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Review

European Cystic Fibrosis Society Standards of Care: Best Practice guidelines

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Abstract

Specialised CF care has led to a dramatic improvement in survival in CF: in the last four decades, well above what was seen in the general population over the same period. With the implementation of newborn screening in many European countries, centres are increasingly caring for a cohort of patients who have minimal lung disease at diagnosis and therefore have the potential to enjoy an excellent quality of life and an even greater life expectancy than was seen previously. To allow high quality care to be delivered throughout Europe, a landmark document was published in 2005 that sets standards of care. Our current document builds on this work, setting standards for best practice in key aspects of CF care. The objective of our document is to give a broad overview of the standards expected for screening, diagnosis, pre-emptive treatment of lung disease, nutrition, complications, transplant/end of life care and psychological support. For comprehensive details of clinical care of CF, references to the most up to date European Consensus Statements, Guidelines or Position Papers are provided in Table 1. We hope that this best practice document will be useful to clinical teams both in countries where CF care is developing and those with established CF centres.

Keywords: Cystic fibrosis; Standards of care; Multidisciplinary management

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1. Newborn screening and access to specialist care from early in life

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The ECFS Neonatal Screening Working Group (Core Committee)

There is clear evidence to support newborn screening for CF. Early recognition provides the foundation for future management and prevents the delay in diagnosis that has affected so many families [1]. Protocols should be designed to reflect the culture and CFTR genetics of each population and minimise potential negative impacts. Please refer to the ECFS guidelines on newborn screening and on the management of young infants with CF diagnosed through screening [2,3].

1.1. 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

Table 1
European consensus statements, guidelines or position papers.

First author and topic	Consensus (C), guideline (G) or position papers (P)	Web URL
Screening		
Castellani C [118]	Benchmarks for cystic fibrosis carrier screening: A European consensus document (C)	http://www.sciencedirect.com/science/article/pii/S1569199310000275
Castellani C [2]	European best practice guidelines for cystic fibrosis neonatal screening (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/Castellani_2009_Journal-of-Cystic-Fibrosis.pdf
Sermet-Gaudelus I [3]	Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening (G)	http://www.sciencedirect.com/science/article/pii/S1569199310000652
Diagnosis		
Mayell SJ [4]	A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis (C)	http://www.elsevier.com/__data/promis_misc/JCF8.pdf
Castellani C [10]	Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice (C)	http://www.elsevier.com/__data/promis_misc/JCF7.pdf
Bombieri C [119]	Recommendations for the classification of diseases as CFTR-related disorders (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S86_S102.pdf
Prevention of progression of lung disease		
Döring G [120]	Early intervention and prevention of lung disease in cystic fibrosis: a European consensus (C)	http://www.elsevier.com/__data/promis_misc/2004.pdf
Optimal nutrition and management of metabolic complications		
Sinaasappel M [49]	Nutrition in patients with cystic fibrosis: a European consensus (C)	http://www.elsevier.com/__data/promis_misc/2002.pdf
Sermet-Gaudelus I [61]	European cystic fibrosis bone mineralisation guidelines (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S16_S23.pdf
Treatment of the complications		
Döring G [31]	Treatment of lung infection in patients with cystic fibrosis: current and future directions (P)	https://www.ecfs.eu/ecfs-standards-care/references
Colombo C [77]	Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S24_S28.pdf
Debray D [68]	Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S29_S36.pdf
Heijerman HJ [121]	Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus (C)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF_article.pdf
Edenborough F [55]	Guidelines for the management of pregnancy in women with cystic fibrosis (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/Pregnancy.pdf
Tranplantation and end of life		
Hirche T [86]	Practical guidelines: lung transplantation in patients with cystic fibrosis (G)	http://dx.doi.org/10.1155/2014/621342
Sands D [87]	End of life care for patients with cystic fibrosis (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S37_S44.pdf
Psychosocial support		
Nobili R [108]	Guiding principles on how to manage relevant psychological aspects within a CF team: interdisciplinary approaches (G)	https://www.ecfs.eu/files/webfm/webfiles/File/documents/JCF%20Articles/JCF10_Sup2_S45_S52.pdf

of CF is less than 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.

1.2. 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.

1.3. 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 less than 0.5%. More than 20 repeats for every 1000 infants are unacceptable (2%).

1.4. 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).

1.5. 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)

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). Mechanisms should be in place for the collection of reliable long-term false negative data.

1.6. 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 normally reported to the family on the same day.

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

The majority of infants with a confirmed diagnosis after NBS should be seen by the CF specialist 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.

1.8. 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 which they may refer later. Information should also be sent to the family primary care physician.
b) The information should be clear that:

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

1.9. 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. The 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.

1.10. What are the minimal acceptable standards for the recognition and management of infants with an equivocal diagnosis 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 infant and have a clear understanding of what to expect with respect to progress and possible symptoms. Information should also be sent to the family primary care physician.

2. Diagnosis

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* 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 [4].

It is mandatory to have a high standard of care for diagnostic evaluation in cystic fibrosis. Diagnostic confirmation is required not only for children and adults presenting with suggestive clinical features, but also for infants with a positive newborn screening test or occasionally a positive family history. The following statements refer to a diagnosis outside of newborn screening.

2.1. What are the minimal requirements to undertake the diagnosis for CF? [5,6]

a) To be able to undertake sweat testing to the standards described below.
b) To be able to perform genetic testing for the most appropriate panel 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.

2.2. What are the diagnostic criteria for CF? [5–7]

A sweat chloride above 59 mmol/L
and/or
two CF causing CFTR mutations in *trans* [†]
and
at birth or clinical features, 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 (males).

2.3. What are the minimal standards for laboratories performing sweat tests? [8]

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. Internal quality control (usually three samples) of the sweat analysis with acceptable limits of agreement for chloride before each sample.
b) Use of a commercially available equipment approved for diagnostic use.
c) A regular external quality assurance for analytes according to national guidelines.

2.4. What are the diagnostic standards of a sweat test? [9]

a) The quantity of sweat should indicate an adequate rate of sweat production (15 μL for Macroduct™ tube system).
b) A sweat chloride value greater than 59 mmol/L is consistent with a diagnosis of CF.
c) In the first six months of life a sweat chloride value less than 30 mmol/L makes the diagnosis of CF unlikely. There is no international agreement on the lower limit of the borderline range after that age, and thresholds of 30 or 40 mmol/L have been suggested.
d) Individuals with sweat chloride values in the borderline range should undergo a repeat sweat test and further evaluation in a CF specialist centre, including a detailed clinical assessment and extensive CFTR gene mutation analysis [9,10].

2.5. What are the minimal standards for a laboratory performing mutation analysis for CFTR? [10]

a) The laboratory should be able to perform DNA testing using dried blood spot samples, whole blood (EDTA) and buccal swabs.
b) Samples should be analysed at least weekly to avoid significant delay in processing.
c) The laboratory should partake in an external quality assurance exercise with at least an 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 more than 90% of the individuals with CF in a local population.
e) When only one mutation is recognised, an extended exon DNA analysis (gene sequencing) should be available in a primary laboratory or a secondary laboratory.
f) The disease liability of variants detected by DNA sequencing should be validated against the CFTR2.org database. Novel mutations or variants should be reported to locus specific databases (such as CFTR1 http://www.genet.sickkids.on.ca/app) in order to facilitate future interpretation of variants of unknown clinical significance.

2.6. What is a CF causing mutation?[10]

a) Since CF is an autosomal recessive disease the diagnosis of CF is substantiated in patients who bear two CF causing mutations (classified in the CFTR-2 database) in *trans* (i.e. one on each homologous chromosome). However, absence of two CF-causing mutations after extended DNA testing in the presence of other typical clinical, laboratory features of the disease or abnormal CFTR bioassays (see below) does not rule out CF.
b) Patients with "mutations of varying consequence" require further evaluation in a CF specialist centre.

2.7. What are the minimal acceptable standards of care for reporting a diagnosis of CF to a symptomatic patient? [2]

a) A positive CF diagnostic test result should be reported promptly (ideally within 24 h).
b) The patient or parents/carers should receive clear written and verbal information about the disease and be provided with access to electronic media from the health service/national patient organisation. Contact information of the appropriate

[†] The term "mutation" is synonymous with "pathogenic variant", according to the CFTR-2 database http://www.cftr2.org.

CF centre should be given (in accordance with treatment pathways for newly diagnosed CF in each country).
c) Genetic counselling should be offered and contacts for clinical genetic services provided. This will facilitate prevention of CF in affected families, including their relatives who may have an increased risk of the disease.
d) An early follow-up appointment should be arranged to assess understanding (no more than one week) and contact information of the CF centre should be given.
e) Patients and parents/carers should receive advice on other information resources, in particular the internet.
f) At the initial diagnostic meeting patients and parents/carers should receive information about the model for future clinical care.

2.8. What are the minimal standards of care and follow-up for a newly diagnosed patient?[5]

A patient diagnosed with CF should have immediate access to a CF specialist centre which has the multi-disciplinary capacity to provide care that complies with the ECFS standards of care.

2.9. What are the minimal standards of care and follow-up for patients with symptoms suggestive of CF and intermediate sweat chloride values?[5,6]

a) A patient in whom the diagnosis is suggestive of CF and an intermediate sweat chloride concentration and only one or no mutation is identified should have access to a CF specialist centre for an 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 CF specialist centre.
b) Ancillary tests may help establish a diagnosis of CF by revealing a second organ disease phenotype, such as pancreatic insufficiency (faecal pancreatic elastase), CBAVD in males, lung or sinus involvement, or by identifying an ion channel abnormality (see section 2.10).
c) These patients must be monitored carefully for development of any complications and appropriate therapy implementation.

2.10. Should a patient with equivocal diagnosis have CFTR bioassay tests (nasal potential difference, intestinal current measurement)? [11]

Patients with a diagnosis that is not clearly CF, should be assessed by a CF specialist. In cases with intermediate sweat test results, further electrophysiological investigations (nasal potential difference, intestinal short circuit current measurement) should be arranged if available.

3. Prevention of progression of lung disease by ensuring all patients have access to therapies of proven effectiveness

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Life expectancy in CF has improved dramatically in the last 4 decades [12]. However, the majority of CF patients still die of respiratory failure [13] 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 [14]. 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.

3.1. 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 [15]. There is no clear evidence how quickly an eradication therapy should be commenced, but treatment should be started promptly (not more than 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 [16]. Options include 28 days of tobramycin solution for inhalation (TIS) and up to 3 months of a combination of nebulised colistin and oral ciprofloxacin [17]. Follow-up cultures to document eradication after treatment are crucial.

3.2. How should chronic bacterial infection with Pseudomonas aeruginosa be treated?

When eradication therapy has failed, the diagnosis of chronic infection is made and long term inhaled antibiotic therapy should be commenced [18]. 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 [19]. Whilst studies are lacking for children younger than 6 years, treatment at equivalent doses is also recommended in this age group. The licenced 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 [20]. Inhaled aztreonam lysine [21] is recommended as an alternative by both European and US guidelines. Colistin (2 MU twice daily) is used widely in Europe and is now also available as a dry powder preparation [22]. A specialist physiotherapist should advise on the timing of inhalational drugs and in an appropriate inhalation technique.

3.3. 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*.

3.4. 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 [17]. There is no evidence to support prophylactic therapy for other bacteria.

3.5. 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 [23] and US [24] guidelines and should be available to all CF patients. A recent head-to-head trial [25] 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 [26]. Flexibility and appreciation of patient preference are essential when prescribing a suitable airway clearance technique [27]. 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 [26]. 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 [28].

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

a) 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 a PEX but it is essential that these episodes are diagnosed and treated promptly. Patients having 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 PEXs include lung function measurements, microbiological testing and radiological tests. Treatment of a PEX usually requires antibiotics which can be administered orally via inhalation or intravenously. If the patient needs hospital admission for intravenous antibiotic therapy it is important that this is not delayed.

b) 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.

c) 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) [29]. For *P. aeruginosa*, a combination of two or more antibiotics is recommended and, although evidence is lacking, 14 days of intravenous treatment is routine [30]. 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.

d) Evaluating response to therapy.

It is important to monitor lung function at the beginning and end of treatment of a PEX. Despite intensive treatment about 25% of patients experiencing a PEX requiring intravenous antibiotic therapy will have a persisting decline in lung function [14], emphasising the need for maintenance therapies to prevent exacerbations.

3.7. 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 [19,31]. Airway clearance techniques, physical activity and nutritional support are important components in maintaining lung health; here we focus on drug therapy only.

3.7.1. 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 pulmonary exacerbations in patients regardless of disease severity [32]. Recent evidence from an analysis of a large data base suggests that dornase alfa reduces lung function decline [33]. 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 [34].

3.7.2. 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 complimentary. Hypertonic saline and mannitol are available as inhaled agents in Europe. Hypertonic saline (7%) has been shown to reduce pulmonary exacerbations and marginally improve lung function in a

systematic review [35]. H ypertonic saline is currently used in many patients with moderate to severe lung disease and is supported by guidelines [19]. Mannitol has been introduced more recently and improves lung function [36,37]. 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.

3.7.3. 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 question 1 above) 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 [18] and is therefore part of standard of care [17,19]. Inhaled antibiotic therapy should be administered as long term maintenance therapy with either single agent therapy or alternating therapy of different antibiotics. The benefits of treatment outweigh the risks associated with the development of antimicrobial resistance which is often overcome by high topical antibiotic concentrations.

3.7.4. 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 PEXs in chronically infected patients [38] and is part of recommended care [19]. A reduction in pulmonary exacerbations has also been observed in younger patients not infected with *P. aeruginosa* [39]. Some concerns remain, regarding the durability of their effect and their impact on inducing resistance for other bacteria.

3.8. 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 [40]. 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.

3.9. CFTR modulator therapy — which treatments address the underlying defect in CF?

Current treatment largely addresses the symptoms caused by the defective gene whilst CFTR pharmacotherapy aims to increase protein expression at the cell surface, or its function, with drug therapy. This treatment strategy could make a major difference in altering or even halting the disease process. Different drugs targeting specific classes of CFTR defects are currently being studied; to date only one drug has clearly demonstrated clinical efficacy. Ivacaftor, a CFTR potentiator studied in the gating mutation G551D, not only enhanced ion transport reflected by reductions in sweat chloride concentrations but also improved clinical measures such as lung function and PEXs [41]. The effect size of lung function changes exceeded that observed for any drug therapy available for CF patients to date. Whilst this mutation is found in less than 5% of patients worldwide, ivacaftor is a proof of principle demonstrating the potential impact of CFTR pharmacotherapy. In patients with the G551D mutation ivacaftor should be part of standard of care.

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

Aspergillus fumigatus as well as other fungi are commonly found in sputum of CF patients. Whilst their relevance is not entirely clear, more recent evidence suggests that *A. fumigatus* may act as a pathogen in at least in some CF patients [42]. Sputum cultures in CF patients should therefore include assessments for fungi. Allergic bronchopulmonary aspergillosis is a well characterised complication in CF patients and should be considered in any patient with clinical deterioration not responding to antibiotic therapy [17]. 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 [17].

3.11. How should we monitor lung disease?

- A multi-disciplinary team is needed to assess and discuss all aspects of CF care.
- Regular monitoring includes assessment of competence of airway clearance and inhalation technique and monitoring of adherence.
- Clinical assessments that should be performed at least every 3 months and at times of symptomatic deterioration [43].
- As airway infection is a major driver of CF lung disease airway cultures should be obtained at every clinic visit [17]. The microbiological assessment needs to include specific culture media for the range of CF pathogens to ensure that relevant organisms are not overlooked.
- Lung function testing guides therapy and should be performed at every clinic visit in patients old enough to cooperate (usually 5 years and older) [43]. Tests for younger children are currently under development. Routine lung function testing should include spirometry performed according to ATS/ERS criteria [44] and testing pre and post bronchodilator should be available.

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.

4. Optimal nutrition and management of metabolic complications of cystic fibrosis

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

4.1. 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 achieve 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 [3,5,45–51].

4.2. 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 [3,43,45–53].

4.3. 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 simple and reliable 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. Inappropriate doses of PERT may result in abdominal pain and constipation.

Guidelines for testing for EPI and dosing of enzymes are available [3,46–51,54].

4.4. What are the main strategies to providing preventive nutritional care?

CF centres should be familiar with the recommendations for age-appropriate dietetic advice directed by CF dietitians [3,5,43,45-51,54–56]. This includes:

- Assessment of EPI and administration of PERT.
- Selection of appropriate diet, with attention to a high fat intake.
- Behavioural therapy to achieve positive mealtime experiences.
- Providing sodium supplementation, when necessary, with special awareness in newborn screened infants.
- Supplementing fat soluble vitamins, as indicated by laboratory testing.

Women with CF who plan their pregnancies should receive pre-conception advice to improve their nutritional status [55].

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

Evaluation should be triggered by weight loss, or decline in weight or length/height percentile (<2 years of age), or decline in BMI percentile for age and gender (>2 years of age), or 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.

4.6. 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.

- *Anticipatory guidance.* Reinforcement of adherence to diet, sodium and enzyme recommendations, using behavioural modification or motivational interviewing
- *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
- *Severe malnutrition.* Enteral feeding via NG or gastrostomy tubes usually improves and maintains nutrition in a patient with CF

Other therapies: Cyproheptadine and growth hormone are not part of routine management. Parenteral nutrition is only appropriate when enteral nutrition is impossible or fails.

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) [45–49,56].

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

All CF patients who have not been diagnosed with 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 OGTT requires confirmation with a second test. Refer to the published guidelines for additional detail.

Published guidelines [57–59] 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.

4.8. 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 [57–59].

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.

4.9. 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 [60–62].

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 [60–62].

4.10. 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 [60–62].

5. Treatment of the complications of cystic fibrosis in a timely and effective way

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5.1. Pulmonary complications

Patients with cystic fibrosis (CF) may develop a variety of complications which, although infrequent, occur commonly enough that 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.

5.1.1. 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 [63]. 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, CT chest). Management guidelines have been published [64]; 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.

5.1.2. 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/day or >100 ml/day for several days [65]. Management guidelines have been published [64]. 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 embolisation) and/or thoracic surgery.

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

The natural history CF lung disease is progression to advanced stage airways obstruction and eventual respiratory failure. The Centre should recognize progression to this stage and have discussions about lung transplant and advanced healthcare directives (see Section 6). 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 [56]. Ventilatory support (e.g. non-invasive ventilation) should be provided in accordance with the patient's wishes for palliation of dyspnea [43]. The Centre should be able to assess the need for opiates to relieve dyspnea and pain associated with advanced stage disease [66,67].

5.2. Liver and pancreas complications

5.2.1. 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. Cystic fibrosis related liver disease (CFLD) is a biliary cirrhosis that usually presents before age 20 years and can lead to portal hypertension and hepatic failure [68,69]. 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 [68–70].

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 immunisation 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). The Centre should have a pathway for referral to a liver transplant programme, for those patients with advanced stage liver disease.

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

Cholelithiasis is not always symptomatic [71]. The Centre should be suspicious when evaluating the patient with non-specific 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.

5.2.3. 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 [72]. Recurrent acute pancreatitis may contribute to the transition from pancreatic sufficiency to insufficiency in CF. The presentation may be a nonspecific abdominal pain, so there should be a high suspicion when seeing a patient with a 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 not different than for non-CF pancreatitis. However, acute pancreatitis is associated with severe dehydration and in the CF population, this may be more severe and attention to rehydration and electrolyte monitoring is crucial.

5.3. Gastrointestinal complications

5.3.1. What is the best way to manage gastroesophageal reflux disease (GORD) in patients with CF?

GORD occurs commonly in patients with CF, affecting approximately 30% [73]. The Centre should be aware of the signs and symptoms of GORD and be able to provide appropriate diagnostic testing (i.e. impedance and pH probe, upper endoscopy) and treatment [74].

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

Constipation has a slow onset with reduced stool frequency [75]. It is common in CF and may be exacerbated by the use of narcotics. Most of the time constipation responds to hydration therapy, stool softeners (e.g., polyethylene glycol) or laxatives [76]. Enemas are rarely needed.

5.3.3. 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 [75]. The Centre should be able to recognise this complication (and its variants) and have standard protocols for diagnosis and treatment based upon published recommendations [43,75,77]. 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. Surgical intervention should be considered only in extreme situations and so the Centre should have surgeons who know about the gastrointestinal complications of CF.

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

This is an uncommon complication. 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 [49].

5.3.5. What is the best treatment for appendiceal mucocele?

Ultrasonography will aid the diagnosis [78]. In case of symptoms, appendectomy with resection of the appendix edges and resection of the caecal tip will avoid risk of recurrence.

5.3.6. What is the best way to manage small bowel overgrowth in patients with CF?

Small bowel overgrowth is suspected when patients have diffuse or periumbilical abdominal pain, excessive bowel gas, nausea, and malabsorption despite adequate enzyme intake. Risk is higher in patients who have had previous intestinal surgery or are using narcotics. It is recommended that diagnosis be made by clinical therapeutic trial of metronidazole [79]. An opinion from a gastroenterologist is essential.

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

MI is a neonatal emergency best handled by a pediatric surgeon (and pediatric radiologist) with expertise in MI, who should liaise promptly with the CF centre. The surgical team should be familiar with both non-surgical and surgical management [80,81]. Complicated MI is more severe, more difficult to treat, and may require prolonged hospitalisation. Post-operative management may require a centre familiar with nutritional management of short bowel syndrome.

5.4. Other complications

5.4.1. 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).

The Centre should utilise standard protocols for therapeutic drug monitoring when using aminoglycosides following recommended treatment dosing [17]. There should be strict avoidance of NSAIDs when using intravenous (IV) aminoglycosides 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 have access to a clinician experienced in vestibular assessment.

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

Nephrolithiasis is common in CF patients [82]. The Centre should be aware of the signs and symptoms associated with nephrolithiasis and able to evaluate by urinalysis and CT-IVP. The metabolic disorder causing kidney stones should be determined. The Centre should have access to a urology specialist and interventional radiologist for complicated nephrolithiasis.

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

Arthralgias are common symptoms in CF patients [73] but arthropathy remains poorly understood. The Centre should be aware of this problem and have access to a rheumatologist who has knowledge of CF.

5.4.4. 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 [73]. The Centre should routinely evaluate sinus disease and offer a recommended treatment, recognizing that this could be a source for lower airways infection [83]. The Centre should have access to diagnostic testing (i.e. CT sinus) and to an otolaryngologist experienced with CF-related sinus disease.

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

With the exception of ABPA, discussed elsewhere in this document, the prevalence of allergic disease is not increased in CF patients and can be managed as for the general community. However patients can develop drug allergies (e.g. antibiotics) that can complicate treatment decisions. The Centre should be aware of the signs and symptoms of possible allergic response to treatment and should know when to stop that therapy accordingly. The Centre should have established protocols for desensitisation.

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

An indwelling IV 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. Port-A-Cath). Only trained individuals should 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) [84,85]. The Centre should have a keen awareness of the signs and symptoms of catheter-related complications and be able to perform proper testing including blood cultures (to assess for infection), ultrasonography and contrast radiology studies (CT or MRI) for vascular occlusion.

5.4.7. 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 as having 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 [55].

5.4.8. 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 counselling regarding fertility options including assisted reproductive techniques.

6. Transplantation and appropriate management of end of life issues

Scott Bell (Aus)
Alistair Duff (UK)

6.1. Summary

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 success transplant. In some patients, transplant is not a suitable treatment option or does not occur. 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. These standards include a series of questions about the approach to transplantation assessment and end of life care, utilising available published evidence and published transplant 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 [86] and the ECFS End of Life Care Guidelines [87].

6.2. Questions

6.2.1. What are the important determinants for the 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 that are associated with increased mortality [88,89] and where transplantation referral [89] is recommended are in patients with:

- FEV_1% predicted of ≤ 30% predicted,
- Rapid decline, particularly female and younger patients,
- Oxygen therapy for hypoxaemia,
- Hypercapnia,
- Frequent exacerbation that responds poorly to intravenous antibiotics.

Earlier referral should be considered in patients with refractory pneumothorax and recurrent massive haemoptysis [89]. 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 [90,91]. 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.

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

Priority for transplantation [88,89,92] should be given to CF patients with:

- Oxygen-dependent respiratory failure,
- Chronic hypercapnia,
- Pulmonary hypertension,
- Undernutrition, 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.

Regular and detailed communication with the Transplant Service is vital to allow regular updates of the clinical progress of all wait-listed patients.

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

Exclusions for lung transplantation [89] include:

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

Most transplant services do not assess patients with:

- Chronic *Burkholderia cenocepacia*
- *Mycobacteria abscessus*.

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

Combined 'liver/lung' or 'lung only' transplantations require careful consideration in patients with advanced lung disease and portal hypertension.

6.2.4. 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 [92].

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. Optimising control of CFRD is important whilst wait-listed [93,94].

Chronic kidney disease (CKD) occurs in many adults with CF and where practical, limiting exposure to nephrotoxic drugs pre-transplant should be considered [95]. The impact of long-term systemic use of aminoglycosides before transplantation on post-transplant renal function is uncertain [96]. Calcineurin inhibitors, hypertension and CFRD have been associated with CKD following transplantation.

Osteoporosis (24%) and osteopenia (38%) is reported in patients with CF [97]. Biphosphonate 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. APBA). Limiting daily dose of prednisolone to <15 mg/day will assist in healing and reduce post-operative infection risk and limit further reduction in bone density.

Psychologically it is vital to help patients maintain hope and counter demoralisation or exhaustion.

6.2.5. 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 [98].

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) [98,99].

Transplantation from the ventilator is associated with higher early mortality [100] 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 Extracorporeal Membrane Oxygenation (ECMO) for severe respiratory failure. Case reports have suggested excellent outcomes [101]. Close communication between the CF Team and the Transplant Service is mandatory prior to ECMO initiation.

6.2.6. 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) [102].

Symptoms that frequently require control include dyspnoea, chest pain, headaches, fatigue and poor sleep quality [103]. The use of narcotic analgesic, anxiolytics, airway clearance support, psychological strategies, oxygen and non-invasive ventilation support are important [67]. Teams should access support from palliative care colleagues to optimise symptom control, when required [103,104].

The balance between effective active treatments whilst providing adequate symptom control can be difficult especially in patients waiting for transplant [103,105]. Symptom control does not preclude lung transplantation, however close communication between CF and Transplant teams is vital [103].

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 [103].

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

Patients' and families' wishes should be the key to making decisions about where to manage the dying patient and where practical, measures taken to assist facilitating these wishes. 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 prefer to have care by a staff that they know well in a familiar environment [106] and, in many cases, prefer to receive care in a hospital [103,107].

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.

6.2.8. 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).

7. Psychosocial support

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Living with CF can be emotionally and physically challenging for the patient 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 medical team and there is a substantial body of literature that establishes the essential elements of the psychosocial role [5,108]. The focus of this paper is to prioritise key psychosocial issues and make recommendations for appropriate management.

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

Diagnosis of CF for the majority is by newborn screening. Screening for CF aims to minimise morbidity and mortality, yet potential disadvantages must be recognised and effects minimised [2]. 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 [109]. Preventative counselling 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 balance between managing a complex health condition and enabling their child to grow with good self-esteem and concept. Families should be hopeful that their child will enter adulthood having a good quality of life with achievements similar to non-CF peers.

Key tasks are to advise on:

- Establishing treatment with baby's daily-routine
- Helping parents accept and administer treatment
- Communicating to family and friends about the medical condition
- The availability of psychosocial follow-up for parents if required including couple counselling
- Available financial support/benefits/allowances and other sources of support.

7.2. International Depression/Anxiety Epidemiology Study (TIDES)

European data emerging from the International Depression/Anxiety Epidemiology Study (TIDES) show that elevated depression scores are no different to general populations although higher anxiety scores have been reported, particularly amongst women. Several risk factors have emerged for increased depression and anxiety scores amongst patients. Anxiety and depression also appear particularly problematic in parents. Support for these problems should be available from the CF service. In what ways should they be identified and addressed?

The CF team needs to assess the psychological well-being of people with CF routinely (see Centre Framework for access to psychological professionals). Surveillance for depression and anxiety in patients and parents should be conducted during annual review with psychometrics (e.g. HADS, CES-D) or discussion.

Elevated psychometric scores require diagnostic confirmation. This should be undertaken by the CF Team psychologist via clinical interview. Where there is no integrated psychologist, referral should be considered to mental health agencies.

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

7.3. 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:

i. Parental adaptation to diagnosis
ii. Commencement of schooling; nursery, primary and secondary
iii. Parental- to self-guided treatment
iv. Transition of care from paediatric to adult services
v. Entering the workplace or further education
vi. Loss of independence (e.g. retirement, loss of activities and functioning, increased reliance on intrusive treatments and carers, and facing transplantation or end of life).

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 [110]. The primary focus should be to increase social 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.

7.4. 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 progression of disease. Successful psychosocial intervention is determined by: (i) the Team ethos to patient care, (ii) collaboration with patients to increase their motivation and (iii) identifying barriers and actively supporting patients' efforts to increase treatment.

i. 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 needs for involvement and making informed choice. Psycho-social professionals need to support team-members' efforts to engage patients in conversation using active-listening skills
ii. 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 [111]
iii. A range of psychological strategies are effective (e.g., reinforcement scheduling, problem-solving). Clinical trials of interventions are ongoing. Psychosocial professionals must achieve competence and provide leadership about techniques.

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

CF diagnosed beyond childhood may be for a range of reasons, mild or mis-diagnosed symptoms or less severe phenotype [112]. Patients often are angry and overwhelmed by information (prognosis, infertility) and 'technical' aspects of busy CF clinics. This leads to challenges in building a trusting alliance. A flexible and individualised approach to clinical management is needed for the particular patient which differs from the routine care provided to those diagnosed in early childhood. Emphasis must be placed on prognosis, fertility issues, personal support, and reviewing what CF knowledge patients may have acquired and from where (some sources being misleading) [113].

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

Competing demands from CF management including monitoring of nutritional status emphasising weight gain within a culture emphasising thinness contribute to confused attitudes towards eating. Disordered eating and body image problems have been reported in people with CF [114].

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 idea.

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 is recommended.

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

Key issues of adulthood are (i) normal tasks of adulthood being made more complex due to CF, (ii) making complex decisions (e.g. making vocational plans or making treatment decisions) and, (iii) coping with deterioration in health and loss of mobility and independence, as well as new complications diagnoses (e.g., CFRD), that can lead to, for example, increased anxiety and depression (demoralisation), low self-esteem and relationship difficulties.

Key approaches are:

i. A pro-active approach during routine clinics and assessment during annual review can help identify emotional, practical and social support requirements (e.g., employment, fertility, risk-taking behaviours). Patients tend not to initiate these [115,116]
ii. Referral to a CF team's psychosocial professional or external specialist mental health services.

CF teams must be aware of the likelihood of demoralisation occurring as a consequence of multiple health problems. This resembles, but is different from, depression in personal impact and treatment [117].

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

All members of the Team need to have some psychosocial skills. A 4-step skills model is described;

i. Team members should have training to enable recognition of psychological needs and provide information and general psychological support. Be able to access psychiatric services in an emergency.
ii. A team member can have additional training to: enable screening and referral for psychological distress, administer psychological first-aid following traumatic medical events (e.g., haemoptysis) and implement particular psychological techniques (e.g., desensitisation to painful procedures).
iii. Trained and accredited team member to assess for psychological distress and implement specific therapeutic techniques (e.g. counselling or therapy delivered according to an explicit framework). Requires supervision from a qualified mental health trained professional.
iv. Qualified mental health specialist (e.g. clinical psychologist), who can diagnose psychopathology and treat using specialist psychological interventions.

Conflict of interest

A.R. Smyth: personal fees from Gilead, other from MPEX, other from Pharmaxis, other from Vertex, grants from Forest Labs, outside the submitted work; S.C. Bell: grants and non-financial support from Vertex Pharmaceuticals, personal fees and other from Novartis, other from Gilead, personal fees and other from Rempex, outside the submitted work; P. Flume: grants and personal fees from Aptalis, grants and personal fees from Gilead Sciences, Inc, grants and personal fees from Bayer Healthcare AG, grants and personal fees from Novartis, grants and personal fees from Vertex Pharmaceuticals, Inc, grants and personal fees from Pharmaxis Limited, grants from Boehringer Ingelheim Pharmceuticals, grants from Grifols, grants from Savara Pharma, grants from KaloBios, grants from Cystic Fibrosis Foundation, grants from National Institutes of Health, grants and personal fees from Genentech, outside the submitted work; A. Munck: personal fees from Vertex, Novartis, personal fees from Vertex, outside the submitted work; F. Ratjen: personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Vertex, personal fees from Novartis, personal fees from Bayer, personal fees from Talecris, personal fees from CSL Behring, personal fees from Roche, personal fees from Gilead, grants from Novartis, personal fees from Genetech, personal fees from Genetech, personal fees from Pari, outside the submitted work; S.J. Schwarzenberg: consulting for Spark HealthCare, outside the submitted work; G. Ullrich: personal fees from Chiesi Pharma GmbH, personal fees from Novartis Pharma GmbH, personal fees from Gilead Sciences GmbH, personal fees from GSK GmbH & Co. KG, personal fees from Activaero GmbH, personal fees from Axcan Pharma GmbH, outside the submitted work. S. Bojcin, M. Bryon, A. Duff, N. Kashirskaya, I. Sermet-Gaudelus, K.W. Southern, G. Taccetti, and S. Wolfe have no conflicts of interest to report.

References

[1] Southern KW, Mérelle MME, Dankert-Roelse JE, Nagelkerke A. Newborn screening for cystic fibrosis. Cochrane Database Syst Rev 2009(1). http://dx.doi.org/10.1002/14651858.CD001402.pub2 [Art. No.: CD001402].
[2] Castellani C, Southern KW, Brownlee K, Dankert Roelse J, Duff A, Farrell M, et al. European best practice guidelines for cystic fibrosis neonatal screening. J Cyst Fibros 2009;8:153–73.

[3] Sermet-Gaudelus I, Mayell SJ, Southern KW. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. J Cyst Fibros 2010;9:323–9.

[4] Mayell SJ, Munck A, Craig JV, Sermet I, Brownlee KG, Schwarz MJ, et al. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. J Cyst Fibros 2009;8:71–8.

[5] Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros 2005;4:7–26 [S1569–1993(04)00213–9 [pii]1016/j.jcf.2004.12.002.].

[6] Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153: S4–S14.

[7] De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J, et al. Cystic fibrosis: terminology and diagnostic algorithms. Thorax 2006;61:627–35.

[8] ECFS CTN SOP on sweat testing; 2013.

[9] Goubau C, Wilschanski M, Skalicka V, Lebecque P, Southern KW, Sermet I, et al. Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. Thorax 2009;64:683–91.

[10] Castellani C, Cuppens H, Macek Jr M, Cassiman JJ, Kerem E, Durie P, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros 2008;7:179–96.

[11] De Boeck K, Kent L, Davies J, Derichs N, Amaral M, Rowe SM, et al. CFTR biomarkers: time for promotion to surrogate end-point. Eur Respir J 2013;41:203–16. http://dx.doi.org/10.1183/09031936.00057512.

[12] Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947–2003. Eur Respir J 2007;29:522–6.

[13] Cystic Fibrosis Foundation Patient Registry. 2005 Annual data report to the center directors. Bethesda, MD: Cystic Fibrosis Foundation; 2006.

[14] Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med 2010;182: 627–32.

[15] Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL, Emerson J, et al. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002;34:91–100.

[16] Langton-Hewer SC, Smyth AR. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. Cochrane Database Syst Rev 2006(4). http://dx.doi.org/10.1002/14651858.CD004197.pub3 [Art. No.: CD004197.(updated 2010)].

[17] Antibiotic treatment for cystic fibrosis. Report of the UK Cystic Fibrosis Trust Antibiotic Group. London: UK Cystic Fibrosis Trust; 2009.

[18] Ryan G, Singh M, K. D. Inhaled antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev 2011(3). http://dx.doi.org/10.1002/14651858.CD001021.pub2 [Art. No.: CD001021].

[19] Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Am J Respir Crit Care Med 2013;187:680–9. http://dx.doi.org/10.1164/rccm.201207-1160OE.

[20] Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: the EAGER trial. J Cyst Fibros 2011;10:54–61.

[21] Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010;45:1121–34.

[22] Schuster A, Haliburn C, Döring G, Goldman MH. Group ftFS. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. Thorax 2013;68:344–50.

[23] Association of Chartered Physiotherapists in Cystic Fibrosis. Standards of care and good clinical practice for the physiotherapy management of cystic fibrosis. London: UK Cystic Fibrosis Trust; 2011.

[24] Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand D-B, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care 2009;54:522–37.

[25] McIlwaine MP, Alarie N, Davidson GF, Lands LC, Ratjen F, Milner R, et al. Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. Thorax 2013. http://dx.doi.org/10.1136/thoraxjnl-2012-202915.

[26] International physiotherapy group for cystic fibrosis. Physiotherapy for people with Cystic Fibrosis: from infant to adult; 2009 [http://www.cfww.org/docs/ipg-cf/bluebook/bluebooklet2009websiteversion.pdf].

[27] Homnick DN. Making airway clearance successful. Paediatr Respir Rev 2007;8:40–5.

[28] Wilkes DL, Schneiderman JE, Nguyen T, Heale L, Moola F, Ratjen F, et al. Exercise and physical activity in children with cystic fibrosis. Paediatr Respir Rev 2009;10:105–9. http://dx.doi.org/10.1016/j.prrv.2009.04.001.

[29] de Groot R, Smith AL. Antibiotic pharmacokinetics in cystic fibrosis. Differences and clinical signifance. Clin Pharmacokinet 1987;13: 228–53.

[30] Flume PA, Mogayzel PJ, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med 2009;180:802–8. http://dx.doi.org/10.1164/rccm.200812-1845PP.

[31] Döring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. J Cyst Fibros 2012;11:461–79.

[32] Jones AP, Wallis CE. Dornase alfa for cystic fibrosis. Cochrane Database Syst Rev 2010(3). http://dx.doi.org/10.1002/14651858.CD001127.pub2 [Art. No.: CD001127.].

[33] Konstan MW, Wagener JS, Pasta DJ, Millar SJ, Jacobs JR, Yegin A, et al. Clinical use of dornase alfa is associated with a slower rate of FEV1 decline in cystic fibrosis. Pediatr Pulmonol 2011;46:545–53. http://dx.doi.org/10.1002/ppul.21388.

[34] Nash E, Stephenson A, Ratjen F, Tullis E. Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. Cochrane Database Syst Rev 2009(1). http://dx.doi.org/10.1002/14651858.CD007168.pub2 [Art. No.: CD007168].

[35] Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev 2009(2). http://dx.doi.org/10.1002/14651858.CD001506.pub3 [Art. No.: CD001506].

[36] Bilton D, Robinson P, Cooper P, Gallagher CG, Kolbe J, Fox H, et al. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. Eur Respir J 2011;38:1071–80.

[37] Aitken ML, Bellon G, De Boeck K, Flume PA, Fox HG, Geller DE, et al. Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. Am J Respir Crit Care Med 2012;185: 645–52.

[38] Southern KW, Barker PM, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev 2012(11). http://dx.doi.org/10.1002/14651858.CD002203.pub4 [Art. No.: CD002203].

[39] Saiman L, Anstead M, Mayer-Hamblett N, Lands LC, Kloster M, Hocevar-Trnka J, et al. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA 2010;303:1707–15.

[40] Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Cochrane Database Syst Rev 2007(4). http://dx.doi.org/10.1002/14651858.CD001505.pub2 [Art. No.: CD001505.].

[41] Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med 2010;363:1991–2003. http://dx.doi.org/10.1056/NEJMoa0909825.

[42] Amin R, Dupuis A, Aaron SD, Ratjen F. The effect of chronic infection with Aspergillus fumigatus on lung function and hospitalization in patients with cystic fibrosis. Chest 2010;137:171–6.

[43] Standards for the clinical care of children and adults with cystic fibrosis in the UK. London: UK Cystic Fibrosis Trust; 2011.

[44] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38. http://dx.doi.org/10.1183/09031936.05.00034805.

[45] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108:832–9 [S0002-8223(08)00179-X [pii] 10.1016/j.jada.2008.02.020].
[46] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:246–59.
[47] UK cystic fibrosis trust nutrition working group. Bromley: Nutritional management of cystic fibrosis; 2002.
[48] Stapleton D, Ash C, King S, E V. Australasian clinical practice guidelines for nutrition in cystic fibrosis; 2006.
[49] Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002;1:51–75 [S1569199302000322 [pii]].
[50] Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155:S73–93 [S0022-3476(09)00881-6 [pii] 10.1016/j.jpeds.2009.09.001].
[51] Robinson KA, Saldanha IJ, McKoy NA. Management of infants with cystic fibrosis: a summary of the evidence for the cystic fibrosis foundation working group on care of infants with cystic fibrosis. J Pediatr 2009;155:S94–S105 [S0022-3476(09)00882-8 [pii] 10.1016/j.jpeds.2009.09.002].
[52] Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC growth charts for the United States: methods and development. Vital Health Stat 2002;11:1–190.
[53] Multicentre Growth Reference Study Group WHO. WHO child growth standards: methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: Switzerland; 2006.
[54] Anthony H, Collins CE, Davidson G, Mews C, Robinson P, Shepherd R, et al. Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines. Pediatric Gastroenterological Society and the Dietitians Association of Australia. J Paediatr Child Health 1999;35:125–9.
[55] Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. J Cyst Fibros 2008;7(1):S2–S32 [S1569-1993(07)00129-4 [pii] 10.1016/j.jcf.2007.10.001].
[56] Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. Chest 2004;125:1S–39S.
[57] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–708 [33/12/2697 [pii] 10.2337/dc10-1768].
[58] Middleton PG, Wagenaar M, Matson AG, Craig ME, Holmes-Walker DJ, Katz T, et al. Australian standards of care for cystic fibrosis-related diabetes. Respirology 2013;33. http://dx.doi.org/10.1111/resp.12227 [in press].
[59] American Diabetes Association. Clinical practice recommendations. Diabetes Care 2010;33(1):S1–S100 [33/Supplement_1/S3 [pii] 10.2337/dc10-S003].
[60] Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90:1888–96 [jc.2004-1629 [pii] 10.1210/jc.2004-1629].
[61] Sermet-Gaudelus I, Bianchi ML, Garabedian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros 2011;10(2):S16–23 [S1569-1993(11)60004-0 [pii] 10.1016/S1569-1993(11)60004-0].
[62] Cystic Fibrosis Trust UK. Bone mineralisation in cystic fibrosis. Cystic Fibrosis Trust: Bromley; 2007.
[63] Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL, et al. Pneumothorax in cystic fibrosis. Chest 2005;128:720–8.
[64] Flume PA, Mogayzel PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med 2010;182:298–306. http://dx.doi.org/10.1164/rccm.201002-0157OC.
[65] Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL, Flume PA, et al. Massive hemoptysis in cystic fibrosis. Chest 2005;128:729–38.
[66] Robinson WM, Ravilly S, Berde C, Wohl ME. End-of-life care in cystic fibrosis. Pediatrics 1997;100:205–9. http://dx.doi.org/10.1542/peds.100.2.205.
[67] Clayton JM, Hancock KM, Butow PN, Tattersall MH, Currow DC, Adler J, et al. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. Med J Aust 2007;186:S77–S108.
[68] Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros 2011;10(2):S29–36. http://dx.doi.org/10.1016/S1569-1993(11)60006-4.
[69] Sokol RJ, Durie PR. Consensus document recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation: Bethesda; 1999.
[70] Sokol RJ, Durie PR, Group CFFHDC. Recommendations for management of liver and biliary tract disease in cystic fibrosis. J Pediatr Gastroenterol Nutr 1999;28:S1–S13.
[71] Modolell I, Alvarez A, Guarner L, De Gracia J, Malagelada J-R. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. Pancreas 2001;22:395–9.
[72] Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in pancreatitis. J Cyst Fibros 2012;11:355–62. http://dx.doi.org/10.1016/j.jcf.2012.05.001.
[73] Cystic Fibrosis Foundation Patient Registry. Annual data report to the centre directors. Bethesda: Cystic Fibrosis Foundation; 2012.
[74] Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498–547.
[75] Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50:38–42.
[76] Evaluation and treatment of constipation in children: summary of updated recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2006;43:405–7.
[77] Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros 2011;10(Suppl. 2):24–8.
[78] Munck A, Belbari N, de Lagausie P, Peuchmaur M, Navarro J. Ultrasonography detects appendicular mucocele in cystic fibrosis patients suffering recurrent abdominal pain. Pediatric 2000;105:921.
[79] Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am 2010;24:943–59 [viii-ix].
[80] Karimi A, Gorter RR, Sleeboom C, Kneepkens CM, Heij HA. Issues in the management of simple and complex meconium ileus. Pediatr Surg Int 2011;27:963–8.
[81] Carlyle BE, Borowitz DS, Glick PL. A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon. J Pediatr Surg 2012;47:772–81.
[82] Gibney EM, Goldfarb DS. The association of nephrolithiasis with cystic fibrosis. Am J Kidney Dis 2003;42:1–11.
[83] Bonestroo HJC, de Winter-de Groot KM, van der Ent CK, Arets HGM. Upper and lower airway cultures in children with cystic fibrosis: do not neglect the upper airways. J Cyst Fibros 2010;9:130–4. http://dx.doi.org/10.1016/j.jcf.2010.01.001.
[84] Garwood S, Flume PA, Ravenel J. Superior vena cava syndrome related to indwelling intravenous catheters in patients with cystic fibrosis. Pediatr Pulmonol 2006;41:683–7.

[85] Munck A, Malbezin S, Bloch J, Gerardin M, Lebourgeois M, Derelle J, et al. Follow-up of 452 totally implantable vascular devices in cystic fibrosis patients. Eur Respir J 2004;23:430–4. http://dx.doi.org/10.1183/09031936.04.00052504.
[86] Hirche TO, Knoop C, Hebestreit H, et al. Practical guidelines: lung transplantation in patients with cystic fibrosis. Pulm Med 2014;2014:621342.
[87] Sands D, Repetto T, Dupont LJ, Korzeniewska-Eksterowicz A, Catastini P, Madge S. End of life care for patients with cystic fibrosis. J Cyst Fibros 2011;10(Suppl. 2):S37–44.
[88] Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326:1187–91.
[89] Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745–55.
[90] Liou TG, Adler FR, Cahill BC, FitzSimmons SC, Huang D, Hibbs JR, et al. Survival effect of lung transplantation among patients with cystic fibrosis. JAMA 2001;286:2683–9.
[91] Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML, Mayer-Hamblett N, et al. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med 2002;166:1550–5.
[92] Snell GI, Bennetts K, Bartolo J, Levvey B, Griffiths A, Williams T, et al. Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant 1998;17:1097–103.
[93] Bradbury RA, Shirkhedkar D, Glanville AR, Campbell LV. Prior diabetes mellitus is associated with increased morbidity in cystic fibrosis patients undergoing bilateral lung transplantation: an 'orphan' area? A retrospective case–control study. Intern Med J 2009;39:384–8.
[94] Hofer M, Schmid C, Benden C, Speich R, Inci I, Weder W, et al. Diabetes mellitus and survival in cystic fibrosis patients after lung transplantation. J Cyst Fibros 2012;11:131–6.
[95] Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk factors for chronic kidney disease in adults with cystic fibrosis. Am J Respir Crit Care Med 2011;184:1147–52.
[96] Quon BS, Mayer-Hamblett N, Aitken ML, Goss CH. Risk of post-lung transplant renal dysfunction in adults with cystic fibrosis. Chest 2012;142:185–91.
[97] Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int 2010;86:1–7.
[98] Slieker MG, van Gestel JP, Heijerman HG, Tramper-Stranders GA, van Berkhout FT, van der Ent CK, et al. Outcome of assisted ventilation for acute respiratory failure in cystic fibrosis. Intensive Care Med 2006;32:754–8.
[99] Bartz RR, Love RB, Leverson GE, Will LR, Welter DL, Meyer KC. Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. J Heart Lung Transplant 2003;22:433–8.
[100] Mason DP, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. J Thorac Cardiovasc Surg 2010;139:765–73 [e1].
[101] Nosotti M, Rosso L, Tosi D, Palleschi A, Mendogni P, Nataloni IF, et al. Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. Interact Cardiovasc Thorac Surg 2013;16:55–9.
[102] Sage N, Sowden M, Chorlton E, Edeleanu A. CBT for chronic illness and palliative care. Chicester: Wiley; 2008.
[103] Robinson WM. Palliative and end-of-life care in cystic fibrosis: what we know and what we need to know. Curr Opin Pulm Med 2009;15:621–5.
[104] Braithwaite M, Philip J, Tranberg H, Finlayson F, Gold M, Kotsimbos T, et al. End of life care in CF: patients, families and staff experiences and unmet needs. J Cyst Fibros 2011;10:253–7.
[105] Macdonald K. Living in limbo–patients with cystic fibrosis waiting for transplant. Br J Nurs 2006;15:566–72.
[106] Chapman E, Landy A, Lyon A, Haworth C, Bilton D. End of life care for adult cystic fibrosis patients: facilitating a good enough death. J Cyst Fibros 2005;4:249–57.
[107] Mitchell I, Nakielna E, Tullis E, Adair C. Cystic fibrosis End-stage care in Canada. Chest 2000;118:80–4.
[108] Nobili RM, Duff AJA, Ullrich G, Smrekar U, Havermans T, Bryon M, et al. Guiding principles on how to manage relevant psychological aspects within a CF team: interdisciplinary approaches. J Cyst Fibros 2011;10:S45–52. http://dx.doi.org/10.1016/S1569-1993(11)60008-8.
[109] Grob R. Is my sick child healthy? Is my healthy child sick?: changing parental experiences of cystic fibrosis in the age of expanded newborn screening. Soc Sci Med 2008;67:1056–64. http://dx.doi.org/10.1016/j.socscimed.2008.06.003.
[110] Olsson CA, Bond L, Burns JM, Vella-Brodrick DA, Sawyer SM. Adolescent resilience: a concept analysis. J Adolesc 2003;26:1–11.
[111] Duff AJA, Latchford GJ. Motivational interviewing for adherence problems in cystic fibrosis. Pediatr Pulmonol 2010;45:211–20. http://dx.doi.org/10.1002/ppul.21103.
[112] Widerman E. Communicating a diagnosis of cystic fibrosis to an adult: what physicians need to know. Behav Med 2002;28:45–52.
[113] Widerman E. The experience of receiving a diagnosis of cystic fibrosis after age 20: implications for social work. Soc Work Health Care 2004;39:415–33.
[114] Randlesome K, Bryon M, Evangeli M. Developing a measure of eating attitudes and behaviours in cystic fibrosis. J Cyst Fibros 2013;12:15–21. http://dx.doi.org/10.1016/j.jcf.2012.05.005.
[115] Sawyer SM. Sexual and reproductive health. In: Hodson ME, Geddes D, Bush A, editors. Cystic Fibrosis. London: Arnold; 2007. p. 279–90.
[116] Hogg M, Braithwaite M, Bailey M, Kotsimbos T, Wilson JW. Work disability in adults with cystic fibrosis and its relationship to quality of life. J Cyst Fibros 2007;6:223–7. http://dx.doi.org/10.1016/j.jcf.2006.10.004.
[117] Griffith JL, Gaby L. Brief psychotherapy at the bedside: countering demoralization from medical illness. Psychosomatics 2005;46:109–16.
[118] Castellani C, Macek M, Cassiman J-J, Duff A, Massie J, ten Kate LP, et al. Benchmarks for Cystic Fibrosis carrier screening: a European consensus document. J Cyst Fibros 2010;9:165–78.
[119] Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros 2011;10(Suppl. 2):S86–S102.
[120] Doring G, Hoiby N, Consensus Study G. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. J Cyst Fibros 2004;3:67–91.
[121] Heijerman H, Westerman E, Conway S, Touw D, Doring G. consensus working g. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. J Cyst Fibros 2009;8:295–315.