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Original Article

Standards for the care of people with cystic fibrosis (CF); recognising and addressing CF health issues

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ABSTRACT

This is the third in a series of four papers updating the European Cystic Fibrosis Society (ECFS) standards for the care of people with CF. This paper focuses on recognising and addressing CF health issues. The guidance was produced with wide stakeholder engagement, including people from the CF community, using an evidence-based framework. Authors contributed sections, and summary statements which were reviewed by a Delphi consultation.

Monitoring and treating airway infection, inflammation and pulmonary exacerbations remains important, despite the widespread availability of CFTR modulators and their accompanying health improvements. Extrapulmonary CF-specific health issues persist, such as diabetes, liver disease, bone disease, stones and other renal issues, and intestinal obstruction. These health issues require multidisciplinary care with input from the relevant specialists. Cancer is more common in people with CF compared to the general population, and requires regular screening. The CF life journey requires mental and emotional adaptation to psychosocial and physical challenges, with support from the CF team and the CF psychologist. This is particularly important when life gets challenging, with disease progression requiring increased treatments, breathing support and potentially transplantation. Planning for end of life remains a necessary aspect of care and should be discussed openly, honestly, with sensitivity and compassion for the person with CF and their family.

CF teams should proactively recognise and address CF-specific health issues, and support mental and emotional wellbeing while accompanying people with CF and their families on their life journey.

ABPA	allergic bronchopulmonary aspergillosis
ACT	airway clearance techniques
BAL	bronchoalveolar lavage
BMD	bone mineral density
BMI	body mass index
CF	cystic fibrosis
CFLD	cystic fibrosis liver disease
CFRD	cystic fibrosis related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CGM	continuous glucose monitoring
CKD	chronic kidney disease
CT	computed tomography
DIOS	distal intestinal obstruction syndrome
DXA	double X-ray absorptiometry
ETI	elexacaftor-tezacaftor-ivacaftor
FEV_1	forced expiratory volume in one second
FIT	faecal immunochemical testing
GFR	glomerular filtration rate
HFNO	High flow nasal cannula oxygen
HRCT	high-resolution computed tomography
LCI	lung clearance index
MBW	multiple breath washout
MRI	magnetic resonance imaging
MRSA	methicillin resistant *Staphylococcus aureus*
NIV	non-invasive ventilatory
NTM	nontuberculous mycobacteria
OGTT	oral glucose tolerance test
ONS	oral nutritional supplements
PERT	pancreatic enzyme replacement therapy
PEx	pulmonary exacerbation
RCT	randomised controlled trials
TIS	tobramycin inhalation solution

1. Introduction

This is the third of a series of four papers outlining standards for the care of people with CF. The first two papers considered "timely and accurate diagnosis" and "establishing and maintaining a healthy life" [1, 2]. In this paper we reflect on the challenges that people with CF may face during their life journeys. These are often specific to people with CF, reflecting the multi-system impact of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene defect and sometimes iatrogenic sequelae of necessary treatments. It is important that CF-specific health issues are identified and addressed promptly and appropriately, including for people with CF established on CFTR modulator therapy.

The paper begins with a section on identifying and addressing airway infection and inflammation, reflecting the most important cause of ill health in the CF population. The section builds on a framework of exercise and airway clearance proposed in the second paper ("establishing and maintaining healthy life") and reinforces the importance of maintaining "clean airways" even in the era of CFTR modulator therapy, including strategies for antibiotic therapy. Important non-pulmonary complications are covered, including CF-related diabetes (CFRD), CF liver disease (CFLD) and CF bone disease. We also reflect on the emotional and psychological journey for people with CF and how the CF team can support them through challenges, highlighting the key role of the CF psychologist. The final section considers the period of life when treatment needs increase and life becomes more challenging. The pathway to solid organ transplantation includes discussion of post-

transplant care. Finally, we reflect on the support and care needed at the end of life, highlighting the need for preparation and transparency.

The final paper in the series ("Planning for a longer life") will build on many of the issues covered in this and earlier papers and explore challenges that have arisen from the success of achieving better life expectancy [3].

We previously described the methodology used to construct and gain consensus on this update and expansion of the ECFS Standards of Care [1]. Briefly, a multidisciplinary core committee commissioned and reviewed author contributions and statements. ECFS members and CF community members identified through CF Europe were invited to review statements via a Delphi consultation (a threshold of ≥80% indicated consensus) (Table 1). Delphi consultation participants and results are detailed in the Supplementary Tables 1 and 2.

2. Identifying and addressing airway infection and inflammation

2.1. Monitoring for lung health decline

Felix Ratjen, Andrea Gramegna, Lucy Perrem, Edward McKone

Monitoring lung health includes evaluating the effectiveness of airway clearance techniques (ACT) and inhalation techniques, and monitoring adherence to prescribed treatments. Clinical assessments should be performed at least every 3 months or when symptoms, especially cough, suggest an exacerbation of CF airway infection and inflammation [4,5]. Virtual visits and remote patient monitoring may help tailor care to an individual's clinical symptoms and extent of lung involvement [2].

Spirometry should be performed at every clinic appointment in people with CF to guide therapy needs and impact [4] (Statement 1). However, spirometry is relatively insensitive in detecting early structural lung disease. More sensitive tests such as multiple breath washout (MBW) to measure lung clearance index (LCI) are being increasingly used, especially in children and in adults with normal spirometry, as their clinical relevance and validity improves [6].

Access to chest X-rays should be available, although the evidence to support routine use is not robust [7]. More sensitive imaging modalities to evaluate structural lung disease such as high-resolution computed tomography (HRCT) are used routinely in some centres, and should be available [8]. Every attempt should be made to ensure the lowest radiation dose possible for each scan and X-ray. Structural magnetic resonance imaging (MRI) technology is being developed and may provide functional and structural information. Further evaluation is required to determine the role of MRI in clinical practice [9].

2.2. Inhaled mucoactive agents

Felix Ratjen, Edwin Brokkar, Isabelle Durieu

Mucoactive therapies, including mucolytics and hydrators, have an important role in the respiratory management of people with CF (Statement 2). Currently, dornase alfa is the only mucolytic agent with proven efficacy in CF [10], with improved lung function, less frequent PEx and reduced rate of percent predicted forced expiratory volume in one second (FEV_1) decline in patients aged 6 years and older regardless of disease severity [11]. Long-term maintenance treatment is required as treatment effects are lost upon discontinuation [10,12]. The timing of the once daily inhalation (morning or evening) does not appear to impact effectiveness. Nonetheless, after taking dornase alfa, people with CF should wait at least 30 minutes before undertaking ACT. In addition, it is advisable to leave a period of at least an hour between nebulised antibiotics and dornase alfa. With these considerations in mind, most people with CF take the dornase alfa dose in the evening [13]. Current guidelines recommend the use of mucoactive therapies in all children with CF above 5 years of age [10] and there is evidence to support the

Table 1
Statements.

1	Respiratory function testing and lung imaging should be regularly performed, as per previous guidance [4].
2	Inhaled mucoactive therapies have an important role in the respiratory management of people with CF.
3	CF teams should work in partnership with people with CF and their families to determine the most appropriate regimen for inhaled mucoactive therapies.
4	Airways should be sampled for infection at each clinic visit and with each respiratory exacerbation (expectorated or induced sputum sample preferred; otherwise, oropharyngeal sample).
5	Induced sputum should be performed at least once a year in people with CF who cannot expectorate sputum even if they are asymptomatic.
6	Lower airway sampling via bronchoalveolar lavage should be considered in people with CF who have persistent symptoms despite appropriate culture-directed therapy from expectorated or induced sputum.
7	There is good evidence to support eradication protocols for *Pseudomonas aeruginosa* identified on respiratory culture of any airway sample.
8	A proactive approach to managing CF pathogens other than *Pseudomonas aeruginosa* is reasonable with antibiotic choice determined by local protocols, patient tolerability, and adverse effects.
9	The CF team should work closely with the microbiology department to ensure targeted therapy, good antibiotic husbandry and appropriate cross infection strategies.
10	A respiratory sample should be obtained at least annually (sputum, induced sputum or bronchoalveolar lavage) for non-tuberculous mycobacteria detection.
11	A diagnosis of allergic bronchopulmonary aspergillosis (ABPA) should be considered for people with CF who are symptomatic and not responding to antibiotic therapy.
12	Formal annual screening for glucose intolerance should commence from ten years of age for people with CF, although a low threshold for screening should be practised if there is clinical concern.
13	Management of CF diabetes requires multi-disciplinary care, including diabetes specialists, and support for the person with CF through the significant psychological impact of this diagnosis.
14	Therapy for CF diabetes is insulin based and should aim for usual standards of glycaemic control, but not at the expense of high-nutrient dietary support
15	Routine assessment for liver disease is recommended in people with CF, including annual blood tests and regular ultrasonography.
16	Early referral to a gastroenterologist or hepatologist with CF expertise should be initiated for persistent abnormal scan findings, evidence of portal hypertension or persistent transaminitis.
17	Double X-ray absorptiometry (DXA) should be performed on children and adults with CF, who are at risk of low mineral density, for example: low BMI, low FEV_1, history of steroid therapy, history of hypogonadism.
18	Bisphosphonates should be considered for people with CF with significant osteoporosis on DXA scan despite standard therapy (adequate nutrition, physical activity, and calcium/vitamin D supplementation).
19	CF teams should take active measures to minimise the risk for people with CF of renal compromise or stones, including routinely assessing for acute kidney injury and chronic kidney disease, modifying potentially nephrotoxic treatments, and ensuring adequate hydration.
20	Constipation and DIOS are common comorbidities and CF physicians should routinely assess if people with CF are experiencing symptoms suggestive of these conditions.
21	Screening for colorectal cancer in people with CF should commence at an earlier age than the general population.
22	Colonoscopy is the most suitable screening method, other less invasive screening tests (faecal immunochemical testing and CT colonoscopy) need further evaluation.
23	The CF psychologist promotes mental health and quality of life through education, prevention, screening and intervention; helping to facilitate a more holistic approach of treatment for people with CF and their families.
24	People with more advanced CF disease should receive holistic individualised care aimed at balancing quality of life, treatment burden and clinical outcomes.
25	People with advanced CF disease must be assessed regularly for respiratory failure using a combination of clinical evaluation, pulse oximetry and blood gas analysis (including nocturnal and ambulatory assessments).
26	To improve symptoms and quality of life for those with advanced CF lung disease, supplemental oxygen should be offered to people with CF with chronic hypoxaemia and nocturnal non-invasive ventilatory support offered with evidence of chronic hypercarbia.
27	In acute or decompensated chronic respiratory failure, non-invasive ventilatory support should be considered, with appropriate plans for escalation made including consideration of invasive ventilation if appropriate.
28	Lung and/or liver transplant should remain available for people with end-stage CF lung or liver disease.

(*continued on next page*)

Table 1 (*continued*)

29	CF teams and transplant centres should collaborate to establish optimal transplant assessment and post-transplant care.
30	For people with CF with advanced disease, planning for end of life care is important.
31	Clear lines of communication are important between the CF and palliative care teams to minimise anxiety and stress for people with CF and their families.

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis, BMI=body mass image, CF=cystic fibrosis, CT=computed tomography, DIOS=distal intestinal obstruction syndrome, DXA=double X-ray absorptiometry, FEV1=forced expiratory volume in one second

use of inhaled hypertonic saline in younger children as well [14]. Hydrators are thought to increase airway surface liquid volume by creating an osmotic gradient. The mechanism of action for hypertonic saline differs from dornase alfa and the approaches are considered complementary. A systematic review concluded that nebulised 7% saline (hypertonic saline) may reduce pulmonary exacerbations (PEx) and improve lung function in older children and adults with CF [15]. Subsequent studies have demonstrated improvements in LCI and reduced mucus plugging on computed tomography (CT) in preschool children with CF [14,16]. Hypertonic saline use appears to be safe in infants with CF [17]. Using a lower concentration of saline is an option to improve tolerability, but recent evidence suggests improved efficacy for 6% compared to 3% hypertonic saline [18]. Mannitol dry powder is an alternative to hypertonic saline available in some countries [19]. Both agents can irritate the airways so initial tolerability testing is recommended, often with use of pre-treatment bronchodilators.

In people with CF established on elexacaftor-tezacaftor-ivacaftor (ETI) CFTR modulator therapy, evidence from the SIMPLIFY study suggests that discontinuing mucoactive inhaled therapies is not associated with short-term deterioration in lung function [20]. It is important that mucoactive therapies, including dornase alfa and hypertonic saline, remain available for people with CF on ETI. Whilst data from SIMPLIFY provide short term reassurance, further data are needed to assess the impact of stopping therapies on longer term outcomes and several projects are actively evaluating this [2]. Long-term maintenance treatment with dornase alfa and/or hypertonic saline is important for all people with CF who are not treated with CFTR modulator therapy. CF teams should work in partnership with people with CF and their families to determine the most appropriate regimen for inhaled mucoactive therapies (Statement 3).

2.3. Surveillance for airway infection

Julian Forton, Pavel Drevinek, Miquel Ekkelenkamp

Surveillance for airway infection guides the management of people with CF even when asymptomatic, to identify promptly appropriate eradication treatments, guide management of chronic bacterial infection, and inform infection control measures. Bacteria, including non-tuberculous mycobacteria (NTM), fungi, and viruses can all contribute to CF lung disease.

Bacteria identified from sputum correlate closely with those identified from direct sampling of the lower airways via bronchoalveolar lavage (BAL) [21]. Sputum (either direct sampling or induced) remains the best sample for surveillance for people with CF. Many children with CF, and increasingly adults on CFTR modulator therapy, are unable to spontaneously expectorate. Therefore oropharyngeal sampling continues to have a role (for example, cough swab or oropharyngeal sampling) [5]. Previously productive patients may still expectorate sputum early in the morning, after physiotherapy, or during exercise. Approaches to accommodate opportunistic sputum collection should be organised. The impact of remote monitoring and sampling on airway surveillance needs to be considered as these models of care become more common [2].

Airways should be sampled for infection at each clinic visit and with each respiratory exacerbation. The preferred sample is sputum, either expectorated or induced (following hypertonic saline, airway clearance manoeuvres and/or exercise); otherwise, oropharyngeal sampling is acceptable (cough swab, oropharyngeal suction, or throat swab) (Statement 4). Induced sputum should be performed at least once a year in people with CF who cannot expectorate sputum even if they are asymptomatic (Statement 5). Lower airway sampling via bronchoalveolar lavage (BAL) should be considered in people with CF who have persistent symptoms despite appropriate culture-directed therapy from expectorated or induced sputum (Statement 6). These approaches are increasingly invasive, but are also increasingly sensitive to detect lower airway bacterial infection [22–26]. Upper airway sampling, especially nasopharyngeal, is unpleasant for infants and children.

In children with CF, lower airway sampling via BAL is about twice as sensitive for pathogen identification than oropharyngeal sampling [22]. Sputum induction following nebulised hypertonic saline is feasible in most children and has a higher yield of pathogens than matched cough swabs. In symptomatic patients, sputum induction is equivalent to BAL for pathogen identification [26]. Sputum induction and BAL have been shown to be superior to oropharyngeal sampling for the detection of NTM [27,28].

As part of the CF team, the CF microbiologist should be involved in establishing local policies for infection control and surveillance, antibiotic treatment and stewardship. If it is not possible for CF team to work closely with a specialist microbiologist, it is essential that microbiological testing is undertaken following CF-specific guidelines [29]. The microbiologist should support interpretation of diagnostic test results and guide individual patient therapy [29–31]. Pathogens, including fast-growing mycobacteria should be identified from samples according to international standards. PCR techniques and systemic antibody assays are not routinely used but may be useful for early diagnosis of airway infection.

2.4. Approaches to antibiotic therapy

Margaret Rosenfeld, Alan Smyth, Giovanni Taccetti, Claire Wainwright

There is good evidence to support eradication protocols for *Pseudomonas aeruginosa* identified on respiratory culture of any airway sample (Statement 7). A proactive approach to managing CF pathogens other than *P. aeruginosa* is reasonable with antibiotic choice determined by local protocols, patient tolerability, and adverse effects (Statement 8). The CF team should work closely with the microbiology department to ensure targeted therapy, good antibiotic husbandry and appropriate cross infection strategies (Statement 9).

2.4.1. Prophylaxis

The early reports of CF describe a suppurative bronchitis in the presence of *Staphylococcus aureus* [32]. This led to the routine use of anti-staphylococcal antibiotic for primary prophylaxis in CF centres in some countries, such as the UK, but this practice was not routinely established in most other countries including the US. A systematic review showed that, during the first 6 years of life, anti-staphylococcal prophylaxis leads to fewer children having respiratory isolates of *S. aureus* [33] (Table 2). There was a non-significant trend towards more children on prophylaxis having one or more isolates of *P. aeruginosa* over the same period. A large, ongoing multicentre trial (CF START, ISRCTN18130649) will establish whether prophylaxis with flucloxacillin predisposes to earlier *P. aeruginosa* infection and impacts LCI. There is no evidence for the use of antibiotic prophylaxis for other CF pathogens.

2.4.2. Eradication

The detection of initial bacterial infection justifies early antibiotic treatment to try to eradicate CF pathogens. There are no trial data to

Table 2
Prophylaxis, eradication and suppression of key CF pathogens, systematic review evidence

	Prophylaxis	Eradication	Suppression
S. aureus	Significantly fewer children have one or more isolates of *S. aureus* up to age 6 years [33]	No systematic review	Systematic review but no eligible trials [34]
MRSA	No systematic review	Significantly fewer patients had MRSA after 28 days of active treatment. No difference at 3 & 6 months [35]	No systematic review
P. aeruginosa	No evidence of benefit in a systematic review of vaccines against *P. aeruginosa* [36]	Nebulised (± oral) antibiotics achieve eradication significantly more often than no treatment. Intravenous antibiotics confer no advantage [37]*	Long-term inhaled antibiotics improve lung function and reduce exacerbation rates [38]
Nontuberculous mycobacteria	No systematic review	Systematic review but no eligible trials [39]**	No systematic review
B. cepacia	No systematic review	Systematic review but no eligible trials [40]	No evidence of benefit in systematic review (one eligible trial) [41]
S. maltophilia	No systematic review	Systematic review but no eligible trials [42]	Systematic review but no eligible trials [42]

Abbreviations: MRSA = methicillin resistant *Staphylococcus aureus*
*The m.1555A>G mitochodrial gene variant increases susceptibility to aminoglycoside induced hearing impairment and is rare in the general population. It should be tested for, if possible, before starting aminoglycoside therapy [43].
**Although eradication is frequently attempted where NTM pulmonary disease is present.

support early eradication treatment for *S. aureus* [44]. Regarding MRSA, one study indicated active treatment for 28 days to be superior to observation only, albeit with a low certainty of evidence [45].

Initial *P. aeruginosa* infection can often be eradicated if treatment is started early, preferably within 4 weeks after the first positive culture [37,46,47] (Statement 7). Clinical trial data support the use of tobramycin inhalation solution (TIS) for 28 days, or up to 3 months of nebulised colistin with oral ciprofloxacin [4,37,46,48]. There is no evidence favouring one regimen over the other [37]. Intravenous antibiotics are no more effective than inhaled treatment when combined with oral ciprofloxacin [46]. A 12-month microbiological follow-up period is suggested to assess whether eradication is sustained [37,46,49,50]. Eradication of *P. aeruginosa* can slow lung function decline [51].

While the early detection of CF bacterial pathogens on respiratory culture may justify an eradication approach, there is no clinical trial evidence to recommend early eradication treatment for CF pathogens other than *P. aeruginosa* [42,52].

2.4.3. Suppression

Once chronic *P. aeruginosa* infection is established [53], European and US guidelines recommend treatment with long-term inhaled anti-pseudomonal antibiotics [4,48]. Both guidelines recommend TIS as first line therapy, in 28 days on/off cycles, with aztreonam lysine as a recommended alternative. European guidelines recommend inhaled colistin as an additional alternative to TIS. While not included in current guidelines of care, aerosolised levofloxacin and liposomal amikacin have been evaluated in randomised controlled trials (RCTs) and may be considered in patients with suboptimal response to first line inhaled antibiotics [54,55]. Of the inhaled antibiotics prescribed for suppressive therapy in CF, TIS has the strongest evidence base, with improved lung function and reduced rates of PEx demonstrated in studies undertaken prior to the CFTR modulator era [38]. Inhaled antibiotic powders may represent an alternative topical delivery mode to aerosolised antibiotics [56]. There is no evidence to guide decisions on *P. aeruginosa* eradication or suppressive therapy for people with CF established on CFTR modulator therapy. There are insufficient data to recommend suppressive inhaled antibiotics for other CF pathogens.

2.4.4. Recognising and treating nontuberculous mycobacterium lung disease

Culturing NTM from respiratory samples requires specific laboratory identification of the organism [57]. The diagnosis of pulmonary disease with NTM is based on clinical, radiological and microbiological criteria as described in international guidelines [58]. In people with CF, these criteria are also used but require validation. Diagnosing NTM lung disease in people with CF can be challenging due to existing CF pulmonary disease and overlapping chronic infection with typical CF pathogens [59,60]. A respiratory sample should be obtained at least annually (sputum, induced sputum or BAL) for NTM detection (Statement 10). Before initiating NTM treatment, drug susceptibility testing is strongly suggested, particularly to macrolides as macrolide resistance (including inducible macrolide resistance for the *Mycobacterium abscessus* group of NTM) is associated with less effective antimicrobial clearance [61]. Treatment is reserved for those with evidence of NTM pulmonary disease based on guidelines as well as optimisation of all clinical aspects including airway clearance, treatment of other airway infections, management of CFRD and nutritional management. Treatments which are not based on evidence from clinical trials should follow international guidelines [62], and include complex antimicrobial combinations for at least 12 months after first negative culture. These complex treatments can be associated with short- and long-term toxicity. Therapeutic drug monitoring is recommended to reduce toxicity, particularly from intravenous amikacin use (Table 2) [58]. The absorption and pharmacokinetics of antibiotics may vary for people with CF. [63]. The ongoing FORMaT trial (Finding the Optimal Regimen for *M. abscessus* treatment, NCT04310930) will determine the best regimen for *M. abscessus* eradication, with tolerance of adverse effects. CFTR modulator treatment may reduce the risk of acquiring NTM infection and may play a role in treatment, but current evidence is limited [64].

2.5. Addressing pulmonary exacerbations

Natalie West, Don Sanders, Barry Plant, Pierre-Régis Burgel

PEx are intermittent clinical deteriorations in CF lung disease, usually treated with oral or intravenous antibiotics [65]. While there is no agreed definition, a PEx is generally described as an acute clinical worsening from baseline, and/or an acute decline in lung function.

PEx are a major cause of morbidity and disease progression, leading to loss of lung function, worsened quality of life, and shorter survival [66–70]. In recent PEx clinical trials, almost half the participants had been treated with oral and/or inhaled antibiotics before treatment with IV antibiotics [65,67], and 25-35% of individuals failed to recover towards baseline lung function [67,71]. Some interventions (for example, CFTR modulator therapy, chronic azithromycin, mucolytics, and inhaled antibiotics for *P. aeruginosa*) decrease the frequency of PEx [72].

PEx treatment usually requires oral and/or IV antibiotics, and sometimes inhaled antibiotics. For a PEx associated with *P. aeruginosa*, a combination of two or more antibiotics is recommended, yet evidence is lacking. The Standardised Treatment of Pulmonary Exacerbations (STOP) programme conducts clinical trials in PEx [65–67]. One STOP clinical trial showed that longer durations (>14 days) of IV antibiotic

therapy in adults with CF were not associated with improved lung function, symptom recovery, or time to next PEx [66]. Therefore, a reasonable treatment duration for IV-treated PEx is considered to be 10–14 days. PEx treatment may require hospital admission for IV antibiotics. In the same STOP trial, mean improvement in lung function was greater in people with CF who spent *any* time in hospital receiving IV antibiotic therapy compared to those treated solely at home [68].

There is some limited evidence that early recognition and treatment of PEx may lead to an overall improvement in lung health, but more research is required to identify and validate biomarkers and patient reported outcomes for this strategy [73].

2.6. Fungal diseases in the CF lung

Gina Hong, Jean-Philippe Bouchara, Carsten Schwarz

Aspergillus fumigatus and other fungi are commonly observed in the respiratory samples of children and adults with CF [74,75]. *Aspergillus*-related lung disease in CF can present as Aspergillus colonisation, *Aspergillus* bronchitis, *Aspergillus* sensitization, allergic bronchopulmonary aspergillosis (ABPA), and rarely, aspergilloma. Agreed diagnostic criteria only exist for ABPA [76,77]. Mycological culture media with antibiotics, including a *Scedosporium*-selective culture medium, are recommended for detection of fungi in CF, although standardised mycological laboratory protocols are not universally adopted. Recurrent positive cultures are necessary to diagnose fungal bronchitis [74,76].

Screening guidelines for fungal surveillance vary between regions and countries, but fungal culture of sputum or BAL fluid should be considered in cases of clinical deterioration [77,78]. ABPA is a common complication in people with CF, and is characterised by cough, wheezing, chest X-ray or CT changes and increased sputum production [79]. Annual total serum IgE screening is recommended to monitor baseline levels. Diagnosis of ABPA relies on elevated total IgE (usually greater than 1000 IU/mL) and also includes allergy skin testing, detection of Aspergillus-specific serum IgE and IgG antibodies, and CT scan [80,81]. A diagnosis of ABPA should be considered in patients with clinical deterioration not responding to antibiotic therapy [77] (Statement 11).

For patients on CFTR modulator therapy who may not readily expectorate sputum, detection of fungi in respiratory culture may be more challenging [5].

ABPA is treated with oral corticosteroids with or without antifungal therapy [77,79], as there is no established evidence for the use of antifungal therapy [82]. Triazoles, the preferred antifungal therapy in susceptible strains, interact with CFTR modulator therapy, requiring dose adjustment of the modulator. There is an increasing evidence base to support the use of anti-IgE therapy (omalizumab and other biologics) to treat ABPA in CF and reduce steroid use [83,84].

The clinical significance of *Aspergillus fumigatus* and other fungi beyond ABPA is debated. Some data suggest that *Aspergillus fumigatus* may play a role in CF disease progression [85–87]. There is weak evidence for the treatment of *Aspergillus fumigatus* and other filamentous fungi in the absence of ABPA [78]. Case reports mostly published before the CFTR modulator era suggest antifungals to have clinical benefit in people with CF with fungal bronchitis and no evidence of IgE-mediated disease [88–90].

3. Cystic fibrosis specific health issues

3.1. CF-related diabetes

Peter Middleton, Claire Berry, Alberto Battezzati

It was traditionally recommended that all people with CF should be screened annually for CFRD with an oral glucose tolerance test (OGTT) from the age of 10 years [91,92] (Statement 12). Increasingly more centres are screening for CFRD with the one-hour OGTT [93,94] or continuous glucose monitoring (CGM) [95]. Thresholds for diagnosis and treatment are not currently established. Glycosylated haemoglobin (HbA1c) should not be used in isolation for CFRD screening, since it is a less sensitive marker of glucose tolerance in people in CF than other biomarkers. HbA1c can however help assess glycaemic control for people with CF on insulin therapy.

Guidelines [92] advise more frequent screening of fasting, post-prandial glucose and/or OGTT when there are symptoms of diabetes, and in the following specific scenarios: PEx, initiation of glucocorticoid therapy, enteral tube feeding, pregnancy, and organ transplantation. Impaired glucose tolerance in people with CF needs close monitoring, particularly to determine if insulin therapy is needed.

Management of CF diabetes requires multi-disciplinary care, including diabetes specialists, and support for the person with CF through the significant psychological impact of this diagnosis (Statement 13).

Insulin is the recommended treatment for CFRD [91,92,96] (Statement 14). but for some people with CF insulin resistance may be an issue. The role of other diabetic therapies requires further research. Optimal insulin strategies should balance the need for maintenance of good nutrition and exercise, and should aim for normoglycemia.

People with CFRD should have a joint quarterly review by a diabetes specialist and the CF team, including provision of diabetes education and dietary support. Psychological support for people with CFRD must be available, especially at the time of diagnosis.

Although there are no clinical trial data to guide the optimal diet for people with CFRD, good nutritional status is linked to good clinical outcomes [97]. Dietary support should be individually tailored with emphasis on quality, quantity and timing of food in relation to exercise and insulin dosing. People with CFRD should be encouraged to maintain exercise and provided with information to manage hypoglycaemia and to avoid inappropriate dietary restrictions to improve glucose tolerance.

There is some observational evidence that CFTR modulator therapy may impact glucose metabolism [98], but there is no evidence that CFTR modulator therapy reverses established diabetes. For people with CFRD or glucose intolerance initiating CFTR modulator therapy, regular glucose measures or CGM should be performed to optimise insulin dose.

3.2. CF-related liver disease

Chee Ooi, Andrea Gramegna, Michael Wilschanski

There is a wide spectrum of hepatobiliary manifestations in CF. Severe CF liver disease often manifests as portal hypertension. Historically, this was considered secondary to biliary stasis with progressive cirrhosis and eventual portal hypertension. More recent evidence suggests obliterative portal venopathy resulting in non-cirrhotic portal hypertension is an important alternative pathophysiological process [99]. Severe CF liver disease (CFLD) has been associated with greater pulmonary and extra-pulmonary disease burden, and worsening survival [100,101].

Evidence of liver disease in people with CF is often subtle and asymptomatic. The earliest signs of emerging or established CFLD may be in the form of hepatomegaly and/or splenomegaly (on palpation or imaging) and consistently raised liver transaminases in blood. Routine assessment for liver disease is recommended in people with CF, including annual blood tests and regular ultrasonography (Statement 15). Blood tests to assess liver function should be performed at least annually in people with CF, and include measurement of transaminases). People with CF have naturally fluctuating liver transaminase levels. Consistently raised transaminase levels (>3 x upper limit of normal) and abnormal clinical findings should prompt an abdominal ultrasound. Early referral to a gastroenterologist or hepatologist with CF expertise is appropriate to investigate for portal hypertension and its complications, exclude non-CF-related liver diseases, and consider further management (Statement 16). The clinical role for non-invasive markers (e.g. serum biomarkers [102], elastography [103]) in early diagnosis and follow-up

of CFLD is emerging but not fully established. Early recognition of significant liver involvement in the preschool years is associated with severe CFLD in adult life [104]. People with CFLD should be referred early to specialist liver centres. The timing of liver transplantation is complex, and should consider the negative impact of severe liver disease on the CF lung versus liver function that is often stable and without impact on quality of life.

Up to 25% of people with CF on CFTR modulator therapy have raised liver transaminase levels. Elevations are usually transient and not clinically significant. CFTR modulator dose adjustment is recommended in those with persistent transaminitis or significant liver disease [2,105].

Cholelithiasis is common and usually asymptomatic in people with CF. Biliary-colic pain or gallstone-related symptoms should prompt ultrasonography of the gallbladder and hepatobiliary tree, and specialist referral [4]. People with CF are at risk of pancreatitis, especially those with pancreatic sufficiency and certain CFTR gene variants [106,107]. This diagnosis should be considered in all people with CF presenting with abdominal pain.

3.3. CF bone disease

Andrea Gramegna, Pilar Azevedo

In the pre-CFTR modulator era, bone disease was noted to be common in people with CF, especially adults [108]. In a systematic review of young adults with CF (median age 28 years), a prevalence of 10-20% was reported for osteoporosis and 35-45% for osteopenia [109]. Vertebral fractures (most frequently at the thoracic level) were reported in 5-31% of adults with CF [109]. With an aging CF population, bone complications are likely to become more relevant.

Low bone mineral density (BMD) likely results from several factors, including malabsorption of calcium and vitamin D, malnutrition, lack of physical activity, low-grade chronic inflammation with increase in osteoclast activity and exposure to bone toxic medications [110]. Risk factors for low BMD include low body mass index (BMI), low FEV_1, history of steroid therapy, history of hypogonadism and history of fractures [108].

Detecting low BMD is important for osteoporosis prevention and existing guidelines recommend early screening for bone health [108, 110]. The use of double X-ray absorptiometry (DXA) is the gold standard for measuring bone mineral content and has been shown to predict fracture risk in older ages [111]. A DXA score was created for post-menopausal women without CF, and further research is needed to validate its use in children and young adults with CF.

Baseline DXA should be performed in all people with CF from age 8 years, especially when exposed to the risk factors listed above (Statement 17). The frequency of DXA monitoring is guided by the baseline DXA score as recommended in previous guidelines [108,110].

Preventative treatment is based on calcium and vitamin D supplementation, and optimising nutritional status and lung health [108,110]. Bisphosphonates have been shown to increase BMD in both adults and children with CF [112]. Bisphosphonate treatment should be considered when optimal preventative treatment has not resolved low BMD (Statement 18). When to intervene requires specialist consideration of DXA score, significant bone loss on subsequent DXA and transplant status [110].

3.4. Stones and other renal issues

Andrew Prayle, Barry Plant

The prevalence of kidney stone formation is 4.6% in people with CF [113]. Ultrasonography was the most common investigation for diagnosis. There is no apparent sex difference, and surgical intervention was required in 38% of cases. Recurrence was reported in 43% of cases [113]. Kidney stones commonly presents in late childhood and early adulthood [114]. People with CF have a risk 2 to 4 fold higher than age-specific prevalence in individuals without CF [115]. Similarly to the general population, the renal stones in CF are typically composed of calcium oxalate [116], with hyperoxaluria contributing as a consequence of the effects of systemic antibiotics and chronic malabsorption [116]. Measures to prevent kidney stone formation include adequate hydration. CF teams should take active measures to minimise the risk for people with CF of renal compromise or stones, including routinely assessing for acute kidney injury (AKI) and chronic kidney disease (CKD), modifying potentially nephrotoxic treatments, and ensuring adequate hydration and appropriate pancreatic enzyme replacement therapy (PERT) dosing (Statement 19).

Renal compromise in CF results from reduced glomerular filtration and/or tubulopathy [117]. AKI in people with CF is typically temporary and primarily caused by fluid depletion secondary to sepsis and drug toxicity, which occurs 110 times more frequently in people with CF than in the general population [118,119]. CKD becomes more common as people with CF age. The prevalence of Stage 3 CKD (estimated glomerular filtration rate [GFR] < 60 mL/min/1.73m^2) doubles with each decade of life in people with CF, with an annual prevalence of 2.3% [120]. Risk factors include increasing age, diabetes, duration of chronic infection, prolonged ibuprofen use, transplantation, and duration of aminoglycoside use [121,122]. Post-transplant CKD has a prevalence exceeding 50% at 5 years post-transplant [123] and may require kidney transplant in some patients.

Simple assays of serum creatinine can be inaccurate for monitoring CF renal disease. When CKD is suspected, a formal test of GFR (such as a EDTA or DTPA based radioisotope method) is more accurate and can be obtained to guide therapy [124]. Annual screening should include urine testing for protein, GFR estimation, and blood pressure measurement. At each face to face clinic visit, blood pressure should be measured, and in people with current or previous kidney impairment, a urine sample should be tested for protein. CFRD can exacerbate renal compromise and should be identified and treated appropriately [124].

Measures to protect renal function focus on ensuring adequate hydration and careful prescribing practices. These include: therapeutic drug monitoring, once daily aminoglycoside dosing regimens [46] (tobramycin rather than gentamicin) [118] and avoiding the combination of intravenous aminoglycoside and colistin [125].

3.5. Intestinal obstruction

Anne Munck, Michael Wilschanski

Constipation and distal intestinal obstruction syndrome (DIOS) are common comorbidities and CF physicians should routinely assess if people with CF are experiencing symptoms suggestive of these conditions (Statement 20). Definitions of DIOS and constipation in CF are specific and make a clear distinction between these two entities. Constipation in people with CF is defined with specific criteria [126]: gradual onset of reduced frequency of stooling and/or an increased stool consistency, combined with abdominal pain and/or distension and symptoms relieved by laxatives. Often the faecal impaction is throughout the colon, with the rectum full of stool.

Constipation is a common problem experienced by almost half of people with CF [126,127]. The pathogenesis likely relates to the underlying CF salt transport defect with disturbed water and electrolytes transport leading to reduced bowel motility [128] and sticky mucus combined with low grade intestinal inflammation and an abnormal gut microbiota [129]. In the absence of evidence-based interventions, management reflects best practice. Constipation responds to oral laxatives (e.g., polyethylene glycol) [126] in association with life style modifications individually tailored for correct hydration, good stool habits, appropriate salt intake, good PERT dosing and physical activity.

DIOS is unique to people with CF, and ranges from incomplete to complete intestinal obstruction. Incomplete DIOS has a short history of days with abdominal pain and/or distension, often with a faecal mass

palpated in the ileocaecum area without signs of complete obstruction. Completely obstructive DIOS can present rapidly with bilious vomiting and/or radiological fluid levels on abdominal X-ray [126]. Again, the pathogenesis reflects the disturbed water and electrolytes transport associated with CF, loss of bile salt-triggered secretion in terminal ileum and impaired motility due to fat malabsorption [130]. Risk factors for DIOS episodes include severe *CFTR* genotype, pancreatic insufficiency, history of meconium ileus, poorly controlled fat malabsorption, previous DIOS episode, organ transplantation, CFRD and dehydration [130]. The prevalence ranges from 5 to 12 episodes/1000 patients per year [126,131] and is similar in children and adults [132]. Some cases may present with less characteristic symptoms or atypical radiography and require careful evaluation to establish a DIOS diagnosis. Other surgical conditions with a similar presentation include appendiceal abscess or mucocoele, intussusception, obstruction with adhesions or volvulus, Crohn disease, severe constipation and gastrointestinal cancer.

Although clinical trial data is lacking, there is guidance available for the management of DIOS [130,133–135]. Incomplete non-obstructive DIOS resolves with appropriate oral hydration and laxatives (e.g., polyethylene glycol) using preparation with iso-osmotic water and electrolytes, or alternatively orally diluted sodium meglumine diatrizoate laxative (Gastrografin®). In complete DIOS, hospitalisation is recommended with bowel rest, nasogastric aspiration, intravenous rehydration, pain relief and lavage diluted Gastrografin®). This can be repeated under medical surveillance as it may cause important fluid shift. Medical treatment is unsuccessful in 11% of cases of complete obstructive DIOS and delayed medical care is a factor predisposing to surgery [132]. For selected medically refractory cases, colonoscopy with Gastrografin® delivery to the caecum or colonic irrigation is a potential approach. Surgery is required with persistent obstruction or evidence of bowel perforation, despite appropriate medical management. Individuals prone to DIOS tend to be at risk for repeated episodes. These individuals require maintenance therapy with adequate PERT, hydration and laxatives (preferably osmotic laxatives such as polyethylene glycol) [133].

3.6. Early identification of cancer

Charlotte Addy, Andrea Gramegna

The increased incidence of malignancy in people with CF compared with the healthy population [136–138], suggests the basic CF defect may cause an increased cancer risk, although inflammation, dietary factors or other comorbidities may be also be factors [137]. The cancer risk is further increased by the use of immunosuppressive therapy after solid organ transplantation [136]. Registry data confirm increased rates of gastrointestinal, renal, thyroid, testicular, skin and haematological malignancies for people with CF [136–139]. Gynaecological and breast cancers may also be more common but further research is needed [140]. The incidence of cancers appears higher in females [137,140].

Colorectal is the cancer with the most robust evidence for people with CF. Colorectal cancer risk is increased 5-10 times (25-30 times post-transplantation) [136–138], with earlier onset in people with CF compared to the healthy population [136]. US consensus guidelines recommend a screening colonoscopy, initiated at age 40 years in non-transplanted and 30 years in transplanted individuals with CF (Statement 21). Re-screening should occur at 5 years, reduced to 3 years if polyps were present on the initial examination [136]. High quality bowel preparation is needed to effectively visualise polyps at colonoscopy [136]. CF-specific bowel preparation may be needed to achieve adequate views [136]. Less invasive screening modalities, including faecal immunochemical testing (FIT) or CT colonoscopy, may be more acceptable to people with CF, but require further evaluation in this population [136] (Statement 22). FIT testing is the most cost-effective screening tool but further evidence is needed to define its role in future screening pathways [136,141].

To date no CF-specific guidance on screening for other malignancies is available, but it is recommended that people with CF actively engage with local, age and disease specific screening pathways [136].

4. Supporting mental and emotional well being

Eddie Landau, Johanna Gardecki, Pavla Hodkova

4.1. The unique risks that people with CF and their families face

The CF life journey requires mental and emotional adaptation to psychosocial and physical challenges. These include significant mental health issues around diagnosis, especially when this is unexpected, as is often the case following newborn bloodspot screening [142–144]. Other factors that impact on wellbeing include a higher prevalence of anxiety and depression [145,146], concerns over quality of life [147,148], the relentless challenge of adhering to a heavy treatment burden [149,150] and adapting to new medications (such as CFTR modulator therapy) [105,151], as well as adjusting to life/illness transitions [152]. People with CF and their families can struggle with managing the demands of everyday life against the backdrop of CF [153]. Supporting the mental health needs of people with CF requires specialized attention and the skills of the entire CF team [154].

4.2. Consider screening tools for mental health issues

Identifying mental health issues through regular screening provides the opportunity for early intervention and improved outcomes throughout life [142,155]. Additional mental health screening prior to and during CFTR modulator therapy can recognise people who are at risk of or already affected by depression or anxiety [105]. Screening tools can identify a range of mental health issues and psychosocial risk factors. Screening may include self-reporting tools and parental/teacher inputs, and can be used as an intervention to acknowledge, identify and address mental health difficulties [143,156,157]. However, screening is not a definitive diagnosis, and is not a strategy to replace the key role of the psychologist within the CF team.

There are a wide number of free screening tools that are available in different languages (Supplementary Table 3) [158]. These mental health tools are used for screening, to identify people with CF who need further psychological support. They evaluate distinct properties and feelings, but all have excellent psychometric properties as well as being straightforward to administer and score.

4.3. The role of the psychologist

The psychologist works holistically with all family members for sustained mental health and quality of life through education, prevention, screening and intervention [155] (Statement 23). Key tasks include supporting adjustment processes [105,151] and helping balance CF-management and “normal” life demands [154,159,160]. Psychosocial care is essential in crucial phases (e.g. diagnosis, transition) [144] and general issues throughout life (e.g. adherence, procedural anxiety and dealing with uncertainty). Mental health issues may become severe for some people with CF, and partnership working with the psychiatric team should support therapeutic interventions.

The psychologist works closely with and strengthens the psychological understanding of the whole CF team [105] to promote skills in patient-centred communication, patient empowerment and cooperative relationship-building [151,160].

5. When life gets challenging

5.1. Supporting increased treatment demands

Clémence Martin, Charlie Addy, Jacqueline Lowdon

5.1.1. Supporting complex care needs and treatment burden

With disease progression, people with CF often face increasingly complex and burdensome treatment regimens [161]. Balance between optimising clinical outcomes, quality of life, symptoms and perceived burden should drive shared decision making between people with CF and the CF team [150]. A holistic approach identifying unmet needs, physiological and psychological issues promotes shared decision making and facilitates advance care planning [162] (Statement 24). Enhanced support may be needed at home and in hospital.

Coping strategies influence adherence, survival and ability to manage complex treatment regimens [163]. Psychosocial support can help individuals manage complex care needs but further research is needed to optimise interventions [164]. Integration of palliative care specialists and education for CF teams helps enhance supportive care for people with complex CF needs [165,166].

5.1.2. Maintaining nutritional status and optimising nutritional support

Nutritional care requires frequent assessment and modification with disease progression [167,168]. Optimal nutritional status is linked to improved quality of life, lung function and longer survival [168]. Nutritional support can be required over prolonged periods, given the longer CF lifespan and ageing population [169]. More intensive support may be needed to optimise nutritional status in people with advanced disease, with chronically diminished oral intake, CFRD, frequent respiratory infections and reduced nutrition due to non-invasive ventilation [168,170].

Oral nutritional supplements (ONS) may benefit people with CF with poor nutritional status, despite efforts to encourage dietary intake, address behavioural factors and optimise PERT [168,171]. While providing a practical solution to increase calorie intake, the evidence base to support ONS for people with CF is poor [171]. Further research is required to evaluate the long-term impact of ONS [167].

Enteral tube feeding is recommended for persistently undernourished people with CF, following optimisation of less invasive nutritional interventions and appropriate evaluation [168,172–174]. The positive impact of enteral feeding, generally delivered through an overnight pump, must be balanced against the treatment burden [168,174]. Approaches to overnight feeding vary based on clinical scenario and individual preference [174].

Nutritional status pre- and post-transplant should be closely monitored and adjusted according to changes in nutritional and clinical status, with risks of CFRD increased by steroid and immunosuppressive use

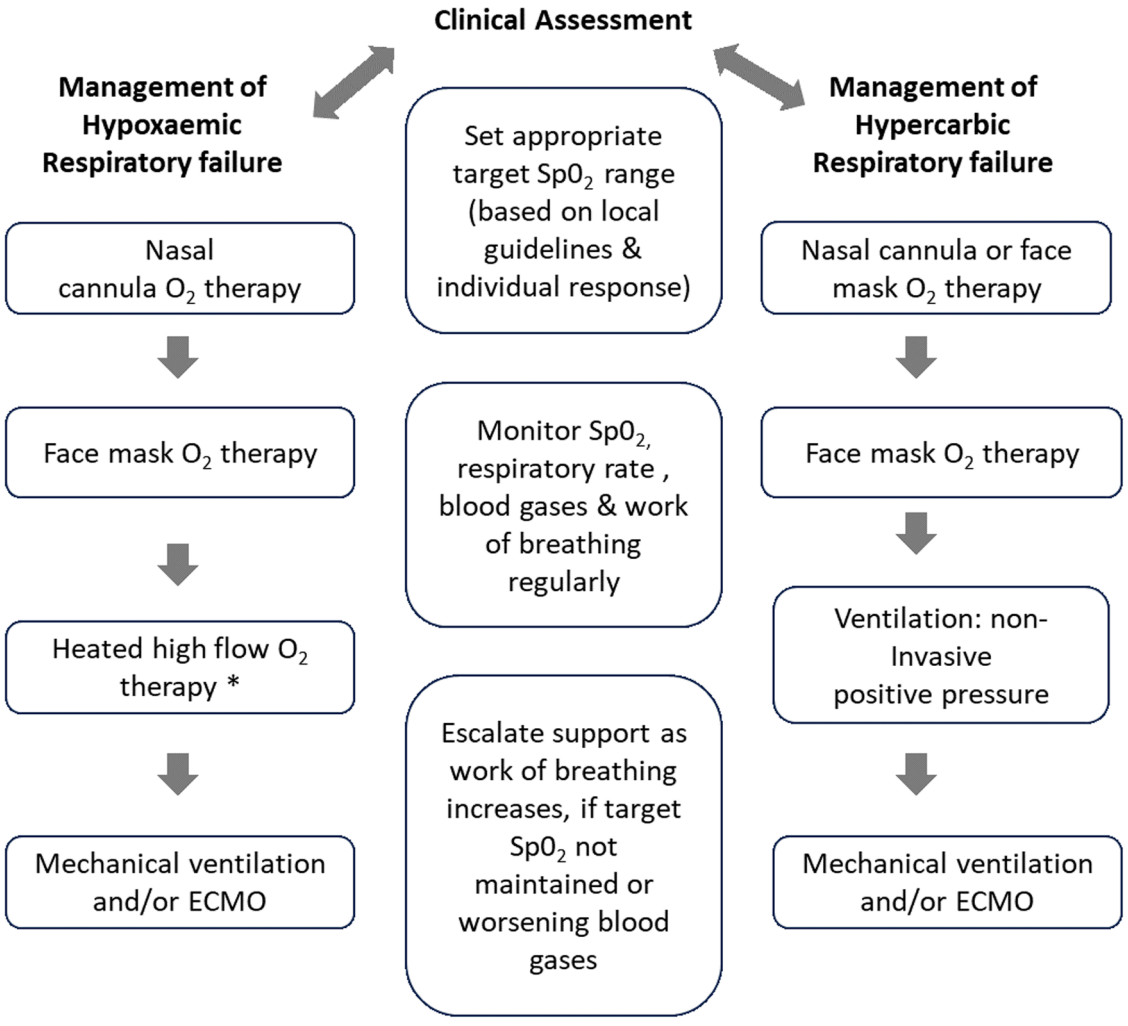

Fig. 1. Clinical assessment, management and current escalation pathway of people with CF in hypoxaemic and hypercarbic respiratory failure. Although two pathways are presented, hypoxaemic and hypercarbic respiratory failure are closely linked and often coexist. * If available; can be considered for use in transient or mild hypercarbia. Abbreviations: ECMO=extracorporeal membrane oxygenation, 0_2 = oxygen, $Sp0_2$=oxygen saturation.

[171,175].

5.2. Supporting breathing

Whitney Brown, Amanda Piper, Charlotte Addy

5.2.1. Detecting and treating respiratory failure

People with advanced CF lung disease are at risk of hypoxemic and or hypercapnic respiratory failure [176]. Respiratory failure can also occur in those with less severe disease following cute complications including PEx. Pneumothorax and haemoptysis are significant complications that need to be addressed promptly as per previous guidance [177,178].

Symptoms of respiratory failure vary by age, duration and presence of hypercarbia. Even with advanced lung disease, symptoms can be subtle, with physiological compensation and lifestyle adjustments impacting clinical presentation [176]. Assessment includes regular screening for symptoms, hypoxaemia, hypercarbia and pulmonary hypertension including nocturnal and ambulatory assessments [176] (Statement 25). Pulse oximetry is used to assess hypoxemia. Arterial blood gases detect hypercarbia, measures bicarbonate and base excess levels to allow assessment of compensation and chronicity [176].

5.2.2. Delivering oxygen and non-invasive ventilatory (NIV) support

In the presence of hypoxaemia, supplemental oxygen is recommended (Fig. 1). Oxygen therapy can improve exercise capacity and quality of life but impacts minimally on exacerbation frequency or survival [176,179,180].

For people with CF with chronic respiratory failure, especially with hypercarbia, domiciliary nocturnal NIV may slow the progression of lung disease [176,181–185], improve symptoms and exercise tolerance [186] but does not reduce hospitalisation rates or improve survival [176,181,182,187] (Statement 26). Hypercarbia is an indication for transplant referral, with NIV used as a bridge to transplantation [176, 186,188].

In acute respiratory failure, including in individuals with advanced disease, options for respiratory support are broader [176]. High flow nasal cannula oxygen (HFNO) offers an alternative method of non-invasive respiratory support which is well tolerated, may offer greater comfort and reduce respiratory rate compared to standard oxygen therapy [176,189,190] (Statement 27). Sinonasal symptoms may also be improved [176,191]. The CF Foundation recommends a trial of HFNO and/or NIV for advanced disease with acute respiratory failure [176]. Close monitoring is required to escalate care or modify the care plan if non-invasive respiratory support options prove ineffective [176, 188,192].

5.3. Solid organ transplantation

Whitney Brown, Pierre-Régis Burgel

Solid organ transplantation is an established therapeutic intervention for end organ disease due to CF, most commonly lung and liver [4]. Additionally, some people with CF may develop chronic kidney disease due to complications of CF (including CFRD and post-transplant complications) and require renal transplantation [120]. The CF and transplant teams should work closely to establish optimal referral and assessment pathways. Early discussion about lung transplantation has been recommended for people with CF with reduced lung function (FEV_1<50% predicted) [188] and referral has been recommended for those with rapidly declining FEV_1<50% and/or with FEV_1<40% predicted and markers of reduced survival [188].

Assessment of lung transplant candidates by transplant teams have been the subject of consensus documents [193] and practical guidelines [194], recognizing the specific needs of people with CF. Determining the optimal timing for lung transplantation remains difficult and may differ between countries based on health system and organ allocation differences [195,196]. Previous guidance on lung transplantation for CF preceded the recent progress in variant-specific therapy. Because treatment with CFTR modulator therapy may induce rapid [197] and sustained [198] improvement in respiratory disease in lung transplant candidates, it is suggested that all people with CF with eligible variants should undergo CFTR modulator therapy before undergoing lung transplantation. Recent data from multiple countries demonstrate the reduction in the number of people with CF undergoing lung transplantation in the CFTR modulator era [199–201]. However, some people with advanced CF lung disease on CFTR modulator therapy may still require lung transplantation. In addition, re-transplantation is a viable option for allograft failure [202]. Therefore, maintaining access to lung transplantation for people with CF appears important (Statement 28).

Post-transplant care in people with CF should aim to maximize survival and quality of life, as well as address specific considerations for CF care in an ageing population [203]. There is no universal model of care following lung transplantation for people with CF [204], however, close coordination of care should be established between the transplant team and the CF team, especially when these teams are different and located in distinct institutions (Statement 29).

5.4. Planning for end of life

Su Madge, Felicity Finlayson

The predicted survival for people with CF is steadily increasing. However there will continue to be progression through advanced disease, potential transplantation and premature death [205,206]. This journey can be unpredictable and take time. Planning for end of life, therefore remains a necessary aspect of care for people with CF [207, 208] (Statement 30).

The CF team can struggle to address this issue with people with CF they have often known and worked with for many years [209–211]. Referral to transplant services and maximising treatment regimens requires proactive and positive partnership working. Individual or group training for the CF team in end of life management and communication skills can help [212]. When quality of life is impaired and the disease course is unlikely to be reversible, people with CF and their significant carers are grateful for an open and honest exploration of options. Initiation of discussions must be handled sensitively and with compassion. Early discussion is preferable and preferences for information should be guided by the person with CF [210,213] (Fig. 2).

Working in partnership with a palliative care team supports the CF team, the person with CF and their carers [213,214]. This collaboration allows concurrently administration of CF treatments (e.g., intravenous antibiotics, airway clearance, analgesia, oxygen) and palliative symptom relief. The patient's wishes around preferred place of death and the Advance Care Directive should guide decision making. Supportive treatment that relieves discomfort and minimises distress allows for a peaceful death.

End of life is often supported in hospital where the familiarity of the CF ward and the relationship with the CF team reassures the individual and their carers [214]. However, home or hospice may be a preferred place of death, particularly for those with non-pulmonary organ failure or cancer. Working in partnership with the hospice or home visiting teams, the person with CF and their carers ensures continuity of care. Every effort should be made to create a safe environment that provides opportunities for the person with CF, carers and friends to come to terms with the approaching end of life.

To ensure successful collaborative working, clear lines of communication are paramount. Regular communication between the different clinical teams, and open and honest discussion with the people with CF and carers reduces unnecessary anxiety and distress (Statement 31). It may be helpful that the carers of the person with CF nominate a contact person to liaise with the wider family and friends with updates on progress, to optimise communication and information sharing.

Areas of discussion around end of life care should include:

- Acknowledging the unpredictability of disease progression and (un)availability of organ transplant.
- Reassurance that disease-modifying therapies and symptom management will be offered for as long as the person with CF wishes.
- Preferences for the provision of spiritual or pastoral care will be supported.
- Documenting an Advanced Care Plan/Directive (specifying limits of treatment and preferred place of death).
- In the event of a lack of capacity, nominating a preferred decision-maker or Medical Power of Attorney.

Fig. 2. Areas of discussion around end of life care.

Care and support in the period following death is important for the family. Time with the deceased loved one is important for significant others. Follow-up contact from the CF team should be offered as well as referral to formal bereavement support and practical information around funeral arrangements. The CF team and ward staff should also be offered an opportunity to debrief and receive psychological support as needed.

6. Conclusion

People with CF continue to face challenges on a scale many could not comprehend. That they continue to live such full and rewarding lives reflects well on their resilience and support from family and the CF team. Much of the advice in this paper revolves around proactively recognising and addressing issues. A regular theme of this paper is partnership working to achieve common goals and support people with CF and their families.

Much of the advice provided in this paper builds on previous guidance from the ECFS Standards of Care group. In a fast-changing field there has been some significant increase in the amount of evidence that people with CF and their carers can access to guide management of complications. A good illustration of this is the series of “STOP” studies evaluating management of pulmonary exacerbation. Despite this, and reflecting the pace of change, many treatments have a poor evidence base, especially in the era of CFTR modulator therapy. The Delphi methodology has enabled us to provide guidance that is pragmatic and impactful in a manner that is inclusive and transparent.

Moving forward, the success of interventions and strategies reviewed in the first three papers in this series will be built on in the final paper (“Planning for a longer life”). In that paper we will provide practical advice on navigating life, as well as placing people with CF in the context of a complex planet, considering subjects such as inequalities and respect for values. Issues of grower older, which mirror those in the general population, have an added layer of complexity for people with CF and we will outline those, as well as the potential and enthusiasm that many with CF have for engaging with research.

Author credit

The core committee established the framework for the exercise and identified experts to produce each section (highlighted in the paper). All members of the faculty contributed to the Delphi process and had oversight of the final paper. Fiona Dunlevy provided overall administrative support and medical writing skills to produce a consistent document. Conflict of interest statements are fully recorded in supplemental materials.

Declaration of competing interest

The authors had no declarations of interest in relation to the current work. Declarations of interest for each author outside the current work are summarised in Supplementary Table 4.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.01.005.

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