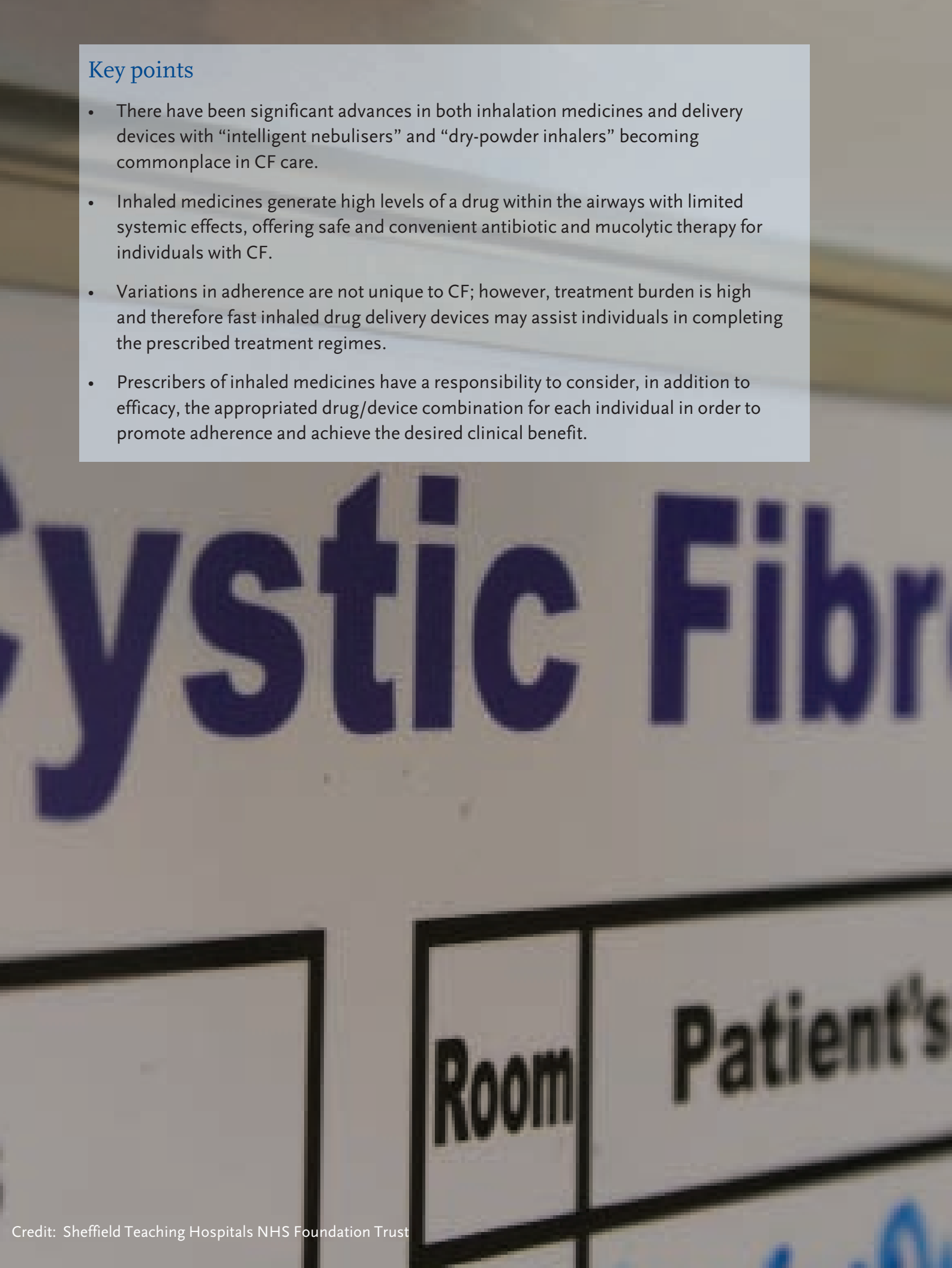
Key points

- There have been significant advances in both inhalation medicines and delivery devices with “intelligent nebulisers” and “dry-powder inhalers” becoming commonplace in CF care.
- Inhaled medicines generate high levels of a drug within the airways with limited systemic effects, offering safe and convenient antibiotic and mucolytic therapy for individuals with CF.
- Variations in adherence are not unique to CF; however, treatment burden is high and therefore fast inhaled drug delivery devices may assist individuals in completing the prescribed treatment regimes.
- Prescribers of inhaled medicines have a responsibility to consider, in addition to efficacy, the appropriated drug/device combination for each individual in order to promote adherence and achieve the desired clinical benefit.



Credit: Sheffield Teaching Hospitals NHS Foundation Trust

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Inhaled therapy in cystic fibrosis: agents, devices and regimens

Summary

The recognised mainstay daily treatments for cystic fibrosis (CF) focus on inhaled and oral medications, airway clearance and optimised nutrition. This review discusses recent advances in inhaled therapies for the management of CF, including devices such as intelligent nebulisers, drug formulations and supporting evidence for inhaled antibiotics (for the management of chronic *Pseudomonas aeruginosa*) and muco-active drugs. We include practical advice for clinicians regarding the optimisation of inhalation technique and education. The influence of adherence on the use of inhaled therapies in CF is also reviewed.

Educational aims

- To inform readers about the history and progression of inhaled therapies for people with CF with reference to the literature supporting current practice.
- To highlight the factors that may impact the success of inhaled therapies, including those which are device specific such as drug deposition and those which influence adherence.

Conflict of interest
None declared.

The recognised mainstay daily treatments for cystic fibrosis (CF) focus on inhaled and oral medications, airway clearance and optimised nutrition [1]. Inhaled therapies offer targeted drug delivery and are relatively simple and quick to take [2]. There have been significant improvements in both delivery devices and the formulation of drugs with "intelligent nebulisers" [3] and dry-powder inhalers becoming commonplace. These developments have occurred in conjunction with development of a wider variety of therapeutic strategies, a greater availability of types of inhaled antibiotics and options to augment physiotherapy airway clearance techniques.

CF is experiencing exciting developments in therapeutic strategies that target various aspects of the physiological cascade in CF (fig. 1). Oral agents such as ivacaftor [4], which works for selected genotypes to directly potentiate the

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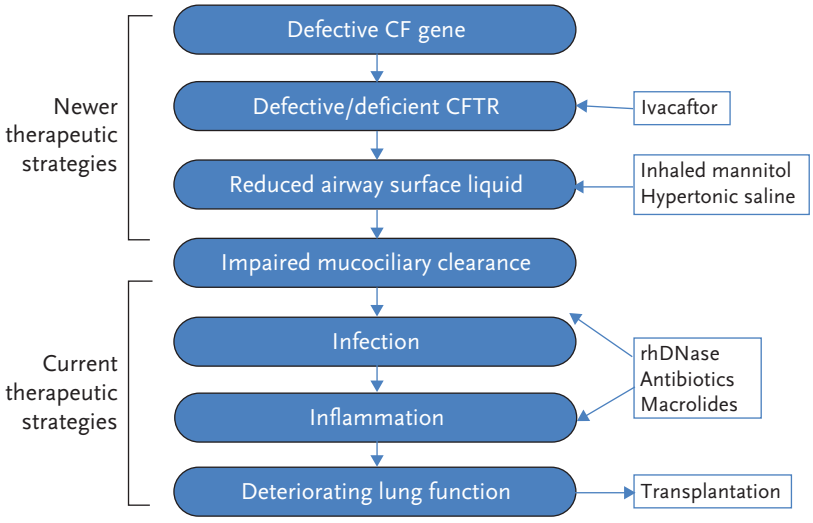

Figure 1
Physiological cascade in CF with therapeutic strategies.

cystic fibrosis transmembrane conductance regulator (CFTR) protein so that rehydration of the airway and clearance are improved, are delivering encouraging and significant improvements in clinical practice. However, the vast majority of people with CF are yet to benefit from these developments as the drugs are specific to selected genotypes. The majority of individuals, and in particular those with established disease, must incorporate an individualised daily treatment regimen into their life, which is often time consuming and complex to complete.

The advantages of using inhaled medications mean that their use generates high drug levels within the airways coupled with limited systemic toxicity. They are relatively fast acting (depending on the drug type) and their precise particle sizes enables them to be directed at the target site with optimal deposition. These factors result in inhaled medications offering convenient long-term home therapy options and can provide treatment options in instances where systemic route drug availability is reduced, *e.g.* in pregnancy. However, optimising delivery of inhaled medications is dependent on both the inhalation technique used and device performance. Appropriate education and training is key to performance, but the use of multiple inhaled therapies is known to be time consuming and adherence to these treatment strategies is often variable [5].

Nebuliser devices

The type of nebuliser used is critical to the efficiency of inhalation and deposition of the drug. Although traditional jet-nebulisers are still in use in a minority of centres, the use of "intelligent nebulisers" [3] such as the eflow (Pari Medical, West Byfleet, UK) and Ineb (Profile Pharma, Zambon SpA, Chichester, UK) is far more commonplace. These are smaller, quicker devices that give improved deposition of a range of medications [6, 7], and ultimately impact on reducing the burden of care. Although inhaled therapies are commonplace in CF care, many factors contribute to reducing their efficiency, with adherence to a prescribed regime often being the most variable [8]. Other contributory factors include the generated aerosol particle size, the inhalation-breathing pattern used and the individual's airway geometry. These newer "intelligent" devices offer improved delivery of medications by addressing some of these factors.

Two technological developments in how nebulisers work have been significant in advancing these devices. Vibrating mesh technology (VMT), which both the eflow and Ineb use, couples the vibration (~116 kHz) of a piezoelectric crystal or column directly to a metallic mesh membrane, with thousands of precisely tapered holes. This results in a uniform aerosol particle size (2.5 µm) being generated as the drug liquid is forced through these precise holes. Adaptive aerosol delivery (AAD) only delivers aerosol on inhalation during the individual's breathing cycle. There is a continuous adaptation to the individual's breathing pattern [9] so that aerosol is typically released only at a predetermined portion (~80%) of the inspiratory time, therefore optimising the deposition of particles [7]. Devices that utilise AAD are programmed

to deliver a specific preset drug dose and use reduced volumes of drug, as they are not continuous flow devices delivering drug throughout the inspiratory and expiratory cycle (*i.e.* they reduce drug wastage during exhalation). The Ineb combines the use of VMT with AAD. However, at present, widespread use is limited by its link to the requirement for prescription of Promixin. Combination of these two technologies in future devices without a specific drug link is ultimately going to be of benefit to the wider CF community.

Inhaled antibiotics

Chronic lower airway infection in CF is a hallmark of CF lung disease and is caused by opportunistic pathogens. Although there are a variety of pathogens, the most common is *Pseudomonas aeruginosa* and its acquisition and persistence is associated with increased morbidity, a decline in lung function and increased mortality [10]. Antibiotics are considered to be the mainstay of treatment for pulmonary disease in CF and their aggressive use and the availability of effective antimicrobials have been significant factors in improving the health and prognosis of people with CF today. The advantages of nebulised antibiotics for the management of chronic *P. aeruginosa* have long been recognised [11], and clinicians in the UK have been prescribing inhaled antibiotics for >30 years, since nebulised carbenicillin and gentamycin were first used [12]. Advances in both the type and efficacy of inhaled antibiotic available and in drug delivery has resulted in the consensus view in the UK that 90% of patients chronically infected with *P. aeruginosa* (~3000 patients in the UK) should be prescribed at least one nebulised antibiotic [13]. UK national registry data indicate that there is great variety in the types of antibiotic used, but polymyxin products are most common overall (Colomycin 39.6%; Promixin 29.8%), followed by the aminoglycoside tobramycin (31.4%) and β-lactam aztreonam (6.8%) [13].

With regards to the evidence base for inhaled antibiotic therapy, tobramycin has been shown to be the most efficacious in significantly improving lung function, reducing the number of exacerbations and bacterial load, and improving quality of life [14]. Findings among adolescents were similar [15]. Chronic therapy is taken as an intermittent regime of 28-day on/off cycles, and although there is little or no supporting evidence base, in clinical practice many physicians prescribe an alternative inhaled antibiotic for use during the "off" cycle. Further studies are required evaluating this approach.

Nebulised aztreonam (Cayston; Gilead Sciences, Foster City, CA, USA) is a relatively new inhaled antibiotic and the first new inhaled drug for CF for a decade. It has proven efficacy in significantly improving lung function [16, 17], and respiratory symptoms such as cough, wheeze and sputum production [16]. It is prescribed three times daily, which at first may be considered less attractive for both clinicians and patients due to adherence concerns. However, the drug fill volume is only 1 mL and it must be taken through an eflow device (with an Altera handset) resulting in a nebulisation time of ~1 min. This is significantly less than the majority of nebulised drugs and the outcomes are maximised when the full therapeutic dose is taken. Specialist CF clinicians can assist patients in successfully incorporating this three times daily regimen and this support should be facilitated as the patient benefit from use of this antibiotic may be significant.

Colistin products (Colomycin and Promixin) have been used as a first line approach to chronic *P. aeruginosa* suppressive therapy for many years in the UK and Europe. However, the long-term efficacy of these drugs is less well documented, with many of the studies having a small subject size although a meta-analysis confirmed the benefit of use [18]. Their use is widely acknowledged in paediatric and adult CF patients, particularly the low rates of microbial resistance despite continuous use [19, 20].

Although nebulised antibiotics have been available for >30 years, recent advances have focused on dry-powder developments, with formulations currently available for tobramycin (TOBI Podhaler; Novartis Pharmaceuticals, East Hanover, NJ, USA) and colistin (Colobreathe; Forest Laboratories, Dartford, UK). This progress has offered simple, fast and convenient delivery of inhaled antibiotics, while delivering similar efficacy to nebulised formulations. In addition, dry-powder inhalers require minimal cleaning compared with a nebuliser system, which is also time-consuming and often not performed to recommended manufacturer's guidance. For the TOBI Podhaler, the EVOLVE study [21] demonstrated efficacy over placebo in 95 patients. The EAGER study [22] then compared the use of three treatment cycles of tobramycin inhalation powder (TIP) with the nebuliser solution (TOBI) in 553 patients. This larger study resulted in the demonstration of similar efficacy

of microbial response coupled with a higher treatment satisfaction (perceived effectiveness, convenience and global satisfaction) with TIP. However, there was a significantly higher rate of cough with TIP (25.3% *versus* 4.3%), although at the time of these trials, very little education was provided with regards to the optimal inhalation technique for dry powders and cough control principles, which are essential in their successful use today.

The only study, to date, to assess the safety and efficacy of the Colobreathe dry-powder inhaler (CDPI) is the Freedom study by Schuster *et al*. [23]. This was an open label study (n=380) evaluating CDPI (1.6 IU) twice daily with three 28-day cycles of tobramycin inhalation solution (TIS) (300 mg). CDPI demonstrated non-inferiority to TIS in terms of change in baseline lung function after 24-weeks of treatment and was well tolerated. As Colobreathe is a single capsule taking 1–2 inhalations, and therefore making it the simplest and quickest inhaled antibiotic, it was no surprise that CDPI rated more highly for ease of use (90.7%) than TIS (53.9%).

Future developments in inhaled antibiotics are anticipated with drugs such as dry-powder ciprofloxacin [24] undergoing phase 2 studies, and nebulised levofloxacin [25] and amikacin (Arikace; Insmed Incorporated, Bridgewater, NJ, USA) [26] in phase 3 studies.

The increasing number of antibiotic formulations now on offer encourages the prescriber to not only consider the drug efficacy and published guidance (UK National Institute for Health and Care Excellence (NICE)), but also essential indicators of success such as drug deposition and adherence.

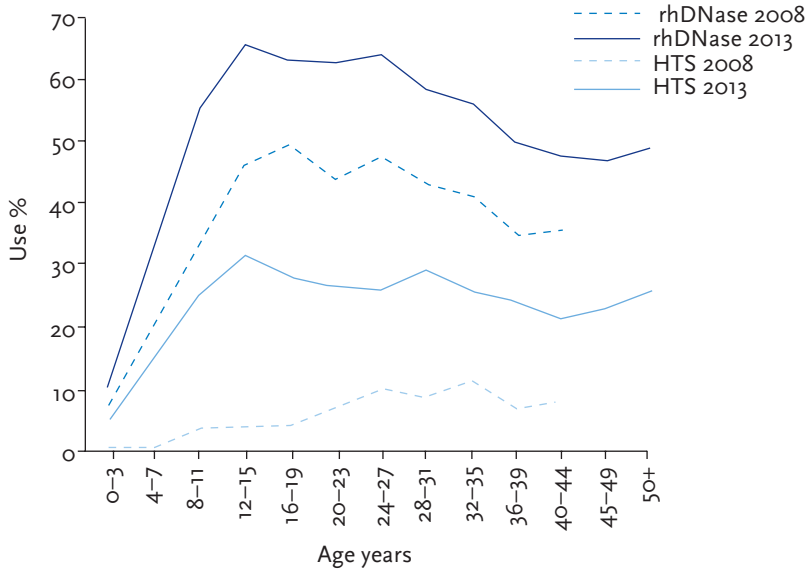

Figure 2
Change in nebulised hypertonic saline (HTS) and rhDNase. Data from [13].

Other inhaled therapies

As well as significant increases in the use of inhaled antibiotics, clinical practice has benefitted from advances in the use of mucolytic and muco-active agents. The benefits of nebulised dornase alfa (recombinant human deoxyribonuclease I (rhDNase)) are widely acknowledged throughout the CF lifespan, both for positive improvements in lung function and airway inflammation [27–29], and augmented airway clearance [30, 31]. UK national registry data reports evidence of significant increases in the use of both rhDNase and hypertonic saline in the past 5 years or so [13], following noteworthy studies of efficacy [32–34] (fig. 2). The physiological importance of increasing the CF-reduced airway surface liquid height to enable and augment effective airway clearance is clearly understood. Agents such as hypertonic saline and inhaled mannitol (Bronchitol; Pharmaxis Pharmaceuticals, Burnham, UK) are potentiators of this effect, and although hypertonic saline is widely used, at a patient level some individuals complain of the obviously salty taste and burden of adding in another nebulised treatment to an already complex treatment regime. The advent of Bronchitol and its demonstrated clinical efficacy [35–37] has provided a dry-powder alternative that has the support of NICE guidance as an add-on therapy. Although inhaling ten capsules may seem time-consuming, clinical studies have been supported by use in clinical practice demonstrating that the majority of patients easily take the full dose in around 5 min, and are encouraged by the positive impact and outcomes that taking the full treatment dose results in. As both Bronchitol and hypertonic saline induce coughing it is vital that inhalation techniques, cough control measures and education are provided for optimal benefit.

Delivery optimisation

The choice of type of device or formulation is fundamental to enabling patients to optimise their delivery and adherence to inhaled therapies. Clinicians such as physiotherapists are ideally placed to deliver individually tailored education with regards to inhalation and device-specific techniques (box 1).

Box 1 Optimising inhalation techniques for dry-powder inhaler devices

- Full exhalation is required at the beginning: lung deposition is related to the extent of the initial exhalation.
- Don't exhale through the device: moisture and the drug dose can be blown out.
- Aim for slow steady inhalation from the beginning to full inspiratory capacity, followed by a breath hold (>5 s).
- Make at least two separate inhalations for the capsule. Follow the steps recommended in specific drug guidelines (education support booklets)
- Exhale through the nose if possible.

It is essential to ensure that inspiratory flow rates are not excessively high. High inspiratory flow rates can cause impaction of the drug in the upper airway, resulting in cough and irritation, and thereby reducing its efficacy in the lower airway. A first test-dose challenge test (box 2) is recommended for all new inhaled therapies and provides an opportunity for the clinician to teach the correct technique while advising on the likelihood of side-effects that can occur in some individuals. This is essential for enabling ongoing adherence and assessing the presence of true drug intolerances. Centres should adhere to local policies and protocols for these tests. In children under the age of 6 years, this will include an observed dose with oxygen saturation monitoring and chest auscultation. In adults (and children who are able to perform spirometry), pre- and post-inhalation dose spirometry should be performed, in addition to oxygen saturation monitoring, and the percentage constriction (if any) should be calculated. If patients are already prescribed a bronchodilator, they may benefit from the inhalation of this prior to the antibiotic [38] (or hypertonic saline or Bronchitol) inhalation, in order to reduce bronchospasm [39].

Box 2 Example of a first test-dose challenge test procedure

In all cases local policies and protocols should be referred to.

1) Pre-test bronchodilator: yes/no
2) Baseline spirometry: forced expiratory volume in 1 s (FEV_1) plus arterial oxygen saturation measured by pulse oximetry (S_{pO_2})
3) Education
4) Inhalation of the test dose drug with continuous S_{pO_2} monitoring
5) Symptoms assessment
6) Spirometry immediately post-inhalation: FEV_1
7) Calculate % constriction (if any): (Pre-inhalation FEV_1 – Post-inhalation FEV_1/Pre-inhalation FEV_1) × 100
8) Assess as pass/fail (*e.g.* pass if <15% constriction)

Treatment regimens and adherence

People with CF have individualised daily treatment regimens for their inhaled therapies and airway clearance. For the majority of drugs there is a generalised consensus as to what is the optimal order to take them: with bronchodilators and muco-active agents taken prior to airway clearance, and inhaled antibiotics always taken after airway clearance in order to have maximal effect (box 3). rhDNase may be used at different times for maximal benefit [30, 31, 40], it can be used pre-airway clearance to reduce the viscosity of secretions and facilitate easier clearance, or alternatively it may be used post-airway clearance to work on secretions that could not be cleared. Individualised assessment is essential. A recent Cochrane review [34] was inconclusive for recommending the optimal timing.

Patients are constantly making their own judgments about balancing the benefits of treatment against the burden imposed, and clinicians frequently make assumptions as to reasons why adherence is variable. In a structured interview study evaluating the patient's perspective of nebulised therapies [41] most patients knew their correct prescription and the purpose of the drug. They reported variable adherence to their individualised regimens with the top reasons listed as: patient choice (17%), treatment burden (15%), time (15%), adverse effects (11%), and perception of benefit (9%), although actual adherence rates were not reported in this study.

It is generally acknowledged that adherence to therapies is the most difficult aspect of managing CF and poor adherence is the primary cause of treatment failure [42]. Variations in adherence are not unique to CF, but the

Box 3 Recommendations for individualised inhalation treatment strategy

1) Individualised but with basic core principles
2) Bronchodilators: given prior to hypertonic saline, airway clearance and inhaled antibiotics
3) Hypertonic saline/mannitol: given prior to/during airway clearance
4) Inhaled antibiotics: always given post-airway clearance techniques
5) rhDNase: individually assess benefit of giving ~1 h pre-airway clearance or immediately post-airway clearance (but >30 min away from taking inhaled antibiotics)

complexity of the daily treatments required to manage symptoms and slow disease progression is substantial. Many treatments (*e.g.* most physiotherapy treatments) are time consuming and interfere with daily lifestyle, just as we are encouraging people to live as normal lives as possible, with normal life goals and aspirations. Greater adherence is generally correlated with optimism about life in general and those who perceive themselves to be in control of situations generally. However, the unpredictability of the course of CF can present a challenge to an individual's adherence. Adherence does not necessarily improve with an increased understanding, and knowledge of the illness may not equate with responsibility and skill in managing the day-to-day treatment regimens.

Although much credibility is given to rigorously regulated randomised controlled trials, these clinical trials often only describe the efficacy of an intervention under optimal conditions. In the area of inhaled therapies and monitoring adherence, their interpretation is difficult as adherence to the trial intervention is a prerequisite for continued involvement in the trial. Therefore, comparative effectiveness research using real world comparison studies can offer valuable insights into patient experience. Harrison *et al.* [43] compared the safety, efficacy and tolerability of TIP (112 mg total dose in four capsules *via* the turbospin inhaler) *versus* TIS (300 mg in 5 mL nebuliser solution) in 78 patients, *via* a questionnaire based study at baseline and during 12 months of therapy. All patients had previously used TIS and were then changed to TIP, with 94% preferring TIP. Self-reported "excellent adherence" at baseline was 43% (using TIS), with a significant increase to 83% after the transition to TIP. While self-reporting may have over-estimated adherence rates the questionnaire did not mention the word "adherence" and instead asked about the use of TIP, and was not asked by a member of the CF multidisciplinary team. Not only did patient's self-report improved adherence post-transition to TIP, they also improved tolerability. Significantly reduced exacerbation rates (measured by the number of intravenous antibiotic courses in 12 months retrospectively during TIS and prospectively during TIP) were also shown, which clearly individuals could not exaggerate. In addition, in a multicentre evaluation of treatment burden following the initiation of TOBI Podhaler and after completion of three treatment cycles, significant improvements in perceived treatment burden, global satisfaction and convenience were observed and sustained at 5 months post-initiation [44].

Several studies have evaluated self- or clinician-reported adherence compared with objective electronic monitoring [45, 46]. Objective recording is only possible through specific nebuliser devices (Ineb) and it has already been discussed that these do not permit use of all nebulised medications. Electronic monitoring uses downloadable data from the device, which can then feedback information to the clinician and the patient, and can be used as an accurate reflection of nebuliser use. This information can be used to facilitate adherence discussions but can also highlight both device performance issues (*e.g.* longer inhalation times) and potential patient complexities such as difficulty achieving the optimal breathing pattern, and can trigger the need for a device or technique review. These devices also provide opportunities to understand adherence patterns, *e.g.* schoolchildren who were more adherent on weekdays than on weekends and during school terms rather than holidays [47]. With greater understanding of adherence rates and patterns intervention can be individually tailored to be more efficacious and achievable. With the advent of dry powders, there is also no current objective monitoring available, so an open, honest and trust-based relationship between CF teams and their patients is essential.

An alternative method is to study prescription collection rates, known as medication possession ratios, and a vast study in the USA assessed 12-month composite medication possession ratios (CMPR) in 3287 patients with CF (aged over 6 years) for a variety of pulmonary medications [48]. The results showed the highest CMPR for rhDNase (57%), followed by inhaled tobramycin (51%) and inhaled aztreonam (47%). Age was related to the CMPR with highest adherence recorded among

6–10 year olds (59%), which then steadily fell with increasing age, only improving again in those aged over 35 years. Findings were consistent across all drug categories. Lower levels of adherence were associated with more CF-related hospital admissions and higher healthcare costs. Clinicians frequently assume worsening adherence occurs with increasing numbers or types of medication, however this study demonstrated higher CMPR in those who were prescribed more than one medication, with incremental increases as the number of medications increased. Overall, adherence to inhaled medications was generally poor (40–57%), although as this study was based on collection of pharmacy refill prescriptions, the true adherence rates may be even worse.

Points to consider

- Do you have an increased awareness of the progression of inhaled medicines technology and products suitable for use in people with CF?
- Do you have an enhanced awareness of the advantages and disadvantages of using inhaled medications in the context of a chronic lifelong disease like CF?
- Do you have an understanding of the impact of adherence on inhaled medication use and how the choice of both inhaled drug and inhalation device may influence this?
- Do you understand the importance of timing of inhaled medications in relation to other inhaled products and their desired action, *i.e.* in pre- and post-airway clearance?
- Are you able to refer to the key reference material for the main inhaled medicines in use for people with CF and gain further information if required?

Conclusion

The management of CF includes frequent use of multiple inhaled therapies, some of which have been discussed here. It is important to acknowledge the evidence base and adherence to national recommendations and standards, but also to apply this on an individual basis to determine what is best for each individual at that particular point in time. The majority of patients have access to "intelligent nebulisers" that optimise nebulised drug delivery and the CF community has welcomed the emergence of dry-powder inhalers with the potential to improve adherence with comparable efficacy. Although many therapies require repeated applications throughout the day, a positive approach from the CF multidisciplinary team can ensure that the patient is fully informed and aware that taking the full prescribed dose is recommended to achieve the maximal possible benefit. Adherence is a huge challenge and is often difficult to evaluate accurately, but a number of adherence support programmes are emerging that include using technological advances and applications, with support materials and adherence motivators suitable for all ages.

The treatment burden for some individuals with CF is unquestionable, with inhaled therapies contributing only in part to the entire daily treatment regime. The specialist CF multidisciplinary team of today is well informed with efficacy data, national guidance [1] and a growing number of drug/device delivery options to consider. The responsibility is therefore not solely in choosing and prescribing the appropriate medication, it is also essential to evaluate the delivery device and the patients' lifestyle and adherence requirements to ensure CF individuals experience the desired clinical benefit of inhaled therapy.

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