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Considerations for the use of inhaled antibiotics for *Pseudomonas aeruginosa* in people with cystic fibrosis receiving CFTR modulator therapy

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ABSTRACT

The major cause of mortality in people with cystic fibrosis (pwCF) is progressive lung disease characterised by acute and chronic infections, the accumulation of mucus, airway inflammation, structural damage and pulmonary exacerbations. The prevalence of *Pseudomonas aeruginosa* rises rapidly in the teenage years, and this organism is the most common cause of chronic lung infection in adults with cystic fibrosis (CF). It is associated with an accelerated decline in lung function and premature death. New *P. aeruginosa* infections are treated with antibiotics to eradicate the organism, while chronic infections require long-term inhaled antibiotic therapy. The prevalence of *P. aeruginosa* infections has decreased in CF registries since the introduction of CF transmembrane conductance regulator modulators (CFTRm), but clinical observations suggest that chronic *P. aeruginosa* infections usually persist in patients receiving CFTRm. This indicates that pwCF may still need inhaled antibiotics in the CFTRm era to maintain long-term control of *P. aeruginosa* infections. Here, we provide an overview of the changing perceptions of *P. aeruginosa* infection management, including considerations on detection and treatment, the therapy burden associated with inhaled antibiotics and the potential effects of CFTRm on the lung microbiome. We conclude that updated guidance is required on the diagnosis and management of *P. aeruginosa* infection. In particular, we highlight a need for prospective studies to evaluate the consequences of stopping inhaled antibiotic therapy in pwCF who have chronic *P. aeruginosa* infection and are receiving CFTRm. This will help inform new guidelines on the use of antibiotics alongside CFTRm.

INTRODUCTION

Cystic fibrosis (CF) is a life-limiting autosomal recessive condition caused by variants in the gene encoding the CF transmembrane conductance regulator (CFTR) protein.[1] More than 160 000 people are estimated to be living with CF worldwide.[2] The major cause of mortality in people with CF (pwCF) is progressive lung disease characterised by bacterial, fungal and viral infections, the accumulation of viscous mucus, airway inflammation, structural damage and recurrent pulmonary exacerbations.[3–5] Dysfunctional mucociliary clearance in the CF airway allows pathogens to colonise the respiratory tract, where they can cause chronic airway infections and persistent inflammation, resulting in structural damage (eg, bronchiectasis and airway destruction) and deteriorating respiratory function.[6 7]

Pseudomonas aeruginosa, a gram-negative bacterium, is one of the most prevalent and important pathogens in adult CF lungs,[6] with the prevalence of infection rising steeply in the teenage years (figure 1).[8 9] The prevalence of *P. aeruginosa* infection increases with age,[10] affecting 5%–20% of children with CF aged ≤2 years[11] and approximately 40%–50% of adults with CF aged approximately 30–45 years (figure 1).[8 9] Acquisition occurs from environmental sources or via transmission from other pwCF[4 6 12]; most first infections are caused by unique, non-clonal strains, whereas shared strains are disproportionally observed in older pwCF.[10] *P. aeruginosa* evades the immune system via several adaptive behaviours, including downregulation of flagella expression and production of exopolysaccharides, which facilitate biofilm formation.[4] Chronic infection with *P. aeruginosa* is associated with increased pulmonary exacerbations, accelerated decline in lung function and premature death in pwCF; therefore, antibiotics should be initiated in response to the first *P. aeruginosa*-positive respiratory culture, with the aim of eradication, as chronic infections require long-term antibiotic therapy.[13–17] Inhaled antibiotics achieve higher airway concentrations and have limited toxicity compared with systemic regimens; therefore, selected

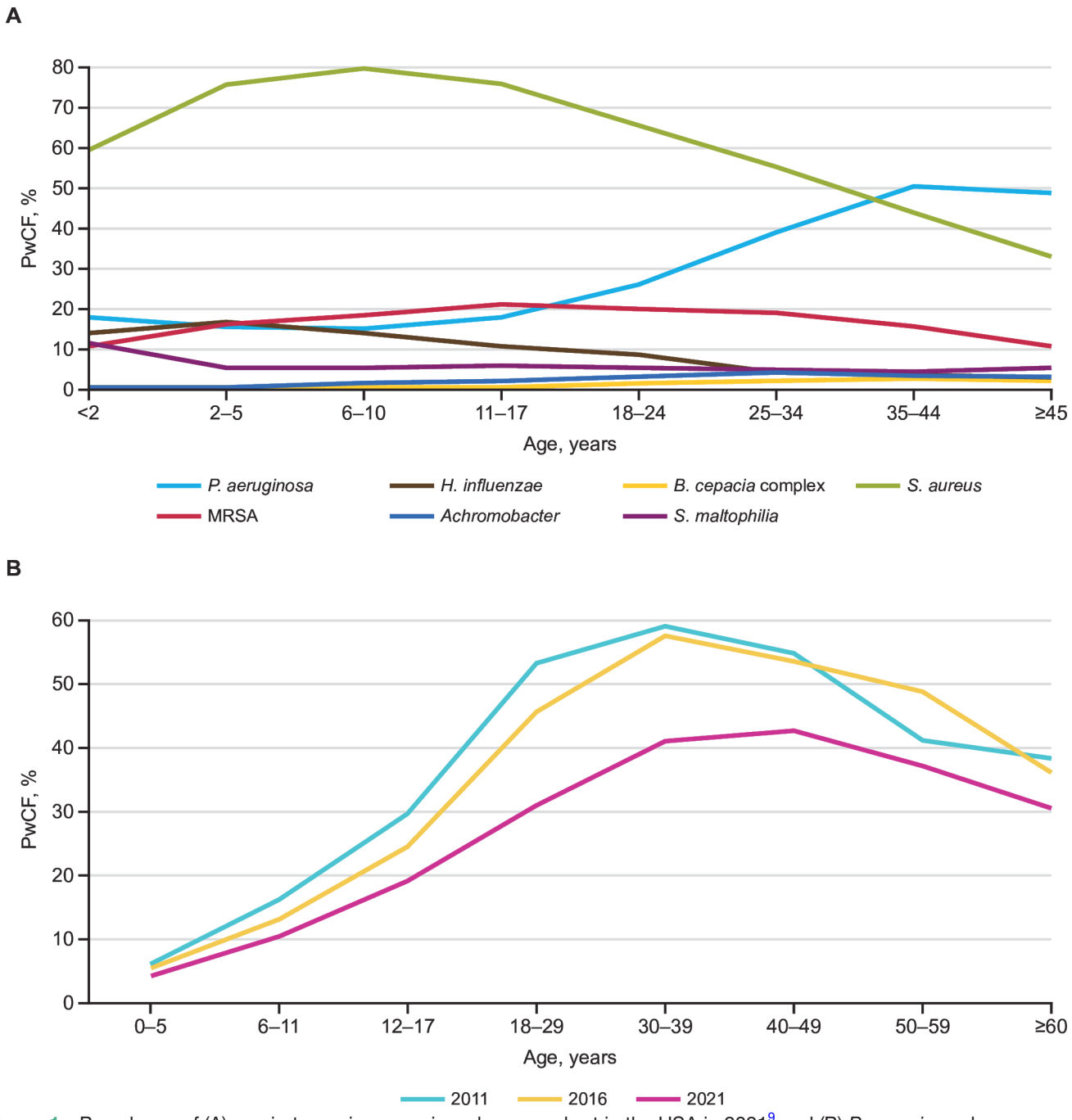

Figure 1 Prevalence of (A) respiratory microorganisms by age cohort in the USA in 2021[9] and (B) *P. aeruginosa* by age cohort in Europe.[8] Reproduced with permission: (A) Cystic Fibrosis Foundation Patient Registry. 2021 Annual Data Report. Bethesda, Maryland copyright 2022 Cystic Fibrosis Foundation[9] and (B) ECFSPR Annual Report 2021, Zolin A, Orenti A, Jung A, van Rens J, *et al,* 2023.[8] Availability of pathogen surveillance data may have been impacted by the COVID-19 pandemic during 2020 and 2021. *B. cepacia* complex, *Burkholderia cepacia* complex; *H. influenzae*, *Haemophilus influenzae*; MRSA, methicillin-resistant *S. aureus; P. aeruginosa*, *Pseudomonas aeruginosa*; pwCF, people with cystic fibrosis; *S. aureus*, *Staphylococcus aureus; S. maltophilia*, *Stenotrophomonas maltophilia*.

antipseudomonal antibiotics have been developed as inhaled formulations.[18]

CFTR modulators (CFTRm) are novel drugs that bind to the CFTR protein during or after protein processing.[19] The most commonly used CFTRm are a combination of three modulator drugs (elexacaftor, tezacaftor and ivacaftor (ETI), originally indicated for pwCF with ≥1 copy of the F508del variant but now approved in some regions for pwCF without a F508del variant[20 21]) and ivacaftor alone (indicated for pwCF with selected gating mutations[22 23]). These agents have demonstrated remarkable efficacy in reducing sweat chloride concentrations, respiratory symptoms (eg, cough and sputum production) and pulmonary exacerbations while enhancing the

quality of life and increasing forced expiratory volume and body mass index in pwCF with appropriate *CFTR* variants.[24–29] By the end of 2021, 88% and 62% of eligible patients in the US-based Cystic Fibrosis Foundation and European Cystic Fibrosis Society registries, respectively, were prescribed CFTRm, with the majority receiving ETI.[8 9] It is important to note, however, that ETI is not readily available in some European countries and many non-European countries,[2 30] and that pwCF without an F508del variant are currently not eligible for this treatment in many regions.[31]

In addition to beneficial effects on lung function, there is evidence that CFTRm may reduce bacterial infections[32 33] and potentially act in conjunction with some antibiotics to decrease infections via changes in airway surface liquid and pH, improvements in microbiome diversity, modified inflammatory and immune responses and activation of innate molecules.[34] However, our understanding of the interactions between CFTRm and antibiotics is limited, and investigations into the effects of CFTRm on CF pathogens have been inconclusive. Despite observations from CF registries that the prevalence of *P. aeruginosa* infections has markedly decreased since the introduction of CFTRm,[8 9] recent evidence showed that chronic *P. aeruginosa* infections often persist in pwCF treated with CFTRm, suggesting that these patients may benefit from inhaled antibiotics to maintain long-term control of infections.[33–35] It is also important to note that the COVID-19 pandemic may have impacted the availability of *P. aeruginosa* prevalence data, with a widespread lack of access to telehealth specimen collections for pathogen surveillance.[36]

This article provides an overview of the changing perceptions of how to diagnose and manage *P. aeruginosa* infections in pwCF during the CFTRm era, including considerations of the CF treatment burden and the future role of inhaled antibiotics.

CURRENT PERSPECTIVES OF PWCF AND HEALTHCARE PROFESSIONALS (HCPS)

With the advent of CFTRm, pwCF are feeling healthier, with many experiencing a significant reduction in sputum volume,[34] which may lead them to believe they are free from airway pathogen infection.[37] Indeed, some pwCF decide to stop taking inhaled antibiotics when they feel better (eg, upon reduction of their previously abundant sputum), despite continuing to have positive cultures for *P. aeruginosa*.[38]

Inhaled antibiotics are among the most burdensome treatments for CF,[39] and pwCF are known to be less adherent to inhaled therapies than to oral medications.[40 41] The reasons behind this include the complex management and time associated with inhaled medications, including correct inhalation technique, nebulisation time and the burden of cleaning devices.[37 40] Furthermore, pwCF are more likely to adhere to treatments that give instant symptom relief (eg, bronchodilators) or that result in immediate consequences in the event of non-adherence (eg, pancreatic enzyme replacement therapy).[40 41] In contrast, treatments offering mostly long-term benefits, such as inhaled antibiotics, require considerable motivation to maintain.[40] One study reported that 42% of adolescent pwCF found it difficult to comply with treatment in the absence of symptoms,[42] and a survey found that pwCF would accept substantial reductions in lung function and life expectancy in exchange for reduced treatment time and burden.[43] It is notable that treatment complexity in CF increases with age; therefore, with growing numbers of adult pwCF, more are now living with established disease and chronic *P. aeruginosa* infection and the associated treatment burden.[39]

The pwCF wish to simplify their treatment. Registry data suggest there has been a slight decrease in reported long-term antibiotic usage in recent years (figure 2)[8 9]; potentially, some pwCF who are benefiting from CFTRm may have discontinued one or more of their long-term antibiotic therapies.[9] The discontinuation of other CF therapies was addressed in the SIMPLIFY study, which evaluated discontinuation versus continuation of mucoactive therapies for 6 weeks in pwCF with mild or moderate disease who were also being treated with ETI.[44] The results suggested that it is acceptable to discontinue treatment over a short period of time, with no clinically meaningful differences in pulmonary function between the two treatment groups; however, long-term follow-up data are not yet available, and patients with more advanced lung disease were not included.

HCPs may expect the incidence of new *P. aeruginosa* infections to decrease in the future due to the widespread use of CFTRm in young pwCF, although this remains to be established. Furthermore, studies have suggested that pwCF have structural defects in the respiratory system early in life, with CF airways demonstrating wall thickening and dilatation in comparison with healthy infants[45 46]; it is unclear if the presence of structural defects in the youngest recipients of CFTRm continues to predispose them to chronic bacterial infection.

Despite a potential reduction in new infections, the overall number of pwCF chronically infected with *P. aeruginosa* may increase due to the prolonged survival of pwCF in whom CFTRm were started when lung damage and chronic *P. aeruginosa* infection were already established. The prevalence of *P. aeruginosa* infection increases rapidly in the teenage years (figure 1), and early diagnosis of infection, followed by eradication therapy, will help to prevent chronic infection from developing in a proportion of young adults with CF. HCPs treat increasing numbers of adults with CF lung disease; most pwCF are now ≥18 years of age,[8 9] with a median survival of up to 65.9 years of age in countries with well-established CF care.[47] Although there has been a decrease in chronic *P. aeruginosa* infections in recent years, it still persists, affecting approximately 50% of pwCF >35 years of age in the USA (figure 1A)[9] and approximately 30%–43% of pwCF >30 years of age in Europe (figure 1B).[8] While the

Figure 2 Medication prescriptions in (A) eligible pwCF from 1999 to 2021 in the USA[9]; (B) adult pwCF from 2011 to 2021 in Europe[8] and (C) children with CF from 2011 to 2021 in Europe.[8] Reproduced with permission: (A) Cystic Fibrosis Foundation Patient Registry. 2021 Annual Data Report. Bethesda, Maryland copyright 2022 Cystic Fibrosis Foundation[9] and (B) and (C) ECFSPR Annual Report 2021, Zolin A, Orenti A, Jung A, van Rens J, *et al*, 2023.[8] CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; pwCF, people with CF; rhDNase, recombinant human deoxyribonuclease.

efficacy of CFTRm is well established, the partial restoration of CFTR function is suboptimal for normal physiological function and is considered unlikely to resolve all chronic structural lung damage,[34] leaving pwCF susceptible to bacterial infection. Indeed, chronic *P. aeruginosa* infections seem to persist in pwCF receiving CFTRm, despite an initial reduction in bacterial load.[35 48]

Some aspects of CF care may need redefining following the introduction of CFTRm. For example, pulmonary exacerbations still occur in pwCF receiving CFTRm, but the symptom profile may be different versus the pre-CFTRm era.[34] Concern also exists around the detection of *P. aeruginosa* in pwCF receiving CFTRm due to the significant reduction in sputum, which has limited the frequency and quality of sample collections. Pathogens have been detected via PCR months after cultures became negative following the initiation of CFTRm.[35] It is, therefore, becoming increasingly apparent that several aspects of CF management require updated guidance, including how *P. aeruginosa* infections are monitored and managed in a manner that works for pwCF and minimises treatment burden.

DIAGNOSIS OF *P. AERUGINOSA* INFECTION

Traditionally, spontaneous sputum was the routine specimen to evaluate airway microbiology in pwCF attending CF clinics,[49] demonstrating a strong concordance between the organisms detected in sputum and those present in the lower respiratory tract.[50] However, the introduction of CFTRm has resulted in many pwCF being unable to provide spontaneous expectorated sputum samples during appointments.[49] Effective sampling for lower airway microbiology remains crucial for the treatment of infections, but it will increasingly rely on alternative techniques such as sputum induction or bronchoscopy with lavage.[51 52] Sample types and methods of *P. aeruginosa* detection are summarised in table 1.[51 53–58]

When spontaneous sputum is not produced during clinic visits, pwCF can sample sputum at home and submit it via post for analysis.[59] Alternatively, sputum induction by inhalation of hypertonic saline and/or support from specialist physiotherapists has been associated with a twofold to threefold increase in pathogen detection versus oropharyngeal sampling in young children.[51–53 60] However, this technique requires a trained specialist and a well-ventilated space with sufficient time between appointments.[60] Furthermore, some pwCF receiving CFTRm are unable to produce sputum even after sputum induction techniques are employed. Bronchoalveolar lavage is a highly effective sampling technique but is invasive, time-consuming and, in children, requires general anaesthesia.[52 53]

While the upper airways do not directly represent the lower airways, studies have shown that, in the long term, bacterial colonies can adapt and converge in the upper and lower airways as a united system.[61] Oropharyngeal swabs are well tolerated but lack sensitivity and can be

Table 1 Summary of sample types and methods of bacterial infection detection in pwCF

Sample type	Advantages of sample type	Disadvantages of sample type	Applicable detection methods (target)	Advantages of detection methods	Disadvantages of detection methods
Swab (oropharyngeal, throat, cough)[51 53–55]	Easy to carry out	Not as sensitive as samples from lower airways	Culture (viable bacterial cells) Species-specific PCR (gene specific to *P. aeruginosa*) NGS* (16S rRNA gene, whole genome)	Culture: ▲ Detection of specific phenotypes (mucoidy, small colony variant) ▲ Permits antibiotic susceptibility testing PCR: ▲ High sensitivity and specificity NGS: ▲▲ Very high sensitivity ▲ Provides the complex picture (microbiome)	Culture: ▲ Lower sensitivity PCR: ▲ May detect DNA from dead cells NGS: ▲ Risk of detection of low quantities, not clinically relevant ▲ Limited discriminatory power (on species level)
Spontaneous expectorated sputum[55]	Representative of lower airways	Not available in young children with CF and many pwCF receiving CFTRm			
Induced sputum[51 53 55]	Representative of lower airways	Need to use specific techniques			
Bronchoalveolar lavage[51 53 55]	Representative of lower airways	Invasive procedure			
Serum[56]	A potential alternative method to diagnose infection if lower airway sample is not available	Inconvenient in young children with CF	Enzyme immunoassay (anti-*P. aeruginosa* IgG)	–	Indirect detection of *P. aeruginosa* Lack of standardisation
Exhaled breath* or urine*[57 58]	Alternatives if lower airway sample is not available	–	Mass spectrometry (metabolites, siderophores)	–	–

*Experimental approach; not currently used in clinical practice.
CF, cystic fibrosis; CFTRm, CF transmembrane conductance regulator modulators; IgG, immunoglobulin G; NGS, next-generation sequencing; *P. aeruginosa*, *Pseudomonas aeruginosa*; PCR, polymerase chain reaction; pwCF, people with CF; rRNA, ribosomal RNA.

poorly representative of the lower airway.[52 53 62] Indeed, studies have shown that throat or cough swabs provide a far lower pathogen yield than sputum induction.[51 63] Nasal lavage is a promising non-invasive technique that can potentially be self-administered by pwCF; however, this technique is not suitable for young children and its representativeness of the lower airway is unclear.[61 64]

With the increasingly observed reduction in sputum in pwCF receiving CFTRm, there is renewed interest in detection techniques other than bacterial culture. Measuring serum antibodies against *P. aeruginosa* antigens may complement other monitoring methods, with positive antibody results prompting a thorough search for infection.[65] Novel culture-independent technologies (eg, quantitative PCR and next-generation sequencing using lower airway samples) can detect bacterial DNA at extremely low concentrations,[53 66] perhaps reflecting an early or low-level infection. However, this raises the question of how clinically important infections should be defined when using these highly sensitive technologies.[53] This concern depends on the context of detection; for example, a pathogen detected at low levels for the first time may be considered relevant, but low levels after an eradication attempt may reflect DNA remnants from dead bacteria and, thus, not be considered relevant. It is important to note that a positive PCR result indicates the presence of bacterial DNA, but not necessarily viable organisms.

Effective infection surveillance is critical and underpins the management of asymptomatic pwCF who demonstrate disease progression despite a lack of symptoms.[52] The quality of the sample, rather than the overall number of samples, may be important; therefore, annual sputum induction may be an effective way to obtain at least one high-quality sample in patients who produce little or no sputum. There is currently inconsistency in the diagnosis of *P. aeruginosa* infection due to differing sampling and analytical techniques that may result in undiagnosed infections. The definition criteria for chronic *P. aeruginosa* infection are also currently unclear, as definitions based on multiple samples (eg, the Leeds criteria) may become irrelevant for patients who do not produce enough sputum for repeated samples.[67] Ideally, detection methods should be standardised while taking into account the wishes of, and burden on, patients.

INHALED ANTIBIOTICS ALONGSIDE CFTRM THERAPY

Chronic *P. aeruginosa* infections are managed using long-term suppressive therapy with inhaled antibiotics,[14] with clinical guidelines providing specific recommendations.[15 16] In recent years, studies have reported that CFTRm may reduce *P. aeruginosa* bacterial load[32 33]; however, the mechanisms behind this apparent effect are not clear.[35 68–70] In addition, there have been suggestions of a molecular synergy between inhaled antibiotics and CFTRm,[33 68] but this evidence is inconclusive, with one study reporting that while the bacterial density of *P. aeruginosa* decreased in highly responsive pwCF receiving CFTRm alongside intensive antibiotics, very few individuals cleared their infection.[33] Those with persistent infections retained their pretreatment strains during 2.5 years of follow-up.[33] The pharmacokinetics of inhaled antibiotics may also be affected by CFTRm; for example, reduced airway mucus plugging could increase the deposition and absorption of inhaled antibiotics, although there is currently no data on the deposition and pharmacokinetics of inhaled antibiotics in pwCF treated with CFTRm.

Consequently, there is insufficient data to support either the discontinuation or continuation of inhaled antibiotics in pwCF receiving CFTRm. It is possible that a reservoir of chronic infection remains in pwCF with established lung disease receiving CFTRm, which may necessitate continued treatment with antibiotics. Thus, it may be considered that antibiotics should not be discontinued in pwCF receiving CFTRm with prior evidence of chronic *P. aeruginosa* infection, unless subsequent investigations confirm clearance of the pathogen. Such investigations may include the use of induced sputum to monitor infection, with multiple negative cultures indicating clearance. More data are needed before clear guidelines can be developed.[34] Despite the lack of evidence on this topic, anecdotal observations suggest that many pwCF receiving CFTRm are keen to reduce their treatment burden by discontinuing antibiotics once they are asymptomatic.[34] A large, well-designed, randomised controlled trial (RCT) of stopping versus continuing inhaled antibiotic therapy in pwCF who have chronic *P. aeruginosa* infection is necessary to resolve this uncertainty and inform new guidance on the use of inhaled antibiotics for chronic *P. aeruginosa* infection alongside CFTRm.

AREAS OF FUTURE RESEARCH

The transformation of CF treatment and outcomes since the introduction of CFTRm has exposed a need for research in several areas; indeed, new research priorities for the CFTRm era have been jointly proposed by pwCF and clinicians.[71] The dynamics of *P. aeruginosa* infection during treatment with CFTRm should be investigated and further studies of the interactions and potential synergies between inhaled antibiotics and CFTRm will help to develop treatment strategies. Research is also required on the optimal dosing of inhaled antibiotics in pwCF receiving CFTRm; for example, evaluating the deposition of inhaled antibiotics in these individuals may result in dosing adjustments, which could reduce the treatment burden. Optimisation of aerosolised antibiotics and improvements to aerosol devices to reduce the time required for preparation, administration and cleaning would also help to alleviate the burden of CF therapy.

As outlined earlier, an RCT of stopping versus continuing inhaled antipseudomonal antibiotic therapy in pwCF with chronic *P. aeruginosa* infection should be

a priority. However, there are significant challenges in designing clinical studies of antibiotic use in the CFTRm era. These include patient recruitment and selection of outcome measures; for example, many pwCF treated with CFTRm experience very low rates of exacerbations, and there is currently no standardised definition of an exacerbation in these patients.[52] Nevertheless, some traditional endpoints (eg, forced expiratory volume in 1 s) are likely to remain relevant, and many pwCF treated with CFTRm are still able to provide induced sputum samples.

The initial clinical studies of CFTRm included pwCF who were receiving inhaled antibiotics.[72–74] Studies in *P. aeruginosa*-negative pwCF are now essential to provide information relevant for pwCF receiving CFTRm who were previously *P. aeruginosa*-positive but have become culture negative and continue to take inhaled antibiotics, despite their culture-negative status. Research into the effects of CFTRm in younger pwCF without long-standing infection and less structural lung damage will provide key prognostic information for early disease cohorts,[35] including the impact of early CFTRm treatment on structural damage, inflammation and persistence of airway bacteria. Indeed, recent data have supported the potential for early disease modification with CFTRm in children as young as 2 years of age.[75] BEGIN (NCT04509050) is an ongoing longitudinal evaluation of the impact of CFTRm on growth and disease progression in children aged <6 years, with results expected in late 2025. These studies may help to further our understanding of how *P. aeruginosa* infections should be diagnosed and managed in this population. Another area of interest is whether the benefits of CFTRm are maintained when long-term antibiotics are stopped.

Future research should also seek to determine whether progress against infection in the CFTRm era requires new antimicrobial approaches[35]; investigational products include gallium, antimicrobial peptides, antibiofilm agents and phages,[76] with bacteriophage BX004 recently granted Fast Track designation from the US Food and Drug Administration for the treatment of chronic respiratory infections caused by *P. aeruginosa* in pwCF.[77]

Finally, research is needed to determine the extent to which ongoing infections affect the health of pwCF treated with CFTRm, particularly those detected only by highly sensitive culture-independent technologies.[33 35 53]

CONCLUSIONS

The introduction of CFTRm has transformed the lives of many pwCF.[78] When sufficient data-driven evidence is available, clear clinical practice guidelines are needed to reflect the changes in the treatment landscape, taking into account the perceptions and wishes of pwCF.

Meanwhile, updated guidance is required on the detection of *P. aeruginosa* to ensure that all infections, including undiagnosed infections in pwCF receiving CFTRm, are identified and treated optimally. Sampling and analytical techniques should be reviewed and further developed for pwCF receiving CFTRm and then standardised to provide a consistent approach across centres and regions.

It is important that younger pwCF and their caregivers continue to be educated about the need for early *P. aeruginosa* detection and treatment while keeping in mind the patients' and caregivers' perspectives on the treatment burden. The current evidence base does not support cessation of inhaled antibiotics upon initiation of CFTRm; therefore, guidelines should provide practical advice on the use of antibiotics alongside CFTRm.

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