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Original Article

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

Pierre-Régis Burgel [a], Kevin W Southern [b,*], Charlotte Addy [c], Alberto Battezzati [d], Claire Berry [e], Jean-Philippe Bouchara [f], Edwin Brokaar [g], Whitney Brown [h], Pilar Azevedo [i], Isabelle Durieu [j], Miquel Ekkelenkamp [k], Felicity Finlayson [l], Julian Forton [m], Johanna Gardecki [n], Pavla Hodkova [o], Gina Hong [p], Jacqueline Lowdon [q], Su Madge [r], Clémence Martin [s], Edward McKone [t], Anne Munck [u], Chee Y Ooi [v], Lucy Perrem [w], Amanda Piper [x], Andrew Prayle [y], Felix Ratjen [z], Margaret Rosenfeld [aa], Don B Sanders [ab], Carsten Schwarz [ac], Giovanni Taccetti [ad], Claire Wainwright [ae], Natalie E West [af], Michael Wilschanski [ag], Amanda Bevan [ah], Carlo Castellani [ai], Pavel Drevinek [aj], Silvia Gartner [ak], Andrea Gramegna [al], Elise Lammertyn [am], Eddie (Edwina) C Landau [an], Barry J Plant [ao], Alan R Smyth [ap], Silke van Koningsbruggen-Rietschel [aq], Peter G. Middleton [ar]

[a] *Respiratory Medicine and Cystic Fibrosis National Reference Center, Cochin Hospital, Assistance Publique Hôpitaux de Paris (AP-HP), Institut Cochin, Inserm U1016, Université Paris-Cité, Paris, France*
[b] *Department of Women's and Children's Health, Institute in the Park, Alder Hey Children's Hospital, University of Liverpool, Eaton Road, Liverpool L12 2AP, UK*
[c] *All Wales Adult Cystic Fibrosis Centre, University Hospital Llandough, Cardiff and Vale University Health Board, Cardiff, UK*
[d] *Clinical Nutrition Unit, Department of Endocrine and Metabolic Medicine, IRCCS Istituto Auxologico Italiano, and ICANS-DIS, Department of Food Environmental and Nutritional Sciences, University of Milan, Milan, Italy*
[e] *Department of Nutrition and Dietetics, Alder Hey Children's NHS Trust, Liverpool, UK*
[f] *University of Brest, Fungal Respiratory Infections Research Unit, SFR ICAT, University of Angers, Angers, France*
[g] *Department of Pharmacy, Haga Teaching Hospital, The Hague, the Netherlands*
[h] *Cystic Fibrosis Foundation, Inova Fairfax Hospital, Bethesda, Maryland, USA, Falls Church, VA, USA*
[i] *Cystic Fibrosis Reference Centre-Centro, Hospitalar Universitário Lisboa Norte, Portugal*
[j] *Cystic Fibrosis Reference Center (Constitutif), Service de médecine interne et de pathologie vasculaire, Hospices Civils de Lyon, Hôpital Lyon Sud, RESearch on HealthcAre PErformance (RESHAPE), INSERM U1290, Université Claude Bernard Lyon 1, 8 avenue Rockefeller, 69373 Lyon Cedex 08, France; ERN-Lung Cystic Fibrosis Network, Frankfurt, Germany*
[k] *Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands*
[l] *Department of Respiratory Medicine, The Alfred Hospital, Melbourne, Australia*
[m] *The Children's Hospital for Wales, Cardiff, UK*
[n] *CF Centre at Goethe University Frankfurt, Frankfurt am Main, Germany*
[o] *CF Center at University Hospital Motol, Prague, Czech Republic*
[p] *Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA*
[q] *Clinical Specialist Paediatric Cystic Fibrosis Dietitian, Leeds Children's Hospital, UK*
[r] *Royal Brompton Hospital, Part of Guys and StThomas's Hospital, London, UK*
[s] *Institut Cochin, Inserm U1016, Université Paris-Cité and National Reference Center for Cystic Fibrosis, Hôpital Cochin AP-HP, ERN-Lung CF Network, Paris 75014, France*
[t] *St.Vincent's University Hospital and University College Dublin School of Medicine, Dublin, Ireland*
[u] *Hospital Necker Enfants-Malades, AP-HP, CF Centre, Université Paris Descartes, Paris, France*
[v] *School of Clinical Medicine, Discipline of Paediatrics and Child Health, Faculty of Medicine & Health, Department of Gastroenterology, Sydney Children's Hospital, University of New South Wales, Sydney, NSW, Australia*
[w] *Department of Respiratory Medicine, Children's Health Ireland, Dublin, Ireland*
[x] *Central Clinical School, Faculty of Medicine, University of Sydney, Sydney, Australia*
[y] *Child Health, Lifespan and Population Health & Nottingham Biomedical Research Centre, School of Medicine, University of Nottingham, Nottingham, UK*
[z] *Division of Respiratory Medicine, Department of Pediatrics and Translational Medicine, Research Institute, Hospital for Sick Children, Toronto, Canada*
[aa] *Department of Pediatrics, Seattle Children's Research Institute, University of Washington School of Medicine, Seattle, WA, USA*
[ab] *Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA*
[ac] *Division Cystic Fibrosis, CF Center, Clinic Westbrandenburg, HMU-Health and Medical University, Potsdam, Germany*

* Corresponding author.
E-mail address: kwsouth@liv.ac.uk (K.W. Southern).

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[ad] Meyer Children's Hospital IRCCS, Cystic Fibrosis Regional Reference Centre, Italy
[ae] University of Queensland, South Brisbane, QLD, Australia
[af] Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
[ag] Pediatric Gastroenterology Unit, CF Center, Hadassah Medical Center, Jerusalem, Israel
[ah] University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[ai] IRCCS Istituto Giannina Gaslini, Via Gerolamo Gaslini 5, Genova 16147, Italy
[aj] Department of Medical Microbiology, Second Faculty of Medicine, Motol University Hospital, Charles University, Prague, Czech Republic
[ak] Cystic Fibrosis Unit and Pediatric Pulmonology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[al] Department of Pathophysiology and Transplantation, Respiratory Unit and Adult Cystic Fibrosis Center, Università degli Studi di Milano, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
[am] Cystic Fibrosis Europe, Brussels, Belgium and the Belgian CF Association, Brussels, Belgium
[an] The Graub CF Center, Pulmonary Institute, Schneider Children's Medical Center, Petah Tikva, Israel
[ao] Cork Centre for Cystic Fibrosis (3CF), Cork University Hospital, University College Cork, Ireland
[ap] School of Medicine, Dentistry and Biomedical Sciences, Belfast and NIHR Nottingham Biomedical Research Centre, Queens University Belfast, Nottingham, UK
[aq] CF Center Cologne, Children's Hospital, Faculty of Medicine, University Hospital Cologne, Cologne, Germany
[ar] Westmead Clinical School, Department Respiratory & Sleep Medicine, Westmead Hospital, University of Sydney and CITRICA, Westmead, Australia

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ABSTRACT

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

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

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

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

1. Introduction

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

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

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

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

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

2. Identifying and addressing airway infection and inflammation

2.1. Monitoring for lung health decline

Felix Ratjen, Andrea Gramegna, Lucy Perrem, Edward McKone

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

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

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

2.2. Inhaled mucoactive agents

Felix Ratjen, Edwin Brokkar, Isabelle Durieu

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

Table 1
Statements.

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

(*continued on next page*)

Table 1 (*continued*)

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

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

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

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

2.3. Surveillance for airway infection

Julian Forton, Pavel Drevinek, Miquel Ekkelenkamp

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

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

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

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

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

2.4. Approaches to antibiotic therapy

Margaret Rosenfeld, Alan Smyth, Giovanni Taccetti, Claire Wainwright

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

2.4.1. Prophylaxis

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

2.4.2. Eradication

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

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

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

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

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

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

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

2.4.3. Suppression

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

2.4.4. Recognising and treating nontuberculous mycobacterium lung disease

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

2.5. Addressing pulmonary exacerbations

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

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

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

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

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

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

2.6. Fungal diseases in the CF lung

Gina Hong, Jean-Philippe Bouchara, Carsten Schwarz

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

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

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

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

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

3. Cystic fibrosis specific health issues

3.1. CF-related diabetes

Peter Middleton, Claire Berry, Alberto Battezzati

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

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

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

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

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

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

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

3.2. CF-related liver disease

Chee Ooi, Andrea Gramegna, Michael Wilschanski

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

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

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

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

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

3.3. CF bone disease

Andrea Gramegna, Pilar Azevedo

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

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

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

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

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

3.4. Stones and other renal issues

Andrew Prayle, Barry Plant

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

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

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

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

3.5. Intestinal obstruction

Anne Munck, Michael Wilschanski

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

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

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

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

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

3.6. Early identification of cancer

Charlotte Addy, Andrea Gramegna

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

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

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

4. Supporting mental and emotional well being

Eddie Landau, Johanna Gardecki, Pavla Hodkova

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

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

4.2. Consider screening tools for mental health issues

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

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

4.3. The role of the psychologist

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

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

5. When life gets challenging

5.1. Supporting increased treatment demands

Clémence Martin, Charlie Addy, Jacqueline Lowdon

5.1.1. Supporting complex care needs and treatment burden

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

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

5.1.2. Maintaining nutritional status and optimising nutritional support

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

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

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

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

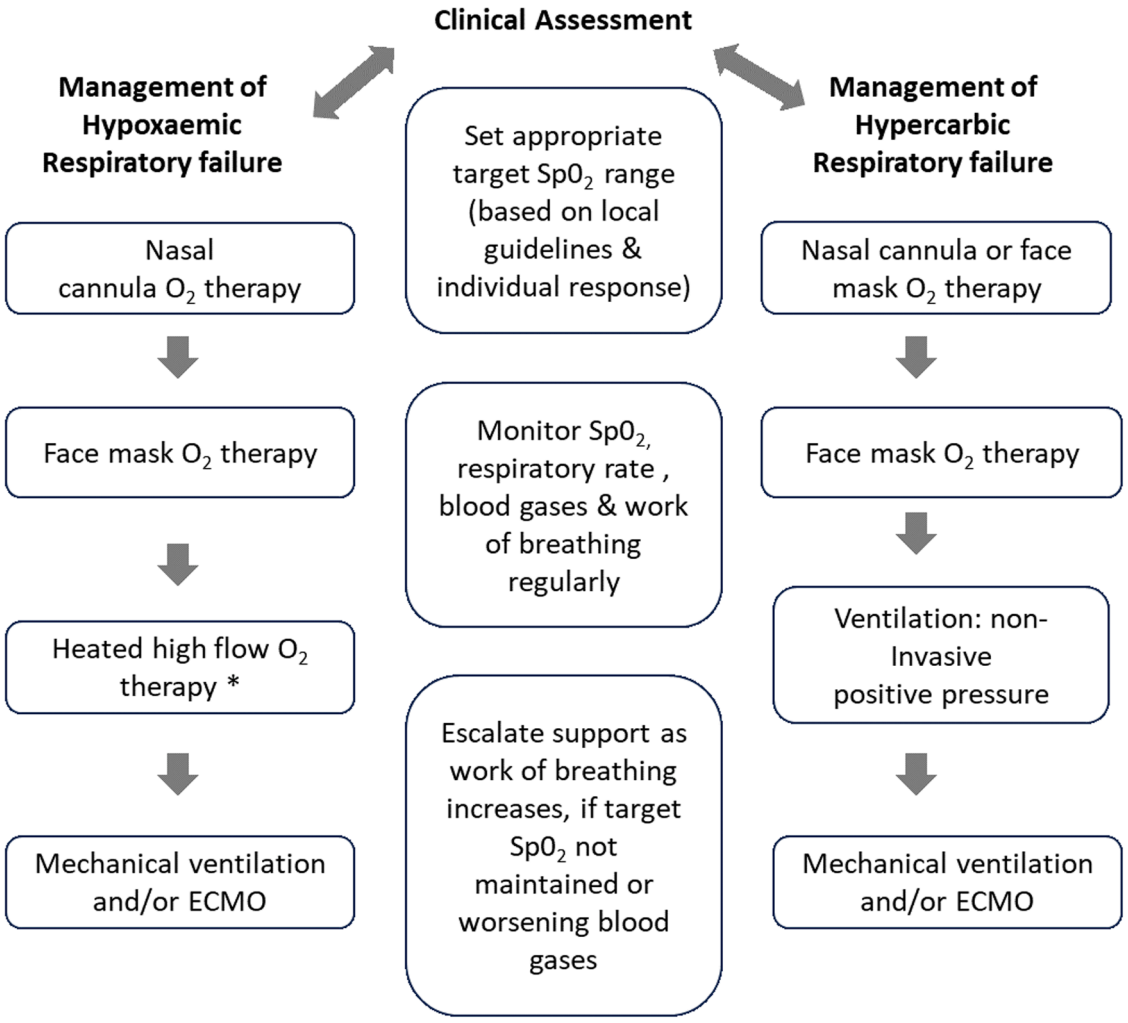

Fig. 1. Clinical assessment, management and current escalation pathway of people with CF in hypoxaemic and hypercarbic respiratory failure. Although two pathways are presented, hypoxaemic and hypercarbic respiratory failure are closely linked and often coexist. * If available; can be considered for use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

[171,175].

5.2. Supporting breathing

Whitney Brown, Amanda Piper, Charlotte Addy

5.2.1. Detecting and treating respiratory failure

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

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

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

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

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

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

5.3. Solid organ transplantation

Whitney Brown, Pierre-Régis Burgel

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

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

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

5.4. Planning for end of life

Su Madge, Felicity Finlayson

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

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

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

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

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

Areas of discussion around end of life care should include:

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

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

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

6. Conclusion

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

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

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

Author credit

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

Declaration of competing interest

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

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Supplementary materials

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

References

[1] 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.
[2] Southern KW. Standards for the care of people with cystic fibrosis; establishing and maintaining health. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.12.002.
[3] 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 DOI.
[4] 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.
[5] Nichols DP, Morgan SJ, Skalland M, Vo AT, Van Dalfsen JM, Singh SB, et al. Pharmacologic improvement of CFTR function rapidly decreases sputum pathogen density but lung infections generally persist. J Clin Invest 2023. https://doi.org/10.1172/jci167957.
[6] Bayfield KJ, Douglas TA, Rosenow T, Davies JC, Elborn SJ, Mall M, et al. Time to get serious about the detection and monitoring of early lung disease in cystic fibrosis. Thorax 2021;76:1255–65. https://doi.org/10.1136/thoraxjnl-2020-216085.
[7] Ciet P, Booij R, Dijkshoorn M, van Straten M, Tiddens H. Chest radiography and computed tomography imaging in cystic fibrosis: current challenges and new perspectives. Pediatr Radiol 2023;53:649–59. https://doi.org/10.1007/s00247-022-05522-4.
[8] Ciet P, Bertolo S, Ros M, Casciaro R, Cipolli M, Colagrande S, et al. State-of-the-art review of lung imaging in cystic fibrosis with recommendations for pulmonologists and radiologists from the "iMAging managEment of cySTic fibROsis" (MAESTRO) consortium. Eur Respir Rev 2022;31. https://doi.org/10.1183/16000617.0173-2021.
[9] Woods JC, Wild JM, Wielpütz MO, Clancy JP, Hatabu H, Kauczor HU, et al. Current state of the art MRI for the longitudinal assessment of cystic fibrosis. J Magn Reson Imaging 2019;10.1002:jmri.27030. https://doi.org/10.1002/jmri.27030.

[10] Yang C, Montgomery M. Dornase alfa for cystic fibrosis. Cochrane Database Syst Rev 2021;3:CD001127. https://doi.org/10.1002/14651858.CD001127.pub5.
[11] Konstan MW, Pasta DJ, VanDevanter DR, Wagener JS, Morgan WJ, Scientific Advisory G, et al. Epidemiologic study of cystic fibrosis: 25 years of observational research. Pediatr Pulmonol 2021;56:823–36. https://doi.org/10.1002/ppul.25248.
[12] Hodson ME, Shah PL. DNase trials in cystic fibrosis. Eur Respir J 1995;8:1786–91. https://doi.org/10.1183/09031936.95.08101786.
[13] Dentice R, Elkins M. Timing of dornase alfa inhalation for cystic fibrosis. Cochrane Database Syst Rev 2021;3:CD007923. https://doi.org/10.1002/14651858.CD007923.pub6.
[14] Ratjen F, Davis SD, Stanojevic S, Kronmal RA, Hinckley Stukovsky KD, Jorgensen N, et al. Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2019;7:802–9. https://doi.org/10.1016/S2213-2600(19)30187-0.
[15] Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev 2009:CD001506. https://doi.org/10.1002/14651858.CD001506.pub3.
[16] Tiddens H, Chen Y, Andrinopoulou ER, Davis SD, Rosenfeld M, Ratjen F, et al. The effect of inhaled hypertonic saline on lung structure in children aged 3-6 years with cystic fibrosis (SHIP-CT): a multicentre, randomised, double-blind, controlled trial. Lancet Respir Med 2022;10:669–78. https://doi.org/10.1016/S2213-2600(21)00546-4.
[17] Stahl M, Wielputz MO, Ricklefs I, Dopfer C, Barth S, Schlegtendal A, et al. Preventive inhalation of hypertonic saline in infants with cystic fibrosis (PRESIS). A randomized, double-blind, controlled study. Am J Respir Crit Care Med 2019;199:1238–48. https://doi.org/10.1164/rccm.201807-1203OC.
[18] Dwyer TJ, Elkins MR, Dentice R, Forbes S, Cooper P, Jaffe A, et al. Saline at lower tonicity in cystic fibrosis (SALTI-CF) trial comparing 0.9% versus 3% versus 6% nebulised saline. Eur Respir J 2023;62. https://doi.org/10.1183/13993003.00960-2021.
[19] Nevitt SJ, Thornton J, Murray CS, Dwyer T. Inhaled mannitol for cystic fibrosis. Cochrane Database Syst Rev 2020;5:CD008649. https://doi.org/10.1002/14651858.CD008649.pub4.
[20] 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.
[21] Jung A, Kleinau I, Schonian G, Bauernfeind A, Chen C, Griese M, et al. Sequential genotyping of Pseudomonas aeruginosa from upper and lower airways of cystic fibrosis patients. Eur Respir J 2002;20:1457–63. https://doi.org/10.1183/09031936.02.00268002.
[22] Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol 1999;28:321–8. https://doi.org/10.1002/(sici)1099-0496(199911)28:5<321::aid-ppul3>3.0.co;2-v.
[23] Blau H, Linnane B, Carzino R, Tannenbaum EL, Skoric B, Robinson PJ, et al. Induced sputum compared to bronchoalveolar lavage in young, non-expectorating cystic fibrosis children. J Cyst Fibros 2014;13:106–10. https://doi.org/10.1016/j.jcf.2013.05.013.
[24] Hoppe JE, Towler E, Wagner BD, Accurso FJ, Sagel SD, Zemanick ET. Sputum induction improves detection of pathogens in children with cystic fibrosis. Pediatr Pulmonol 2015;50:638–46. https://doi.org/10.1002/ppul.23150.
[25] Zampoli M, Pillay K, Carrara H, Zar HJ, Morrow B. Microbiological yield from induced sputum compared to oropharyngeal swab in young children with cystic fibrosis. J Cyst Fibros 2016;15:605–10. https://doi.org/10.1016/j.jcf.2016.01.001.
[26] Ronchetti K, Tame JD, Paisey C, Thia LP, Doull I, Howe R, et al. The CF-Sputum Induction Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. Lancet Respir Med 2018;6:461–71. https://doi.org/10.1016/s2213-2600(18)30171-1.
[27] De Bel A, De Geyter D, De Schutter I, Mouton C, Wellemans I, Hanssens L, et al. Sampling and decontamination method for culture of nontuberculous mycobacteria in respiratory samples of cystic fibrosis patients. J Clin Microbiol 2013;51:4204–6. https://doi.org/10.1128/JCM.02035-13.
[28] Plongla R, Preece CL, Perry JD, Gilligan PH. Evaluation of RGM medium for isolation of nontuberculous mycobacteria from respiratory samples from patients with cystic fibrosis in the United States. J Clin Microbiol 2017;55:1469–77. https://doi.org/10.1128/jcm.02423-16.
[29] 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.
[30] Boutin S, Weitnauer M, Hassel S, Graeber SY, Stahl M, Dittrich AS, et al. One time quantitative PCR detection of Pseudomonas aeruginosa to discriminate intermittent from chronic infection in cystic fibrosis. J Cyst Fibros 2018;17:348–55. https://doi.org/10.1016/j.jcf.2017.12.007.
[31] CF Trust. CF trust guidelines: laboratory standards for processing microbiological samples from people with cystic fibrosis. UK: The Cystic Fibrosis Trust; 2022. Second editionDec.
[32] Andersen DH. Therapy and prognosis of fibrocystic disease of the pancreas. Pediatrics 1949;3:406–17.
[33] Rosenfeld M, Rayner O, Smyth AR. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. Cochrane Database Syst Rev 2020;9:Cd001912. https://doi.org/10.1002/14651858.CD001912.pub5.
[34] Ahmed MI, Mukherjee S. Treatment for chronic methicillin-sensitive staphylococcus aureus pulmonary infection in people with cystic fibrosis. Cochrane Database Syst Rev 2018;7:CD011581. https://doi.org/10.1002/14651858.CD011581.pub3.
[35] Lo DK, Muhlebach MS, Smyth AR. Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis. Cochrane Database Syst Rev 2022;12:CD009650. https://doi.org/10.1002/14651858.CD009650.pub5.
[36] Johansen HK, Gotzsche PC. Vaccines for preventing infection with pseudomonas aeruginosa in cystic fibrosis. Cochrane Database Syst Rev 2015:Cd001399. https://doi.org/10.1002/14651858.CD001399.pub4.
[37] Langton Hewer SC, Smith S, Rowbotham NJ, Yule A, Smyth AR. Antibiotic strategies for eradicating pseudomonas aeruginosa in people with cystic fibrosis. Cochrane Database Syst Rev 2023;6:CD004197. https://doi.org/10.1002/14651858.CD004197.pub6.
[38] Smith S, Rowbotham NJ. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev 2022;11:Cd001021. https://doi.org/10.1002/14651858.CD001021.pub4.
[39] Waters V, Ratjen F. Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis. Cochrane Database Syst Rev 2020;(6):CD010004. https://doi.org/10.1002/14651858.CD010004.pub5. IssueArt. No.:.
[40] Regan KH, Bhatt J. Eradication therapy for Burkholderia cepacia complex in people with cystic fibrosis. Cochrane Database Syst Rev 2019;(4):CD009876. https://doi.org/10.1002/14651858.CD009876.pub4. IssueArt. No.:.
[41] Frost F, Shaw M, Nazareth D. Antibiotic therapy for chronic infection with burkholderia cepacia complex in people with cystic fibrosis. Cochrane Database Syst Rev 2021;(12):CD013079. https://doi.org/10.1002/14651858.CD013079.pub3. IssueArt. No.:.
[42] Amin R, Jahnke N, Waters V. Antibiotic treatment for Stenotrophomonas maltophilia in people with cystic fibrosis. Cochrane Database Syst Rev 2020;3:CD009249. https://doi.org/10.1002/14651858.CD009249.pub5.
[43] McDermott JH, Wolf J, Hoshitsuki K, Huddart R, Caudle KE, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for the use of aminoglycosides based on MT-RNR1 Genotype. Clin Pharmacol Ther 2022;111:366–72. https://doi.org/10.1002/cpt.2309.
[44] Dalboge CS, Pressler T, Hoiby N, Nielsen KG, Johansen HK. A cohort study of the Copenhagen CF Centre eradication strategy against Staphylococcus aureus in patients with CF. J Cyst Fibros 2013;12:42–8. https://doi.org/10.1016/j.jcf.2012.06.005.
[45] Muhlebach MS, Beckett V, Popowitch E, Miller MB, Baines A, Mayer-Hamblett N, et al. Microbiological efficacy of early MRSA treatment in cystic fibrosis in a randomised controlled trial. Thorax 2017;72:318–26. https://doi.org/10.1136/thoraxjnl-2016-208949.
[46] Langton Hewer SC, Smyth AR, Brown M, Jones AP, Hickey H, Kenna D, et al. Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and Pseudomonas aeruginosa infection: the TORPEDO-CF RCT. Health Technol Assess 2021;25:1–128. https://doi.org/10.3310/hta25650.
[47] Ratjen F, Moeller A, McKinney ML, Asherova I, Alon N, Maykut R, et al. Eradication of early P. aeruginosa infection in children <7years of age with cystic fibrosis: the early study. J Cyst Fibros 2019;18:78–85. https://doi.org/10.1016/j.jcf.2018.04.002.
[48] Mogayzel Jr PJ, Naureckas ET, Robinson KA, Brady C, Guill M, Lahiri T, et al. Cystic fibrosis foundation pulmonary guideline. pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. Ann Am Thorac Soc 2014;11:1640–50. https://doi.org/10.1513/AnnalsATS.201404-166OC.
[49] Mayer-Hamblett N, Kloster M, Rosenfeld M, Gibson RL, Retsch-Bogart GZ, Emerson J, et al. Impact of sustained eradication of new pseudomonas aeruginosa infection on long-term outcomes in cystic fibrosis. Clin Infect Dis 2015;61:707–15. https://doi.org/10.1093/cid/civ377.
[50] Taccetti G, Denton M, Hayes K, Drevinek P. Sermet-Gaudelus I. A critical review of definitions used to describe pseudomonas aeruginosa microbiological status in patients with cystic fibrosis for application in clinical trials. J Cyst Fibros 2019. https://doi.org/10.1016/j.jcf.2019.08.014.
[51] Casaredi IG, Shaw M, Waters V, Seeto R, Blanchard AC, Ratjen F. Impact of antibiotic eradication therapy of Pseudomonas aeruginosa on long term lung function in cystic fibrosis. J Cyst Fibros 2023;22:98–102. https://doi.org/10.1016/j.jcf.2022.08.007.
[52] Lord R, Jones AM, Horsley A. Antibiotic treatment for Burkholderia cepacia complex in people with cystic fibrosis experiencing a pulmonary exacerbation. Cochrane Database Syst Rev 2020;4:CD009529. https://doi.org/10.1002/14651858.CD009529.pub4.
[53] Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. J Cyst Fibros 2003;2:29–34. https://doi.org/10.1016/S1569-1993(02)00141-8.
[54] Elborn JS, Flume PA, Cohen F, Loutit J, VanDevanter DR. Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. J Cyst Fibros 2016;15:634–40. https://doi.org/10.1016/j.jcf.2016.01.005.
[55] Bilton D, Pressler T, Fajac I, Clancy JP, Sands D, Minic P, et al. Amikacin liposome inhalation suspension for chronic Pseudomonas aeruginosa infection in cystic

fibrosis. J Cyst Fibros 2020;19:284–91. https://doi.org/10.1016/j.jcf.2019.08.001.
[56] Tiddens HA, Bos AC, Mouton JW, Devadason S, Janssens HM. Inhaled antibiotics: dry or wet? Eur Respir J 2014;44:1308–18. https://doi.org/10.1183/09031936.00090314.
[57] Wallace E, Hendrickson D, Tolli N, Mehaffy C, Peña M, Nick JA, et al. Culturing mycobacteria. Methods Mol Biol 2021;2314:1–58. https://doi.org/10.1007/978-1-0716-1460-0_1.
[58] Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Andrejak C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 2020;71:905–13. https://doi.org/10.1093/cid/ciaa1125.
[59] Leung JM, Olivier KN. Nontuberculous mycobacteria: the changing epidemiology and treatment challenges in cystic fibrosis. Curr Opin Pulm Med 2013;19:662–9. https://doi.org/10.1097/MCP.0b013e328365ab33.
[60] Leung JM, Olivier KN. Nontuberculous mycobacteria in patients with cystic fibrosis. Semin Respir Crit Care Med 2013;34:124–34. https://doi.org/10.1055/s-0033-1333574.
[61] Woods GL, Brown-Elliott BA, Conville PS, Desmond EP, Hall GS, Lin G, et al. CLSI standards: guidelines for health care excellence. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes. Wayne (PA): Clinical and Laboratory Standards Institute; 2011.
[62] Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US cystic fibrosis foundation and European cystic fibrosis society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax 2016;71(Suppl 1):i1–22. https://doi.org/10.1136/thoraxjnl-2015-207360.
[63] Gilljam M, Berning SE, Peloquin CA, Strandvik B, Larsson LO. Therapeutic drug monitoring in patients with cystic fibrosis and mycobacterial disease. Eur Respir J 1999;14:347–51. https://doi.org/10.1034/j.1399-3003.1999.14b18.x.
[64] Wiesel V, Aviram M, Mei-Zahav M, Dotan M, Prais D, Cohen-Cymberknoh M, et al. Eradication of nontuberculous mycobacteria in people with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor: a multicenter cohort study. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.05.003.
[65] Sanders DB, Solomon GM, Beckett VV, West NE, Daines CL, Heltshe SL, et al. Standardized treatment of pulmonary exacerbations (STOP) study: observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations. J Cyst Fibros 2017;16:592–9. https://doi.org/10.1016/j.jcf.2017.04.005.
[66] Goss CH, Heltshe SL, West NE, Skalland M, Sanders DB, Jain R, et al. A randomized clinical trial of antimicrobial duration for cystic fibrosis pulmonary exacerbation treatment. Am J Respir Crit Care Med 2021;204:1295–305. https://doi.org/10.1164/rccm.202102-0461OC.
[67] West NE, Beckett VV, Jain R, Sanders DB, Nick JA, Heltshe SL, et al. Standardized treatment of pulmonary exacerbations (STOP) study: physician treatment practices and outcomes for individuals with cystic fibrosis with pulmonary Exacerbations. J Cyst Fibros 2017;16:600–6. https://doi.org/10.1016/j.jcf.2017.04.003.
[68] Sanders DB, Khan U, Heltshe SL, Skalland M, West NE, VanDevanter DR, et al. Association of site of treatment with clinical outcomes following intravenous antimicrobial treatment of a pulmonary exacerbation. J Cyst Fibros 2022;21:574–80. https://doi.org/10.1016/j.jcf.2021.11.009.
[69] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002;121:64–72. https://doi.org/10.1378/chest.121.1.64.
[70] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153:345–52. https://doi.org/10.1093/aje/153.4.345.
[71] Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med 2010;182:627–32. https://doi.org/10.1164/rccm.200909-1421OC.
[72] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del Allele. N Engl J Med 2019;381:1809–19. https://doi.org/10.1056/NEJMoa1908639.
[73] Schechter MS, Schmidt HJ, Williams R, Norton R, Taylor D, Molzhon A. Impact of a program ensuring consistent response to acute drops in lung function in children with cystic fibrosis. J Cyst Fibros 2018;17:769–78. https://doi.org/10.1016/j.jcf.2018.06.003.
[74] Delhaes L, Touati K, Faure-Cognet O, Cornet M, Botterel F, Dannaoui E, et al. Prevalence, geographic risk factor, and development of a standardized protocol for fungal isolation in cystic fibrosis: Results from the international prospective study "MFIP". J Cyst Fibros 2019;18:212–20. https://doi.org/10.1016/j.jcf.2018.10.001.
[75] Breuer O, Schultz A, Turkovic L, de Klerk N, Keil AD, Brennan S, et al. Changing prevalence of lower airway infections in young children with cystic fibrosis. Am J Respir Crit Care Med 2019;200:590–9. https://doi.org/10.1164/rccm.201810-1919OC.
[76] Tracy MC, Moss RB. The myriad challenges of respiratory fungal infection in cystic fibrosis. Pediatr Pulmonol 2018. https://doi.org/10.1002/ppul.24126.
[77] Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis–state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 2003;37(Suppl 3):S225–64. https://doi.org/10.1086/376525.
[78] Hong G, Desai S, Moss RB, Eschenhagen P, Quon BS, Schwarz C. Clinician variability in the diagnosis and treatment of aspergillus fumigatus-related conditions in cystic fibrosis: an international survey. J Cyst Fibros 2022;21:136–42. https://doi.org/10.1016/j.jcf.2021.07.008.
[79] Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy 2013;43:850–73. https://doi.org/10.1111/cea.12141.
[80] Li BCM, Huh SM, Prieto MD, Hong G, Schwarz C, Moss RB, et al. Biomarkers for the diagnosis of allergic bronchopulmonary aspergillosis in cystic fibrosis: a systematic review and meta-analysis. J Allergy Clin Immunol Pract 2021;9:1909-30 e4. https://doi.org/10.1016/j.jaip.2020.12.064.
[81] Refait J, Macey J, Bui S, Fayon M, Berger P, Delhaes L, et al. CT evaluation of hyperattenuating mucus to diagnose allergic bronchopulmonary aspergillosis in the special condition of cystic fibrosis. J Cyst Fibros 2019;18:e31–ee6. https://doi.org/10.1016/j.jcf.2019.02.002.
[82] Burgel PR, Paugam A, Hubert D, Martin C. Aspergillus fumigatus in the cystic fibrosis lung: pros and cons of azole therapy. Infect Drug Resist 2016;9:229–38. https://doi.org/10.2147/IDR.S63621.
[83] Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev 2021;9:Cd010288. https://doi.org/10.1002/14651858.CD010288.pub5.
[84] Koutsokera A, Corriveau S, Sykes J, Coriati A, Cortes D, Vadas P, et al. Omalizumab for asthma and allergic bronchopulmonary aspergillosis in adults with cystic fibrosis. J Cyst Fibros 2020;19:119–24. https://doi.org/10.1016/j.jcf.2019.07.011.
[85] Amin R, Dupuis A, Aaron SD, Ratjen F. The effect of chronic infection with aspergillus fumigatus on lung function and hospitalization in patients with cystic fibrosis. Chest 2010;137:171–6. https://doi.org/10.1378/chest.09-1103.
[86] O'Dea AL, Feng R, Glaser LJ, Kubrak C, Rubenstein RC, Dorgan DJ, et al. The Clinical Association between Aspergillus fumigatus and Respiratory Outcomes in Adolescents and Adults with Cystic Fibrosis. Ann Am Thorac Soc 2023. https://doi.org/10.1513/AnnalsATS.202210-852OC.
[87] Düesberg U, Wosniok J, Naehrlich L, Eschenhagen P, Schwarz C. Risk factors for respiratory aspergillus fumigatus in german cystic fibrosis patients and impact on lung function. Sci Rep 2020;10. https://doi.org/10.1038/s41598-020-75886-w.
[88] Brandt C, Roehmel J, Rickerts V, Melichar V, Niemann N, Schwarz C. Aspergillus bronchitis in patients with cystic fibrosis. Mycopathologia 2018;183:61–9. https://doi.org/10.1007/s11046-017-0190-0.
[89] Shoseyov D, Brownlee KG, Conway SP, Kerem E. Aspergillus bronchitis in cystic fibrosis. Chest 2006;130:222–6. https://doi.org/10.1378/chest.130.1.222.
[90] Schwarz C, Brandt C, Melichar V, Runge C, Heuer E, Sahly H, et al. Combined antifungal therapy is superior to monotherapy in pulmonary scedosporiosis in cystic fibrosis. J Cyst Fibros 2019;18:227–32. https://doi.org/10.1016/j.jcf.2018.08.012.
[91] Middleton PG, Wagenaar M, Matson AG, Craig ME, Holmes-Walker DJ, Katz T, et al. Australian standards of care for cystic fibrosis-related diabetes. Respirology 2014;19:185–92. https://doi.org/10.1111/resp.12227.
[92] Ode KL, Ballman M, Battezzati A, Brennan A, Chan CL, Hameed S, et al. ISPAD clinical practice consensus guidelines 2022: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2022;23:1212–28. https://doi.org/10.1111/pedi.13453.
[93] Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A. Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. Diabetes Care 2011;34:292–5. https://doi.org/10.2337/dc10-1604.
[94] Prentice BJ, Chelliah A, Ooi CY, Hameed S, Verge CF, Plush L, et al. Peak OGTT glucose is associated with lower lung function in young children with cystic fibrosis. J Cyst Fibros 2020;19:305–9. https://doi.org/10.1016/j.jcf.2019.05.005.
[95] Weiss L, Reix P, Mosnier-Pudar H, Ronsin O, Beltrand J, Reynaud Q, et al. Screening strategies for glucose tolerance abnormalities and diabetes in people with cystic fibrosis. Diabetes Metab 2023;49:101444. https://doi.org/10.1016/j.diabet.2023.101444.
[96] Cystic Fibrosis Trust. Management of cystic fibrosis diabetes. 2022. https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Diabetes%20Consensus%20FINAL_0.pdf Date accessed: 23 October 2023.
[97] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108:832–9. https://doi.org/10.1016/j.jada.2008.02.020.
[98] Salazar-Barragan M, Taub DR. The effects of elexacaftor, tezacaftor, and ivacaftor (ETI) on blood glucose in patients with cystic fibrosis: a systematic review. Cureus 2023;15:e41697. https://doi.org/10.7759/cureus.41697.
[99] Witters P, Libbrecht L, Roskams T, Boeck KD, Dupont L, Proesmans M, et al. Noncirrhotic presinusoidal portal hypertension is common in cystic fibrosis-associated liver disease. Hepatology 2011;53:1064–5. https://doi.org/10.1002/hep.24183.
[100] Singh H, Coffey MJ, Ooi CY. Cystic fibrosis-related liver disease is associated with increased disease burden and endocrine comorbidities. J Pediatr Gastroenterol Nutr 2020;70:796–800. https://doi.org/10.1097/mpg.0000000000002694.
[101] Chryssostalis A, Hubert D, Coste J, Kanaan R, Burgel PR, Desmazes-Dufeu N, et al. Liver disease in adult patients with cystic fibrosis: a frequent and independent prognostic factor associated with death or lung transplantation. J Hepatol 2011;55:1377–82. https://doi.org/10.1016/j.jhep.2011.03.028.
[102] Calvopina DA, Lewindon PJ, Ramm LE, Noble C, Hartel GF, Leung DH, et al. Gamma-glutamyl transpeptidase-to-platelet ratio as a biomarker of liver disease

and hepatic fibrosis severity in paediatric cystic fibrosis. J Cyst Fibros 2022;21:236–42. https://doi.org/10.1016/j.jcf.2021.10.014.
[103] Sakhuja S, Staples HM, Minard CG, Ramm LE, Lewindon PJ, Ramm GA, et al. Risk factors for more rapid progression of severe liver fibrosis in children with cystic fibrosis-related liver disease: a multi-center study validated by liver biopsy. Liver Int 2023;43:1277–86. https://doi.org/10.1111/liv.15572.
[104] Stonebraker JR, Ooi CY, Pace RG, Corvol H, Knowles MR, Durie PR, et al. Features of severe liver disease with portal hypertension in patients with cystic fibrosis. Clin Gastroenterol Hepatol 2016;14:1207. https://doi.org/10.1016/j.cgh.2016.03.041. 15.e3.
[105] 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.
[106] McKay IR, Ooi CY. The exocrine pancreas in cystic fibrosis in the era of cftr modulation: a mini review. Front Pediatr 2022;10:914790. https://doi.org/10.3389/fped.2022.914790.
[107] Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology 2011;140:153–61. https://doi.org/10.1053/j.gastro.2010.09.046.
[108] Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90:1888–96. https://doi.org/10.1210/jc.2004-1629.
[109] Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int 2010;86:1–7. https://doi.org/10.1007/s00223-009-9316-9.
[110] Sermet-Gaudelus I, Bianchi ML, Garabedian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros 2011;10(Suppl 2):S16–23. https://doi.org/10.1016/S1569-1993(11)60004-0.
[111] NIH Consensus Development Panel on Osteoporosis Prevention D, Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785–95. https://doi.org/10.1001/jama.285.6.785.
[112] Jeffery TC, Chang AB, Conwell LS. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database Syst Rev 2023;1:CD002010. https://doi.org/10.1002/14651858.CD002010.pub5.
[113] Moryousef J, Kwong J, Kishibe T, Ordon M. Systematic review of the prevalence of kidney stones in cystic fibrosis. J Endourol 2021;35:1693–700. https://doi.org/10.1089/end.2021.0151.
[114] Gibney EM, Goldfarb DS. The association of nephrolithiasis with cystic fibrosis. Am J Kidney Dis 2003;42:1–11. https://doi.org/10.1016/s0272-6386(03)00403-7.
[115] Hiatt RA, Dales LG, Friedman GD, Hunkeler EM. Frequency of urolithiasis in a prepaid medical care program. Am J Epidemiol 1982;115:255–65. https://doi.org/10.1093/oxfordjournals.aje.a113297.
[116] Bohles H, Gebhardt B, Beeg T, Sewell AC, Solem E, Posselt G. Antibiotic treatment-induced tubular dysfunction as a risk factor for renal stone formation in cystic fibrosis. J Pediatr 2002;140:103–9. https://doi.org/10.1067/mpd.2002.120694.
[117] Downes KJ, Patil NR, Rao MB, Koralkar R, Harris WT, Clancy JP, et al. Risk factors for acute kidney injury during aminoglycoside therapy in patients with cystic fibrosis. Pediatr Nephrol 2015;30:1879–88. https://doi.org/10.1007/s00467-015-3097-3.
[118] Bertenshaw C, Watson AR, Lewis S, Smyth A. Survey of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2007;62:541–5. https://doi.org/10.1136/thx.2006.067595.
[119] Smyth A, Lewis S, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2008;63:532–5. https://doi.org/10.1136/thx.2007.088757.
[120] Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk factors for chronic kidney disease in adults with cystic fibrosis. Am J Respir Crit Care Med 2011;184:1147–52. https://doi.org/10.1164/rccm.201105-0932OC.
[121] Stehling F, Büscher R, Grosse-Onnebrink J, Hoyer PF, Mellies U. Glomerular and tubular renal function after repeated once-daily tobramycin courses in cystic fibrosis patients. Pulm Med 2017;2017:2602653. https://doi.org/10.1155/2017/2602653.
[122] Berg KH, Ryom L, Faurholt-Jepsen D, Pressler T, Katzenstein TL. Prevalence and characteristics of chronic kidney disease among Danish adults with cystic fibrosis. J Cyst Fibros 2018;17:478–83. https://doi.org/10.1016/j.jcf.2017.11.001.
[123] Quon BS, Mayer-Hamblett N, Aitken ML, Goss CH. Risk of post-lung transplant renal dysfunction in adults with cystic fibrosis. Chest 2012;142:185–91. https://doi.org/10.1378/chest.11-1926.
[124] KDIGO CKD Work Group. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;3:1–150.
[125] M L. Al-Aloul M, Miller H, Alapati S, Stockton P, Walshaw M. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use Pediatr Pulmonol 2005;39:15–20.
[126] Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50:38–42. https://doi.org/10.1097/MPG.0b013e3181a6e01d.
[127] Stefano MA, Sandy NS, Zagoya C, Duckstein F, Ribeiro AF, Mainz JG, et al. Diagnosing constipation in patients with cystic fibrosis applying ESPGHAN criteria. J Cyst Fibros 2022;21:497–501. https://doi.org/10.1016/j.jcf.2021.08.021.
[128] van der Doef HPJ, Houwen RHJ. Constipation and cystic fibrosis. Slow movement. J Cyst Fibros 2022;21:385–6. https://doi.org/10.1016/j.jcf.2022.04.003.
[129] Marsh R, Gavillet H, Hanson L, Ng C, Mitchell-Whyte M, Major G, et al. Intestinal function and transit associate with gut microbiota dysbiosis in cystic fibrosis. J Cyst Fibros 2022;21:506–13. https://doi.org/10.1016/j.jcf.2021.11.014.
[130] Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros 2011;10(Suppl 2):S24–8. https://doi.org/10.1016/S1569-1993(11)60005-2.
[131] Ooi CY, Jeyaruban C, Lau J, Katz T, Matson A, Bell SC, et al. High ambient temperature and risk of intestinal obstruction in cystic fibrosis. J Paediatr Child Health 2016;52:430–5. https://doi.org/10.1111/jpc.13096.
[132] Munck A, Alberti C, Colombo C, Kashirskaya N, Ellemunter H, Fotoulaki M, et al. International prospective study of distal intestinal obstruction syndrome in cystic fibrosis: associated factors and outcome. J Cyst Fibros 2016;15:531–9. https://doi.org/10.1016/j.jcf.2016.02.002.
[133] Gilchrist FJ, Green J, Carroll W. Interventions for treating distal intestinal obstruction syndrome (DIOS) in cystic fibrosis. Cochrane Database Syst Rev 2021;12:CD012798. https://doi.org/10.1002/14651858.CD012798.pub3.
[134] Carroll W, Green J, Gilchrist FJ. Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis. Cochrane Database Syst Rev 2021;12:CD012619. https://doi.org/10.1002/14651858.CD012619.pub3.
[135] Groves T, Kench A, Dutt S, Gaskin K, Fitzgerald DA. Question 8: How should distal intestinal obstruction syndrome [DIOS] be managed? Paediatr Respir Rev 2017;21:68–71. https://doi.org/10.1016/j.prrv.2016.04.001.
[136] Hadjiliadis D, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels AB. Cystic fibrosis colorectal cancer screening consensus recommendations. Gastroenterology 2018;154:736. https://doi.org/10.1053/j.gastro.2017.12.012. 45.e14.
[137] Birch RJ, Peckham D, Wood HM, Quirke P, Konstant-Hambling R, Brownlee K, et al. The risk of colorectal cancer in individuals with mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene: An English population-based study. J Cyst Fibros 2023;22:499–504. https://doi.org/10.1016/j.jcf.2022.10.001.
[138] Maisonneuve P, Lowenfels AB. Cancer in cystic fibrosis: a narrative review of prevalence, risk factors, screening, and treatment challenges: adult cystic fibrosis series. Chest 2022;161:356–64. https://doi.org/10.1016/j.chest.2021.09.003.
[139] Johannesson M, Askling J, Montgomery SM, Ekbom A, Bahmanyar S. Cancer risk among patients with cystic fibrosis and their first-degree relatives. Int J Cancer 2009;125:2953–6. https://doi.org/10.1002/ijc.24679.
[140] Appelt D, Fuchs T, Steinkamp G, Ellemunter H. Malignancies in patients with cystic fibrosis: a case series. J Med Case Rep 2022;16:27. https://doi.org/10.1186/s13256-021-03234-1.
[141] Gini A, Zauber AG, Cenin DR, Omidvari AH, Hempstead SE, Fink AK, et al. Cost-effectiveness of screening individuals with cystic fibrosis for colorectal cancer. Gastroenterology 2017. https://doi.org/10.1053/j.gastro.2017.12.011.
[142] Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Sole A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. Thorax 2014;69:1090–7. https://doi.org/10.1136/thoraxjnl-2014-205983.
[143] Landau EC, Verkleij M, Graziano S, Quittner AL, Georgiopoulos AM, Smith BA, et al. Mental health screening in cystic fibrosis as an intervention: patient and caregiver feedback on improving these processes. Respir Med 2022;202:106955. https://doi.org/10.1016/j.rmed.2022.106955.
[144] Bryon M. Breaking the diagnosis of cystic fibrosis to parents: a process not a one-off event. Paediatr Respir Rev 2020;35:103–5. https://doi.org/10.1016/j.prrv.2020.04.006.
[145] Kimball H, Douglas T, Sanders M, Cobham VE. Anxiety in children with cystic fibrosis and their parents: a systematic review. Clin Child Fam Psychol Rev 2021;24:370–90. https://doi.org/10.1007/s10567-021-00345-5.
[146] Lord L, McKernon D, Grzeskowiak L, Kirsa S, Ilomaki J. Depression and anxiety prevalence in people with cystic fibrosis and their caregivers: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2023;58:287–98. https://doi.org/10.1007/s00127-022-02307-w.
[147] Cronly JA, Duff AJ, Riekert KA, Fitzgerald AP, Perry IJ, Lehane EA, et al. Health-related quality of life in adolescents and adults with cystic fibrosis: physical and mental health predictors. Respir Care 2019;64:406–15. https://doi.org/10.4187/respcare.06356.
[148] Habib AR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. Ann Am Thorac Soc 2015;12:420–8. https://doi.org/10.1513/AnnalsATS.201408-393OC.
[149] 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.
[150] Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. J Cyst Fibros 2009;8:91–6. https://doi.org/10.1016/j.jcf.2008.09.007.
[151] Havermans T, Duff AJA. Changing landscape: psychological care in the era of cystic fibrosis transmembrane conductance regulator modulators. Curr Opin Pulm Med 2020;26:696–701. https://doi.org/10.1097/mcp.0000000000000727.

[152] Singh J, Towns S, Jayasuriya G, Hunt S, Simonds S, Boyton C, et al. Transition to adult care in cystic fibrosis: The challenges and the structure. Paediatr Respir Rev 2022;41:23–9. https://doi.org/10.1016/j.prrv.2020.07.009.
[153] Chudleigh J, Browne R, Radbourne C. Impact of cystic fibrosis on unaffected siblings: a systematic review. J Pediatr 2019;210:112. https://doi.org/10.1016/j.jpeds.2019.03.035. 7.e9.
[154] 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 2020;8:65–124. https://doi.org/10.1016/S2213-2600(19)30337-6.
[155] Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, et al. International committee on mental health in cystic fibrosis: cystic fibrosis foundation and european cystic fibrosis society consensus statements for screening and treating depression and anxiety. Thorax 2016;71:26–34. https://doi.org/10.1136/thoraxjnl-2015-207488.
[156] Georgiopoulos AM, Christon LM, Filigno SS, Mueller A, Prieur MG, Boat TF, et al. Promoting emotional wellness in children with CF, part II: mental health assessment and intervention. Pediatr Pulmonol 2021;56(Suppl 1):S107–Ss22. https://doi.org/10.1002/ppul.24977.
[157] Filigno SS, Miller J, Moore S, Peugh J, Weiland J, Backstrom J, et al. Assessing psychosocial risk in pediatric cystic fibrosis. Pediatr Pulmonol 2019;54:1391–7. https://doi.org/10.1002/ppul.24414.
[158] Georgiopoulos A., Smith B., Quittner A. Integrating patient-reported outcomes into research a clinical practice: measures of health-related quality of life and mental health. In: Wilmott RW, Boat TF, Bush A, Chernick V, Deterding RR, Ratjen F, editors. Kendig textbook of disorders of the respiratory tract in children. 10th ed. Philadelphia, PA: Elsevier Health Sciences; in press.
[159] Flewelling KD, Sellers DE, Sawicki GS, Robinson WM, Dill EJ. Social support is associated with fewer reported symptoms and decreased treatment burden in adults with cystic fibrosis. J Cyst Fibros 2019;18:572–6. https://doi.org/10.1016/j.jcf.2019.01.013.
[160] Eaton CK, Beachy S, McLean KA, Nicolais CJ, Bernstein R, Sáez-Clarke E, et al. Misunderstandings, misperceptions, and missed opportunities: perspectives on adherence barriers from people with CF, caregivers, and CF team members. Patient Educ Couns 2020;103:1587–94. https://doi.org/10.1016/j.pec.2020.02.025.
[161] Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. J Cyst Fibros 2013;12:461–7. https://doi.org/10.1016/j.jcf.2012.12.009.
[162] Trandel ET, Pilewski JM, Dellon EP, Jeong K, Yabes JG, Moreines LT, et al. Prevalence of unmet palliative care needs in adults with cystic fibrosis. J Cyst Fibros 2020;19:394–401. https://doi.org/10.1016/j.jcf.2019.11.010.
[163] Abbott J, Hurley MA, Chadwick H, Peckham D. Ways of coping and survival in cystic fibrosis: a 20-year longitudinal study. J Cyst Fibros 2023;22:112–8. https://doi.org/10.1016/j.jcf.2022.04.011.
[164] Dawson S, Girling C-J, Cowap L, Clark-Carter D. Psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis. Cochrane Database Syst Rev 2023;3. https://doi.org/10.1002/14651858.CD013766.pub2. CD013766-CD.
[165] Goggin J, Cohen RI. CF healthcare workers feel unprepared in providing suitable end of life care and desire more education: results of a nationwide survey. J Cyst Fibros 2016;15:85–9. https://doi.org/10.1016/j.jcf.2015.08.005.
[166] Kapnadak SG, Ramos KJ, Dellon EP. Enhancing care for individuals with advanced cystic fibrosis lung disease. Pediatr Pulmonol 2021;56(Suppl 1):S69–s78. https://doi.org/10.1002/ppul.24937.
[167] 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;121:1591. https://doi.org/10.1016/j.jand.2020.03.015. 636.e3.
[168] 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.
[169] George PM, Banya W, Pareek N, Bilton D, Cullinan P, Hodson ME, et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. BMJ 2011;342:d1008. https://doi.org/10.1136/bmj.d1008.
[170] Collins S. Nutritional management of cystic fibrosis - an update for the 21st century. Paediatr Respir Rev 2018;26:4–6. https://doi.org/10.1016/j.prrv.2017.03.006.
[171] Smyth RL, Rayner O. Oral calorie supplements for cystic fibrosis. Cochrane Database Syst Rev 2014:Cd000406. https://doi.org/10.1002/14651858.CD000406.pub4.
[172] Mielus M, Sands D, Woynarowski M. Improving nutrition in cystic fibrosis: a systematic literature review. Nutrition 2022;102:111725. https://doi.org/10.1016/j.nut.2022.111725.
[173] Schwarzenberg SJ, Hempstead SE, McDonald CM, Powers SW, Wooldridge J, Blair S, et al. Enteral tube feeding for individuals with cystic fibrosis: cystic fibrosis foundation evidence-informed guidelines. J Cyst Fibros 2016;15:724–35. https://doi.org/10.1016/j.jcf.2016.08.004.
[174] Shimmin D, Lowdon J, Remmington T. Enteral tube feeding for cystic fibrosis. Cochrane Database Syst Rev 2019;7:Cd001198. https://doi.org/10.1002/14651858.CD001198.pub5.
[175] Hollander FM, de Roos NM, Heijerman HGM. The optimal approach to nutrition and cystic fibrosis: latest evidence and recommendations. Curr Opin Pulm Med 2017;23:556–61. https://doi.org/10.1097/mcp.0000000000000430.
[176] Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, et al. Cystic fibrosis foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros 2020;19:344–54. https://doi.org/10.1016/j.jcf.2020.02.015.
[177] Flume PA, Mogayzel Jr PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med 2010;182:298–306. https://doi.org/10.1164/rccm.201002-0157OC.
[178] Mingora CM, Flume PA. Pulmonary complications in cystic fibrosis: past, present, and future: adult cystic fibrosis series. Chest 2021;160:1232–40. https://doi.org/10.1016/j.chest.2021.06.017.
[179] Zinman R, Corey M, Coates AL, Canny GJ, Connolly J, Levison H, et al. Nocturnal home oxygen in the treatment of hypoxemic cystic fibrosis patients. J Pediatr 1989;114:368–77. https://doi.org/10.1016/s0022-3476(89)80553-0.
[180] Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Cochrane Database Syst Rev 2013;2013:CD003884. https://doi.org/10.1002/14651858.CD003884.pub4.
[181] Archangelidi O, Carr SB, Simmonds NJ, Bilton D, Banya W, Cullinan P. Non-invasive ventilation and clinical outcomes in cystic fibrosis: Findings from the UK CF registry. J Cyst Fibros 2019;18:665–70. https://doi.org/10.1016/j.jcf.2018.11.006.
[182] Milross MA, Piper AJ, Dwyer TJ, Wong K, Bell SC, Bye PTP. Non-invasive ventilation versus oxygen therapy in cystic fibrosis: a 12-month randomized trial. Respirology 2019;24:1191–7. https://doi.org/10.1111/resp.13604.
[183] Wadsworth LE, Belcher J, Bright-Thomas RJ. Non-invasive ventilation is associated with long-term improvements in lung function and gas exchange in cystic fibrosis adults with hypercapnic respiratory failure. J Cyst Fibros 2021;20:e40–ee5. https://doi.org/10.1016/j.jcf.2021.05.011.
[184] Flight WG, Shaw J, Johnson S, Webb AK, Jones AM, Bentley AM, et al. Long-term non-invasive ventilation in cystic fibrosis – experience over two decades. J Cyst Fibros 2012;11:187–92. https://doi.org/10.1016/j.jcf.2011.11.006.
[185] Papale M, Parisi G, Spicuzza L, Rotolo N, Mulè E, Aloisio D, et al. Nocturnal non invasive ventilation in normocapnic cystic fibrosis patients: a pilot study. Acta Biomed 2021;92:e2021164. https://doi.org/10.23750/abm.v92i2.11261.
[186] Young AC, Wilson JW, Kotsimbos TC, Naughton MT. Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. Thorax 2008;63:72–7. https://doi.org/10.1136/thx.2007.082602.
[187] Spoletini G, Pollard K, Watson R, Darby MJ, Johnstone A, Etherington C, et al. Noninvasive ventilation in cystic fibrosis: clinical indications and outcomes in a large UK adult cystic fibrosis center. Respir Care 2021;66:466–74. https://doi.org/10.4187/respcare.07862.
[188] Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, et al. Lung transplant referral for individuals with cystic fibrosis: cystic fibrosis foundation consensus guidelines. J Cyst Fibros 2019;18:321–33. https://doi.org/10.1016/j.jcf.2019.03.002.
[189] Piper AJ, Parker S, Torzillo PJ, Sullivan CE, Bye PT. Nocturnal nasal IPPV stabilizes patients with cystic fibrosis and hypercapnic respiratory failure. Chest 1992;102:846–50. https://doi.org/10.1378/chest.102.3.846.
[190] Sklar MC, Dres M, Rittayamai N, West B, Grieco DL, Telias I, et al. High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. Ann Intensive Care 2018;8:85. https://doi.org/10.1186/s13613-018-0432-4.
[191] Davis MD, Brockbank J, Hayden R, Schechter MS, Rubin BK. Nocturnal high-flow nasal cannula therapy and sinonasal symptoms during cystic fibrosis exacerbations. Respir Care 2023. https://doi.org/10.4187/respcare.09890.
[192] King CS, Brown AW, Aryal S, Ahmad K, Donaldson S. Critical care of the adult patient with cystic fibrosis. Chest. 2019;155:202–14. https://doi.org/10.1016/j.chest.2018.07.025.
[193] Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: an update from the international society for heart and lung transplantation. J Heart Lung Transplant 2021;40:1349–79. https://doi.org/10.1016/j.healun.2021.07.005.
[194] Hirche TO, Knoop C, Hebestreit H, Shimmin D, Sole A, Elborn JS, et al. Practical guidelines: lung transplantation in patients with cystic fibrosis. Pulm Med 2014;2014:621342. https://doi.org/10.1155/2014/621342.
[195] Coriati A, Sykes J, Lemonnier L, Ma X, Stanojevic S, Dehillotte C, et al. Impact of a high emergency lung transplantation programme for cystic fibrosis in France: insight from a comparison with Canada. Eur Respir J 2021;59:2100014. https://doi.org/10.1183/13993003.00014-2021.
[196] Lehr CJ, Skeans M, Dasenbrook E, Fink A, Fernandez G, Faro A, et al. Effect of including important clinical variables on accuracy of the lung allocation score for cystic fibrosis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2019;200:1013–21. https://doi.org/10.1164/rccm.201902-0252oc.
[197] Burgel PR, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. Am J Respir Crit Care Med 2021;204:64–73. https://doi.org/10.1164/rccm.202011-4153OC.
[198] Martin C, Reynaud-Gaubert M, Hamidfar R, Durieu I, Murris-Espin M, Danner-Boucher I, et al. Sustained effectiveness of elexacaftor-tezacaftor-ivacaftor in lung transplant candidates with cystic fibrosis. J Cyst Fibros 2022;21:489–96. https://doi.org/10.1016/j.jcf.2022.01.012.
[199] Martin C, Legeai C, Regard L, Cantrelle C, Dorent R, Carlier N, et al. Major decrease in lung transplantation for patients with cystic fibrosis in France. Am J Respir Crit Care Med 2022;205:584–6. https://doi.org/10.1164/rccm.202109-2121LE.
[200] Ringshausen FC, Sauer-Heilborn A, Büttner T, Dittrich AM, Schwerk N, Ius F, et al. Lung transplantation for end-stage cystic fibrosis before and after the availability

of elexacaftor–tezacaftor–ivacaftor, Germany, 2012–2021. Eur Respir J 2022;61: 2201402. https://doi.org/10.1183/13993003.01402-2022.
[201] Bower JK, Volkova N, Ahluwalia N, Sahota G, Xuan F, Chin A, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study. J Cyst Fibros 2023;22: 730–7. https://doi.org/10.1016/j.jcf.2023.03.002.
[202] Chan EG, Hyzny EJ, Ryan JP, Morrell MR, Pilewski J, Sanchez PG. Outcomes following lung re-transplantation in patients with cystic fibrosis. J Cyst Fibros 2022;21:482–8. https://doi.org/10.1016/j.jcf.2021.12.002.
[203] Shah P, Lowery E, Chaparro C, Visner G, Hempstead SE, Abraham J, et al. Cystic fibrosis foundation consensus statements for the care of cystic fibrosis lung transplant recipients. J Heart Lung Transplant 2021;40:539–56. https://doi.org/10.1016/j.healun.2021.04.011.
[204] McKone E, Ramos KJ, Chaparro C, Blatter J, Hachem R, Anstead M, et al. Position paper: models of post-transplant care for individuals with cystic fibrosis. J Cyst Fibros 2023;22:374–80. https://doi.org/10.1016/j.jcf.2023.02.011.
[205] Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with cystic fibrosis. J Cyst Fibros 2021;20:243–9. https://doi.org/10.1016/j.jcf.2020.07.017.
[206] Burgel PR, Burnet E, Regard L, Martin C. The changing epidemiology of cystic fibrosis: the implications for adult care. Chest 2023;163:89–99. https://doi.org/10.1016/j.chest.2022.07.004.
[207] Cathcart F, Wood J, Madge S. Improving end-of-life care for adults with cystic fibrosis: an improvement project. BMJ Open Qual 2020;9. https://doi.org/10.1136/bmjoq-2019-000861.
[208] Dhingra L, Walker P, Berdella M, Plachta A, Chen J, Fresenius A, et al. Addressing the burden of illness in adults with cystic fibrosis with screening and triage: an early intervention model of palliative care. J Cyst Fibros 2020;19:262–70. https://doi.org/10.1016/j.jcf.2019.08.009.
[209] Obregon LL, Jeong K, Hoydich ZP, Yabes J, Pilewski J, Richless C, et al. Associations between demographic characteristics and unmet supportive care needs in adults with cystic fibrosis. BMJ Support Palliat Care 2022;12:e281–e4. https://doi.org/10.1136/bmjspcare-2019-001819.
[210] 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.
[211] Basile M, Jojan L, Hobler MR, Dellon EP, Georgiopoulos AM, Goggin JL, et al. Assessing practices, beliefs, and attitudes about palliative care among people with cystic fibrosis, their caregivers, and clinicians: results of a content analysis. J Palliat Med 2021;24:1650–6. https://doi.org/10.1089/jpm.2020.0725.
[212] Marmor M, Jonas A, Mirza A, Rad E, Wong H, Aslakson RA. Opportunities to improve utilization of palliative care among adults with cystic fibrosis: a systematic review. J Pain Symptom Manag 2019;58:1100. https://doi.org/10.1016/j.jpainsymman.2019.08.017. 12.e1.
[213] Bonvicini KA, Perlin MJ, Bylund CL, Carroll G, Rouse RA, Goldstein MG. Impact of communication training on physician expression of empathy in patient encounters. Patient Educ Couns 2009;75:3–10. https://doi.org/10.1016/j.pec.2008.09.007.
[214] Linnemann RW, O'Malley PJ, Friedman D, Georgiopoulos AM, Buxton D, Altstein LL, et al. Development and evaluation of a palliative care curriculum for cystic fibrosis healthcare providers. J Cyst Fibros 2016;15:90–5. https://doi.org/10.1016/j.jcf.2015.03.005.