Cystic fibrosis

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Cystic fibrosis is a monogenic disease considered to affect at least 100 000 people worldwide. Mutations in *CFTR*, the gene encoding the epithelial ion channel that normally transports chloride and bicarbonate, lead to impaired mucus hydration and clearance. Classical cystic fibrosis is thus characterised by chronic pulmonary infection and inflammation, pancreatic exocrine insufficiency, male infertility, and might include several comorbidities such as cystic fibrosis-related diabetes or cystic fibrosis liver disease. This autosomal recessive disease is diagnosed in many regions following newborn screening, whereas in other regions, diagnosis is based on a group of recognised multiorgan clinical manifestations, raised sweat chloride concentrations, or *CFTR* mutations. Disease that is less easily diagnosed, and in some cases affecting only one organ, can be seen in the context of gene variants leading to residual protein function. Management strategies, including augmenting mucociliary clearance and aggressively treating infections, have gradually improved life expectancy for people with cystic fibrosis. However, restoration of CFTR function via new small molecule modulator drugs is transforming the disease for many patients. Clinical trial pipelines are actively exploring many other approaches, which will be increasingly needed as survival improves and as the population of adults with cystic fibrosis increases. Here, we present the current understanding of *CFTR* mutations, protein function, and disease pathophysiology, consider strengths and limitations of current management strategies, and look to the future of multidisciplinary care for those with cystic fibrosis.

Lancet 2021; 397: 2195–211

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Introduction

Cystic fibrosis is an autosomal recessive inherited disease affecting multiple body systems. Recorded observations of children with this disease from the 1940–50s focused on pancreatic damage leading to severe malabsorption, wasting, and childhood mortality.[1] Children were noted to be at risk of lung infections, although the pathogenic links between these disparate disease processes were unclear. A heatwave in 1948 in New York, NY, USA, which resulted in many children with cystic fibrosis developing severe hyponatraemic dehydration, led to the discovery of salt loss through sweat and the development of diagnostic testing via sweat sodium and chloride testing.[2] Since 1989, the discovery of the *CFTR* gene that causes cystic fibrosis has underpinned substantial increases in the understanding of pathophysiology.[3] Over time, cystic fibrosis has become a model for the harmonisation of research development and clinical advances, wherein scientific progress in pathophysiology and cellular biology has led to therapeutic advances directly linked with major improvements in patient care and survival. Such examples are nutritional supplementation including pancreatic enzyme supplementation,[1,4] airway clearance,[5] and long-term antimicrobial treatment for the suppression of airway infection.[6] The development of small molecules to improve CFTR protein function, termed CFTR modulators, has substantially benefitted people with cystic fibrosis. The resultant changing epidemiology of cystic fibrosis creates new challenges, which might require different approaches to health-care delivery.

Since the original discovery of the most common *CFTR* mutation, NM_000492.3:1521_1523delCTT(Phe508del), more than 2000 mutations in *CFTR* have been described, with clinical—ie, sweat chloride, lung function, pancreatic status, and *Pseudomonas aeruginosa* infection rates—information available on an increasing number of *CFTR* mutations, variants of varying clinical consequence, and cystic fibrosis-causing variants that are conclusively non-disease causing.

Pathogenic mutations in *CFTR* have conventionally been categorised into classes I–VI according to defects in the protein production process (figure 1).[7,8] Some classes are defective in more ways than one.[8] Disease severity in cystic fibrosis might be genetically influenced by mutation class, modifier genes,[9] and the presence of complex alleles (ie, two or more mutations on the same allele that interact to modify protein quantity or function).[10] For example, in Phe508del homozygotes, lung disease might vary widely,[11] and additional *CFTR* mutations in promoter, intronic, and exonic regions are associated with disease severity,[11] which might affect responsiveness to new CFTR modulators.[12]

Function and pathophysiological mechanisms of the CFTR protein

The CFTR protein transports chloride and bicarbonate across the apical surface of secretory epithelia, most notably the sweat gland, airway, gastrointestinal tract, pancreas, and vas deferens. In the lungs, CFTR-mediated chloride secretion and sodium absorption by the epithelial sodium channel regulate airway surface liquid hydration, which is essential for ciliary function and antimicrobial activity.[13] Defective CFTR dehydrates the airway surface resulting in thick mucopurulent

Search strategy and selection criteria

We searched PubMed, ClinicalTrials.gov, and Cochrane Library for research related to cystic fibrosis between 2000 and 2020. We also did a manual search and review of reference lists. We largely selected publications from the past 10 years, but also included original descriptions and highly regarded older publications. We only considered papers published in English.

For more on ***CFTR* mutations** see https://cftr2.org and http://www.genet.sickkids.on.ca

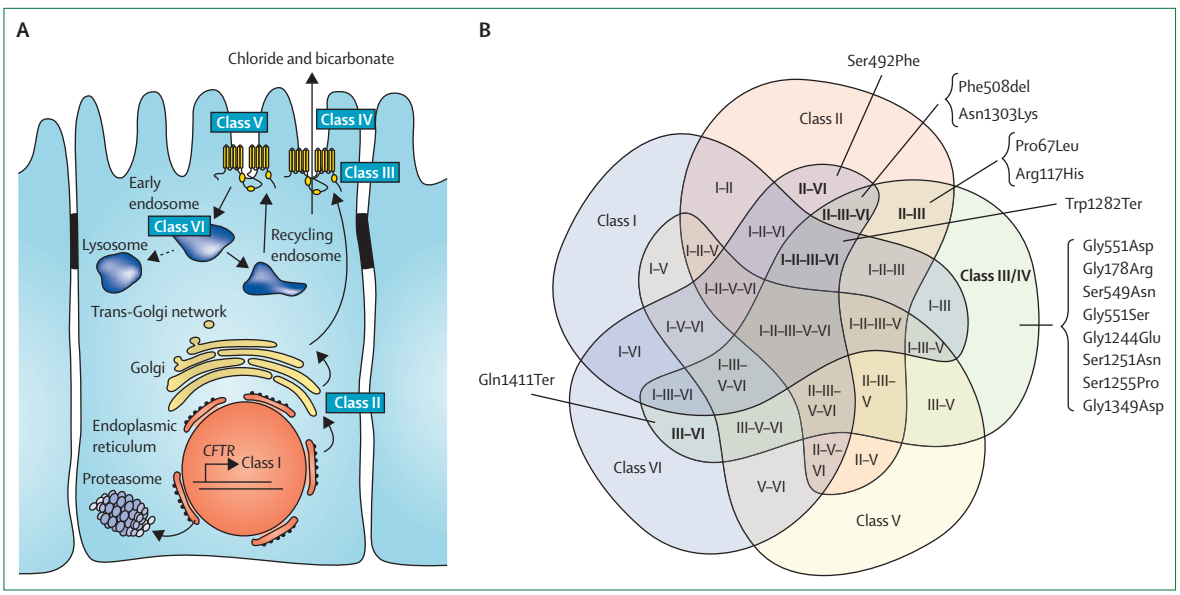

Figure 1*: Classes and effects on function of pathogenic mutations in *CFTR

(A) *CFTR* mutations have conventionally been classified according to their effect on CFTR protein expression and function: class I mutations result in the production of no full-length proteins, and many of these proteins are premature truncation codons leading to short, unstable mRNA and absence of full-length *CFTR*; class II mutations produce misfolded CFTR leading to failure of maturation and trafficking to the cell surface; class III mutations result in CFTR to be correctly located at the cell surface but failure in opening in response to chemical signalling (abnormal gating); class IV mutations decrease conductance through the ion pore; class V mutations reduce the amount of CFTR; Class VI mutations produce unstable CFTR with a short half-life; classes IV–VI retain some ability to transport ions, hence might be termed residual function mutations. (B) The limitations to the classification system are clearly illustrated by this diagram showing that, although some mutations fall clearly into one class, others lead to several functional defects—eg, the *CFTR* mutation, Phe508del, which is an archetypal misfolding (class II) mutation, leads to gating and stability problems. Reproduced from Veit and colleagues,[8] by permission of the American Society for Cell Biology.

secretions, impaired mucociliary clearance, chronic infection, inflammation, and progressive structural lung damage.[14] Dysfunctional CFTR also affects bicarbonate-dependent mechanisms, such as the unfolding and expanding of mucins affecting mucus viscosity, and regulation of airway surface liquid pH, with effects on antimicrobial peptide functions.[15–18] Airway surface acidification has been shown in human cystic fibrosis airway epithelial cells, the cystic fibrosis pig, exhaled human breath condensate, and the nasal pH of newborn babies with cystic fibrosis.[17,19,20] However, a bronchoscopic study with the use of pH-sensitive probes showed no pH differences in children with and without cystic fibrosis;[21] clinical relevance thus remains unclear.

CFTR-mediated chloride and bicarbonate secretion in pancreatic ducts alkalinises ductal fluid, neutralises peptic acid, and optimises pH for digestive enzyme function.[22] Pancreatic disease in people with cystic fibrosis begins in the uterus and is caused by ductal obstruction and epithelial damage. Pancreatic proteins build up behind the obstructed ducts leading to increased blood concentrations of these proteins, including trypsinogen, an immunoreactive test for which forms the basis of most newborn screening systems. Ongoing duct obstruction, inflammation, fibrosis, and fatty infiltration cause eventual pancreatic destruction.[23] In the gastrointestinal tract, defective bicarbonate secretion can result in intestinal mucus obstruction and meconium ileus.[24] Similarly, cystic fibrosis liver disease is characterised by hyperviscous biliary secretions, cholestasis, and eventual cirrhosis.[25]

Diagnosis of cystic fibrosis

Clinical diagnosis

Updates to diagnostic consensus guidelines were published in 2017 by the Cystic Fibrosis Foundation in collaboration with global partners.[26–29] In regions without newborn screening programmes, diagnostic criteria are suggestive clinical features (table 1; figure 2), or family history and evidence of CFTR dysfunction, or family history and detection of two disease-causing *CFTR* mutations.[28] The CFTR2 website is a useful resource providing evidence of disease liability. Genotypes of varying clinical consequence—eg, NM_000249.3:350G>A(Arg117His)—require a diagnostic sweat chloride or advanced electrophysiological testing for a firm cystic fibrosis diagnosis. Sweat testing,[30] done in an accredited clinical laboratory, remains the gold standard test of CFTR function: chloride concentrations of more than 60 mmol/L are diagnostic; concentrations between 30–59 mmol/L are in the intermediate range; and concentrations less than 30 mmol/L are considered normal.

Newborn screening

Several newborn screening strategies are in use, most of which use an initial biochemical screen (commonly

	Cystic fibrosis manifestations	CFTR-related disorders*	Multifactorial complications of cystic fibrosis†
Lungs	Recurrent or chronic bacterial and fungal infections, bronchiectasis, pneumothorax, haemoptysis, and respiratory failure	Bronchiectasis (non-cystic fibrosis)	Infection with multidrug resistant microorganisms
Upper airways	Chronic sinusitis and nasal polyps	Chronic sinusitis and nasal polyps	..
Ears	..	..	Hearing and vestibular impairment (aminoglycoside toxicity)
Pancreas	Pancreatic destruction with exocrine pancreatic insufficiency, and pancreatitis (common in pancreatic sufficient patients)	Recurrent pancreatitis	..
Liver	Neonatal jaundice, liver disease, fatty liver, cirrhosis, and biliary calculi	Primary sclerosing cholangitis	Drug-related liver disease (eg, antifungals and CFTR modulators)
Gut	Meconium ileus, distal intestinal obstruction syndrome, malnutrition, and dyslipidaemia	..	Obesity and gastrointestinal malignancy
Kidneys	Urinary tract calculi	..	Renal failure
Musculoskeletal	..	..	Osteoporosis, osteopenia, cystic fibrosis arthropathy, and muscular dysfunction
Male genitals	Congenital bilateral absence of the vas deferens, and azoospermia and infertility	Congenital bilateral absence of the vas deferens	..
Female genitals	Cervical mucus abnormality	..	Female subfertility and urinary incontinence
Endocrine	Cystic fibrosis-related diabetes	..	Abnormal reproductive hormone composition
Tab	..	..	Anxiety and depression
Sweat glands and skin	Hypochloremic metabolic alkalosis, dehydration, and aquagenic palmoplantar keratoderma	Aquagenic palmoplantar keratoderma	..
Others	..	..	Antimicrobial allergy, polypharmacy, and non-gastrointestinal tumours (eg, lymphomas)

*Single organ disease with evidence of CFTR dysfunction in the absence of a cystic fibrosis diagnosis. †Emerging manifestations of multifactorial causes include conditions prevalent in people with cystic fibrosis that might result from treatment and associated complications (eg, renal failure from cystic fibrosis-related diabetes and aminoglycoside use); some complications might fit into more than one category—for example, cystic fibrosis-related diabetes complicated by corticosteroid use.

Table 1: **Manifestations of cystic fibrosis, CFTR-related disorders, and emerging complications**

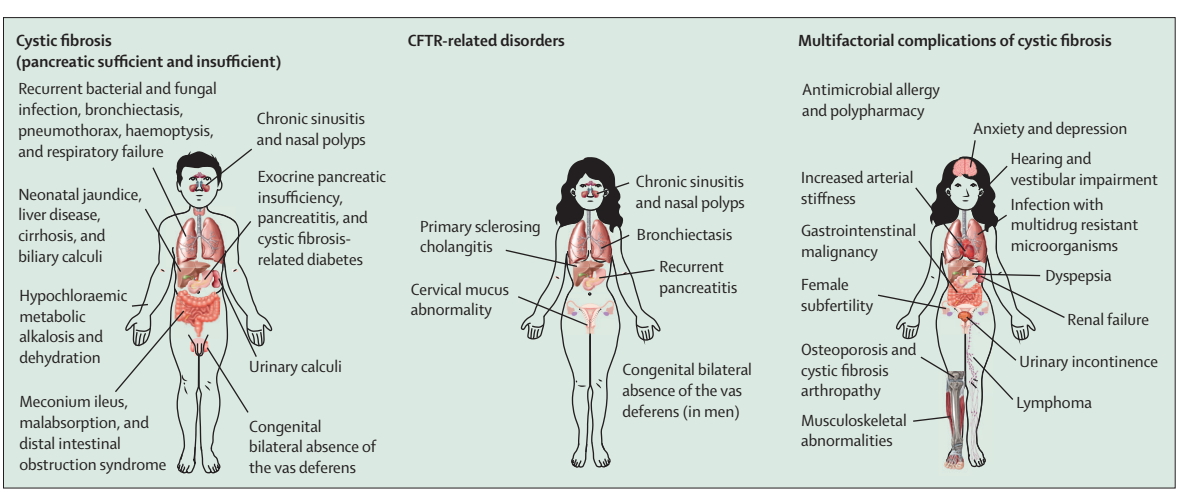

Figure 2: **Clinical manifestations of cystic fibrosis and cystic fibrosis-related disorders**
Single-organ disease (ie, cystic fibrosis-related disorders) with evidence of CFTR dysfunction in people who do not fulfil diagnostic criteria for cystic fibrosis is being increasingly recognised, and further complications, which are often multifactorial and relate to the burden of chronic disease, consequences of therapy, and the misunderstood consequences of CFTR deficiency (eg, gastrointenstinal malignancies; table 1), might emerge later in life for people with cystic fibrosis.

immunoreactive trypsinogen measurement from dried blood spot) followed by genetic testing or sweat chloride testing, or both.[31] The selection of *CFTR* mutations included in newborn screening panels is based on local population prevalence, in general, seeking to detect as many patients with cystic fibrosis as possible while trying to minimise false positives. Benefits of newborn screening for people with cystic fibrosis and their

families have been numerous, with positive effects to both physical (ie, nutrition and survival) and psychological health.[26] Future health benefits from highly effective CFTR modulator therapies might prove synergistic with newborn screening, as new animal uterine studies and postnatal therapy show disease attenuation.[32]

Cystic fibrosis screen-positive, inconclusive diagnosis or CFTR-related metabolic syndrome

Cystic fibrosis screen-positive, inconclusive diagnosis (the European term) and CFTR-related metabolic syndrome (the North America term) describe the same situation: a child with hypertrypsinaemia at newborn screening who does not fulfil the diagnostic criteria for cystic fibrosis and is apparently healthy.[29,33] The most common reason for this apparent paradox is the possession of one or more *CFTR* variants of varying clinical consequence. Babies with this syndrome will either have a sweat chloride concentration of less than 30 mmol/L and two *CFTR* variants (one or both variants being a varying clinical consequence), or a sweat chloride concentration of 30–59 mmol/L with zero or one *CFTR* mutations and zero or one varying clinical consequence. Updated consensus guidelines on this terminology, and management and follow-up of these infants, have been published.[34] Most children with this syndrome will not develop a biochemical or clinical picture of cystic fibrosis, but follow-up (at lesser frequency than people with cystic fibrosis) through adolescence and adulthood will yield a proportion with clinical disease if there is sufficient oversight to detect such issues in a timely fashion.

In contrast, CFTR-related disorders[35] are established end-organ clinical disorders associated with evidence of CFTR dysfunction without an individual fulfilling diagnostic cystic fibrosis criteria. The over-representation of CFTR heterozygosity in conditions, such as congenital bilateral absence of the vas deferens (present in most men with cystic fibrosis), recurrent pancreatitis, and airway disease (eg, bronchiectasis, allergic bronchopulmonary aspergillosis, or asthma), might point to the under-recognised contribution of CFTR dysfunction along with non-CFTR genetic, epigenetic, or environmental factors,[36] and remains an important area of study (table 1; figure 2).

Advanced tests of CFTR function

The passage of charged ions across cell surfaces leads to measurable electrical currents. Electrophysiological testing can thus measure CFTR function in the nose (on the basis of ease of access) or alternatively in the intestinal tract. Nasal potential difference and intestinal (rectal) current protocols each allow assessment of sodium and chloride transport, and have been standardised globally.[37] Ion transport in the gastrointestinal tract might also be tested by assessment of short-circuit current on rectal biopsy.[38] Techniques have been established to culture biopsy cells into spherical organoids, the induced swelling of which can be measured in real time to measure ion and water transport.[39] Such an approach has proved useful in complex diagnostic cases and assessment of response to CFTR modulators.[40] These tests are highly specialised and not widely available; therefore, patients are referred to specialised centres. Patients with CFTR-related disorders will frequently have intermediate values indicating a degree of CFTR dysfunction.

Manifestations of disease and conventional therapies

Lung disease: monitoring and assessment

Chronic upper (ie, rhinosinusitis and nasal polyps) and lower (ie, muco-obstructive, neutrophilic inflammation, and chronic infection) respiratory tract disease are hallmarks of cystic fibrosis.[41,42] Structural lung disease can be seen in infancy,[43] although this disease might become less frequent with newborn screening.[44] Findings from one single cohort study showed the presence of bronchiectasis in approximately 33% of preschool-aged children,[45] with many studies replicating these estimates.[46] The classic vicious cycle of infection and inflammation is then soon established, with uncertainty around which presents first. Studies in systems ranging from CFTR knockout ferrets[47] to bronchoalveolar lavage and CT imaging[48] support the concept that hypoxia, dysregulated mucus, and neutrophilic inflammation can precede infection. However, chronic airway infection also develops in early life, with pathogens, such as meticillin-sensitive *Staphylococcus aureus*, yielding to a higher prevalence of microbes, such as *P aeruginosa*, which is present in most adults.[49] Fungal (most commonly *Aspergillus fumigatus*) and mycobacterial infections are increasing in prevalence.[50] Infection and inflammation are contributors in recurring acute pulmonary exacerbations,[51] which lead to progressive loss of lung function; advanced, end-stage bronchiectasis and respiratory failure develop over time.

For many decades, spirometry has been the mainstay of lung function monitoring. A forced expiratory manoeuvre allows measurement of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (total volume of air exhaled). Global quality guidelines are available for performance and interpretation.[52] Volumes require normalising for age, size, and sex of the patient, with reference values being harmonised globally.[53] FEV_1 is lost gradually over the lifetime of a person with cystic fibrosis. This loss is a combination of gradual, chronic decline and the acute effects of intermittent pulmonary exacerbations from which, in some cases, lung function is never regained.[54] FEV_1 is a familiar concept, guiding decisions on day-to-day management, assessment of treatment response, and referral for lung transplantation. However, FEV_1 has its limitations: cooperation is required from patients and some (particularly young children) find it difficult to perform reliably; measurements from very young children cannot be taken outside of specialist laboratories; and the test is insensitive to early stage

disease, with signals being dominated by the large airways rather than peripheral small airways in which cystic fibrosis disease begins. For these reasons, incorporation of sensitive methods, such as lung clearance index measured by multibreath washout techniques, is being considered. The test requires specialised equipment and trained staff adhering to standardised protocols,[55] and is also more time consuming than spirometry. Despite these limitations, FEV_1 is being used increasingly in clinical contexts[56,57] and is proving valuable as a clinical trial outcome measure.[58,59]

Imaging has long been a key component of cystic fibrosis lung disease monitoring, and as population health has improved over the last few decades, the use of plain chest x-rays has decreased, giving way to newer imaging modalities. Chest x-rays remain useful, for example, in the identification of lobar collapse (which could require intensification of treatments or bronchoscopy), detection of pneumonias, and detection of specific features of allergic bronchopulmonary aspergillosis (eg, characteristic wedge-shaped consolidation). CT scans are more sensitive than chest x-rays in revealing mucus plugging, airway wall thickening, and gas trapping indicative of distal small airways disease.[60] CT scans are sensitive to early disease but cannot be employed frequently because, even with the most modern scanners, there is a radiation burden. Novel techniques based on MRI with or without hyperpolarised gases are being increasingly explored, predominantly as research tools.[61]

Precise and timely pathogen identification is essential for targeted treatment. Current practice for pathogen detection involves respiratory sampling at hospital visits and during pulmonary exacerbations, with expectorated sputum culture established as the standard of care. Less sensitive oropharyngeal swabs are used in non-expectorating patients[62] when sputum induction does not work, and bronchoalveolar lavage might be used to identify treatable pathogens if needed (albeit neither technique is frequently repeatable).[62,63] In addition to culture-based methods, advanced molecular techniques with 16S ribosomal RNA sequencing have increased characterisation of bacterial diversity.[64] However, detection of previously unrecognised microbes in the cystic fibrosis lung yields crucial challenges in determining pathogenic relevance in an evolving cystic fibrosis microbial landscape.

Lung disease: management

Person-to-person transmission of cystic fibrosis-related pathogens present in people with cystic fibrosis associated with adverse health outcomes has been widely shown in people with cystic fibrosis.[65] There is evidence of severe outcomes in patients with transmissible strains of *P aeruginosa*,[66,67] *Burkholderia* species, meticillin-resistant *S aureus*, and non-tuberculous mycobacteria.[68] Measures to prevent pathogen transmission among people with cystic fibrosis (which might occur during encounters outside health-care settings and at cystic fibrosis clinics and hospitals[67]) have been recommended in international guidelines:[69–71] individual segregation of all people with cystic fibrosis; hand hygiene and protective equipment; and cleaning of medical devices, such as nebulisers. Although widely adopted by cystic fibrosis centres globally, infection control measures are mostly on the basis of low quality evidence, most of which are retrospective assessments of infection rates of pathogens before and after adopting an infection control strategy[72] for people with cystic fibrosis. However, it might be that these infection control measures contributed to the relative sparing of people with cystic fibrosis during the 2020 coronavirus pandemic.[73]

Conventional and future antimicrobial approaches are outlined in table 2;[74–91] currently, respiratory pathogens are targeted through prophylaxis (most commonly for *S aureus*), eradication of early infection thereby delaying or preventing chronic infection, long-term suppressive antimicrobial treatment with oral or inhaled antimicrobials to prevent progression of exacerbations and lung damage, and treatment of acute exacerbations. *S aureus* prophylaxis is recommended for the first 3 years of life in the UK, and

	Properties and clinical improvement	Development phase
Inhaled antibiotics		
Tobramycin (nebuliser or dry powder inhaler); colistimethate (nebuliser or dry powder inhaler); aztreonam	*Pseudomonas aeruginosa* eradication[74] and treatment;[75] *P aeruginosa* treatment;[75] *P aeruginosa* treatment[76] and FEV_1 improvements[77]	All available
Levofloxacin	*P aeruginosa* treatment; FEV_1 improvements[78]	Available
Amikacin	Additive therapy for *Mycobacterium avium* complex[79]	Available in the USA for refractory *Mycobacterium avium* complex disease
Vancomycin	Reduction in meticillin-resistant *Staphylococcus aureus* density *vs* placebo in phase 2 trials[80]	Phase 3 trial in children (older than 6 years) and adults (NCT03181932)
Non-antibiotic		
Inhaled nitric oxide	Targets *P aeruginosa* biofilm[81]	Phase 2 trial in adults (NCT02498535)
Inhaled gallium	Targets *P aeruginosa* biofilm and quorum sensing inhibition[82]	Phase 1 trial in adults (NCT03669614)
Inhaled OligoG (alginate oligosaccharide)	Targets *P aeruginosa* biofilm;[83] alters mucus properties;[84] potentiates antibiotic function[85]	Phase 2 trial in adults (NCT02157922)
Bacteriophage	Reduce bacterial load of *P aeruginosa* and airway inflammation[86,87]	Preclinical and case reports
Cysteamine	Mucolytic properties;[88] targets *P aeruginosa* biofilm;[88] enhances antibiotic activity;[88] improves CFTR function;[89] restores macrophage clearance of *P aeruginosa*[90]	Phase 2b trial in adults (NCT03000348)
IgY (antipseudomonal antibody)	Potential for reducing *P aeruginosa* in oropharynx and reduced infection[91]	Phase 3 trial in adults (NCT01455675)
Inhaled molgramostim (GM-CSF)	Targets infections caused by non-tuberculous mycobacteria	Phase 2 trial in adults (NCT03597347)

FEV_1=forced expiratory volume in 1 second.

Table 2: **Current and future anti-infective therapies for cystic fibrosis**

	Properties	Administration	Clinical effect
Dornase alfa	Recombinant human deoxyribonuclease; breaks down polymerised DNA produced by degrading neutrophils	No specific timing with airway clearance; no differences with daily, twice daily, or alternate day regimens	FEV_1 improvement; reduced pulmonary exacerbations; little evidence in less than 6 years
Hypertonic saline (3% or 7%)	Osmotic agent; airway surface liquid hydration	Before or during airway clearance; tolerability testing required for bronchospasm; bronchodilator pretreatment recommended	No change or improvement in FEV_1; reduced pulmonary exacerbations; symptom resolution; quality of life improvement; $FEV_{0·5}$ and $LCI_{2·5}$ improvement
Mannitol	Osmotic agent; airway surface liquid hydration	Available in dry powder; before or during airway clearance techniques; tolerability testing needed for bronchospasm	FEV_1 improvement; reduced pulmonary exacerbations; low efficacy in children

FEV_1=forced expiratory volume in 1 seconds. $FEV_{0·5}$=forced expiratory volume in 0·5 seconds. LCI=lung clearance index.

Table 3: **Licensed mucoactive agents[71,110] as adjuncts to airway clearance**

clinical benefits remain controversial. Due to concerns over links to increased risk of *P aeruginosa* infection,[71] a UK-led trial[92] is randomising infants to long-term anti-staphylococcal prophylaxis or culture-guided treatment to identify associated risks of *P aeruginosa* infection development. Global standards of care include eradication of early *P aeruginosa*, a common bacterium that chronically infects the lungs of people with cystic fibrosis and is associated with adverse outcomes. There is little evidence to distinguish between current antibiotic strategies, which are delivered by inhaled, oral, or intravenous (most commonly an aminoglycoside with a β-lactam) routes.[74]

Pulmonary exacerbations, which are poorly understood flares of symptoms (eg, cough, increased sputum production or change in colour, shortness of breath, fatigue, anorexia, and fevers) accompanied by a drop in lung function, are treated with either oral or intravenous antibiotics.[51,93] Specific drugs are tailored to the individual's pathogens, although in-vitro sensitivity testing shows little relationship to clinical outcomes.[94] Best practice, including the optimal duration of therapy, is the focus of a large research programme (Standardized Treatment of Pulmonary Exacerbations study).[95]

Once *P aeruginosa* infection is chronic, the emphasis shifts to long-term suppression with inhaled antibiotics; several drugs have been approved and dry-powder formulations have, in some cases, reduced the burden-some need for nebulised therapy.[75] Inhaled tobramycin has shown the greatest effect for *P aeruginosa* infection; a cycling approach is adopted to reduce antibiotic resistance; trials were done in a month-on and month-off basis, although many clinical teams now adopt an alternating approach with two (or more) agents. Azithromycin is not bactericidal against *P aeruginosa* but has immunomodulatory and anti-inflammatory properties,[96] and might interfere with biofilm formation.[97] Chronic administration of azithromycin in adults reduced pulmonary exacerbations and lung function decline, and improved quality of life.[98–100] A multicentre randomised trial in children older than 6 months showed reduced pulmonary exacerbations and increased weight gain with azithromycin treatment but did not show added benefit with inhaled tobramycin.[101]

With rising prevalence of non-tuberculous mycobacteria and associated clinical challenges, guidelines have been developed for diagnosis, monitoring, and treatment.[102] Treatment regimens are intensive, particularly for *Mycobacterium abscessus*, and patients should be counselled for side-effects, potential drug allergy, intolerance, and toxicity.[102,103] Drug-to-drug interactions need consideration, including reduction of ivacaftor efficacy with rifamycins.[103] Chronic azithromycin treatment should be withheld while evaluating suspicion of pulmonary disease caused by non-tuberculous mycobacteria to minimise the risk of macrolide resistance.[102] Evidence for antifungal use in Aspergillus bronchitis and allergic bronchopulmonary aspergillosis is inadequate due to the low number clinical trials.[104] Treatment for this condition generally involves administration of systemic corticosteroids, and might include antifungal therapy.[105] Biological treatment with anti-IgE antibody has little evidence of efficacy;[106] and therapy based on anti-IL-5 might be a potential therapeutic strategy.

Recommendation guidelines for regular airway clearance and physiotherapy are available and are introduced early at diagnosis under the guidance of specialist physiotherapists.[71] Techniques, which can be individually tailored to the patient, evolve as the child matures. These techniques include active cycle of breathing, autogenic drainage, positive expiratory pressure, oscillatory devices, intermittent positive pressure breathing. and non-invasive ventilation.[107] A 2019 Cochrane review concluded a significant reduction in pulmonary exacerbations with a positive expiratory pressure and mask versus high frequency chest wall oscillation.[108] However, comparing techniques is challenged by the apparently low sensitivity of outcome measures, an area requiring further research.

Mucoactive drugs improve airway clearance, with mucus hydrators (ie, hypertonic saline and mannitol) acting via osmotic principles and mucolytics (ie, dornase alfa) breaking tenacious bonds. Current guidelines support the use of dornase alfa and hypertonic saline, with mannitol available as an alternative agent (table 3).[71,109,110] The absence of high quality data comparing these agents limits evidence to suggest treatment superiority. Selection should be pragmatic, determined by tolerability, adherence, response, and, cost (in some regions).

Lung transplantation has been a viable option for people with advanced cystic fibrosis lung disease[111] since the 1980s, with evidence showing that people with cystic fibrosis have better median survival rates than those with other lung diseases.[112] During 1995–2018, cystic fibrosis was the cause of approximately 15% of all lung transplantations and was the third most common diagnosis.

Referral is generally recommended in the setting of advanced disease with rapid lung function decline, rapid weight loss, refractory pneumothorax, or massive haemoptysis.[113] The transplantation process requires comprehensive evaluation of key considerations and centre-specific assessment criteria. Some consider chronic infections with pathogens (eg, *Burkholderia cenocepacia* or *M abscessus*) absolute contraindications. However, an analysis of more than 3000 lung transplant recipients with such pathogens showed no significant association with a 90-day or 1-year mortality.[114] Cystic fibrosis-related comorbidities (ie, gastro-oesophageal reflux disease, cystic fibrosis-related diabetes, bone disease [particularly with systemic glucocorticoid treatment], and kidney disease) affect outcomes and require optimisation. Malnutrition has been associated with reduced median post-transplantation survival and is a contraindication in some centres.[115] Pretransplantation evaluation of mental health is essential due to the issues faced by people with cystic fibrosis and the substantial additional psychosocial demands of the transplantation process.[111] Early referral for lung transplant evaluation is increasingly recommended to allow people with cystic fibrosis the opportunity to cultivate strong relationships with the medical teams, and to optimise such medical or social issues.[116]

Pancreatic exocrine disease and nutrition

Approximately 85% of babies born with cystic fibrosis have pancreatic insufficiency, typically those with severe *CFTR* mutations in classes I–IV and VI. Around 3% of newborn babies with severe mutations can be pancreatic sufficient, with transition to insufficiency over time.[23] People with milder mutations in classes IV and V are likely to be pancreatic sufficient but have an increased prevalence of pancreatitis.[117] Faecal elastase is used as a marker for pancreatic exocrine function (<200 µg/g of stool in insufficiency) and to guide treatment. Patients with pancreatic insufficiency require lifelong pancreatic enzyme replacement therapy and fat-soluble vitamin (A, D, E, and K) supplementation.[23] Current pancreatic enzyme replacement therapy preparations are porcine-derived capsules prescribed according to oral intake and lipase requirements. Alternative liquid preparations might be more practical for younger children and patients with nasogastric or gastrostomy feeds, although trial data on this are scarce.[118] Novel non-porcine therapies, including liprotamase, have shown benefit in phase 3 trials and are awaiting approval.[119] Partial restoration of pancreatic exocrine function has been seen with CFTR modulators in young children and alternative non-CFTR channels involved in ductal bicarbonate secretion might also play a role in future therapy.

Close monitoring of weight, nutrition (eg, serum vitamin levels), metabolic demands, and respiratory function by specialised dietitians is essential. Malnutrition is associated with impaired lung function, increased risk of pulmonary exacerbations, hospitalisations, and mortality.[120] To prevent these consequences, current guidelines recommend maintaining a body-mass index (BMI) of 22 kg/m² for women, 23 kg/m² for men, and Z scores above the 50th percentile for children.[121] Although being simple and accessible, these measurements might underestimate sarcopenia (low muscle mass): in a systematic review of four studies that assessed body composition by methods, including dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or MRI, 21 of 45 patients who had fat-free mass depletion had BMI values above the cutoffs for malnutrition.[122]

International guidelines recommend a daily energy intake of 110–200% of the recommended daily allowance (at least 35–40% from fat) and supplementation of fat-soluble vitamins and minerals.[121] However, inadequate intake of nutrients is common in people with cystic fibrosis[123] and a substantial proportion of people with cystic fibrosis are underweight.[124] Severely malnourished patients might benefit from enteral feeding by nasogastric tube or gastrostomy, with evidence for positive effects on BMI, lung function, and hospitalisation frequency.[125] Conversely, obesity in people with cystic fibrosis is increasing in prevalence and is also associated with a decrease in lung function;[126] and might become a more prevalent problem once effective CFTR modulators are in widespread use.

Intestinal disease

Intestinal disease such as meconium ileus can be simple or complex; the simple form involves small bowel dilatation proximal to the obstruction, and the complex form results in complications including volvulus, necrosis, atresia, or perforation (which requires surgery). Simple meconium ileus can be managed conservatively via disimpaction with the use of hyperosmolar enemas including gastrografin or acetylcysteine, or surgery if conservative approaches are unsuccessful.[24] Distal intestinal obstruction syndrome occurs after the newborn period and affects 15% of people with cystic fibrosis and 44–50% of those with a history of meconium ileus.[127] Accumulation of viscous material within the bowel lumen of the terminal ileum and caecum causes complete or incomplete obstruction. Like meconium ileus, distal intestinal obstruction syndrome is more prevalent in class I, II, and III mutations than in people with one or more residual function mutations. Other risk factors are pancreatic insufficiency, dehydration, fat malabsorption, previous distal intestinal obstruction syndrome, cystic fibrosis-related diabetes, and organ transplantation.[127] Differential diagnoses include appendicitis, volvulus, intussusception, adhesions, and malignancy. Current management of distal intestinal obstruction syndrome involves oral rehydration and osmotic laxatives containing polyethylene glycol, oral gastrografin, or acetylcysteine.

Intravenous rehydration, nasogastric aspiration, and gastrografin are used in patients that have vomited or when oral treatment has not worked; close monitoring for substantial fluid shifts, shock, and intestinal perforation is required. Other common gastrointestinal manifestations include gastro-oesophageal reflux disease and small bowel bacterial overgrowth.[128] Despite small studies suggesting a beneficial effect of probiotics in people with cystic fibrosis, a randomised controlled trial was not successful in showing the positive effects of probiotics on BMI, lung function, abdominal pain, or exacerbations.[129]

Cystic fibrosis liver disease

Cystic fibrosis liver disease is the third leading cause of death in people with cystic fibrosis[25,130] with two general phenotypes: (1) focal biliary cirrhosis beginning early in life in a few patients and yielding to multilobular cirrhosis, or (2) obliterative portal venopathy occurring in adulthood and gradually evolving over time. Early studies reported 5–10% rates of cirrhosis during the first decade of life;[131] and prevalence rates of 20–40%, with a rise in adult cases, have been reported.[25] An international study of severe cystic fibrosis liver disease (cirrhosis and portal hypertension) reported prevalence rates of 3–5%; diagnosis was made at a median age of 10 years (with boys being diagnosed earlier) with 94% of diagnoses at younger than 20 years.[130] In contrast, analysis of cystic fibrosis liver disease cases from the UK Cystic Fibrosis Registry reported prevalence of cystic fibrosis liver disease increasing from 203 to 228·3 per 1000 people over a 5-year period. Median age of cirrhosis was at age 19 years and several factors suggested a higher risk in people with severe cystic fibrosis.[25] In contrast, a study of 179 people with severe cystic fibrosis liver disease showed no difference in lung function decline compared with other people with cystic fibrosis of the same age, sex, and height.[132] Diagnostic modalities are improving, which might contribute to apparent rising cystic fibrosis liver disease prevalence in adulthood. A US National Institutes of Health study reported that 47% of people with cystic fibrosis had cystic fibrosis liver disease on the basis of the new diagnostic criteria, compared with 22% of the same population assessed on the basis of the previous criteria.[131] Future risk-stratification algorithms might incorporate non-*CFTR* genes (eg, *SERPINA1*) as modifiers.[133] Treatment options are scarce; ursodeoxycholic acid remains the mainstay of therapy despite meta-analysis evidence showing low efficacy.[134]

Cystic fibrosis-related diabetes

Cystic fibrosis-related diabetes is a common complication of cystic fibrosis affecting approximately 35% of adults.[135] In a European Cystic Fibrosis Patient Registry study, prevalence increased by approximately 10% with every decade after age 10 years.[135] Cystic fibrosis-related diabetes bears features of both type 1 and type 2 diabetes, with loss of islet cells and varying degrees of insulin resistance leading to impaired glucose tolerance.[136,137] Cystic fibrosis-related diabetes screening, which consists of a 2 h oral glucose tolerance test, is recommended in all people with cystic fibrosis beginning at age 10 years;[71,135,137] haemoglobin A1C is not recommended for screening as it might be spuriously low in cystic fibrosis-related diabetes. Diagnosis of this disease during clinical stability follows standard criteria, including 2 h oral glucose tolerance test values of more than or equal to 11·1 mmol/L (200 mg/dL), fasting plasma glucose concentrations of more than or equal to 7·0 mmol/L (126 mg/dl), haemoglobin A1C rates of more than or equal to 6·5%, or random glucose concentrations more than or equal to 11·1 mmol/L (200 mg/dl).[137,138] Once cystic fibrosis-related diabetes develops, there are numerous aspects of care to consider: psychosocial support, blood glucose monitoring, blood pressure monitoring, and monitoring of microvascular complications. At present, insulin remains the only guideline recommended treatment for cystic fibrosis-related diabetes, with oral hypoglycaemics recommended only in clinical trials.[71,135,137,138]

Other physical complications

Adults with cystic fibrosis have a reduction in bone mass compared with healthy people when matched by age, sex, and BMI,[139,140] and is contributed to by low vitamins D and K,[141] poor nutrition, physical inactivity, and glucocorticoid treatment. Low bone mass is correlated with severity of lung disease and was present in 50% of people with cystic fibrosis who were on the transplant waiting lists.[142] The European Cystic Fibrosis Society best practice guidelines[71] recommend periodically screening people with cystic fibrosis from age 8–10 years with dual-energy X-ray absorptiometry scans. Treatment recommendations are similar to other causes of reduced bone mass.

Autoantibodies, including anti-*Saccharomyces cerevisiae*, antineutrophil cytoplasmic antibodies, and less commonly anticitrullinated peptide, have been identified in up to 78% of people with cystic fibrosis.[143] Most people do not have clinical manifestations of autoimmune disease. Antineutrophil cytoplasmic antibodies against neutrophil-derived basic permeability-increasing protein are present in 20–80% of people with cystic fibrosis, and are associated with *P aeruginosa* infection and increased severity of lung disease.[144] *P aeruginosa* is hypothesised to induce cleavage of permeability-increasing protein, creating cryptic epitopes that induce formation of autoantibodies and trigger inflammation.[145,146]

Other manifestations of inflammation are cystic fibrosis arthropathy (in up to 29% of adults[147]) and vasculitis. Arthropathy, of multiple large and small joints, is common with age and in women, and correlates with the presence of autoantibodies, frequency of pulmonary exacerbations, and elevated IgG concentrations. Treatment is usually with non-steroidal anti-inflammatory drugs and corticosteroids. Cutaneous vasculitis is not

frequent in cystic fibrosis but has been described in patients chronically infected with *Burkholderia cepacia* complex organisms.[148]

There is increasing evidence of endothelial dysfunction in children and adults with cystic fibrosis, with and without conventional risk factors such as diabetes.[149,150] These changes might be responsive to antioxidants[151] or the phosphodiesterase type 4 inhibitor, sildenafil.[152]

Mental health, psychosocial, and social support

With cystic fibrosis being a chronic, life-shortening disease with complex and time-consuming management requirements, depression and anxiety are relatively common (prevalence of 10–19% *vs* 22–32%[153]) among people with cystic fibrosis. Both mental health issues are associated with older age, women, a worse health status, and reduced adherence to treatment.[153,154] The European Cystic Fibrosis Society and the Cystic Fibrosis Foundation international committee on mental health developed recommendations for prevention, screening, and treatment of people with cystic fibrosis and their caregivers for anxiety and depression. Briefly, these recommendations focus on identifying a health setting dedicated to treating mental health issues, annual screening for anxiety and depression by questionnaires, and stepwise management of these conditions, including pharmacotherapy in severe or resistant cases.[155] Recommended screening tools are simple and quick but might miss substantial psychopathology.[156]

The importance of administering palliative care to people in advanced stages of cystic fibrosis is increasingly acknowledged. Advanced care planning includes palliative care focused on the relief of symptoms while maintaining usual care, and planning ahead for death.[157] In one study, only a few people with cystic fibrosis had received advanced care planning before their final hospitalisation, despite people with cystic fibrosis and their caregivers reporting a willingness to receive care.[158] Implementation of an advanced care planning programme was associated with relief of anxiety and depression scores among 47 people with cystic fibrosis, although only half of them had severe disease.[159]

Newer therapies and clinical trials pipelines

CFTR modulators

Until the group of small molecule drugs, now termed CFTR modulators, were developed, all available therapies targeted symptoms and downstream consequences of CFTR dysfunction rather than the root cause itself. The goal of treating disease by restoring CFTR activity was considered to be game-changing, but was challenging in the early stages. Two main groups of molecules have been developed: potentiators that improve the function of CFTR at the cell surface, and correctors that aid trafficking of CFTR to the cell surface. In 2020, amplifiers, which increase the amount of CFTR mRNA (and thus protein) within the cell,[160] entered clinical trials. As the CFTR produced from amplifiers remains in a mutated form, such agents will be used in conjunction with correctors and potentiators.

Ivacaftor was the first CFTR modulator to enter the clinic and has now been licensed as an oral preparation for several years. As a potentiator, ivacaftor is used as a monotherapy for mutations with cell surface protein. These mutations could be gating (failing to open) mutations, conductance mutations, or mutations resulting in low concentrations of CFTR. Pivotal trials in gating mutation groups—most commonly NM_000249.3:1652G>A(Gly551Asp)—have shown a substantial increase in FEV_1 (by approximately 10%), fewer exacerbations, improved weight gain, and improved quality of life scores.[161] There was a drop in sweat chloride of approximately 50 mmol/L, which serves as a useful biomarker on a group basis, but did not correlate with lung function changes within individuals. Young children have shown restoration of pancreatic exocrine function,[162] confirming for the first time that pancreatic disease is not completely irreversible. Longer term registry data are available showing that clinical benefit is durable and loss of lung function is slowed, which results in a reduced need for lung transplantation and mortality.[163]

Phe508del, a globally common *CFTR* mutation, requires a different approach. Attempts were made to aid trafficking of this misfolded mutation with the first corrector, lumacaftor. As a single agent, this agent was inadequate for clinical efficacy,[164] but when CFTR function was further boosted with ivacaftor, statistically significant improvements were seen in FEV_1 (of approximately 3–4%) in Phe508del homozygous patients.[165] The effect on exacerbation frequency and the longer-term effect on FEV_1 rate of decline were impressive.[166] Limitations of this combination, which has since been licenced and is marketed as Orkambi (Vertex Pharmaceuticals, Boston, MA, USA), include several drug-to-drug interactions and chest-related side-effects in a number of patients. In trials, the second dual combination of tezacaftor and ivacaftor showed similar levels of efficacy without the same limitations;[167,168] this combination is now licenced and marketed as Symkevi or Symdeko (Vertex Pharmaceuticals, Boston, MA, USA) for both Phe508del homozygous patients and those with several residual function mutations.

The development of triple modulator combinations has been a large step forward. The combination of two correctors with different mechanisms of action and ivacaftor has shown to restore Phe508del CFTR function to very high levels, both in the laboratory and in clinical trials, and has had a clinically significant effect on Phe508del homozygotes[169] and on a single copy of Phe508del in combination with a non-modulable mutation (eg, a premature stop mutation).[170] Marketing approval was rapid in the USA, where the drug is approved for all patients with one or two copies of Phe508del (85–90% of the currently characterised

global population). The drug is being assessed by the European Marketing Authority. The positive results from the development of these agents have encouraged competitive research and development activity in this field. Drugs and combinations of drugs are progressing through mid-stage trials done by several companies (figure 3).[171]

Read-through agents

Premature stop mutations, possessed by approximately 10% of the global cystic fibrosis population, lead to truncated unstable mRNA and a lack of full-length CFTR proteins. These mutations are thus not amenable to current CFTR modulator therapies. Read-through agents are molecules with ribosomal binding that allow full-length protein translation.[172] Ataluren was the first of these agents in late phase clinical trials but did not produce effective results.[173] Academic and commercial programmes are currently developing new agents. Several studies have researched the development of chemically modified aminoglycosides to provide higher activity and less toxicity than aminoglycoside antibiotics in clinical use.[174–176]

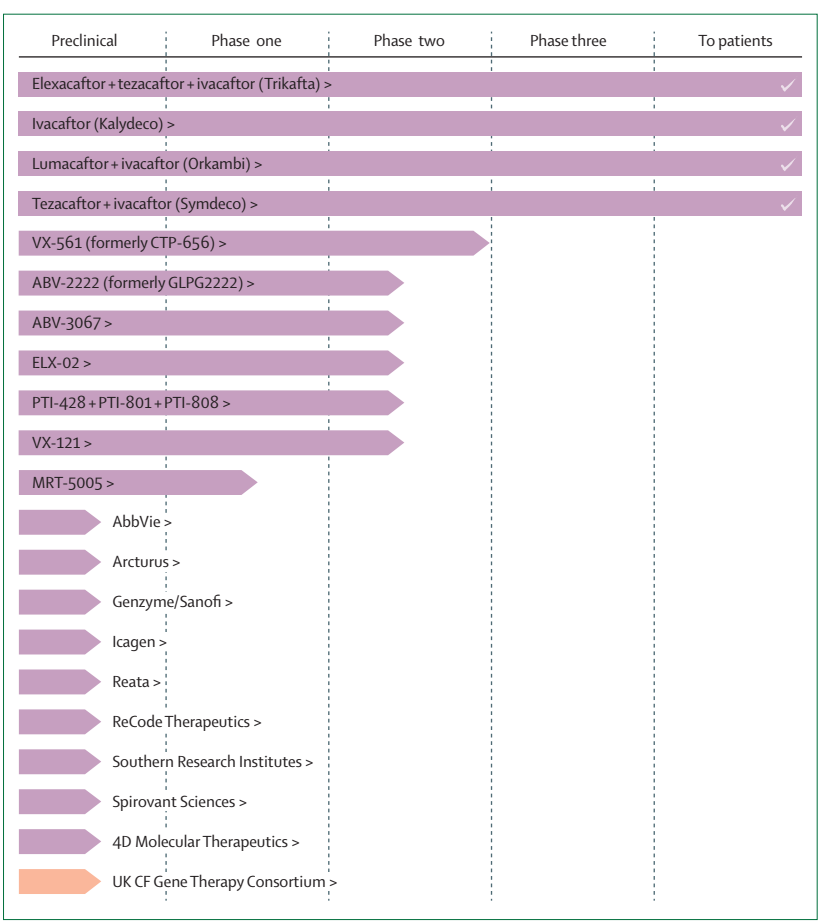

***Figure 3*: Strategies to restore CFTR function**

The Cystic Fibrosis Foundation clinical trials pipeline[171] illustrates the wide range of approaches to restore CFTR function with: CFTR modulators, potentiators, and correctors (from Vertex Pharmaceuticals [ivacaftor, lumacaftor, tezacaftor, elexacaftor, VX-561, VX-121], AbbVie [ABBV], Proteostasis Therapeutics [PTI], Sanofi Genzyme, and Reata Pharmaceuticals); CFTR mRNA amplifiers (proteostasis); agents for premature stop mutations (from Eloxx Pharmaceuticals [ELX-02], Icagen, ReCode, and Southern Research Institutes); mRNA replacement (Translate Bio, MRT-5005; Arcturus Therapeutics); and *CFTR* gene delivery (Spirovant Sciences, 4D Pharma), which the UK Cystic Fibrosis Gene Therapy Consortium is engaged with although outside the Cystic Fibrosis Foundation pipeline.

Gene and mRNA-based therapies

Since the discovery of *CFTR* just over 30 years ago, gene therapy for cystic fibrosis has been a tantalising, if somewhat elusive, goal. Over 20 clinical trials have been done with either a modified viral vector or synthetic vector to carry DNA into cells lining the airway.[177] Viral vectors have been difficult to administer repeatedly due to immunogenicity. The largest non-viral clinical trial was reported by the UK Cystic Fibrosis Gene Therapy Consortium in 2012.[178] After monthly nebulisation for a year, there was a 3–4% difference in FEV_1 between active and placebo groups due to stabilisation in the active group. The consortium is developing a pseudotyped lentivirus with an aim of greater clinical effect. Other approaches are being explored in preclinical and early phase trials including antisense oligonucleotide-mediated therapy, mRNA delivery, stem-cell therapy, and gene repair and editing.[171,179] For the approximately 10–15% of people worldwide who might not have gene mutations suitable for small molecule modulators, a different approach for these people will be needed. However, long-lasting expression without the need for regular dosing, if achievable, would make such an approach potentially useful for all patients.

Novel anti-infective approaches

The emerging threat of antimicrobial resistance has pronounced implications in cystic fibrosis. Resistance can be acquired via chromosomal mutations, horizontal transfer of resistance genes from other bacteria, alterations in gene or protein expression in response to environmental stimuli (as with biofilm formation), and antibiotic tolerance in chronic infection.[180,181] New antibiotics are being developed, but novel non-antibiotic antimicrobials might help overcome resistance mechanisms. Many of these antimicrobials are in the early phases of development and include targeting quorum sensing and *P aeruginosa* biofilm formation, bacterial virulence, and epithelial damage (table 2).[182]

Trials of anti-inflammatory therapies

Dysregulated inflammation is a hallmark feature of cystic fibrosis with contributing factors of membrane lipid imbalance, oxidative stress, and exaggerated cytokine responses in the setting of chronic infection. Despite advances in CFTR modulator therapies, studies of people with cystic fibrosis receiving these drugs have shown that airway inflammation persists.[183,184] Clinical trials are underway to test new agents that attenuate inflammation or promote its resolution without blocking the critical anti-inflammatory response. Acebilustat (Celtaxsys,

Atlanta, GA, USA) is a leukotriene inhibitor that inhibits neutrophil accumulation without preventing activation of transmigration in response to inflammatory stimulus.[185] Early phase cystic fibrosis clinical studies showed significant reductions in sputum neutrophils, and larger phase 2 studies are underway. Fenretinide (LAU-7B; Laurent Pharmaceuticals, Montreal, QC, Canada) promotes anti-inflammatory docosahexaenoic acid in resolving inflammation.[186] Lenabasum (Corbus Pharmaceuticals Holdings, MA, USA) is a cannabinoid receptor 2 agonist with both antifibrotic and anti-inflammatory properties.[187] A phase 2 randomised controlled trial in adults reported reduced inflammatory markers and pulmonary exacerbations.[188] A further phase 2 randomised controlled trial in people with cystic fibrosis aged 12 years and older is underway.

Airway hydrating and mucoactive drugs

Phase 2 trials of OligoG (AlgiPharma, Sandvika, Norway), an oligosaccharide derived from seaweed that possesses both mucolytic and biofilm disrupting properties, are ongoing. Several companies are developing epithelial

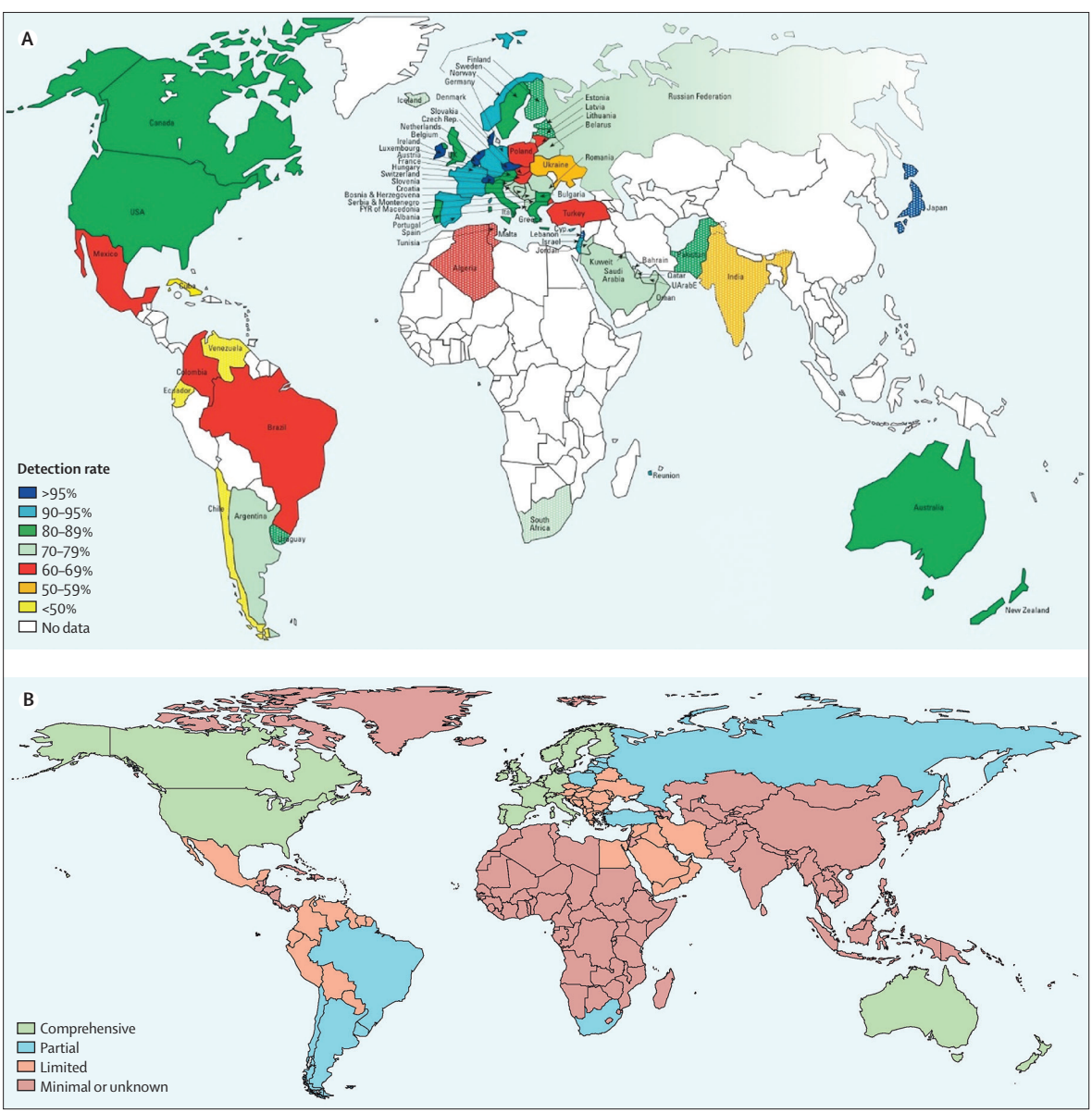

***Figure 4*: Global genetic epidemiology and standards of care for cystic fibrosis**
(A) The detection rate of cystic fibrosis-causing *CFTR* mutations. The names of several regions have since been updated as follows: Bosnia and Herzegovina, Cyprus, Czech Republic, Kuwait, Montenegro, North Macedonia, Russia, Serbia, and United Arab Emirates. (B) Global standards of care for cystic fibrosis defined according to factors such as resources, training, coverage, outcomes, access, and data management. Comprehensive=all factors present. Partial=at least half of these factors present. Limited=more than one factor present. Minimal or unknown=one or no factors present. Reproduced from Bell and colleagues,[193] by permission of Elsevier.

sodium channel inhibitors, both as conventional drugs and as mRNA targeted approaches.[171,189,190]

The changing epidemiology of cystic fibrosis and future perspectives

Cystic fibrosis as a global disease

CFTR mutations are increasingly recognised in people of non-European ancestry. In people of African and Asian origin, the frequency of *CFTR* mutations is not known due to the wide genetic heterogeneity (figure 4A),[191] although advanced sequencing might detect previously unreported *CFTR* mutations.[192] The clinical course of people with cystic fibrosis living in Asia, the Middle East, and Africa might be very different from that seen in high-income countries. This difference might be a consequence of late diagnosis, different diet and environmental exposures, different genomic backgrounds (accounting for more people with pancreatic sufficient cystic fibrosis than in European populations), comorbidity with other recessive disorders due to consanguinity in some regions, and possibly, socioeconomic status and poor access to coordinated specialised care and treatments for cystic fibrosis (figure 4B).[193] Differences in access to treatments could account for the extreme differences in survival and other cystic fibrosis outcomes within countries in the European registry.[124]

Cystic fibrosis as a chronic disease of adulthood

Improvement of cystic fibrosis care in previous decades has steadily increased the life expectancy of people with cystic fibrosis, with over 50% of people with cystic fibrosis being adults,[124] and those in high-income countries living longer than 40 years.[194] Between 2015–25, the population of people with cystic fibrosis has been predicted to increase by 50%, and the number of adults with cystic fibrosis by 75%;[195] this estimate does not consider the highly effective CFTR modulators, so is likely to be a conservative estimate. Newer complications are emerging in adults, attributable to the consequences of treatment and to CFTR deficiency (table 1; figure 2). Obesity,[126] diabetes, and dyslipidaemia might be associated with increased cardiovascular morbidity.[194] Increased prevalence of gastrointestinal cancers and lymphomas (especially after transplantation),[196] has led to the development of new screening guidelines.[197]

Although men with cystic fibrosis are mostly infertile due to congenital bilateral absence of the vas deferens, subfertility might be present in women with cystic fibrosis, particularly those with pancreatic insufficiency.[198] The causes of this subfertility are multifactorial, with both endocrine and cervical mucus changes. Pregnancy in women with cystic fibrosis is generally successful, sometimes following assisted reproduction. Complications are more frequent than in healthy women, and reduced lung function is associated with preterm birth. International guidelines on reproduction and pregnancy have recently been published.[199]

Implications for future delivery of cystic fibrosis care

Multidisciplinary health care, coordinated and delivered by highly specialised centres, was globally regarded as best practice. In-person clinic visits, ranging from biannual to quarterly, and hospital admissions for pulmonary exacerbations, were the norm. Intravenous antibiotics were largely delivered to inpatients in many centres, although home intravenous treatments were increasing in others. In the past 5 years, some clinical teams have questioned this one-size-fits-all pattern of surveillance and health-care delivery based on known risks of cross-infection, inconvenience to patients' daily lives, and the growing population of people with cystic fibrosis with improved health. Reviews have discussed pros and cons of remote care (eg, telemedicine). In 2020, the world was affected by the COVID-19 pandemic. The speed at which the virus spread, the unprecedented number of people infected, and the very severe disease and mortality encountered by many has transformed the way society functions, at least for the short term, with possible longer-term implications. The pandemic led to the adoption of teleclinics and provision of home spirometry in many cystic fibrosis centres. Lessons should be learned from the COVID-19 pandemic to allow cystic fibrosis health-care teams to take the best parts of this experience and build a new approach for cystic fibrosis care once the pandemic has passed. We are fortunate to be at a stage of technological development in which systems are available for remote monitoring of activity, lung physiology, nutrition, treatment adherence, and psychological wellbeing. For any such technology to fulfil its potential for people with cystic fibrosis, codevelopment and acceptability testing is essential. As the population of people with cystic fibrosis is increasing, the availability of highly effective modulator therapies might further expedite its growth, as early initiation of these therapies is predicted to have a major effect on survival. Furthermore, the psychosocial complexities of improved survival and prolonged chronic treatment adherence are under study as this landscape evolves. Shared decision making and reliance upon patient reported outcome measures must become essential tools in future studies to improve quality of life within the new paradigm of increased quantity. Movement of the cystic fibrosis community into the next era of widespread availability of CFTR modulator dugs is essential for challenging the status quo and adapting to a changing environment. In this way, we can all aim to maximise physical health and quality of life for patients and families with cystic fibrosis.

Contributors

All authors contributed to the scoping, literature reviews, and writing of this Seminar.

Declaration of interests

MS reports grants, personal fees, and non-financial support from GlaxoSmithKline; grants and non-financial support from Novartis and Trudell pharma; non-financial support from Actelion; and personal fees from Boeringer Ingelheim, AstraZeneca, and Vertex Pharmaceuticals,

outside the submitted work. IJH reports grants from Wellcome Trust Institutional Strategic Support Fund, outside the submitted work. DP reports grants and personal fees from Vertex Pharmaceuticals, and grants from Laurent Pharmaceuticals, outside the submitted work. JCD reports grants from the Cystic Fibrosis Trust outside the submitted work; Advisory Board and clinical trial leadership activities for AlgiPharma, Galapagos NV, and Proteostasis Therapeutics; Advisory Board and trial design assistance for ImevaX; Advisory Board and national coordinator and global coinvestigator for Vertex Pharmaceuticals; Advisory Board activities for Boehringer Ingelheim, Nivalis Therapeutics, Raptor Pharmaceuticals, Enterprise, Novartis, Pulmocide, Flatley, and Arcturus Therapeutics; and has given lectures for Teva.

Acknowledgments

The authors thankfully acknowledge the artwork done by Lia Kresh. JCD is supported by the UK National Institutes for Health Research (NIHR) through a Senior Investigator Award, the NIHR Imperial Biomedical Research Centre, and the Royal Brompton Hospital, National Heart & Lung Institute Clinical Research Facility. IJH is supported by the NIHR through a Clinical Lectureship and the Wellcome Trust through an Institutional Strategic Support Fund at Newcastle University. DP is supported by the US Cystic Fibrosis Foundation and the US National Institutes of Health (P20GM130423).

Editorial note: the *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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