Standards for the care of people with cystic fibrosis; establishing and maintaining health

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Original Article

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ABSTRACT

This is the second 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 establishing and maintaining health. The guidance is produced using an evidence-based framework and with wide stakeholder engagement, including people from the CF community. Authors provided a narrative description of their topic and statements, which were more directive. These statements were reviewed by a Delphi exercise, achieving good levels of agreement from a wide group for all statements.

This guidance reinforces the importance of a multi-disciplinary CF team, but also describes developing models of care including virtual consultations. The framework for health is reinforced, including the need for a physically active lifestyle and the strict avoidance of all recreational inhalations, including e-cigarettes. Progress with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy is reviewed, including emerging adverse events and advice for dose reduction and interruption.

This paper contains guidance that is pertinent to all people with CF regardless of age and eligibility for and access to modulator therapy.

Abbreviations

ACT	Airway clearance techniques
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CPET	Cardiopulmonary exercise testing
CRS	Chronic rhinosinusitis
ECFS	European Cystic Fibrosis Society
ETI	Elexacaftor-tezacaftor-ivacaftor
ETS	Environmental tobacco smoke
NBS	Newborn bloodspot screening
PERT	Pancreatic enzyme replacement therapy
PEx	Pulmonary exacerbation(s)
PhySIIG	Physiotherapy Special International Interest Group
RCT	Randomised controlled trial
VST	Variant-specific therapy

1. Introduction

This is the second of a series of four papers updating standards for the care of people with cystic fibrosis (CF), coordinated by the European Cystic Fibrosis Society (ECFS). These papers have been produced by academic and medical experts in the field of CF in collaboration with people with CF and the CF community. A previous editorial describes the structure, contents and new developments of this 4-paper series [1]. This paper, "Establishing and maintaining health", illustrates the changes in CF care, based on significant developments over the past two decades.

The first paper in the series "A timely and accurate diagnosis" outlines the key development of newborn bloodspot screening (NBS) [2], which has now expanded to most countries in which CF has a significant incidence. Regions with long established NBS programmes are now witnessing the benefits of early diagnosis.

NBS facilitates early treatment to address the pathophysiological consequences of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, allowing people with CF to achieve excellent nutritional status, to keep their airways free of chronic infection, and to establish a healthy and active lifestyle. These "basic" principles underpinning CF care have resulted in a steady improvement in outlook and wellbeing for people with CF.

Over the past decade a further development has emerged that

directly addresses the underlying CF molecular defect. CFTR modulator therapy, to date the only variant-specific therapy (VST) available, has transformed the clinical outcomes for people with CF who are eligible and have access to these therapies [3].

The guidance in this paper reflects the changing CF landscape. Unless otherwise specified, the ethos and principles of care described relates to all people with CF, regardless of age or treatment with CFTR modulator therapy. Where appropriate, guidance may also apply to the parents or caregivers of children and young adults with CF. We support shared decision making with all people with CF and their families.

People with CF and healthcare professionals need to be aware of the changing environment in which they live and work. It is important to have an open mind to innovative approaches, but also to ensure that care continues to be based on the best available evidence and that quality of care is maintained.

The first three sections of this paper cover the essential components of establishing good health: achieving excellent nutrition, maintaining airway health and engaging with exercise. We then reflect on models of care, building on previous ECFS guidance, and consider the potential for remote care. Finally, we describe issues around managing medicines, including developments in the field of VST.

We previously described the methodology used to construct and gain consensus on this update and expansion of the ECFS Standards of Care [2]. Briefly, a multidisciplinary core committee created the framework, invited authors and reviewed author contributions and statements. The statements underwent a Delphi consultation, with a threshold of ≥80 % indicating consensus. The core committee reviewed all comments, and adjusted statements if necessary (Table 1). Delphi consultation participants are listed in Supplementary Table 1, and Delphi results are presented in Supplementary Table 2.

Table 1
Statements.

#	Statement
1	Whenever breast feeding is possible, it should be encouraged and supported for infants with CF.
2	Infants with CF presenting with meconium ileus are at risk of both short and long-term nutritional deficits and require early support from the CF team.
3	Support from a specialist CF dietitian is essential.
4	The CF team should encourage healthy feeding behaviours early in life to promote a good relationship with food and a positive body image.
5	Pancreatic enzyme replacement therapy should be initiated if there is clinical evidence of pancreatic insufficiency.
6	Nutritional status should be monitored at each clinic visit.
7	For people on CFTR modulator therapy, special consideration should be given to the need for salt and vitamin supplementation.
8	Physiotherapy advice for airway clearance, including physical activity and exercise, should begin at diagnosis.
9	Physiotherapy for airway clearance should be individualised and provide a framework for people with CF to self-manage.
10	Adolescents should be supported to take increasing responsibility for airway clearance techniques, in preparation for independent adult life.
11	The CF team should regularly evaluate people with CF for rhino-sinus disease.
12	People with CF should avoid tobacco smoke (direct and environmental).
13	People with CF should avoid e-cigarette use (vaping).
14	Regular standardised exercise testing (as per the guidance of the ECFS Exercise Working Group and PhySIIG) should guide the advice and support given by the CF team.
15	CF teams should support people with cystic fibrosis to be physically active and exercise regularly.
16	Access to a multidisciplinary team with CF expertise and to closely associated specialties remains a key requirement for all people with CF.
17	The CF centre should adapt to reflect the improved life expectancy of people with CF.
18	People with CF should be educated by the CF multidisciplinary team and supported (including with telehealth) to help them best manage their health.
19	Remote care provides an opportunity for monitoring and interventions without hospital visits, but further research is needed to determine optimal strategies.
20	Virtual clinics and homecare offer an alternative to traditional structures but should not replace all face-to-face clinic reviews.
21	As new therapies emerge, the role of the CF pharmacist is increasingly important to optimise drug delivery and management.
22	A variety of approaches are available to monitor adherence to therapies and these should be used in an open manner to support people with CF and their families.
23	CF teams should work in partnership with people with CF and parent/caregivers to support adherence to therapies.
24	Starting and stopping therapies should be guided by the best evidence available and decided in partnership with the person with CF.
25	People with CF with eligible *CFTR* gene variants should be offered CFTR modulator therapy.
26	For young children and infants, certain CFTR modulator therapies may not yet be licensed, and options should be considered on an individual basis.
27	When initiating CFTR modulator therapy, people with CF and families should be encouraged to promptly report any significant physical or mental health changes to the CF team.
28	All adverse events experienced on CFTR modulator therapy should be reported to a post market surveillance scheme and the pharmaceutical company.

Abbreviations: CF=cystic fibrosis, CFTR=cystic fibrosis transmembrane conductance regulator, PhySIIG=Physiotherapy Special International Interest Group.

2. Eating well

2.1. Infant feeding

Chris Smith, Dimitri Declercq

Infant nutritional status has continued to improve in recent decades, largely thanks to early introduction of nutritional support made possible through NBS [4–7]. US registry data show that median weight for length of infants is above the recommended 50th percentile in the first two years of life, however median length remains below expected [8,9]. Close monitoring, as per previous guidelines, is associated with improved growth outcomes. Optimal early growth impacts long-term outcomes, including respiratory function [10–15].

Breast milk is the best nutrition for all infants, including those with CF (Statement 1) [5,16,17]. Breast feeding rates vary but are reported as being lower than in infants without CF [16]. The CF team should encourage and support breast feeding, and where available locally, seek specialist support such as a breastfeeding counsellor early in the diagnosis [13,18].

Close support and regular follow-up by a CF specialist dietitian are essential following diagnosis. The requirement for pancreatic enzyme replacement therapy (PERT) should be identified promptly through clinical assessment and stool measurement of faecal elastase (FE-1) and, if available, faecal fat microscopy. Key moments regarding dietetic support and PERT dosage advice during infancy are periods when feeding methods change, such as the introduction of alternative milks and solid foods.

If growth falters, the infant may require fortification of breast milk or additional use of appropriately fortified formulas to ensure growth potential is optimised [16].

Up to 20 % of infants with CF present with meconium ileus shortly after birth and many require surgical intervention [19]. Growth failure may occur in approximately 40 % of infants with meconium ileus [20,21]. This highlights the need for proactive nutritional management, including parenteral nutrition for infants requiring surgery [21]. Early referral and involvement of the CF team is essential for these families (Statement 2).

Food intake in early life predicts longer-term eating habits [21]. The aim is to balance the importance of infant nutrition while avoiding excessive focus on weight gain that can cause unnecessary concern for the family and negatively influence eating behaviours in the child.

2.2. Supporting good eating; content and behaviours

Eddie Landau, Monika Mielus, Tacjana Pressler

Achieving optimal nutritional status for people with CF addresses malnutrition, while recognising the growing prevalence of excessive weight in all ages [22–25]. The CF specialist dietitian is essential to

support people with CF in developing and maintaining healthy nutritional habits through their life (Statement 3), with consistent support and messaging from all members of the CF team. The CF team should play an active role in nutritional surveillance, as well as collecting data to understand the changing nutritional needs of people with CF [3].

Children and adolescents with CF may require increased intake of protein and calories [13-15,26]. To achieve a high calorie intake, people with CF have often consumed poor quality highly processed diets [27–29]. It is reasonable to include nutrient-dense foods in the diet, but people with CF should not rely on higher fat diets to achieve energy intake, as evidence does not link this to CF health benefits [30]. These foods should provide essential nutrients such as protein, healthy fats, vitamins, minerals, fibre and complex carbohydrates [14,15,30]. People with CF initiating CFTR modulator therapy should be encouraged to continue a high-quality balanced diet [3].

Encouraging healthy feeding behaviours early in life promotes a healthy relationship with food and a positive body image (Statement 4). Feeding principles for infants/toddlers with and without CF are similar, including responsiveness to hunger cues, and encouraging eating without coaxing and bribing [31]. It is important to support young children with CF to listen to their bodily cues, and to avoid confrontation around meals, as this can increase the likelihood of future problematic eating behaviours [13,32]. For older children with CF, behavioural strategies can reduce conflict and lay framework for healthy eating in adult life. Strategies include viewing mealtimes as an opportunity for routine and connection [33], and involving the person with CF in meal planning [34,35].

Guidance for people with CF who have access to CFTR modulator therapy should focus on achieving excellent nutrition with acknowledgement of the long-term risks of obesity (for example, cardiovascular disease), which may be a potential issue for some.

Achieving optimal nutrition relies on coordinated support from the whole CF team, and recommendations must be based on current research, clinical guidelines and consensus views [13,36]. The CF team should provide comprehensive support for nutritional, physiotherapeutic and psychological aspects of care. This includes offering advice on nutrition, providing guidance on physical activity tailored to individual abilities, and addressing psychological factors that may impact eating habits [37].

2.3. Pancreatic enzyme replacement therapy

Chris Smith, Dimitri Declercq

Over 80 % of people with CF have exocrine pancreatic insufficiency and require PERT [38]. CF pancreatic disease obstructs exocrine enzyme delivery and causes a reduced bicarbonate secretion with prolonged acidity in the proximal duodenum [14]. Clinical features indicating pancreatic insufficiency include poor weight gain and loose frequent stools despite a good appetite (Statement 5). Low faecal elastase-1 (FE-1) levels in stool indicate pancreatic insufficiency ($\leq$100 μg/g stool) and supports the use of PERT [39]. For people with CF with an intermediate FE-1 measurement (100–200 μg/g stool), a diagnosis of pancreatic insufficiency is likely, and a trial of PERT is appropriate if clinically indicated.

Appropriate PERT dosage and delivery is essential to correct nutrient maldigestion and malabsorption. PERT should be taken with all food containing fats, proteins, and complex carbohydrates. Guidance varies for PERT dosing and timing, especially the recommended dose with snacks [14,40,41]. Factors influencing dosage include the amount of dietary fat, the PERT formulation being used, weight gain and clinical response [14,42]. Projects, including MyCyFAPP (mycyfapp.eu) and CF Tummy Tracker (cftummytracker.org), are evaluating abdominal symptoms for people with CF to better understand and inform PERT dosage.

PERT consists of lipase, protease, and amylase. Formulations vary in strength, content, and form, including enteric-coated microspheres, tablets, non-enteric-coated tablets, lipase cartridge or powder [14,43]. People with CF and their caregivers should be advised that switching between PERT formulations may initially lead to gastrointestinal problems that can be overcome by adjustment of dosing. The enteric-coated capsules release enzymes effectively when the pH in the duodenum reaches approximately 5.5 [44].

Adherence to PERT is challenging and an individual approach is warranted. Emerging data suggest CFTR modulator therapy may impact pancreatic insufficiency in some people [45,46]. More data are required to guide PERT management in this context.

2.4. Monitoring nutritional progress

Eddie Landau, Monika Mielus, Tacjana Pressler, Anne Munck, Kevin Southern

Nutritional status should be monitored at each clinic visit (Statement 6). Monitoring weight and height (length if aged under 2 years) is a key component of CF care, to support optimal growth in childhood and as a marker of wellbeing in adult life. For older children and adults, body mass index (BMI) should be calculated [14]. BMI and BMI percentiles (or z-scores) have limitations in distinguishing whether deficits, excess stores, or changes in weight are related to fat or fat-free mass compartments. Assessment of body composition as part of nutritional assessment may provide clearer information to guide people with CF [47], particularly in the context of CFTR modulator therapy [3].

Non-judgemental weight monitoring needs to be undertaken with the family, and later with the person with CF, to support the good eating behaviours outlined. This is challenging and requires skilled partnership working by the whole CF team [36]. Comparing growth rates to standard charts is essential. Targets should be ambitious, but also reflect genetic growth potential.

For children and adults on CFTR modulator therapy, improved condition, nutrient absorption, and appetite may result in accelerated weight gain [48]. This should be anticipated and addressed sensitively, appreciating that it is difficult to alter established eating patterns.

It is important to monitor serum levels for fat soluble vitamins, A, D and E at least annually, to assess the need for supplementation [3]. CF-specific multi-vitamin preparations have become more widely available and may improve adherence. These preparations and the impact of CFTR modulator therapy means that vitamin levels (especially vitamin A) can sometimes rise above the normal reference range, requiring adjustment of supplementation [49]. Awareness of the sequelae of excessive vitamin intake should be emphasised [50–52].

There is poor evidence to guide the need for salt supplementation and its dosage [53]. However, for infants and small children, the rationale is compelling, especially when weight gain has been suboptimal [53]. In addition, some older children and adults who are very active may benefit from salt supplementation, but again the supporting evidence is limited. Salt requirements for people with CF increase in hot weather and during periods of fever. Most “western” diets have a high salt content, and this should be monitored and considered when advising families about salt supplementation. The impact of CFTR modulator therapy on reducing sweat salt loss needs to be considered when determining salt requirements and dietary advice [3] (Statement 7). Blood pressure should also be recorded at each clinic visit for people on CFTR modulator therapy [36], given the impact on salt homeostasis and reports of hypertension in clinical trial participants (see Section 7.2).

Dietary advice (intake of calcium and vitamin D) should aim to establish and support bone growth and strength. An assessment of bone mineral density (DXA scan) should be undertaken before puberty to establish baseline data and then repeated at a frequency determined by the baseline results [54]. DXA scan results also provide useful information on body composition. Vitamin K is essential for bone formation; however, more research is required to determine a reliable biomarker to monitor supplementation requirements [50].

3. Towards optimal lung health; staying ahead of the curve

3.1. Physiotherapy for airway clearance

Lisa Morrison, Brenda Button, Sandra Gursli, Catherine Brown

3.1.1. Working with the family from diagnosis through transition to adult life

Following diagnosis, the specialist CF physiotherapist and the family should establish a management plan for physiotherapy and airway clearance techniques (ACT) [55,56] (Statement 8). Physiological principles and age-appropriate ACT should be used to clear airway secretions [57–60]. A range of physiotherapy interventions, ACT types and combinations exist [57], with limited evidence to guide practice [61–64].

Physiotherapists should guide and support parents to manage changing ACT needs and ongoing therapies within their family [65–67]. Parents of children with CF develop expertise and adapt to changes as their child grows and develops [68]. From an early age, physiotherapy management supports children to perform treatment with assistance, supervision, and gradual independence to attain self-mastery and self-confidence [57,59,69]. Children should be taught to understand their respiratory condition, monitor symptoms, appreciate airway secretions and tailor ACT accordingly [59,70].

Aspirations may differ between parents and children, especially between the age of 8 to18 years. Physiotherapists must understand both perspectives and help establish mutual goals [71]. Participation in shared decision making, which is internationally recognised as a young person's right, empowers the person with CF [72] and could promote adherence to treatments.

Regular physiotherapy review and treatment adjustments allow families to develop good habits, treatment routines and motivation to maintain adherence [57,59,69,73]. Regular follow-up should continually optimise treatments to adapt to changing needs and minimise treatment complexity [59,74]. Reducing the burden of ACT promotes adherence [75,76].

Individualising treatment to the person's experience of benefit, perceived usefulness and preferences can help the person adhere to the regimen. [55,74] (Statement 9). The individual management plan should be consistent with the emerging ethos of "gentle, efficient, motivating and self-supporting" (GEMS) [74], and should include age-appropriate physical activity and exercise.

3.1.2. Adapting airway clearance in older children and adults

As older children with CF move to adulthood, they should be encouraged and supported to manage their ACT independently through shared decision making [62,77], establishing self-efficacy and a readiness for transition to adult care [78] (Statement 10). Transition should include early introduction of the adult team, collaboration between teams, and engagement with the young person [79–81]. Clear, high quality physiotherapy information, adequate support and anticipatory guidance for caregivers and young people will promote successful transition to adult care, and may improve transition experiences [82]. Motivational interviewing may support this approach [83,84].

3.1.3. Airway clearance approaches for the productive patient

Airway clearance has positive short-term effects on mucus transport and sputum rheology [64,85,86]. There is little evidence to support one technique over another with respect to short-term clinical outcomes, although more active techniques such as Positive Expiratory Pressure (PEP) reduce the frequency of pulmonary exacerbations (PEx) compared to more passive techniques such as high frequency chest wall oscillation (vests) [87]. Individualising and combining ACTs for people with CF [88] may increase effectiveness and enhance adherence [89].

A priority research question for people with CF was whether regular exercise can replace ACT [90] but more evidence is needed [91]. During an exacerbation, it is important that people with CF can competently perform airway clearance, since the person may have increased sputum load and reduced energy for exercise.

For those who are eligible and have access, CFTR modulator therapy has had a significant impact on people with established airways disease, with many becoming unproductive. The longer-term effects of VST on chronic airway infection and PEx are relatively unknown, and people with CF should remain engaged with ACT approaches [92–94].

3.1.4. The upper airways; problems and solutions

The most common upper airway disorder in people with CF is chronic rhinosinusitis (CRS), with nasal polyposis recognised as a common complication [95]. The CF team should regularly evaluate people with CF for rhino-sinus disease (Statement 11). Virtually all adults and older children with CF have radiological evidence of CRS, yet only a third report symptoms [8,95-97]. CRS can lead to increased bronchial reactivity, chronic lower airway infection and increased frequency of PEx via postnasal drip, negatively impacting quality of life [97]. CF physiotherapists play an important role in the assessment and treatment of CRS [88].

The validated SNOT-20/22 score is a generic tool to recognise CRS and upper airway disease, guide severity, prompt referral to otolaryngology, and assess treatment response [88,95].

There is evidence to support nasal irrigation (douche) and topical steroids to relieve symptoms [88,95]. Isotonic irrigation solutions are preferred, with evidence of effectiveness for 0.9 % sodium chloride solution [95]. A trial of topical steroids may be appropriate for some people with CF, but the evidence base is not strong [98,99]. Effectiveness is enhanced when gravity is harnessed during application, with the person with CF positioned with their head over the edge of the bed [95].

Evidence supports delivery of topical nebulised solutions to the sinuses using a sinus specific nebuliser compared to a standard nebuliser [96]. Tobramycin or colistin delivered topically to the sinuses may reduce *Pseudomonas aeruginosa* infection [100,101]. Nasal nebulisation of dornase alfa may reduce CRS symptoms and improve quality of life scores [102]. Further research is needed to fully establish the benefits of these therapies.

Surgical intervention such as functional endoscopic sinus surgery (FESS) can be effective for people with CF not responding to medical management of CRS. Nasal polyps recur in approximately 80 % of people following polypectomy [95]. CFTR modulator therapy appears to profoundly improve CRS symptoms and radiological findings [95,97,103].

3.2. Clean air

Ross Langley, Kevin Southern, Lisa Morrison

3.2.1. Cigarette smoking and vaping

Evidence that people with CF should not smoke is unequivocal (Statement 12), and we recommend that people with CF should also avoid electronic cigarettes (also known as e-cigarettes, vapes, or electronic nicotine delivery systems [ENDS]) (Statement 13). In the past, advice was less clear and sometimes supportive of e-cigarettes. Children are increasingly exposed to e-cigarettes, with a rapid rise in uptake and regular use in young people [104]. E-cigarettes generate a vapour by heating a liquid that may contain very high levels of nicotine, making them highly addictive. The vapour can also contain vegetable glycerine, polyethylene glycol plus multiple chemical flavourings. The user can be exposed to toxic levels of heavy metals including nickel, lead and cadmium. Many devices currently exist, some disposable, and some that can be easily modified to vaporise other harmful and addictive drugs such as cannabis.

The long-term outcomes for these relatively new products are still unclear. E-cigarettes can cause pulmonary inflammation, oxidative stress leading to epithelial damage and necrosis, airway hyper-reactivity

and altered host defences [105]. In vitro studies have shown that e-cigarette liquids can impair ion channel function including the epithelial sodium channel (ENaC) and CFTR, as well as containing high levels of acrolein which is associated with chronic bronchitis [106].

3.2.2. Hookah smoking

Hookah smoking is also known as shisha or water-pipe smoking. The user inhales through a tobacco pipe with a long flexible hose that draws smoke through water in a bowl. This form of smoking has existed for many years, traditionally in Arabic countries, and is becoming popular in the USA and Europe [107]. Variation in hookah devices and hoses (porous versus non-porous) can influence exposure to the smoke and chemicals, particularly nicotine and carbon monoxide. For these reasons the side effects may be over or underestimated. Furthermore, the humidity associated with hookah smoking facilitates deeper inhalation, potentially increasing the side effects [107]. Hookah sessions generally take 45 min in social environments, including long deep "puffs" and sharing equipment with others [107]. The levels of tar inhaled during these sessions is thought to be over 35 times greater than smoking one cigarette [108]. Sharing of mouthpieces during a hookah session can contribute to transmission of CF pathogens [109].

People with CF should avoid all forms of smoking/vapour inhalation including e-cigarettes and hookahs.

3.2.3. Passive smoking

Environmental tobacco smoke (ETS) is also known as passive or second-hand smoke. ETS is a combination of "mainstream smoke" exhaled by the smoker, or "sidestream smoke" from the burning end of a cigarette, pipe, or cigar, or tobacco burning in a hookah. Sidestream smoke has higher concentrations of nicotine and cancer-causing agents than mainstream smoke [110]. Repeated exposure to ETS increases the risk of lung cancer in adults who have never smoked by 20–30 % [106]. There are no safe levels of exposure to ETS for people with CF of all ages (Statement 12).

4. Being active

Thomas Radtke, Zoe Saynor, Anna Middleton

4.1. The rationale for physical activity and exercise

Physical activity involves activities of daily living and recreation, while exercise is purposeful and structured towards improvements in fitness and airway clearance. The type, duration and intensity of exercise depends on personal goals. Exercise facilitates mucociliary clearance, slows the progression of decline in lung function, and improves exercise capacity, which, when reduced, is a predictor for lung transplantation and death in people with CF [111–114].

The World Health Organisation recommends at least 60 min of moderate-to-vigorous physical activity per day for school-aged children and 150 min per week for adults, with the inclusion of muscle strengthening activities 2–3 times per week. Pre-schoolers should spend at least 180 min per day in a variety of different activities and reduce screen time to a maximum of one hour per day [66]. These fundamental guidelines for physical activity and sedentary behaviour are applicable and important for people with CF. CF-related comorbidities need to be considered when recommending physical activity, but people with CF should be aiming to maximise their physical activity by increasing habitual physical activity (especially moderate-to-vigorous intensity), reducing sedentary time, participating in structured exercise training and promoting positive long-term physical activity behaviours [115, 116]. Other approaches to exercise, for example resistance training which can build muscle and alter body composition, should be considered and encouraged if appropriate.

Availability of CFTR modulator therapy presents new opportunities for people with CF to lead active lifestyles, but also challenges. For example, some respond to CFTR modulator therapy with excessive weight gain [117], which seems to be fat mass rather than muscle, which is an important issue since the prevalence of obesity is steadily rising throughout the CF population [8,24,118,119].

For overweight individuals, regular physical activity and exercise are key to minimising the risk of cardiovascular and metabolic disease [120–122], comorbidities which are becoming more relevant with the ageing CF population. Some people with CF have chosen to modify their treatment regimens and use exercise as a substitute for traditional airway clearance therapy. The long-term effectiveness of exercise as an airway clearance therapy requires further research and is shorter-term effects are currently under investigation in the ExACT clinical trial (NCT05482048) [123,124] .

4.2. Approaches to measuring and monitoring exercise capability

CF-specific consensus recommendations for standardised functional and laboratory exercise testing are available [125,126]. Indications for exercise testing include establishing aerobic fitness and/or muscle strength, evaluation of potential exercise-induced risks, monitoring disease progression, guiding individualised exercise prescription, and evaluating the response to exercise programmes [125,126]. Exercise testing can also serve as a motivational tool. Dynamic endpoints, such as exercise capacity, can provide valuable insights into the integrated functioning of multiple organ systems (cardiovascular, musculoskeletal, respiratory). These modalities provide a more comprehensive understanding of an individual's health status.

The ECFS Exercise Working Group (EWG) and the Physiotherapy Special International Interest Group (PhySIIG) suggest a small selection of exercise tests performed consistently and to a high standard [126] (Statement 14). Cardiopulmonary exercise testing (CPET) provides a measure of aerobic fitness and helps assess exercise-related symptoms [125]. If CPET is not available, standardised guidance is available for other less-complex tests [125,126].

4.3. Strategies to support and maintain an active lifestyle

The CF team should promote an active lifestyle as early as possible [115]. Family engagement in physical activity influences long-term behaviours by promoting enjoyment and adherence [127]. Children with CF are encouraged to participate in club activities, integrating exercise into normal lifestyle (Statement 15).

The CF team should review exercise capacity and progress at each clinic, ideally with a psychologist to support goal setting, self-regulation and management of barriers and setbacks [127]. The most effective type, duration and intensity of exercise for people with CF remains unknown [113,115]. Programmes should be individualised with focused guidance for specific subgroups considering age, gender, disease severity, extra-pulmonary complications, access and psychological factors modulating physical activity behaviours [115,128]. Physical activity and exercise plans should be developed in consultation with the person with CF and their family [127], facilitating individual preferences for environment, modality, duration, intensity and frequency. Offering choice, diversity and flexibility can improve engagement, enjoyment and long-term physical activity behaviour, and can promote self-efficacy and adaptability in the management of unplanned setbacks [115,127].

For people with more advanced or severe CF lung disease, exercise remains important, although advice needs to be more pragmatic and alternative interventions considered, such as stationary cycling and strength training [115]. Consistent messaging from the CF team promotes favourable body composition changes and accrual of lean tissue mass (skeletal muscle) for people with CF who undertake high levels of exercise [20]. People with CF can be reassured that physical activity is safe [129,130], by identifying individual safety considerations through exercise testing and musculoskeletal assessment, followed by appropriate education. Initial supervision of prescribed programmes

(in-person or via telemedicine [20]) can monitor the impact, enjoyment and avoidance of undesired physiological responses which can negatively impact long-term physical activity behaviour [115]. Regular review of progress using recommended tests is recommended to modify the programme and maximise benefits [91,115].

Adherence to exercise programmes is often poor and strategies should evolve and adapt as the person ages [131]. The CF team should work with the individual to identify factors that impact adherence, including facilitators, enabling and re-enforcing factors, and physical and psychosocial barriers. Support should focus on coping and behavioural strategies to promote motivation. These strategies can include goal setting and self-monitoring, integrating structured exercise into daily life and influencing long-term physical activity behaviour [127,128,132-134]. Digital media and wearable technology are valuable tools for self-monitoring and motivation [132], however future research is needed to determine the best physical activity assessment tool and their effectiveness in promoting engagement [135].

5. Working with the CF team and other healthcare professionals

5.1. Expectations and models of care

Isabelle Fajac, Kris De Boeck, Audrey Chansard, Dominique Pougheon Bertrand, Scott Bell

The model of care for people with CF is based on the CF centre and the framework first described in the 2014 ECFS Standards of Care [136]. The success of centre-based care in improving survival and other key clinical metrics is clear and the principles driving this model remain relevant today [137]. However, it is appropriate to reflect on changes to the traditional care model given the continued improved life expectancy [137] (Statement 17), the health benefits following initiation of CFTR modulators [138], and the new approaches to providing care that emerged with the Covid-19 pandemic [139]. Changes that facilitate care closer to home with less frequent hospital visits may be appropriate and are popular with people with CF and their families but must not compromise quality of care. Strategies to be considered include networks with a central specialised hub, regional clinics and remote care, as described in following sections.

Whichever model of care is adopted, the multidisciplinary CF team remains key, and access to this team is a requirement for people with CF (Statement 16). The CF team provides the support that people with CF and families require for their journey (Statement 18) and must include respiratory paediatricians or pulmonologists with specialist CF knowledge. Other members of the CF team should include clinical nurse specialists, respiratory physiotherapists, physical activity coaches/exercise physiologists, dietitians, clinical psychologists, social workers (and youth workers), microbiologists and pharmacists, all of whom should be experienced in CF care [136]. Although the roles of these professionals are well established, they continue to evolve with the changing CF landscape (see Section 6.1 on the increasing importance of the CF pharmacist). Youth workers are being increasingly utilised in a healthcare setting to support young people with chronic conditions on their journey into adult life [140].

With the development of CFTR modulators, it is critical that all people with CF have access to *CFTR* gene testing for diagnosis and information on their eligibility for CFTR modulators [3]. Moreover, the CF team should be knowledgeable about eligibility for CFTR modulators, modalities of prescription, possible complications, drug interactions, and follow-up [3]. The CF team should discuss the potential impact and prescribing of CFTR modulators with the person with CF as soon as eligibility is confirmed.

It is essential that the CF team establishes links with closely associated specialties, including clinical genetics, and radiology. Strong links should also exist with a wide range of other medical and surgical specialties including gastroenterology and hepatology, endocrinology with expertise in CF-related diabetes, otorhinolaryngology, cardiothoracic and general surgery, interventional radiology, specialist anaesthesia and pain control, rheumatology, psychiatry, intensive care, urology/nephrology, assisted fertility services and gynaecology/obstetric services [136]. Because of the growing number of pregnancies since the availability of the triple therapy combination, elexacaftor-tezacaftor-ivacaftor (ETI) [141], there is a need to enhance links with obstetric care teams delivering high-risk pregnancy care.

Transplant services for lung and liver should be easily accessible and approachable for case discussion focusing on CF-specific complications, education, and consideration of the appropriate use of CFTR modulators in post-transplant patients [142,143]. With the increased survival of people with CF, primary care expertise should be integrated into the CF care pathway, especially for non-CF-related diseases and disease prevention screening. Links with specialists experienced in age-associated comorbidities should also be established.

The regular visits and assessments constituting quality CF care throughout lifetime, as outlined by several guidelines documents [136,144], have been associated with improved survival [137]. The Covid-19 pandemic prompted integration of virtual care with voice and video link consultations [139]; we discuss this further in Section 5.2. Virtual multidisciplinary consultations with the possible use of connected medical devices should be proposed and evaluated in terms of risks and benefits for the person with CF. This will inform on the optimal use of remote monitoring and care, which is still an area for further study [145,146] (Statement 19). Care needs to be individualised to each person with CF, based on their needs and preferences [147,148]. The CF team should have regular pre- and post-clinic visit patient discussions and should have regular quality-management meetings to discuss and update general policies such as infection control, treatment and follow-up protocols [136].

The buildings, facilities, and the computer infrastructure should allow the CF team to provide effective diagnosis, holistic care, treatment and research [136]. CF centres should encourage people with CF to participate in CF registries in order to further the understanding of the disease and improve clinical care through key metrics and benchmarking [149]. Members of the CF team should keep up to date with developments in CF through continued professional development, attendance at conferences, participation in audits, and involvement in clinical research including clinical trials [136]. CF centres should network with other centres, both nationally and internationally, and link with local or national patient representative organisations to offer additional resources to support people with CF and families. Less economically advantaged regions should strive to implement best practice to deliver equality and high standards of care. Patient organisations and the ECFS help translate standards from economically advantaged regions to improve CF care in developing services by supporting skill development and resource allocation [136]. There is an increasingly recognised need to improve diagnosis and management in countries with a low incidence of CF [150] and in regions with limited resources. In these countries, even if a diagnosis is established, access to basic therapies is challenging.

It is a period of significant change for the CF community. Despite this, the basic framework of CF care remains key to good outcomes for people with CF (Fig. 1). It is imperative that CF teams work in partnership with people with CF to deliver care in the most appropriate manner without compromising quality.

5.2. Potential for remote care

Charlotte Addy, Michael Doumit and Ilan Shufer

5.2.1. Remote monitoring

Remote monitoring can supplement face to face care at CF centres to assist early detection of clinical decline [151] and to support adherence [152]. Multiple modalities are available to remotely monitor clinical progress, including lung function, vital signs, sleep quality, physical

Develop and/or maintain a CF centre with all necessary expertise amongst the CF team, with special attention to:

- up-to-date knowledge about CFTR modulator eligibility, prescribing, reimbursement, follow-up of adherence, tolerance
- continued support for people with CF without access to or eligibility for CFTR modulator therapy
- consultations adapted to the needs and disease severity of the person with CF
- combining face to face consultations and virtual consultations
- adapting the service to the growing needs of people with CF (for example, education, work, family, travel, and long-term plans)
- team expertise and quality evaluation management
- developing a research active environment

Develop or maintain strong links with all relevant medical specialties needed, with special attention to:

- links with primary care and enhanced screening for associated comorbidities
- obstetrics
- ageing and CF-related complications
- access to transplant services

Fig. 1. Key principles of CF care.

activity, height/weight and patient reported outcomes. Validity and reliability vary between modalities and devices, with interpretation and follow-up dependent on the monitoring purpose (See Table 2).

While remote monitoring is feasible, caution is needed in application. Concerns include low engagement, particularly in adolescents, and lack of improved clinical outcomes following monitoring-based interventions [152–154]. Increased monitoring can lead to health anxiety, and this may contribute to disengagement with ongoing assessment [155].

A number of accurate home spirometers are available. Disparity between home and hospital measurements exists, with caution needed if results are compared [156]. Daily variability also impacts reliability and should be considered when interpreting results [157–159]. Further data is necessary regarding individual variability using remote monitoring, both with technique and the device. Performing tests, for example spirometry, during a video link may prove beneficial. Research is needed to determine optimal monitoring strategies and subsequent interventions to improve clinical outcomes, promote engagement and balance the additional burden of remote monitoring with benefit for people with CF.

5.2.2. *Virtual clinics*

The use of virtual clinics for CF care was accelerated by the Covid-19 pandemic, with interest sustained by feasibility and the benefits to people with CF and healthcare teams [159,160]. Benefits include reduced financial/travel burden, reduced impact on home life and reduced risk of cross-infection. Virtual clinics promote sustainability and flexibility, and are cost effective, although funding to support equipment may be complex to access [161]. Accessibility and engagement in virtual clinics vary across racial, ethnic and socioeconomic groups [162], so care models must account for this, providing additional support as needed. Virtual clinics and homecare offer an alternative to traditional

Table 2
Summary of remote monitoring modalities.

Remote monitoring modality	Benefits	Limitations	Current level of evidence
Home spirometry	• Ease of use • Reduced Infection Control risk • Small and Portable • Enables more frequent measurement	• Variable reliability and reproducibility • Multiple devices • Variable technique between devices • Cost of device and replacement devices • Cannot be used interchangeably with clinic spirometry • Potential for inaccurate calculation of predicted values by using historical height measures (especially for children)	Single and multi-centre studies
Home physical activity monitoring	• Ease of use • Small and portable • Multiple options dependent on age and level of information required	• Variable reliability and reproducibility • Multiple devices making standardisation difficult • Limited data linkage with healthcare systems • Devices with high accuracy are costly	Single and multi-centre studies
Quality of life /symptom measures	• Early detection of illness • Increased focus on patient reported outcomes	• Variable engagement with monitoring, especially in adolescents • Lack of standardisation of symptom scores	Single and multi-centre studies
Home sputum collection	• Results available prior to clinical review • Possibility of postage to CF centre	• Limited results linkage with healthcare systems • Reduced availability of sputum in children and those on CFTR modulator therapy • Location/country dependent policies on postage	Few single centre studies
Pulse oximetry	• Device accuracy • Small and portable	• Limited benefit outside of acute exacerbations	Few single centre studies
Height/weight measurement	• Easily accessible to most • Contemporary height measures useful for lung function values	• Variable accuracy of measurements depending on user/equipment • Cannot be used interchangeably with clinic measurements	Multiple non-CF single centre studies

structures but should not replace all face to face clinic reviews (Statement 20). The initiation of new therapies should be monitored directly in clinic.

To address safety concerns and ensure effective monitoring, virtual clinics should mirror "traditional" face to face clinics, including provision for multidisciplinary assessments, lung function, mental health screening, blood, nutritional and microbiological monitoring. CF healthcare professionals should be trained in the principles of remote consultation, establishing a safe and meaningful consultation, and recognising cues that should trigger an intervention or face to face consultation (Fig. 2). Coming out of the Covid-19 pandemic, most centres have adopted a hybrid approach, with the balance between face to face and virtual consultations determined by the person with CF and CF team, annual screening requirements and individual clinical needs. Further large-scale evidence capturing the experiences of people with CF is needed to optimise hybrid models which minimise burden while maintaining quality.

5.2.3. Ambulatory care

As outcomes for people with CF improve, there is a move towards proactive ambulatory or outpatient interventions to promote health and quality of life. These include exercise programmes [163], psychological support [164], adherence interventions [152], diabetes education [165] and weight management. Virtual formats overcome the need for segregation based on infection control issues and allow provision of group-based support previously inaccessible to people with CF. There is also potential for clinical practitioners embedded in the CF team to provide assessment, support and interventions in the home of the person with CF.

6. Managing medicines

Medicines are a large part of daily life of people with CF and their families. The rationale for each intervention should be clear and evidence reviewed regularly. In these sections we consider the expanding role of the pharmacist in the CF team, the challenge of supporting adherence and the increasing importance of stopping/starting strategies. Finally, we review developments in the field of VST, with CFTR modulator therapy now an established and important intervention for many people with CF.

6.1. Role of the pharmacist in the CF team

Amanda Bevan, Carina Hansen

The role of the CF pharmacist has become increasingly important to optimise drug delivery and management (Statement 21). Activities defined in previously published standards of care [136,166-168] have been expanded and are outlined below.

The pharmacist is a core member of the CF team, advising on all aspects of medicines. The CF pharmacist should review each person with CF and complete a full medicine history at least annually. This will include evaluation of relevant drug interactions, difficulties with adherence or medicines taking behaviour, medicines which might be discontinued, problems with medicines administration and availability, especially of new generic options. The pharmacist should review medicines against current evidence as part of the annual review. For healthcare regions without a dedicated CF pharmacist, these tasks will need to be taken on by other members of the CF team, with potential impact on quality of care.

Environment (for the CF team and the person with CF) • Reduce background noise • Reduce disturbances/interruptions • Ensure comfortable positioning • Ensure privacy – from public and from family/pets if needed • Opportunity to assess home environment – consider safeguarding issues • Dress appropriately and avoid distractions in the background
Technical issues • Ensure effective audio-visual hardware • Appropriate internet connection with suitable speed • Clarify with the person with CF if the sound and visuals functional/acceptable • Have a backup communication option planned in case connection fails • If issues arise ensure troubleshooting carried out before terminating consultation
Communication • Consider whether consultations conducted 1:1 or with person with CF and several CF members – adjust communication style accordingly if group consultation • Consider consent issues if the person with CF is paediatric or vulnerable • Utilise different skill set to face to face assessment which may require upskilling of CF • Effective history taking critical • Reduced reliance on clinical signs • Alter body language assessment to account for limited perspective • Adapt questions as needed considering environment of the person with CF • Consider if others may be present/listening out of sight • Consider comfort of the person with CF in using this format • Maintain eye contact and visual cues – as even more important when only face/upper torso is visible • If looking away from the camera at another screen or paper results, explain what you are doing (and that you are still listening)
Effective use and integration of home monitoring • If remote monitoring in use ensure this is considered as part of consultation • If additional monitoring needed after consultation, ensure results are obtained and a clear plan of action agreed with the person with CF before consultation ended
Outcomes • Clarify wishes of the person with CF regarding future virtual consultations • Ensure outcome clear to the person with CF and the CF team • Consider whether next review is face to face vs virtual

Fig. 2. Guide to conducting effective virtual consultations with people with CF.

People with CF obtain medicines from various routes including hospital pharmacies, outpatient pharmacies, community pharmacies and home delivery services. Obtaining essential medicines from several providers may be challenging [169]. The relationship with the community pharmacy is especially important for people with CF and the services they provide are complementary to those from the hospital. Communication between the two services should be clear, to best support the person with CF. The pharmacist should be available to answer queries related to medicines from people with CF or other healthcare professionals.

The CF pharmacist should attend all CF team meetings to provide input on medicines-related topics and support the team to develop and follow evidence-based guidelines within the service, and across any shared care networks. The CF pharmacist is also well placed to support clinical research.

6.2. Supporting adherence to therapies

Urzula Borawska, Kevin Southern, Ilan Shufer

The therapeutic burden for people with CF and their families is variable but always significant [170]. Supporting people with CF with adherence to therapies requires skilled partnership working, an appreciation of treatment burden and a clear rationale for each therapeutic intervention [171]. Communication should be clear and open, with shared decision making and agreed treatment goals.

Several methods provide insight into how a person with CF manages their daily treatment burden. These include, in order of accuracy and validity: electronic data capture (EDC), medication possession ratio (MPR), regular phone diaries, self-reporting via apps or paper diaries and retrospective surveys [172,173]. Whichever surveillance method is employed to monitor treatment adherence, this should be transparent, with the CF team working openly to support the person with CF and reflect together on results (Statements 22 and 23).

Supporting optimal adherence requires an individualised approach that is flexible and considers the life of the person with CF and their family. Various strategies support improved adherence, with no clear evidence as to a preferred approach (Table 3) [174]. Clinical trial data suggest that an individualised approach can help the person with CF maintain adherence to aerosolised therapies [152]. With the increased availability of technologies to help monitor treatments and wellbeing, it is important that these advances are driven by people with CF to address their needs. Adherence monitoring should be supportive, improve quality of life and not result in an additional perceived burden for people with CF.

Table 3
Strategies to support and improve adherence to CF therapies.

Focused on relationship with CF team

- Establish a relationship with the person with CF and their family based on cooperation, honesty, and trust
- Normalise challenges with adherence and acknowledge the person's efforts
- Ensure that all members of the CF team deliver a consistent message to the person with CF and their family
- Emphasise the potential benefits of therapy and the realistic trajectory of the disease without inducing anxiety (avoid using fear-based approaches)
- Collaboratively develop an individual behaviour change plan with the person with CF, and consider using motivational interviewing

Focused on the person with CF

- Assess patient/family resources, coping skills, and experience of resilience
- Support emotional wellness and provide interventions to prevent decline in mental health
- Monitor mental health – annual screening of depression and anxiety symptoms is recommended
- Offer suitable interventions utilising various treatment modalities if/when symptoms increase, and/or refer to mental health specialists when needed
- Assess the beliefs and attitudes of the person with CF and their family regarding the treatment

Focused on treatment

- Monitor the educational needs of the person with CF and their family, and deliver comprehensive knowledge through diverse methods
- Help to establish treatment routines and habits
- Collaboratively establish an individually tailored treatment plan with the person with CF and their family
- Help to develop accurate time-management strategies e.g., using electronic devices, reminders

6.3. Starting and stopping medicines

Gwyneth Davies, Maarten Ploeger, Nicole Mayer–Hamblett, Bradley Quon

The evidence base for traditional CF medicines largely stems from clinical trials and systematic reviews undertaken before the CFTR modulator era. The implementation of CFTR modulator therapy for many people with CF has been successful but requires a reappraisal of all therapeutic approaches.

Decision making for starting and stopping chronic medicines should be shared between the person with CF/their caregivers and a clinician with expertise in CF (Statement 24), with rationale documented and reviewed at least annually. Recommendations should be guided by clinical trial evidence where available, and tailored to the individual. Factors such as CFTR modulator prescription, pre-existing lung disease, age, comorbidities and treatment burden should be considered. Treatments should balance therapeutic burden and side effects with health optimisation, minimising decline in pulmonary function and occurrence of PEx.

Studies are evaluating if it is safe to stop chronic medicines in people established on triple combination CFTR modulator therapy (ETI). The randomised controlled trials (RCTs) SIMPLIFY (NCT04378153) and CF STORM (EudraCT 2020–005,864–77) explore stopping nebulised mucoactive therapies, according to the research priorities set by the CF community. Observational studies such as HERO-2 (NCT04798014) and NEEMO (NCT05519020) are evaluating the role of long-term treatments more broadly. In SIMPLIFY, people with CF on ETI who discontinued inhaled mucoactive therapies did not have a drop in lung function. However, the study participants had predominantly mild to normal lung function and the 6-week study period was short [175].

There is no evidence to support or refute stopping medicines in young children (<12 years) on CFTR modulators, and at present there is inconclusive evidence to guide decision making in individuals with moderate to severe CF lung disease (ppFEV$_1$<60 %). Similarly, there is no evidence available to inform when chronic therapies should be newly initiated in those already established on CFTR modulators. These remain important questions for the CF community.

When applying clinical trial findings to clinical practice, it is important to consider these results in the context of study design, participant demographics, intervention and timing of outcome measurement. Where high quality evidence is available, it may be appropriate to monitor treatment reduction (dose-tapering or stopping). Short- and long-term treatment-specific considerations should be discussed, acknowledging any unknowns and communicating clear criteria for re-starting.

Data collection in CF registries regarding treatments and clinical outcomes should be optimised, to maximise the value of these data for the benefit of the community.

7. Variant-specific therapy (CFTR modulator therapy) to correct the underlying defect

7.1. Progress since interim guidance (January 2023)

Kevin Southern, Mark Chilvers, Elise Lammertyn

CFTR modulator therapy has been a significant intervention for people with CF who are eligible (genotype and age) and who have access

[3]. These oral therapies, generally taken twice daily, have proven efficacy and a good safety profile [3]. People with CF with eligible *CFTR* gene variants should be offered CFTR modulator therapy (Statement 25).

The first CFTR modulator, ivacaftor, is licensed for a limited range of responsive *CFTR* gene variants, which are carried by <5 % of people with CF. Ivacaftor has been available for eligible people with CF since 2012 and is currently licensed for people with CF from 1 month of age in the US (4 months in Europe) [176].

The dual modulator therapies, lumacaftor-ivacaftor and tezacaftor-ivacaftor expanded the population eligible for CFTR modulator medicines, but with reduced efficacy compared to ivacaftor. These dual therapies were initially licensed for people with two copies of the c.1521_1523delCTT (F508del) *CFTR* variant, followed by label extensions to some compound heterozygote combinations for tezacaftor-ivacaftor [3,177].

The triple combination therapy ETI has better efficacy than dual modulator therapies and has been licensed for people with just one F508del variant, increasing the pool of eligible people with CF. In 2023, ETI was approved for children from 2 years of age in the US [178]. The approval process is ongoing in Europe.

There is strong evidence to support the use of ivacaftor or ETI for people with CF who have eligible *CFTR* variants. The evidence for dual therapy is less robust [179] and this treatment should be considered on an individual basis.

Some people established on ivacaftor therapy may be eligible for ETI if their second *CFTR* variant is F508del and clinical trial data suggest some additional benefit. The decision to switch to ETI should be made on an individual basis, balancing the potential additional benefit with the risk of adverse reactions caused by the additional agents in the ETI triple combination therapy.

CFTR modulator therapy is expensive, with inequitable access worldwide [150]. In countries and regions that have funded access to CFTR modulator therapy, CF teams should promptly offer these medicines to eligible people with CF, with systems in place to monitor response and adverse reactions [3]. Independent lists of eligible variants are available and should be checked regularly for updates [3,180]. For people with rare uncharacterised *CFTR* variants, n-of-1 trials are appropriate to assess efficacy, although funding may be a challenge for off-licence indications, reflecting a licence that is genotype dependent. For young children and infants, certain CFTR modulator therapies may not yet be licensed, and options should be considered on an individual basis (Statement 26).

The impact of CFTR modulator therapy on the lives of people with CF is considerable and these updated guidelines reflect that changing landscape. A small but significant number of people with CF do not have *CFTR* gene variants that are responsive to current CFTR modulator therapy. For these people, emerging technologies such as gene replacement or editing to correct the underlying CF defect are required [3]. The principles of care outlined in this paper remain essential to achieve good outcomes in all people with CF, especially for people who are ineligible for CFTR modulator therapy or who live in a country or region without access.

7.2. Monitoring for adverse events on CFTR modulator therapy

Kevin Southern, Martin Hug and Anna Georgiopoulos

The safety profile of CFTR modulator therapy for people with CF is good. Preclinical studies were reassuring and concerns over lens opacities from animal studies have not manifested significantly in humans. This has been confirmed by regular eye examination of people with CF exposed to CFTR modulator therapy [3].

However, despite the overall safety profile, impactful side effects from CFTR modulator therapy are seen. Side effects related to the physiological changes associated with the therapy include increased airway secretions, abdominal pain, rhinorrhoea (especially in younger children), sinusitis, and testicular pain [3]. Adverse reactions relating to the mechanism of action are generally transient and resolve in days or weeks. Idiosyncratic side effects include skin rash, headache, drug-induced acne [181], mastitis, transaminitis (raised liver enzymes), muscle pain, creatinine kinase elevation and raised blood pressure. Raised blood pressure was most clearly associated with the dual combination of lumacaftor-ivacaftor but has also been reported with other modulator combinations [182,183]. Elevated liver transaminases have been reported in up 25 % of people with CF taking ETI and the summary of product characteristics recommends routine monitoring, with more frequent evaluation if there is evidence of liver disease [184]. Transient dyspnoea was often observed on initiation of lumacaftor-ivacaftor [185]. This side effect was not regularly reported with other CFTR modular combination therapies [179].

Neuropsychiatric side effects have been reported for all available CFTR modulator therapies [186]. An increasing number of reports have accompanied the widespread availability of ETI, including alterations in mood, anxiety, sleep and neurocognition, as well as suicidal ideation/-attempts. Most remain limited to case reports/series and single-centre studies [187–190], although national survey data are emerging [191, 192]. Some changes in mental health may be positive or unrelated to starting a CFTR modulator, while negative experiences may reflect psychological adjustment to living in the modulator era, direct physiologic impact of the modulator, or drug-drug interactions, highlighting the importance of careful assessment [190,192]. The Pharmacovigilance Risk Assessment Committee (PRAC) for the European Commission recently determined that there is at least a reasonable possibility of a causal relationship between ETI and depression [193].

When discussing the risks and benefits of CFTR modulator therapy, potential physical and mental health impacts should be considered. People with CF and their families should be encouraged to report both positive and adverse experiences to the CF team, regardless of presumed causality (Statement 27). As people with CF are established on modulator therapy, surveillance is required based on the above events, including eye examination, measurement of liver transaminases [194] and blood pressure. Mental health should be monitored in accordance with CFF/ECFS guidelines, including screening for depression and anxiety before and no later than 3 months after initiating VST [3].

The importance of post market surveillance was illustrated by reports of five cases of raised intracranial pressure in younger children on ETI [195,196]. In three children, this was identified from papilloedema seen on routine eye examination, and in two children because of sixth nerve palsy.

As with any new drug, all adverse events, regardless of causality should be reported on a national database or registry and to the company as part of a post market surveillance schedule (Statement 28).

7.3. Adjusting the dose of CFTR modulator therapy after adverse reactions

Mark Chilvers, Martin Hug, Peter Middleton, Jane Davies

No evidence-based approach to dose interruption, reduction and re-introduction of CFTR modulators has been reported. Side effect management is based on clinical context, local experience and emerging evidence from case studies (Table 4).

Mild skin rashes or acne can be unpleasant but can often be managed with symptom-based treatment without CFTR modulator dose interruption [181,197]. More severe rashes may require dose interruption and initiation of desensitisation protocols ranging from weeks [198] to several months [199,200].

Real world data show that variations in transaminases with CFTR modulators rarely lead to liver injury [201] but may be managed with dose interruption or adjustment.

Neuropsychiatric issues have been effectively relieved by dose interruption or reduction [187,188,202] (Table 4). Some people with CF have chosen to not re-introduce CFTR modulator therapy because of the

Table 4
Suggested dose adjustment of CFTR modulator therapy
Note: some countries may apply stricter criteria for discontinuation, especially with transaminitis.

Event	Severity	Dose adjustment	*Re*-introduction	Other actions
Rash	Mild	Continue standard dose[1] [197]	N/A	Treat with antihistamines, topical steroids
	Severe	Stop	Once symptoms resolve, restart at full dose, or start desensitisation process [198–200]	Treat with antihistamines, topical steroids
Transaminitis	>3 X ULN	Continue standard dose	N/A	Repeat LFTs monthly
	>5 X ULN	Dose reduction[2] [211]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride	Repeat LFTs after 2 weeks
	>8 X ULN	Stop [211]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride[2]	Repeat LFTs 1–2 weekly [188]
Pre-existing liver disease	Moderate hepatic impairment: VST treatment if clear medical need & benefits outweigh risks [184].	Dose reduction[2] [184]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride[2]	Repeat LFTs 1–2 weekly [188]
Insomnia / daytime fatigue		Standard dose	Consider switching am/pm dosing times	
Neuropsychiatric, mood or anxiety symptoms	Moderate	Dose reduction[3]	12 weeks after[4] symptoms resolve, increase dose [203] Titrate dose with clinical response ± sweat chloride[2] [188,190,203]	Consider initiation or dose adjustment of psychopharmacologic therapy [190]
	Severe	Stop	Once symptoms resolve, consider re-introduction with a reduced dose[3] or alternate drug[5] Titrate dose with clinical response ± sweat chloride[2] [190,203]	Consider initiation or dose adjustment of psychopharmacologic therapy [190]
Pregnancy		Standard dose [3] or stop VST to 2nd trimester		Review with obstetrician CF clinic[6]

Abbreviations: LFTs=Liver Function Tests, ULN=upper limit of normal, VST=variant-specific therapy.
Footnotes:
[1] Currently three different age and weight based dosage formulations are available for modulator treatment [184]. All are based on the following Standard Dose Regimen: 2 tablets each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening.
[2] Dose reduction to: 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening, OR 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning 3 times a week.
[3] Dose reduction to: 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening.
[4] Consider earlier reestablishment of standard dose if clinically indicated.
[5] Consider alternative agent, either a dual or mono modulator combination dependent on patient genotype.
[6] *In utero* VST exposure may reduce neonatal serum immunoreactive trypsinogen and result in a false negative newborn screening result.

adverse reaction [188,190,203].

There have been reports of benign intracranial hypertension in people on CFTR modulator therapy which, in some cases, may have been associated with hypervitaminosis A. Dose interruption was needed for some people, whereas in others symptoms resolved with reduction of vitamin supplementation [195,196,204].

Ultimately the decision to continue CFTR modulator therapy is determined by patient preference and clinical guidance. Sweat chloride as a marker of CFTR modulation can be used to support dosing regimens [188,203]. Recently developed drug assays [205,206] can measure drug levels and titrate drug dose against clinical markers of benefit. This has helped resolve CFTR modulator therapy side effects in some cases [207]. Further work to standardise these assays and make them more widely available is a clinical priority.

7.4. Adjusting the dose of CFTR modulator therapy during pregnancy

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The number of pregnancies has tripled for women with CF established on ETI therapy [8]. Interrupting CFTR modulator therapy during or before pregnancy is an option but has been associated with clinical deterioration in pregnant and non-pregnant women [3]. Real world safety data are emerging [208] and clearly many women with CF are choosing to continue ETI throughout pregnancy [209], however some may choose to interrupt medication throughout pregnancy. In certain jurisdictions access to CFTR modulator therapy is denied for pregnant women with CF. The decision to continue or stop CFTR modulator therapy during pregnancy and breastfeeding should be made considering the risks for the mother and the baby [195,210].

8. Conclusion

This comprehensive paper provides guidance for people with CF and healthcare professionals, based on the best available evidence. The paper provides background and context, while the accompanying statements (Table 1) are more directive. The tone of the guidance reflects the changing landscape for the CF community and promotes activities and interventions to both establish and maintain a healthy life. The pro-active ethos that runs through this paper is illustrated by sections and statements on physical activity and exercise, clean air and models of care. The next paper in this series will explore interventions for complications of CF and when life gets more challenging.

The guidance was developed in partnership with people with CF and the wider CF community. Whilst a good level of evidence was identified for some recommendations (13 Cochrane systematic reviews cited), overall, the evidence base to support guidance was not strong. This reflects the rapidly evolving CF field. The Delphi methodology enabled us to develop relevant statements in a timely manner. Responses to the Delphi exercise were informative and resulted in statements being modified (improved) or rejected by the Core Committee. The process

helps to identify research questions that require new or further clinical trials to provide an answer and improve the evidence base. The guidance is translatable to both established and emerging CF care services and provides a framework for living a healthy life.

CRediT authorship contribution statement

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 to produce a consistent document.

Declaration of competing interest

KWS has no competing interests. See supplementary materials for full CoI statements for all authors.

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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.2023.12.002.

References

[1] Southern K, Burgel P, Castellani C, De Boeck K, Davies J, Dunlevy F, et al. Standards for the care of people with cystic fibrosis (CF). Editorial J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.09.009. published online.

[2] Castellani C, Simmonds NJ, Barben J, Addy C, Bevan A, Burgel PR, et al. Standards for the care of people with cystic fibrosis (CF): a timely and accurate diagnosis. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.09.008.

[3] Southern KW, Castellani C, Lammertyn E, Smyth A, VanDevanter D, van Koningsbruggen-Rietschel S, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. J Cyst Fibros 2023; 22:17–30. https://doi.org/10.1016/j.jcf.2022.10.002.

[4] Leung DH, Heltshe SL, Borowitz D, Gelfond D, Kloster M, Heubi JE, et al. Effects of diagnosis by newborn screening for cystic fibrosis on weight and length in the first year of life. JAMA Pediatr 2017;171:546–54. https://doi.org/10.1001/jamapediatrics.2017.0206.

[5] Munck A, Boulkedid R, Weiss L, Foucaud P, Wizla-Derambure N, Reix P, et al. Nutritional status in the first 2 years of life in cystic fibrosis diagnosed by newborn screening. J Pediatr Gastroenterol Nutr 2018;67:123–30. https://doi.org/10.1097/mpg.0000000000001956.

[6] Martins JP, Forte GC, Simon M, Epifanio M, Pinto LA, Marostica PJC. The role of neonatal screening in nutritional evolution in the first 12 months after diagnosis of cystic fibrosis. Rev Assoc Med Bras (1992) 2018;64:1032–7. https://doi.org/10.1590/1806-9282.64.11.1032.

[7] Coffey MJ, Whitaker V, Gentin N, Junek R, Shalhoub C, Nightingale S, et al. Differences in outcomes between early and late diagnosis of cystic fibrosis in the newborn screening era. J Pediatr 2017;181. https://doi.org/10.1016/j.jpeds.2016.10.045. 137-45.e1.

[8] Cystic Fibrosis Foundation. Cystic fibrosis foundation patient registry 2021 annual data report. 2022.

[9] Martiniano SL, Elbert AA, Farrell PM, Ren CL, Sontag MK, Wu R, et al. Outcomes of infants born during the first 9 years of CF newborn screening in the United States: a retrospective cystic fibrosis foundation patient registry cohort study. Pediatr Pulmonol 2021;56:3758–67. https://doi.org/10.1002/ppul.25658.

[10] Sanders DB, Zhang Z, Farrell PM, Lai HJ. Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis. J Cyst Fibros 2018;17: 528–35. https://doi.org/10.1016/j.jcf.2018.01.006.

[11] Macdougall A, Jarvis D, Keogh RH, Bowerman C, Bilton D, Davies G, et al. Trajectories of early growth and subsequent lung function in cystic fibrosis: an observational study using UK and Canadian registry data. J Cyst Fibros 2023;22: 388–94. https://doi.org/10.1016/j.jcf.2022.09.001.

[12] Ong T, Onchiri FM, Britto MT, Heltshe SL, Kessler LG, Seid M, et al. Impact of guideline-recommended dietitian assessments on weight gain in infants with cystic fibrosis. J Cyst Fibros 2022;21:115–22. https://doi.org/10.1016/j.jcf.2021.08.005.

[13] McDonald CM, Alvarez JA, Bailey J, Bowser EK, Farnham K, Mangus M, et al. Academy of nutrition and dietetics: 2020 cystic fibrosis evidence analysis center evidence-based nutrition practice guideline. J Acad Nutr Diet 2021;121. https://doi.org/10.1016/j.jand.2020.03.015. 1591-636.e3.

[14] Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr 2016;35:557–77. https://doi.org/10.1016/j.clnu.2016.03.004.

[15] van der Haak N, King SJ, Crowder T, Kench A, Painter C, Saxby N. Highlights from the nutrition guidelines for cystic fibrosis in Australia and New Zealand. J Cyst Fibros 2020;19:16–25. https://doi.org/10.1016/j.jcf.2019.05.007.

[16] Colombo C, Alicandro G, Daccò V, Consales A, Mosca F, Agostoni C, et al. Breastfeeding in cystic fibrosis: a systematic review on prevalence and potential benefits. Nutrients 2021;13. https://doi.org/10.3390/nu13093263.

[17] Hoen AG, Li J, Moulton LA, O'Toole GA, Housman ML, Koestler DC, et al. Associations between gut microbial colonization in early life and respiratory outcomes in cystic fibrosis. J Pediatr 2015;167. https://doi.org/10.1016/j.jpeds.2015.02.049. 138-47.e1-3.

[18] Miller T, Antos NJ, Brock LA, Wade T, Goday PS. Lactation Consultation Sustains Breast Milk Intake in Infants With Cystic Fibrosis. J Pediatr Gastroenterol Nutr 2019;69:358–62. https://doi.org/10.1097/mpg.0000000000002415.

[19] Long AM, Jones IH, Knight M, McNally J. Early management of meconium ileus in infants with cystic fibrosis: a prospective population cohort study. J Pediatr Surg 2021;56:1287–92. https://doi.org/10.1016/j.jpedsurg.2021.02.047.

[20] Tan SMJ, Coffey MJ, Ooi CY. Differences in clinical outcomes of paediatric cystic fibrosis patients with and without meconium ileus. J Cyst Fibros 2019;18:857–62. https://doi.org/10.1016/j.jcf.2019.09.008.

[21] Padoan R, Cirilli N, Falchetti D, Cesana BM. Risk factors for adverse outcome in infancy in meconium ileus cystic fibrosis infants: a multicentre Italian study. J Cyst Fibros 2019;18:863–8. https://doi.org/10.1016/j.jcf.2019.07.003.

[22] Orenti A., A. Z, A. J, van Rens J. ECFSPR Annual Report 2020. 2022. https://www.ecfs.eu/sites/default/files/ECFSPR_Report_2020_v1.0%20%2807Jun2022%29_website.pdf Date accessed: 16/8/2023.

[23] Bailey J, Krick S, Fontaine KR. The changing landscape of nutrition in cystic fibrosis: the emergence of overweight and obesity. Nutrients 2022;14:1216. https://doi.org/10.3390/nu14061216.

[24] Szentpetery S, Fernandez GS, Schechter MS, Jain R, Flume PA, Fink AK. Obesity in Cystic fibrosis: prevalence, trends and associated factors data from the US cystic fibrosis foundation patient registry. J Cyst Fibros 2022;21:777–83. https://doi.org/10.1016/j.jcf.2022.03.010.

[25] Gabel M, Fox C, Grimes R, Lowman J, McDonald C, Stallings V, et al. Overweight and cystic fibrosis: an unexpected challenge. Authorea, Inc.; 2021. https://doi.org/10.22541/au.163252745.50364958/v1.

[26] Mariotti Zani E, Grandinetti R, Cunico D, Torelli L, Fainardi V, Pisi G, et al. Nutritional care in children with cystic fibrosis. Nutrients 2023;15:479. https://doi.org/10.3390/nu15030479.

[27] Tham A, Katz TE, Sutherland RE, Garg M, Liu V, Tong CW, et al. Micronutrient intake in children with cystic fibrosis in Sydney, Australia. J Cyst Fibros 2020;19: 146–52. https://doi.org/10.1016/j.jcf.2019.08.028.

[28] Sutherland R, Katz T, Liu V, Quintano J, Brunner R, Tong CW, et al. Dietary intake of energy-dense, nutrient-poor and nutrient-dense food sources in children with cystic fibrosis. J Cyst Fibros 2018;17:804–10. https://doi.org/10.1016/j.jcf.2018.03.011.

[29] Poulimeneas D, Grammatikopoulou MG, Devetzi P, Petrocheilou A, Kaditis AG, Papamitsou T, et al. Adherence to dietary recommendations, nutrient intake adequacy and diet quality among pediatric cystic fibrosis patients: results from the GreeCF study. Nutrients 2020;12. https://doi.org/10.3390/nu12103126.

[30] McDonald CM, Bowser EK, Farnham K, Alvarez JA, Padula L, Rozga M. Dietary macronutrient distribution and nutrition outcomes in persons with cystic fibrosis: an evidence analysis center systematic review. J Acad Nutr Diet 2021;121: 1574–90. https://doi.org/10.1016/j.jand.2020.03.016. e3.

[31] McNally J, Hugh-Jones S, Caton S, Vereijken C, Weenen H, Hetherington M. Communicating hunger and satiation in the first 2 years of life: a systematic review. Matern Child Nutr 2016;12:205–28. https://doi.org/10.1111/mcn.12230.

[32] Cystic Fibrosis Foundation, D Borowitz, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic fibrosis foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155:S73–93. https://doi.org/10.1016/j.jpeds.2009.09.001.

[33] Hammons AJ, Fiese B. Mealtime interactions in families of a child with cystic fibrosis: a meta-analysis. J Cyst Fibros 2010;9:377–84. https://doi.org/10.1016/j.jcf.2010.07.002.

[34] Ryan JL, Filigno SS, Stark LJ. Behavioral interventions and anticipatory guidance. Nutrition in Cystic Fibrosis 2015:239–54. https://doi.org/10.1007/978-3-319-16387-1_17.

[35] Lahiri T, Hempstead SE, Brady C, Cannon CL, Clark K, Condren ME, et al. Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. Pediatrics 2016;137. https://doi.org/10.1542/peds.2015-1784.

[36] Leonard A, Bailey J, Bruce A, Jia S, Stein A, Fulton J, et al. Nutritional considerations for a new era: a CF foundation position paper. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.05.010.
[37] Bradley JM, Madge S, Morton AM, Quittner AL, Elborn JS. Cystic fibrosis research in allied health and nursing professions. J Cyst Fibros 2012;11:387–92. https://doi.org/10.1016/j.jcf.2012.03.004.
[38] Orenti A., Zolin A., Jung A., van Rens J. ECFSPR Annual Report 2021. 2023. https://www.ecfs.eu/sites/default/files/Annual%20Report_2021_09Jun2023.pdf Date accessed: 26 August 2023.
[39] Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. J Cyst Fibros 2017;16(Suppl 2):S70–SS8. https://doi.org/10.1016/j.jcf.2017.06.011.
[40] Ng C, Major G, Smyth A. Timing of pancreatic enzyme replacement therapy (PERT) in cystic fibrosis. Cochrane Database Syst Rev 2021;8:CD013488.
[41] Calvo-Lerma J, Hulst J, Asseiceira I, Claes I, Garriga M, Colombo C, et al. Nutritional status, nutrient intake and use of enzyme supplements in paediatric patients with Cystic Fibrosis; a European multicentre study with reference to current guidelines. J Cyst Fibros 2017;16:510–8.
[42] Somaraju URR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2020;8:CD008227. https://doi.org/10.1002/14651858.CD008227.pub4.
[43] Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2016;11:Cd008227. https://doi.org/10.1002/14651858.CD008227.pub3.
[44] Trang T, Chan J, Graham DY, Trang T, Chan J, Graham DY. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21st century. World J Gastroenterol 2014;20:11467–85.
[45] Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med 2018;6:545–53. https://doi.org/10.1016/s2213-2600(18)30202-9.
[46] Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5years (KLIMB). J Cyst Fibros 2019;18:838–43. https://doi.org/10.1016/j.jcf.2019.03.009.
[47] Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: a systematic review. Nutrition 2018;55-56:131–9. https://doi.org/10.1016/j.nut.2018.03.052.
[48] Bass R, Brownell JN, Stallings VA. The impact of highly effective CFTR modulators on growth and nutrition status. Nutrients 2021;13:2907. https://doi.org/10.3390/nu13092907.
[49] Sankararaman S, Hendrix SJ, Schindler T. Update on the management of vitamins and minerals in cystic fibrosis. Nutr Clin Pract 2022;37:1074–87. https://doi.org/10.1002/ncp.10899.
[50] Gerasimidis K, Bronsky J, Catchpole A, Embleton N, Fewtrell M, Hojsak I, et al. Assessment and interpretation of vitamin and trace element status in sick children: a position paper from the european society for paediatric gastroenterology hepatology, and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr 2020;70:873–81. https://doi.org/10.1097/MPG.0000000000002688.
[51] Hergenroeder GE, Faino A, Bridges G, Bartlett LE, Cogen JD, Green N, et al. The impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in people with cystic fibrosis. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.08.002.
[52] Schembri L, Warraich S, Bentley S, Carr SB, Balfour-Lynn IM. Impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in children with cystic fibrosis. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.04.019.
[53] Declercq D, Van Braeckel E, Marchand S, Van Daele S, Van Biervliet S. Sodium status and replacement in children and adults living with cystic fibrosis: a narrative review. J Acad Nutr Diet 2020;120:1517–29. https://doi.org/10.1016/j.jand.2020.05.011.
[54] Putman MS, Anabtawi A, Le T, Tangpricha V, Sermet-Gaudelus I. Cystic fibrosis bone disease treatment: current knowledge and future directions. J Cyst Fibros 2019;18(Suppl 2):S56–65. https://doi.org/10.1016/j.jcf.2019.08.017.
[55] Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA. Early lung disease in infants and preschool children with cystic fibrosis. What have we learned and what should we do about it? Am J Respir Crit Care Med 2017;195:1567–75. https://doi.org/10.1164/rccm.201606-1107CI.
[56] Kieninger E, Yammine S, Korten I, Anagnostopoulou P, Singer F, Frey U, et al. Elevated lung clearance index in infants with cystic fibrosis shortly after birth. Eur Respir J 2017;50. https://doi.org/10.1183/13993003.00580-2017.
[57] IPG/CF. Physiotherapy for people with Cystic Fibrosis: from infant to adult. 2018. www.ecfs.eu/ipg_cf/booklet.
[58] McIlwaine M, Mc Cormack P, Lee Son N. Airway clearance and activity in the early pre-school years of children with cystic fibrosis. In: Be Doeck K, Southern K, editors. The early cystic fibrosis years. European Cystic Fibrosis Society; 2018. p. 297.
[59] Rand S, Hill L, Prasad SA. Physiotherapy in cystic fibrosis: optimising techniques to improve outcomes. Paediatr Respir Rev 2013;14:263–9. https://doi.org/10.1016/j.prrv.2012.08.006.
[60] Filipow N, Stanojevic S, Raywood E, Shannon H, Tanriver G, Kapoor K, et al. Real-world effectiveness of airway clearance techniques in children with cystic fibrosis. Eur Respir J 2023;62. https://doi.org/10.1183/13993003.00522-2023.
[61] 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. https://doi.org/10.1016/j.jcf.2010.04.008.
[62] Wilson LM, Morrison L, Robinson KA. Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2019;1:Cd011231. https://doi.org/10.1002/14651858.CD011231.pub2.
[63] Chapman N, Watson K, Hatton T, Cavalheri V, Wood J, Gucciardi DF, et al. Methods used to evaluate the immediate effects of airway clearance techniques in adults with cystic fibrosis: a systematic review and meta-analysis. J Clin Med 2021;10. https://doi.org/10.3390/jcm10225280.
[64] Warnock L, Gates A. Airway clearance techniques compared to no airway clearance techniques for cystic fibrosis. Cochrane Database Syst Rev 2023;4:CD001401.
[65] Andrews K, Smith M, Cox NS. The physiotherapy consultation: a qualitative study of the experience of parents of infants with cystic fibrosis in Australia. Physiother Theory Pract 2023;39:540–6. https://doi.org/10.1080/09593985.2021.2023932.
[66] World Health Organisation. WHO guidelines on physical activity and sedentary behaviour. 2020. https://www.who.int/publications-detail-redirect/9789240015128.
[67] Fisher V, Fraser L, Taylor J. Experiences of fathers of children with a life-limiting condition: a systematic review and qualitative synthesis. BMJ Support Palliat Care 2023;13:15–26. https://doi.org/10.1136/bmjspcare-2021-003019.
[68] Tluczek A, Grob R, Warne E, Van Gorp S, Greene L, Homa K. Parenting children with cystic fibrosis: developmental acquisition of expertise. J Dev Behav Pediatr 2022;43:e463–ee72. https://doi.org/10.1097/dbp.0000000000001089.
[69] McIlwaine M, Mc Cormack P, Lee Son N. Airway clearance and activity in the early pre-school years of children with cystic fibrosis. editor. In: Kris De Boeck KWS, editor. The early cystic fibrosis years. European Cystic Fibrosis Society; 2018. p. 297.
[70] Gursli S, Sandvik L, Bakkeheim E, Skrede B, Stuge B. Evaluation of a novel technique in airway clearance therapy - specific Cough Technique (SCT) in cystic fibrosis: a pilot study of a series of N-of-1 randomised controlled trials. SAGE Open Med 2017;5:2050312117697505. https://doi.org/10.1177/2050312117697505.
[71] Nap-van der Vlist MM, Berkelbach van der Sprenkel EE, Nijhof LN, Grootenhuis MA, van der Ent CK, Swart JF, et al. Daily life participation in childhood chronic disease: a qualitative study on the child's and parent's perspective. BMJ Paediatr Open 2021;5:e001057. https://doi.org/10.1136/bmjpo-2021-001057.
[72] Fairweather NH, Jones FW, Harris SA, Deiros Collado M, Shayle A. Thriving alongside cystic fibrosis: developing a grounded theory of empowerment in children and young people with cystic fibrosis during key life transitions. Child Care Health Dev 2021;47:484–93. https://doi.org/10.1111/cch.12860.
[73] Sherman AC, Simonton-Atchley S, Campbell D, Reddy RM, O'Brien CE, Guinee B, et al. Persistent adherence to airway clearance therapy in adults with cystic fibrosis. Respir Care 2019;64:778–85. https://doi.org/10.4187/respcare.06500.
[74] Gursli S, Quittner A, Jahnsen RB, Skrede B, Stuge B, Bakkeheim E. Airway clearance physiotherapy and health-related quality of life in cystic fibrosis. PLoS One 2022;17:e0276310.
[75] Nicolais CJ, Bernstein R, Saez-Flores E, McLean KA, Riekert KA, Quittner AL. Identifying factors that facilitate treatment adherence in cystic fibrosis: qualitative analyses of interviews with parents and adolescents. J Clin Psychol Med Settings 2019;26:530–40. https://doi.org/10.1007/s10880-018-9598-z.
[76] Calthorpe RJ, Smith SJ, Rowbotham NJ, Leighton PA, Davies G, Daniels T, et al. What effective ways of motivation, support and technologies help people with cystic fibrosis improve and sustain adherence to treatment? BMJ Open Respir Res 2020;7. https://doi.org/10.1136/bmjresp-2020-000601.
[77] Cronly J, Savage E. Developing agency in the transition to self-management of cystic fibrosis in young people. J Adolesc 2019;75:130–7. https://doi.org/10.1016/j.adolescence.2019.07.006.
[78] Torun T, Çavuşoğlu H, Doğru D, Özçelik U, Ademhan Tural D. The effect of self-efficacy, social support and quality of life on readiness for transition to adult care among adolescents with cystic fibrosis in Turkey. J Pediatr Nurs 2021;57:e79–84. https://doi.org/10.1016/j.pedn.2020.11.013.
[79] Willis LD. Transition from pediatric to adult care for young adults with chronic respiratory disease. Respir Care 2020;65:1916–22. https://doi.org/10.4187/respcare.08260.
[80] Sezgin E, Weiler M, Weiler A, Lin S, Hart L. It is a life journey: a roadmap of teens with chronic diseases in transitioning to independence. J Pediatr Health Care 2020;34:346–55. https://doi.org/10.1016/j.pedhc.2020.02.001.
[81] Lonabaugh KP, O'Neal KS, McIntosh H, Condren M. Cystic fibrosis-related education: are we meeting patient and caregiver expectations? Patient Educ Couns 2018;101:1865–70. https://doi.org/10.1016/j.pec.2018.06.004.
[82] Coyne I, Malone H, Chubb E, While AE. Transition from paediatric to adult healthcare for young people with cystic fibrosis: parents' information needs. J Child Health Care 2018;22:646–57. https://doi.org/10.1177/1367493518768448.
[83] Cooley L, Hudson J, Potter E, Raymond KF, George C, Georgiopoulos AM. Clinical communication preferences in cystic fibrosis and strategies to optimize care. Pediatr Pulmonol 2020;55:948–58. https://doi.org/10.1002/ppul.24655.
[84] Magill M, Apodaca TR, Borsari B, Gaume J, Hoadley A, Gordon REF, et al. A meta-analysis of motivational interviewing process: technical, relational, and conditional process models of change. J Consult Clin Psychol 2018;86:140–57. https://doi.org/10.1037/ccp0000250.
[85] Abrami M, Maschio M, Conese M, Confalonieri M, Salton F, Gerin F, et al. Effect of chest physiotherapy on cystic fibrosis sputum nanostructure: an experimental and theoretical approach. Drug Deliv Transl Res 2022;12:1943–58. https://doi.org/10.1007/s13346-022-01131-8.

[86] Dwyer TJ, Daviskas E, Zainuldin R, Verschuer J, Eberl S, Bye PTP, et al. Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial. Eur Respir J 2019;53. https://doi.org/10.1183/13993003.01793-2018.
[87] 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;68:746–51. https://doi.org/10.1136/thoraxjnl-2012-202915.
[88] CF Trust. Physiotherapy standards of care and good clinical practice for the physiotherapy management of cystic fibrosis. 2020. https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/Standards%20of%20Care%20and%20Good%20Clinical%20Practice%20for%20the%20Physiotherapy%20Management%20of%20Cystic%20Fibrosis%20Fourth%20edition%20December%202020.pdf.
[89] Raywood E, Shannon H, Filipow N, Tanriver G, Stanojevic S, Kapoor K, et al. Quantity and quality of airway clearance in children and young people with cystic fibrosis. J Cyst Fibros 2023;22:344–51. https://doi.org/10.1016/j.jcf.2022.09.008.
[90] Rowbotham NJ, Smith S, Leighton PA, Rayner OC, Gathercole K, Elliott ZC, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. Thorax 2018;73:388–90. https://doi.org/10.1136/thoraxjnl-2017-210473.
[91] Saynor ZL, Cunningham S, Morrison L, Main E, Vogiatzis I, Reid S, et al. Exercise as airway clearance therapy (ExACT) in cystic fibrosis: a UK-based e-Delphi survey of patients, caregivers and health professionals. Thorax 2023;78:88–91. https://doi.org/10.1136/thorax-2022-219213.
[92] Britto CJ, Taylor-Cousar JL. Cystic fibrosis in the era of highly effective CFTR modulators. Clin Chest Med 2022;43:xiii–xxvi. https://doi.org/10.1016/j.ccm.2022.07.003.
[93] Perrem L, Ratjen F. Anti-inflammatories and mucociliary clearance therapies in the age of CFTR modulators. Pediatr Pulmonol 2019;54(Suppl 3):S46–s55. https://doi.org/10.1002/ppul.24364.
[94] Saluzzo F, Riberi L, Messore B, Loré NI, Esposito I, Bignamini E, et al. CFTR modulator therapies: potential impact on airway infections in cystic fibrosis. Cells. 2022;11. https://doi.org/10.3390/cells11071243.
[95] Krajewska J, Zub K, Słowikowski A, Zatoński T. Chronic rhinosinusitis in cystic fibrosis: a review of therapeutic options. Eur Arch Oto-rhino-Laryngol: Official J Eur Federat Oto-Rhino-Laryngol Soc (EUFOS): Affiliated German Soc Oto-Rhino-Laryngol - Head Neck Surgery 2022;279:1–24. https://doi.org/10.1007/s00405-021-06875-6.
[96] BJ Johnson, Choby GW, O'Brien EK. Chronic rhinosinusitis in patients with cystic fibrosis-current management and new treatments. Laryngoscope Investigat Otolaryngol 2020;5:368–74. https://doi.org/10.1002/lio2.401.
[97] Uyttebroek S, Dupont L, Jorissen M, Van Gerven L. Upper airway disease in adults with cystic fibrosis in the era of <scp>CFTR</scp>modulators. Laryngoscope 2023. https://doi.org/10.1002/lary.30642.
[98] Liang J, Higgins T, Ishman SL, Boss EF, Benke JR, SY Lin. Medical management of chronic rhinosinusitis in cystic fibrosis: a systematic review. Laryngoscope 2013;124:1308–13. https://doi.org/10.1002/lary.24503.
[99] Karanth TK, Karanth V, Ward BK, Woodworth BA, Karanth L. Medical interventions for chronic rhinosinusitis in cystic fibrosis. Cochrane Database Syst Rev 2022;4:CD012979. https://doi.org/10.1002/14651858.CD012979.pub3.
[100] Mainz JG, Schädlich K, Schien C, Michl R, Schelhorn-Neise P, Koitschev A, et al. Sinonasal inhalation of tobramycin vibrating aerosol in cystic fibrosis patients with upper airway Pseudomonas aeruginosa colonization: results of a randomized, double-blind, placebo-controlled pilot study. Drug Des Devel Ther. 2014;8:209–17. https://doi.org/10.2147/DDDT.S54064.
[101] Aanaes K, von Buchwald C, Hjuler T, Skov M, Alanin M, Johansen HK. The effect of sinus surgery with intensive follow-up on pathogenic sinus bacteria in patients with cystic fibrosis. Am J Rhinol Allergy 2013;27:e1–4. https://doi.org/10.2500/ajra.2013.27.3829.
[102] Shah GB, De Keyzer L, Russell JA, Halderman A. Treatment of chronic rhinosinusitis with dornase alfa in patients with cystic fibrosis: a systematic review. Int Forum Allergy Rhinol 2018;8:729–36. https://doi.org/10.1002/alr.22082.
[103] Stapleton AL, Kimple AJ, Goralski JL, Nouraie SM, Branstetter BF, Shaffer AD, et al. Elexacaftor-tezacaftor- ivacaftor improves sinonasal outcomes in cystic fibrosis. J Cyst Fibros 2022;21:792–9. https://doi.org/10.1016/j.jcf.2022.03.002.
[104] Action on Smoking and Health (ASH). Use of e-cigarettes (vapes) among young people in Great Britain. 2023. https://ash.org.uk/uploads/Use-of-vapes-among-young-people-GB-2023.pdf?v=1686042690 Date accessed: 1 August 2023.
[105] Novelli CE, Higginbotham EJ, Kapanke KA, Webber-Ritchey KJ, Parker CH, Simonovich SD. A systematic review examining the pulmonary effects of electronic vapor delivery systems. J Clin Anesth 2022;82:110952. https://doi.org/10.1016/j.jclinane.2022.110952.
[106] Gaurav R. Vaping away epithelial integrity. Am J Respir Cell Mol Biol 2019;61:127–9. https://doi.org/10.1165/rcmb.2019-0016ED.
[107] Boskabady MH, Farhang L, Mahmodinia M, Boskabady M, Heydari GR. Comparison of pulmonary function and respiratory symptoms in water pipe and cigarette smokers. Respirology 2012;17:950–6. https://doi.org/10.1111/j.1440-1843.2012.02194.x.
[108] Boskabady MH, Farhang L, Mahmoodinia M, Boskabady M, Heydari GR. Prevalence of water pipe smoking in the city of Mashhad (North East of Iran) and its effect on respiratory symptoms and pulmonary function tests. Lung India 2014;31:237–43. https://doi.org/10.4103/0970-2113.135763.
[109] Strulovici-Barel Y, Shaykhiev R, Salit J, Deeb RS, Krause A, Kaner RJ, et al. Pulmonary abnormalities in young, light-use waterpipe (Hookah) smokers. Am J Respir Crit Care Med 2016;194:587–95. https://doi.org/10.1164/rccm.201512-2470OC.
[110] American Cancer Society. Health risks of secondhand smoke. 2023. prevention/tobacco/health-risks-of-tobacco/secondhand-smoke.html#:~:text=Secondhand%20smoke%20(SHS)%20is%20also,tobacco%20burning%20in%20a%20hookah Date accessed: 1 August 2023.
[111] Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, et al. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J Respir Crit Care Med 2019;199:987–95. https://doi.org/10.1164/rccm.201806-1110OC.
[112] Hebestreit A, Kersting U, Basler B, Jeschke R, Hebestreit H. Exercise inhibits epithelial sodium channels in patients with cystic fibrosis. Am J Respir Crit Care Med 2001;164:443–6.
[113] Radtke T, Smith S, Nevitt SJ, Hebestreit H, Kriemler S. Physical activity and exercise training in cystic fibrosis. Cochrane Database Syst Rev 2022. https://doi.org/10.1002/14651858.CD002768.pub5.
[114] Schneiderman JE, Wilkes DL, Atenafu EG, Nguyen T, Wells GD, Alarie N, et al. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. Eur Respir J 2014;43:817–23. https://doi.org/10.1183/09031936.00055513.
[115] Gruet M, Saynor ZL, Urquhart DS, Radtke T. Rethinking physical exercise training in the modern era of cystic fibrosis: a step towards optimising short-term efficacy and long-term engagement. J Cyst Fibros 2022;21:e83–98. https://doi.org/10.1016/j.jcf.2021.08.004.
[116] Bianchim MS, McNarry MA, Barker AR, Williams CA, Denford S, Holland AE, et al. Sleep, sedentary time and physical activity levels in children with cystic fibrosis. Int J Environ Res Public Health 2022;19:7133. https://doi.org/10.3390/ijerph19127133.
[117] Gramegna A, Majo F, Alicandro G, Leonardi G, Cristiani L, Amati F, et al. Heterogeneity of weight gain after initiation of Elexacaftor/Tezacaftor/Ivacaftor in people with cystic fibrosis. Respir Res 2023;24:164. https://doi.org/10.1186/s12931-023-02451-0.
[118] Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. J Clin Transl Endocrinol 2021;26:100276. https://doi.org/10.1016/j.jcte.2021.100276.
[119] Gramegna A, Aliberti S, Contarini M, Savi D, Sotgiu G, Majo F, et al. Overweight and obesity in adults with cystic fibrosis: an Italian multicenter cohort study. J Cyst Fibros 2021. https://doi.org/10.1016/j.jcf.2021.05.002. S1569-993(21)00129-6.
[120] Saunders T, Burgner D, Ranganathan S. Identifying and preventing cardiovascular disease in patients with cystic fibrosis. Nature Cardiovasc Res 2022;1:187–8. https://doi.org/10.1038/s44161-022-00030-y.
[121] Poore TS, Taylor-Cousar JL, Zemanick ET. Cardiovascular complications in cystic fibrosis: a review of the literature. J Cyst Fibros 2021. https://doi.org/10.1016/j.jcf.2021.04.016. S1569-993(21)00126-0.
[122] Frost F, Nazareth D, Fauchier L, Wat D, Shelley J, Austin P, et al. Prevalence, risk factors and outcomes of cardiac disease in cystic fibrosis: a multinational retrospective cohort study. Eur Respir J 2023. https://doi.org/10.1183/13993003.00174-2023.
[123] Heinz KD, Walsh A, Southern KW, Johnstone Z, Regan KH. Exercise versus airway clearance techniques for people with cystic fibrosis. Cochrane Database Syst Rev 2022. https://doi.org/10.1002/14651858.CD013285.pub2.
[124] Ward N, Morrow S, Stiller K, Holland AE. Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review. Thorax 2021;76:763–71. https://doi.org/10.1136/thoraxjnl-2020-215836.
[125] Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH, et al. Statement on exercise testing in cystic fibrosis. Respiration 2015;90:332–51. https://doi.org/10.1159/000439057.
[126] Saynor ZL, Gruet M, McNarry MA, Button B, Morrison L, Wagner M, et al. Guidance and standard operating procedures for functional exercise testing in cystic fibrosis. Eur Respir Rev 2023;32. https://doi.org/10.1183/16000617.0029-2023.
[127] Shelley J, Dawson EA, Boddy LM, Stewart CE, Frost F, Nazareth D, et al. Developing an ecological approach to physical activity promotion in adults with Cystic fibrosis. PLoS ONE 2022;17:e0272355. https://doi.org/10.1371/journal.pone.0272355.
[128] Cox NS, Holland AE. Current perspectives of physical activity in cystic fibrosis. Expert Rev Respir Med 2019;13:13–22. https://doi.org/10.1080/17476348.2019.1552833.
[129] Ruf K, Winkler B, Hebestreit A, Gruber W, Hebestreit H. Risks associated with exercise testing and sports participation in cystic fibrosis. J Cyst Fibros 2010;9:339–45. https://doi.org/10.1016/j.jcf.2010.05.006.
[130] Ruf K, Hebestreit H. Exercise-induced hypoxemia and cardiac arrhythmia in cystic fibrosis. J Cyst Fibros 2009;8:83–90. https://doi.org/10.1016/j.jcf.2008.09.008.
[131] Williams CA, Barker AR, Denford S, van Beurden SB, Bianchim MS, Caterini JE, et al. The Exeter Activity Unlimited statement on physical activity and exercise for cystic fibrosis: methodology and results of an international, multidisciplinary, evidence-driven expert consensus. Chron Respir Dis 2022;19:14799731221121670. https://doi.org/10.1177/14799731221121670.
[132] Shelley J, Fairclough SJ, Knowles ZR, Southern KW, McCormack P, Dawson EA, et al. A formative study exploring perceptions of physical activity and physical activity monitoring among children and young people with cystic fibrosis and health care professionals. BMC Pediatr 2018;18:335. https://doi.org/10.1186/s12887-018-1301-x.
[133] Dillenhoefer S, Stehling F, Welsner M, Schlegtendal A, Sutharsan S, Olivier M, et al. Barriers for sports and exercise participation and corresponding barrier

management in cystic fibrosis. Int J Environ Res Public Health 2022;19:13150. https://doi.org/10.3390/ijerph192013150.
[134] Wietlisbach M, Benden C, Koutsokera A, Jahn K, Soccal PM. Radtke T. Perceptions towards physical activity in adult lung transplant recipients with cystic fibrosis. PLoS One 2020;15:e0229296. https://doi.org/10.1371/journal.pone.0229296.
[135] Pinto ACPN, Piva SR, Rocha A, Gomes-Neto M, Atallah ÁN, Saconato H, et al. Digital technology for delivering and monitoring exercise programs for people with cystic fibrosis. Cochrane Database Syst Rev 2023;6:CD014605. https://doi.org/10.1002/14651858.CD014605.pub2.
[136] Conway S, Balfour-Lynn IM, De Rijcke K, Drevinek P, Foweraker J, Havermans T, et al. European cystic fibrosis society standards of care: framework for the cystic fibrosis centre. J Cyst Fibros 2014;13(Suppl 1):S3–22. https://doi.org/10.1016/j.jcf.2014.03.009.
[137] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2019. https://doi.org/10.1016/s2213-2600(19)30337-6.
[138] Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.02.004.
[139] Sabadosa KA, Faro A, Nelson EC, Marshall BC. Impact of the COVID-19 pandemic: how our response is shaping the future of cystic fibrosis care. J Cyst Fibros 2021;20(Suppl 3):1–2. https://doi.org/10.1016/j.jcf.2021.09.002.
[140] Marshall M, Waring G. Youth work in the hospital setting: a narrative review of the literature. Compr Child Adolesc Nurs 2023;46:240–57. https://doi.org/10.1080/24694193.2021.1936294.
[141] Jain R, Taylor-Cousar JL. Fertility, pregnancy and lactation considerations for women with CF in the CFTR modulator era. J Pers Med 2021;11. https://doi.org/10.3390/jpm11050418.
[142] O'Carroll M. Advanced cystic fibrosis lung disease and lung transplantation in the era of cystic fibrosis transmembrane conductance regulator modulators. Semin Respir Crit Care Med 2023;44:260–8. https://doi.org/10.1055/s-0042-1758731.
[143] Pilewski JM. Update on lung transplantation for cystic fibrosis. Clin Chest Med 2022;43:821–40. https://doi.org/10.1016/j.ccm.2022.07.002.
[144] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018;17:153–78. https://doi.org/10.1016/j.jcf.2018.02.006.
[145] Prickett MH, Flume PA, Sabadosa KA, Tran QT, Marshall BC. Telehealth and CFTR modulators: accelerating innovative models of cystic fibrosis care. J Cyst Fibros 2023;22:9–16. https://doi.org/10.1016/j.jcf.2022.07.002.
[146] Vagg T, Shanthikumar S, Ibrahim H, O'Regan P, Chapman WW, Kirwan L, et al. Telehealth in Cystic Fibrosis. A systematic review incorporating a novel scoring system and expert weighting to identify a 'top 10 manuscripts' to inform future best practices implementation. J Cyst Fibros 2023;22:598–606. https://doi.org/10.1016/j.jcf.2023.05.012.
[147] George C, Raymond KF, Collins L, Arefy Z, Kazmerski TM. Partnership enhancement program: piloting a communication training program for cystic fibrosis care teams. J Patient Exp 2021;8:23743735211014049. https://doi.org/10.1177/23743735211014049.
[148] Pougheon Bertrand D, Fanchini A, Lombrail P, Rault G, Chansard A, Le Breton N, et al. A conceptual framework to develop a patient-reported experience questionnaire on the cystic fibrosis journey in France: the ExPaParM collaborative study. Orphanet J Rare Dis 2023;18:31. https://doi.org/10.1186/s13023-023-02640-6.
[149] McIntyre K, Bertrand DP, Rault G. Using registry data to improve quality of care. J Cyst Fibros 2018;17:566–72. https://doi.org/10.1016/j.jcf.2018.06.006.
[150] Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022. https://doi.org/10.1016/j.jcf.2022.01.009.
[151] Wong CH, Smith S, Kansra S. Digital technology for early identification of exacerbations in people with cystic fibrosis. Cochrane Database Syst Rev 2023;4:Cd014606. https://doi.org/10.1002/14651858.CD014606.pub2.
[152] Wildman MJ, O'Cathain A, Maguire C, Arden MA, Hutchings M, Bradley J, et al. Self-management intervention to reduce pulmonary exacerbations by supporting treatment adherence in adults with cystic fibrosis: a randomised controlled trial. Thorax 2022;77:461–9. https://doi.org/10.1136/thoraxjnl-2021-217594.
[153] Cox NS, Eldridge B, Rawlings S, Dreger J, Corda J, Hauser J, et al. Web-based physical activity promotion in young people with CF: a randomised controlled trial. Thorax 2023;78:16–23. https://doi.org/10.1136/thorax-2022-218702.
[154] Lechtzin N, Mayer-Hamblett N, West NE, Allgood S, Wilhelm E, Khan U, et al. Home monitoring of patients with cystic fibrosis to identify and treat acute pulmonary exacerbations. eICE study results. Am J Respir Crit Care Med 2017;196:1144–51. https://doi.org/10.1164/rccm.201610-2172OC.
[155] Beaufils F, Enaud R, Gallode F, Boucher G, Macey J, Berger P, et al. Adherence, reliability, and variability of home spirometry telemonitoring in cystic fibrosis. Front Pediat 2023;11:1111088. https://doi.org/10.3389/fped.2023.1111088.
[156] Paynter A, Khan U, Heltshe SL, Goss CH, Lechtzin N, Hamblett NM. A comparison of clinic and home spirometry as longtudinal outcomes in cystic fibrosis. J Cyst Fibros 2022;21:78–83. https://doi.org/10.1016/j.jcf.2021.08.013.
[157] Thornton CS, Magaret AS, Carmody LA, Kalikin LM, Simon RH, LiPuma JJ, et al. Quantifying variation in home spirometry in people with cystic fibrosis during baseline health, and associations with clinical outcomes. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.05.011.
[158] Kruizinga MD, Essers E, Stuurman FE, Zhuparris A, van Eik N, Janssens HM, et al. Technical validity and usability of a novel smartphone-connected spirometry device for pediatric patients with asthma and cystic fibrosis. Pediatr Pulmonol 2020;55:2463–70. https://doi.org/10.1002/ppul.24932.
[159] Davis J, Ryan M, Marchetti P, Dahlberg SE, Greenberg J, Bacon C, et al. Real-world feasibility of short-term, unsupervised home spirometry in CF. Pediatr Pulmonol 2022;57:3129–35. https://doi.org/10.1002/ppul.26147.
[160] Perkins RC, Davis J, NeSmith A, Bailey J, Powers MR, Chaudary N, et al. Favorable clinician acceptability of telehealth as part of the cystic fibrosis care model during the COVID-19 pandemic. Ann Am Thorac Soc 2021;18:1588–92. https://doi.org/10.1513/AnnalsATS.202012-1484RL.
[161] Nash EF, Choyce J, Carrolan V, Justice E, Shaw KL, Sitch A, et al. A prospective randomised controlled mixed-methods pilot study of home monitoring in adults with cystic fibrosis. Ther Adv Respir Dis 2022;16:17534666211070133. https://doi.org/10.1177/17534666211070133.
[162] Albon D, Van Citters AD, Ong T, Dieni O, Dowd C, Willis A, et al. Telehealth use in cystic fibrosis during COVID-19: association with race, ethnicity, and socioeconomic factors. J Cyst Fibros 2021;20(Suppl 3):49–54. https://doi.org/10.1016/j.jcf.2021.09.006.
[163] Hillen B, Simon P, Schlotter S, Nitsche O, Bähner V, Poplawska K, et al. Feasibility and implementation of a personalized, web-based exercise intervention for people with cystic fibrosis for 1 year. BMC Sports Sci Med Rehabil 2021;13:95. https://doi.org/10.1186/s13102-021-00323-y.
[164] Graziano S, Boldrini F, Righelli D, Milo F, Lucidi V, Quittner A, et al. Psychological interventions during COVID pandemic: telehealth for individuals with cystic fibrosis and caregivers. Pediatr Pulmonol 2021;56:1976–84. https://doi.org/10.1002/ppul.25413.
[165] Hasan S, Cecilia Lansang M, Salman Khan M, Dasenbrook E. Managing Cystic Fibrosis related diabetes via telehealth during COVID-19 pandemic. J Clin Transl Endocrinol 2021;23:100253. https://doi.org/10.1016/j.jcte.2021.100253.
[166] Abraham O, Li JS, Monangai KE, Feathers AM, Weiner D. The pharmacist's role in supporting people living with cystic fibrosis. J Am Pharm Assoc (2003) 2018;58:246–9. https://doi.org/10.1016/j.japh.2018.01.006.
[167] Zobell JT, Moss J, Heuser S, Roe L, Young DC. Understanding the expanding role of pharmacy services in outpatient cystic fibrosis care. Pediatr Pulmonol 2021;56:1378–85. https://doi.org/10.1002/ppul.25283.
[168] Thompson K, Shaw N, Bentley S, Harrison M, Bowman E, Makhecha S. Role of the clinical pharmacist in the management of CF. Hospital pharmacy Europe. 2016.
[169] Herbert S, Rowbotham NJ, Smith S, Wilson P, Elliott ZC, Leighton PA, et al. Exploring the challenges of accessing medication for patients with cystic fibrosis. Thorax 2022;77:295–7. https://doi.org/10.1136/thoraxjnl-2021-217140.
[170] Glasscoe C, Hope HF, Lancaster GA, McCray G, West K, Patel L, et al. Development and preliminary validation of the challenges of living with cystic fibrosis (CLCF) questionnaire: a 46-item measure of treatment burden for parent/carers of children with CF. Psychol Health 2022:1–25. https://doi.org/10.1080/08870446.2021.2013483.
[171] Macdonald M, Martin-Misener R, Helwig M, Smith LJ, Godfrey CM, Curran J, et al. Experiences of adults with cystic fibrosis in adhering to medication regimens: a qualitative systematic review. JBI Database System Rev Implement Rep 2016;14:258–85. https://doi.org/10.11124/JBISRIR-2016-002362.
[172] Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. Chest 2011;140:425–32. https://doi.org/10.1378/chest.09-3074.
[173] Smith S, Calthorpe R, Herbert S, Smyth AR. Digital technology for monitoring adherence to inhaled therapies in people with cystic fibrosis. Cochrane Database Syst Rev 2023;2:CD013733. https://doi.org/10.1002/14651858.CD013733.pub2.
[174] Dawson S, Girling CJ, Cowap L, Clark-Carter D. Psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis. Cochrane Database Syst Rev 2023;3:CD013766. https://doi.org/10.1002/14651858.CD013766.pub2.
[175] Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. Lancet Respir Med 2023;11:329–40. https://doi.org/10.1016/S2213-2600(22)00434-9.
[176] Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, et al. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation. results of a two-part phase 3 clinical trial. Am J Respir Crit Care Med 2021;203:585–93. https://doi.org/10.1164/rccm.202008-3177OC.
[177] European Medicines Agency. Orkambi EPAR. 2023. https://www.ema.europa.eu/en/documents/product-information/orkambi-epar-product-information_en.pdf Date accessed: 28 September 2023.
[178] Goralski JL, Hoppe JE, Mall MA, McColley SA, McKone E, Ramsey B, et al. Phase 3 open-label clinical trial of elexacaftor/tezacaftor/ivacaftor in children aged 2-5 years with cystic fibrosis and at least one F508del allele. Am J Respir Crit Care Med 2023;208:59–67. https://doi.org/10.1164/rccm.202301-0084OC.
[179] Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database Syst Rev 2020;12:CD010966. https://doi.org/10.1002/14651858.CD010966.pub3.
[180] Cystic Fibrosis Foundation Patient Registry. 2021 Annual data report. 2023.
[181] Hudson BN, Jacobs HR, Philbrick A, Zhou XA, Simonsen MM, Safirstein JA, et al. Drug-induced acne with elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis. J Cyst Fibros 2022;21:1066–9. https://doi.org/10.1016/j.jcf.2022.09.002.

[182] Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. J Cyst Fibros 2022;21:265–71. https://doi.org/10.1016/j.jcf.2021.11.012.
[183] Gramegna A, De Petro C, Leonardi G, Contarini M, Amati F, Meazza R, et al. Onset of systemic arterial hypertension after initiation of elexacaftor/tezacaftor/ivacaftor in adults with cystic fibrosis: a case series. J Cyst Fibros 2022;21:885–7. https://doi.org/10.1016/j.jcf.2022.04.010.
[184] European Medicines Agency. Kaftrio summary of product characteristics. 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio Date accessed: 1 July 2021.
[185] Burgel PR, Munck A, Durieu I, Chiron R, Mely L, Prevotat A, et al. Real-life safety and effectiveness of lumacaftor-ivacaftor in patients with cystic fibrosis. Am J Respir Crit Care Med 2020;201:188–97. https://doi.org/10.1164/rccm.201906-1227OC.
[186] Dagenais RVE, Su VCH, Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: a systematic review. J Clin Med 2020;10. https://doi.org/10.3390/jcm10010023.
[187] Arslan M, Chalmers S, Rentfrow K, Olson JM, Dean V, Wylam ME, et al. Suicide attempts in adolescents with cystic fibrosis on Elexacaftor/Tezacaftor/Ivacaftor therapy. J Cyst Fibros 2023;22:427–30. https://doi.org/10.1016/j.jcf.2023.01.015.
[188] Spoletini G, Gillgrass L, Pollard K, Shaw N, Williams E, Etherington C, et al. Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis. J Cyst Fibros 2022;21:1061–5. https://doi.org/10.1016/j.jcf.2022.05.001.
[189] Zhang L, Albon D, Jones M, Bruschwein H. Impact of elexacaftor/tezacaftor/ivacaftor on depression and anxiety in cystic fibrosis. Ther Adv Respir Dis 2022;16:17534666221144211. https://doi.org/10.1177/17534666221144211.
[190] Baroud E, Chaudhary N, Georgiopoulos AM. Management of neuropsychiatric symptoms in adults treated with elexacaftor/tezacaftor/ivacaftor. Pediatr Pulmonol 2023;58:1920–30. https://doi.org/10.1002/ppul.26412.
[191] Van Citters A, Aliaj E, Cary J, King J, Alvarez J, Brown C, et al. Highly-effective modulator therapies: impact on the well-being of people living with cystic fibrosis and implications for the CF care model. Journal of Cystic Fibrosis 2022. S191 - S2.
[192] Bathgate CJ, Muther E, Georgiopoulos AM, Smith B, Tillman L, Graziano S, et al. Positive and negative impacts of elexacaftor/tezacaftor/ivacaftor: healthcare providers' observations across US centers. Pediatr Pulmonol 2023. https://doi.org/10.1002/ppul.26527.
[193] European Medicines Agency. Committee for medicinal products for human use (CHMP) Minutes for the meeting on 22-25 May 2023. 2023. https://www.ema.europa.eu/en/documents/minutes/minutes-chmp-meeting-22-25-may-2023_en.pdf Date accessed: 28 September 2023.
[194] Agency MaHpR. Ivacaftor, tezacaftor, elexacaftor (Kaftrio▼) in combination with ivacaftor (Kalydeco): risk of serious liver injury; updated advice on liver function testing. 2023. https://www.gov.uk/drug-safety-update/ivacaftor-tezacaftor-elexacaftor-kaftriov-in-combination-with-ivacaftor-kalydeco-risk-of-serious-liver-injury-updated-advice-on-liver-function-testing Date accessed: 28 September 2023.
[195] Southern KW, Barben J, Goldring S, Kneen R, Southward S, Rajeev Y, et al. Raised intracranial pressure in three children with cystic fibrosis receiving elexacaftor-tezacaftor-ivacaftor modulator therapy. Am J Respir Crit Care Med 2023;208:103–5. https://doi.org/10.1164/rccm.202303-0380LE.
[196] Miller MJ, Foroozan R. Papilledema and hypervitaminosis A after elexacaftor/tezacaftor/ivacaftor for cystic fibrosis. Can J Ophthalmol 2022;57:e6–10. https://doi.org/10.1016/j.jcjo.2021.04.018.
[197] Bhaskaran D, Bateman K. A case of Elexacaftor-Tezacaftor-Ivacaftor induced rash resolving without interruption of treatment. J Cyst Fibros 2022;21:1077–9. https://doi.org/10.1016/j.jcf.2022.06.011.
[198] Cheng A, Baker O, Hill U. Elexacaftor, tezacaftor and ivacaftor: a case of severe rash and approach to desensitisation. BMJ Case Rep 2022;15:e247042. https://doi.org/10.1136/bcr-2021-247042.
[199] Diseroad ER, Mogayzel Jr PJ, Pan A. Rechallenge of elexacaftor/tezacaftor/ivacaftor after skin rash in two pediatric patients. J Pediatric Pharmacol Therapeut: JPPT: Official J PPAG 2022;27:463–6. https://doi.org/10.5863/1551-6776-27.5.463.
[200] Balijepally R, Kwong D, Zhu L, Camacho JV, Liu A. Elexacaftor/tezacaftor/ivacaftor outpatient desensitization. Ann Allergy, Asthma Immunol 2022;128:104–5. https://doi.org/10.1016/j.anai.2021.08.010.
[201] Tewkesbury DH, Athwal V, Bright-Thomas RJ, Jones AM, Barry PJ. Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on liver tests at a large single adult cystic fibrosis centre. J Cyst Fibros 2023;22:256–62. https://doi.org/10.1016/j.jcf.2023.01.007.
[202] Talwalkar JS, Koff JL, Lee HB, Britto CJ, Mulenos AM, Georgiopoulos AM. Cystic fibrosis transmembrane regulator modulators: implications for the management of depression and anxiety in cystic fibrosis. Psychosomatics 2017;58:343–54. https://doi.org/10.1016/j.psym.2017.04.001.
[203] Ibrahim H, Danish H, Morrissey D, Deasy KF, McCarthy M, Dorgan J, et al. Individualized approach to elexacaftor/tezacaftor/ivacaftor dosing in cystic fibrosis, in response to self-reported anxiety and neurocognitive adverse events: a case series. Front Pharmacol 2023;14:1156621. https://doi.org/10.3389/fphar.2023.1156621.
[204] Wisniewski BL, Aylward SC, CO Jordan, Kopp BT, Paul GR. Hypervitaminosis A with fulminant secondary intracranial hypertension following personalized medicine-based Elexacaftor/Tezacaftor/Ivacaftor initiation in a preadolescent with cystic fibrosis. J Cyst Fibros 2022;21:e217–ee20. https://doi.org/10.1016/j.jcf.2022.01.010.
[205] Choong E, Sauty A, Koutsokera A, Blanchon S, André P, Decosterd L. Therapeutic Drug Monitoring of Ivacaftor, Lumacaftor, Tezacaftor, and Elexacaftor in Cystic Fibrosis: where Are We Now? Pharmaceutics 2022;14:1674. https://doi.org/10.3390/pharmaceutics14081674.
[206] Pigliasco F, Cafaro A, Stella M, Baiardi G, Barco S, Pedemonte N, et al. Simultaneous Quantification of Ivacaftor, Tezacaftor, and Elexacaftor in Cystic Fibrosis Patients' Plasma by a Novel LC-MS/MS Method. Biomedicines 2023;11:628. https://doi.org/10.3390/biomedicines11020628.
[207] Hong E, Li R, Shi A, Almond LM, Wang J, Khudari AZ, et al. Safety of elexacaftor/tezacaftor/ivacaftor dose reduction: mechanistic exploration through physiologically based pharmacokinetic modeling and a clinical case series. Pharmacotherapy: J Human Pharmacol Drug Therapy 2023;43:291–9. https://doi.org/10.1002/phar.2786.
[208] Jain R, Magaret A, Vu PT, VanDalfsen JM, Keller A, Wilson A, et al. Prospectively evaluating maternal and fetal outcomes in the era of CFTR modulators: the MAYFLOWERS observational clinical trial study design. BMJ Open Respir Res 2022;9. https://doi.org/10.1136/bmjresp-2022-001289.
[209] Montemayor K, Tullis E, Jain R, Taylor-Cousar JL. Management of pregnancy in cystic fibrosis. Breathe (Sheff) 2022;18:220005. https://doi.org/10.1183/20734735.0005-2022.
[210] Taylor-Cousar JL, Shteinberg M, Cohen-Cymberknoh M, Jain R. The impact of highly effective cystic fibrosis transmembrane conductance regulator modulators on the health of female subjects with cystic fibrosis. Clin Ther 2023;45:278–89. https://doi.org/10.1016/j.clinthera.2023.01.016.
[211] Cystic Fibrosis Canada. Canadian clinical consensus guideline for initiation. Monitoring and discontinuation of CFTR modulator therapies for patients with cystic fibrosis 2022. https://www.cysticfibrosis.ca/uploads/Consensus%20Guideline%20-%20CFTR%20Modulators%20June%202022%20(004)%20FINAL-ua.pdf. Date accessed: 13 August 2023.