The ageing of people living with cystic fibrosis: what to expect now?

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The ageing CF population brings new challenges: emerging comorbidities and uncertain long-term effects of CFTR modulators. Early treatment is crucial, but the evolving landscape requires constant updating of care. https://bit.ly/3AevNrX

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Abstract

The prognosis of people with cystic fibrosis (pwCF) has improved dramatically with the introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators (CFTRm). The ageing of the cystic fibrosis (CF) population is changing the disease landscape with the emergence of different needs and increasing comorbidities related to both age and long-term exposure to multiple treatments including CFTRm. Although the number of pwCF eligible for this treatment is expected to increase, major disparities in care and outcomes still exist in this population. Moreover, the long-term impact of the use of CFTRm is still partly unknown due to the current short follow-up and experience with their use, thus generating some uncertainties. The future spread and initiation of these drugs at an earlier stage of the disease is expected to reduce the systemic burden of systemic inflammation and its consequences on health. However, the prolonged life expectancy is accompanied by an increasing burden of age-related comorbidities, especially in the context of chronic disease. The clinical manifestations of the comorbidities directly or indirectly associated with CFTR dysfunction are changing, along with the disease dynamics and outcomes. Current protocols used to monitor slow disease progression will need continuous updates, including the composition of the multidisciplinary team for CF care, with a greater focus on the needs of the adult population.

Introduction

In the late fifteenth century, long before cystic fibrosis (CF) was recognised as a pathological entity, an Irish poet wrote: "Woe to that child which when kissed on the forehead tastes salty. He is bewitched and soon must die" [1].

Described more than 80 years ago [2], CF still has no definitive cure. However, its prognosis has significantly improved, allowing the vast majority of people with CF (pwCF) to live well into adulthood.

CF transmembrane conductance regulator (CFTR) modulators (CFTRm), together with the introduction of neonatal screening, multidisciplinary teams (MDTs) in specialised centres, lung transplant programmes, the introduction of new antibiotics, nutritional support and respiratory physiotherapy, have revolutionised the survival rates for pwCF [3].

Search methods

A PubMed search was conducted for articles published in the last 30 years on CF treatments. After this, the search focused on articles published from 2010 to date on CFTRm. Subsequently, different PubMed

search methods were combined according to the sections of this review (comorbidities in pwCF, ageing, inflammation, fragility, pregnancy, transplantation, *etc*.).

CFTRm: transforming CF treatment

The treatment landscape for CF has evolved significantly, especially with the introduction of CFTRm. These therapies aim to address the genetic defect that causes CF, either by increasing the opening time of the CFTR channel (potentiators) or by improving CFTR protein synthesis and correcting its folding (correctors). Since the launch of ivacaftor in 2012 as the first CFTRm [4], other combinations of potentiators and correctors have emerged, such as lumacaftor/ivacaftor [5–9], tezacaftor/ivacaftor [10–15] and elexacaftor/tezacaftor/ivacaftor (ETI) [16–22] (table 1). The latter combination, together with ivacaftor

TABLE 1 Evolution of the approval of cystic fibrosis transmembrane conductance regulator modulators (CFTRm) and their indications

Molecule name	CFTRm	Modulator type	Commercial name	FDA first approval	EMA first approval	Current indications
VX-770	Ivacaftor	Potentiator	Kalydeco®	2012	2012	Kalydeco® (USA) Age: ⩾1 month Mutations: at least one of the 97 mutations listed at www.cff.org/media/25171/download Kalydeco® (EU[#] and UK) Age: ⩾4 months Mutations: at least one of the following 10 mutations: *R117H*, *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* and *S549R*
VX-809/ VX-770	Lumacaftor/ ivacaftor	Corrector/ potentiator	Orkambi®	2015	2015	Orkambi® (USA) Age: ⩾2 years Mutations: homozygous for *F508del* mutation Orkambi® (EU and UK) Age: ⩾1 year Mutations: homozygous for *F508del* mutation
VX-661/ VX-770	Tezacaftor/ ivacaftor	Corrector/ potentiator	Symdeko® in USA Symkevi® in EU and UK	2018	2018	Symdeko® (USA) Age: ⩾6 years Mutations: homozygous for *F508del* mutation or at least one copy of the *F508del* mutation and one of the 154 mutations listed at www.cff.org/sites/default/files/2022-02/Symdeko-Approved-Mutations.pdf Symkevi® (EU and UK) Age: ⩾6 years Mutations: homozygous for the *F508del* mutation or at least one copy of the *F508del* mutation and one of the following 14 mutations: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3AàG*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5GàA*, *3272 26AàG* and *3849 +10kbCàT*
VX-445/ VX-661/ VX-770	Elexacaftor/ tezacaftor/ ivacaftor	Corrector/ corrector/ potentiator	Trikafta® in USA Kaftrio® in EU and UK	2019	2020	Trikafta® (USA) Age: ⩾2 years Mutations: at least one copy of the *F508del* mutation or any of the 177 mutations listed at www.cff.org/sites/default/files/2022-02/Trikafta-Approved-Mutations.pdf Kaftrio® (EU[¶] and UK[+]) Age: ⩾6 years Mutations: at least one copy of the *F508del* mutation

FDA: US Food and Drug Administration; EMA: European Medicines Agency; EU: European Union. [#]: The Committee for Medicinal Products for Human Use of the EMA adopted on 23 February 2024 a positive opinion for the label extension of Kalydeco® for the treatment of infants with cystic fibrosis (CF) from ages 1 month and older with at least one of the 10 mutations. [¶]: The European Commission approved on 23 November 2023 the label extension of Kaftrio® for the treatment of children with CF aged 2–5 years with at least one copy of the F508del mutation. [+]: In the UK, following Medicines and Healthcare products Regulatory Agency approval on 15 November 2023, children aged 2 years and older have access to this expanded indication for Kaftrio®. In addition, Kaftrio® is also approved for the same 177 mutations as Trikafta®.

TABLE 2 New cystic fibrosis transmembrane conductance regulator modulators (CFTRm) and future combinations

	Molecule name	Sponsor	CFTRm	Modulator type
New CFTR modulators	VX-121	Vertex Pharmaceuticals	Vanzacaftor	Corrector
	PTI-801	Proteostasis	Posenacaftor	Corrector
	VX-561	Vertex Pharmaceuticals	Deutivacaftor	Potentiator
	PTI-808	Proteostasis	Dirocaftor	Potentiator
	PTI-428	Proteostasis	Nesolicaftor	Amplificator
	Molecule name	**ClinicalTrials.gov ID**	**Phase**	**Status**
Combinations under study	Vanzacaftor/tezacaftor/deutivacaftor	NCT05033080	3	Closed to enrolment
		NCT05076149	3	Closed to enrolment
		NCT03912233	2	Completed with results
	Dirocaftor/posenacaftor/nesolicaftor	NCT03500263	1/2	Completed with results

for gating mutations, is considered a highly effective modulator therapy (HEMT). All these treatments have demonstrated good efficacy, safety and effectiveness in clinical trials and real-life studies, significantly transforming the outlook for pwCF and allowing most to reach adulthood with life expectancy and comorbidities becoming more similar to those of the general population [23, 24]. Nevertheless, several factors, such as socioeconomic conditions and local access to HEMTs and MDTs, can significantly affect clinical outcomes across different countries [25].

Nonetheless, with the currently available CFTRm, it is estimated that the coverage of CF genotypes is 90–95% [26]; however, in some regions where some genotypes, such as *F508del*, are less prevalent, this coverage drops to only 70% [27]. The emergence of new CFTRm, future new combinations and expanded coverage for mutations other than *F508del* in existing CFTRm offer hope for those who cannot yet benefit from this therapy (table 2).

The role of inflammation in ageing

Ageing is a natural process that we all experience throughout our lives, but what happens when illness becomes a companion from the very moment we come into the world?

Some studies have suggested that pwCF may experience accelerated ageing due to factors such as chronic inflammation from recurrent infections, oxidative stress, malnutrition and exposure to multiple drugs, all of which are key components of the disease [28]. Specifically, it is suspected that this chronic inflammatory state and oxidative stress may also contribute to the development of various comorbidities [29], including cancer in the respiratory, digestive and reproductive systems [28].

In the general population, it has been observed that the combination of chronic inflammation and oxidative stress may induce telomere dysfunction, which could accelerate telomere shortening and trigger premature ageing [30, 31]. A study published in 2021 suggested that telomere length may be related to overall health and disease severity in pwCF. The researchers observed shorter telomeres in CF patients with potential markers of more severe disease, such as the chronic use of inhaled corticosteroids or antibiotics use at the time of blood sampling, more hospitalisations, and comorbidities [32].

Moreover, we cannot overlook the importance of the gut microbiota and more specifically the gut–lung axis, which plays a crucial role in regulating the immune system [33–36]. Any alteration in this dynamic, as could be the case with antibiotics and, potentially, with the new CFTRm, could also predispose individuals to the onset of other diseases.

The use of CFTRm seems to offer relevant advances in ameliorating airway inflammation and infection, but these topics are still under investigation [37, 38].

Nevertheless, advances in the early diagnosis and the initiation of therapy at younger ages may be changing the landscape of the disease. In fact, on one hand, the early initiation of CFTRm should reduce the time of exposure to inflammation and stop disease progression. However, on the other hand, prolonged life expectancy will contribute to increasing the burden of comorbidities on the health of pwCF (figure 1).

Health challenges in ageing pwCF: emerging comorbidities

One of the main characteristics of CF disease is the patient's frailty from an early age, which may increase with ageing. So far, only a few studies have examined the characteristics of adults with CF (awCF) and suggested possible similarities to the frailty syndrome seen in elderly people without CF. These studies considered CF as an early expression of this geriatric syndrome [39–41]. In these individuals, susceptibility to recurrent respiratory infections, impaired lung capacity, difficulty in maintaining adequate nutritional status due to malabsorption, polypharmacy and associated genetics may be associated factors.

Although most of the understanding of frailty comes from the field of geriatric medicine, its importance as a treatable aspect in people with chronic diseases such as CF is increasingly being recognised [42]. Due to CFTRm, CF has now become a chronic and manageable disease for many pwCF, but the role of comorbidities related to both the disease and ageing will now play a greater role.

Within comorbidities, we can clearly identify some that are strongly and directly related to CFTR and chloride channel dysfunction (common CF comorbidities) and those whose pathophysiology is more complex and related not only to CFTR but also to ageing, chronic inflammation and prolonged use of certain drugs used in CF such as antibiotics or CFTRm (emerging comorbidities) (figure 2). The current evidence on all these comorbidities is detailed below.

Comorbidities

Pancreatic disorders

The pancreas is one of the most affected organs in CF and plays a crucial role in both exocrine and endocrine function.

The exocrine function of the pancreas involves the production and release of digestive enzymes, such as amylase, lipase and trypsin. In pwCF, mucosal obstruction of the pancreatic ducts can lead to recurrent pancreatitis. Studies have suggested that CFTRm may reduce the number of episodes of pancreatitis by reducing mucosal obstruction of the pancreatic duct and, therefore, prevent or delay pancreatic insufficiency (PI) [43, 44].

The endocrine function of the pancreas involves the production and release of hormones, mainly insulin and glucagon. Although CFTRm are primarily expected to improve pancreatic exocrine function, some studies suggest that they may also benefit endocrine function by improving glycaemic homeostasis and reducing the risk of CF-related diabetes (CFRD), as discussed below [45].

CFRD

CFRD is one of the most common nonrespiratory comorbidities in pwCF.

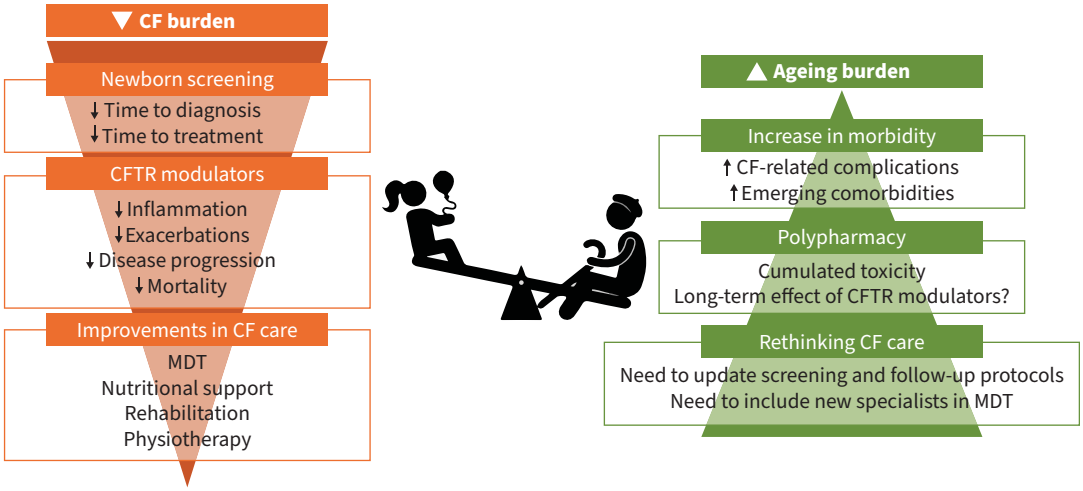

FIGURE 1 Factors potentially influencing the natural history of cystic fibrosis (CF) in the future. CFTR: CF transmembrane conductance regulator; MDT: multidisciplinary team.

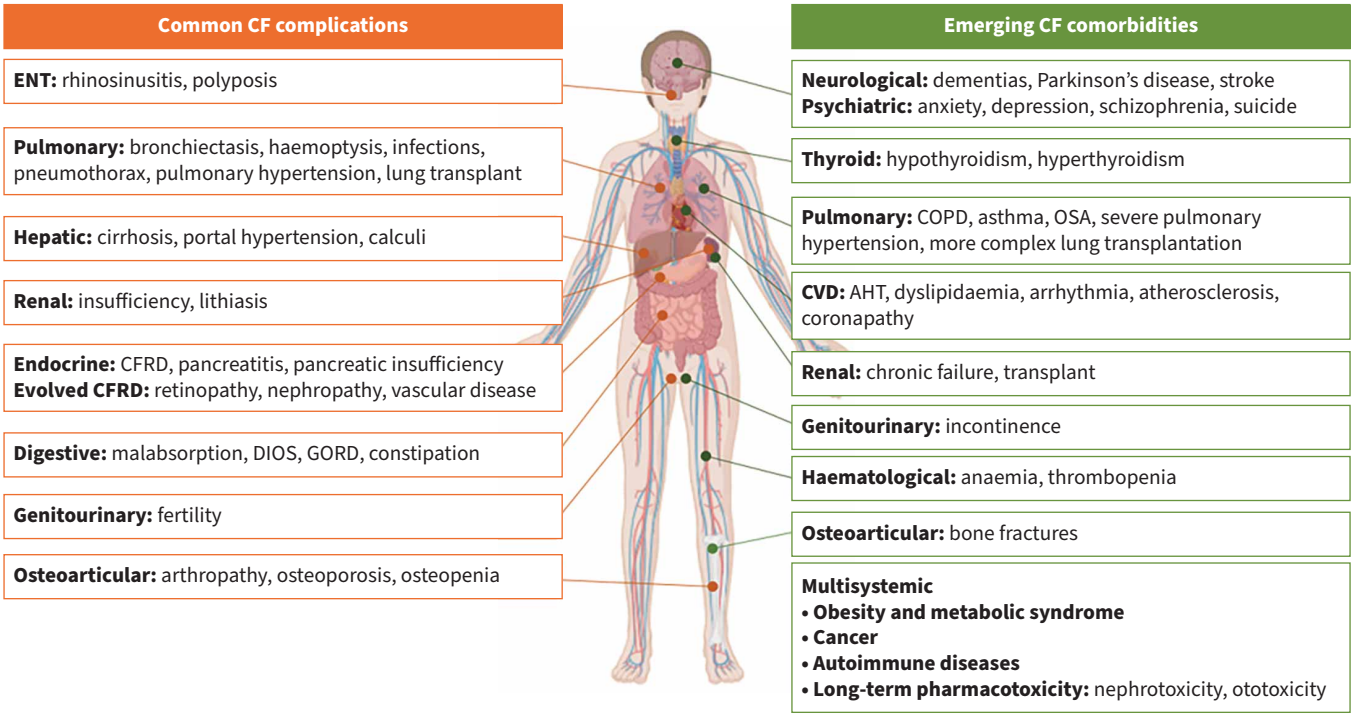

FIGURE 2 Cystic fibrosis (CF) morbidity with ageing. AHT: arterial hypertension; CVD: cardiovascular disease; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; ENT: ear, nose and throat; GORD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea.

The exact mechanism by which diabetes develops in CF has not yet been fully elucidated. It is now recognised that the main pathophysiological factor is endogenous insulin deficiency secondary to fibrotic destruction of pancreatic islet beta cells. However, other factors also play a role, such as impaired functioning of other pancreatic hormones (glucagon, somatostatin, pancreatic polypeptide), enteroinsular axis dysfunction, impaired insulin clearance and insulin resistance. PwCF can exhibit varying degrees of insulin resistance, influenced by multiple factors including chronic disease-associated inflammation, recurrent infections, nutritional status and the use of medications such as corticosteroids [46].

This form of diabetes therefore shares characteristics of both type 1 diabetes (due to lack of insulin) and type 2 diabetes (due to insulin resistance), but its management and treatment require strategies tailored specifically to the needs of pwCF.

CFTRm have helped to reduce insulin requirements and have led to better control of the disease [45]. As this population ages, CFRD is likely to be associated with more microvascular (retinopathy, nephropathy and neuropathy) [47] and macrovascular complications (cardiovascular disease, cerebrovascular disease and peripheral arterial disease) [48]. The CF Foundation/American Diabetes Association clinical practice guidelines recommend that all individuals begin annual screening with an oral glucose tolerance test at 10 years of age, [49]. Despite this, only 25–50% of the population is tested annually [50]. The guidelines recommend annual monitoring of microvascular complications starting 5 years after a diagnosis of CFRD, but there is currently insufficient evidence to justify recommending routine screening for macrovascular complications in people with CFRD and PI [51]. Early detection of these complications is crucial and should be systematically integrated into the routine clinical practice of healthcare professionals.

CF-related liver disease (CFLD)

CFLD is characterised by a wide variety of manifestations, including biliary tract disease (cholangiopathies, cholestasis and gallbladder disease), focal or multifocal biliary cirrhosis, and liver function abnormalities ranging from hepatic steatosis to cirrhosis with or without portal hypertension [52].

The pathophysiological processes of CFLD are complex [53, 54]. This pathogenic cycle includes chronic obstruction of intrahepatic bile ducts, leading to accumulation of bile and other fluids within the liver,

triggering a persistent inflammatory response. This inflammation, in turn, promotes activation of hepatic cells such as stellate cells, which are responsible for excessive production of collagen and other fibrotic proteins. However, it is believed that innate immunity and intestinal dysbiosis, *via* translocation of bacterial endotoxins, may further elucidate the pathophysiology by disrupting bile acid homeostasis.

Hepatic steatosis has been observed to be present in pwCF who have a higher body mass index (BMI) and better preserved lung function. It appears to exhibit similarities to nonalcoholic fatty liver disease found in people without CF [55]. CFTRm could enhance exocrine function of the pancreas and promote an increase in BMI. As a result, we may see an increased frequency of hepatic steatosis in this population [56].

Current recommendations suggest annual pancreatic and coagulation parameter screening in all pwCF from the time of diagnosis and imaging tests according to the results [57, 58].

To date, the impact of CFTRm on CFLD is unknown and little research has been conducted on this topic [59]. It is believed that CFTRm may have beneficial effects on liver function by correcting defects in ion transport and fluid secretion within liver cells, improving the viscosity of bile secretions, and preventing ductal obstruction and subsequent progression to liver cirrhosis.

CF bone disease (CFBD)

As patients age, an increase in the incidence of CFBDs such as osteopenia and osteoporosis is observed [60].

Both diseases are characterised by a loss of bone mineral density, which increases the risk of fractures. In pwCF, these disorders can develop due to several factors. Chronic inflammation and prolonged corticosteroid use increase osteoclast activity, resulting in increased bone resorption. At the same time, nutrient malabsorption, CFRD and vitamin and mineral deficiency (especially vitamin D, K and calcium) compromise the ability of osteoblasts to form new bone tissue [61, 62].

Current guidelines recommend early detection of bone disease in pwCF by bone densitometry from the age of 8–10 years, with periodic repeats every 1–5 years depending on the results [63, 64].

The use of CFTRm is expected to reduce the incidence of CFBDs by improving nutrient absorption and decreasing the frequency of exacerbations, leading to a reduction in systemic inflammation. In addition, it has been observed that CFTRm may improve quality of life and lung function, which could have positive indirect effects on musculoskeletal health by facilitating increased physical activity [65].

Arthropathies, including reactive arthritis, autoimmune-induced arthritis and arthralgias, are also common in pwCF [66]. Although its pathophysiology is not fully understood, there appears to be a complex interaction between the bone, joint and immune systems [67, 68]. These conditions may be the result of chronic systemic inflammation, pro-inflammatory cytokine production (elevated levels of tumour necrosis factor-α, interleukin (IL)-1 and IL-6), circulating immune complex formation, antibiotic use (quinolones) and limited mobility due to respiratory problems [69].

Metabolic syndrome

Metabolic syndrome encompasses several metabolic risk factors that increase the likelihood of developing cardiovascular disease. The diseases commonly included within metabolic syndrome are obesity, arterial hypertension (AHT), dyslipidaemia (DLP) and diabetes mellitus. Obesity in pwCF has increased significantly since the inception of CFTRm. In the phase III ETI clinical trial, an increase in BMI of 1.1 $kg \cdot m^{-2}$ was observed after 6 months of treatment initiation [17]. Real-life studies suggest that those pwCF with an initial BMI within a normal range before the onset of ETI can return to their initial weight within 3 years, while those starting from a low BMI may continue to gain weight [70]. However, socioeconomic factors and local dietary traditions can also impact weight.

It is very likely that the traditional recommendation, since 1988 [71], of a hypercaloric diet to pwCF will require considerable changes due to the increased risk of DLP and AHT with improved patient nutrition [72].

In fact, the use of ETI has been associated with increased total cholesterol, low-density and high-density lipoprotein levels [73, 74].

Currently, there are limited data on the cardiovascular safety of CFTRm. Cases of pwCF developing AHT following the use of ETI [75] and other cases where the presence of cardiovascular risk factors has led to acute myocardial infarction in this population have been reported in the literature [76, 77].

Renal disorders

Renal function in pwCF may be related to factors such as recurrent respiratory exacerbations, aminoglycosides and metabolic imbalances (hyperoxaluria, hyperuricosuria and hypercalciuria) favouring kidney stone development [78, 79].

Respiratory exacerbations can contribute to renal dysfunction by favouring sepsis, hypovolaemia and salt wasting; these can lead to recurrent acute kidney injury or chronic renal failure. Although the latter is rare in pwCF, its incidence increases with age due to the gradual loss of nephrons [79]. Other risk factors include lung transplantation due to the use of immunosuppressants, CFRD, female gender, worse lung function and recurrent episodes of acute kidney injury [80].

In addition, new age-related renal complications have been identified in pwCF, such as glomerular lesions (amyloidosis and IgA nephropathy), microalbuminuria, proteinuria, diabetic nephropathy, as well as tubulointerstitial lesions [79, 81, 82].

CFTRm could have indirect beneficial effects on renal function. By improving lung function and reducing respiratory exacerbations, they may indirectly contribute to the preservation of renal function. However, further studies are required to fully understand these effects and determine their impact on renal function in pwCF.

Obstructive sleep apnoea (OSA)

OSA is currently a largely unknown disorder in pwCF. The severity of symptoms and manifestations may vary from patient to patient. The combination of airway obstruction, chronic inflammation, structural alterations of the oropharynx, chronic upper airway obstruction (rhinosinusitis and polyps), increased obesity and muscle weakness associated with CF may predispose patients to develop OSA [83, 84]. In a currently published series, the occurrence of OSA in awCF is very low (3–7%) but is likely to be underestimated [84, 85]. With increasing obesity and other vascular comorbidities this percentage could increase. Furthermore, the link between this disease and metabolic, cardiovascular and neurocognitive effects is well known [85]. Other sleep disorders, such as nocturnal hypoxaemia and excessive daytime sleepiness, are also present in this population group, but associated risk factors have not yet been identified [83–85]. Current studies suggest incorporating screening for OSA and nocturnal hypoxaemia with polysomnography in pwCF regardless of disease severity [84, 85].

Neuropsychiatric disorders

In awCF, medical care should always include the psychological and neurological challenges that may arise from the disease. The constant need for healthcare and an uncertainty about the future can create a significant emotional burden, affecting psychological well-being from a very early age and throughout life. Anxiety, depression and neurocognitive disorders are conditions that can significantly affect the quality of life of these patients. The prevalence rates of depression and anxiety in awCF are about 19% and 30%, respectively [86]. In children, these disorders can be two to three times more frequent than in the general population [87].

These disorders can be triggered by uncertainty about the future, worries about deteriorating health and challenges in maintaining a good quality of life. The introduction of ETI is expected to reduce the triggers of these conditions; however, case reports and studies describing new mental health events in pwCF taking this modulator have begun to emerge [88, 89].

A recent review, including clinical trials of ETI, post-marketing reports, interim results from a registry-based safety study of ETI and peer-reviewed literature, concluded that, to date, there is no robust evidence that ETI is associated with increased mental health problems [90]. It is possible that the onset of the coronavirus disease 2019 pandemic, which coincided with its commercialisation, could play a role in increasing the cases of anxiety and depression. Furthermore, higher levels of anxiety and depression have also been described in pwCF who cannot access new CFTRm. Despite these results, caution is warranted and further studies are needed to fully elucidate the effects of CFTRm and their potential association with the increase in neuropsychiatric disorders in order to provide better clinical evaluation and guidance.

In the case of anxiety and depression, there is a consensus that suggests a specific screening through the GAD-7 (Generalised Anxiety Disorder seven-item scale) and the PHQ-9 (Patient Health Questionnaire nine-item) [86]. However, milder cases cannot be detected by questionnaires, so the inclusion of psychologists in the MDT is usually recommended [87].

In addition, it is likely that in the future we may observe an increase in eating disorders and behavioural disturbances due to weight gain in a population used to a hypercaloric diet [91–93].

The incidence of neurocognitive problems, such as dementia and memory impairment, is another important aspect to consider in the ageing population. Significant structural changes in areas of the brain related to cognitive, autonomic and mood functions (cerebellum, hippocampus, *etc.*) have been observed in pwCF through magnetic resonance imaging (MRI) [94]. The pathophysiology of these alterations is not clear but hypoxia and chronic inflammation could potentially play contributing roles.

Cancer

With increasing life expectancy in pwCF, an increased risk of developing cancer is expected. The risk factors for cancer in CF could include high-fat and low-fibre diets, repeated exposure to radiation, chronic inflammation from recurrent infections, and comorbidities such as CFRD, gastro-oesophageal reflux and inflammatory bowel disease [95]. The role of the CFTR gene in this context has also been discussed with different results [95]. For example, in the intestinal setting, it has been shown that overexpression of CFTR can have an inhibitory effect on tumour growth in colorectal cancer by suppressing cancer cell proliferation, migration and invasion [96, 97]. Interestingly, CFTR overexpression has also been shown to suppress tumour progression in prostate cancer cell lines [98] and in some cases may even be a protective factor [99]. However, increased tumour progression has been observed in both ovarian [100] and cervical cancer [101] in these cases.

The risk of cancer is markedly increased in pwCF who have received a solid organ transplant. In the specific case of lung transplantation, the most common in this population, the risk of developing any type of cancer reaches almost 10% [102]. Within lung-transplanted pwCF, non-Hodgkin's lymphoma and colorectal cancer are the most prevalent cancers [102].

Overall, in pwCF, colorectal cancer is the most common neoplasm. Given this reality, international recommendations suggest that nontransplanted pwCF should undergo colonoscopy for colorectal cancer screening from the age of 40 [103]. For transplanted pwCF, it is advised to start screening at age 30 or 2 years after transplantation [103]. Therefore, pwCF are encouraged to undergo regular colonoscopies, even in the absence of bowel symptoms, as a preventive measure against colorectal cancer [103].

The faecal immunochemical test (FIT) has not been evaluated in the CF population and is therefore not currently recommended as a screening method. However, the modelling results suggest that screening with the FIT may be more cost-effective for pwCF than colonoscopy screening, provided the method is sensitive and specific [103].

In addition to gastrointestinal cancer, a significant incidence of other cancers affecting different body systems is observed in the CF population, such as lung cancer, various gynaecological cancers (*e.g.* breast, ovarian, uterine and cervical), sarcomas, melanoma, thyroid cancer, bladder cancer, prostate cancer, kidney cancer, nasosinusal cancer, *etc.* [104, 105].

The role of CFTRm in the risk of cancer is still unknown, but surely the ageing process can further contribute to increase it along with immunosenescence.

Polypharmacy and drug toxicity

Polypharmacy, which is already prevalent among pwCF, will possibly persist with aging of this population [106] and the need to incorporate new treatments for managing their comorbidities. All of this will increase the risk of drug interactions that could alter the effectiveness and safety of treatments. In addition, the elderly are more susceptible to medication side-effects due to age-related physiological changes, such as decreased renal and hepatic function, reduced lean body mass, and decreased nutrient absorption, which can increase the risk of serious side-effects such as falls, gastrointestinal disorders, cognitive impairment and cardiovascular events [107, 108].

On the other hand, the improvement in symptoms with CFTRm can lead to a significant decrease in the treatment burden for these patients. For example, the SIMPLIFY study [109] (impact of discontinuing chronic therapies in people with cystic fibrosis on highly effective CFTR modulator therapy) concluded that, in pwCF with mild lung disease who are on ETI therapy, the use of hypertonic saline solution or alpha dornase could be discontinued for 6 weeks without affecting their functional tests. Similar studies include HERO-2 (ClinicalTrials.gov ID: NCT04798014) [110] and CF-STORM (Trials Tracker ID: TT005796).

Impact of CFTRm on comorbidities and follow-up in CF units

Despite the evident benefits of CFTRm, their long-term impact and role in comorbidities are not entirely clear. Initiatives such as the PROMISE study (prospective study to evaluate biological and clinical effects of significantly corrected CFTR function) [111] aim to assess the impact of triple therapy with ETI on various organs. So far, only the results of the effect of ETI on the gastrointestinal tract (PROMISE-GI) have been published [112], demonstrating improvements in gastrointestinal symptoms and inflammation after 6 months of treatment, without achieving reversal of established PI.

Specific protocols for managing comorbidities in awCF are crucial for addressing their health needs comprehensively. To date, there are few consensus guidelines on how to address comorbidities in awCF. Specific protocols have been established for managing CFRD [49], nutrition [113], mental illness [86] and hepatobiliary disease [57, 58].

However, there are only three specific protocols for addressing emerging comorbidities related to the aging of pwCF, namely those for colorectal cancer [103], bone disease management [67, 68] and advanced lung disease management [114]. For other comorbidities, we still need to rely on existing disease-specific protocols in each country for diagnosis, management and treatment. The emergence of new comorbidities and the incorporation of CFTRm may generate the need to establish new screening protocols for pwCF or to modify the existing ones. It is important to consider that CFTRm also have an impact on follow-up protocols in CF units. It is becoming less common for pwCF to require hospitalisation, so outpatient care is playing a major role in disease control and management. Monitoring the sputum microbiology of pwCF is challenging as patients rarely produce spontaneous expectoration after using CFTRm. Therefore, several studies have attempted to define new methods of microorganism isolation, such as induced sputum [115, 116] or bronchoalveolar lavage [117].

Furthermore, with CFTRm use lower radiological and functional deterioration is expected; therefore, more sensitive tests such as MRI [118, 119] or the lung clearance index [120–122] could replace X-rays or spirometry to detect earlier changes.

Changes in the age profile of this population should also lead to changes in the composition of the MDT [123]. The inclusion of gynaecologists, oncologists, nephrologists, cardiologists, geriatricians, neurologists and other professionals could now become essential for managing this changing population [124].

CFTRm in special populations

The inclusion of CFTRm has not only improved patient survival, but also transformed their outlook on life and long-term concerns.

With the possibility of motherhood or fatherhood now becoming a reality for pwCF [125], a somewhat unexpected effect of CFTRm has been the increase in female fertility, leading to a dramatic rise in the number of pregnancies [126, 127]. Research on the effects of CFTRm during pregnancy and breastfeeding is controversial because these patients are excluded from clinical trials [128]. Studies in animal models have revealed that the use of CFTRm could cause cataracts in newborns [129, 130]. In addition, bilateral congenital cataracts have been reported in the first 6 months of life in children of women treated with ETI [130]. Therefore, it is crucial to thoroughly assess the potential fetal risks against the likelihood of maternal worsening if treatment is discontinued. The multicentre prospective study MAYFLOWERS (study evaluating maternal and fetal outcomes in the era of modulators) [131] aims to evaluate the effects of CFTRm during pregnancy and 2 years after, thus shedding light on this field. However, there are currently several clinical cases documented in the literature of successful pregnancies with the use of CFTRm, both at the fetal and maternal levels [129, 132, 133]. There have even been reports of reversal of meconium ileus and delay in PI in a homozygous *F508del* baby whose mother was a carrier of the disease [134]. This development opens up the possibility of prenatal treatment for the disease, offering hope for future interventions [135].

The possibility of initiating CFTRm at increasingly early stages may increase the proportion of asymptomatic or minimally symptomatic awCF.

Additionally, advances in diagnostics have revealed milder cases of CF with unusual clinical presentations, such as recurrent pancreatitis, male infertility (bilateral agenesis of the vas deferens), liver cirrhosis, idiopathic bronchiectasis, allergic bronchopulmonary aspergillosis, difficult-to-control asthma, COPD, recurrent haemoptysis or primary infections with *Pseudomonas aeruginosa* [136].

In these patients, it is not clear whether CFTRm have an indication due to the lower potential for improvement and the significant economic burden it entails. Moreover, it is known that adherence to CFTRm and other targeted therapies substantially decreases as health improves [137, 138]. In these cases, adherence to CFTRm can be a significant challenge.

Additionally, with the introduction of new CFTRm, there has been a decrease in the number of lung transplants required, reaching historically low levels since registry data has been available [27]. CFTRm have contributed to improved lung function and slower disease progression. Since lung transplant is expected to be postponed for several years, these patients may have a higher burden of comorbidities with more post-transplant complications and much more complex management [139–142]. This could require the creation of new models of care to achieve optimal care for pwCF after transplantation [143]. To date, current guidelines for referring pwCF for lung transplantation do not take into account the use of CFTRm in determining the optimal time for referral, patient assessment and inclusion on the waiting list [144–147]. The use of CFTRm in transplant patients is currently controversial and pharmaceutical companies contraindicate their use in any solid-organ transplant due to their interaction with immunosuppressants and some antimicrobial prophylaxis [148, 149]. In some studies, the concomitant use of CFTRm and immunosuppressants required a reduction in the dose of immunosuppressant [150–155], while in others, no significant differences in immunosuppressant dose requirements were observed [156–158]. Despite the lack of guidelines [144], the use of CFTRm is increasingly in the hands of the healthcare professional [143, 159], making strict monitoring essential [160, 161]. Moreover, it is still unclear whether there is any clinical benefit in continuing these treatments after transplantation or if modulators play a role in preventing long-term organ rejection. In some cases, CFTRm have been shown to be beneficial in managing extrapulmonary comorbidities after lung transplantation, especially in nutritional, gastrointestinal, rhinosinusal and endocrine aspects [156, 157, 162, 163].

It is important to remember that CFTRm also aim to slow down or halt disease progression, but patients with advanced lung disease (forced expiratory volume in 1 s $\leqslant$40% pred) are not included in most CFTRm clinical trials [164]. Nevertheless, the limited data available so far suggest that CFTRm may delay the need for lung transplantation and improve the quality of life of these patients [21, 165–167].

In conclusion, these “special” populations have unique characteristics that would require specific studies to carefully evaluate the efficacy, safety and cost-effectiveness of CFTRm in order to ensure the appropriate and beneficial use of these drugs and to minimise side-effects [168].

Therapeutic gaps and challenges

Given the high cost of CFTRm, we face significant challenges regarding access to this treatment, often based on the different health coverage systems across countries [169, 170]. Additionally, part of the lack of access may be due to the limitations of CFTRm use for specific mutations [26]. The frequency of mutations varies by race and, for example, the Mediterranean region (Spain, Italy, Turkey and Israel) has the lowest prevalence of the *F508del* variant [27]. Therefore, there are far fewer patients eligible for ETI therapy in this region compared to the rest of Europe.

Furthermore, the approval of CFTRm by local drug regulatory agencies can vary significantly between countries [170].

Babies and children who could likely benefit from early initiation of CFTRm are still not eligible for some combinations in some regions. Unfortunately, it seems that postcode has a much greater influence on the health of pwCF than genetic code.

Additionally, there may be patients with tolerability issues or severe side-effects with CFTRm (hepatotoxicity, allergic reactions, gastrointestinal problems, *etc.*).

Based on what has been previously discussed, we are currently facing a scenario with three groups of pwCF that can be easily differentiated according to the availability or access to CFTRm treatment, namely pwCF without access to CF therapy, pwCF with delayed access and pwCF with early access (table 3). This diversity in treatment is shaping a landscape where the disease course may evolve differently between these groups in the near future.

In the not-too-distant future, it will be necessary to consider new treatments that allow for the coverage of 100% of pwCF. This could include the development of new CFTRm with improved mechanisms of action,

TABLE 3 Distribution of cystic fibrosis (CF) patients according to the availability or accessibility of CF transmembrane conductance regulator modulator (CFTRm) treatment

	Causes of no access to CFTRm	Causes of late access to CFTRm	Causes of early access to CFTRm
Regulatory and administrative	Lack of approval by the local regulatory agency Requires updating or revision of clinical guidelines Limitations or lack of insurance coverage	Long approval process in the country/region Delays in getting on reimbursement lists Lack of sufficient funding in the health system	Inclusion in early clinical trials Accelerated approval by regulatory agencies
Economic and financial	Cost prohibitive for the patient or the health system Budgetary constraints in the health system Need for price negotiations and agreements		Inclusion in early access programmes
Logistics and distribution	Lack of access to specialised CF centres or units Problems of distribution and access to medicines		Availability and access to specialised CF centres or units Responsiveness to initial demand
Eligibility criteria	Specific genotype not eligible Lack of evidence for other genotypes	Exclusion based on a specific genotype not initially approved Limited knowledge of efficacy in other genotypes	Availability for specific genotypes Genetic suitability for CFTRm response
Clinical and safety	Specific medical contraindications Patient intolerance to the drug	Limited knowledge of effectiveness or safety	Routine access to an experienced and fully equipped CF unit with known engagement in clinical trials

such as the combination of vanzacaftor/deutivacaftor/tezacaftor [171] or dirocaftor/posenacaftor/nesolicaftor, which have shown promising preliminary results [172, 173].

The personalised approach to treatment [174, 175], based on the individual characteristics of the patient such as specific mutations of the CFTR gene, disease severity and response to CFTRm, known as CFTRm theratyping, is currently a crucial strategy [176]. The main advantage of theratyping is the ability to group CFTR variants their effect on the CFTR protein, regardless of the mutation class, and their response to different CFTRm [177].

The use of intestinal organoids [178, 179] and nasospheroids [180] as complementary tools in this process allows us to evaluate the impact of CFTRm on those populations for which they have not yet been authorised. Additionally, this technique helps us identify patients who are likely to respond better to treatment, predict individual responses that could justify requests for compassionate use and explore combination drug strategies to maximise therapeutic benefits [181, 182].

The development of therapies targeting other aspects of the disease, such as inflammation and infection, is another key point. Phage therapy offers a promising adjunctive therapy for combating infections from multi-drug-resistant microorganisms, thus decreasing the chronic inflammatory state of these patients [183–186].

Ultimately, our goal should be to find a permanent cure for this disease and different clinical trials of gene therapy are already underway in this population, using both mRNA and DNA [187–189].

Clinical gaps and challenges

In addition to advancing treatment, it is crucial to address other unmet needs. The most evident aspect of CF today is the continuous change in many aspects of the disease. Most evident changes after CFTRm are improvements of the respiratory and digestive manifestations of the disease with increasing life expectancy. However, depending on disease severity and age at the time of HEMT initiation, clinical goals, challenges and expectation can be different. In fact, we assume that an earlier administration of HEMT can significantly reduce permanent organ damage at different levels. In the future, we can imagine starting some kind of CFTR modulating therapy at birth and to reduce quite consistently any clinical expression of the disease. Nevertheless, the majority of patients on HEMT today have a variable disease expression related to both genetics and a variable period of previous organ exposure to CFTR dysfunction. Additionally, despite the use of modulators, CFTR expression remains variable and far from being fully restored. The clinical implications of this are still unknown, including the room for improvement in this area.

We are currently beginning to describe a new ageing process in pwCF who have a variety of underlying mutations, treatments and comorbidities. This process will require constant and frequent reflection and updating of guidelines/clinical protocols. Moreover, the current emerging needs, such as recommendations to detect, monitor and manage emerging comorbidities, could change in few years from now. At present, there is particular concern regarding the risk of cardiovascular diseases and nongastrointestinal cancer due to increasing longevity and nutritional changes. In particular, there is urgent need to identify the modifiable risk factors for these conditions and develop specific monitoring and preventive protocols.

This constant need for observations also includes the need to monitor the long-term consequences of HEMT and other therapeutic interventions, such as gene therapy, including potential interactions with other commonly used drugs.

Socioeconomic implications of growing older with CF

Ageing with CF brings with it a number of significant economic challenges for both patients and healthcare systems.

As patients age, direct healthcare costs increase considerably due to the need for more intensive and specialised treatments to manage the chronic complications of the disease. These costs include frequent visits to specialists, recurrent hospitalisations, medical tests and the use of expensive medications, such as CFTRm and other specific treatments. Additionally, access to CFTRm is variable, which can affect the uniformity of treatment and outcomes among different patients and regions [27].

Beyond these conventional costs, people ageing with CF may face increased indirect costs. With increased life expectancy, a larger proportion of awCF may experience disease progression that could lead to a decline in the ability to work full-time, resulting in a significant loss of income and, in many cases, early retirement [190]. Physical limitations, such as reduced lung function, affect work capacity and may increase dependence on income support or disability pensions.

Published data indicate that awCF represent a higher socioeconomic burden compared to the paediatric population [191, 192]. This increased economic burden is due to the greater complexity and cost of managing long-term complications in adults.

However, with the introduction of more effective treatments, there are also fewer severe patients, which implies, for example, a reduced need for transplants and hospitalisations [193].

Moreover, this group of patients will face the physical and emotional challenges of ageing with a chronic disease. This may include difficulties in maintaining independence, managing disease-related emotional stress and adjusting to changes in quality of life. The psychological impact of ageing with CF should not be underestimated, as it can profoundly affect patients' overall well-being.

To effectively address the socioeconomic implications of ageing with CF, it is essential to implement comprehensive strategies. These strategies should include equitable access to care, providing adequate financial support, strengthening psychosocial support and promoting medical and scientific research. Ongoing research is crucial to develop new therapies and improve understanding of the mechanisms that contribute to ageing and associated complications in pwCF.

Conclusions

The evolution of CF since its initial description in 1938 has undergone significant changes, particularly after the introduction of CFTRm. While studies have demonstrated the effectiveness of CFTRm in various aspects, it is important to recognise that longer-term monitoring is needed to investigate any potential beneficial or side-effects. Moreover, the initiation of these drugs at an earlier stage of the disease is expected to reduce the systemic burden of systemic inflammation and its consequences on health. On the other hand, the prolonged life expectancy results in an increasing burden of age-related comorbidities within the context of a chronic disease. The balance between these factors is expected to further change in the future. The clinical manifestations of the comorbidities associated with CFTR dysfunction will also continue to change along with the disease dynamics and outcomes. Current protocols to screen, monitor and slow disease progression will need continuous revision, including the composition of the MDT for CF care, with a greater focus on the needs of the older adult population. Many uncertainties remain to be resolved, particularly in areas such as associated comorbidities, the impact of CFTRm on microbiology and their use in special populations.

Points for clinical practice

- Evaluating the effects of CFTRm beyond the pulmonary system. As a consequence of systemic expression of CFTR, the introduction of CFTRm is contributing to improving the general health of pwCF beyond the lungs. Numerous benefits are being described, including improved gastrointestinal absorption of nutrients, bone density and reduced systemic inflammation in areas such as the bowel, renal system and reproductive system.
- Comprehensive health management of pwCF (new MDT). Due to the constant changes in the clinical manifestations and outcomes of the disease after the introduction of CFTRm, current protocols to monitor and slow disease progression will require constant review, including the composition of the MDT for CF care, with a greater focus on the needs of an older population.
- Education and empowerment of pwCF. These are milestones in the management of the disease, particularly in the transition to a chronic disease and with the lifelong use of CFTRm. The landscape of the disease is evolving for both pwCF and healthcare professionals. It will require a progressive adaptation to current and future clinical developments of the disease and the adoption of new precautions for the ageing-related comorbidities that will start to play a more prominent role.
- Long-term care planning. Monitoring the evolving manifestations of the disease and the changing needs of patients is crucial in the context of both clinical care and research. A continuous review of the current protocols will be necessary to address the emerging needs and potential health issues of ageing pwCF.

Questions for future research

- To what extent will the introduction of CFTRm modify the different aspects of CF disease beyond the lungs?
- What are the long-term effects of CFTRm in pwCF?
- How should the current protocols be adapted to address the changing landscape of the disease in an ageing population?
- Do we need new screening and monitoring protocols for comorbidities directly or indirectly related to CFTR dysfunction?
- Will it be possible to optimise the functioning of existing CFTRm?
- What other CFTRm and therapies are in development for pwCF?

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