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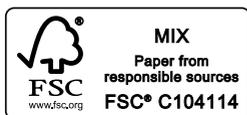
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OPTIMIZING PHARMACEUTICAL CARE IN CYSTIC FIBROSIS

Editors

Siân Bentley, Carlo Castellani, Daniel Peckham, Nicola Shaw

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LIST OF CONTRIBUTORS

Siân Bentley, BPharm (Hons)

Royal Brompton and Harefield NHS Foundation Trust, UK

Amanda Bevan, BSc (Hons), DPharm, IPP

Southampton University Hospitals NHS Trust

Mieke Boon, MD, PhD

Cystic fibrosis Centre, University Hospital of Leuven, Leuven, Belgium

Naim Bouazza, PhD

Université de Paris, Pharmacologie et évaluations thérapeutiques chez l'enfant et la femme enceinte F-75006 Paris, France

Elaine Bowman, BSc (Hons), MSc, IPP

Specialist Respiratory Pharmacist, Royal Brompton and Harefield NHS Foundation Trust

Edwin Brokaar, PharmD

Haga Teaching Hospital, The Hague, The Netherlands

Veerle Bulteel, MSc

Executive Coordinator, ECFS Clinical Trials Network

Giuliana Cangemi, Bsc

Central Laboratory of Analyses, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Elio Castagnola, MD

Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Carlo Castellani, MD

IRCCS Istituto Giannina Gaslini, Genoa, Italy

Anna Connolly, MPharm. PGDip. MPSI

National Referral Centre for Adult Cystic Fibrosis, St. Vincent's University Hospital, Dublin, Ireland

Clare Cox, BPharm (Hons), DipClinPharm

Royal Papworth Hospital, UK

[Grainne Crealey](#), MSc Finance, Ph
National University of Ireland, Galway

[Kris De Boeck](#), MD, PhD
Cystic fibrosis Centre, University Hospital of Leuven, Leuven, Belgium

[Alistair Duff](#), MA, MSc, DClinPsych
Leeds Teaching Hospitals NHS Trust, Leeds, UK

[Nichola MacDuff](#), Advanced clinical nurse specialist
The Royal Wolverhampton NHS Trust, UK

[Fiona Dunlevy](#), PhD
Quality Manager, ECFS Clinical Trials Network

[Isabelle Fajac](#), MD, PhD
APHP.Centre - Université de Paris, Paris, France

[Frantz Foissac](#), PhD
Université de Paris, Pharmacologie et évaluations thérapeutiques chez l'enfant et la femme enceinte F-75006 Paris, France

[Silvia Gartner](#), Pediatric pulmonologist
University Hospital Vall d'Hebron, Barcelona

[Trudy Havermans](#), PhD
Cystic Fibrosis and Transplant Centre, University Hospital Leuven, Belgium

[Kate Hayes](#), PhD
Standardization Coordinator, ECFS Clinical Trials Network

[Hettie M. Janssens](#), MD, PhD
Department of Pediatrics, Division of Respiratory Medicine and Allergology,
Erasmus MC-Sophia Children's Hospital, University Hospital Rotterdam,
The Netherlands

[Jim Littlewood](#), MD, OBE
Cystic Fibrosis Trust

[Francesca Mattioli](#), MD

Department of Internal Medicine, Clinical Pharmacology and Toxicology Unit,
University of Genoa

[Douglas McCabe](#), MPharm (Hons), DipClinPharm, IPP

NHS Lothian, Western General Hospital, Edinburgh.

[Alessio Mesini](#), MD

Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[Lutz Naehrlich](#), MD

Justus-Liebig-University Giessen, Department of Pediatrics, Germany

[Ciaran O'Neill](#), BSc(Econ), PhD

Queens University Belfast

[Olivia K. Paulin](#), MPharm

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde,
Glasgow, United Kingdom

[Daniel Peckham](#), MBBS, DM, FRCP

Regional Adult CF Unit, St James's University Hospital, Leeds, LS97TF, UK

[George Retsch-Bogart](#), MD

Faculty Director of Network Operations, CFF Therapeutics Development Network (TDN)
Coordinating Center and Cystic Fibrosis Center, University of North Carolina at Chapel Hill,
Chapel Hill, NC, USA

[Nicola Rowbotham](#), BSc, PhD, BMBS, PGcert Health Research, MRCPCH

Evidence Based Child Health Group, University of Nottingham, UK

[Michele Samaja](#), Professor of Biochemistry, School of Medicine

Department of Health Science, University of Milan, Italy

[Lisa Sammons](#), Advanced clinical nurse specialist

The Royal Wolverhampton NHS Trust, UK

[Elena K. Schneider-Futschik](#), PharmD, PhD

Department of Pharmacology & Therapeutics, School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, VIC, 3010, Australia

[Michaela Semeraro](#), MD PhD

Centre d'Investigation Clinique Unité de Recherche Clinique-CIC P1419, Hôpital Necker Enfants Malades, Université de Paris, Paris France

[Isabelle Sermet-Gaudelus](#), MD, PhD

Centre de référence Maladies rares, Mucoviscidose et maladies de CFTR, Hôpital Necker Enfants Malades, INSERM U1151, Université paris Sorbonne, ERN Lung

[Nicola Shaw](#), BSc (Hons)

Leeds Teaching Hospitals NHS Trust, UK

[Beth Smith](#), MD

Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York, USA

[Alan Smyth](#), MA, MBBS, MRCP, MD, FRCPCH

Evidence Based Child Health Group, University of Nottingham, UK

[Harm A.W.M. Tiddens](#), MD, PhD

Department of Pediatrics, Division of Respiratory Medicine and Allergy, Erasmus MC-Sophia Children's Hospital, University Hospital Rotterdam, The Netherlands

[Jean-Marc Treluyer](#), MD, PhD

Université de Paris, Pharmacologie et évaluations thérapeutiques chez l'enfant et la femme enceinte F-75006 Paris, France

[Silke van Koningsbruggen-Rietschel](#), MD, PhD

Director ECFS-CTN and Cystic Fibrosis Centre, University Hospital, Faculty of Medicine, University of Cologne, Cologne, Germany

[Paul Whitaker](#), MBBS, MD, FRCP

Department of Respiratory Medicine, Bradford Teaching Hospitals NHS Foundation Trust, Leeds, UK

Erik Wilms, Advanced clinical pharmacist
Apotheek Haagse Ziekenhuizen, The Hague, The Netherlands

PREFACE

Over the last decades, major advances have occurred in the care and treatment of cystic fibrosis (CF) leading to more people with CF living longer, reaching adulthood and enjoying a better quality of life. Advances have gone even more quickly recently with new very innovative genomically-guided therapies becoming available for many patients. Over the last years, the European Cystic Fibrosis Society has published three books describing how to give the best care at different critical ages of life, from early years to adolescence and adulthood. This new book is devoted to the transversal issue of pharmaceutical care in CF.

The goal of this book is not to go into details on how to treat each condition seen in CF which can be found in many other publications, but to inform on issues very specific to CF when using pharmaceutical drugs. For example, the very unique pharmacokinetics seen in CF, the preferred regimens for antibiotic infusions, or the challenges of hospital or home parenteral administrations. The specificities of nebulized delivery, the interactions between medicines used in CF, the evaluation and management of frequent drug reactions, adherence and new challenges in the management of many drugs during pregnancy or breast feeding are covered. Chapters are also devoted to new precision medicines, from development, to access and evaluation in real life.

The European Cystic Fibrosis Society expresses a most heartfelt appreciation to Carlo Castellani, Daniel Peckham, Nicola Shaw and Siân Bentley for their huge work in bringing together international experts in the field to produce this excellent textbook. We are sure that this book will be very useful and informative to caregivers specializing in CF across all ages since the crucial issues are approached in a novel and very pragmatic way.

Isabelle Fajac

President of the European Cystic Fibrosis Society

INTRODUCTION

The care of a chronic and multi-system disease like cystic fibrosis demands a multifaceted therapeutic strategy. This includes the involvement of trained professionals working in a dedicated setting, their close interaction with people with cystic fibrosis and their families, and of course effective medications. The past years have seen a gradual increase in the cystic fibrosis specific armamentarium, with a more recent acceleration towards precision medicine, made possible by the new mutation-specific compounds. This has added to the control of the disease, but also increased the complexity of care management, with added drug interactions, monitoring, administration and adherence issues.

This book is intended to support cystic fibrosis professionals to promote medicines optimization in their practice. We hope it will prove helpful and thank all the authors who contributed and ECFS for believing in it.

Siân Bentley

Carlo Castellani

Daniel Peckham

Nicola Shaw

CHAPTER 1

The role of medicines in changing the clinical history of cystic fibrosis

Authors

Jim Littlewood, Daniel Peckham

Introduction

The survival of children with cystic fibrosis (CF) beyond infancy and early childhood is largely due to medicines that have gradually become available to treat their various respiratory and nutritional problems, amongst others. Dorothy Andersen's first clear description of CF as a specific condition in 1938, in the pre-antibiotic era, was based entirely on autopsy material [1]. Even in the 1940s, severe progressive pulmonary infection and malnutrition, with death in infancy or early childhood was the rule. At this time, available treatments focused mainly on nutrition, and there was still a widespread belief that intestinal malabsorption and malnutrition contributed to the intractable respiratory infections. There was much discussion as to whether the changes in other organs were part of a primary disease process, or secondary to various nutritional deficiencies. This chapter will focus on a brief history of medicines in CF, focusing on drugs which have had a significant benefit to patients as well as those that have not. More detailed infor-

mation is freely available on the website <http://cysticfibrosis.online>.

1 Antibiotics

In 1946, Paul di Sant'Agnese, a pediatrician colleague of Dorothy Andersen in New York, was the first to report the use of penicillin in CF infants and advised *"an appropriate diet begun promptly and continued consistently, use of sulphadiazine during the stage of chronic cough and the use of nebulized penicillin."* In 1943 a small quantity of penicillin became available from the US Army to treat three children with CF and a further two in 1944. The results were variable. However, years later in 2001, di Sant'Agnese [2] recalled *"In most patients the results (of penicillin treatment) were dramatic. From death's door, slowly dying from chronic pulmonary disease while we watched helplessly, patients revived in a few days"* [3]. The main pathogen was *Staphylococcus aureus* which was very sensitive to penicillin and responded impressively to the small doses used.

Harry Shwachman in Boston was more impressed by the wide spectrum antibiotics and later recalled that *“before 1948 there was no antibiotic for CF. There was penicillin and streptomycin: they were not effective. So 1948 was the year of aureomycin and in 1949 we had terramycin”* [4]. Shwachman reported his experience with the broad-spectrum antibiotics, aureomycin and terramycin, from 1949 and their successful long-term use for 6 months to over 6 years [5]. Although there was no evidence that therapy prevented the onset of chest disease, it could control symptoms for prolonged periods and had improved the survival. Between 1945 and 1954 the average age of death was 45.2 months; up to 1949 the age of death had been only 12.8 months [5].

In 1958 Shwachman and Kulczycki in Boston published their classic review of experience with 105 patients [6]. Courses of antibiotics such as chlortetracycline (Aureomycin) or oxytetracycline (Terramycin) were recommended for infections but used continuously only for those who were chronically infected; large doses combined with chloramphenicol or erythromycin were recommended for those with more severe infections. Aerosol antibiotics, penicillin and streptomycin or neomycin and polymyxin (both of which were later recognized as ototoxic), were added for more severe infections. In contrast to present day practice, antibiotics were seldom given intravenously or even intramuscularly. More antibiotics gradually became available with definite benefits, but also with various toxic effects such as ototoxicity from neomycin aerosols [7], staining of the

teeth from tetracycline [8], aplastic anemia and optic neuritis with chloramphenicol [9], renal problems with aminoglycosides [10], and allergic reactions [11]. Nevertheless, oral, intravenous and inhaled antibiotics, continue to have a pivotal role in delaying the onset chronic pulmonary infections and slowing the progression when infection becomes established.

2 A comprehensive therapeutic regimen

Care at a CF center by a team of professionals was pioneered by Leroy Matthews and Carl Doershuk in Cleveland. In 1957 a comprehensive treatment program was started with funding from the local parents and the support of Dr William Wallace, Chairman of Pediatrics, who appointed Dr Leroy Matthews “to plan and initiate a comprehensive treatment and research program for CF patients.” This was essentially an intensive program treating the obstructive pulmonary lesion, the secondary pulmonary infections, the pancreatic exocrine deficiency and the nutritional aspects. The program involved meticulous attention to detail, monthly clinic attendances, early interventions, nebulizer and mist tent therapy, physiotherapy and postural drainage, monthly respiratory cultures and intermittent (but if necessary prolonged oral or intramuscular) vigorous antibiotic treatment of any pathogenic organisms isolated, high protein low fat diet with vitamin supplements and pancreatic replacement therapy. Annual mortality fell from 10% in 1950 to 2% in

1960. From 1961 their program spread nationwide through the CF Foundation's Centers program and was associated with a general fall in the annual mortality rate [12].

3 Long-term anti-staphylococcal antibiotics

A short anecdotal report of long-term use of oxacillin (an anti-staphylococcal antibiotic available from 1962) showed the drug to be safe and that *S. aureus* did not develop resistance. The organism was eradicated in 3/15 patients, as most children had "advanced pulmonary involvement" with chronic entrenched infection by the time the treatment was started [13]. As *S. aureus* was the main pathogen, long-term prophylactic anti-staphylococcal therapy from birth was first recommended in the UK by David Lawson [14], and subsequently supported by experience from East Anglia, UK in infants diagnosed via newborn screening [15]. However, it has long been debated whether prophylactic long-term anti-staphylococcal therapy encourages the growth of *Pseudomonas aeruginosa* [16]. In Copenhagen, a successful alternative to long-term antibiotics for treating *S. aureus*, was based on 15 years experience with 209 patients. If the organism was cultured from the airways of a person with CF "anti-staphylococcal therapy was given whether there were clinical symptoms or not – usually courses of oxacillin and dioxacillin with fusidic acid for 14 days. Chronic infections were given long-term treatment for one to three months" [17]. The UK CF START trial finishing in 2023 should answer the ques-

tions surrounding long-term prophylactic anti-staphylococcal treatment.

4 Increasing use of intravenous antibiotics for *P. aeruginosa*

The earlier, more frequent and more "professional" use of intravenous antibiotics at all stages of infection was a major development during the 1970s. Choosing two antibiotics with the help of expert microbiological support, ensuring adequate blood levels of aminoglycosides and allowing for the altered pharmacokinetics of antibiotics in people with CF, all became routine in most CF centers during the 1980s. Intensive courses of intravenous antibiotics became routine treatment for exacerbations of the chest infection [18], or as regular three-monthly courses in patients who were chronically infected with *P. aeruginosa* [19]. New anti-pseudomonal antibiotics became available giving clinicians wider choice: azlocillin in 1980, piperacillin in 1982, netilmicin in 1982, ceftazidime in 1983, aztreonam in 1986, and oral ciprofloxacin in 1986. Improved delivery systems and intravenous access facilitated more aggressive intravenous antibiotic therapy.

5 Three-monthly intravenous antibiotics for chronic *Pseudomonas* infection

Improved survival was reported by the Copenhagen CF center since starting three-monthly courses of intravenous anti-pseudomonal antibiotics for all chronically

infected patients from 1976 (5-year survival 82%) [19]. During the period 1971 to 1975, 51 chronically infected CF patients were treated with intravenous antibiotics but only when their condition deteriorated (5-year survival 54%). These results were largely ignored outside Denmark, or the treatment was regarded as over intensive. True, this was not a controlled trial and there were problems outside Denmark with the cost of the antibiotics, drug allergies, the patients' time and quality of life. It is important to note that long-term nebulized antibiotics [20] that frequently stabilize the respiratory function of chronically infected patients were not yet used at the time of this Danish study. However, the regimen is a measure of the more intensive treatment at the Copenhagen center. Clinicians elsewhere, including the UK, were still using intravenous antibiotics only as a last resort, even in the early 1980s. With the advent of long-term inhaled anti-pseudomonal therapy, intervals between courses of intravenous antibiotics could be extended in those patients who remained quite stable. During the 1980s the increasing reliance on and the more frequent use of intravenous antibiotics increased pressure on hospital beds and also on families' domestic arrangements. Therefore home administration of antibiotics, supervised by specialized CF staff gradually became more frequent in most CF centers [21-23]. The first home intravenous antibiotic series was reported from Texas in 1974. A scalp vein needle and tube were used as a heparin lock [21] to administer gentamicin and also colistin for 127 courses in 67 patients with no major complications.

6 An effective oral anti-pseudomonal antibiotic

As *P. aeruginosa* gradually replaced *S. aureus* as the main pathogen, ciprofloxacin, an effective oral anti-pseudomonal antibiotic was very welcome in the mid-1980s, sparing many patients intravenous antibiotic treatment and hospitalization [24]. It became widely used for oral administration in chest infections in patients with CF and as part of early eradication treatment [25].

7 Nebulized antibiotics to stabilize chronic *Pseudomonas* chest infection and eradicate early infection

In 1981 an early paper by Margaret Hodson from the Royal Brompton Hospital in London had a major influence on treatment in the UK [20]. Although nebulized penicillin had been used in the 1940s when *S. aureus* was the main pathogen [2], Hodson's present paper revived the interest in nebulized antibiotics for patients chronically infected with *P. aeruginosa* to significantly reduce the frequency of exacerbations. As a direct result of this paper, patients with chronic *Pseudomonas* chest infection were increasingly treated with intravenous preparations of nebulized anti-pseudomonal antibiotics gentamicin and tobramycin, with or without a synthetic penicillin. This contrasted with North America where, even in 1986, McLusky and colleagues at the Toronto clinic advised that, "until additional well-controlled trials were completed, their routine use (of inhaled antibiotics) was

not justified because of cost, potential side effects and the propensity to select resistant organisms” [26].

Nebulized antibiotic therapy became widely used to treat people with CF, eventually reducing the proportion of patients with chronic *P. aeruginosa* infection. Interest was revived in nebulized colomycin by a 1985 short report from Leeds [27] of the successful eradication of early colonization with *P. aeruginosa* in CF using nebulized colomycin – an observation later confirmed in Copenhagen [25] and in a number of other small studies from Europe. According to Hoiby, nebulized colomycin was also introduced into the treatment of chronically infected patients in Copenhagen in 1987 on the strength of the initial 1985 report from Leeds [28]. Over the next couple of decades, colistin, inhaled preservative free tobramycin, aztreonam lysine, levofloxacin and amikacin have been introduced into clinical practice.

The possibility of eradicating early *Pseudomonas* infection, first suggested in a 1985 letter to the Lancet from Leeds [27], was confirmed in this first Copenhagen clinical trial of early eradication therapy for *Pseudomonas* [25]. Early *P. aeruginosa* infection could be eradicated in 80% of patients with CF by three weeks treatment with oral ciprofloxacin and nebulized colistin. As historical controls were used, many clinicians did not accept the results, delaying the benefits of early eradication to many patients for a further decade. Early eradication of *P. aeruginosa* is now standard practice although multiple different regimens are often used, including nebulized

antibiotics as single agents or in combination with oral or intravenous antibiotics [29].

8 Macrolides

The initial interest in the use of macrolides (such as erythromycin) in chronic *P. aeruginosa* infection followed impressive results from Japan in diffuse panbronchiolitis [30, 31]. Mark Everard believes the first report of the use of macrolides in CF was in a Japanese publication by Nakanishi *et al.* in 1995 describing a 16-year-old boy with CF admitted to hospital with a severe chest infection, diffuse reticulonodular shadows and over inflation on X-ray, and pulmonary function tests showing obstructive and restrictive impairment. Erythromycin and lomefloxacin were administered by mouth, and aminoglycosides were administered by inhalation. His symptoms were alleviated, and at the time of reporting he was an outpatient. In this case, low-dose and long-term erythromycin administration was very effective [32, 33]. The beneficial effect of 600 mg/day of erythromycin for 1 to 12 months in chronic panbronchiolitis in Japanese patients had been reported previously [30]. The effect appeared to be independent of the presence of chronic *Pseudomonas* infection and an anti-inflammatory action was suggested. The first use of macrolides in CF from Sheffield UK and Perth Western Australia showed an anti-inflammatory effect in people with CF. Four of six patients with CF had significant reduction in IL-8 sputum levels after one-month treatment

with low dose oral erythromycin (200 mg three times per day) [33].

The use of macrolides in CF was approved in the US following a study from the US showing that participants in the azithromycin group had less risk of experiencing an exacerbation than participants in the placebo group, and at the end of the study weighed an average of 0.7 kg more than participants receiving placebo. The authors concluded that azithromycin treatment was associated with improvement in a clinically relevant endpoint and should be considered for patients with CF who are 6 years or older and chronically infected with *P. aeruginosa* [34].

The OPTIMIZE (Optimizing Treatment for Early *Pseudomonas aeruginosa* Infection in CF) trial was a multicenter, double-blind, randomized, placebo-controlled, 18-month trial in children with CF, 6 months to 18 years of age, with early *P. aeruginosa*. Azithromycin or placebo was given 3 times weekly with standardized tobramycin inhalation solution. The trial demonstrated a significant reduction in the risk of pulmonary exacerbation and sustained improvement in weight associated with azithromycin use as compared with placebo among children recently infected with *P. aeruginosa*.

A more recent study assessed 1065 children and 990 adults in the French CF Registry from 2 years before to 5 years after long-term azithromycin treatment initiated between 2001 and 2011. The results supported the beneficial effect of low dose macrolides. In children, long-term azithromycin treatment was associated with immediate and sustained beneficial changes in lung function and sustained

beneficial changes in the frequency of pulmonary exacerbations. In adults, it was associated with immediate beneficial changes in lung function.

9 Recombinant human DNase

The effect of various enzymes on the viscosity of CF sputum showed that pancreatic dornase had the most marked effect showing complete dissolution of the fibrous structure of the sputum [35]. This finding supported the theory that the excessive viscosity of CF sputum was related to a fibrous network observed in the sputum, primarily the result of deoxyribonucleoproteins. These early studies eventually led to the introduction of DNase as an effective mucolytic, but only after the unacceptable side effects of the biological product (a bovine preparation) were circumvented by producing a genetically engineered product rhDNase (Pulmozyme) [36].

Following two small efficacy and safety studies [37], a randomized, double-blind, placebo-controlled study was conducted to determine the effects of once-daily and twice-daily administration of rhDNase on the frequency of exacerbations of respiratory symptoms, parenteral antibiotic usage and decline in pulmonary function. A total of 968 adults and children with CF were treated for 24 weeks as outpatients. The administration of rhDNase once and twice daily reduced the age-adjusted risk of respiratory exacerbations by 28% and 37%, respectively, and improved forced expiratory volume in one second (FEV₁)

during the study by a mean of 5.8% and 5.6%, respectively. Transient voice alteration and laryngitis were more frequent in rhDNase-treated patients [38].

A 96-week, randomized, double-blind, placebo-controlled trial involved 49 CF centers and 474 children aged 6 to 10 years. At 96 weeks the treated group had maintained their respiratory function levels; the treatment benefit for dornase alfa compared with placebo in percent predicted mean was 3.2% for forced expiratory volume in one second (FEV_1), 7.9% for average forced expiratory flow during the forced expiratory fraction ($FEF_{25-75\%}$) and 0.7% for forced vital capacity (FVC). The risk of respiratory tract exacerbation was reduced by 34% [39]. The results of this trial influenced some pediatricians to try young CF patients on dornase alpha before they developed chronic infection and this became routine practice in some centers. In Copenhagen, treatment was found to reduce the frequency of respiratory exacerbations and new positive respiratory tract cultures [40].

Dornase alpha has proved to be one of the most successful therapies introduced during the past 20 years. It is undoubtedly a medicine that has had a major positive effect on people with CF of all ages and all severity of involvement.

10 Hypertonic saline

In an early study in 1996, the inhalation of hypertonic (7%) saline alone, and with amiloride, significantly increased the

amount of radio aerosol cleared from the right lung at 60 and 90 minutes [41]. The authors suggested that inhaled hypertonic saline was a potentially useful treatment for CF. Peter Bye's group at the Adult CF Center at St Vincent's Hospital in Sydney continued their work on hypertonic saline and eventually carried out a successful clinical trial of hypertonic saline in adults with CF, confirming its value in the treatment of CF [42].

In a much quoted double-blind, parallel-group trial from Sydney, 164 patients with stable CF who were at least six years old were randomly assigned to inhale 4 mL of either 7% hypertonic saline or 0.9% (control) saline twice daily for 48 weeks, each dose preceded by a bronchodilator. Compared with the control group, the hypertonic saline group had significantly higher FVC (by 82 mL) and FEV_1 (68 mL) values, but similar FEF_{25-75} . The hypertonic saline group also had significantly fewer pulmonary exacerbations and higher percentage of patients without exacerbations. The authors concluded that hypertonic saline preceded by a bronchodilator is an inexpensive, safe, and effective additional therapy for patients with CF [42].

A major study to determine if inhaled hypertonic saline reduced the frequency of exacerbations in patients less than six years was undertaken by Rosenfeld *et al.* [43], involving 321 children aged 4 to 60 months. The authors found that among infants and children with CF younger than six years, the use of inhaled hypertonic saline compared with isotonic saline did not reduce the rate of pulmonary exacerbations over the course of 48 weeks of treatment.

The most recent Cochrane review (in 2018) concludes that regular use of nebulized hypertonic saline by adults and children over the age of 12 years with CF results in improved lung function after four weeks (very low-quality evidence from three trials), but this was not sustained at 48 weeks (low-quality evidence from one trial). The review did show that nebulized hypertonic saline reduced the frequency of pulmonary exacerbations in patients aged over 6 years. Hypertonic saline does appear to be an effective adjunct to physiotherapy during acute exacerbations of lung disease in adults [44]. However it is not a replacement for rhDNase.

11 Mannitol

It had been suggested that hypertonic saline might impair the antimicrobials effects of defensins in the airways, so in 1999 Robinson *et al.* reported their experience with another osmotic agent - dry powder mannitol (300 mg) in 12 patients with CF [45]. They compared the effect of mannitol and its control (empty capsules plus matched voluntary cough) and a 6% solution of hypertonic saline (HS) on bronchial mucus clearance (BMC), measured by a radio aerosol / gamma camera technique. There was a significant improvement in cough clearance with the mannitol ($9.7 \pm 2.4\%$) compared to control ($2.5 \pm 0.8\%$). Despite premedication with a bronchodilator, a small fall in FEV₁ was seen immediately after administration of both the mannitol (7.3%) and hypertonic saline

(5.8%) with values returning to baseline by the end of the study.

Subsequently a short term study of the effect of 420 mg of inhaled mannitol twice daily significantly improved lung function in patients with CF [46].

A pooled analysis was performed of the two phase 3 trials in which 600 patients inhaled either mannitol (400 mg) or control (mannitol 50 mg) twice a day for 26 weeks [47]. Both the mean absolute change in FEV₁ (73.42 mL) and relative change in FEV₁ by % predicted from baseline for mannitol 400 mg (3.56%) versus control were statistically significant (both $p < 0.001$). Increases in FEV₁ were observed irrespective of rhDNase use. Significant improvements in FEV₁ occurred in adults but not children aged 6-11 years or adolescents aged 12-17. Pulmonary exacerbation incidence was reduced by 29% ($p = 0.039$) in the mannitol 400 mg group. The authors concluded there were sustained six-month improvements in lung function and decreased incidence of pulmonary exacerbations, indicating that inhaled mannitol is an important additional drug in the treatment of CF.

12 N-acetylcysteine

The N-acetylcysteine (NAC) story in relation to CF is quite remarkable. Although declared to be well tolerated with no significant adverse effects and without evidence of significant clinical benefit in CF, reports of its use keep appearing. A systematic review in 1999 from Groningen considered 23 studies of NAC in CF. There were only

three randomized controlled trials on nebulized NAC, none showing any effect on lung function. Six trials of oral NAC in CF showed an insignificant tendency towards beneficial effect on lung function. A more recent systematic review identified 23 trials, of which nine trials (255 participants) were included in the review analysis (seven of the ten trials were more than 10 years old) [48]. Three trials of nebulized thiol derivatives were identified. The authors found no evidence to recommend the use of inhaled or oral NAC.

13 Denufosal

Denufosal is a selective P2Y2 agonist that stimulates ciliary beat frequency and chloride secretion in normal and CF airway epithelia via both P2Y2 activation and inhibition of epithelial sodium transport. The early clinical trials funded by the CF Foundation (CFF) were encouraging, but the drug failed to achieve significance in the second phase 3 study [49]. Dr Robert J. Beall, Ph.D., President and CEO of the CFF at the time, said *“This is a serious disappointment to the entire CF community. We have long understood that drug development is not predictable, but we are always hopeful that promising therapies will prove effective for those with CF. Inspire’s latest data underscores the importance of our pursuing multiple new therapies that can control and cure CF.”*

14 Alpha-1-antitrypsin

Alpha-1-antitrypsin, the main inhibitor of neutrophil elastase, was given in aerosol form to 12 CF patients, and was found to suppress neutrophil elastase in respiratory lining fluid. CF epithelial lining fluid inhibits neutrophil-mediated killing of *P. aeruginosa* but this was reversed by alpha-1-antitrypsin [50]. Apparently, the material used in this trial (purified human plasma alpha-1-antitrypsin [Prolastin] from Cutter Biological) was very difficult to obtain in sufficient quantities. A subsequent trial, with a genetically engineered product, disappointingly failed to show significant benefit to patients with CF [51]. The clear reduction in airway inflammation has sustained research interest in this area, even though no improvement in lung function was observed [52].

15 Amiloride

Michael Knowles first discovered the increased bioelectrical potential difference across CF respiratory epithelium [53]. In a key study, Knowles and Boucher investigated whether inhibition of excessive sodium absorption by inhaled amiloride might favorably affect the course of CF lung disease. Fourteen of eighteen patients completed a one year double-blind, cross-over trial comparing aerosolized amiloride four times daily to control solution. The

mean loss of FVC was reduced from 3.39 mL per day during treatment with vehicle alone to 1.44 mL per day with amiloride. Sputum viscosity and elasticity, and mucociliary and cough clearance improved during treatment, suggesting a beneficial effect. This trial created considerable interest but the effect of amiloride was modest and short-lived; also, the loss of FVC in the control group seemed excessive. A small UK study found no added benefit from nebulized amiloride [54], as did a larger French study of 64 patients with CF, chronically infected with *P. aeruginosa* who received nebulized amiloride or placebo three times daily for 6 months [55].

16 Gentamicin and ataluren (PTC124)

In 1996 Howard and co-workers demonstrated in cells carrying *CFTR* nonsense mutations, that gentamicin induced a dose-dependent increase in expression of full-length *CFTR* [56]. Subsequently Bedwell and coworkers showed in a CF bronchial epithelial cell line carrying the *CFTR* W1282X premature stop mutation, that gentamicin was capable of restoring *CFTR* expression on the apical membrane [57]. Michael Wilschanski and colleagues from Haddash University Hospital, Israel, were the first to show that gentamicin *in vivo* could activate mutant *CFTR* in CF patients carrying stop mutations as had been suggested by Howard *et al.* (1996) and Bedwell *et al.* (1997) [56, 57]. Nine people with CF carrying stop mutations received gentamicin nasal drops for 14 days.

The abnormal nasal potential difference improved after gentamicin treatment, suggesting that chloride transport had increased. The authors concluded that gentamicin may influence the underlying chloride transport abnormality in patients with CF carrying stop mutations (i.e. those mutations containing an X) [58].

Subsequently another compound, PTC124 (later called ataluren), was identified and seemed to do the job more efficiently and went into clinical trials. The new chemical entity selectively induces ribosomal read through of premature but not normal termination codons.

Early studies showed modest improvements in pulmonary function and a reduction in quantitative cough assessment. These effects were not observed in a larger phase 3 trial but sub-analysis suggested that these results could have been affected by the concomitant treatment with inhaled tobramycin [59]. A further phase 3 placebo-controlled efficacy trial was therefore undertaken in the absence of tobramycin. Neither percent predicted (pp) FEV₁, change nor pulmonary exacerbation rate over 48 weeks was statistically different between active and placebo groups. Development of a nonsense-mutation CF therapy remains elusive.

17 Intestinal malabsorption, malnutrition and pancreatic enzymes

Fibrocystic disease of the pancreas was identified most clearly by Dorothy Andersen, a pediatric pathologist in New

York [1]. Most infants died in infancy from pneumonia and virtually all had severe intestinal malabsorption, which was documented in a number of studies. In the 1940s the nutritional aspects of CF were regarded of major importance in pathogenesis, even with regard to vitamin A. Andersen's early recommendations were "a diet low in fat, high in protein with liberal allowance of fruit and vegetables and moderate restriction of starch. Supplementary vitamin A is essential and pancreatin and vitamin B complex are given." Some of the first objective evidence that treatment with pancreatin had a favorable effect on absorption showed that treatment improved fat absorption and halved nitrogen output [60, 61]. In 1958 as part of a very extensive review, Andersen described the malnutrition and growth retardation which occurred in most CF patients, including deficiency of fat-soluble vitamins with overt vitamin A deficiency, bleeding from vitamin K deficiency, vitamin D deficiency and tocopherol deficiency. During the 1970s there was increasing interest in the extent and severity of nutritional problems, and survival steadily improved.

From the early 1970s Crozier in Toronto abandoned the traditional low-fat diet believing that "to deprive the child with CF, who usually has very little subcutaneous fat of this important nutrient seems ridiculous" [62]. As early as 1972 he changed his patients to a high saturated fat diet of whole milk, butter, eggs and animal fats. This new regimen resulted in improved body weight, an 11% increase in cholesterol and 12% increase in triglycerides. However, the increased fat intake did require the patients to take 60 to 100 Cotazym capsules a day.

Crozier had laid the foundations for the nutrition philosophy of the Toronto clinic, later considered to be a major factor in the exceptional survival of their patients.

During the 1980s the tendency to stop restricting dietary fat to increase energy intake was slow to be adopted, with some senior pediatricians believing "steatorrhea is seldom controlled by pancreatin alone and reduction of fat in the diet is necessary".

18 New acid-resistant microsphere enzyme preparations were a major advance

Pancreatic enzyme preparations available at the end of the 1970s were crude, impure and inefficient, regarded more as a food supplement than a new drug. The modest effect of these preparations was explained by the fact that up to 90% of that activity was destroyed by gastric acid. In the late 1970s, the new acid-resistant microspheres Pancrease became available in North America. A comparison between the new pH-sensitive microspheres (Pancrease) and encapsulated enzyme powder (Cotazym) showed the new enteric coated product significantly improved fat absorption compared to the conventional enzyme capsule.

In 1992 onwards, a number of studies showed that recently introduced new high lipase enzymes were as effective as the standard enzymes, reducing the number of capsules required to achieve control and the same lipase intake [63].

In 1993 a new complication, fibrosing colonoopathy, was observed in five CF children with unusual strictures of the ascending colon [64]. Studies in the UK and US showed a relationship with the very high dose of lipase achieved with the new enzymes; in the UK study there was also an association with Eudragit L30D55, the copolymer in the covering of certain brands of high-strength preparation. Although there was lack of agreement on the role of copolymer in causing fibrosing colonopathy, all agreed that high doses of the new lipase preparations were relevant to the etiology of the complication.

19 CF related diabetes

With increasing survival, CF related diabetes (CFRD) affects a greater number of patients. An early important observation was that the gradual onset of glucose intolerance was associated with a worse prognosis [65]. The details of the identification and treatment of glucose intolerance receive increasing attention as the age of the CF population increases. Insulin remains the mainstay of treatment.

20 Ibuprofen

In the late 1980s, the CFF funded a major study to determine the benefits of treating inflammation in the CF airways with long-term oral ibuprofen. The authors concluded that in patients with CF and

“mild” lung disease, high-dose ibuprofen, taken consistently for four years, significantly slows the progression of the lung disease without serious adverse effects [66]. Despite these results, the benefits of ibuprofen in this trial were not convincing to most clinicians. Subsequently the modest effect and frequent side effects prevented the widespread use of ibuprofen and the treatment never became popular even in the US – only some 5% of patients on the CFF’s registry reported taking the drug. The most recent evidence from Michael Konstan [67] reported that high-dose ibuprofen treatment was associated with the rate of FEV₁ decline and mortality among children followed in the Epidemiologic Study of CF (ESCF) and subsequently in the US CF Foundation Patient Registry (CFFPR). In a propensity-score matched cohort study of children with CF, the authors observed an association between high-dose ibuprofen use and both slower lung function decline and improved long-term survival.

21 A new era of treatment

Most of the medicines discussed above have had a favorable effect on people with CF by improving symptom control and slowing disease progression. They have contributed to a steady increase in survival and improvements in quality of life. The recent introduction of CFTR modulators into clinical practice has resulted in a paradigm shift in treatment, where targeting the origin of CF rather than the secondary

effects of CFTR dysfunction has become a reality. The potential impact of these medications was first highlighted by Ramsey *et al.* in their landmark paper reporting on the effects of ivacaftor in patients with the G551D (c.1652G>A/p.Gly551Asp) mutation [68]. These results surpassed expectation and have recently been replicated in clinical trials of triple CFTR modulator therapy in people with CF and a F508del (c.1521_1523delCTT/p.Phe508del) mutation [69]. The long-term effectiveness of these small molecules is still unknown but they are likely to change the natural history of the disease and modify the clinical effectiveness of many conventional therapies. New studies will be needed to evidence base drug withdrawal and improve treatment burden.

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CHAPTER 2

Cystic fibrosis medication: present and future

Authors

Siân Bentley, Daniel Peckham,
Carlo Castellani, Nicola Shaw

Introduction

The treatment of cystic fibrosis (CF) has dramatically improved over the past few decades with life expectancy increasing to over 40 years of age in many countries [1, 2]. This change in clinical outcome reflects a proactive multidisciplinary approach to treatment, with a focus on early interventions to avoid disease progression. The international culture of clinical, scientific and patient collaboration in the field of CF has also been pivotal in driving an evidence-based approach to treatment and provided the foundation for translational research and drug development.

High standards of care are essential if clinical outcome is to continue improving. This includes facilities for neonatal screening and systems and processes in place to ensure prompt and accurate diagnosis, delivery of care in a multidisciplinary center with appropriate expertise, and easy access to medications which will minimize disease progression and reduce CF related complications.

Therapeutic intervention in CF can be challenging due to the complex multi-system nature of the disease, variability in concordance and limited effectiveness of some drug therapies [3]. Treatment should ultimately aim to maximize quantity and quality of life for people with CF, while minimizing treatment burden. The pharmacological management of CF care is particularly challenging due to the polypharmacy nature of prescribing, variability in doses and regimens schedules, drug interactions, frequency of side effects, drug accessibility issues and adherence to treatment.

1 Antibiotics

Despite the growing number of drugs available for the treatment of CF, there is often limited evidence to support interventions. Surprisingly this can relate to everyday practice, including routine administration of antibiotics. Treatment decisions are often made based on the best possible evidence in combination with clinical experience. A recent systematic review identified 148 gaps in the evidence base available when making treatment decisions for the management of CF [4]. Most of these evidence

gaps are related to drug therapy, especially the use of antibiotics, where there has long been diversity in clinical practice. This is highlighted by the differences reported in a survey assessing the dosing schedule for 24 intravenous antibiotics used in the management of CF. The authors found significant disparity between units, with the average consensus rate for the most commonly prescribed dosing schedule being 58.2% (range = 23.1–100%). Full concordance was reported for only two antibiotics [5]. This does not mean that treatment is ineffectual as the introduction of aggressive antibiotic therapy, including evidence-based nebulized antibiotics, has played a major role in reducing morbidity and mortality in people with CF [6]. The low level of consensus partly reflects the complex nature of CF, variations between individuals in the clinical response to treatment, the inextricable link between infection and inflammation, and the limited effectiveness of antibiotic treatment in some patients [7, 8]. Developing an evidence-based and standardized approach towards antibiotic treatment has become particularly important in the global context of growing antimicrobial resistance and the proliferation of multiresistant organisms [9]. In patients with CF, antibiotic resistance has significant implications as it will limit treatment options, reduce the effectiveness of antimicrobial activity and may preclude lung transplantation. Similarly the overuse of antibiotics can also result in an increased prevalence of drug allergy and other drug-related complications [10]. Indeed, the seemingly simple question of “which antibiotics, when, at what dose, and for how long?” lacks a robust evidence

base to support the basis for all current CF supportive care. Without rational evidence-based use of antibiotics, we could potentially do more harm than good, given the growing insight into the lung microbiota, in particular the links between lower lung microbiota diversity, increased airway inflammation and current antibiotic use [11].

This is also borne out with potential links between the use of anti-staphylococcal prophylaxis and acquisition of *Pseudomonas aeruginosa* [12], and use of antimicrobial medicines and increasing incidence of fungus [13] and nontuberculous mycobacterium [14]. Similarly, antibiotics can influence lung immunity by altering the gut microbiota through the gut lung axis [15, 16]. Antibiotics tend to shift the gut microbiota towards decreased abundance of beneficial bacterial species and increase the outgrowth of pathogenic ones such as *Clostridium difficile*. Alteration of gut bacterial diversity can change local and systemic metabolism, immunity and can increase susceptibility to pulmonary infection and inflammation [15-17].

With an increasing burden of highly resistant pathogenic organisms affecting patients with CF, new antibiotic classes and non-antimicrobial adjuncts are urgently needed. At the same time, we must optimize existing medicines by collaborating to develop robust evidence to guide best practice, and reduce the negative effects of antimicrobial use.

2 Antifungals

Fungal disease is another area where robust evidence is lacking despite the increase in prevalence of fungal infections in people with CF [18]. Treatment is made even more difficult due to similarities between the symptoms of bronchiectasis, *Aspergillus* bronchitis and bronchopulmonary aspergillosis and the limitation in the specificity and sensitivity of biomarkers used to monitor disease activity. The use or perhaps overuse of antifungals has resulted in increased resistance. Resistance of *Aspergillus fumigatus* isolates to at least one azole has been reported to be as high as 16.2% of patients with CF [19]. This is compounded by a lack of routine drug level monitoring to ensure therapeutic levels, which can vary significantly between individuals [20, 21]. Contrary to antimicrobials, there are comparatively limited options available to treat fungal infections and this is further compounded by systemic toxicity that characterizes some of the key classes of antifungal medicines, such as triazoles and amphotericin. Azoles interact with CFTR modulators while voriconazole enhances UV-induced DNA damage and may be associated with malignancies. Work is ongoing to improve the accuracy of diagnostic and monitoring tools and to develop new antifungal compounds that will be less toxic to patients, while still combatting resistance. This includes the development of designer drugs which can be delivering directly to the site of action, by nebulization or inhalation.

3 Treating comorbidities

The increase in patient survival and the advent of a generation of older patients with CF brings new challenges. The complications arising from CF, drug therapy and growing old will need to be tackled in an extended multidisciplinary team. Examples include complications such as retinopathy, nephropathy and microalbuminuria associated with CF related diabetes (CFRD). There is evidence that CFTR modulator therapy improves pancreatic exocrine function and, although only time will tell, this is most likely to benefit young patients.

CFRD increases treatment burden and can be associated with reduced adherence. The introduction of devices such as insulin pumps, non-invasive sensors such as Free-style libre and access to remote monitoring platforms is helping to simplify treatment. While insulin remains the gold standard and the only treatment proven to improve CFRD outcomes [22], alternative therapies, particularly effective oral medicines, are needed to circumvent the need for regular subcutaneous injections, and their associated practical and social difficulties.

Similarly, CF related liver disease is an area which lacks treatment options, and robust evidence is lacking for existing treatment options such as ursodeoxycholic acid [23].

4 CFTR modulators

The introduction of effective CFTR modulators into clinical practice has resulted in a paradigm shift in treatment, where targeting the clinico-pathogenic origin of CF rather than the secondary effects of CFTR dysfunction has become a reality [24]. The first drug to be licensed was ivacaftor, a CFTR potentiator which increased the open probability of the CFTR channel when expressed in the membrane [24]. This drug is ineffective for CF associated with the F508del CFTR mutation (Phe508del, p. [phe508del]/c.[1521_1523delCTT]) and ivacaftor treatment is limited to specific gating and residual function mutations, such as G551D (c.1652G>A/p.Gly551Asp). Clinical trials have demonstrated significant clinical benefit from this drug, with improvements in quality of life, lung function, weight and sweat chloride [24].

The most common CF mutation worldwide is F508del, which results in inadequate processing and retention of CFTR protein in the endoplasmic reticulum (ER). Recently approved treatments for individuals homozygous for this mutation combine the correctors lumacaftor or tezacaftor to increase CFTR folding and cell surface location, with ivacaftor to increase CFTR channel activity. This treatment regimen results in modest improvements in lung function with a reduction in pulmonary exacerbations [25-27]. Phase 3 studies have now shown promising results using triple combination molecules (the correctors elexacaftor/tezacaftor plus ivacaftor) for patients who are

heterozygous for F508del with a minimal function allele, as well as improved results for F508del homozygous patients [28, 29]. The drug has now been approved in the USA and could provide CFTR modulation for up to 90% of patients [23]. However, such therapies remain elusive for those patients with Class 1 (nonsense) mutations and further research is needed to ensure that precision medicine is available to all patients.

To realize their potential, CFTR modulator therapies must overcome several challenges. Drug availability is probably the most pressing challenge for patients, with many healthcare systems unable to support the prohibitive high cost of supplying these medicines.

Secondly, drug approval bodies must consider how patients with very rare mutations, who are generally not included in large trials necessary for approval by regulatory bodies, can gain access to potentially effective treatments.

Lastly, the evidence base must be extended to treat children at first diagnosis, and potentially *in utero*, if we are to maximize the potential benefits and avoid the sequela of disease progression. This goes hand in hand with the need to gather long-term safety and efficacy data to support the use of CFTR modulators, and provide a platform to drive the development of new CFTR disease modifying medicines. We also must consider the impact of CFTR modulators on the need for current supportive therapies. There are early signals that pancreatic

function may be restored in some patients treated with CFTR modulators [30]. If the benefits of CFTR modulators extrapolate to other key therapy areas, such as airway clearance, more research will be required to ascertain if and when supportive therapies are still required to modify disease progression.

5 Adherence

People with CF often use more than ten medications per day [31] and a large proportion of them are non-adherent to their treatment regimens [32-35]. A recent survey reported that the median daily time for taking treatments was 2 hours (interquartile range was 2-3 hours) [31]. The perceived treatment burden and daily treatment activities are reported to be high amongst adults with CF regardless of age and disease severity [36].

Poor adherence has been associated with a decline in lung function and an increase in pulmonary exacerbations requiring IV antibiotics [37]. Poor adherence also has economic implications, with an increased utilization of health resources and time spent away from employment or education [32, 38].

In CF, non-adherence to medication is multifactorial with multiple reasons being cited for not taking treatment as prescribed, including lack of time, forgetfulness, and unwillingness to take medication in public [39]. Perception of the effectiveness of

treatment and treatment beliefs are also important determinants that need to be considered [40]. Higher perceived need for treatment and lower perceived concerns regarding treatment are associated with better adherence [41]. However, it is interesting that adherence has been shown to be suboptimal with the CFTR modulators, a class of medication with an assumed high perceived treatment need [42].

Adherence is a complex behavior, varies between individuals [43]. Understanding the reasons for non-adherence is crucial to address the problem and to assist with intervention design. Interventions should be individualized as a “one size fits all” solution is unlikely to be successful [44]. At present, there is little evidence to support which interventional strategies are effective in supporting adherence in the CF population. A qualitative approach to explore in greater detail which barriers and facilitators influence adherence is crucial to designing a successful intervention for an individual with CF [44-46]. Some of the identified facilitators for adherence include recognizing the importance of therapies, developing a strong relationship with the care teams and establishing a structured routine [45]. The development of routines or habits is one of the behaviors that has been associated with high adherence rates [44, 47]. The delivery of advice to encourage habit formation (taking treatments in a specific context which does not alter) is recommended

to be part of the intervention package to improve adherence [47].

It is also essential that intervention design and execution involve the individual person with CF, that it is acceptable, and the goals are achievable. Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments [48].

CF specialist pharmacists within the multi-disciplinary team for every center in Europe.

In the following chapters we explore a selection of topical issues and address some of the current pharmaceutical challenges in CF care (**Table 1**).

6 The CF pharmacist

While most of this article has focused on the prescribing of medicines, the benefits of a dedicated CF pharmacist cannot be understated. They provide an invaluable role in the day-to-day management of CF, especially in an era of increasing prescribing complexity. Their role is highly cost effective and has the added advantage of directly supporting patient education and helping the delivery of effective homecare. The European CF Society Best Practice Guidelines [31] state that “the inclusion of a CF specialized pharmacist in the CF team is important”. While many teams in the UK and Ireland include a CF pharmacist, this is not the case for many centers in Europe. One survey suggested that less than half of respondents have access to a clinical pharmacist [32]. With the advent of increasingly complex personalized medicine and the potential for polypharmacy when treating an ageing population, it is imperative that the CF community works towards including

Main Theme	Topics
Pharmacology themes	Pharmacodynamics, pharmacokinetics, infusion strategies, plasma drug level monitoring Major common interactions
The CF pharmacist	Role of pharmacist in the multidisciplinary team, including: prescription monitoring and medication review service, managing formularies, clinical guidelines and treatment protocols, identifying patient and medication risk factors, preventing, detecting and reporting adverse drug reactions, individualizing drug and dosage requirements, educating and counselling patients and carers, evaluating medicine use and financial management, antimicrobial stewardship, providing medication closer to home, pharmacist prescribing
Administration routes	Access, monitoring and support of parenteral lines Physiology of drug inhalation and deposition Types of nebulizer and inhaler devices.
Special populations and situations	Peculiarities of pediatric dosages and administration Contraception in CF CF therapies during pregnancy and breast feeding Diabetic control in pregnancy Preventing and managing drug reactions and desensitization models
New therapies	The CF pharmaceutical pipeline Precision medicine and mutation specific medicines Health Technology Assessment and access to medicines
Patients' contribution	The adherence challenge Interactions between multidisciplinary team and patient Patients' priorities
The contribution of the European CF Society to development and monitoring of medicines	The Clinical Trial Network The role of the European CF Patient Registry in post-marketing studies

Table 1: Topics addressed in this book

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CHAPTER 3

Pharmacokinetics/pharmacodynamics guided approach to antibacterial administration in cystic fibrosis

Authors

Elio Castagnola, Giuliana Cangemi, Alessio Mesini, Francesca Mattioli

1 General concepts of pharmacokinetics/pharmacodynamics

Antibiotic resistance is a major problem in modern medicine. “Standard” therapeutic regimens do not always achieve plasma concentrations capable to guarantee pathogen eradication, while minimizing undesirable effects. Pharmacokinetic (PK) principles can help predict antimicrobial efficacy and therefore the pharmacodynamic (PD) response [1]. An antibiotic’s effectiveness is related both to patient’s exposure to the drug, defined by different PK properties such as maximum plasma concentration (C_{max}), area under plasma concentration curve over 24 hours as a function of time (AUC), minimum pre-dose concentration (C_{min}) [2], and to microorganism susceptibility, estimated *in vitro* by the minimal drug concentration inhibiting the bacterial growth (minimum inhibitory concentration [MIC]).

PK/PD parameters normalized to MIC can be used to manage difficult to treat infections [3].

The antibacterial effect of antibiotics depends on the antibiotic concentration or the time of exposure of the bacteria to the drug [4].

Time-dependent antibiotics (beta-lactams, macrolides, tetracyclines, glycopeptides) are characterized by an *in vivo* activity related to the proportion of time that drug plasma levels persist above the MIC during the administration interval (% $t > MIC$), and to the fact that C_{min} can be higher than the MIC. To reduce the risk of resistance selection and to maximize therapeutic effectiveness, a drug plasma concentration 4-5 times above MIC, or at least at MIC level, is desirable at the end of dose interval. Therefore, the total daily dose should ideally be administered in 3-4 doses, each infused over 2-3 hours, or over 24 hours (continuous infusion). This method of administration is important mainly for time-dependent antibiotics which have no post-antibiotic effect (PAE). PAE is defined as the persistent suppression of bacterial growth even when

the plasma concentrations of the antibiotic fall below the MIC [5-7].

Concentration-dependent antibiotics (such as aminoglycosides and quinolones) exert their activity *in vivo* on the basis of the C_{max} reached and of a prolonged PAE. For these drugs, C_{max}/MIC indicates efficacy and a single daily dose is appropriate.

For both time-dependent and concentration-dependent antibiotics, the AUC/MIC ratio can effectively express the extent of pharmacologically active exposure. Probably the most important risk factor for selecting antibiotic-resistant strains is repeated exposure of bacteria to suboptimal concentrations (often due to inappropriate dose) [8]. In the presence of suboptimal antibiotic concentrations at the site of infection, the presence of a single bacterial mutation might confer a survival advantage. This could lead to selection of resistant pathogens, even with antibiotic concentrations above the MIC [8, 9]. Therefore, antibiotic concentrations at the site of infection should be maintained high enough that a second mutation is needed to confer full antibiotic resistance. These higher concentrations, called “mutant prevention concentrations”, are therefore desirable, and can be achieved only with dosages greater than that required for clinical cure [10].

2 Pathophysiological changes in CF: impact on PK/PD

In CF, the PK of a medicine can vary significantly between patients, and even within the same patient, making it difficult to predict the PK trend of a drug and its PD

response. This variability is due to the multiple *CFTR* mutations possible, the general clinical condition of the patient, the level of multiorgan impairment, and the patients' life expectancy, which has decidedly increased with the introduction of new therapeutic strategies. Full understanding PK in CF patients is further complicated by the extreme heterogeneity of PK data in the literature. Robust statistical interpretation is not always possible because the relevant studies were conducted in different historical periods, were often uncontrolled, with heterogeneous patient populations. Studies published before 1985 reported, for example, that beta-lactam clearance (CL) and volumes of distribution (V_d) at steady state were higher in CF patients than in healthy volunteers. More recent studies have shown a smaller difference between the two comparison groups.

The pathophysiology of CF can affect the PK and PD of drugs in many different ways. In the following section, we describe these challenges to understanding PK and PD in the context of CF.

2.1. Gastrointestinal tract changes

Defective CFTR protein causes decreased chloride secretion in the airways, associated with an increase in sodium absorption mediated by the epithelial sodium channel (ENaC). The pathological triad of obstruction, infection and inflammation, which is responsible for respiratory disease, also causes gastrointestinal tract malfunction. Absorption of orally administered drugs can be altered by gastrointestinal tract changes in CF, such as hypersecretion of gastric acid, malabsorption and lesions of

the proximal mucosa of the small intestine. Some studies have not shown significant changes in bioavailability, while others seem to suggest an increase in the oral bioavailability of some drugs. Although the extent of absorption is highly variable, the absorption rate is generally slower. Once absorbed, most drugs circulate in the blood bound to plasma proteins such as albumin, α 1-acid glycoprotein, and α -globulins. The degree of plasma protein binding differs from drug to drug and may affect activity, tissue distribution, and hepatobiliary and urinary excretion.

2.2. Serum protein

The success of antibiotic treatment in CF can be significantly affected by changes in body mass, imbalances in plasma protein concentration, and endothelial dysfunction [11].

People with CF have low levels of many serum proteins (such as albumin, globulin, prothrombin and coagulation factors), mainly because of reduced synthesis. This can also result from hypervolemic conditions up to 1.4-fold higher than in healthy people due to reduced arterial oxygen saturation associated with pulmonary dysfunction. Reduced serum protein levels in CF could result in increased free drug concentrations, especially for drugs that bind tightly to serum protein. Patients with hypervolemia and/or hypoalbuminemia can therefore have increased Vd and CL, complicating the maintenance of adequate plasma drug concentrations. Of note, Vd and CL differences in CF patients compared to healthy people seem less pronounced when these parameters are

normalized to height or body surface area (BSA) rather than body weight [12]. For example, tobramycin Vd was similar in CF patients compared to healthy people, when normalized to BSA; but Vd was significantly higher in people with CF, when normalized to body weight. In patients with CF, the lean body mass (LBM) represents the largest percentage of total body weight. Therefore drugs with wide distribution in lean tissue will have high Vd (e.g. ceftazidime) whilst drugs with high distribution in adipose tissue will have high CL. Indeed, if we adjust the values for LBM, Vd in CF patients in good health does not differ from Vd in healthy people [13].

2.3. Hepatic clearance

The hepatic clearance of drugs largely depends on hepatic blood flow or on intrinsic clearance for molecules with high and low extraction ratios, respectively. Depending on the molecule, altered hepatic blood flow or impaired liver enzyme activity will impact hepatic drug clearance. About 30-40% of CF patients have some degree of hepatobiliary dysfunction including elevation of the liver enzymes γ -glutamyl transpeptidase, aspartate amino transferase and alanine amino transferase. Nonetheless, many drugs appear to have greater hepatic clearance in people with CF. Some studies do not exclude increased hepatic blood flow [14], but at the moment it is considered unlikely that the *CFTR* gene defect is directly involved [15]. It is difficult to predict to what extent drug metabolism, dependent on phase 1 and/or phase 2 hepatic biotransformation, may significantly differ in CF compared to healthy subjects. The

relationship between possibly increased enzyme activity, mediated by cytochromes CY1A2 and CYP2C8, and CF disease (severity, genotype) has not yet been defined, with only divergent evidence from small studies available.

2.4. Kidney changes

In the kidney, *CFTR* is highly expressed in the apical membrane of all segments of the nephron, where it mediates the secretion of Cl^- in the distal tubule [14]. *CFTR* is also expressed in the main cells of the collecting duct, and modulates the activity of other ion channels, in particular reducing ENaC activity. Changes in cell membrane composition and tubular transport characteristics seem to be the basis of increased Na^+ reabsorption in the proximal tubule in CF patients. These changes appear to reduce Na^+ delivery to the distal convoluted tubule and to increase glomerular filtrate (GFR) through a feedback tubuloglomerular mechanism or through the activation of the atrial natriuretic peptide secondary to hypervolemia [16]. Glomerulomegaly, glomerular hyperfiltration and abnormalities in renal tubular function, which precede microalbuminuria and the following nephropathy, have been described in adults with CF, in association with disease severity. However, the supporting studies do not include a control group, are based on historical controls, or use non-comparable equations for the estimation of GFR. The mechanisms involved in renal drug elimination are glomerular filtration, active secretion and tubular reabsorption. It has been shown that people with CF have more acidic urine than healthy volunteers [17], which would

increase the degree of ionization of basic drugs (e.g. aminoglycosides) and their renal CL. However the lower degree of ionization in acidic urine could favor tubular reabsorption of weakly acidic drugs (e.g. beta-lactams), reducing CL.

CFTR also acts as an ABC-transporter for anions other than Cl^- . The *CFTR* defect in CF patients implies, in theory, that bidirectional transport of organic anions could be reduced; this would justify the increased renal CL, which is often observed for some beta-lactams [18]. The two contrasting mechanisms described may partially explain why renal CL does not significantly differ between CF and healthy subjects. Some drugs, such as beta-lactams can fail due to augmented renal clearance ($\text{CL} > 130\text{-}160 \text{ mL/min/1.73m}^2$, according to different definitions) [19]. This should be considered in when treating CF patients with severe infections.

3 Using PK/PD parameters to optimize antibiotic therapy

In CF, the airways often become the site of chronic polymicrobial infection and inflammation. Antibiotics are widely prescribed to eradicate pathogens or control acute respiratory exacerbations [20] and are administered repeatedly, with prolonged cycles. This practice has substantially contributed to increased life expectancy [21]. However, it has also been observed that the diverse microbiota observed in younger patients narrows over lifetime, with establishment of specialized communities of pathogens associated with poor pulmonary function

in older patients [22]. Antibiotic concentrations can be lower than desired in the lung, due to high concentrations of bacteria (frequently with high MIC), repeated prolonged treatment and abnormal PK due to underlying disease. These sub-therapeutic antibiotic concentrations at the site of lung infection increase the risk for resistance selection [21, 22]. Considering the PK/PD parameters of a drug [3], along with the MIC of the pathogen involved and the site of infection (mainly the lung) could improve effectiveness of treatment, concomitantly reducing the risk of selecting resistant strains. Optimizing the PK and PD involves finetuning the dose and route of administration, and evaluating plasma concentrations, as a proxy of organ concentration. The effectiveness of this concept has been recently demonstrated for meropenem in children with CF [23].

3.1. The tissue/plasma ratio

A barrier to using this technique for optimizing drugs administered by the intravenous or oral route is that plasma concentrations cannot easily be directly linked to target concentrations on the surface of the lung or in the epithelial lining fluid (ELF). Antibiotic concentrations in ELF can be estimated from drug concentrations in bronchoalveolar lavage (BAL) samples [24]. First the “apparent” volume of ELF is estimated, based on the fact that urea concentrations are the same in plasma, BAL and ELF, using the equation:

$$ELF \text{ volume} = (\text{volume aspirated in BAL} \times \text{urea in BAL aspirate}) / \text{urea in plasma}$$

Then, drug concentration in ELF can be estimated with the equation:

$$\text{Drug concentration in ELF} = (\text{BAL volume} / \text{estimated ELF volume}) \times \text{drug concentration in BAL}$$

The ratio of antibiotic concentration in ELF/plasma provides only a moderate level of understanding of antibiotic disposition in the lung. Evaluation of target PK/PD achievement in the ELF with current dosing regimens is necessary to define the optimal antibiotic dosing strategies for treatment of lung infections. However, at present it is nearly impossible to accurately estimate the concentration-time profile in the lungs [25]. Therefore it remains inferential to correlate the plasma and/or tissue concentrations with target PK/PD indices.

3.2. Impact of the administration route

Lipophilic antibiotics (fluoroquinolones, macrolides, tetracyclines, oxazolidinones) generally penetrate well into the lung tissue, and thus standard dosing will achieve the PK/PD targets for susceptible pathogens, with aggressive dosing for treatment of less susceptible pathogens. For hydrophilic antibiotics (beta-lactams, aminoglycosides, glycopeptides), standard dosing regimens rarely achieve the PK/PD targets in the lung tissue. Higher doses may be necessary for CF patients, who have altered antibiotic CL and/or an increased Vd. Nebulization can increase drug delivery into the lungs. However when antibiotics are administered via inhalation, it is even more complex to establish a link between PK and clinical performance. The concentration-time profile of inhaled antibiotics is complicated by variables such

as aerosol deposition, particle dissolution, permeation into lung tissue, binding, and transfer to the systemic circulation [25]. For example, for time-dependent drugs such as beta-lactams, the rate of clearance from the lungs is needed to maximize the known PK/PD index of antibacterial efficacy. This rate is often not known, and dosing regimens are based arbitrarily on systemic doses or those used in animal models. Moreover, different PK/PD targets may exist for the same agent when administered by inhalation or systemically. For example maximal tobramycin concentrations >25 times the pathogen MIC are needed to overcome the inhibitory effect of sputum in CF patients, compared to 10 times the MIC in plasma [25]. Since inhaled administration of antibiotics achieves exponentially higher lung concentrations than systemic administration, inhaled drugs may achieve the required PK/PD index of antibacterial efficacy, even if the target pathogen is reported to be resistant by conventional interpretations [25]. However, it must be stressed that nebulized antibiotics can be associated with a higher risk of respiratory complications in patients with severe hypoxemia or with signs of poor pulmonary reserve [26].

3.3. PK/PD of frequently used antibiotics

In the following sections, we summarize PK/PD data on systemic administration of the antibiotics (or class of antibiotics) most frequently used in CF, with specific information (when available) on lung concentrations. PK/PD targets, together with available data on tissue/plasma concentration ratios, are reported in **Table 1** [3,

10, 27-36]. Parameters related with other, less frequently administered drugs are also summarized in **Table 1**.

3.3.1. Beta-lactams

Beta-lactams are a time-dependent class of drugs, and should be administered as fractionated doses (every 6-8 h) in prolonged (2-3 h) or in continuous (24 h) infusion to achieve the best PK/PD target at the end of dosing interval. This is demonstrated for piperacillin-tazobactam in cancer patients [37-39] and for 3 h infusion of meropenem in CF [40]. In general, penetration in lung tissues is variable and higher dosages are required in the case of severe pulmonary infections, with prolonged or even continuous infusion [29, 33], depending on the drug in question.

Nearly 20% of an intravenous infusion of aztreonam penetrates in bronchial secretion, but very high concentrations can be achieved by means of aerosolized administration of its lysine salt [41]. It can be hypothesized that effectiveness toward bacterial strains with higher MIC could be obtained by increasing the daily dose (i.e. the AUC of the drug). Ceftolozane-tazobactam is a combination of a cephalosporin with a beta-lactamase inhibitor that is highly effective against multidrug resistant *P. aeruginosa* in CF [42], with a lung/plasma ratio of about 46% [43], which explain the need of doubling the recommended dose (3000 mg instead of 1500 mg of the combination every 8 h) both for patients with severe (nosocomial) pneumonia [44] and in CF [45]. Ceftolozane-tazobactam is usually administered via a 1 h infusion [46], but administration of 6000 mg

in 24 h continuous infusion (with 3000 mg as load) has been reported effective in a patient with CF [47]. Ceftazidime-avibactam is another beta-lactam/beta-lactamase inhibitor combination with potential activity against some carbapenemase (KPC, OXA-48, but not VIM or NDM) producing Gram-negative bacteria including *P. aeruginosa* and *Burkholderia cepacia* [43, 48]. Its penetration in the lungs is estimated as about 30% based on concentrations in the ELF [48]. This drug should be infused every 8 h over 2 h [46].

Ceftaroline and ceftobiprole are new cephalosporins highly effective against methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline can be administered every 12 h. However administration every 8 h via 1 h infusion [46] is recommended for severe systemic infections (e.g. pneumonia or bacteremia) [49] and especially for CF patients, in whom the drug's half-life has been shown to be shorter [50]. This way, a $t > \text{MIC}$ greater than 60% of dose interval is obtained, although could be still suboptimal for strains with higher MIC values [51]. Ceftobiprole should be administered every 8 h via 2 h infusion, but no data are available in CF.

3.3.2. Aminoglycosides

This is a concentration-dependent class of drugs with poor penetration in lungs after intravenous infusion [25, 29], leading to difficulties in achieving optimal PK/PD. Nebulization could allow more effective concentrations in the lungs, with negligible plasma concentrations [26, 41]. For example, it has been shown that lung concentrations of gentamicin after

systemic and inhaled administrations were ≤ 1.0 mg/liter and 400 mg/liter, respectively. Therefore, a hypothetical isolate of *P. aeruginosa* with MIC up to 0.1 mg/L could be treated with systemic infusion; however an isolate with a MIC up to 40 mg/L would need treatment by inhalation. For tobramycin, administration of capsules by dry-powder inhaler achieved peak lung concentrations 2 times higher than by nebulizer, permitting larger doses to be delivered [25]. In contrast to gentamicin and tobramycin, nebulized amikacin rapidly diffuses into systemic circulation, potentially exposing the patient to systemic toxicity. Therefore, for this drug, plasma concentration (C_{min}) monitoring is advised [25]. Liposomal amikacin could improve effectiveness and reduce potential systemic toxicity [25]. Finally, it must be stressed that combining intravenous and inhaled administration of the same aminoglycoside could increase the risk of renal toxicity without improving effectiveness [26].

3.3.3. Colistin

The activity of colistin is time-dependent and concentration-dependent. Colistin (polymyxin E) is a cationic polypeptide that consists of more than 30 components, the major ones being colistin A and colistin B. It is available in Europe as colistin sulfate or colistin methanesulfonate (colistimethate sodium [CSM]), an inactive pro-drug that is slowly, and in small amounts, converted *in vivo* to the active drug colistin. For intravenous administration, a loading dose is necessary; otherwise therapeutic concentrations of colistin would be reached only after at least 48 h of CSM administration.

Drug/route of administration	PK/PD		
	Parameters for efficacy	Target for Therapy	Target for resistance suppression
Amikacin, intramuscular	C _{max} /MIC	< 10	> 20
Gentamycin, intravenous single-daily			
Tobramycin, intravenous multiple daily doses			
Aztreonam, intravenous	%t>MIC	C _{min} > 4-5 x MIC, for 50-80% of dose interval	C _{min} 6 x MIC, for 100% dose interval
Ceftazidime intravenous			
Cefepime intravenous			
Meropenem, intravenous			
Amoxicillin-clavulanate oral			
Piperacillin intravenous			
Piperacillin-tazobactam, intravenous			
Ticarcillin, intravenous			
Ciprofloxacin oral/intravenous			
Levofloxacin oral/intravenous	C _{max} /MIC as secondary determinant	> 8	>22
Tigecyclin, intravenous	AUC/MIC	> 20 for tigecycline	-
Doxycyclin oral/intravenous			-
Azithromycin, oral Clarithromycin, oral	AUC/MIC for azithromycin	> 25	-
	%t>MIC as secondary determinant	> 50-80%	
Colistin, intravenous	AUC/MIC	> 20-50	none
	C _{min}	2 mg/l	

Table 1: Pharmacokinetic/pharmacodynamic indices and lung concentrations of antibiotics most frequently administered in patients with cystic fibrosis [3, 10, 27-36]

Tissue/plasma ratio		Notes
Sputum or bronchial secretion or epithelial lining fluid	Lung	
0.21	0.40	Toxicity is mainly related to elevated concentrations in inner ear and kidney, and C _{min} has been linked to the risk of an increase in serum creatinine
0.66	-	
0.12	-	
0.21	-	Recommended administration in prolonged (2-3 h) or continuous (24 h) infusion.
0.18	-	
0.60	0.94-1.04	
0.20-0.47	-	
0.14	0.32	
0.04	0.28	
-	0.78-0.92	
0.01	-	
0.26-0.89/1.06	2.75/6.24	
185/-	-/0.67	
-	2.0	Not active against <i>P. aeruginosa</i>
0.17/-	-/0.73	
16.92	30.00 azithromycin 4.2 clarithromycin	Azithromycin administered mainly as anti-inflammatory drug
0		Active against Gram-negatives only, with the exclusion of <i>Proteus</i> (not effective) and possible reduced/absent efficacy on <i>Providencia</i> , <i>Burkholderia</i> , <i>Serratia</i> , <i>Moraxella</i> , <i>Helicobacter</i> , <i>Campylobacter</i> , <i>Vibrio</i> , <i>Brucella</i> , <i>Aeromonas</i> , <i>Morganella</i> , <i>Edwardsiella</i> C _{min} ≥ 2.5 mg/L is associated with renal toxicity

Drug/route of administration	PK/PD		
	Parameters for efficacy	Target for Therapy	Target for resistance suppression
Fusidic acid, oral	AUC/MIC	> 4	-
Linezolid oral/intravenous	AUC/MIC	> 80-120	
	%t > MIC as secondary determinant	> 80%	
Fosfomycin, intravenous	AUC/MIC	> 9	> 3150
	%t > MIC as secondary	40-70%	
Trimethoprim-sulfamethoxazole, oral	t > MIC	> 50%	
	C _{min}	≥ 2 mg/L for trimethoprim and ≥ 38 mg/L for sulfamethoxazole	
Rifampin, oral	AUC/MIC C _{max} /MIC,	≥ 8	
Vancomycin	AUC/MIC	> 400	> 200
Teicoplanin	C _{min}	≥ 10 mg/l	
Chloramfenicol	t > MIC	at least 50% of the dose interval	

Table 1 (contd): Pharmacokinetic/pharmacodynamic indices and lung concentrations of antibiotics most frequently administered in patients with cystic fibrosis [3, 10, 27-36]

Tissue/plasma ratio		Lung	Notes
Sputum or bronchial secretion or epithelial lining fluid			
0.57			Active only against Gram-positive, including MRSA. In order to rapidly achieve effective concentrations and reduce the occurrence of resistance should be administered with a loading dose
4.14/0.70-8.57		3.2	Active only against Gram-positive, including MRSA. Can be administered in 2 divided doses (3 in patients < 12 years) or as continuous infusion, mainly in case of infections due to strains with reduced susceptibility (e.g. MIC \geq 2 mg/L)
		0.52	Hypernatremia and hypokalemia are possible adverse events: the first related to the high sodium content of the IV formulation and the second to the enhanced potassium urinary excretion.
		Trimethoprim 4.03-5.47 Sulfamethoxazole < 0.01	Higher concentrations and doses seem to be necessary for treatment of infections due to <i>S. maltophilia</i> .
		0.33	To be used in combination with other antibiotics for the risk of resistance selection; breakpoints for Gram-negatives are not defined
0.68		0-20-0.30	Not considered effective for <i>S. aureus</i> with MIC > 1 mg/L
1.46			
-		-	

- = not available; AUC=area under the time-concentration curve; MIC=Minimal Inhibitory Concentrations; C_{max}=Maximal Concentration; C_{min}=Minimal Concentration; t=time

Comparing recommended doses of CSM from different manufacturers and different countries, it is important to remember that 1 million IU (1 MU) corresponds to 80 mg of CSM, and 150 mg of “colistin base activity” are equal to 360 mg or 4.5–5 MU of CSM, while 1 mg of polymyxin B (available in USA) contains 10,000 IU. All these different compounds may present differences in *in vivo* PK [3]. At present the dosage recommended for intravenous administration in adults and adolescents is 1 h infusion of 9 MU as a loading dose, followed by 4.5 MU every 12 h. The loading dose applies to patients with normal and impaired GFR including those on renal replacement therapy, while maintenance must be modified according to GFR. On the contrary, polymyxin B does not need to be metabolized, and therefore, higher plasma concentrations in relation to steady state (65% of steady state) are attained after the first dose. Therefore a loading dose can be recommended but not considered mandatory [3]. After intravenous administration of CSM, colistin is undetectable in BAL [29]. On the contrary, the few PK studies on inhaled colistin in CF patients showed that high drug concentrations were achieved in the sputum even 12 h from after administration, with low levels in serum and urine [26, 52]. At present EMA recommends 1 to 2 MU every 8–12 h for nebulized administration [53]. However, in patients with ventilator-associated pneumonia due to multidrug resistant *P. aeruginosa* or *A. baumannii*, nebulized colistin administered at doses up to 5 M every 8 h was well tolerated and not inferior to an intravenous combination of beta-lactams and aminoglycosides [54,

55]. The PK/PD characteristics of high-dose CSM suggest that nebulized administration could be considered, especially for strains with increased MIC values [25]. Formulations for administration by dry-powder inhaler could increase drug delivery to the lungs, with a higher local AUC and effectiveness, without any increase in systemic toxicity [25].

3.3.4. Fluoroquinolones

The activity of fluoroquinolones is time-dependent and concentration-dependent. These antibiotics are a cornerstone of treatment in CF patients, thanks to good penetration in lung tissue [29, 33]. PK/PD parameters suggest a single daily administration, but gastrointestinal toxicity limits this possibility, at least for ciprofloxacin. A nebulized formulation has become available for levofloxacin, with encouraging results [25, 41]. However, the EMA recently warned about the risk of severe adverse events (especially muscular-skeletal or neurologic) related to fluoroquinolones, that can occur from two days to many months after stopping treatment. These adverse events are more frequent in older patients, those receiving solid organ transplantation, or treated with steroids [56].

3.3.5. Glycopeptides

This is a class of drugs with different PK/PD parameters. Vancomycin presents a time-dependent and concentration-dependent (i.e. AUC) activity and achieves relatively low pulmonary concentrations [29, 57]. Therefore high dosages and probably continuous infusion (with a loading dose) could be recommended for pneumonia [3,

33]. Of note, vancomycin should be considered ineffective in presence of MRSA strains with increased MIC (> 1 mg/L) [30, 58]. Teicoplanin activity is time-dependent and penetrates better into lung tissue than vancomycin [32].

Antibiotic classes	Preferred administration
Beta-lactams, vancomycin or linezolid (at least in presence of high MIC values),	Intravenous infusion: prolonged (2-3 h) or continuous (24 h)
Aminoglycosides, colistin	Inhalation via nebulizer and/or with the use specific formulations (powder) and devices (dry-powder inhalers)
Fluoroquinolones (levofloxacin).	Systemic or inhalation route

Table 2: Administration of key antibiotics, optimized for PK/PD

4 Technical considerations therapeutic drug monitoring of antibiotics

Optimizing dose, administration schedule and route and evaluating drug concentrations in plasma (and in ELF or sputum where possible) can help optimize drug effectiveness while minimizing toxicity.

For bacterial strains that are less sensitive to antibiotics, combination therapy can be required to overcome treatment failure, achieve clinical cure, and avoid resistance. Large prospective studies are needed to confirm whether increasing doses and/or monitoring drug concentrations could be a cost-effective strategy to optimize antibiotic use in CF.

Finally, the wide inter-patient variability in drug disposition in CF strongly supports the adoption of therapeutic drug monitoring

(TDM). The availability of reliable analytical methods for TDM of antibiotics in clinical laboratories is crucial for the individualization of antimicrobial therapies based on PK/PD strategies. Analytical methods employed for TDM need to be highly specific, accurate and reproducible for measuring a wide range of concentrations of analytes in plasma or complex matrices (such as ELF or sputum), and in the presence of co-medications. The gold standard technique is currently high performance liquid chromatography (HPLC) coupled to tandem mass (MS/MS) spectrometry. This guarantees accurate three-step identification and quantification of the drug of interest [59]. The first step is chromatographic separation, based on the chemo-physical properties of the analytes, the second step is selection of the ionized drug in the first stage of the tandem mass spectrometer, and the third

step is the selection of a product ion of a fragmentation reaction of the precursor ion in the second mass spectrometer stage [60]. In comparison to immunoassays, LC-MS/MS allows very high accuracy [61, 62], a wide range of measurable concentrations, as well as low-cost and rapid simultaneous measurement of multiple drugs in a single run (multiplexing) [63]. An advantage of LC-MS/MS compared to HPLC coupled to UV detection (HPLC-UV) requires time-consuming sample preparation such as solid phase extraction or evaporation to dryness. In contrast, the sample preparation for LC-MS/MS is based on protein precipitation methods, and is therefore fast and easy. Moreover, LC-MS/MS allows the use of micro-samples. Such alternative sampling strategies are essential for pediatric patients [64-66].

The performance of each single or multiple methods should be validated following international guidelines [67], paying particular attention to the evaluation of artifacts due to the presence of pro-drugs [68]. Stability is an issue for most antibiotics, especially beta-lactams [69, 70], therefore stability should be evaluated in different operative conditions, when defining reliable operative protocols to be applied in clinical practice.

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CHAPTER 4

Treatment challenges associated with drug-drug interactions in cystic fibrosis

Authors

Olivia K. Paulin, Elena K. Schneider-Futschik

Introduction

Advances in our understanding of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulation and of the contribution of airway infection and inflammation to the pathogenesis of CF have motivated efforts to initiate therapy in early childhood. With the marked increase in the number of CF medications approved in the last decade, there is greater potential for a more complex treatment regimen. A 2006 study of a CF patient cohort reported a median daily number of medications of seven (range 0–20), including two nebulized medications, and found that patients spent a mean duration of 2–3 hours on daily treatment activities, including airway clearance [1]. In 2019, the reported average likely exceeds 40 tablets per day (<https://www.cysticfibrosis.org.au/about-cf/life-with-cf>).

Polypharmacy, defined as the concurrent use of five or more drugs, is common in people with CF. Potential drug-drug interactions can be predicted by identifying agents that alter drug metabolism and either substituting them or adjusting their dose.

CF-specific treatment regimens have been recognized as potential causes of adverse drug reactions, including drug-drug interactions, given the frequency with which short-term treatments (e.g. antibiotics) overlap with chronic treatments such as CFTR modulators [2].

This chapter reviews the available evidence of drug-drug interactions involving CFTR modulators and the subsequent effects on patient outcomes.

Drug-related events and drug interactions account for approximately 10% and 1% of hospital admissions, respectively [3]. Knowledge of factors that contribute to drug interactions is often limited, and “high-risk” patient cohorts need to be identified. People with CF can be considered “high-risk”, as they are commonly exposed to polypharmacy. Furthermore, certain CF-specific risk factors may be associated with drug interactions (**Table 1**). These include demographic risk factors, female sex, very young age, liver and kidney dysfunction, and, importantly, genetic polymorphisms [3].

■ Polypharmacy
■ Demographic risk factors
■ Female sex
■ Age (very young and elderly)
■ Liver dysfunction
■ Renal dysfunction
■ Hypoproteinemia
■ Pharmacogenetic risk factors
■ Genetic polymorphisms
■ Dehydration
■ Others

Table 1: Potential risk factors for drug interactions in CF

Adapted from Andersen and Feingold, 1995 [3].

1 General drug absorption pathways

1.1. Drug absorption

The mechanisms of drug interactions that modify drug absorption usually involve formulation and variations in gastric pH and/or gastrointestinal motility. CF drugs that increase gastric pH include proton pump inhibitors (PPIs), antacids and H₂ antagonists. These drugs can reduce the absorption of azole antifungals (e.g. ketoconazole) that are ideally absorbed in an acidic environment.

1.2. P-glycoprotein mediated drug metabolism

Drug disposition is also influenced by membrane-bound transport proteins (e.g.

P-glycoprotein), which protect the body from harmful substances. P-glycoprotein acts as a pump, which uses energy created by ATP hydrolysis to drive drug efflux. P-glycoprotein is expressed at high levels in the epithelial cells of the small intestine, the proximal tubules of the kidney, and in epithelial cells of the capillaries of the blood-brain barrier and placenta. CF-specific P-glycoprotein inhibitors that affect the rate of drug absorption include antimicrobials such as clarithromycin, erythromycin, and rifampicin, and azole antifungals such as itraconazole and ketoconazole.

Drugs that bind strongly to plasma proteins may cause drug interactions due to alterations in drug distribution. Ivacaftor (Kalydeco) is >97% bound to the plasma proteins human serum albumin (HSA) and α -1-acid glycoprotein (AGP), and can potentially compete with coadministered CF drugs for binding sites at AGP and HSA, altering their free concentrations [4, 5]. We have investigated drug-drug interactions between ivacaftor and several co-administered CF drugs by measuring HSA and AGP binding affinities using fluorometric and surface plasmon resonance binding techniques, together with molecular docking techniques [4, 5]. We found that, thanks to their high binding affinities, montelukast, ibuprofen, dicloxacillin, omeprazole, and loratadine can significantly displace ivacaftor from its binding sites at AGP and HSA. Co-administration of these drugs with ivacaftor *in vivo* could effectively increase free plasma concentrations of ivacaftor. The effect could be negligible though, unless the displaced drug has a low therapeutic index, limited distribution in the body, and/

or is slowly eliminated (and could therefore potentially accumulate).

It is important to take into account the effects of concomitant ivacaftor administration on the pharmacokinetic/pharmacodynamic parameters, including half-life, C_{max} , and dosage, of other CF drugs. Based on the 12 h mean plasma half-life of ivacaftor, the recommended oral dosage regimen is twice daily (every 12 h) administration of a 150 mg film-coated tablet (mean C_{max} 768 ng/mL) with fat-containing food to facilitate intestinal absorption (due to its low aqueous solubility, <0.05 µg/mL). The leukotriene receptor antagonist montelukast (which strongly competes for plasma protein binding sites) has a plasma half-life of 2.7–5.5 h and is generally administered orally in the evening at 10 mg/day (mean C_{max} 353 ng/mL). Therefore, to effectively increase free plasma concentrations of ivacaftor, montelukast is best taken together with the second evening dose of ivacaftor. However, further clinical trials are required to substantiate the validity of any dosage regimen based on data obtained from the aforementioned *in vitro* study [5].

2 Drug biotransformation

The most clinically relevant drug interactions are those that cause alterations in drug metabolism. In general, *in vitro* studies can provide very accurate data on the interactions between drugs that selectively affect cytochrome (CY) P450 enzymes. However, translating findings to a clinical setting can be difficult. CYP450 enzymes are divided

into families 1–3 and sub-families A–E, and individual gene numbers. About ~90% of drug metabolism is attributed to 6 enzymes: 1A2, 2C9, 2C19, 3A4, 2C9, and 2C19 [6]. The ability of a single CYP450 enzyme to metabolize several substrates underlies many drug interactions associated with CYP450 inhibition [7]. Drug interactions can also occur as a result of the induction of several human CYPs following long-term drug treatment. Enzyme induction leads to increased substrate metabolism, usually diminishing exposure and potentially reducing therapeutic efficacy (**Figure 1**) [2]. Conversely, CYP450 inhibition results in increased drug concentrations, potentially increasing toxicity.

In addition to the properties of the drug in question, the individual genetic make-up of each patient can strongly influence drug metabolism. Genetic polymorphisms in a given CYP450 gene can result in variations in the activity of the encoded enzyme. Based on these variations, patients can be classified as poor metabolizers, extensive metabolizers, or ultra-rapid metabolizers. A classic example is the response to codeine, which is metabolized by CYP2D6. Ultra rapid metabolizers experience increased toxicity, whereas poor metabolizers are unable to convert codeine to its active metabolite morphine, and hence do not experience its analgesic effect. Commonly used CF drugs that have moderate to strong CYP450 enzyme interactions are summarized in **Table 2**.

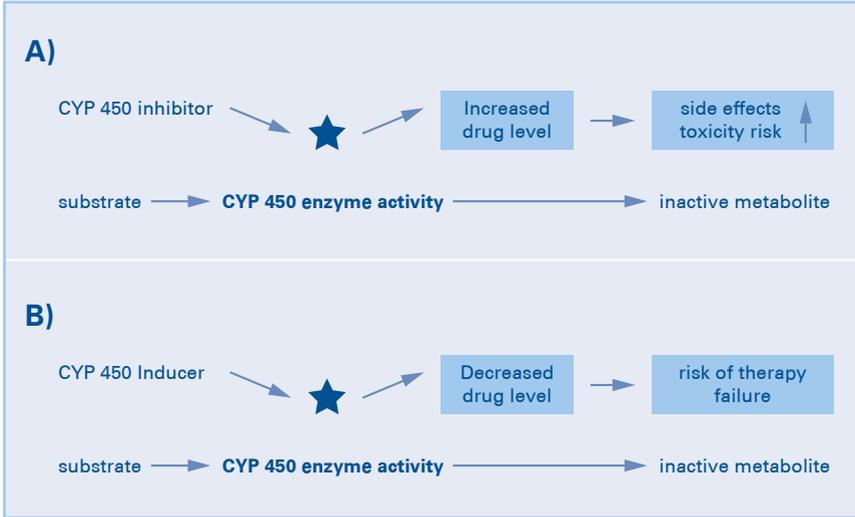


Figure 1: Effects of CYP450 inhibitors (A) and inducers (B) on drug substrates

Reproduced from Jordan et al., 2016 [2]

2.1. CYP3A4 inhibitors

The CYP3A4 inhibitors most relevant to CF therapy include antibiotics (e.g. clarithromycin, ciprofloxacin, erythromycin), selective serotonin-reuptake inhibitors (SSRIs) (e.g. fluoxetine), PPIs (e.g. omeprazole), and azole antifungals (e.g. fluconazole) (**Table 2**). These medications inhibit the CYP3A4 enzyme, resulting in increased concentrations of the corresponding substrates, potentially leading to toxicity. A well-documented example of this interaction is the concomitant administration of azole antifungals in patients treated chronically with inhaled corticosteroids; this combination leads to suppression of the hypothalamic-pituitary axis, adrenal insufficiency, and growth failure [8-10].

2.2. CYP3A4 inducers

The most problematic CYP3A4 inducers used in CF therapy are the antibiotics rifampicin and rifabutin. Rifampicin is especially challenging when administered in combination with azole antifungals (CYP3A4 inhibitors) or antibiotics such as clarithromycin (**Table 2**). Several case studies have reported that rifampicin reduces concentrations of the antifungals voriconazole and itraconazole to barely detectable and undetectable levels, respectively [11]. A less marked effect is observed on the antifungals fluconazole and posaconazole [2]. Rifampicin also significantly reduces concentrations of the antibiotics clarithromycin and doxycycline, potentially necessitating more frequent dosing if these antibi-

otics are administered concomitantly with rifampicin [12]. Concentrations of azithromycin, which is metabolized via different pathways, remain unaffected. Increases in drug dose and/or frequency of administration should be individualized according to the specific medication administered concomitantly with CYP3A4 inducers.

2.3. CYP2C9/2C19 inhibitors

CYP2C19 inhibitors used to treat CF include azole antifungals (e.g. fluconazole and voriconazole) and proton pump inhibitors. Substrates of CYP2C19 include SSRIs, such as citalopram and escitalopram (Table 2) [2]. Some PPIs like omeprazole inhibit CYP2C9 to varying degrees. Monitoring of plasma concentrations of azole antifungals is also recommended when used in combination with PPIs, as absorption of some azole antifungal formulations is pH-dependent and is therefore impacted by PPI-induced increases in gastric pH [2]. Dose adjustment and monitoring for efficacy may be necessary if the CYP2C19 inhibitor omeprazole is administered concomitantly with citalopram [2].

2.4. CYP2C9/2C19 inducers

In addition to its effects on CYP3A4, rifampicin is a potent inducer of both CYP2C9 and CYP2C19 (Table 2). By contrast, the CYP3A4 inducer rifabutin does not affect CYP2C9 or CYP2C19. While the roles of CYP2C9 and CYP2C19 in drug metabolism are not as important as that of CYP3A4, these two enzymes are nonetheless implicated in several drug-drug interactions. Many non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and

the CYP2C9 substrate diclofenac, can be affected by concomitant administration of the CYP2C9 inducer rifampicin, in some cases requiring monitoring of ibuprofen concentrations and dose adjustment [13]. CYP2C9 inhibitors include antibacterial agents (sulfonamides, trimethoprim), azole antifungals, H₂ antagonists, PPIs, and SSRIs [6].

2.5. CYP1A2

CYP1A2 inhibitors used in CF treatment include ketoconazole (azole antifungal), ciprofloxacin (fluoroquinolone antibiotic), clarithromycin and erythromycin (macrolide antibiotics), and cimetidine (H₂ antagonist) (Table 2) [6]. Patients taking CYP1A2 substrates such as amitriptyline (a tricyclic antidepressant) should be monitored for efficacy when concurrently taking CYP1A2 inhibitors. CYP1A2 inducers include rifampicin and the PPI omeprazole.

3 Drug interactions specific to CF

3.1. QT prolongation

Macrolides and fluoroquinolones are two classes of antibiotics that are commonly used in CF and can contribute to additive QT prolongation. The FDA has issued a Drug Safety Communication for the macrolide antibiotic azithromycin, describing the potential risk of fatal heart rhythms associated with this drug, and notes that erythromycin and clarithromycin contribute most significantly to potential QT prolongation [14]. Ciprofloxacin and levofloxacin, two quinolone antibiotics commonly used to

treat lung infections in CF, also appear to contribute to QT prolongation, albeit not to extent described for moxifloxacin [15].

3.2. Nephrotoxicity

Many antimicrobials used to treat infections in CF can contribute to nephrotoxicity, especially if administered concomitantly. Antibiotic classes for which this phenomenon has been described include aminoglycosides and carbapenems, as well as vancomycin, colistin, and sulfamethoxazole/trimethoprim. A 2005 study reported that extended interval dosing of tobramycin (once daily instead of three times daily) resulted in decreased nephrotoxicity [2]. Close monitoring of patients who require multiple potentially nephrotoxic drugs is thus essential. Alternatively, combination therapy using these compounds can be avoided.

3.3. CFTR modulators

The discovery and development of CFTR modulators that directly target dysfunctional chloride channels have the potential to significantly alter the CF treatment landscape. In Europe, ivacaftor monotherapy (Kalydeco) is approved for children aged 6 months or older who carry gating mutations. Ivacaftor/lumacaftor (Orkambi) is approved for children aged 2 years or older homozygous for c1521_1523delCTT/p.Phe508del (F508del). Ivacaftor/tezacaftor (Symkevi/Symdeco) is approved for children aged 6 years or older who have two copies of F508del or F508del and one residual function mutation [16]. In a real-world setting, 14% of patients discontinued ivacaftor/lumacaftor therapy

within a year of beginning treatment; in two thirds of cases discontinuation was due to adverse reactions [17]. Ivacaftor, a CYP3A4 substrate, undergoes extensive liver metabolism, and its concentration is therefore affected when administered concurrently with CYP3A4 inducers such as rifampicin, the herbal treatment St John's wort, and even lumacaftor [18]. Ivacaftor and ivacaftor/lumacaftor drug-drug interactions are listed in **Tables 3-5**, respectively. According to the prescribing information, dosing should be reduced to once daily for patients concomitantly taking moderate CYP3A4 inhibitors such as fluconazole, and to twice weekly for patients concomitantly taking strong CYP3A4 inhibitors such as certain azole antifungals (e.g. ketoconazole, itraconazole, posaconazole, and voriconazole), ketolide antibiotics (telithromycin), and macrolide antibiotics (clarithromycin). Additionally, ivacaftor concentration should be monitored in individuals who consume grapefruit juice and Seville oranges, which inhibit CYP3A4 and can increase ivacaftor levels. *In vitro* data indicate that lumacaftor and ivacaftor-carboxylate, one of the main metabolites of ivacaftor, are strong inducers of CYP3A4, and may reduce ivacaftor concentrations *in vivo* [18, 19].

A series of clinical drug-drug interaction studies were recently conducted to measure the effects of ivacaftor on sensitive substrates of CYP2C8 (rosiglitazone), CYP3A (midazolam), CYP2D6 (desipramine), and P-glycoprotein (digoxin) [20]. The same group evaluated the effect of ivacaftor on a combined oral contraceptive increasingly used by women with CF upon reaching adulthood. Ivacaftor was found to

weakly inhibit CYP3A and P-glycoprotein, but had no effect on CYP2C8 or CYP2D6. Moreover, ivacaftor caused non-clinically significant increases in ethinylestradiol and norethisterone exposure. Based on these results, caution and appropriate monitoring are recommended when substrates of CYP2C9, CYP3A, and/or P-glycoprotein are coadministered with ivacaftor, particularly drugs with a narrow therapeutic index, such as warfarin (**Table 3**) [20].

Lumacaftor/ivacaftor induces several CYP450 enzymes, including 3A4, 2C9, 2C19, 2B6, and P-glycoprotein (**Table 4**). Specifically, the strong induction of CYP3A4 by ivacaftor/lumacaftor can significantly reduce concentrations of azole antifungals, potentially rendering them ineffective. Concomitant administration of ivacaftor/lumacaftor and drugs that have a narrow therapeutic index or those that are sensitive substrates (e.g. midazolam, cyclosporin, tacrolimus, clarithromycin, or erythromycin) should be avoided, or alternatives considered.

bioavailability in CF through the induction or inhibition of CYP450. These combinations may necessitate drug substitution, specific monitoring, or dose adjustment to avoid potential toxicity issues. Close communication between the prescribing clinician, the CF multidisciplinary team, and the CF specialist pharmacist, together with the use of web-based evaluation tools such as Crediblemeds (<https://www.crediblemeds.org/>), will aid the management of potential drug interactions.

4 Perspectives

Further research during the early stages of drug development is essential to recognize previously unknown interactions, characterize the mechanisms underlying known interactions, and study novel compounds from drug classes implicated in drug-drug interactions. Screening for potential drug-drug interactions and vigilance are of the utmost importance to identify combinations of treatments that can alter drug

Cytochrome					
	CYP1A2	CYP2B6	CYP2C19	CYP2C8	
Inducers	Rifampicin Fluvoxamine Phenytoin	Lumacaftor Rifampicin Carbamazepine Ritonavir	Lumacaftor Rifampicin Enzalutamide Ritonavir	Lumacaftor Rifabutin Rifampicin	
Inhibitors	Ciprofloxacin Ivacaftor* Levofloxacin Propranolol Amiodarone Carbamazepine Isoniazid Cimetidine	Itraconazole Ketoconazole Paroxetine Sertraline Venlafaxine Voriconazole	Amitriptyline Esomeprazole Fluconazole Fluoxetine Omeprazole Sertraline Voriconazole	Montelukast Clopidogrel	
Substrates	Duloxetine Mirtazapine Theophylline Tizanidine	Dosulepin Fluoxetine Sertraline Bupropion Desipramine Dextromethorphan Nebivolol	Citalopram Escitalopram Esomeprazole Lansoprazole Omeprazole Pantoprazole Posaconazole Voriconazole	Omeprazole Rifampicin Repaglinide	

Table 2: Effects (strong or moderate) on cytochrome P450 of drugs commonly used in cystic fibrosis (*weak interaction)

	CYP2C9	CYP2D6	CYP3A4	CYP3A5
	Lumacaftor Rifampicin		Lumacaftor Rifabutin Rifampicin Carbamazepine Phenytoin St. John's Wort	Ciclosporin Lumacaftor
	Fluconazole Ivacaftor* Lumacaftor Omeprazole Sulfamethoxazole Voriconazole Amiodarone Ivacaftor	Duloxetine Fluoxetine Haloperidol Paroxetine Sertraline Bupropion Cimetidine Quinidine Terbinafine	Clarithromycin Erythromycin Fluconazole Itraconazole Ivacaftor* Levofloxacin* Posaconazole Voriconazole Ciprofloxacin Ritonavir Verapamil	Clarithromycin Itraconazole Ketoconazole
	Fluoxetine Ibuprofen Voriconazole Celecoxib Tolbutamide Warfarin	Amitriptyline Atomoxetine Fluoxetine Haloperidol Mirtazapine Paroxetine Propranolol Venlafaxine Nortriptyline	Citalopram Clarithromycin Corticosteroids Ciclosporin Doxycycline Erythromycin Escitalopram Guanfacine Itraconazole Ivacaftor Lansoprazole Midazolam Mirtazapine Rifabutin Tacrolimus Tezacaftor Voriconazole Simvastatin	Citalopram Clarithromycin Escitalopram Erythromycin Ivacaftor Tacrolimus Tezacaftor

Adapted from Jordan et al., 2016 [2].

Drug class	Drug	Nature of interaction	
Anticoagulants	Warfarin	CYP2C9 inhibition via ivacaftor	
Antiepileptics	Carbamazepine Phenobarbital Phenytoin	CYP3A4 induction via AEDs	
Antimycobacterials	Rifampicin	CYP3A4 induction via rifampicin	
Azole antifungals	Itraconazole Ketoconazole Voriconazole Posaconazole Fluconazole	CYP3A4 inhibition via anti-fungals	
Benzodiazepines	Diazepam Midazolam	Weak CYP3A4 inhibition via ivacaftor	
CFTR modulators	Lumacaftor	CYP3A induction via lumacaftor	
Glycosides	Digoxin	PgP-inhibition via ivacaftor	
Herbal remedies	St John's Wort	CYP3A4 induction via St John's Wort	
Immunosuppressants	Ciclosporin Everolimus Sirolimus Tacrolimus	PgP-inhibition via ivacaftor	
Macrolides	Clarithromycin Erythromycin	CYP3A4 inhibition via macrolide	
NSAIDs	Ibuprofen	CYP2C9 inhibition via ivacaftor	
Rifamycins	Rifabutin	CYP3A4 induction via rifabutin	
Sulfonylureas	Glimepiride Glipizide	CYP2C9 inhibition via ivacaftor	

Table 3: Drug-drug interactions described for ivacaftor

Result of interaction	Recommended intervention
Increased warfarin exposure	Monitor INR
Decreased ivacaftor exposure	Avoid where possible
Significantly decreased ivacaftor exposure	Avoid
Moderately increased ivacaftor exposure	When used in combination decrease ivacaftor dose to twice weekly (decrease to once daily for fluconazole)
Increased benzodiazepine exposure	Consider an alternative drug; use with caution and monitor for toxicity
Decreased ivacaftor exposure	Dose adjustments already accounted for in ivacaftor/lumacaftor dosage unit to compensate, so no action necessary
Increased digoxin exposure	Use with caution, monitor digoxin concentration, and adjust dose if necessary
Decreased ivacaftor exposure	Avoid where possible
Increased levels of immunosuppressants	Monitor immunosuppressant concentration; decreased doses may be required
Increased ivacaftor exposure	If used with clarithromycin, decrease ivacaftor dose to twice weekly; if used with erythromycin decrease ivacaftor dose to once daily Azithromycin does not require dose adjustments
Increased ibuprofen exposure	Check NSAID levels 2–4 weeks after initiation; dose decrease may be required
Decreased ivacaftor exposure	Avoid where possible
Increased sulfonylurea exposure	Use with caution

Abbreviations: AED=anti-epileptic drug; CFTR=cystic fibrosis transmembrane conductance regulator; INR=international normalized ratio; PgP=P-glycoprotein.

Adapted from Jordan et al., 2016 [2].

Drug class	Drug	Mechanism of interaction	
Antiepileptics	Carbamazepine Phenobarbital Phenytoin	CYP3A4 induction via luma- caftor	
Antimycobacterials	Rifampicin	CYP3A4 induction via rifam- picin	
Azole antifungals	Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	CYP3A4 induction and inhibition	
Benzodiazepines	Midazolam	CYP3A4 induction via luma- caftor	
Corticosteroids	Dexamethasone Methylprednisolone Prednisone Prednisolone	CYP3A4 induction via luma- caftor	
H2-receptor antagonists	Famotidine Ranitidine	CYP2C19 induction via lumacaftor	
Hormonal contraceptives	Ethinylestradiol Norethisterone Other progestogens	CYP3A induction via luma- caftor	
Immunosuppressants	Ciclosporin Everolimus Sirolimus Tacrolimus	CYP3A4 induction (luma- caftor) and PgP inhibition (ivacaftor and lumacaftor)	
Leukotriene receptor antagonists	Montelukast	CYP2C9 inhibition/induction via lumacaftor/ivacaftor	
Macrolides	Clarithromycin Erythromycin	CYP3A4 induction via lumacaftor and inhibition via macrolides	

Table 4: Lumacaftor/ivacaftor drug-drug interactions

Result of interaction	Recommended intervention
Decreased exposure of antiepileptic	Avoid where possible
Decreased ivacaftor exposure	Avoid where possible
Decreased azole exposure and increased lumacaftor/ivacaftor exposure	Avoid where possible; azoles may be ineffective. If starting lumacaftor/ivacaftor in patient already on azole begin with one tablet daily for 1 week then increase to recommended daily dose
Decreased benzodiazepine exposure	Consider an alternative agent
Decreased steroid exposure	Monitor for effectiveness; higher steroid doses may be required
Decreased H ₂ -receptor antagonist exposure	Monitor for effectiveness
Decreased contraceptive exposure/effectiveness Increased menstrual abnormality events	Avoid where possible; should not be used as sole contraception method. Applies to oral injectable transdermal and implantable contraceptives. Alternative methods of contraception include progestogen-only injections the copper IUD or levonorgestrel intra-uterine system
Decreased immunosuppressant levels	Avoid where possible; higher immunosuppressant doses will be required
Altered exposure of montelukast	Monitor for effectiveness
Decreased macrolide exposure Increased lumacaftor/ivacaftor exposure	If starting lumacaftor/ivacaftor in patient receiving macrolides, begin with one tablet daily for 1 week then increase to recommended daily dose. Azithromycin does not require dose adjustments

Drug class	Drug	Mechanism of interaction	
NDRIs	Bupropion	CYP2B6 induction via lumacaftor	
NSAIDs	Ibuprofen	CYP2C19 induction via ivacaftor/lumacaftor	
Proton pump inhibitors	Esomeprazole Lansoprazole Omeprazole Pantoprazole	CYP2C19 induction via lumacaftor	
Rifamycins	Rifabutin	CYP3A4 induction via lumacaftor	
SSRIs	Citalopram Escitalopram Sertraline	CYP2C19 induction via lumacaftor	
Sulfonylureas	Glimepiride Glipizide Tolbutamide	CYP2C9 inhibition/induction	

Table 4 (contd): Lumacaftor/ivacaftor drug-drug interactions

Result of interaction	Recommended intervention
Decreased bupropion exposure (<i>in vitro</i>)	Reduce dose of bupropion
Decreased ibuprofen exposure	Levels should be re-checked 2–4 weeks after initiation; higher ibuprofen doses may be required
Decreased PPI exposure	Monitor for increased adverse events or decreased efficacy
Decreased rifabutin exposure	Increase in rifabutin dose may be necessary
Decreased SSRI exposure	Monitor for effectiveness; higher SSRI doses may be necessary
Altered exposure	Monitor for increased adverse events or decreased efficacy

Adapted from Jordan et al., 2016 [2].

Abbreviations: NDRI=norepinephrine-dopamine reuptake inhibitor, NSAID=non-steroidal anti-inflammatory drug, PPI=proton pump inhibitor, SSRI=selective serotonin reuptake inhibitor, IUD=intra-uterine device

Drug Class	Drug	Mechanism of interaction	
Anticoagulants	Warfarin	CYP2C9 inhibition via ivacaftor/tezacaftor	
Antiepileptics	Carbamazepine Phenobarbital Phenytoin	CYP3A4 induction via antiepileptics	
Antimycobacterials	Rifampicin	CYP3A4 induction via rifampicin	
Azole antifungals	Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	CYP3A4 inhibition via azoles	
Calcium channel blockers	Diltiazem Verapamil	CYP3A4 inhibition via calcium channel blockers	
Glycosides	Digoxin	PgP-inhibition via ivacaftor/tezacaftor	
Herbal Remedies	St John's Wort	CYP3A4 induction via St John's Wort	
Macrolides	Clarithromycin Erythromycin Telithromycin	CYP3A4 inhibition via macrolides	
Rifamycins	Rifabutin	CYP3A4 induction via rifabutin	
Sulfonylureas	Glimepiride Glipizide	CYP2C9 inhibition via ivacaftor/tezacaftor	
Tyrosine kinase inhibitors	Crizotinib Imatinib Nilotinib	CYP3A4 inhibition via tyrosine kinase inhibitors	

Table 5: Ivacaftor-Tezacaftor Drug-Drug Interactions

Result of Interaction	Recommended Intervention
Increased warfarin exposure	Monitor INR
Decreased exposure of ivacaftor/tezacaftor	Avoid where possible
Decreased ivacaftor/tezacaftor exposure	Avoid where possible
Increased ivacaftor/tezacaftor exposure	When used in combination, decrease ivacaftor/tezacaftor dose to twice weekly (decrease to alternate days if combined with fluconazole)
Increased ivacaftor/tezacaftor exposure	Adjust dose of ivacaftor/tezacaftor if necessary
Increased digoxin exposure	Use with caution, monitor digoxin concentration and adjust dose if necessary
Decreased ivacaftor/tezacaftor exposure	Avoid where possible
Increased ivacaftor/tezacaftor exposure	If used with clarithromycin or telithromycin, decrease ivacaftor/tezacaftor dose to twice weekly; if used with erythromycin, decrease ivacaftor/tezacaftor dose to alternate days. Azithromycin does not require dose adjustments
Decreased ivacaftor/tezacaftor exposure	Avoid where possible
Increased exposure of sulfonylurea	Monitor for increased adverse events and adjust dose if necessary
Increased exposure of ivacaftor/tezacaftor	Adjust dose of ivacaftor/tezacaftor if necessary

Abbreviations: INR=international normalized ratio, P-gP=P-glycoprotein

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CHAPTER 5

The role of the CF specialist pharmacist in everyday practice and in clinical trials

Authors

Amanda Bevan, Elaine Bowman

Introduction

In recent years the role of the cystic fibrosis (CF) pharmacist has received greater recognition, and it is now established that the CF pharmacist should be an integral part of the CF multidisciplinary team [1].

In the UK, Pharmacy Standards of Care produced in conjunction with the CF Trust have existed since 2002. The most recent version was produced in 2016 [2].

In 2014, the European Cystic Fibrosis Society produced “Standards of Care: Framework for the Cystic Fibrosis Centre” [3]. These included a framework for medicines management and outlined the role of the CF pharmacist.

Common roles and responsibilities of the CF pharmacist include:

- Medication reconciliation/history taking
- Prescription monitoring and medication review service
- Managing formularies, clinical guidelines, and treatment protocols
- Identifying patient and medication risk factors

- Preventing, detecting, and reporting adverse drug reactions
- Individualizing drug and dosage requirements
- Educating and counselling patients and carers
- Evaluating medicine use and financial management
- Antimicrobial stewardship
- Providing medication closer to home
- Pharmacist prescribing

This chapter provides more detail on what these roles entail and how they benefit the patient with CF and the CF multidisciplinary team (MDT).

Despite the recommendation that the CF MDT should include a specialist clinical pharmacist, less than half of the European CF centers have access to one [4]. This is most likely due to the fact that decentralized clinical pharmacy services are uncommon in Europe, and are only significantly developed in the UK and Ireland [5]. However, the appointment of specialist CF clinical pharmacists provides clear benefits to patients and services. The majority of the UK CF centers and some European centers, mainly located in EU member states, have access to a CF pharmacist who fulfils all

the roles detailed in this chapter. However, some CF centers do not have access to a CF pharmacist, and only have access to a dispensing service. We have endeavored to distinguish between European countries in which these arrangements differ, and acknowledge that some European countries, particularly non-EU member states, do not have access to the broad range of drugs required on a daily basis to optimize the health of people with CF. The manner in which people with CF pay for medication also varies widely across Europe. However, a discussion of the details of medication provision in each country is beyond the scope of this chapter.

1 Role of the CF pharmacist within the multidisciplinary team (MDT)

The CF pharmacist is now recognized as a key member of the CF MDT. The NHS England Specialized Respiratory Service Specifications for CF include a CF pharmacist [6, 7].

The CF pharmacist can advise the MDT on all aspects of medication. This is increasingly important as patients are living longer and medications are becoming ever more complex. The CF pharmacist should attend the CF inpatient ward rounds, attend CF multidisciplinary team meetings, see CF patients at the annual review and during inpatient stays, and be available for consultation at outpatient appointments. Some CF pharmacists regularly see people with CF at outpatient clinics, although this is not routine practice.

Role of the CF pharmacist outside the MDT

The CF pharmacist should interact with other healthcare professionals as part of the care of CF patients. This includes liaising with and providing support and advice to community pharmacists. Commissioning colleagues within relevant organizations should be supported. During transition of patient care from pediatric to adult centers, the pharmacist should support and liaise with relevant colleagues. The CF pharmacist should also support and educate pharmacy, nursing, and medical colleagues both at centers within a shared care network and in the main center. The CF pharmacist should be an active member of the European CF Pharmacists Group and the UK CF Pharmacists Group if living in the UK. Attendance at study days and at national and international conferences ensures up to date knowledge. Membership of the CF Pharmacists groups enables CF pharmacists to support each other to provide best pharmaceutical care to people with CF.

2 Pharmacy support services

Alongside the CF pharmacist, there will be various other pharmacy personnel involved in providing support services to people with CF. Depending on the CF service, these may include the following:

- A Clinical Pharmacy Technician to support inpatient one-stop dispensing schemes, including medicines reconciliation, use of patients' own medicines, self-medication schemes, and patient counselling.
- Outpatient, inpatient, and discharge dispensing services to ensure timely supply of medication. This ensures patients have all their medication available to them when they need it.
- Aseptic dispensing service to provide aseptically manufactured products while in hospital (e.g. intravenous antibiotic desensitization regimes, total parenteral nutrition). This may be provided in-house or outsourced. See also the section on home intravenous (IV) antibiotic provision.
- Access to a medicines information service with experience providing information regarding the treatment of children and/or adults with CF as appropriate.
- Access to an on-call pharmacy service for the supply of urgent medication, information, and advice.
- Procurement and distribution to provide an efficient medicine supply service for inpatients and dispensing services.
- Homecare service to ensure the long-term supply of medication in the most cost-effective and convenient manner, taking into account the needs of the individual. Also, provision of home intravenous antibiotic treatment to people with CF where deemed appropriate by the service.

See section on homecare service provision (Sections 16 and 17 of this chapter).

3 Medicines optimization

The principal role of the CF pharmacist is to ensure that medicines are optimized at an individual level for all people with CF.

Medicines optimization is a patient-centered approach to safe and effective medicines use that ensures that people obtain the best possible outcomes from their medicines [8]. It is the process through which the pharmacy team co-operates with an individual and other healthcare professionals in designing, implementing, and monitoring a therapeutic plan to achieve these specific health outcomes while keeping the individual at the center of the decision-making process. Demonstrated benefits of a dedicated CF pharmacist include reducing medication errors, improving patient care, increasing access to medications, and financial savings [9].

4 Medicines reconciliation

Accurate medicines reconciliation ensures that medicines are taken correctly, potential adverse effects are identified, and an allergy history is documented. There are various points of care at which medicines reconciliation can occur: during inpatient admission, at an annual review, or at an outpatient appointment. Medicines recon-

ciliation should be undertaken at every clinic review and within 24 hours of admission to secondary care. It should include a review of alternative and over-the-counter medicine usage, as well as a review of the individual's adherence. All relevant information regarding medication should be effectively disseminated to primary care to ensure continuity of care.

4.1. Inpatient admission

When a person with CF is admitted to hospital, they should be seen by a CF pharmacist to ensure an accurate medication list is available to the MDT and to discuss any medication issues the patient may have. The patient may be in hospital for several days or longer, so an in-depth patient consultation is more likely to be achieved.

4.2. Annual review

It is recommended that CF patients are seen at annual review by a CF pharmacist. During the annual review, a comprehensive medication review is undertaken. Prior to the review, the patient's most recent clinic or discharge letter and the general practitioner's medication records are reviewed. Discrepancies, inappropriate prescribing, and potential adherence issues can therefore be identified in advance, and thus can be discussed during the review. At annual reviews, pharmacists make an average of 4.75 interventions per patient, most of which are deemed significant or very significant [10].

4.3. Outpatient appointments

A CF pharmacist should be available at each outpatient appointment to discuss medication issues that the CF patient or any member of the CF MDT may have. Some centers have a CF pharmacist as part of the outpatient clinic, while others have a CF pharmacist that can be contacted on an ad hoc basis.

5 Newborn screening

Newborn screening for CF is available in most European countries. Consequently, CF is most often diagnosed within the first 6–8 weeks of life. As part of a series of initial MDT meetings the pharmacist meets new CF families to explain the purpose of the medicines prescribed for the baby, and how to administer them. They also provide details about the medicine supply process via hospital and community services and about solving any problems that may arise. This meeting also provides an opportunity for the family to ask questions about CF medications that may have arisen since the diagnosis. The information covered should include:

- The purpose of the medicine, its intended benefits, and common adverse effects
- The baby's dose, how to administer it, and for how long it will be needed
- How to use an oral syringe or other administration aids, including maintenance instructions
- Safe storage and expiry of the medicine once opened

- How to obtain ongoing supplies of medication

The session is also an opportunity for the CF pharmacist to introduce the pharmacy service that is offered, and to begin to build what will likely be a longstanding professional relationship [11].

6 Prescription monitoring and medication review service

A key part of the role of the CF pharmacist is monitoring prescriptions and providing a comprehensive medication review service. This involves ensuring all medication and formulations are appropriate for the individual at that point in time.

Perhaps the most important part of the medication review is identifying and managing drug interactions, optimizing the effectiveness of medication while minimizing the risks of adverse effects. As people with CF live longer, they are prescribed more and more medication, much of which is complex. The potential for drug interactions increases with each new medication prescribed. In particular, new CFTR modulators interact with a large number of drugs, and it is therefore essential that the CF pharmacist carefully checks the patient's other medications before starting these drugs.

The CF pharmacist supports people with CF to help them make informed decisions about their medication. This leads to improved adherence and outcomes. The CF pharmacist helps detect and report medication errors and puts systems in place to minimize the risk of harm (e.g. monitoring

aminoglycoside and azole antifungal levels). Some CF pharmacists have studied to become qualified as independent non-medical prescribers, allowing them to support the CF service in prescribing for both inpatients and outpatients (e.g. homecare prescriptions). It is common for CF patients to be treated outside of the specialist CF unit (e.g. on a surgical or maternity ward). In these situations, the CF pharmacist can provide support and treatment advice.

7 Managing formularies, clinical guidelines, and treatment protocols

The CF pharmacist can assist in completing formulary applications to ensure medicines are introduced into clinical practice via local joint hospital and primary care formulary processes, developing shared care protocols where appropriate. CF pharmacists support the CF MDT in understanding the commissioning and reimbursement of high-cost medicines used in CF within the context of the responsible commissioner. The CF pharmacist also assists in completing any required forms and, where no mechanism exists to routinely fund a particular treatment, can help identify possible ways of requesting funding and coordinating this process. They liaise with the responsible commissioner to resolve inequality of access to medicines and to set budgets for high-cost medicines based on predicted usage. Moreover, the CF pharmacist ensures effective communication with other members of the CF MDT. They provide horizon scanning and critical evalu-

ation of recent studies on new and existing therapies.

The CF pharmacist compares practice with that of other centers, both nationally and internationally, to ensure that evidence-based treatments are being offered. They advise on the legal and ethical framework for the use of medicines, including additional requirements when prescribing unlicensed/off-label medicines, and ensure that prescribers are aware when they are prescribing unlicensed/off-label medicines. CF pharmacists provide expert advice on the administration of medicines, including the safe administration of IV drugs, administration via enteral feeding tubes, and the selection of formulations most appropriate to an individual person with CF. They can source medicines, including unlicensed medicines of a suitable quality when required (e.g. if a licensed medicine is unavailable due to a manufacturing issue, but an ongoing supply is essential for patient care). The CF pharmacist can resolve medication supply problems and liaise with primary care to ensure that ongoing supply is available to all patients or to suggest alternative medication where necessary. They collaborate with and contribute to CF research and development, and routinely work collaboratively with other members of the MDT to optimize the use of medicines in individual patients (e.g. working with physiotherapists to optimize nebulized therapy or with dietitians to optimize pancreatic enzyme replacement therapy).

8 Adherence

Adherence to treatment is a complex, multi-factorial issue and the subject of much discussion in the context of CF management, where appropriate polypharmacy is the norm. Patients are often required to take 10 or more different medications. The James Lind Alliance Priority Setting Partnership for Cystic Fibrosis identified the following as the number one research question for both people with CF and healthcare professionals: “What are the effective ways of simplifying the treatment burden of people with Cystic Fibrosis?” [12]. Using two or more nebulized medications and performing airway clearance for 30 mins or more each day were the treatment activities deemed most burdensome [13]. Alongside the patient-centered aim of reducing or halting disease progression, optimizing adherence is essential to ensure judicious use of valuable resources by avoiding inappropriate escalation of treatment, particularly given the increasing cost of CF therapies.

The pharmacist also has a significant role to play in supporting adherence, particularly in CF, where forced expiratory volume in one second (FEV₁) and body mass index (BMI) may decline due to inadequate treatment. Self-reported adherence has been identified as the most common method of measuring adherence in practice, and it has been suggested that greater specialist pharmacist involvement in CF patient care could facilitate improved adherence monitoring [14]. The CF pharmacist can ensure that medication is appropriate for the individual, can educate the patient about the

medication, and can discuss any medication-related issues (e.g. adverse effects or supply problems) that may be affecting the patient's adherence.

9 Identifying patient and medication risk factors

The CF pharmacist ensures that patient characteristics, including age, treatment expectations, pregnancy, breastfeeding, and organ dysfunction are taken into account whenever a drug is prescribed or a patient characteristic changes. They guide treatment using their knowledge of the evidence base and of the individual's response to previous and current medication. The CF pharmacist advises on the risks and benefits of non-drug and complementary therapies.

10 Preventing, detecting and reporting adverse drug events

The CF pharmacist can help the CF MDT and the person with CF identify a medication that may be causing a specific adverse event. This medication can then be discontinued, and an alternative prescribed if necessary. CF pharmacists proactively check for and document toxicity caused by medication, including allergies/hypersensitivity, contraindications, and other adverse drug reactions. They also advise on the appropriate use, storage, and disposal of medicines to minimize adverse events and the risk to others and to the environment.

They have a responsibility to document and report all reactions to newer medicines, as well as any serious reactions, to the Medicines and Healthcare products Regulatory Agency (MHRA) if based in the UK or the European Medicines Agency (EMA) if based in Europe. The CF pharmacist provides expert advice on the use of medicines during pregnancy and ensures that all exposure to medication during pregnancy is recorded and documented via the UK Teratology Information Service or the European Network of Teratology Information Services, as appropriate.

11 Individualizing drug and dosage requirements

It is the responsibility of the CF pharmacist to maximize the therapeutic potential and minimize the adverse effects of medicines by individualizing the treatment regimen to the specific person with CF. CF pharmacists manage therapeutic drug monitoring of relevant medicines (e.g. aminoglycosides, antifungals, and immunosuppressants) depending on the pharmacokinetic variables of the individual in question. Moreover, they monitor and review outcomes of an individual's need for medication, and advise on de-prescribing where appropriate. CF pharmacists also work with individuals to promote adherence to their prescribed treatments, and optimize use of medicines, taking account of and respecting the patient's wishes and lifestyle. Finally, the CF pharmacist advises on the most appropriate treatments for people with CF approaching the end of life.

12 Educating and counselling healthcare professionals, patients, and carers

The CF pharmacist contributes to the education and training of other healthcare professionals, including those working in primary care, other members of the MDT, and other secondary care professionals. They should lead the training of others within the pharmacy department, and provide education and counselling to people with CF to enable the safe and effective use of their medicines. They can provide patient information, both written and verbal, in a format that the person with CF can understand. Appropriate education can contribute to improved adherence to medicines by identifying intentional and unintentional non-adherence and can provide support to individuals to empower them to improve adherence. The CF pharmacist can support people with CF by helping them access prescription exemption certificates (if eligible) and pre-payment options.

13 Evaluating medicines use and financial management

The CF medication landscape is an increasingly expanding field of complex and expensive treatments. As such, the introduction of new therapies needs to be carefully managed. The CF pharmacist can identify patients eligible for treatment, will have knowledge of local funding arrangements, and will be able to review and implement patient access schemes, write any required guidelines, educate patients and health-

care professionals on new medications, and monitor outcomes and adverse events to new treatments, as well as adherence. The CF pharmacist can provide financial reporting to the CF MDT, the wider organization, and commissioners, as necessary. They can also contribute to budget planning, especially for high-cost drugs, and to business cases involving CF medicines. Finally, they can audit treatment guidelines and new therapies.

14 Antimicrobial management/ stewardship

Antimicrobial stewardship describes systems and processes designed for effective antimicrobial medicine use [15]. Pharmacists play a key role in this process, especially in the context of secondary care [16]. Because antibiotics are the mainstay of treatment for respiratory exacerbations in CF, and inhaled antibiotic formulations help reduce these exacerbations, the CF pharmacist plays a crucial role in antimicrobial stewardship within the CF team. They work closely with prescribers to ensure that the most appropriate antimicrobials are selected, taking into account specific organisms cultured and individual factors. It is well recognized that the use of effective antibiotics is one of the therapeutic advances that has helped increase the longevity of CF patients [17]. However, the use of antibiotics is not without issues. Adverse effects such as progressive renal toxicity following repeated courses of aminoglycosides is just one of the many challenges faced by the CF physician [18].

The CF pharmacist can help manage and minimize these adverse effects by ensuring the correct dose using patient-individualized parameters such as renal and hepatic function and body weight. The CF pharmacist will also ensure that correct monitoring is undertaken throughout the treatment course (e.g. therapeutic drug monitoring with aminoglycoside therapy and continual monitoring of renal, hepatic, electrolyte, and blood indices).

Hypersensitivity reactions, particularly to antibiotics, are common occurrences in the CF patient [19]. These reactions can lead to the prescribing of suboptimal treatment in hypersensitive patients. CF pharmacists can assist with the identification and documentation of allergies and, in the case of IgE-mediated reactions, can suggest an alternative antibiotic regimen or a desensitization regimen [20]. This will ensure that the CF patient receives optimal treatment and will therefore reduce the risk of further loss of lung function.

The CF pharmacist plays a central role in the production of CF center antimicrobial guidelines. New antimicrobials such as ceftazidime/avibactam, ceftolozone/tazobactam (Zerbaxa) and isavuconazole (Cresemba) have become available in recent years. CF pharmacists can facilitate the introduction of these new agents and help with hospital formulary applications, educate nursing staff and patients about administration, and audit the use of these agents to ensure appropriate usage.

15 Communication across different interfaces

People with CF are prescribed many different types of medicines. Some are prescribed by their general practitioner (GP) and provided via a community pharmacy, while others are prescribed by the CF center and provided either by the hospital pharmacy or a homecare company. Some of these medicines are prescribed outside of their product license, or are not routinely available. A GP/community pharmacy may only have a very small number of patients with CF and will be unfamiliar with much of the necessary medication. It is therefore important that regular and detailed information is communicated from the CF center to the GP and community pharmacists, particularly when medicines are newly started, stopped, or changed, along with information about prescribing responsibility. The CF pharmacist will liaise with GPs, clinical commissioning pharmacists, and community pharmacists to prevent delays to patients receiving their medicines, maximizing patient safety and convenience. Unlike hospital pharmacies, community pharmacies may experience drug shortages. The CF pharmacist can either advise the community pharmacy about where to source the medication or alternatively can arrange for the hospital pharmacy to supply the medication to the patient on a short-term basis. Communication between CF pharmacists, the CF MDT, and CF patients is essential to ensure that supplies of medication are not interrupted, thereby avoiding jeopardizing adherence.

16 Providing medication closer to home

In recent years in the UK and in some European countries, provision of some CF medication has moved away from prescribing and supply via the primary care route, instead opting for prescribing by the hospital and supply via the hospital pharmacy or a third-party homecare company. The drugs supplied via this route tend to be high-cost drugs such as nebulized antibiotics, dornase alfa (Pulmozyme), CFTR modulators, and antifungals such as voriconazole and posaconazole.

In the UK, homecare services are used to provide these medications to minimize the impact of value added tax (VAT) on the cost of medicines supplied to people with CF. This also applies to hospitals whose out-patient pharmacies are provided by a community pharmacy. Significant savings can be made using these companies. In Europe, whether VAT is paid on medicines by hospital pharmacies varies from country to country. If a third party is providing a pharmacy service to people with CF, it should be overseen by the CF pharmacist and audited against set standards at regular intervals. Where available, homecare services should be audited against professional standards [21].

17 Provision of IV antibiotics for home use

People with CF commonly receive a partial or entire course of IV antibiotics in the

home setting. Home IV antibiotic treatment can be beneficial for the patient, and does not differ from hospital-based treatment in terms of clinical outcomes [22]. How these antibiotics are provided varies widely within the UK and within Europe. A variety of models are used:

- IV antibiotics, diluents, flushes, and ancillaries are dispensed by the hospital pharmacy for the patient to make up and administer themselves
- IV antibiotics and flushes are compounded by the hospital pharmacy and dispensed to the patient, along with the necessary ancillaries
- An external company compounds the IV antibiotics and flushes and delivers these to the patient's home, along with necessary ancillaries.

Many hospitals use a combination of these models. It is more costly to use an external company to compound and deliver IV antibiotics. Moreover, not all antibiotics can be compounded due to lack of stability data. The CF pharmacist has a crucial role to play in ensuring successful IV antibiotic therapy. They ensure that the patient has a complete and timely supply of all items required including antibiotics, diluents, and ancillaries. They check that the flushes prescribed for each patient are appropriate for the type of IV access that the patient has *in situ*. Communication between the CF pharmacist, CF MDT, and CF patient is essential to ensure successful home IV antibiotic therapy. The CF pharmacist also ensures that the provision of home IV antibiotic therapy is the most cost-effective modality for their CF center.

18 Patient access schemes

In recent years, CFTR modulators have become available via patient access schemes (PAS) in countries in which these drugs are either not routinely funded or not yet commercially available. PAS involve complex agreements between a drug company and the hospital pharmacy at the CF center. These agreements must be entered into before patients can be prescribed these drugs. The CF pharmacist plays a central role in managing these PAS by ensuring that the agreement is approved by the chief pharmacist and assisting with the formulary applications to introduce the drug into clinical practice. Because these drugs are not supplied to the patient via the GP/community pharmacy route, the CF pharmacist also coordinates the prescribing and supply of these drugs to patients.

19 Pharmacist prescribing

Many CF pharmacists complete further training to become qualified pharmacist prescribers. In these cases, the additional skills of the CF pharmacist should be used to maximize the impact on the quality of the care provided. CF pharmacist prescribers can help with prescribing for CF inpatients, and can attend annual reviews or outpatient appointments for patients who are prescribed medication via a homecare company.

20 Clinical trials

According to the World Health Organization a clinical trial is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes”. For the purposes of this chapter, the intervention could be a medicine, a biological substance, or gene therapy. Clinical trials must be conducted in accordance with the European Union clinical trials directive 2001/20/EC (Europe 2001) [23] and Good Clinical Practice (GCP) (Europe 2005) [24].

A clinical trial can involve a new medicinal product or an old drug for a new indication. It may investigate drug pharmacokinetics or pharmacodynamics within a specific population, or may examine a novel route of administration for a drug currently administered via another route.

According to Brown *et al.* [25], “the role of the pharmacist in clinical trials is to ensure that drugs, whether classified as investigational medicinal products (IMPs) or not, are procured or, if necessary, manufactured correctly, maintaining the highest standards for medication safety practices and ultimately, the quality, efficacy, and safety of the results of a study”.

For trial medicines, storage with regular temperature monitoring is provided within a clinical trials pharmacy. If a trial drug is to be stored outside of the clinical trials pharmacy, a pharmacist should perform a risk assessment of the storage facility. Trial drugs should be stored away from other non-trial drugs wherever possible. In

cases in which a clinical trial drug requires on-site assembly or manufacturing, this is undertaken within a sterile manufacturing facility, usually located within the pharmacy department. All products that form part of the manufacturing process must have a corresponding certificate of analysis and be supervised by a clinical trials pharmacist. Manufacturing, dispensing, supply, and return records for trial medication must be meticulously maintained by the pharmacy in accordance with the relevant trial protocol.

During trial design, a pharmacist will advise on the source, quality (including packaging and labelling), and cost of the medicines involved. A designated pharmacist should review each protocol to assess the feasibility of the study and provide costing data for any work to be undertaken by the pharmacy. This preliminary work should include involvement in site initiation visits with the sponsor to agree upon pharmacy details. All packaging, labelling and drug accountability forms must be assessed for suitability for use, and each trial will require a validated pharmacy procedures document prior to the first trial subject visit [26]. Before initiating supplies for a clinical trial, the pharmacist will ensure that all relevant authorizations (from the sponsor and local healthcare and research organizations) are in place, and that the final version of the investigators brochure is available. All IMP prescriptions must be validated by a pharmacist before dispensing to ensure that the drug dose and frequency of administration conform to the trial protocol.

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CHAPTER 6

Parenteral administration in hospital and at home: challenges and solutions

Authors

Edwin Brokaar, Nichola MacDuff,
Lisa Sammons, Silvia Gartner, Erik Wilms,
Douglas McCabe

Introduction

Pulmonary exacerbations (PEX) are a common complication in cystic fibrosis (CF) and are associated with morbidity, mortality, and decreased quality of life. Approximately 45% of CF patients aged 18 years and older have at least one PEX every year [1]. Often, optimal treatment is with intravenous (IV) antibiotics. The clinician should consider not just the most appropriate antibiotic but also the optimal means and method of administration for each individual patient. Depending on the characteristics of the antibiotic, patient preferences, and the facilities available, the therapy may be administered in the hospital or at home. In this chapter we describe the properties of various access devices, possible complications and the management thereof, support that inpatients and outpatients may require, various characteristics of antibiotics to consider, home-care infusion devices, and the patient perspective of IV antibiotic treatment.

1 IV access options, associated complications, and their management

Practitioners should be familiar with a wide variety of IV access devices, to ensure that the correct method of delivery is selected. Recent years have seen considerable interest in the importance of focusing on vessel health rather than on the IV access device itself [2]. The health of peripheral veins, the suitability of the medication to be administered, the appropriate line choice for the length of treatment, and ongoing assessment of the line during treatment are all important considerations. The UK Vessel Health and Preservation (VHP) working group came up with a framework to support practitioners in selecting the most appropriate device [2]. Placement of any vascular device is an aseptic procedure and should only be undertaken by staff with appropriate training [3, 4].

1.1. Line selection

1.1.1. Peripheral cannula

A peripheral cannula is defined as one of less than 7.5 cm in length, and should be

selected for short term therapy (for bolus injections or short infusions) of 3–5 days duration [3]. Because CF treatment regimens tend to last at least 14 days, a cannula would not be the optimal choice of device in most circumstances. The average peripheral line lasts only 44 hours, mainly due to phlebitis and infiltration [5].

1.1.2. Midline catheter

Midline catheters range from 7.5–20 cm in length and are used to administer fluid, blood products, and medication for treatments expected to last between 1 and 4 weeks. Midline catheters should be placed above or below the fold of the antecubital area to avoid patient discomfort when flexing the arm. This will also reduce the chance of a kink forming [6]. Ultrasound should be used to facilitate insertion. Because the tip of a midline catheter does not extend beyond the axillary vein there is no need for radiological confirmation of tip placement prior to use. Midline catheters provide easy, short-term access to administer antibiotic treatment courses of a specific duration, and appear to be associated with fewer and less serious complications than peripherally inserted central venous catheter (PICC) lines. Midline bloodstream infections and thrombosis occur over 10 times more often in patients with PICC lines versus midlines [7, 8].

1.1.3. Central lines

A PICC is a catheter that is inserted into the veins of the upper arm and then advanced into the central veins. The choice of a PICC line over a midline should balance the risks of infection and other complications against

the purpose for which the line is to be used and the duration of treatment [9]. A study by May *et al.* reported marked differences in the frequency of complications among centers in the USA and attributed this to variability in the approaches used to manage PICC lines within institutions [10]. A totally implanted vascular access device (TIVAD) consists of two components: a reservoir with a self-sealing septum that is permanently placed under the skin and a catheter that is tunneled into a central vein. In the context of CF, TIVADs have traditionally been inserted in patients who require regular courses (≥ 2 per year) and whose vessel health is compromised due to repeated access. A 20-year retrospective study by Royle *et al.* reported an overall complication rate (infection, thrombosis, leakage, extravasation) of 0.58 per 1000 catheter-days [8]. The results of the majority of studies of the safety of implanted ports also indicate a lower infection rate than that associated with tunneled external lines (e.g. PICC and Hickman devices) [6]. A 2018 multicenter study by May *et al.* supported this finding, and noted that polyurethane catheters are more likely to require removal than those made of silicone [10]. The duration of function of a TIVAD is up to 4,440 days (approximately 12 years).

1.2. Complications and their management

Most guidelines recommend regular site care (observation and evaluation of the device and surrounding tissue) [6]. In circumstances in which patients are self-administering medications in their own home, suitable education should be provided and

a modified visual infusion phlebitis (VIP) score used to guide appropriate action should complications arise (**Figure 1**).

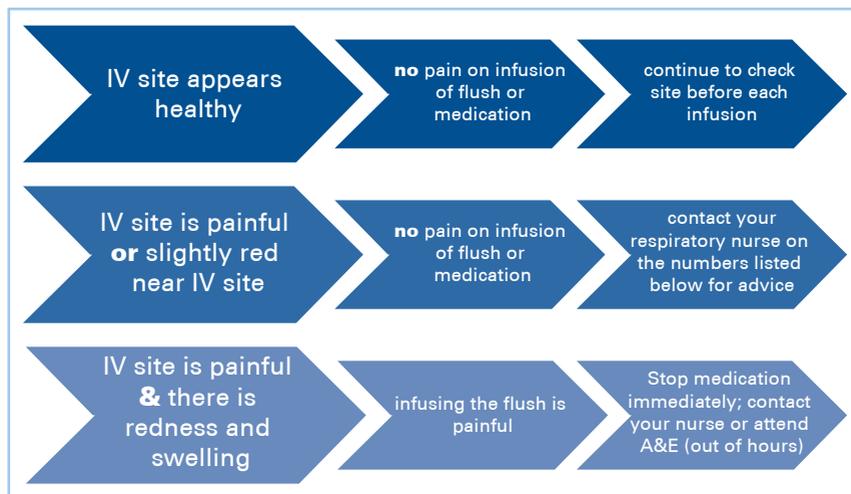


Figure 1: Modified visual infusion phlebitis score

Original VIP score developed by Andrew Jacks: Consultant Nurse, Rotherham General Hospital. Modified for patient use by Nichola MacDuff, CF CNS, The Royal Wolverhampton NHS Trust.

1.2.1. Infiltration and extravasation

Infiltration should be managed as per local policies. The infusion or bolus injection should be immediately discontinued upon observation of infiltration. Similarly, if extravasation (the inadvertent administration of vesicant solutions into the surrounding tissue) is observed, the infusion or bolus injection should be promptly discontinued and immediate intervention performed to mitigate the effects of the vesicant on the tissue. Treatment should be determined before removal of the catheter,

which may be used to remove some of the drug. Ongoing treatment will depend on the properties of the agent and the severity of the extravasation.

1.2.2. Occlusion

There is no clear evidence to support the use of anticoagulants as a preventative measure in thrombotic occlusion. A variety of retrospective multicenter studies have examined the use of high-strength heparin (100 IU/ml) and low-strength heparin (10 IU/mL), but failed to establish conclu-

sive findings owing to variation in practice within and across centers.

In the absence of blood return, an attempt should be made to flush midline catheters and central venous access devices. Force should not be applied if resistance is encountered. Thrombolytic agents specifically indicated for dissolving clots should be prescribed and administered in line with local policy. The instilled volume of thrombolytic agent should not exceed the volume capacity of the catheter. Patients should be monitored for secondary effects of thrombosis (pulmonary embolism, interruption in limb perfusion). If a device is not functioning correctly, a linogram can be performed using radio-opaque dye to establish the patency and integrity of the device. This can then inform the clinician's decision to remove the device if it has fractured or to use thrombolytic medication if the device is blocked.

1.2.3. Infection

When accessing the device, it is important to adhere to local protocols and procedures for the prevention of catheter-related bloodstream infections, including those pertaining to aseptic catheter insertion and aseptic non-touch technique (ANTT). If infection is suspected, blood culture samples can potentially be obtained through the device and/or via peripheral venipuncture.

2 Patient selection and patient support

2.1. Patient-related determinants

Persons with CF require numerous courses of IV antibiotics during their life. Because the duration and frequency of antibiotic therapy increases with disease severity, the optimal choice of intravenous access device will also change correspondingly. It is therefore important to choose the method of administration that is most suitable for the patient's disease stage, while also considering previous experiences, body image, past medical history, and lifestyle [3]. Home IV antibiotic therapy has become standard practice in CF patients with stable infection who require long-term administration of intravenous antibiotics [11]. Home therapy offers some advantages over hospital-based treatment, including improved psychological wellbeing, less disruption of family life, reduced incidence of hospital-acquired infections, and greater cost-effectiveness for the healthcare system [12].

2.1.1. Selecting patients suitable for home IV antibiotic therapy

Several models have been developed for the provision of home IV antibiotic therapy: administration by a healthcare professional at an ambulatory care center or at home, administration by the patient's caregiver at home, or self-administration (adults). The first and second options have the advantage of supervised administration, although the first requires that the patient travels and the second entails the added cost of visits by a healthcare professional. The second two options offer greater cost savings,

but require training of both the patient and the caregiver, and involve less professional supervision [12, 13]. Hospital discharge can be planned once patients and caregivers are considered to be sufficiently well prepared and to have sufficient knowledge and aptitude.

Patients and caregivers should be informed about the benefits and risks of home IV antibiotic therapy and should be given the opportunity to decline or accept this type of therapy. Careful selection of patients and caregivers is key to ensuring therapeutic success. Patients should be selected using a team approach, and the home IV antibiotic therapy specialist nurse should be primarily responsible for assessing and managing patient criteria for acceptance of this treatment modality. In addition, the patient's home should have a dedicated procedure area that is clean and equipped with the appropriate facilities for storage of medication [13]. Some patients may require a short hospital stay to receive the necessary training. In any case, the first dose of antibiotic should always be administered in hospital under the supervision of a health-care professional to ensure that the patient has no anaphylactic reactions.

Home IV antibiotic therapy can be considered in the following scenarios:

- Stable respiratory infection without other complications or specific treatments (hemoptysis, failure to clear secretions, need for intensive chest physiotherapy)
- Mild respiratory infection that cannot be resolved exclusively with oral antibiotics
- Additional hospital care or frequent monitoring is not required
- Patients or caregivers who are able to safely administer treatment at home

While a number of studies have compared hospital versus home antibiotic treatments, no definitive conclusions can be drawn as to which is most suitable or preferable [14]. In most of these studies, analyses of improvements in pulmonary function parameters have revealed large variation, indicating that some patients improve greatly while others do not. A recent Cochrane review concluded that home IV antibiotic therapy in CF is not harmful and that the decision to treat at home should be made on an individual basis [15].

2.1.2. Monitoring patients at home

Once patients are discharged, weekly evaluations in an outpatient clinic should be scheduled. This evaluation should include physical examination, oxygen saturation testing, spirometry, and nursing evaluation of vascular access and drug administration, the absence of progression to severe PEx, and the presence of adverse reactions. The timing of these follow-up visits can be modified according to the patient's condition, family situation, and complications. The CF unit should be available for consultation at any time in case complications arise. It is crucial to delineate clear recommendations on how to monitor patient progress during therapy, developing pathways for rapid access to clinical care and early detection of potential complications. Patients should also receive mandatory training and clear

instructions on the management of their home IV antibiotic therapy.

Clear and timely communication between disciplines, coherent and non-contradictory information, and the possibility of 24/7 contact in case of emergencies are essential to establish the trust a patient needs to leave the hospital with an IV catheter in place [16]. Because the shelf life of ready-to-use IV products may be shorter than the total antibiotic course, accurate planning and communication with the patient in conjunction with the dispensing pharmacy are essential. Patients may find that elastomeric devices run somewhat quicker or slower than expected, and may require advice on how to handle these situations both before and during home treatment.

2.1.3. Inpatient support

The main aim of PEx treatment with IV antibiotics is to achieve and maintain optimal lung function, since lung function, particularly forced expiratory volume in one second (FEV₁), is the most important objective clinical outcome measure in CF. The entire CF multidisciplinary team (including doctors, specialist nurses, physiotherapists, dieticians, pharmacists, clinical psychologists, microbiologists, and social workers) should work together to evaluate and treat PEx and associated complications, such as pneumothorax and hemoptysis. During inpatient treatment, patients are monitored more closely than during outpatient care. Therefore, the risk associated with inpatient treatment is potentially lower. For hospitalized patients, recommendations include more intensive physiotherapy as well as treatment with the usual airway surface

liquid hydrators, mucolytics, and inhaled antibiotics.

Conventionally, antibiotic selection for PEx treatment has been based on the results of microorganism and antibiotic susceptibility testing. Respiratory tract cultures should be mandatorily obtained at the moment of exacerbation. The CF team should regularly evaluate hospitalized patients to detect improvements that could allow transition from “requiring in-hospital treatment” to “home IV antibiotic therapy possible”.

2.2. Antibiotic-related determinants

2.2.1. Choosing the antibiotic for home IV antibiotic therapy

Home IV drug administration requires the application in the home of nursing techniques or skills that are usually only available in a clinical setting. Reconstitution of the solution for infusion and IV administration can be performed by trained nurses at home or by the patients themselves. Providing ready-to-use infusion devices may be beneficial for patients, but this option is not appropriate for all antibiotics. The following criteria should be fulfilled when selecting drugs for home IV treatment:

- There should be no alternative, less invasive means of administration
- The drug of choice should be well known to the treating physician and the caregivers
- The drug of choice should be well accepted with little chance of causing adverse drug reactions

- The dosage regimen should be feasible for a home-care setting, requiring as few manipulations or device changes as possible
- The drug of choice should be chemically stable if used in conjunction with ready-to-use infusion devices

Aminoglycoside antibiotics can be used to treat exacerbation of CF pulmonary infection. This group of antibiotics is not free of side effects, but is so familiar to physicians that the risks can be minimized, even at home. Aminoglycosides can be administered once daily as a bolus injection or as a short infusion. Renal function, drug levels, and hearing function can be monitored using approaches similar to those used in a clinical setting.

Owing to their low level of toxicity, cephalosporins and beta-lactams antibiotics can be administered at home. Cephalosporins can be administered by continuous infusion to overcome the need for frequent (>2 times daily) administration. While amoxicillin lacks sufficient stability for home administration, piperacillin (with tazobactam) and flucloxacillin can be administered at home. Carbapenems are generally well tolerated, but have the disadvantage of being unstable in solution. To guarantee stability, prepared solutions can be kept deep frozen, and kept cool using cold packs during administration. Other antibiotics with activity against *Pseudomonas aeruginosa* such as colistin and fosfomycin are also suitable for home administration. For certain newer combinations such as ceftazidime plus avibactam, stability and compatibility with home infusion devices should be assessed before deciding upon home IV administration.

Treatment with certain antibiotics such as tigecycline is, in our opinion, best initiated in a clinical setting, given its limited tolerability. Adverse drug reactions such as nausea should be observed and treated, as failure to do so will significantly diminish treatment. Patients who tolerate tigecycline in a clinical setting may be suitable candidates for home administration. Antibiotics with a sufficient level of oral absorption, such as quinolones and co-trimoxazole, should always be given orally provided the oral route is available and appropriate. IV administration should be considered only in specific cases in which gastrointestinal absorption is compromised.

2.2.2. Intermittent or continuous infusion

Dosing schedules for home IV antibiotic therapy should be as simple as possible. Ideally, only a single administration or change of a home infusion device should be required per day. The use of ready-to-use IV (elastomeric or portable electronic) pumps allows continuous infusion in a manner that negligibly affects patient mobility.

For aminoglycoside antibiotics, a single daily bolus infusion is both safe and effective. Other antibiotics tend to be more effective with a prolonged period of exposure above the minimum effective concentration. For these antibiotics, which include cephalosporins, carbapenems and beta-lactams, continuous administration can be considered. Owing to its short half-life, the cephalosporin ceftazidime must be administered two or three times per day in most patients. Continuous administration is an alternative that offers clinical and practical

advantages over 3-times-daily administration, and can be achieved using an electronically controlled portable pump or an elastomeric pump. Continuous administration of meropenem is complicated by its poor stability, although cold packs can be used to keep solutions sufficiently cold to enable infusion over 24 hours. Older antibiotics with activity against *P. aeruginosa*, such as colistin, can be administered once daily, although continuous infusion is also possible. The stability and safety of other, newer antibiotics, such as the combination of ceftazidime and avibactam, will have to be evaluated before continuous infusion can be considered.

2.2.3. Antibiotic-related monitoring

Monitoring of serum drug concentrations can facilitate determination of optimal dosing level and frequency. In persons with CF who have pulmonary infections, high serum levels of antibiotics are often necessary to overcome (partial) resistance. Furthermore, it is necessary to take into account various patient-specific characteristics, including renal function, which varies widely. For aminoglycosides, therapeutic drug monitoring is considered necessary to guide proper dosing and minimize toxicity. For cephalosporins, beta-lactam antibiotics and carbapenems, therapeutic drug monitoring can be helpful to optimize the dosage regimen, but is less accepted and not generally available. Aminoglycoside dose can be optimized after the first administration. If IV tobramycin is administered in a home setting, serum levels can be measured once weekly, together with serum creatinine levels (to monitor renal function).

For aminoglycosides, a mid-concentration 4–8 hours after administration will provide a detectable concentration that can be used to monitor clearance. When interpreted correctly, preferably using pharmacokinetic interpretation and modelling software, changes in clearance can be considered indicative of loss of renal function. Alternatively, trough levels can be monitored, although one disadvantage is that this approach only reveals large decreases in renal clearance. In addition to renal toxicity, aminoglycoside ototoxicity should be monitored in the same way as during clinical administration. The characteristics of various IV antibiotics used in CF treatment are shown in **Table 1**. Only general information on toxicity and monitoring is provided: more detailed information can be found in the product information accompanying each antibiotic.

Antibiotic	Continuous infusion	Home administration	Toxicity	Monitoring
Piperacillin/tazobactam	+	+		
Ceftazidime	+	+		
Meropenem	+	+		
Aztreonam	+	+		
Tobramycin	n/a	+	Renal toxicity and ototoxicity	Tobramycin levels and renal function
Ciprofloxacin	n/a	+ (preferably oral)		
Levofloxacin	n/a	+ (preferably oral)		
Colistin	Unknown	+ no theoretical objections to continuous administration; little or no experience	Neuropathy, renal toxicity	
Fosfomycin	Unknown	+ no theoretical objections to continuous administration; little or no experience		Serum electrolytes (Na, K)
Ceftolozane/tazobactam	Unknown	No theoretical objections to continuous administration and home administration; little experience		
Tigecyclin	-	Not advisable due to side effects	Nausea	
Ceftazidim/Avibactam	Unknown	+ no theoretical objections to continuous administration and home administration; little experience		
Linezolid	-	+ (preferably oral)	Headache, metal taste, hypertension	Blood pressure
Moxifloxacin	-	+ (preferably oral)		
Amikacin	-	+	Renal and ototoxicity	Amikacin levels and renal function

Table 1: Overview of the most common IV antibiotics used in CF treatment

3 Home-care infusion devices, patient perspective, quality of life

3.1. Home-care infusion devices

There are two main formulations used for patients receiving home IV antibiotic therapy: vials or ampoules that the patient must reconstitute, and subsequently draw-up and self-administer; and ready-made IV products packaged in syringes, medication cassettes, or elastomeric pumps that patients can connect and self-administer using a centralized intravenous additive service (CIVAS). This can be commercial or provided in-house by the health service unit.

In both cases, patients will need to be trained and obtain practical experience, often in a ward setting with qualified staff who can demonstrate, supervise, and document adequate competency before patients can self-administer IV at home. This should include the practical ability to administer IV medication, aseptic technique, and knowledge of the medication, IV line care, and the necessary action to take in the event of an adverse effect. The training record should be completed in detail and stored in the patient record. Refresher training is recommended every 1–2 years to ensure maintenance of competency, especially if patients have intervals of many months between courses of IV antibiotics. Some CF centers opt to refresh and verify knowledge and competencies with each new course of IV antibiotics.

Patients are given large amounts of medication and equipment in order to complete the treatment course at home, as summarized in **Table 2**.

Medicines	Equipment
IV antibiotics – usually at least 2 different medicines (supplied ready-made or in vials and ampoules)	Syringes
	Needles (may include filter needles for glass ampoules)
Water for injection (to reconstitute powder vials)	Alcohol wipes
Sodium chloride 0.9% flush	Syringe caps
Heparin - usually 100 units/mL for TIVADs and 10 units/mL for long lines (depending on local policy and type of IV access)	Yellow incineration bin (“Cin bin”)
Oral medication (additional antibiotics, antiemetics, analgesics, antifungals, antihistamines as required)	Ampoule cutters (optional)

Table 2: Equipment and sundries required for home IV antibiotic therapy

Abbreviations: IV=intravenous, TIVAD=totally implantable vascular access device

To complete a course of home IV antibiotic therapy, a patient can be provided with information leaflets explaining how to make up and administer the medication, together with a list of any side effects to report. It is

important that adequate follow up and monitoring is agreed upon at the start of each course (e.g. repeat spirometry, blood tests, and measurement of tobramycin levels). It may be possible to perform these tests at the patient's local medical practice to avoid travelling long distances. Patients should also be given contact details for 24-hour, 7-day-a-week access to professional advice in the event of any complications such as line blockage or severe adverse reactions at home. The contact point will usually be the inpatient ward where experienced nursing and medical staff will be available, including out of hours and on weekends. Some centers provide adrenaline pens to cover the rare event of anaphylaxis at home. Patients are educated and shown how to use these pens and provided with an action plan should anaphylaxis occur at home, including emergency numbers to call (e.g. 999 in the UK) [17].

In the case of patients supplied with ready-made products, once it is decided to treat with IV antibiotics an order is placed to the CIVAS pharmacy (which may be an in-house service or may be outsourced to an external manufacturer). There may be an interval of several days between placing the order and receipt of the product, although some CIVAS pharmacies may offer same-day preparation. The urgency of treatment should therefore be taken into account. In some cases it may be appropriate to admit the patient to begin treatment immediately, and then place the CIVAS order, which will arrive a few days later. The stability of each medicine also affects how many days-worth can be supplied at a time: several deliveries may be required and reconstituted

medicines may need to be refrigerated. Adequate cold storage is also required, since products are bulky, and a 2-week course may consist of 42–84 doses.

IV bolus is often the preferred route, provided this is appropriate for the chosen medicine. This is the simplest form of IV drug administration for the patient to carry out at home. Many medicines can be administered by IV bolus via a central, PICC, or long line. When administered via peripheral IV cannula, some medicines may need to be infused or administered at larger volumes or for longer periods (e.g. colistimethate sodium). The CF pharmacist and nurse have detailed knowledge about the administration options for each medicine and will usually select the easiest method for home administration (see product literature). Many medicines used today can only be administered by IV infusion. In this case, ready-made products are preferable for home administration to avoid the need for multiple manipulations and use of an IV infusion pump. Occasionally, it may be possible to train carefully selected patients to perform IV infusions at home in cases in which CIVAS is unavailable. Local policies and guidelines can be produced to summarize all required information.

There is little published information on outcomes of home IV antibiotic therapy in CF patients. The most recent Cochrane review included only one such study, and stressed the need for large randomized controlled trials comparing treatment outcomes in hospital and home settings [15, 18]. Clinical outcomes also vary between studies: while some show a greater improvement in FEV₁ in the hospital

group, this may be due to a lower FEV₁ in this group at the beginning of treatment. Other studies have reported no differences in lung function. **Tables 3** and **4** summarize the advantages and disadvantages associated with each setting [15, 18-21].

Advantages	Disadvantages
Access to full multidisciplinary team, including daily physiotherapy and dietetics support	More frequent investigations
Greater degree of mastery (control of disease)	Hospital-acquired infection
Potential for greater improvement in lung function and nutritional status	Increased disruption to life, sleep
Monitoring and treatment of complications (e.g. insulin, oxygen, non-invasive ventilation)	Lack of food choices
Adherence and regular drug administration with a set routine	
Adequate rest to recover	

Table 3: Advantages and disadvantages of hospital IV antibiotic therapy

Advantages	Disadvantages
Less disruption to daily life (family, study, work, sleep)	Increased fatigue due to burden of care plus usual activities during illness
Reduced cost and pressure on inpatient beds	Potential missed doses or early discontinuation of treatment course
Reduced cost to patients and families (travel, loss of earnings)	Increased incidence of line infections and bacteremia
Preferable food and exercise options at home	Self-diagnosis and self-reporting of adverse effects such as drug allergy
Patients may prefer to choose the timing of drug administration	Lack of access to physiotherapy or dietetic support
Reduced risk of cross infection	

Table 4: Advantages and disadvantages of home IV antibiotic therapy

3.2. Patient perspective

CF patients and caregivers tend to prefer home over hospital IV treatment, for several reasons. Treatment in hospital is considered disruptive for patients, especially children, and their families, depriving them of school, work, and social activities for extended periods of time. It is very important that the MDT provides patients and caregivers with all necessary information in a written document.

Parents and/or caregivers should be familiar with antibiotic regimens, and should know how to prepare and administer antibiotics, avoiding risks of contamination and dosing errors. These risks can be reduced by limiting the number of antibiotics and their frequency of administration.

One of the most important issues for patients or caregivers is the choice of IV access device. Patients who prefer a PICC line typically do not want a more permanent device (e.g. a TIVAD): the PICC line gives patients the option of removing the intravenous access immediately after completing antibiotic administration. Patients using PICC lines also find them more cosmetically acceptable, as they allow insertion of the catheter in the upper arm rather than the dorsum of the hand (as is the case with a peripheral line). Patients should be informed about the benefits and possible drawbacks of each access device in order to be able make a well-informed choice.

Patients using infusion pumps find them very convenient owing to the short preparation time prior to administration and the minimal amount of equipment needed to mix the medication, which saves on storage space and generates less waste.

Ready-made infusion pumps offer further convenience. Parents and caregivers also feel that home IV antibiotic therapy reduces the likelihood of cross infection.

The potential disadvantages of home IV antibiotic therapy include less professional supervision and monitoring and initial feelings of insecurity on beginning the treatment process [14].

3.3. Quality of life

The rationale for home IV antibiotic therapy is that patients and caregivers can continue their daily activities with minimal disruption while undergoing antibiotic treatment essential for their quality of life (QoL). Some patients and families, although motivated, cannot manage the additional stress and time commitments associated with home IV antibiotic therapy. In terms of QoL, family disruption and sleeping and eating problems are less significant in patients receiving home- versus hospital-based treatment. Home therapy may be also less expensive both for the family and the attending hospital. Moreover, new drug administration devices provide patients with increased mobility and independence. Few studies have examined QoL in patients undergoing home IV antibiotic therapy. A Canadian study of adults receiving home- or hospital-based IV antibiotic therapy [22] reported significant improvements in the home IV antibiotic therapy cohort in 3 domains: physical functioning, role-emotional, and the mental component summary (MCS) scale score. The improvement in the MCS score indicates that the greatest benefits of home therapy are improvements in psychological distress,

social functioning, and role disabilities due to emotional problems.

A Greek study assessed QoL in 35 stable pediatric CF patients colonized with *P. aeruginosa* and treated with IV antibiotics for 2 weeks either in hospital or at home [23]. QoL was measured using the DISABKIDS questionnaire (condition-specific module for CF), a validated questionnaire completed by children and their parents. In the home group significant improvements were observed in all QoL domains, while in the hospital group significant improvements were observed only in physical and impact domains. Moreover, home treatment was associated with substantial economic savings as compared with hospital treatment.

4 Summary

CF patients frequently receive IV antibiotic treatment for PEx. These treatments have a major impact on daily life, but are necessary to maintain health. Many antibiotics used to treat persons with CF can be administered either the hospital or at home, and the latter option is usually preferred. The choice of line used depends on patient characteristics, patient preferences, and care facilities. Most antibiotics can be prepared for infusion by both the patient and caregiver or provided as a ready-made infusion. In both cases, thorough instruction and training are required to ensure safe administration, and patients should have 24/7 access to health-care providers for support.

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CHAPTER 7

Aerosol therapy for CF lung disease: the basics

Authors

Hettie M. Janssens, Harm A.W.M. Tiddens

Introduction

Aerosol treatment plays an important role in the treatment of lung disease for most patients with cystic fibrosis (CF). This treatment starts early in life and is continued throughout life. A large variety of therapies are delivered as an aerosol, including mucolytics, antibiotics, bronchodilators, oligonucleotides, and gene therapy. A similarly wide array of aerosol delivery devices are used to deliver these therapies, ranging from nebulizers to dry powder inhalers (DPIs) and pressurized metered dose inhalers (pMDIs). The general view is that aerosol therapies provide high concentrations throughout the airways. In reality however, many factors determine the aerosol distribution in the lungs of CF patients, and concentrations vary widely throughout the bronchial tree. In order to optimize aerosol therapy from infancy into adulthood, prescribers of CF medication must have an in-depth understanding of the ins and outs of aerosol therapy. In this chapter we first cover the basics of aerosol therapies, and then discuss the various aerosol delivery devices.

1 The target area

CF lung disease results in abnormal secretions in the lung that foster infection and inflammation [1, 2]. The vicious cycle of infection, inflammation, and thick pulmonary secretions leads to early structural lung damage. In addition to bronchiectasis, small airway disease plays an important role in CF lung disease [3]. In advanced lung disease the geometrical changes associated with small airway disease are significantly more severe than alterations affecting large airways. Progressive bronchiectasis and small airway disease eventually lead to end-stage lung disease [4]. The severity and distribution of the structural changes, in addition to mucus in the airways, all have a considerable impact on the distribution of inhaled aerosols. When prescribing aerosol therapy, it is therefore crucial to take these patient-specific structural changes into account. The most direct and sensitive means of visualizing these changes is chest computed tomography (CT) [5]. Another important issue to take into account when treating the airways is that the combined surface area of all small airways is in the range of several square meters. In general, drug inhalation results in very high concen-

trations in central airways but much lower concentrations in the small airways. Unfortunately, it is even more challenging to efficiently target the small airways in diseased areas of the lung.

2 Aerosol particles and deposition

From infancy, we inhale thousands of liters of air per day containing all sorts of aerosol particles, including microorganisms and *Aspergillus* spores. Upper and lower airways are highly efficient at trapping aerosol particles and transporting these particles out of the lungs through mucociliary and cough clearance mechanisms. For efficient aerosol treatment of both central and small airways it is important to consider a number of factors that determine whether a sufficient fraction of the inhaled particles can bypass the upper airways to be deposited onto the walls of large and small airways in diseased lung areas. These factors can be divided into particle-related factors and patient-related factors [6].

The most important particle-related factors that determine their aerodynamic behavior are shape, size, and density. The size distribution of an aerosol is usually described as the mass median aerodynamic diameter (MMAD), which refers to the droplet diameter above and below which 50% of the mass of drug is contained. The second important parameter is the geometric standard deviation (GSD), which is a measure of the spread of an aerodynamic particle size distribution. Aerosol particles smaller than 5 μm are often described as

being “respirable.” This means that these particles have a relatively high probability of bypassing the upper airways. However, particles with a MMAD of 2–5 μm have a lower probability of being transported to and deposited in the small airways than particles of 1–2 μm (**Figure 1**). Unfortunately, small particles carry little drug. In addition to the geometric size of the particle, the particle density determines transport velocity and deposition probability. Spheres that have the same transport velocity exhibit the same aerodynamic behavior and have similar deposition patterns in the lung. This means that particles that are geometrically large and are porous (i.e. have a low density) can behave aerodynamically like particles that are geometrically small and are nonporous (i.e. have a high density). This effect of density on aerodynamic diameter has been utilized in the development of dry porous particles for DPI tobramycin formulations.

Among the most important patient-related determinants of lung deposition and distribution within the airways is the diameter of the large airways [6]. Young children have smaller airways and higher inspiratory airflows relative to adults, and both these parameters facilitate central airway deposition (**Figure 1**) [7]. A second patient-related factor determining particle deposition is the quality of the inhalation maneuver. This quality depends on age, physical capability, disease severity, and the cognitive ability of the patient to perform specific inhalation maneuvers. It is well recognized that even well-trained and capable patients can vary their inhalation technique considerably from day to day [8, 9]. A high inspiratory flow rate

results in more turbulence in the central airways, meaning that a larger fraction of the inhaled drug is deposited in the upper airways [10]. Conversely, a slow inhalation maneuver will result in less turbulence in the central airways and a greater probability that aerosol particles will bypass the central large airways. Ideally, an aerosol should be inhaled with slow and deep inhalation, so that even large particles containing a high drug mass have a greater probability of bypassing the turbulent central large airways to reach the diseased small airways. The third patient-related factor that determines particle deposition is the presence of structural abnormalities of the airways and/or mucus in the airways, which disturb the airflow pattern and increase deposi-

tion at the sites of obstruction [10-12]. The fourth patient-related factor is the ability of the lung to expand homogeneously. Recent modelling studies have shown that lobes with substantial structural damage receive less inhaled drug particles [9, 12]. It is likely that structural abnormalities such as fibrosis in CF lungs have a negative impact on lung expansion [13] (**Figure 2**). As a result, there is a preferential airflow to the healthier regions of the lungs.

In order to select the most appropriate inhalation device for a patient we should not only take into account the aerosol characteristics of the inhaled drug, but also the patient's age, the required inhalation flow pattern associated with the device, and the severity of CF lung disease.

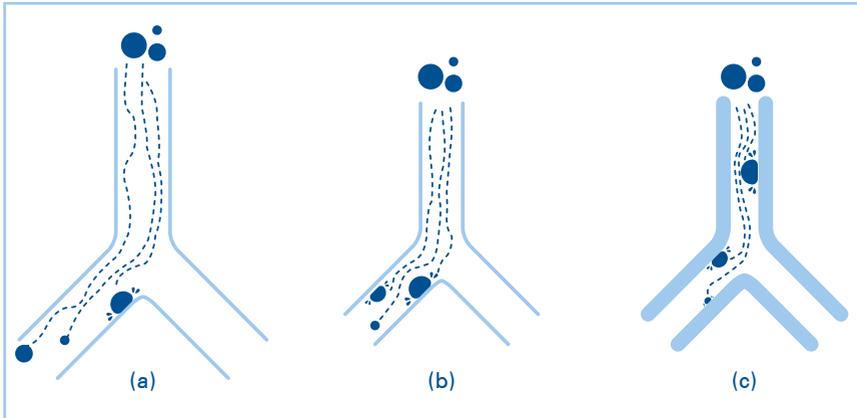


Figure 1: Schematic view of the bronchial tree showing the relation between airway size, flow velocity, and deposition of three differently sized aerosol particles (1, 3, and 5 μm).

(a) In the healthy lung, the 5 μm particle has the highest probability of being deposited onto the mucosa of the central airways due to inertial impaction. (b) In the healthy lung of a child, the airways are narrower and flow velocities of the inhaled particles are higher. As a result, the 3 and 5 μm particles are deposited on the central airway mucosa. (c) In the diseased lung of a child, the airways are thickened due to mucosal

swelling by inflammation and mucus. As a result, the cross-sectional diameter of the central airways is even smaller relative to the healthy lung (b). In addition, mucus depositions cause more turbulence of the inhaled air. As a result the 1, 3 and 5 μm particles are deposited on the central airway mucosa. Figure and legend reproduced with permission from the publisher [38].

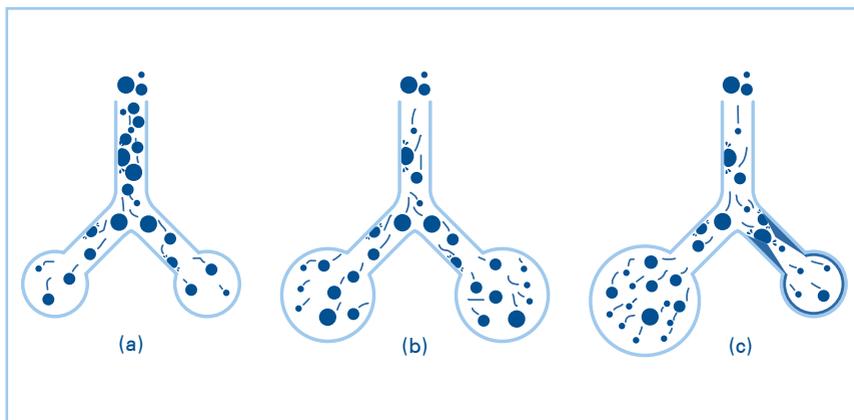


Figure 2: Schematic representation of the distribution of aerosol particles throughout the lung for the normal lung and the diseased lung.

(a) Distribution of aerosol particles for a patient with normal lung lobes while the patient is inhaling the antibiotic using tidal volume breathing. Note that there is homogeneous distribution of the antibiotic between lung segments, and deposition is higher in the central airways relative to the small airways and parenchyma. (b) Same patient as in (a) inhaling deeply. Note that more drug reaches the small airways and parenchyma. Furthermore, there is equal expansion of the two lung lobes. (c) The patient has considerable lung disease in one lobe, and is inhaling quickly and deeply.

The diseased lobe has a higher airway resistance and reduced compliance relative to the healthier parts of the lung. The expansion of the diseased lobe is slower relative to the healthier parts. As a result, there is preferential flow to the healthier lobe. In addition, the partial obstruction of the airway to the diseased lung lobe causes a turbulent flow pattern and increased aerosol deposition. The overall result is that the healthy lung lobe receives more antibiotic relative to the diseased lobe. Figure and legend reproduced with permission from the publisher [38].

3 Inhalation devices

There are different devices to administer inhaled drugs. The choice of inhalation device is dependent on the available formulations of the drug, the ability of the patient to perform an inhalation maneuver, and device availability in the country in question. Current inhalation devices can be classified into four categories: (i) nebulizers; (ii) pMDIs, which can be used with a press-and-breathe technique, such as a breath actuated pMDI (BA-pMDI) device, or in combination with a valved holding chamber (VHC); (iii) DPIs; and (iv) soft-mist inhalers [14]. Most inhaled drugs for CF are administered via nebulizers. Currently, two inhaled antibiotics and mannitol are available as DPIs. Drugs that are also used for asthma and chronic obstructive pulmonary disease such as inhaled corticosteroids and bronchodilators are available in pMDIs and DPIs. Because pMDIs and DPIs are convenient devices to use daily, there is a preference to prescribe these devices over nebulizers whenever possible. The choice of a pMDI or DPI depends on the ability of the patient to perform a specific inhalation maneuver. A DPI can be prescribed from the age of 7 years. For children under the age of 7 years, a pMDI should be used in combination with a VHC. This gives the child more time to inhale the drug after actuation of the pMDI and reduces oropharyngeal deposition. For children of less than 3–4 years the VHC should be equipped with a face mask. Direct placement of the pMDI into the mouth is not recommended for all patients, as the press-and-breathe technique requires

precise hand-mouth coordination, which is often incorrectly performed leading to high oropharyngeal and low lung deposition [15]. As an alternative to a pMDI a BA-pMDI can be used to avoid this co-ordination problem. A soft-mist inhaler is a hand-held device that produces a fine, slowly moving mist in one dose that the patient must inhale using the press-and-breathe technique. The fine particles and the slow release of the dose offset the problems with coordination and oropharyngeal deposition associated with pMDIs. The soft-mist inhaler can be used in combination with a VHC.

For more detailed background information on pMDIs, DPIs, and soft-mist inhalers, it is recommended to read the ERS/ISAM consensus statement on inhaled therapies [14]. Here we will focus on nebulizers and several DPIs that are used for inhaled CF drugs.

3.1. Nebulizers

Nebulizers generate an aerosol from a liquid for inhalation, and can be used to deliver a wide range of drugs. There are various types of nebulizers, which differ in the way the aerosol is generated, and in the efficiency with which they deliver drugs to the lungs [16]. These include jet, ultrasonic, and vibrating mesh nebulizers, with or without smart nebulizer technology. Jet and vibrating mesh nebulizers are most commonly used to treat people with CF.

3.1.1. Jet nebulizers

Most inhaled drugs for CF are licensed for use with jet nebulizers. Traditional jet nebulizers are relatively inefficient and inconvenient to handle, but are still widely used.

Furthermore, cleaning instructions must be followed strictly, as nebulizers can easily become contaminated with microorganisms [17]. A jet nebulizer consists of a nebulizer and suitable compressor, or a nebulizer combined with compressed air or oxygen. Compressed airflow through the nebulizer entrains liquid through a Venturi tube against a baffle, which breaks the liquid into an aerosol. The particle size distribution of the aerosol leaving the device is determined by the design of the baffle and the flow through the device. Usually, optimal operational flow is 6–8 L/min. A lower flow leads to larger particles and prolonged nebulization time [18]. The patient inhales the aerosol with tidal breathing from a reservoir through a mouthpiece or face mask. For children below the age of 5 years, good face mask design and tight placement on the face are important to maximize efficiency [19, 20]. A cooperative child of four years or more can best inhale through a mouthpiece, as this improves lung deposition relative to inhalation via face mask [21, 22]. There are different types of jet nebulizers. Widely used unvented nebulizers with continuous aerosol output are inefficient, due to the loss of aerosol during exhalation and when a patient is not breathing through the nebulizer. For this reason, an exhalation filter must be fitted for use with inhaled antibiotics. This prevents contamination of the surroundings or of carers with antibiotics. Correct connection of the filter to the mouthpiece via a T-piece should be confirmed. Lung deposition from jet-nebulizers ranges from 1.3% in infants to 11% in older children and 15% in healthy adults [14, 22, 23]. More efficient jet nebulizers

have been developed, such as open vent, breath-enhanced (Pari LC Plus, Pari GmbH, Starnberg, Germany), and breath-actuated (AeroEclipse, Trudell Medical International, London, Canada) nebulizers with inhalation and exhalation valves. The use of breath actuated systems results in improved lung deposition, lung dose reproducibility, and reduced loss of aerosol during exhalation. Breath-actuated devices are suitable for children of 4 years and older.

3.1.2. Vibrating mesh nebulizers

Vibrating mesh nebulizers are currently the most widely used nebulizers for CF. Mesh nebulizers use either a vibrating or fixed membrane with a piezo-electric element with microscopic holes to generate an aerosol. Vibrating mesh devices have a number of advantages over jet-nebulizers. They are highly efficient, fast, quiet, generally portable, and run on rechargeable batteries. Lung deposition ranges from 30% to 80%, depending on the device. The disadvantages are that they are relatively expensive and require maintenance and cleaning after each use. Cleaning is necessary to prevent contamination by microorganisms [24] and to prevent build-up of deposits and blockage of the mesh [25]. The mesh should therefore be replaced at regular intervals.

Mesh nebulizers are available with breath-enhanced (E-flow Rapid, Pari GmbH, Starnberg, Germany; Aeroneb Go, Aerogen, Galway, Ireland) or dosimetric (I-neb-adapted aerosol dosimetric (AAD) system, Philips Respironics, Chichester, UK) aerosol delivery. Different mesh nebulizer systems may differ significantly in the amount of

drug delivered to the lungs, and some provide dose recommendations relative to jet-nebulizers (see **Table 1**). In recent years, new inhaled antibiotics have been licensed for use with a specific mesh nebulizer (see **Table 1**). eFlow technology predominantly is used. An eFlow rapid control unit is used for electrical supply, which is combined with a specifically designed mesh nebulizer handset for each inhaled antibiotic. The medication package includes doses for 28 days and a new nebulizer handset with which to replace the old one. Drug-specific nebulizers should not be used for other medications, as this may have unpredictable effects on the dose delivered.

3.1.3. Smart nebulizers

In smart nebulizers the breathing pattern can be electronically controlled (slow and deep) and the aerosol can be delivered during a specific phase of inspiration [14]. A deep and long inhalation shortens nebulizing time and increases the inhaled dose. Smart nebulizers can achieve high lung deposition (60–80%) [14]. In addition, they can improve the delivery of drug to the small airways [26]. Smart nebulizer systems can incorporate either jet or mesh nebulizers. The I-neb AAD system is an example of a system using a mesh nebulizer, while the Akita-Jet (Vectura) is an example of a smart system using a jet nebulizer. Smart nebulizers also allow adherence data to be electronically logged. With nebulizers with E-flow technology the eTrack control unit can be used to electronically monitor adherence, although this is not the standard provided unit. The data can be downloaded and shared with a healthcare provider either via internet from

home or via a computer in a hospital. This provides a useful means of monitoring and discussing in an open way with patients their use of aerosol therapy.

3.2. Dry powder inhalers

For CF medicines, there are currently two DPIs available for inhaled antibiotics (inhaled tobramycin and inhaled colistin) and one for inhaled mannitol. More inhaled antibiotics are being developed for use in DPIs, including ciprofloxacin and vancomycin. The use of DPIs to replace nebulized therapy offers patients greater convenience, and is beneficial for adherence and disease control [27]. In DPIs for inhaled antibiotics and mannitol the drug is present as a dry powder formulation in a capsule. Multiple capsules may be required to inhale a sufficient mass of the antibiotic into the lungs. The technical properties of the dry powder formulation combined with the properties of the inhaler determine how the powder is best inhaled. Both the mass and the aerosol characteristics of the released aerosol depend on the inhaler resistance, the inhaled volume, and the inspiratory flow profile generated by the patient [28]. The DPIs used for CF drugs are all low resistance inhalers. This means that little effort is required to generate high inspiratory flows, but also means that these flows can vary considerably between patients [29]. High inspiratory flows increase oropharyngeal deposition and can reduce lung deposition, especially in the small airways. There are some marked differences in the particles generated owing to the different formulations used for the powders. PulmoSphere technology (Novartis AG, Basel, Switzerland) is used to formulate

tobramycin inhalation powder (TIP) (Tobi Podhaler, Mylan Pharma GmbH, Steinhilfen, Switzerland). This is a spray-drying technique that generates relatively large porous particles that disperse easily, and therefore a low inspiratory flow (30 L/min) is sufficient to release the particles from the inhaler. Large porous particles behave like small particles, and have the potential to be deposited more peripherally in the lungs. Careful instruction demonstrating the low flow and deep inhalation technique is essential to ensure optimal lung deposition. In the colistin DPI (Colobreath, Teva, Haarlem, Netherlands) the powder is formulated as micronized particles that, in general, do not disperse very easily. Therefore, high energy is likely needed to generate small particles. It is claimed that an inspiratory flow of 30 L/min through the inhaler is sufficient for optimal dispersion of the micronized drug into respirable aerosol particles. However, to our knowledge there are no published data available describing the detailed aerosol characteristics of the colistin DPI.

Inhalation of mannitol as a dry powder increases the hydration of the airway surface liquid and stimulates mucociliary clearance [30]. Mannitol dry powder for inhalation (Bronchitol, Teva, Haarlem, Netherlands) is inhaled via a Handihaler, which is also a low resistance inhaler. Inhaled mannitol is provided in capsules containing micronized particles, and should be inhaled using a deep forceful inhalation technique. Ten capsules should be inhaled for one dosage.

In general, when using a DPI with capsules it is recommended to repeat the inhalation maneuver twice for each capsule to ensure that all drug is released. Cough is the most

reported side effect by patients using DPIs for inhaled antibiotics and mannitol [30-32]. Using a bronchodilator prior to inhalation of a DPI with inhaled antibiotics or mannitol may help relieve cough symptoms.

4 Inhaled drugs for CF

Table 1 provides a general overview of inhaled drugs used by persons with CF and the devices used to deliver them. Available drug device combinations can vary from country to country. Off-label combinations are also shown. Indications are not addressed in the table.

It is important to realize that newer inhaled drug solutions are registered as a drug/device combination. Ideally each nebulized drug should only be delivered using the appropriate registered device. When delivering older drugs using modern efficient vibrating mesh or smart nebulizers instead of less efficient jet nebulizers, it should be borne in mind that this off-label use will alter the pharmacokinetics, and that dose adaptation may be required depending on the type of drug in question. Using a nebulizer other than that which is recommended may lead to toxic effects, especially in young children [33]. A recent study of children aged 6–18 years revealed a similar pharmacokinetic and safety profile for inhaled tobramycin using the I-neb (75 mg) and the PariLC-Plus (300 mg) nebulizers [34].

Inhaled drug	Brand name	Device	Dose	Remark
Inhaled antibiotics				
Amikacin liposome inhalation	Arikayce	Lamira nebulizer with E-flow rapid control unit	590 mg/8.4 mL; single-use vial	
Aztreonam lysine for inhalation (AZLI)	Cayston	Altera nebulizer with E-flow rapid control unit	75 mg TID	<ul style="list-style-type: none"> ■ Fixed combination nebulizer/drug ■ Every 28 days new mesh delivered with 84 ampoules ■ License: ≥ 6 years
Ceftazidime	Generic IV fluid	Jet-nebulizer with suitable compressor	1 g BID	<ul style="list-style-type: none"> ■ Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa ■ Use exhalation filter ■ Off-label
Colistin inhalation suspension	Tadim Colistin	Pari-LC Plus with suitable compressor	1–2 million IU BID	<ul style="list-style-type: none"> ■ Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa ■ Use exhalation filter ■ 1 million IU; 1 ampoule of 1 million IU in 3 mL NaCl 0.9% ■ 2 million IU; 2 ampoules of 1 million in 4 mL NaCl 0.9% ■ License: ≥ 1 years
Colistin inhalation suspension	Tadim Colistin	E-flow rapid	1–2 million IU BID	<ul style="list-style-type: none"> ■ 1 million IU; 1 ampoule of 1 million IU in 3 mL NaC 0.9% ■ 2 million IU; 2 ampoules of 1 million in 4 mL NaCl 0.9%

Table 1: Inhaled drug-device combinations used for treatment of CF

Inhaled drug	Brand name	Device	Dose	Remark
Inhaled antibiotics				
Colistin inhalation suspension	Tadim	I-neb	1-2 million IU BID equivalent; 0.3 mL or 0.5 mL	<ul style="list-style-type: none"> Fixed combination nebulizer/drug Suitable from age 6 1 million IU; 1 ampoule of 1 million in 1 mL, fill gray cup, 0.3 mL 2 million IU; 1 ampoule of 1 million in 1 mL, fill violet cup, 0.5 mL
Colistin inhalation powder	Colo-breath	Turbospin DPI	1.662.500 IU 2dd [1 capsule]	<ul style="list-style-type: none"> Twice forceful deep inhalation for 1 capsule Low resistance DPI License: ≥6 years
Levofloxacin	Quinsair	Zirela nebulizer with E-flow rapid control unit	240 mg BID	<ul style="list-style-type: none"> Fixed combination nebulizer/drug New mesh delivered every 28 days with 56 ampoules License: ≥18 years
Meropenem	Generic IV fluid	Jet-nebulizer with suitable compressor	<p>Adults 250 mg BID</p> <p>Children 6–12 years: 125 mg BID ≥12 years: 250 mg BID</p>	<ul style="list-style-type: none"> Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa Use exhalation filter Off/label

Table 1 (contd): Inhaled drug-device combinations used for treatment of CF

Inhaled drug	Brand name	Device	Dose	Remark
Inhaled antibiotics				
Tobramycin inhalation solution (TIS)	Tobi (300 mg/5 mL) Bramitob (300 mg/4mL) Generic TIS (300 mg/5 mL)	Pari-LC Plus with suitable compressor	300 mg BID	<ul style="list-style-type: none"> ■ Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa ■ Use exhalation filter ■ License: ≥6 years
		E-flow rapid	300 mg BID	<ul style="list-style-type: none"> ■ Off-label, pharmacokinetic and deposition data available
		I-neb	60 mg (300 mg/5 mL) BID 75 mg (300 mg/4 mL) BID	<ul style="list-style-type: none"> ■ Off-label, pharmacokinetic and deposition data available
		AKITA-Jet in combination with PariLC-Sprint	150 mg BID	<ul style="list-style-type: none"> ■ Off-label, pharmacokinetic and deposition data available
	Vantobra	Tolero/eFlow rapid control unit	170 mg BID	<ul style="list-style-type: none"> ■ Fixed combination nebulizer/drug ■ Replace mesh every 28 days, delivered with 56 ampoules ■ License: ≥6 years
Tobramycin inhalation powder (TIP)	Tobi Podhaler	Podhaler DPI	112 mg (4 capsules) BID	<ul style="list-style-type: none"> ■ Slow deep inhalation of 30 L/min ■ Low resistance DPI ■ License: ≥6 years

Table 1 (contd): Inhaled drug-device combinations used for treatment of CF

Inhaled drug	Brand name	Device	Dose	Remark
Inhaled antibiotics				
Vancomycin	Generic IV fluid	Jet-nebulizer with suitable compressor	Adults 250 mg BID Children 4 mg/kg (maximum 200 mg) QID	<ul style="list-style-type: none"> ■ Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa ■ Use exhalation filter ■ Off-label ■ Dry powder formulation in development
Inhaled antimycotics				
Liposomal amphotericin B	Ambisome	I-neb	50 mg once per week	<ul style="list-style-type: none"> ■ Fill violet cup (0.5 mL) of I-neb 8x ■ 50 mg in 10 mL water for injections ■ Off-label, pharmacokinetics available, clinical study in adults available
Inhaled mucocactive agents				
Dornase alpha	Pulmozyme	Jet-nebulizer with suitable compressor	2.5 mg QD or BID	<ul style="list-style-type: none"> ■ Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa ■ License: ≥6 years

Table 1 (contd): Inhaled drug-device combinations used for treatment of CF

Inhaled drug	Brand name	Device	Dose	Remark
Inhaled mucoactive agents				
Dornase alpha	Pulmozyme	E-flow Rapid	2.5 mg QD or BID	<ul style="list-style-type: none"> License: ≥6 years
Dornase alpha	Pulmozyme	I-neb	0.5–2.5 mg QD or BID	<ul style="list-style-type: none"> Violet cup of 0.5 mL, fill 1-3 times Off-label
Dornase alpha	Pulmozyme	AKITA-Jet in combination with PariLC-Sprint	2.5 mg QD or BID	<ul style="list-style-type: none"> Off-label, clinical studies available
Hypertonic saline 3%, 6% or 7%	Nebusal 7% Mucoclear 6% Generic NaCl 3%, 6% or 7%	Jet-nebulizer with suitable compressor	4 mL BID	<ul style="list-style-type: none"> Suitable compressor: flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa Use bronchodilator before if coughing and/or bronchospasm Nebusal license: ≥6 years Clinical studies available.
		E-flow Rapid	4 mL BID	<ul style="list-style-type: none"> Off-label
		I-neb	0.3 mL BID	<ul style="list-style-type: none"> Fill 1x green cup (0.3 mL) Off-label
Mannitol powder	Bronchitol	Handihaler DPI	400 mg BID [10 capsules]	<ul style="list-style-type: none"> License: ≥18 years Low resistance DPI

Table 1 (contd): Inhaled drug-device combinations used for treatment of CF

Abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily

5 Correct inhalation technique and adherence

To achieve an optimal therapeutic effect with aerosol therapy, correct inhalation technique and good adherence are both important. Regular revision of the inhalation technique is necessary, as it has been shown that users can make many crucial mistakes [8]. Video recordings in the home setting, performed by the patient's support team, are a great tool to allow the CF team and patient to jointly evaluate the inhalation technique and identify details that can be improved [8].

Aerosol therapy is a great burden for CF patients, given their already time-consuming treatment regimen. Adherence to pulmonary treatment is generally low, leading to greater healthcare use [35]. Several strategies can help improve adherence and reduce treatment burden in patients, including electronic adherence monitoring [36], switching to a faster, smaller new nebulizer or a DPI, and using semi-structured interviews and motivational interviewing techniques to identify solutions in partnership with the patient [37].

6 Conclusions

The respiratory system is well equipped to keep aerosol particles out. Therefore, to optimize efficacy it is important that CF caregivers, patients, and their home support team have a detailed knowledge of aerosol therapy. Achieving an optimal therapeutic effect with an inhaled drug not only depends on patient adherence to the treatment regime, but also on maintenance of correct inhalation technique on a daily basis. The combination of 100% adherence and poor inhalation technique unfortunately results in suboptimal efficacy of the therapy, which is a waste of patient time and financial and healthcare resources. Regular revision of the inhalation technique at home using video can help determine whether crucial mistakes are being made. Adherence barriers such as illness perceptions, medication beliefs, and practical barriers need to be discussed regularly in partnership with the patient, keeping the dialogue open and aiming for concordance [38].

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CHAPTER 8

CF medicines in children

Authors

Michaela Semeraro, Kate Hayes,
Isabelle Sermet-Gaudelus

Introduction

The treatment of cystic fibrosis (CF) has long been the domain of pediatric specialist care due to the complex presentation of the disease in early years and limited life expectancy. Recent advances in the use of antibiotic and antifungal treatments and better understanding of physiopathology and genetics has greatly improved life expectancy and facilitated the transition of ever greater numbers of children into adult care. Current pharmaceutical legislation, both in the US and in the EU, requires initial approval in the adult population for all new therapies, with subsequent extension to pediatric populations. This approach is questionable given the pharmacokinetic (PK) and physiological variability within the pediatric population by age cohort.

1 Overview of CF pediatric drugs

1.1. Symptomatic or presymptomatic therapies

Initial treatments target the downstream effects of cystic fibrosis transmembrane

conductance regulator (CFTR) dysfunction in order to control symptoms and mitigate complications. These include, among others:

- Pancreatic enzyme replacement, necessary in more than 80% of patients with CF to prevent malnutrition and growth failure secondary to pancreatic insufficiency [1].
- Airway clearance therapies (ACTs), whose early initiation, potentiated by mucolytics [2] and osmotic therapies have proven efficacy in fighting the devastating effects of airway obstruction and slowing progressive decline in lung function [3].
- Antimicrobial treatments to eradicate or control respiratory infections with *Staphylococcus aureus* and later *Pseudomonas aeruginosa* [4].

These strategies raise specific issues as there are very few studies specifically assessing antibiotic PK and pharmacodynamics (PD) in pediatric populations. Moreover, inhaled antimicrobial administration may be challenging in the pediatric population due to a lack of suitably adapted devices for this age cohort.

Early introduction of these therapies targeting symptom management, from neonatal screening through to education and maintenance of a healthy lifestyle throughout childhood have demonstrated

success in preserving lung function [5]. Maximizing patient adherence to these therapies is central to their success.

1.2. Targeting the basic defect: CFTR therapies in children

Beyond these supporting treatments, advances in CFTR modulator therapies to fight the basic defect in CF have made remarkable progress. CFTR modulator therapies are designed to correct the malfunctioning protein made by the *CFTR* mutation. In patients with CF, because different mutations cause different defects in the protein, the medications developed so far are effective only in people with some specific mutations. Treatments targeting the CFTR defect already tested in children include:

1. Ivacaftor (Kalydeco) known as a potentiator, opens the CFTR “gate” to promote the flow of chloride (Cl⁻) and is therefore effective only in patients who have some degree of functioning CFTR protein production. Ivacaftor is approved in the EU for children aged 6 months and older who have at least one gating mutation, one residual function mutation, one splice mutation or a conduction mutation [6].
2. Lumacaftor/ivacaftor (Orkambi) is a combination of ivacaftor and lumacaftor, a corrector, designed to increase the quantity of CFTR on the cell surface by targeting defective production and circulation of the CFTR protein due to the mutation F508del (c.1521_1523delCTT/p.Phe508del). Orkambi is approved in the EU for children aged 2 years and older with

two copies of the F508del mutation, the most common mutation of *CFTR*.

3. Tezacaftor/ivacaftor (Symkevi) combines the corrector tezacaftor and the potentiator ivacaftor. It is approved in the EU for patients 12 years old and older with two copies of the F508del mutation and patients who have at least one specific residual function mutation [7].
4. Elexacaftor/tezacaftor/ivacaftor (Trikafta) has been approved in the US for people with CF aged 12 years and older who have at least one copy of the F508del mutation, regardless of their second mutation. The European Medicines Agency (EMA) is currently analysing Trikafta for its safety and clinical effectiveness. In the US this triple combination therapy has demonstrated lung function improvement of between 10 to 14% even in younger study cohorts (two completed phase 3 clinical trials for children ≥12 years old, NCT03525444).

Importantly, ivacaftor and lumacaftor/ivacaftor are the only CFTR-targeted drug therapies approved for patients younger than 6 years and there are no medications currently approved for patients younger than 6 months of age.

Despite recent advances in the development of CFTR modulators, there are still many CF patients who are not eligible for modulator therapy based on current Food and Drug Administration (FDA) or EMA guidelines. For almost 10% of CF patients with non-F508del mutations, who do not respond to the available range of treatments for functional restoration of

F508del, research is ongoing into agents for nonsense mutations, DNA or RNA replacement (gene therapy or RNA therapy), antisense oligonucleotides for splicing mutations and editing of stem cell genes for regenerative medicine. Our rapidly growing understanding of CF disease will help in the development of new and improved therapies.

1.3. The added value of early treatment

Since CF lung disease has been demonstrated to start from birth [8], treatment should commence as early as possible to prevent initiation of the disease cascade. Part of the resultant airway anomalies may even be congenital. Indeed, a recent study in the G551D (c.1652G>A/p.Gly551Asp) ferret model demonstrated that *in utero* therapy offered partial protection from disease, which only subsequently developed when the treatment was stopped in adulthood [9]. This is imperative given that there is evidence of disease progression in both pancreatic, liver and respiratory systems in children with CF from 6 months of age [10], and lung structure and function worsen significantly each year of life in young children aged 0 to 6 years [11].

Due to defective host defense, a variety of bacteria colonize the airway early in life. Clinical studies are needed to evaluate the best preventative treatment. This may involve interventions like airway clearance techniques and prophylactic antibiotic treatment. Moreover, an early intervention with treatments targeting the basic defect in CFTR should improve the natural course of the disease before structural lung disease is established. The KIWI clinical

trial (NCT01705145) conducted on children with CF aged 2 to 5 years and a *CFTR* gating mutation, showed that ivacaftor treatment over the 24-week open-label treatment period improved sweat chloride and nutritional parameters and suggested an improvement in markers of pancreatic exocrine function. Unfortunately, lung function was not assessed since the young population was deemed unsuitable for inclusion of this parameter.

2 Main differences between PK and PD characteristics between adult and children

2.1. Variability factors

Children differ from adults in their response to drugs. These differences may be caused by changes in the PK and/or PD between children and adults and may also vary among children of different ages.

The PK of a drug includes the processes of absorption, distribution, metabolism and elimination of a drug, whereas the PD comprises the physiological and biological response to the administered drug and therefore may represent both efficacy and safety measures. While a child grows, enzyme pathways (involved in the PK), function and expression of receptors and proteins (involved in the PD) mature; this can be referred to as “developmental changes” in childhood. Up to 70% of the drugs in pediatric intensive care, and 90% of the drugs in neonatal intensive care, are prescribed in an off-label or unlicensed manner. Instead of the *a priori* use of body weight for dosing guidelines in children,

detailed information on PK and also potentially PD, should be taken into account to define both effective and safe dosing regimens across the age range. The EMA mandates pharmaceutical companies to perform research across the full pediatric age range for all drugs that are developed for the European market, by requiring the submission of a pediatric investigation plan (PIP).

Several factors interfere with the PK/PD in children compared to adults, including: (i) metabolic enzyme capacity in children (i.e. P-450 cytochromes [CYPs] are expressed during the first week of life and the activity at birth is often low); (ii) renal and liver function which are influenced by physiological changes depending on age; (iii) body composition which is modified continuously, resulting in an age-dependent proportion of body water and fat, influencing drug distribution. For example, hydrophilic drugs like aminoglycosides have a larger volume of distribution in neonates, due to the larger amount of extra-cellular fluid (45% of the body weight) compared with adults (20%). Research is targeting population PK/PD modeling and covariate analysis to individualize dosing regimens at different ages, body weights and according to genetic profile.

2.2. Variability factors in CF

Children with CF present a complex pharmacological challenge with drug metabolism and clearance frequently requiring adjustment of dosage regimens. As for older patients, children with CF will require a different dosage regimen than that recommended for children without CF [12]. This is

due to the fact that organs associated with drug disposition (the gastrointestinal tract, liver and kidney) show a degree of functional impairment. Consequently, the PK of drugs is altered and plasma concentrations of many drugs are lower than those found in individuals without CF. The reason may be the increased activity of specific drug metabolizing enzymes which induce a moderately increased renal and liver clearance of drugs in patients with CF.

2.3. Variability factors according to CF drug class

Several studies have addressed the issue of PK and PD variability in children with CF. Several studies focused on beta-lactam and aminoglycoside antibiotics, which are the most common drugs utilized for pulmonary exacerbations in the CF pediatric population. The higher drug plasma clearance reported in children with CF compared to patients without CF [12, 13] using the same pharmaceutical formulation suggests that patients with CF should receive drug dosages above those normally recommended. Due to large inter-individual variability, individual dosage adjustments based on the monitoring of drug plasma concentrations are highly recommended.

We currently lack sufficient data regarding the optimization of pharmacological dosage of CFTR modulators in children, however, PK data are collected and analyzed for all current trials. Indeed, determining PK/PD of modulator therapies in children is critical, as those drugs will be administered for an indefinite period, and safety profiles may be different according to ages. Recent studies have shown that weight and age

may impact efficacy and safety (mainly liver cytotoxicity) in ivacaftor-treated children with at least one G551D mutation, a finding that may reflect the importance of individual pharmaco-metric analyses (GOAL study; NCT01521338). Despite development of new techniques for determining levels of modulators and their metabolites in body fluids, there have been no recommendations to date for therapeutic monitoring. Other investigators have recognized the importance of metabolism of these drugs and the potential impact on biomarker development, and have incorporated some pharmaco-metric analyses in organoid studies. To date, no studies have compared pharmaco-metric parameters of CFTR modulators *in vitro* and *in vivo*; this may be an important area of future research [14].

2.4. Drug-drug interactions in children

CFTR modulators are a substrate of cytochrome P450 enzymes (CYP3A4 and CYP3A5). Patients with CF frequently take other drugs that are highly likely to interact with modulators, placing them at risk for drug toxicity or decreased modulator efficacy. Because of the prevalence of drugs metabolized by these enzymes, drug-drug interactions with CFTR modulators are a significant and sometimes under-recognized concern. For instance, antibiotics like rifampin are potent inducers of CYP3A and therefore, can strongly accelerate the metabolism of CFTR modulators with consequent decreased effectiveness. On the other hand, many drugs are CYP3A inhibitors (antifungals, macrolides, ibuprofen, midazolam and immunosup-

pressive agents) with consequent elevated levels of these drugs in serum with possible toxicity and associated adverse effects.

3 Most relevant pediatric clinical studies results

3.1. Anti-inflammatory drugs

There are conflicting data about the potential anti-inflammatory effect of CFTR modulators although initial results demonstrating improvement in sweat chloride and lung function test results are encouraging. Therefore, CF anti-inflammatory drug development must continue. The leukotriene receptor antagonist montelukast has been studied in two smaller trials, showing reduction of serum eosinophilic cationic protein, but there are conflicting results on serum IL-8 levels and other clinical outcomes [15]. Cannabinoid receptor 2 (CB2) is found primarily on immune cells and sensory neurons. Activation of CB2 receptors produces a spectrum of anti-inflammatory effects, including inhibiting the generation of inflammation resolution mediators and suppressing leukocyte trafficking. Lenabasum is an orally active small molecule drug that selectively binds as an agonist to CB2 on immune cells. A phase 2 trial in adults demonstrated a reduced rate of pulmonary exacerbations requiring intravenous antibiotics in the intervention group. A phase 2 multicenter, double-blind, randomized, placebo-controlled study assessing the efficacy and safety of lenabasum in patients 12 years of age or older is now active (NCT03451045).

A large phase 2 randomized controlled trial investigated the efficacy and safety of an LT_{B4} receptor antagonist as an anti-inflammatory therapy in CF [16]. Unfortunately, the trial was terminated early because of an increased incidence of pulmonary exacerbations in both adults and children treated with the study drug. The patients included in the trial developed evidence of decreased pulmonary function and increased circulating neutrophils, an effect which was later demonstrated in a preclinical model, showing that the dose used in the clinical trial overly suppressed the inflammatory response. High dose ibuprofen has been investigated in prospective 2 year and 4 year controlled studies and showed a reduction in the rates of lung function decline in children with CF [17]. More recently the same team demonstrated that this beneficial effect of high dose ibuprofen translates to significantly improved survival [18]. Such drugs are likely to be most effective if initiated before the development of bronchiectasis, thus during childhood.

3.2. Mucociliary clearance

Mucociliary clearance in pediatric CF patients can be impacted by mucolytics (such as dornase alpha), hydrators (such as hypertonic saline or mannitol) and other drugs targeting non-CFTR ion channels.

Clinical trials of dornase alpha compared to other medications that improve airway clearance in a pediatric population, showed an improvement in percent predicted forced expiratory volume (ppFEV₁) and a diminution of pulmonary exacerbation rates [19]. Another drug acting upon mucociliary clearance is inhaled amiloride, which inhibits the

epithelial sodium channel (ENaC). In several adult and pediatric studies amiloride was ultimately unsuccessful, potentially due to inadequate potency and duration of action [20]. Newer agents with improved PK and PD properties have been developed. An initial study conducted in adolescents aged 14 years and older taking the ENaC inhibitor VX-371 (NCT02871778) plus hypertonic saline, did not show a significant increase in lung function (measured by ppFEV₁). The addition of VX-371 with or without hypertonic saline was generally well tolerated in participants already taking lumacaftor/ivacaftor. A phase 2 study is now open for recruitment of patients aged 12 and older with inhaled ENaC inhibitor (NCT04059094).

3.3. CFTR modulator therapies in pediatric patients with cystic fibrosis

Many studies have been conducted in the pediatric population in order to establish the safety and efficacy of CFTR modulators in pediatric patients with CF.

3.3.1. Ivacaftor trials

Many recent studies have demonstrated efficacy in a range of outcome measures including improvements in sweat chloride concentration, reduction in pulmonary exacerbation rates and improvements in ppFEV₁.

After successful Phase 3 clinical trials, Rowe *et al.* conducted a multicenter prospective cohort study in patients with CF pre- and post-ivacaftor initiation. Within 6 months of treatment, patients (aged 6 years and older) experienced significant improvements in ppFEV₁ and reductions in sweat chloride concentration [21]. Ramsey

et al. performed a randomized, double-blind, placebo-controlled trial in children 12 years of age and older with at least one G551D *CFTR* mutation which demonstrated an increase in pulmonary function, even in those with normal ppFEV₁ and reduced rates of pulmonary exacerbations [22].

These clinical improvements were also supported by the results of the ENVISION study [6] conducted in children aged 6–11 years of age with at least one G551D *CFTR* mutation and baseline mean ppFEV₁ of 84.2%. This study also showed an increase in pulmonary function and reduced pulmonary exacerbation rates. Studies in younger aged cohorts, such as the open-label,

single-arm KIWI study [23] conducted in children aged 2–5 years of age, with at least one copy of a *CFTR* gating mutation (**Table 1**), demonstrated a PK exposure similar to adults. Compared to the adult population, about 15% of children included in the study, presented with transaminase elevation.

Furthermore, sustained improvement from baseline ppFEV₁ across an 8 week treatment period with ivacaftor was demonstrated in the KONNECTION study, a double-blind, placebo-controlled crossover study for children aged ≥6 years, with at least one copy of a non-G551D gating mutation (**Table 1**) and baseline mean ppFEV₁ of 78.4% [24].

Gating mutation	KIWI [23]	KONNECTION [24]
G551D (c.1652G>A/p.Gly551Asp)	x	
G1244E (c.3731G>A/p.Gly1244Glu)	x	x
G1349D (c.4046G>A/p.Gly1349Asp)	x	x
G178R (c.532G>A/p.Gly178Arg)	x	x
G551S (c.1651G>A/p.Gly551Ser)	x	x
G970R (c.2908G>C/p.Gly970Arg)	x	x
S1251N (c.3752G>A/p.Ser1251Asn)	x	x
S1255P (c.3763T>C/p.Ser1255Pro)	x	x
S549N (c.1646G>A/p.Ser549Asn)	x	x
S549R(A->C) (c.1645A>C/p.Ser549Arg) or (T->G) (c.1647T>G/p.Ser549Arg)	x	x

Table 1: *CFTR* gating mutations eligible for the KIWI and KONNECTION trials of ivacaftor

The KONDUCT study, a double-blind, placebo-controlled parallel group study conducted in children 6 years and older with at least one copy of R117H (c.350G>A/p.Arg117His) and baseline mean ppFEV₁ 72.9%, did not show any difference in the pulmonary function but demonstrated improvement in the sweat chloride concentration [25].

A series of studies have shown improvement in typical outcome measures such as ppFEV₁, sweat chloride and weight/BMI but only approximately 5% of patients with CF have one of the ten mutations approved for ivacaftor use. A serious potential adverse event linked to ivacaftor is elevation of liver transaminases in both adult and pediatric patients; however, the rate of transaminase elevation appeared to be higher in children aged 2–5 years compared with adult studies, reaching 15% in the pediatric study [26].

3.3.2. Lumacaftor-ivacaftor trials

In two randomized, double-blind, placebo-controlled phase 3 clinical trials, combination therapy with the CFTR modulators lumacaftor and ivacaftor improved lung function, BMI and reduced incidence of pulmonary exacerbations in patients with CF aged 12 years and older who were homozygous for the F508del *CFTR* mutation [27].

The open-label phase 3 study of lumacaftor/ivacaftor in patients with CF aged 6–11 years homozygous for the F508del *CFTR* mutation, demonstrated that the combination therapy was well tolerated over 24 weeks of treatment, with a safety profile similar to that observed in older patients. Sweat chloride rapidly improved

after treatment initiation and returned to baseline once therapy was discontinued. Improvements were demonstrated in sweat chloride, BMI z-score, the respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R), and lung clearance index (LCI), a sensitive measure of early CF lung disease [28].

3.3.3. Tezacaftor-ivacaftor clinical trials

Tezacaftor is a second-generation CFTR corrector. In phase 3 trials, tezacaftor/ivacaftor had improved tolerability compared with lumacaftor/ivacaftor especially considering the chest tightness associated with the lumacaftor/ivacaftor treatment, while having similar clinical benefit to lumacaftor/ivacaftor in homozygous F508del patients or those with one F508del allele and a residual function second *CFTR* mutation [29]. Tezacaftor/ivacaftor was generally safe and well-tolerated and improved CFTR function in children aged 6 through 11 years with CF, supporting tezacaftor/ivacaftor use in this age group.

3.3.4. Next generation correctors

Phase 1 and 2 trials adding different next-generation correctors to tezacaftor/ivacaftor to make a triple combination therapy are on-going. Phase 3 trials with VX-661, VX-445 and VX-770 have reported improvements in lung function (absolute increase in ppFEV₁ of 7–12%) incremental to tezacaftor-ivacaftor in children 12 to 18 years.

4 Challenges in trial design for CF medicines in children

4.1. How to define drug efficacy in children with CF

The increased effectiveness of CF therapies has led to a reduction in the feasibility of placebo-controlled designs for the development of new CF therapies. It presents ethical challenges in study design where placebo alternatives may no longer be a viable option. A possible solution would be the choice of an active comparator drug which has already demonstrated clinical efficacy, rather than placebo. Furthermore, the short study duration of most pediatric studies offers limited opportunity to evaluate subtle improvements (for example, pulmonary exacerbations are rare in the early years). Novel endpoints are needed to measure short term responsiveness in cross-over studies. New established biomarkers for such an application in pediatric studies include LCI, fractional exhaled nitric oxide (FENO), lung imaging based on high-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI), and adapted age-appropriate questionnaires for pediatric patients and for their caregivers.

4.2. How to choose the appropriate dosage and the best method of administration

Modeling and simulation tools can provide an algorithm for selecting the appropriate dose for prospective evaluation of safety and efficacy in pediatric clinical trials. We learned from previous experience in the field of antibiotic research that new ther-

apeutic strategies are needed in order to obtain high local (parenchymal) concentrations. Oral and intravenous formulations need dose adjustment according to PK and PD data in the context of the patients' clinical status. A distinction must be made between severe illness with malnutrition and cardio-respiratory insufficiency (with marked changes in distribution and elimination) and milder disease (characterized mainly by a moderate change in absorption).

Inhaled drugs may represent a useful formulation for pediatric patients since they allow both selective and fast administration of high concentrations of antibiotics in the broncho-pulmonary tract (10 to 80 times greater than those obtained by a venous route). Toxicity is low due to weak systemic passage. Inhaled therapies offer targeted drug delivery and are relatively simple and quick to take [30]. However, optimizing delivery of inhaled medications is dependent on both the inhalation technique used and device performance as well as on the frequency of administration considering the impact on social life. It is well known that inhaled administration is difficult for children and toddlers with major problems in coordination of breathing. New technological developments of nebulizers specific to the infant and preschool pediatric populations are needed to improve efficiency in these very young patients.

Moreover the other challenge in developing the right drug in children with CF is the development of age-adapted dosage forms (i.e. oro-dispersible tablets or liquid forms that mask unpleasant taste). This is a

real challenge for manufacturers and more research in this field is required.

5 Conclusion

The 1989 United Nations Convention on the Rights of the Child “recognizes the right of the child to the enjoyment of the highest attainable standard of health”. This includes the right to evidence-based treatments, as foreseen for mutation targeted therapy, and adequate and specifically targeted CFTR therapy. In the exciting era of CFTR modulators, which are reshuffling the therapeutic landscape and the prognosis of the disease, we indeed need to maximize efficiency of the currently used drugs and decrease safety issues of these new life-long medications. This is a challenge that we have to face, by increasing our knowledge of pharmaceutical care in CF children

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CHAPTER 9

Medicines, pregnancy and breast feeding in CF

Authors

Naim Bouazza, Jean-Marc Treluyer,
Michaela Semeraro,
Isabelle Sermet-Gaudelus, Frantz Foissac

Introduction

Over the past years, overall survival in cystic fibrosis (CF) patients has substantially increased, mainly due to better management of nutrition and respiratory infection along with improved antimicrobial treatment. Furthermore, development of multidisciplinary care centers dedicated to CF with systematic screening has allowed early detection of related complications (such as diabetes, osteoporosis or liver disease). These significant improvements in CF care management allow pediatric patients to reach adulthood and has led to the emergence of healthcare providers specialized in adult care. The median age of CF patients in economically developed countries has increased to 40 years and the number of women reaching reproductive age has largely increased. It is noteworthy that women with CF have near-normal fertility, and incorrect perceptions about the likelihood of conception may lead healthcare providers to avoid advice regarding contraception [1]. In the US, the number of pregnancies among women with CF has

increased progressively since the 1990s (2). The most recent data from the Cystic Fibrosis Foundation patient registry showed that 280 women with CF were pregnant in 2018 [2]. The overall pregnancy rate among women with CF has remained relatively constant, in contrast to the pregnancy rate in the general US population, which has declined during this time. The drug regimen in patients with CF is composite, with mainly pancreatic enzyme supplements, vitamins, mucolytics, antibiotics (inhaled, oral or intravenous), and CFTR modulators. In this chapter we will discuss how pregnancy and CF may affect the pharmacokinetics of drugs, and review the available data regarding safety of medications commonly used in CF patients during pregnancy.

1 Drug disposition in pregnancy

Many physiological changes occur during pregnancy, at varying intensities during gestation. These changes are likely to modify the pharmacokinetics and pharmacodynamics of drugs administered to pregnant women.

1.1. Absorption

The absorption of drugs can be modified by a decrease in intestinal motility, but also by a variation in gastric pH, which consequently results in a modification of the ionization state of weak acids and bases [3]. In addition, the nausea and vomiting that can happen from the first days of pregnancy can also modify the absorption of drugs (i.e., delayed, incomplete or even zero).

1.2. Distribution

During pregnancy, an increase in plasma volume and extravascular water is observed. The total water of the body is increased by 45% at the end of pregnancy compared to a nonpregnant woman [4]. This phenomenon leads to an increase in the volume of distribution of hydrophilic molecules and decreases maximal plasma concentrations [5]. Similarly, an increase in adipose tissue may result in a higher volume of distribution of lipophilic molecules, but the clinical consequences are generally not significant [5].

On the other hand, the concentrations of serum albumin and alpha-1 glycoprotein acid decrease by around 30% and 20%, respectively, at the end of pregnancy [4]. Therefore, an increase in the free fraction of drugs (i.e. the pharmacologically active form) is observed for molecules strongly linked to plasma proteins [6].

1.3. Elimination

The two main routes of drug elimination are hepatic metabolism and renal excretion. Modification in hepatic clearance can result from changes in hepatic blood flow (for drugs with high extraction ratios), in

free fraction, or in intrinsic hepatic clearance [7]. Data on changes in hepatic blood flow during pregnancy are contradictory [4, 8]. Several studies do not show significant differences, while others show an increase in hepatic flow, probably explained by an increase in portal vein flow. However, it is more likely that hepatic clearance variations are mainly due to changes in enzyme and transporter activities (i.e. permeability glycoprotein [PGP], organic cation transporter [OCT]) [7]. The increase in estrogen and progesterone may be responsible for the induction or inhibition of liver enzymes, particularly the cytochrome P450 class [5]. Studies on these activity modifications showed an increase in the enzymatic activity of CYP2A6, CYP2C9, CYP2D6, CYP3A4 and CYP2B6 and a decrease in the activity of CYP1A2 and CYP2C19 [5]. On the other hand, an increase in the clearance of drugs metabolized by UGT1A1 and UGT1A4 is also observed [9, 10].

During pregnancy, the renal perfusion rate is increased leading to an increase in glomerular filtration. Changes in renal secretion are poorly documented and it is suggested that an increase during pregnancy might occur. Regarding transporter activities, studies performed on metformin and digoxin estimate that both PGP and OCT increase during pregnancy [7].

2 Drug placental transfer

Most medicinal drugs diffuse through the placenta and reach the fetus. After maternal drug administration, the fetal drug expo-

sure will vary according to the maternal exposure as well as placental transfer characteristics. Depending on the physical and chemical characteristics, a compound could cross the placental barrier by passive, facilitated diffusion or active transport. Lastly, the contribution of feto-placenta drug metabolism could also modify fetal drug exposure. As a result, an alteration of fetus development leading to congenital malformations, growth or functional deficiencies may be observed.

3 Drugs and breastfeeding

Beside *in utero* exposure through placental transfer, medicines can also pass into breast milk in small quantities, therefore, the newborn can be exposed to drugs through breastfeeding after delivery. The question of starting or continuing safely to breastfeed the newborn is challenging. Several factors may inform about drug exposure through breastfeeding the newborn. Firstly, molecules with a long elimination half-life should be evaluated cautiously. Breastfeeding the newborn just before the mother is dosed is preferred but does not necessarily ensure a low exposure to the baby. It is also of interest whether a drug can be orally absorbed by neonates. The drug's presence in breast milk does not mean necessarily that the baby will be exposed to significant drug levels. Drug quantities in milk are not representative of infant plasma levels, especially for poorly absorbed drugs. The most relevant parameter to assess exposure to drugs through

breastfeeding is represented by the relative infant dose (RID). This dose stands for the dose received via breast milk (dose/kg/24 h) relative to the dose administered to the mother (dose/kg/24 h). A relative dose of 10% or above can be considered as the limit of concern [11].

4 Drug disposition in cystic fibrosis patients

CF patients have many pathological changes that can modify both pharmacokinetics and pharmacodynamics of drugs. Apparent changes in pharmacokinetics may be explained by variations in drug absorption, distribution and drug elimination. Intestinal absorption is delayed, and transit is significantly lower compared to healthy subjects, therefore, time to reach the maximal concentration is postponed, and lower bioavailability may be observed in CF patients. Disposition of drugs in the body varies according to the organ systems affected by the disease (such as the lungs, the gastrointestinal tract, and the liver) [12]. Adipose tissue is known to be substantially decreased in CF patients and this also alters the distribution of lipophilic drugs. Hypoalbuminemia is often observed in CF patients and may also disturb disposition of highly protein bound drugs. Both hepatic and renal clearances are increased in patients with CF. Activities of CYP1A2 and CYP2C8 increase, while other CYP isoforms such as CYP2C9 and CYP3A4 remain unchanged. An increase in phase 2 enzyme activities have been also shown [13]. In CF patients, hyperfiltration has been reported to be

associated with disease severity and can impact renal drug clearance [13]. Overall, the total body clearance of medications is increased, often associated with a decrease in drug elimination half-life.

5 Drugs during pregnancy and breastfeeding in cystic fibrosis patients

Most drugs are not properly evaluated during pregnancy and safety is mostly derived from animal studies or clinical experience. Whereas drug prescriptions are usual during pregnancy, women and their fetuses remain an orphan population regarding drug efficacy and safety. Medical decision-making regarding the choice of one drug within a therapeutic class should be primary based on knowledge about efficacy for the mother and safety for the fetus, particularly in the context of CF. **Table 1** is adapted from Kroon *et al.* [14] and summarizes the recommendations during pregnancy and breast feeding for the most common drugs used in CF patients.

5.1. Pancreatic enzyme supplements

Pancreatic enzyme therapy is used to prevent maldigestion due to pancreatic insufficiency in CF patients. Since no proper absorption of pancreatic enzymes into systemic circulation is observed, no risk is expected for the fetus. Similarly, breast feeding is possible as there is no absorption by the mother.

5.2. Antibiotics

Oral, nebulized and intravenous antibiotics are often used in CF. Although the prevalence of *Pseudomonas aeruginosa* is decreasing, CF patients are chronically colonized with this type of pathogen [2]. *Staphylococcus aureus* is also one of the most prevalent pathogen of chronic airway infections in CF [2]. Penicillin and cephalosporin are first-line treatments during pregnancy for susceptible pathogens such as *S. aureus*, and their use during pregnancy appear to be safe. The RID through breast feeding is very low (<2%) with some traces detected in milk. Anti-pseudomonal penicillin (e.g. piperacillin, piperacillin-tazobactam, temocillin), can be also safely administered intravenously. Azithromycin is widely used to improve lung function in CF patients and for treating infectious exacerbations caused by *P. aeruginosa*. Although some clinical data suggest that use of azithromycin during pregnancy seems probably safe and compatible with breast feeding, erythromycin is the first choice macrolide. Carbapenems should be avoided during pregnancy and remain as a second-line treatment, as only limited studies in humans are available, therefore penicillin, cephalosporin or erythromycin should be preferred. The clinical use of aminoglycosides (such as gentamycin and tobramycin) is associated with fetal nephro- and ototoxicity and should be used only in case of life-threatening infections. Similarly, quinolones have been associated with cartilage damage and arthropathy in preclinical studies, and should be avoided during pregnancy. High concentrations in milk have been also reported with this class

of antibiotics (RID >5%) so breast feeding should be avoided when possible. In the absence of safer alternatives, ciprofloxacin should be used as a preferred quinolone. The use of trimethoprim-sulfamethoxazole is not recommended during the first and third trimesters of pregnancy. Trimethoprim was shown to increase neural defects when administered in the first trimester, whereas sulfamethoxazole is associated with icterus of the neonates when used during the last trimester of pregnancy. Colistin is also worthy of mention because of its wide bactericidal spectrum, and its frequent use in nebulized and intravenous formulations. However, there is a lack of safety data in pregnancy, therefore intravenous administration should be avoided. In general, it appears that the inhaled route of antibiotic administration is mostly associated with low absorption into systemic circulation and may be associated with lower risks.

5.3. Mucolytics

The two main types of mucolytics are hypertonic saline and recombinant human DNase (or dornase alfa). Data regarding use of hypertonic saline during pregnancy in CF are limited. However, there is likely no risk for both the fetus and the mother due to limited systemic absorption when administered by inhalation. The same conclusions can be made for recombinant human DNase, for which very few clinical experience is available during pregnancy. The inhaled route of administration of rhDNase results in low systemic absorption, and its presence as an endogenous compound suggest that this treatment may be used safely in pregnant women if

necessary. Recombinant DNase (rhDNase) is also compatible with breast feeding since this large protein molecule is unlikely to be absorbed.

5.4. CFTR modulators

More and more women of childbearing potential with CF are becoming eligible to receive modulators as a chronic therapy and it is difficult to anticipate how many women will remain on this treatment during their pregnancy. The safety of these drugs during pregnancy and their potential harm to the fetus remain insufficiently addressed. To date, few data have been published, and publications consist essentially of case reports. The recent work by Trimble *et al.* [15] reported meaningful data regarding a singleton delivery of a woman treated with lumacaftor/ivacaftor throughout her pregnancy. The authors described the uncomplicated and successful pregnancy as well as a 9-month follow-up of the breastfed infant. Concentrations of lumacaftor and ivacaftor were measured in maternal plasma, cord blood, breast milk and infant plasma. The main conclusion was that both drugs seem to readily cross the placenta. A higher cord-to mother ratio of plasma concentrations was found for lumacaftor compared to ivacaftor (2 versus 0.25). These two drugs have different elimination pathways. While lumacaftor is mainly excreted unchanged into feces, ivacaftor undergoes extensive metabolism by cytochrome P450 (CYP) 3A leading to two active metabolites. Therefore, the possibility of lumacaftor accumulation in the placenta could not be excluded. Similarly, the authors reported that both molecules were found in breast

milk, and were detectable at low levels in infant plasma. However, even if the infant experienced some liver abnormalities, this could not be clearly attributed to the CFTR modulator combination therapy. Presently, the data available for ivacaftor alone or in combination with lumacaftor remain insufficient to inform decision making about CFTR modulator use during pregnancy.

Another CFTR combination therapy (tezacaftor/ivacaftor) was approved in 2018. This combination demonstrated a clinically significant effect across multiple phase 3 studies in patients with CF homozygous or heterozygous for the F508del mutation (p. [phe508del]/c. [1521_1523delCTT]). Furthermore, fewer side effects and drug interactions were reported compared to lumacaftor/ivacaftor combination therapy. However, a recent pharmacokinetic analysis reported that itraconazole co-administration increased substantially the areas under the curve of tezacaftor and ivacaftor by 4-fold and 15.6-fold, respectively [16]. In general, strong CYP3A inhibitors should be used with caution when administered with tezacaftor/ivacaftor. Currently, no clinical data are available during pregnancy for this combination regarding both safety and breast feeding.

The triple combination CFTR modulator therapy comprising ivacaftor, tezacaftor and elxacaftor recently approved in the US is a new step in CF treatment. Even if this new combination probably represents a major breakthrough for improving health and possibly survival in patients carrying at least one F508del mutation, so far little is known about the safety of these modulators during pregnancy and lactation. Thus,

two recent reviews evaluating the safety of drugs during pregnancy and breastfeeding recommend caution or avoiding all CFTR modulator drugs for both pregnancy and breastfeeding due to lack of data [14,17].

6 Conclusions

The number of women with CF reaching reproductive age has largely increased and more women are considering motherhood. The question regarding impact of pregnancy on the prognosis of women with CF has been addressed. There is no evidence that pregnancy is associated with a decline of lung function or mortality, particularly for women with a well-preserved baseline lung function and optimal nutritional status. The drug regimen in CF is very complex and there are concerns regarding the safety of the drugs used in the context of pregnancy and breastfeeding. However, knowledge about these risks for pregnant or lactating women is still limited as these women are commonly excluded from clinical studies. Limited safety data exist for some drug classes such as antibiotics, allowing decision-making to favor one drug over others. However, in general there is an urgent need to gather clinical observations to better investigate drug effects during pregnancy. This is particularly true for CFTR modulators, whose effects on the fetus have not yet been fully investigated.

Drugs	Recommendation in pregnancy	Recommendation for breastfeeding
Pancreatic enzymes	No risk is expected since no absorption by the mother.	Compatible. Poor systemic absorption.
Antibiotics		
Penicillins (+/- beta-lactamase inhibitors)	No risk was demonstrated. Use as first-line treatment.	Compatible. Some trace in milk may alter the gastrointestinal flora of the breastfed neonate.
Cephalosporins	No risk was demonstrated. Use as first-line treatment.	Compatible. Excreted in low concentrations in milk and may alter the gastrointestinal flora of the breastfed neonate.
Macrolides		
Erythromycin	No risk was demonstrated. Preferred drug in this class.	Possibly compatible. Very early exposure to erythromycin is associated with hypertrophic pyloric stenosis in infants. Low RID 1.4-1.7% [11]
Azithromycin	Probably no risk. Erythromycin should be preferred.	Probably compatible. RID is 3.9 % [11]
Carbapenems	Risks not well established. Limited data in human. Preferred drugs are either penicillin, cephalosporin, or erythromycin.	Poor oral bioavailability – unlikely to be absorbed.

Table 1: Recommendations during pregnancy and breast feeding for most common drugs used in CF patients

Drugs	Recommendation in pregnancy	Recommendation for breastfeeding
Aminoglycosides	Risk of fetal nephro- and ototoxicity. Should be used only in case of life-threatening infections. Inhaled route can be used as low systemic absorption.	May alter the gastrointestinal flora of the breastfed neonate. For intravenous administration, avoid breast feeding within the 2 hours following injection. Inhaled route is safe for the breastfed infant.
Quinolones	Not recommended during pregnancy. If necessary, use the most documented drug of the class: ciprofloxacin.	Not recommended. High concentrations found in milk. RID > 10%.
Trimethoprim/ Sulfamethoxazole	Not recommended. Trimethoprim associated with neural defects when used in first trimester. Sulfonamide use in third trimester is associated with an increase in bilirubin in the neonate especially preterm.	Compatible in term neonates but avoid if G6PD deficiency. RID range from 4% to 9%.
Colistin	Risks not well established. Limited data in human. Intravenous route should be avoided. Inhaled route likely to be safe.	Possibly compatible with inhaled route.
Mucolytics		
rhDNase	Probably safe. Inhaled route associated with low systemic absorption.	Compatible since this large protein molecule is unlikely to be absorbed.
Hypertonic saline	Probably safe. Inhaled route associated with low systemic absorption.	Compatible. Poor systemic absorption.

Table 1 (contd): Recommendations during pregnancy and breast feeding for most common drugs used in CF patients

Drugs	Recommendation in pregnancy	Recommendation for breastfeeding
CFTR Modulators	Not recommended. Risks not established. Limited data in human.	Not recommended. Lumacaftor and ivacaftor detectable in milk and at low levels in plasma of breastfed infant [15].

Table 1 (contd): Recommendations during pregnancy and breast feeding for most common drugs used in CF patients

Abbreviations: CFTR=cystic fibrosis transmembrane regulator, RID=relative infant dose

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CHAPTER 10

Evaluation and management of beta-lactam antibiotic drug reactions

Authors

Paul Whitaker, Daniel Peckham

Introduction

Rawlins and Thompson broadly categorized drug reactions into two main groups [1]. Type-A reactions are common and predictable (e.g. ototoxicity and nephrotoxicity caused by aminoglycoside treatment), and account for over 80% of all adverse events seen with drug administration. Type-B reactions are uncommon and cannot be predicted based on the pharmacological actions of the drug. Hypersensitivity reactions account for the majority of Type-B reactions, and were famously sub-classified by Gell and Coombs into four main categories in 1963 (**Table 1**) [2]. In patients with CF, type-I and type-IV reactions predominate. Antibody mediated cytopenia, such as hemolytic anemia secondary to piperacillin, are uncommon.

Type-I reactions are mediated by antigen-specific IgE, with the involvement of mast cells and basophils. Symptoms develop following the rapid release of histamine, leukotrienes, and prostaglandins into the circulation. Rapid vasodilation leads to urticarial reactions, angioedema, bron-

choconstriction, and, in cases of extreme reactions, anaphylaxis. Some drugs, such as vancomycin, can activate mast cells via non-IgE-mediated mechanisms and can precipitate a reaction indistinguishable from an IgE-mediated reaction.

Type-IV reactions are mediated by drug-specific T cells and can produce a wide array of clinical presentations (see **Table 2**). The most common presentations in people with CF are maculopapular reactions and fixed drug eruptions. Severe cutaneous reactions with systemic involvement, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), have been rarely reported in people with CF. *In vitro* studies have identified drug-antigen-responsive T cells from patients with CF and hypersensitivity to sulfamethoxazole, piperacillin, meropenem, and aztreonam [3, 4]. This confirms that T cells are involved in the pathogenesis of these reactions. Beta-lactams are too small in size to act as full antigens. However, they become immunogenic by binding to serum proteins and forming haptens. In people with CF, binding of piperacillin to lysine residues on albumin has been shown to create a hapten that stimulates drug-specific T cells [3].

Type of hypersensitivity	Immune mechanism	Clinical features
Type-I (immediate reactions)	IgE bound to surface of mast cells and basophils. Antigen binding causes degranulation and release of histamines and other vasoactive mediators	Urticaria, bronchospasm, anaphylaxis
Type-II (cytotoxic reactions)	Antigenic determinants on surface of cells are targets for antibodies (IgG or IgM)	Hemolytic anemia, thrombocytopenia, neutropenia, pemphigus
Type-III (immune complex)	Circulating immune complexes are deposited in vascular beds or on the tissue surface. Complement system activation and neutrophilic inflammation	Vasculitis Serum sickness
Type-IV (T-cell-mediated)	Effector T cells produce different responses upon cytokine response	See Table 2

Table 1: Gell and Coombs classification of hypersensitivity [2]

Category of type-IV reaction	Immune mediator	Cell type	Clinical features
Type-IVa	Th1 cells: IFN γ and TNF- α	T cells, macrophages	Contact dermatitis Tuberculin reaction
Type-IVb	Th2 cells: IL-4, IL-5, IL-13	Eosinophils	Maculopapular rash
Type-IVc	Cytotoxic T cells: perforin, granzyme B	T cells	Contact dermatitis Maculopapular rash Bullous eruptions (SJS, TEN)
Type-IVd	T cells: GM-CSF, IL-8	Neutrophils	AGEP

Table 2: Type-IV T-cell mediated hypersensitivity reactions, classified by the cytokine patterns produced

Abbreviations: AGEP=acute generalized exanthematous pustulosis, GM-CSF=granulocyte stimulating factor, IFN=interferon gamma, IL=interleukin, TNF=tumor necrosis factor, TEN=epidermal necrolysis, SJS=Stevens-Johnson syndrome

The timing of the reaction is important. Type-I reactions (immediate) typically develop within one hour and less than six hours after exposure. By contrast, type-IV reactions (non-immediate) develop at least six hours (usually several days) after beginning treatment. Type-IV reactions can accelerate upon repeated exposure; an initial reaction to piperacillin on day six could develop within one day, or less, upon re-exposure.

1 Antibiotic reactions

1.1. Antibiotic reactions in people with CF

Acute respiratory exacerbations are usually treated with a combination of two intravenous antibiotics for 14 days. For patients with chronic *Pseudomonas aeruginosa* infection the antibiotics used are a beta-lactam together with either tobramycin or colistin. The beta-lactams most frequently used are ceftazidime, piperacillin-tazobactam, meropenem, and aztreonam.

The incidence of hypersensitivity reactions during a course of beta-lactam antibiotics in the general population is around 2%. In people with CF, beta-lactams reactions are up to three times more frequent [5-7]. Koch *et al.* studied 121 patients with CF, and found that 4.5% of treatment courses resulted in adverse reactions, with piperacillin and ceftazidime accounting for the majority of reactions [7]. The prevalence of drug hypersensitivity is therefore high. One study found that 36% of patients had a history of beta-lactam hypersensitivity and

19% had multiple beta-lactam reactions [8]. More recently, Roehmel *et al.* conducted a retrospective review of the development of hypersensitivity reactions in 100 patients with CF [9]. They observed a history of drug hypersensitivity in 60% of patients, of whom 31% had a history of three or more hypersensitivity reactions.

The majority of reactions in patients with CF are non-immediate [5, 6]. Pleasants *et al.* found that the mean time to development of non-immediate reactions was nine days [6]. Typical non-immediate reactions include maculopapular rashes, arthralgia, and drug fever [7]. While these reactions are not usually severe, they are sufficient to necessitate treatment discontinuation. Immediate reactions, including anaphylaxis, account for around 15% of all reactions [9]. Given the ever-increasing diversity of antibiotic classes used in people with CF, the range of reactions observed is expanding, and clinicians must remain vigilant for more unusual presentations.

1.2. Why are reactions so frequent in patients with CF?

Antibiotics are delivered intravenously at high doses, for prolonged periods, and on a repeated basis. This alone is likely sufficient to drive sensitization. Studies have identified cumulative exposure, age, and poor lung function as risk factors [8]. In addition, 77% of patients with known hypersensitivity go on to have at least one further reaction [9]. For some drugs, hypersensitivity is associated with a certain allele, such as abacavir (Ziagen) and the major histocompatibility complex (MHC) human leukocyte allele (HLA)-B*5701. However the

reactions are too prevalent in people with CF to be related to single HLA allele. Genetic markers that confer an increased risk may be identified in due course.

CF shares features of auto-inflammation, with an enhanced pro-inflammatory signature [10, 11]. This inflammatory milieu may play an important role in triggering the immune response by inducing dendritic cell maturation and driving antibiotic hypersensitivity. Studies in CF epithelia and monocytes show aberrant responses to bacterial lipopolysaccharide, with increased tumor necrosis factor (TNF)- α , interleukin (IL)-18, IL-1 β , and caspase-1 release [10]. This process is driven by defective ion transport and repeated pulmonary infections due to bacteria such as *P. aeruginosa* and *Burkholderia cepacia* complex [12]. Persistent neutrophilic inflammation is present in CF lungs and is associated with elevated levels of IL-8, IL-1 β , IL-6, IL-17, and TNF- α . Genetic variants of IL-18 and TNF- α have also been associated with beta-lactam-induced reactions [13]. Levels of these two pro-inflammatory cytokines are likely to fluctuate in response to external stimuli, such as gram negative bacterial infections [10].

Other potential factors which may alter immune tolerance and upregulate the immune response include the presence of defective regulatory T cells and dendritic cells [14]. In dendritic cells, *CFTR* regulates MHC II expression and when defective may alter the T cell immune response.

2 Assessing an acute reaction

When patients develop a suspected drug hypersensitivity reaction, their reaction should be documented in a structured approach that includes the following information:

- The generic and proprietary name of the drug or drugs suspected to have caused the reaction and their route of administration
- A description of the reaction and, if possible, an accompanying photograph
- The indication for the drug taken and any specific features of the patient's illness
- The date and time of the reaction
- The number of doses taken or number of days on the drug before onset of the reaction

Records must be updated and included in all hospital discharge letters and primary care communication. It is also considered good practice to provide up to date allergy information to the patient or their carer so they can present it during future consultations.

In patients with suspected drug-related anaphylaxis it is important to take two samples for measurement of mast cell tryptase levels at the time of the reaction, recording the exact timing of both samples. Tryptase is a serine protease and an important prestored pro-inflammatory mast cell mediator that is released upon mast cell degranulation.

2.1. Evaluation of patient labelled as being hypersensitive

Drug reactions to antibiotics make it increasingly difficult to treat infective exacerbations of CF effectively. The label of hypersensitivity has a major impact within the hospital, necessitating prolonged hospital stays and the use of expensive alternative antibiotics. These alternative antibiotics also contribute to antibiotic resistant organisms and increases the risk of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* infections.

Figure 1 shows a simple algorithm for evaluating potentially hypersensitive patients. Whether the reaction was immediate or non-immediate will influence the tests performed and will be discussed later in more detail. First, irrespective of the type of reaction, a detailed history must be taken. This should include a review of any rash, concomitant medication, concomitant diagnoses (e.g. viral infections), and any laboratory data from the time of the reaction.

When reviewed, many patients with CF can have the label of drug allergy removed without further testing. Examples include the following scenarios:

- The patient has since tolerated the drug without adverse effect
- The reaction was strongly suggestive of a non-immune mechanism, such as gastrointestinal disturbance or headache
- An alternative explanation, such as viral infection or chronic urticaria, was later found to be the cause

If the reaction history is consistent with drug hypersensitivity further investigations are warranted. A large number of patients with convincing histories will be demonstrably not hypersensitive [15]. Negative testing may indicate that the patient was never hypersensitive. However, in many patients with IgE-mediated reactions sensitivity can disappear over time [16]. T cell mediated reactions tend to persist and can be lifelong.

2.1.1. Potential immediate reactions

For patients with immediate, potentially IgE-mediated reactions an initial evaluation and risk stratification should be undertaken by the patient's CF team. Patients with signs of more severe immediate reactions, such as anaphylaxis, should be referred to a specialist who is trained and experienced in managing these cases.

Skin Testing

Skin testing is usually the first-line test when assessing potential hypersensitivity. There are three types of skin tests: the skin-prick test, intradermal test, and patch test. Skin-prick tests are performed to identify immediate reactions; they are performed on the volar aspect of the forearm and are usually read at 20 minutes. The result is compared to a positive (histamine) and negative (saline) control. A wheal of 3 mm greater in diameter than the negative control is considered positive. If skin-prick testing is negative intradermal testing can also be performed, with readings taken at 20 minutes. When assessing beta-lactams it is important to test the major and minor penicillin-allergenic metabolites

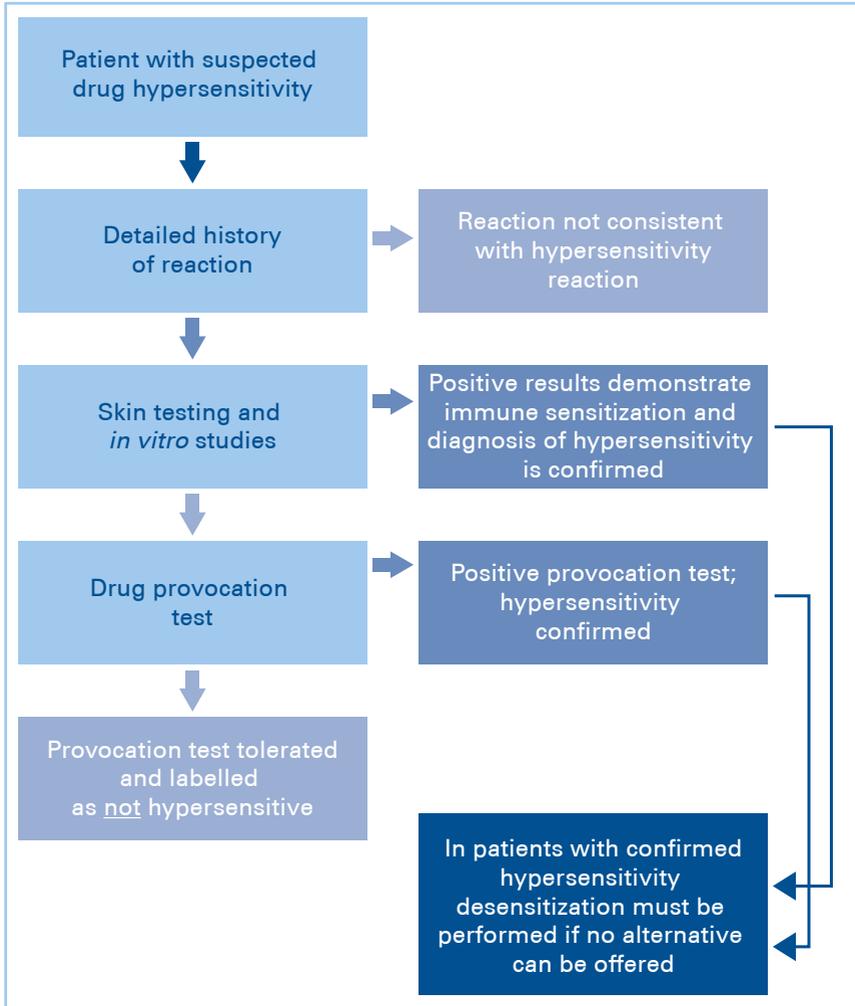


Figure 1: Basic algorithm for the evaluation of a patient with suspected hypersensitivity

(commercially available), benzylpenicillin, amoxicillin, and the beta-lactam under investigation.

It is most appropriate to perform skin testing between 6 weeks and 6 months after the reaction. In IgE-mediated reactions sensitivity can disappear quickly. Thus, skin testing should also be performed after patients have had a sufficient drug-free period without anti-histamines, or glucocorticosteroids. Skin-prick testing and patch testing can be performed with any form of the drug. Intradermal testing requires a commercially available intravenous preparation of the drug. The concentrations used for intradermal testing have been evaluated for most of the common antibiotics [17]. Quinolones and vancomycin can cause non-specific mast cell activation and skin test results may be hard to interpret.

In vitro tests

Drug-specific IgE levels and the basophil activation test (BAT) are potential options to determine sensitivity to the culprit drug [18]. *In vitro* studies can be useful in patients who received several drugs simultaneously or in those who had such severe reactions that drug provocation tests may be contraindicated. Specific IgE determination can be performed using commercially available assays. However, these are only available for a limited number of antibiotics and do not include most of the frequently used CF antibiotics such as piperacillin or ceftazidime. Sensitivity to specific IgE to beta-lactams is low (less than 50%), although it is higher in cases of severe immediate reactions and when tests are performed within three years of the reac-

tion. BAT is based on flow cytometry and measures the activation of basophil surface markers (CD63 and CD203c) by the culprit drugs. Commercially available kits are available but standardized protocols are lacking and the sensitivity for beta-lactam antibiotics is low.

2.1.2. Potential non-immediate reactions

Non-immediate reactions are usually T-cell-mediated and the clinical presentation can be varied. Certain features suggest more severe systemic involvement. These include fever, lymphadenopathy, bullous lesions, mucosal involvement, facial edema, eosinophilia, and abnormal liver function. Patients with features of severe reactions must be referred for specialist review. While skin testing is very safe in patients with a history of benign reactions, there is a possibility of disease reactivation in individuals with severe exfoliative skin reactions, such as SJS/TEN. In these patients tests should be performed with caution, and only if absolutely necessary.

Skin testing

In order to assess sensitization in T-cell-mediated reactions the patch test and intradermal tests are reviewed with delayed readings. These are performed after a negative skin-prick test. Patch testing is performed by applying a drug in a soluble base (usually petroleum), with subsequent patch removal after 48 hours and readings for erythema and induration taken at 48 and 96 hours. Intradermal tests are more convenient for the patient and positive results can be observed after 24 and 48 hours.

Patch tests and intradermal tests are generally considered comparable, although there is some evidence to suggest that intradermal testing is more sensitive [19].

It is now accepted that the sensitivity of skin testing in patients with non-immediate reactions to beta-lactam antibiotics is low. Padia *et al.* [20] found that only 9% of patients developed positive delayed intradermal readings, while Lammintausta *et al.* [21] reported patch test positivity in only 4% of patients with non-immediate reactions to cephalosporins. Blanca-Lopez *et al.* observed positive patch or intradermal test results in only 5% of children with non-immediate beta-lactam reactions and a positive provocation test [22]. In patients with CF only 14% had positive intradermal test results for piperacillin despite testing positive in *in vitro* tests [3].

In vitro tests

The most established assay for identifying drug-specific T cells is the lymphocyte transformation test (LTT). In the LTT the proliferation of activated T cells is measured by the incorporation of radioactive thymidine. This is useful test, with sensitivity ranging from 50–80% for beta-lactam antibiotics [23]. In a cohort of patients with CF and non-immediate reactions to piperacillin the sensitivity was 68% [24]. Unfortunately, the LTT is not widely available and its use is largely limited to research given the complexity of the assay.

2.2. Drug provocation tests

For the majority of patients with CF and suspected hypersensitivity, skin-test results will be negative and *in vitro* studies

unavailable. In this situation, the only means of determining whether someone is truly hypersensitive is by performing a drug provocation test.

- Provocation tests are contraindicated in patients who have had severe hypersensitivity reactions. This includes severe cutaneous reactions and reactions with systemic involvement including hematologic reactions
- Provocation tests may not be needed if an alternative and effective drug is available
- Provocation tests must be performed under the strictest safety conditions. Resuscitation facilities and appropriately trained staff must be available

Different protocols for provocation tests are available and should be tailored to the individual patient's risk [25]. Risk assessment should include information relating to the historical reaction as well as the patient's current health status. Higher-risk patients include those with advanced lung disease or other risk factors such as pregnancy. In cases of patients who are very low risk (e.g. those who had an unknown reaction over 10 years earlier with no evidence to suggest an IgE-mediated reaction), it may be possible to directly perform a single full-dose provocation test without the need for skin testing. In patients with a moderate risk history, such as those with a documented skin reaction without features of anaphylaxis, a graded antibiotic challenge can be performed if the skin test result is negative. An example of a graded challenge would be one-hundredth of the full dose, followed by one-tenth of the full dose, before finally administering the full

therapeutic dose. A 30 to 60 minute observation period is required between steps. Patients with a high risk (e.g. those with a previous anaphylactic reaction) should be referred to a specialist allergy center for assessment, where a risk/benefit analysis specific to the individual will be performed. If the provocation test is tolerated the medical record should be updated and the patient informed that they can receive it in future. In non-CF patients, a negative skin test result plus a negative provocation test result has more than a 99% negative predictive value for excluding IgE-mediated reactions. In people with CF this value will be lower as tests are performed when the patient is clinically stable and additional co-factors, such as infection, are often necessary for the reaction to develop. To completely exclude non-immediate reactions some centers advocate a longer course of antibiotics. However, it is generally felt that the patient should not be unnecessarily exposed to antibiotics.

3 Management of hypersensitive patients

3.1. Use alternative antibiotic

The basic structure of beta-lactams is a four-member beta-lactam ring (**Figure 2**). In penicillin this beta-lactam ring is connected to a five-member thiazolidine ring to form the so-called penicillin nucleus. In cephalosporins the beta-lactam ring is connected to a six-member dihydrothiazine ring. Penicillins have one side chain (R1) while cephalosporins have two (R1 and R2). These side chains determine the pharmaco-

logical and antibacterial properties of each drug, and are important sites of immune recognition and cross-reactivity between antibiotics. Cross-reactivity to the common beta-lactam ring is infrequent. Aztreonam is a monobactam that contains a beta-lactam nucleus with no adjoining ring.

Fortunately, reactions in CF appear to be highly drug specific, with little cross-reactivity. In cases of non-immediate reactions the T cells are stimulated *in vitro* with the chemical entity to which the patient was exposed at the time of the reaction, but not with closely related drugs or other drugs commonly used in people with CF [3]. It is not until the patient has developed several separate drug reactions that their antibiotic options are truly restricted. However, caution is required with ceftazidime and aztreonam, which share an identical side chain, making cross-reactivity possible. Moss *et al.* studied the tolerability of aztreonam in 20 patients with previous beta-lactam hypersensitivity [26], and found that 19 patients tolerated aztreonam; the patient who failed had had a previous reaction to ceftazidime.

In individuals without CF the risk of a penicillin-hypersensitive patient developing a reaction to ceftazidime, meropenem, or aztreonam is very low, as there is little structural similarity [27, 28]. There have been fewer studies of patients who initially developed hypersensitivity to cephalosporins than to penicillins. Romano *et al.* studied 106 patients with a history of immediate reaction to cephalosporins. Skin testing and drug provocation tests revealed that around 25% of patients were also

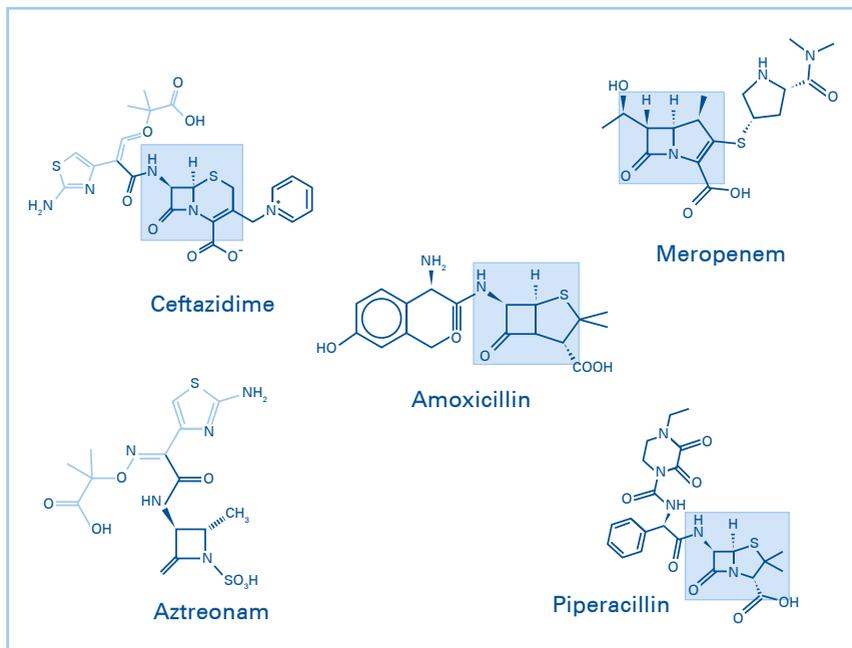


Figure 2: Structure of common antibiotics used to treat patients with CF.

The semi-synthetic beta-lactam compounds share the beta-lactam ring but have modified side chains. Aztreonam differs from the other drugs in that it possesses a monocyclic beta-lactam nucleus instead of a dual ring

penicillin-allergic, but only 3% reacted to aztreonam and only 1% to meropenem [29].

3.2. Treating through

In some patients who experience a mild reaction it may be possible to “treat through” the reaction without suspending treatment. The reaction can be made more tolerable with the addition of anti-histamines and steroids. In others, the symptoms appear to worsen after administration of high-dose antibiotics over a short infusion time. In this situation, initiation of continuous antibiotic infusion can help to combat the severity of reaction symptoms, and in some patients the reaction may even resolve.

3.3. Alternative routes of administration

The intravenous route of administration appears to be the most immunogenic. It is reported that in mild non-immediate reactions the patient will often tolerate the drug when it is given in nebulized form [30]. This is an important option. Moreover, nebulized aztreonam can be used alongside an intravenous antibiotic in patients with multiple drug reactions. The careful use of intravenous antibiotics is important to prevent the development of hypersensitivity. Given the overall improvements in the routine management of CF care there is less of a need for frequent intravenous antibiotics to maintain stability. Indeed, mild exacerbations can be effectively treated with a combination of oral antibiotics and intensified inhaled treatment.

3.4. Desensitization

While alternative regimens can be devised for most patients, there are some for whom all options have been exhausted. In this difficult scenario, drug desensitization represents a safe method of reintroducing a drug to which a patient has been proven hypersensitive. As with provocation tests this approach should be avoided in patients with severe T-cell-mediated reactions. Desensitization results in a temporary state of immune tolerance to the culprit drug by administering gradually increasing suboptimal doses prior to the full therapeutic dose. This is an established procedure in people with CF who have immediate antibiotic reactions [31, 32]. Legere *et al.* reported 52 successful desensitization procedures in 15 patients with immediate reactions [32]. The procedure involves a rapid protocol consisting of either 12 or 16 increments performed in less than six hours (Figure 3). Protocols have also been designed for desensitization to oral antibiotics such as flucloxacillin, co-trimoxazole, and oral ciprofloxacin.

When undertaking rapid intravenous desensitization the patient must be kept in a monitored area with 1:1 nurse supervision. In patients in whom the original reaction was anaphylaxis the procedure should be performed in an intensive care setting. The patient must provide full consent, and accept the risk that a further reaction could occur. There is no clear consensus as to whether pre-medication with anti-histamines and steroids should be administered empirically. Once desensitization is completed, the patient should remain in

hospital for a further 48 hours; this is the interval during which desensitization failure tends to occur. If the patient misses regular doses of the treatment such that more than five half-lives of the drug are omitted, desensitization will need to be repeated, as the temporary tolerance can be lost.

There is very limited information available in the CF literature to support desensitization in cases of non-immediate reactions [33]. While a retrospective study by Burrows *et al.* included a small number of patients with non-immediate reactions, the outcomes of these patients were not distinguished from those of patients with immediate reactions. A later retrospective review of 275 desensitization procedures in 42 patients with a range of non-immediate reactions found that success ranged from 55% with piperacillin to 88% with tobramycin [34]. In patients who failed desensitization the reactions observed were milder than the original reactions and the majority occurred within 48 hours of starting treatment. Prophylactic anti-histamines and steroids did not reduce the risk of reaction.

Name of medication: Ceftazidime					Total mg per bag	Amount of bag infused (mL)
Solution 1	100 mL of	0.200 mg/mL			20.00	9.25
Solution 2	100 mL of	2.000 mg/mL			200.00	18.75
Solution 3	100 mL of	19.607 mg/mL			1960.65	250.00
Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.100	0.100
2	1	5.0	15	1.25	0.250	0.350
3	1	10.0	15	2.50	0.500	0.850
4	1	20.0	15	5.00	1.000	1.850
5	2	5.0	15	1.25	2.500	4.350
6	2	10.0	15	2.50	5.000	9.350
7	2	20.0	15	5.00	10.000	19.350
8	2	40.0	15	10.00	20.000	39.350
9	3	10.0	15	2.50	49.016	88.366
10	3	20.0	15	5.00	98.0325	186.399
11	3	40.0	15	10.00	196.065	382.464
12	3	80.0	61.87	82.50	1617.536	2000.00
Total time = 226.875 minutes (3h 46m)						

Figure 3: Example of a 12-step protocol for rapid intravenous desensitization to ceftazidime.

Reproduced from [32]

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CHAPTER 11

CFTR modulators, CFTR directed therapies and precision medicine

Authors

Mieke Boon, Kris De Boeck

Introduction

Since 1989, when mutation of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was discovered to be the underlying genetic cause of cystic fibrosis (CF), our understanding of the disease has evolved enormously. The CFTR protein is a transmembrane anion channel that regulates chloride and bicarbonate transport through epithelial mucosae. It comprises two membrane-spanning domains, two nucleotide-binding domains (NBD) and a regulatory (R) domain. During channel opening, the R-domain is phosphorylated, ATP binding induces dimerization of the NBDs, and the protein configuration changes so that anions efflux along the concentration gradient.

In the lungs, abnormal CFTR function results in airway surface dehydration and poor expansion of mucins, which both contribute to viscous secretions and defective mucociliary clearance. Obstruction of the intra-pancreatic ducts leads to reduced delivery of digestive enzymes into the intestinal lumen. In addition, reduced bicarbonate

secretion impairs activation of pancreatic enzymes and results in limited absorption of nutrients. Around 85% of people with CF have pancreatic insufficiency. Obstruction of the vas deferens causes infertility in nearly all males with CF.

Symptomatic treatment aims to improve the nutritional status (by pancreatic enzyme supplements and high caloric foods) and to prevent or decrease lung damage (by mucolytic drugs and chest physiotherapy along with anti-infective and anti-inflammatory strategies). In the last decade, we have moved from treating the symptoms to treating the underlying CFTR protein defect with CFTR modulators. When effective, CFTR modulators bring spectacular benefit for the patient and, when instituted early, could prevent major complications like pancreatic insufficiency and maybe even CF related diabetes (CFRD).

1 CFTR mutations and classification

More than 2000 different variants in the *CFTR* gene have been reported; these variants have traditionally been referred to as “mutations.” For 412 of these mutations, the functional defect in the CFTR protein has been described: 346 are CF-causing, 37 have varying clinical consequence, 21 do not cause CF and 8 have unknown significance. Currently there is insufficient information about the clinical relevance of the remaining >1700 variants.

CFTR mutations can be subdivided in 7 classes, according to their effect on CFTR protein synthesis, function and stability [1] (Figure 1). **Class I mutations** (nonsense mutations, frameshift mutations) result in a premature stop codon, premature termination of gene transcription and very short mRNAs, targeted by nonsense mediated mRNA decay and therefore absent protein production (“null mutations”). **Class II mutations** lead to misfolding and abnormal trafficking of the CFTR protein; most of the protein is degraded in the proteasome, with very little protein reaching the plasma membrane. F508del (p. [Phe508del]/c. [1521_1523delCTT]), the most frequent *CFTR* mutation, has class II characteristics. **Class III (gating) mutations** are characterized by a near normal amount of CFTR at the plasma membrane, but with a reduced probability of open status and limited if any anion traffic through the cell membrane. In **Class IV mutations**, the conductivity of the CFTR channel is abnormal, which also results in reduced chloride transport through the cell membrane. **Class V muta-**

tions result in a lower amount of normal CFTR channels. **Class VI mutations** lead to protein with decreased stability at the cell membrane and thus a reduced amount of CFTR channels due to increased turn-over. Large deletions, insertions and frameshift mutations are grouped as **class VII mutations**. These mutations cannot be targeted by small molecule therapies.

As chloride transport at the cell membrane is somewhat preserved in patients with at least one class IV or V mutation, they generally have a milder disease phenotype including lower sweat chloride, lower incidence of pancreatic insufficiency, slower decline in lung function, better life expectancy and lower disease burden. Class IV and V mutations are collectively referred to as residual function (RF) mutations, in contrast with minimal function (MF) mutations leading to no protein or protein with only minimal function (mainly classes I, II and VII).

This classification of mutations has helped to stratify CFTR-directed therapies. However, several mutations have characteristics of different classes. For example, when the class II mutation F508del is rescued (rF508del) by modulatory therapy it becomes present at the cell membrane but has reduced probability of the channel being open and decreased stability, characteristic of classes III and VI, respectively. Therefore, more than one CFTR modulator is needed to correct the F508del defect.

	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
CFTR defect	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable	No mRNA
Mutation examples	Gly542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Phe508del, Asn1303Lys, Ala561Glu	Arg117His, Arg334Trp, Ala455Glu	Ala455Glu, 3272-26A→G, 3849+10 kb C→T	c.120del23, rPhe508del	dele2, 3(21 kb), 1717-1G→A
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability	Unrescuable

Wild-type CFTR

Figure 1: Classification of *CFTR* mutations, adapted from [1]

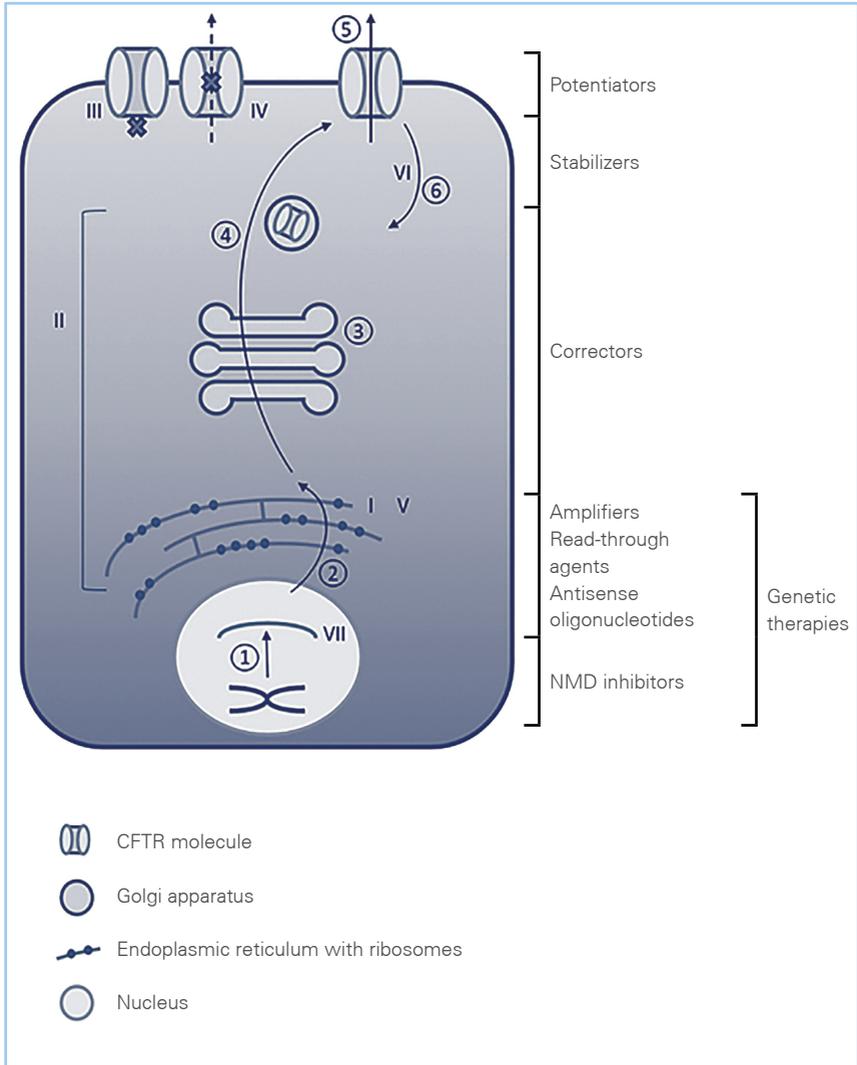


Figure 2: Overview of *CFTR* mutation classes and different therapies, reproduced with permission from [2]

Abbreviations: I=class I mutations (absence of or severe reduction in CFTR), II=class II mutations (defective CFTR processing and trafficking), III=class III mutations (impaired CFTR gating), IV=class IV mutations (impaired CFTR conductance), V=class V mutations (reduction in normal CFTR transcript), VI=class VI mutations (reduced CFTR stability), VII=class VII mutations (no mRNA, unrescuable), 1=transcription, 2=translation, 3=post-translational modification, 4=protein trafficking, 5=surface expression of functional CFTR, 6=CFTR turnover, NMD=nonsense-mediated mRNA decay

2 Therapies targeting CFTR

CFTR modulators are mostly small molecules taken orally to target the CFTR protein in all organs. Several types of CFTR modulators have been described (**Figure 2**).

- CFTR **potentiators** increase the open probability of CFTR at the plasma membrane (targeting class III mutations, rF508del and selected RF mutations).
- CFTR **correctors** improve folding and trafficking of mutant CFTR so that more CFTR protein passes the endoplasmic reticulum control machinery and reaches the plasma membrane (targeting class II defects).
- **Stop codon read through agents** result in a full length mRNA and further translation of the CFTR protein (targeting class I defects).
- CFTR **amplifiers** bind to the nascent CFTR protein, increase the efficiency of translation and therefore result in more CFTR available for other CFTR modulators to work on.
- CFTR **stabilizers** improve the stability of CFTR at the plasma membrane (targeting class VI defects).

Besides CFTR modulators, gene therapy and gene correction are also being studied in CF. Instead of targeting the CFTR protein, a normal *CFTR* gene is administered (via viral or non-viral vectors) or the *CFTR* gene is corrected with technologies such as CRISPR-Cas9. So far, gene therapy hasn't reached the clinic because of limited efficacy. Additional corrective strategies in the pipeline include messenger RNA (mRNA) addition, transfer RNA (tRNA) recoding, and antisense oligonucleotides.

In this chapter, we focus on CFTR modulator therapy and especially on drugs approved for use in the clinic. Most CFTR modulators have been identified via high throughput screening, hence their mechanism of action is often not fully understood.

2.1. CFTR modulators

2.1.1. Ivacaftor (Kalydeco)

Ivacaftor was the first CFTR modulator approved by the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA). It increases the open probability of the channel at the cell membrane. Several clinical trials showed impressive improvements in biomarkers (sweat chloride, fecal elastase), surrogate markers (forced expiratory volume in

one second [FEV₁] and clinical outcomes (weight, body mass index [BMI], pulmonary exacerbations). An overview of the individual trials with their respective outcomes is presented in **Table 1**.

Ivacaftor 150 mg twice daily was trialed in a placebo-controlled phase 3 study in patients 12 years and older with at least one G551D mutation, the most prevalent class III mutation [3]. Treatment with ivacaftor for 48 weeks was associated with a fast and sustained mean increase in percentage predicted (pp) FEV₁ of 10.5%. There were similarly fast and sustained mean decreases in sweat chloride concentration of 48.1 mmol/l (to below the diagnostic threshold of 60 mmol/l), and pulmonary exacerbations decreased by 55.5%. There were also significant improvements in the non-respiratory outcomes of weight gain and quality of life (using the standardized revised Cystic Fibrosis Questionnaire [CFQ-R]). This study was a major milestone and an eye opener for what effective CFTR modulation can achieve.

Subsequent studies confirmed the major benefits of ivacaftor in other populations. In a placebo-controlled trial in patients aged 6 to 11 years, ppFEV₁ improved by 12.5%, despite near-normal lung function at baseline [4]. In patients with baseline ppFEV₁ above 90%, the primary outcome was adapted to the patient group studied. Improvement in ventilation inhomogeneity, measured by multiple breath washout and expressed as lung clearance index (LCI) improved by 2.16 units [5]. But even these

patients had significantly improved ppFEV₁. A cross-over trial in patients with class III mutations other than G551D showed benefits similar to those seen in patients with G551D [6].

Open-label studies explored the safety and efficacy of ivacaftor in children with class III mutations aged 2-5 years [7], 1-2 years [8], and below 1 year (this study is ongoing; NCT02725567). Impressive decreases in sweat chloride concentration were seen in all cohorts, with individual patients reaching levels below 30 mmol/l. Improvement or maintenance of weight and height centiles was also seen. The indicated doses of ivacaftor for treatment of children are shown in **Table 2**.

Surprisingly, in all cohorts below age 6 years, fecal elastase levels increased and immunoreactive trypsinogen (IRT) levels decreased. This suggests a window of opportunity to prevent or revert exocrine pancreatic insufficiency, historically regarded as irreversible because of very early onset, even intrauterine. In the meantime, this hypothesis has been backed up by data in animal models. After ivacaftor treatment of ferrets pregnant with CF offspring, pups were protected against neonatal meconium ileus and 87% of pups remained pancreatic sufficient until at least 3 months of age, with normal growth and preservation of normal pancreatic histology in most pups.

In a placebo-controlled trial, patients with the RF mutation R117H (p. [Arg117His]/c. [350G>A]) had improvements (although of a lower magnitude than in class III mutations) in ppFEV₁, sweat chloride and BMI z-score [9].

Overall, ivacaftor is well tolerated, but there is some concern about liver toxicity, especially in children, with increases in serum transaminase levels 8 times above the upper limit of normal (ULN) at times. Since studies in children aged under 6 years were open-label, the data are difficult to interpret. Cataract, although reported in young rats (only when exposed in pregnancy or at day 7-35 of life) was not seen with an increased frequency in humans treated with ivacaftor. Ivacaftor has EMA approval for CF patients above 6 months of age with at least one of nine gating mutations, and in patients aged over 18 years with at least one R117H mutation. The FDA approval is more extensive, with ivacaftor approved for patients aged over 6 months with a class III mutation or the R117H mutation, and for patients with one of 28 RF mutations (see **Table 3**). FDA approval was in part based on *in vitro* data in Fisher rat thyroid cells expressing these mutations and showing more than 10% improvement in CFTR function on addition of ivacaftor. Also ivacaftor has been trialed in patients with an RF mutation, in a n-of-1 study by Jerry *et al.* and a cross-over trial evaluating the benefit of ivacaftor and tezacaftor-ivacaftor [10].

Overall, ivacaftor offers effective treatment for 5 to 10% of patients with CF, the frequency of class III and RF mutations strongly varying between countries and regions [11].

Despite its high cost, ivacaftor is nowadays available and reimbursed in most developed countries, but sadly not in Portugal, New Zealand, nor in most countries in Eastern Europe and South America.

The real-life benefit of treatment with ivacaftor has been clearly shown. US and UK registry studies have shown an impressive reduction in hospitalization (40%), death (49%), organ transplantation (85%) and pulmonary exacerbations (36%) [12]. There was also decreased prevalence of common CF pathogens (*S. aureus*, *P. aeruginosa*, *Aspergillus*) and lower prevalence of CFRD, bone disease, depression and hepatobiliary complications. In another study, the rate of lung function decline was nearly half that of a matched cohort of homozygous F508del patients (-0.91% versus 1.72% ppFEV₁ per year) [13]. In patients with severe lung disease (ppFEV₁<40% or listed for lung transplantation), ppFEV₁ improved by 16.7%, weight improved and days of intravenous antibiotic therapy decreased [14]. In a small observational study, ivacaftor treatment reduced the density of *P. aeruginosa* in sputum, airway inflammation and improved lung imaging [15]. Sustained improvement in chest CT abnormalities and circulating inflammatory markers were confirmed [16]. However, in another cohort of patients treated with ivacaftor for 6 months, there was no influence on sputum microbiome and inflammatory markers [17]. Real world studies revealed no new safety concerns [18].

The number of quality adjusted life years (QALYs) gained by patients on ivacaftor, representing the number of years in perfect health, varies from 15.8 to 25.6 depending on an optimistic or conservative approach to continuation of treatment benefit [19]. Ivacaftor was thought to bridge 65% of the survival gap between healthy people and people with CF.

Author	Main inclusion criteria	Study type and duration	Number of patients	
In patients with at least one G551D mutation				
Ramsey <i>et al.</i> 2011 [3]	≥12 years ppFEV ₁ 40-90%	Randomized, DB-PC, Parallel groups 48 weeks	161	
Davies <i>et al.</i> 2013 [5]	6-11 years ppFEV ₁ 40-105% Weight ≥ 15 kg	Randomized, DB-PC, Parallel groups 48 weeks	52	
Davies <i>et al.</i> 2013 [5]	≥6 years ppFEV ₁ >90% LCI >74 Weight ≥ 15 kg	Randomized, DB-PC, Cross-over 28 days	20	
In patients with at least one non-G551D gating mutation				
De Boeck <i>et al.</i> 2014 [6]	≥6 years ppFEV ₁ ≥40%	Randomized, DB-PC, Cross-over 8 weeks	39	
In patients with at least one gating mutation				
Davies <i>et al.</i> 2016 [7]	2-5 years Weight ≥8 kg	Open-label, Single arm 24 weeks	34	

Table 1: Main results from clinical trials with ivacaftor

Treatment effect compared to placebo or within group (if open-label)						
Sweat chloride mmol/l (95% CI or SD)	ppFEV ₁ (95% CI)	Pulmonary exacerbations rate ratio (95% CI)	CFQ-R points (95% CI)	Nutritional parameters (95% CI or SD)	Other (95% CI or SD)	
-48.1 (-51.5, -44.7)	+10.5% (8.5, 12.5)	0.43 (0.27, 0.68)	+8.6	Weight +2.7 kg (1.3, 4.1)		
-53.5 (-60.9, -46.0)	+10.0% (4.5, 15.5)	NS	NS	Weight +2.8 kg (1.3, 4.2) BMI z-score +0.45		
-47.5 (-54.6, -40.4)	+8.67% (2.36, 14.97)	ND	NS	ND	LCI -2.16 (-2.88, -1.44)	
-49.2 (-57.0, -41.4)	+10.7% (7.3, 14.1)	ND	+9.6 (4.5, 14.7)	BMI z-score +0.28 (0.12, 0.45)		
-46.9 (26.2)	ND	ND	ND	Weight z-score +0.2 (0.3) BMI z-score +0.4 (0.4) Height Z-score NS	Fecal elastase-1 +99.8 µg/g (138.4) IRT -20.7 ng/mL (24.0)	

Author	Main inclusion criteria	Study type and duration	Number of patients	
In patients with at least one gating mutation				
Rosenfeld <i>et al.</i> 2018 [8]	12-<24 months	Open-label, Single arm 24 weeks	19	
In patients with at least one R117H mutation				
Moss <i>et al.</i> 2015 [9]	≥6 years ppFEV ₁ 40-90% if >12 years ppFEV ₁ 40-105% if 6-11 years	Randomized, DB-PC, Parallel groups 24 weeks	69	

Table 1 (contd): Main results from clinical trials with ivacaftor

Treatment effect compared to placebo or within group (if open-label)						
Sweat chloride mmol/l (95% CI or SD)	ppFEV ₁ (95% CI)	Pulmonary exacerbations rate ratio (95% CI)	CFQ-R points (95% CI)	Nutritional parameters (95% CI or SD)	Other (95% CI or SD)	
-73.5 (17.5)	ND	ND	ND	Weight z-score NS Length z-score NS	Fecal elastase-1 +164.7 µg/g (151.9) IRT -647.1 ng/mL (339.3) Serum lipase -228.4 U/L (263.0) Serum amylase -54.8 U/L (70.5)	
-24.0 (-28.0, -19.9)	NS	NS	+8.4 (2.17, 14.61)	NS		

Abbreviations: 95% CI=95% confidence interval, SD=standard deviation, SEM=standard error of the mean, NS=no significant difference, ND=no data reported, DB-PC=dou-
ble-blind placebo-controlled, FEV₁=forced expiratory volume in 1 second, BMI=body mass
index, LCI=lung clearance index, IRT=immune reactive trypsinogen

Age	Weight	Form	Dose
Ivacaftor			
> 6 years		Tablets	150 mg ivacaftor BID
6 months - 6 years	≥14 kg	Granules	75 mg ivacaftor BID
	7-14 kg	Granules	50 mg ivacaftor BID
	<7 kg	Granules	25 mg ivacaftor BID
Lumacaftor/ivacaftor			
>12 years		Tablets	400 mg lumacaftor + 250 mg ivacaftor, BID
6-11 years		Tablets	200 mg lumacaftor + 250 mg ivacaftor, BID
2-5 years	≥14 kg	Granules	150 mg lumacaftor + 188 mg ivacaftor, BID
	<14 kg	Granules	100 mg lumacaftor + 125 mg ivacaftor, BID
Tezacaftor/ivacaftor			
≥12 years		Tablets	100 mg tezacaftor once daily + 150 mg ivacaftor BID
6-12 years	≥30 kg	Tablets	100 mg tezacaftor once daily + 150 mg ivacaftor BID
	<30 kg	Tablets	50 mg tezacaftor once daily + 75 mg ivacaftor BID
Elexacaftor/tezacaftor/ivacaftor			
≥12 years		Tablets	200 mg elexacaftor once daily + 100 mg tezacaftor once daily + 150 mg ivacaftor BID

Table 2: CFTR modulator doses in children

Consider dose adjustments in children with liver disease or in case of concomitant treatment with e.g. azoles. For full instructions consult drug specification leaflet.

Abbreviation: BID=twice daily.

2.1.2. Ivacaftor plus lumacaftor (Orkambi)

The CFTR corrector lumacaftor improves CFTR protein trafficking and folding so that an increased amount of rF508del appears at the cell surface. However, since rF508del CFTR still has an important gating defect, ivacaftor is needed to significantly increase CFTR protein function. Hence, the combination of a CFTR corrector (lumacaftor, 600 mg daily or 400 twice daily) plus a CFTR potentiator (ivacaftor 250 mg twice daily) was trialed in patients homozygous for F508del.

An overview of the individual trials with their respective outcomes is presented in **Table 4**.

In a phase 2 trial, lumacaftor/ivacaftor combination therapy was assessed in adults with CF homozygous for F508del. The participants had a moderate improvement in sweat chloride (9.1 mmol/l). There was a small improvement in ppFEV₁, compared to baseline (+3.1%). This change from baseline was not significantly different from the change observed in the placebo group [20]. In the placebo-controlled phase 3 trials, lumacaftor/ivacaftor combination therapy resulted in a significant but rather limited improvement in ppFEV₁ (+ 3%) and a decrease in the number of exacerbations in patients aged ≥ 12 years [21]. The moderate improvement in lung function was sustained, but only within the range of approved symptomatic therapies like hypertonic saline and rhDNAse. However there were large differences in benefit between patients. Waterfall plots documenting individual benefits show major improvements in some patients (almost equaling the

mean ivacaftor treatment benefit in G551D patients) to no benefit at all. Sweat chloride concentration was not studied in the phase 3 trial.

In a placebo-controlled trial in children aged 6 to 11 years, lumacaftor/ivacaftor significantly improved LCI (-1.09), ppFEV₁ (+ 2.4%) and sweat chloride (-20 mmol/l) [22]. In an open-label phase 3 study in children aged 2-5 years, the mean decrease in sweat chloride concentration was -32 mmol/l. Weight improved and even a modest increase in fecal elastase was seen [23]. The doses for use in children are shown in **Table 2**.

Overall, ivacaftor/lumacaftor was well tolerated, but serious adverse events related to abnormal liver function were reported in 0.9% of patients on active treatment compared to 0% of patients on placebo. Chest tightness and dyspnea occurred (mostly in patients with severe lung disease), leading to treatment discontinuation in about 1.2% of cases.

Lumacaftor/ivacaftor combination therapy has been approved by the EMA and FDA for people with CF who are homozygous for the F508del *CFTR* mutation and aged 2 years and over (**Table 3**). This could represent a moderately effective treatment for about 50% of people with CF. However, despite EMA marketing authorization, several national health authorities have refused reimbursement because of an unfavorable cost/benefit ratio. Reimbursement in some countries but not in others (despite similar healthcare spending as percent of gross domestic product) leads to major frustration, especially since an alternative treatment is not available at present.

Ivacaftor (Kalydeco)			
EMA approval		FDA approval	
Mutations	From age of	Mutations	From age of
9 class III mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R	6 months	9 class III mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R	6 months
R117H	18 years	R117H	
		28 other ivacaftor responsive mutations (clinically and/or <i>in vitro</i>): E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A>G, E831X, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, 2789+5G>A, 3272-26A>G, 3849+10kbC>T	
Lumacaftor/ivacaftor (Orkambi)			
EMA approval		FDA approval	
Mutations	From age of	Mutations	From age of
F508del homozygous	2 years	F508del homozygous	2 years

Table 3: EMA and FDA approval of CFTR modulators in clinical use (as of November 2019)

Tezacaftor/ivacaftor (Symkevi, Symdeko)			
EMA approval		FDA approval	
Mutations	From age of	Mutations	From age of
F508del homozygous	12 years	F508del homozygous	12 years
Patients heterozygous for F508del and one of the following mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A>G, S945L, S977F, R1070W, D1152H, 2789+5G>A, 3272 26A>G, or 3849+10kbC>T		Patients heterozygous for F508del and one of the following mutations: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A>G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G>A, 3272-26A>G, 3849+10kbC>T	
Elexacaftor/tezacaftor/ivacaftor (Trikafta)			
EMA approval		FDA approval	
Mutations	From age of	Mutations	From age of
No approval yet		F508del homozygous or F508del heterozygous in combination with minimal function mutation	12 years

Table 3 (contd): EMA and FDA approval of CFTR modulators in clinical use (as of November 2019)

Sources:

<https://www.ema.europa.eu/en/medicines/human/EPAR/kalydeco> and [orkambi](https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi) and [symkevi](https://www.ema.europa.eu/en/medicines/human/EPAR/symkevi)

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207925> and [211358](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211358) and [210491](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210491) and [212273](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212273)

Long-term benefit has been shown for patients treated with lumacaftor/ivacaftor. In extension studies and a matched registry cohort of homozygous F508del patients not treated with lumacaftor/ivacaftor, ppFEV₁ rate of decline was reduced by 42% (1.33% per year versus -2.29% per year) [24]. The real-life benefit from lumacaftor/ivacaftor was evaluated in 842 French patients; an increase in ppFEV₁ of 3.7% was noted after one year on continuous treatment, but 18.2% of the patients stopped treatment due to respiratory and non-respiratory adverse events. Patients with severe lung disease (ppFEV₁<40% and high frequency of intravenous antibiotics) were at high risk of intolerance [25].

When initiating treatment in patients with low baseline lung function, it has been advocated that decreasing the starting dose may improve tolerability. According to 2018 CFF registry data, 63.2% of eligible patients were being treated with lumacaftor/ivacaftor [26].

It is difficult to forecast the real long-term benefit from lumacaftor/ivacaftor on quality of life, survival, need for lung transplant and other long-term outcomes. One model predicted an increase of 2.42 QALYs, and increased median survival of 2.9 years. It was estimated that this would bridge 28% of the survival gap with nonCF peers [27]. More recent estimates are more optimistic [28]; with an increase in median survival of 6.1 years, the estimate ranging from 4.8 to 23.4 depending on the age at treatment introduction (which ranged from 6 to 25 years).

2.1.3. Ivacaftor plus tezacaftor (Symdeco, Symkevi)

As lumacaftor can induce side effects such as chest tightness, and interacts with the metabolism of other drugs, the potentiator tezacaftor was trialed (see **Table 5** for an overview of studies). In patients aged ≥ 12 years of age and homozygous for F508del, the combination of ivacaftor (150 mg twice daily) plus tezacaftor (100 mg once daily) led to modest but sustained improvements in ppFEV₁ (+4%) and CFQ-R (+5.1 points) as well as modest mean decreases in sweat chloride concentration (-10 mmol/l) and rate of pulmonary exacerbations (-35%) [30]. A cross-over trial in patients aged ≥ 12 years with one F508del mutation and one RF mutation also showed significant improvements in ppFEV₁ (+6.8%), and CFQ-R (+11.1 points) and modest decreases in sweat chloride (-9.5 mmol/l) [10]. In addition, tezacaftor/ivacaftor combination treatment was superior to ivacaftor monotherapy (+2.1% ppFEV₁, +1.4 CFQ-R points). An open-label study in children aged 6-11 years, (the vast majority homozygous for F508del but including some heterozygous for F508del and a RF mutation) reported good tolerability and non-significant improvements in ppFEV₁ (+0.9%) and CFQ-R (+3.4) as well as a mean decrease in sweat chloride of -14.5 mmol/l [31].

Overall tezacaftor/ivacaftor was well tolerated. Liver function abnormalities and chest tightness were not seen more frequently than in the placebo group.

Tezacaftor/ivacaftor (sold in Europe as Symkevi) has EMA approval for patients from the age of 12 years, who are either homozygous for F508del or compound

heterozygous for F508del and a selected list of RF mutations (see **Table 3**). FDA approval for tezacaftor/ivacaftor (sold in the US as Symdeko) differs by including a longer list of RF mutations. Tezacaftor/ivacaftor could be a moderately effective treatment for around 50% of patients with CF.

At present, there are no data on the real-life benefit of tezacaftor/ivacaftor. The benefit is expected to be similar to that of lumacaftor/ivacaftor, but with better tolerability.

2.1.4. Elexacaftor/ivacaftor/tezacaftor triple combination therapy

Adding a second CFTR corrector greatly improves correction of the mutant F508del protein. If full correction of the F508del allele could be achieved in patients heterozygous for F508del, this would result in 50% of functional protein, equivalent to the functional level of asymptomatic carriers.

The next-generation corrector, VX-445 (elexacaftor), was tested in combination with ivacaftor/tezacaftor in phase 2 trials in patients aged >12 years homozygous for F508del or heterozygous for F508del/MF [32]. When elexacaftor was added to the existing regimen of tezacaftor/ivacaftor, patients homozygous for F508del had improved ppFEV₁ (+11%), CFQ-R (+20.7) and sweat chloride (-39.6 mmol/l). Similar improvements were observed in patients heterozygous for F508del and a MF mutation: ppFEV₁ (+13.9%), CFQ-R (+25.7 points) and sweat chloride (-39.1 mmol/l).

Phase 3 trials with the triple combination (elexacaftor/tezacaftor/ivacaftor) were performed in patients from the age of 12 years on and results were confirmative. After 24 weeks treatment in F508del/MF

heterozygous patients, compared with baseline, ppFEV₁ improved by +14.3%, the rate of pulmonary exacerbations decreased by -63% and CFQ-R improved by +20.2 points. Sweat chloride decreased by -41.8 mmol/l [33]. After 4 weeks of triple therapy in F508del homozygous patients and compared to tezacaftor/ivacaftor, ppFEV₁ increased by 10%, and CFQ-R improved by 17.4 points. Sweat chloride decreased by 45.1 mmol/l [34]. These improvements are very impressive. Such increases in CFQ-R have never been seen before in clinical trials. The fact that heterozygous patients benefit to the same extent as homozygous patients is surprising; it may indicate that close to full correction of the F508del allele has been achieved (meaning that these patients have similar CFTR function to carriers who do not have disease) OR that the maximal possible acute correction of CFTR function has been reached.

The triple combination treatment was tolerated with limited side effects. Apart from the side effects known for the tezacaftor/ivacaftor combination, no new safety concerns were reported.

In October 2019, the FDA approved the elexacaftor/ivacaftor/tezacaftor triple combination (sold as Trikafta) for patients ≥12 years homozygous for F508del or heterozygous for F508del and a MF mutation. EMA approval is expected by the end of 2020.

Around 85-90% of patients with CF could benefit from triple therapy, at least if access to the drug can be guaranteed. Given the enormous efficacy seen in trials, triple combination treatment is expected to significantly change the lives of most patients.

Since FDA approval dates from October 2019, real-life benefit data are not yet available for the triple therapy.

Precautions when using CFTR modulators

Ivacaftor is a substrate for CYP3A4 and CYP2C9. The dose of ivacaftor should be reduced to 150 mg twice weekly when combined with strong inhibitors (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), and to once daily in combination with mild inhibitors (e.g. fluconazole, erythromycin). Ivacaftor should not be prescribed to patients on CYP3A inducers like anti-epileptic drugs (e.g. fenobarbital, carbamazepine, phenytoin), rifampicin or St. John's wort. Ivacaftor increases the bioavailability of warfarin, glimepiride and glipizide by inhibition of CYP2C9 and of digoxin, cyclosporin, everolimus, sirolimus and tacrolimus by inhibition of the efflux pump P-gp (permeability glycoprotein substrate). Patients on ivacaftor should not consume large amounts of grapefruit juice nor Seville oranges. The use of ivacaftor is discouraged in pregnant and breastfeeding women. Because of reported rises in transaminases, it is recommended to evaluate liver enzymes before start of the treatment, every 3 months during the first year of treatment and every year from then on. For patients with a history of transaminase elevations, more frequent monitoring should be considered. If transaminases increase to a level >5 times ULN, or >3 times in combination with bilirubin >2 times ULN, treatment should be interrupted.

Specific dose adjustment regimens are available for young children (see [Table 2](#)). Because of a potential increased risk of cataract, an eye exam is advised in pediatric patients before start and during treatment. The most common side effects are headache, upper respiratory tract infections, abdominal pain, diarrhea, rash, nausea and dizziness.

The above instructions must be followed for monotherapy with ivacaftor as well as for combination therapy with lumacaftor, tezacaftor and elexacaftor.

In contrast with ivacaftor, lumacaftor is a strong inducer of CYP3A. Combination therapy can therefore decrease the therapeutic effect of medications that are substrates of CYP3A, e.g. oral contraceptive drugs. When needed, additional contraceptive measures are therefore advised.

For lumacaftor/ivacaftor combination therapy, the most frequently reported side effects are worsening of liver function, breathing problems, increase in blood pressure and abnormalities in menstruation. Dyspnea usually improved without stopping the treatment. In patients with severe lung disease and $FEV_1 < 40\%$, the dose of lumacaftor/ivacaftor should be restricted to half of the dose.

For elexacaftor/ivacaftor/tezacaftor, the most frequently reported adverse events are rash, headache, abdominal pain, diarrhea and elevation of liver enzymes.

All the currently licensed CFTR modulators above should be consumed with a fat-containing meal. Caution and dose restrictions may be needed in patients with hepatic or renal impairment. For full instructions see drug-specific leaflets.

2.1.5. Other correctors and potentiators

The next-generation Vertex corrector (VX-121) is being trialed in combination with tezacaftor/ivacaftor (NCT03912233). Phase 2 clinical trial results are pending. A deuterated form of ivacaftor, VX-561, that may be more stable and therefore only requires once daily intake, is being tested in a phase 2 study (NCT03911713).

CFTR modulators from pharmaceutical companies other than Vertex are also in clinical development. Galapagos developed the potentiator GLPG-1837. In an open-label phase 2a study in adults with at least one G551D mutation, and after a week of ivacaftor washout, 4 weeks of treatment with GLPG-1837 led to a decrease in mean sweat chloride concentration from 96 to 69 mmol/l and ppFEV₁ returned to the values seen before ivacaftor washout [35]. In the meantime, the Galapagos CFTR modulator program has been continued by Abbvie and compounds were relabeled to ABBV. The first generation corrector ABBV-2222 was tested in two four-week phase 2 placebo-controlled studies. Sweat chloride improved for both populations included in the studies: adults homozygous for F508del (-17.6 mmol/l) and in heterozygotes with one F508del mutation and one gating mutation already treated with ivacaftor (-7.6 mmol/l) [36].

In another study, addition of the second-generation corrector ABBV-2737 to lumacaftor/ivacaftor treatment in F508del homozygous patients resulted in a mean decrease in sweat chloride of -19.6 mmol/l and an increase of ppFEV₁ of +3.4% [37].

Several other pharmaceutical companies such as Flatley Discovery labs, Proteo-

stasis, Novartis have other potentiators and/or correctors in the pipeline.

2.1.6. Amplifier plus lumacaftor/ivacaftor, or third generation corrector plus potentiator

PTI-428 is a first-in-class CFTR amplifier that is thought to improve mRNA stability. It enhances the binding of the nascent CFTR protein to the translocon on the endoplasmic reticulum and therefore increases mRNA translation and protein production. In theory, amplifiers are not only useful for class V mutations, but across genotypes, as more mutant CFTR protein is made available as substrate for other CFTR modulators. In a placebo-controlled, phase 2 study in F508del homozygous adults on lumacaftor/ivacaftor, adding the amplifier PTI-428 resulted in an additional improvement in ppFEV₁ of +5.2% [38]. PTI-428 is currently being evaluated in combination with the corrector PTI-801 and the potentiator PTI-808. Preliminary data show an increase in ppFEV₁ of +8% after 14 days, with good tolerability [39].

Author	Main inclusion criteria	Study type and duration	Number of patients	Sweat chloride mmol/l (95% CI)	
In F508del homozygous patients					
Wainwright <i>et al.</i> 2015 [21]	Lumacaftor 600 mg QD Ivacaftor 250 mg BID	≥12 years FEV ₁ 40-90%	Randomized, DB-PC, Parallel groups 24 weeks	1108	ND
	Lumacaftor 400 mg BID Ivacaftor 250 mg BID				ND
Ratjen <i>et al.</i> 2017 [29]	Lumacaftor 200 mg BID Ivacaftor 250 mg BID	6-11 years FEV ₁ ≥70% LCI ≥75 Weight ≥15 kg	Randomized, DB-PC, Parallel groups 24 weeks	204	-20.8 (-23.4, -18.2)

Table 4: Main results from clinical trials with lumacaftor/ivacaftor

Treatment effect compared to placebo or within group if open-label				
ppFEV ₁ (95% CI)	Pulmonary exacerbations rate ratio (95% CI)	CFQ-R points (95% CI)	Nutritional parameters (95% CI or SEM)	Other (95% CI or SD or SEM)
+3.3% (2.3, 4.3)	0.70 (0.56, 0.87)	+3.1 (0.8, 5.3)	BMI +0.28 (0.15, 0.41)	
+2.8% (1.8, 3.8)	0.61 (0.49, 0.76)	NS	BMI +0.24 (0.11, 0.37)	
+2.4% (0.4, 4.4)	ND	NS	BMI z-score NS	LCI -1.09 (-1.43, -0.75)

Author	Main inclusion criteria	Study type and duration	Number of patients	Sweat chloride mmol/l (95% CI)	
In F508del homozygous patients					
McNamara et al. 2019 [23]	Children weighing <14 kg: Lumacaftor 100 mg BID Ivacaftor 125 mg BID Children weighing ≥ 14 kg Lumacaftor 150 mg BID Ivacaftor 188 mg BID	2-5 years Weight ≥8 kg	Open-label, Single arm 24 weeks	60	-31.7 (-35.7, -27.6)

Table 4 (contd): Main results from clinical trials with lumacaftor/ivacaftor

Treatment effect compared to placebo or within group if open-label				
ppFEV ₁ (95% CI)	Pulmonary exacerbations rate ratio (95% CI)	CFQ-R points (95% CI)	Nutritional parameters (95% CI or SEM)	Other (95% CI or SD or SEM)
ND	ND	NS	BMI z-score +0.29 (0.14, 0.45) Weight z-score +0.26 (0.15, 0.38) Height z-score +0.09 (0.02, 0.15)	LCI NS Fecal elastase-1 +52.6 µg/g (22.5, 82.7) IRT -130.2 ng/mL (-192.3, -68.1) Serum lipase -228.4 U/L (263.0) Serum amylase -54.8 U/L (70)

Abbreviations: BID=twice daily, BMI=body mass index, DB-PC: double-blind placebo-controlled, FEV₁=forced expiratory volume in 1 second, IRT=immune reactive trypsinogen, LCI=lung clearance index, ND=no data reported, NS=no significant difference, QD=once daily, SD=standard deviation, SEM=standard error of the mean, 95% CI=95% confidence interval

Author	Main inclusion criteria	Study type and duration	Number of patients	
In F508del homozygous patients				
Taylor-Cousar <i>et al.</i> 2017 [30]	≥12 years ppFEV ₁ 40-90%	Randomized, DB-PC, Parallel-groups 24 weeks	509	
In patients heterozygous for F508del and a residual function mutation				
Rowe <i>et al.</i> 2017 [10]	≥12 years ppFEV ₁ 40-90%	Randomized, DB-PC, Parallel-groups 8 weeks	246	
In patients F508del homozygous or heterozygous for F508del and a residual function mutation				
Walker <i>et al.</i> 2019 [31]	6-11 years	Open-label, single arm 24 weeks	67	

Table 5: Main results from clinical trials with tezacaftor/ivacaftor

Treatment effect compared to placebo						
Sweat chloride mmol/l (95% CI)	ppFEV ₁ (95% CI)	Pulmonary exacerbations rate ratio (95% CI)	CFQ-R points (95% CI)	Nutritional parameters	Other	
-10.1 (-11.48, -8.8)	+4.0% (3.1, 4.8)	0.65 (0.48, 0.88)	+5.1 (3.2, 7.0)	BMI z-score NS	ND	
-9.5 (-11.7, -7.3)	+6.8% (5.7, 7.8)	NS	+11.1 (8.7, 13.6)	BMI NS	Fecal elastase-1 NS IRT NS	
-14.5 (-17.4, -11.6)	+0.9% (-0.6, 2.3)	ND (trial was open label)	+3.4 (1.4, 5.5)	BMI z-score NS		

Abbreviations: BID=twice daily, BMI=body mass index, DB-PC: double-blind placebo-controlled, FEV₁=forced expiratory volume in 1 second, IRT=immune reactive trypsinogen, LCI=lung clearance index, ND=no data reported, NS=no significant difference, QD=once-daily, SD=standard deviation, SEM=standard error of the mean, 95% CI=95% confidence interval

2.1.7. CFTR stabilizers

Class VI mutations can be targeted by CFTR stabilizers. These compounds improve anchoring of the mutant protein in the plasma membrane, increasing half-life. Again, this is a potentially mutation-independent strategy, and can be used in combination with other CFTR modulators. For example, rF508del has a reduced plasma membrane half-life. Cavosonstat (N91115) was a first-in-class stabilizer that showed potential *in vitro* but failed to improve FEV₁ in the subsequent phase 2 trial. Therefore, its development was discontinued [40].

2.1.8. Read-through agents

Stop or nonsense mutations prematurely halt translation of *CFTR* mRNA into protein, due to the presence of a preterm stop codon. Small molecules can “over-read” and skip this stop codon by including a random or near-cognate amino acid at the stop codon position during ribosomal translation.

Aminoglycosides were shown to have read-through capacity, but were not developed due to known toxicity. High throughput screening identified ataluren as a compound with read-through capacity, and a better toxicity profile. This was the first attempt to modify *CFTR* expression. When ataluren was evaluated in a phase 3 trial in patients with at least one stop codon mutation, it did not meet the primary outcome of FEV₁ improvement. Post hoc analysis showed that FEV₁ improved in the subset of patients not taking aminoglycosides [41], but a subsequent phase 3 trial could not confirm these results [42] and the development of ataluren for CF was

stopped. Ataluren however has received EMA conditional approval for the subgroup of boys with Duchenne muscular dystrophy and a stop codon mutation.

There is a new pipeline for patients with CF and a stop codon (class I) mutation. ELX-02 is an optimized glycoside with read-through capacity. Data from *in vitro* and phase 1 randomized, double-blind placebo-controlled, single-ascending-dose studies showed low toxicity of a single subcutaneous or intravenous administration [43]. A phase 2 clinical trial (NCT04135495) in CF patients with at least one G542X mutation started in November 2019; trial completion and results are pending.

2.2. Other strategies to improve CFTR function

Although CFTR modulators are bringing major benefits for patients with CF today, it still makes sense to develop other strategies that may improve CFTR function in the future. CFTR modulators need to be taken lifelong. Some patients may not tolerate modulators and longer term toxicity may surface. Lifelong treatment is a burden for the patient and the cost is very high. Therefore, strategies that aim at full or lifelong correction are especially appealing. Some of these alternative strategies have already entered the clinical phase of drug development, but most are still in the preclinical pipeline.

2.2.1. Preventing mRNA decay

Inhibition of nonsense-mediated mRNA decay (NMD) is a possible target to increase the amount of available mRNA for translation [44].

2.2.2. Antisense oligonucleotides

Antisense oligonucleotides (ASOs) aim to bind a small stretch of correct mRNA (20 to 30 RNA bases) to the transcribed *CFTR* mRNA at the locus of a point mutation or a splice site. This strategy has been successful in a few diseases, including spinal muscular atrophy, where a survival motor neuron (SMN) oligonucleotide is applied systemically to improve motor function. Eluforsen is a 33-nucleotide (or “mer”) ASO including the 3 missing bases in F508del mRNA. In patients with CF, inhalation of eluforsen improved CFTR function as measured by nasal potential difference [45]. In principle, an ASO can target any individual *CFTR* mutation, for example to block aberrant splice sites or to inhibit micro (mi)RNAs that inhibit *CFTR* transcription.

2.2.3. Gene therapy

Since the discovery of the *CFTR* gene 30 years ago, it has been a goal to introduce normal copies of *CFTR* by gene therapy. The greatest advantage is that gene therapy is mutation agnostic and thus applicable in all patients. There are, however, multiple hurdles, such as developing a suitable vector construct that passes all the natural barriers of the airways and then transfects the correct gene into the nucleus. Some viral vectors (e.g. adenovirus, lentivirus, adeno associated virus) are efficient, but too virulent. In addition, they lose efficacy because the patient produces antibodies targeting the viral vector. As the airway epithelium renews constantly, gene therapy must be repeated at regular intervals, unless airway stem cells can be modified.

A phase 2b clinical trial of 12 months duration with inhaled gene therapy using a liposomal vector showed stabilization of FEV₁, compared to decline in the placebo group [46]. At present the UK Gene Therapy Consortium is preparing to enter clinical trials of *CFTR* gene therapy using a lentiviral vector (rSIV.F/HN) pseudotyped with the F and HN proteins from Sendai virus.

2.2.4. Gene editing

Instead of inserting a correct whole gene or mini gene, an approach could be to “restore” the abnormal gene *in situ*. For example, the CRISPR/Cas9 technology can recognize and “cut” the aberrant *CFTR* DNA sequence and “paste” in the correct sequence. *In vitro* studies with this technique (e.g. in rectal organoids) are very promising [47]. Again, major challenges must be addressed for *in vivo* use, such as determining the optimal vector to deliver the CRISPR/Cas9 system to the nucleus, the specificity of the cutting and pasting, possible influence on nearby genes, and the potential toxicity.

2.2.5. Normal mRNA addition

The nucleus is a major barrier to the introduction of foreign DNA. Therefore, inserting wild type *CFTR* mRNA in the cytoplasm is a reasonable alternative. MRT5005 is a first-in-class mRNA inhaled therapy. Interim results of inhaled MRT5005 in single ascending doses in adults with CF report good tolerability and suggest impact on lung function (NCT03375047). Addition of mRNA via inhalation will however be subject to many of the challenges associated with gene therapy: suitable vectors

must be available, the immune response must be bypassed and upregulation of *CFTR* in non-target cells must be avoided.

2.2.6. Transfer ribonucleic RNA addition

Another approach for correcting nonsense mutations in *CFTR* is to insert tRNA into cells which adds an amino acid at the site of a nonsense codon. This “recodes” the protein produced by translation. Again, correct delivery at the site of action is a main hurdle [48].

3 Where are we with precision medicine for patients with CF?

The concept of precision medicine is not new. Clinicians have been working to “personalize” and tailor healthcare to individual health needs throughout the history of medicine. However until now, it has not been possible to predict how each of our bodies will respond to specific interventions, or identify whom among us is at risk of developing an illness.

We are all unique. Our health is determined by our inherent differences combined with our lifestyles and environment. Precision medicine is an emerging approach for disease treatment and prevention that considers this individual variability in genes, environment, and even the lifestyle of each person. The terms precision medicine, personalized medicine and theranostics are often used interchangeably. But they all refer to a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual

patient based on their predicted response or risk of disease. It is thus a move away from the “one size fits all” approach to one which combines and analyses information about our genome, with other clinical and diagnostic information, to identify patterns that can help to determine our individual risk of developing disease and determine the most effective interventions to help improve our health. This has the potential to tailor therapy with the best response and highest safety margin to ensure better patient care. In the US especially, stakeholders are starting to prefer the term “precision medicine” instead of “personalized medicine” to describe the use of data and genomics to tailor treatments to specific groups. The National Research Council (NRC) has expressed concern that “personalized medicine” may be misconstrued to mean that completely individualized treatments are available for every unique patient, which is not the case.

CFTR modulator therapy can be seen as mutation class-specific (such as ivacaftor for people with a class III mutation) or as mutation-specific (as seen for people homozygous or heterozygous for F508del). This grouping according to a molecular marker such as genotype is a step towards precision medicine, but we can go further than that. As is obvious from waterfall plots in clinical trials of ivacaftor in people with G551D and double combination treatment in people homozygous for F508del, there are large differences in the benefit that individual people experience for both sweat chloride and FEV₁. Similarly, when correction of CFTR function by modulators is tested *in vitro* in patients’ own tissue (organoids,

nasal cells), we see large differences in CFTR rescue between people with exactly the same mutation. *In vitro* testing of intestinal organoids, in particular, has been shown to predict *in vivo* response [49]. In the future, when several treatment options will become available for patients with one particular mutation or mutation class, these *in vitro* predictors will help pinpoint the best treatment for the individual patient, bringing us a step closer to precision. The optimal treatment benefit depends on many factors such as modifier genes, variability in pharmacodynamics, interactions with other drugs and the environment. Testing CFTR function in the patients' own tissue will take into account many of these issues and will certainly outperform testing in heterologous cell types such as Fisher rat thyroid cells.

We can probably already speak of precision medicine in our approach to patients with rare and ultra-rare mutations. Indeed, these patients (unless they have one of the 28 RF mutations known to respond to a modulator or unless they have F508del on the second allele) are not currently benefiting from any modulator therapy and are not targeted by drug development programs. For most of these mutations, the functional effect on the CFTR channel is even not known. When current modulator drugs are tested directly in the tissue of people with ultra-rare mutations, candidates for drug treatment can be identified. CFTR function, and its rescue by modulators, can be evaluated in intestinal organoids by the forskolin induced swelling (FIS) assay. If CFTR is not functional, the organoids do not swell. If CFTR function is rescued, then swelling occurs and can be

quantified. This approach has led to drug reimbursement for patients with rare mutations. The Horizon 2020 HIT-CF project is further validating this approach (www.hitcf.org). Organoids are being collected across Europe from 500 patients with rare mutations and exposed to varying CFTR modulators. Patients with the highest *in vitro* response will enter a clinical trial to study the *in vivo* benefit. Apart from bringing effective treatments to some of these patients, this will allow larger scale correlations between *in vitro* and *in vivo* efficacy.

4 Conclusion

Thanks to symptomatic treatment, the life expectancy of people with CF has improved steadily over several decades. The combination of strict follow-up and intensive symptomatic treatment led to a median life expectancy of around 50 years. But heavy treatment burden and severe morbidity often results in low quality of life.

With CFTR modulator drugs that treat the underlying defect, we have entered a new era. Highly effective CFTR modulators will be available for up to 90% of patients. When CFTR function is majorly improved, the disease is transformed. This benefit is experienced within a few days with large and sustained increases in lung function, decreases in pulmonary exacerbations, improvement in nutritional status and major improvement in the quality of life. Even more exciting is the building evidence that complications like pancreatic insufficiency and CFRD can be prevented, reverted or

improved. This is despite the fact that we do not even know the full potential of highly effective CFTR modulators e.g. when they are introduced at an early age. Is prevention of male infertility possible? It is imaginable that future children with CF will be treated only with CFTR modulators, from a young age.

When patients and families have the opportunity to experience the major health benefits from CFTR modulators they are astonished and become hopeful for the future. Likewise, physicians and paramedical teams are excited that highly effective therapies have finally arrived and are anxious to prescribe these effective treatments as soon as possible to as many patients as possible. But the anticipated high treatment costs, along with the lifelong need for modulators are a challenge. How quickly will the triple modulator combination reach the 90% of eligible patients?

Introduction of these new drugs will also bring new challenges. We need to monitor the safety of long-term treatment. How can we continue the entire drug development pipeline? Whilst it is relatively easy to document the benefit from highly effective first-in-class modulators, it will be difficult to evaluate new modulators. How to prove that they are as good as or better than these highly effective compounds? What will be the best comparator: placebo (is this ethically correct?) or the best in class drug (how will this cost be overcome, but by an open-label comparison group)? Will patients still be willing to participate in clinical trials? How should we continue the non-modulator drug pipeline e.g. anti-inflammatory and anti-infective drugs? How

should we progress the alternative strategies for CFTR correction that might lead to a one-off correction? We badly need clinical trials of how to simplify the treatment burden.

But the bottom line is that CFTR modulators have brought enormous progress and hope to the CF community. Only a few decades ago, children were dying from CF in their mid-teens. Put in that context, our new challenges can be seen as 'luxury problems' and will surely be overcome.

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CHAPTER 12

Optimizing pharmaceutical treatment in cystic fibrosis

Authors

Grainne Crealy, Ciaran O'Neill

1 Introduction

Cystic fibrosis (CF) is a heritable chronic condition with a prevalence of 7.97 to 7.37 per 100,000 in the USA and countries of the European Union (EU) respectively [1]. The average life expectancy in the developed world is the mid-40s or above [2], but half that in Brazil and even less in El Salvador, India, the Middle East, and non-EU countries [2]. Sharp economic-related disparities are also evident for other outcomes including growth and nutrition, lung function and quality of life [3]. Moreover, inequality in CF care and outcomes is evident both between and within countries, typically as a reflection of existing social inequities [4-9]. While these inequalities have narrowed in developed countries, stark differences remain between developed and less developed countries.

CF comprises several distinct classes of genetic mutations, some of which can be treated with specific therapies. Therefore, management can vary, as can prognosis between patient groups differentiated by

disease type. Life expectancy has increased for many patients thanks to the advent of newborn screening, and developments in clinical care such as antibiotics, bronchodilators, steroids, lung transplantation, pancreatic enzyme replacement therapy, dietetics and of novel therapeutics that modulate CFTR protein. As life expectancy has increased though, so too has the need to treat the complications of CF including CF-related diabetes (CFRD), metabolic bone disease, gastrointestinal malignancy, and comorbidities including mental health conditions related to CF (depression and anxiety). Specific expertise has been developed to provide clinical care for patients with these complications [10]. CF complications increase the treatment cost and broader economic impact associated with the condition.

2 Costs

Studies in the US have shown that between 2003 and 2013, the number of hospital discharges with CF as a primary diagnosis rose from 8,328 to 12,590 [11]. Over the same period, mean hospital charges (adjusted for inflation) associated with

an inpatient episode rose from \$60,051 to \$94,644, an increase of almost 58%, even though the length of stay increased by only 0.2 days from 10.1 to 10.3 days. The same research showed the aggregate cost of inpatient stays increased by over 138% from just over \$500 millions \$1.2 billion in real terms. Inpatient mortality fell from 1.44% to 0.71%. The increases in cost were attributed to an increase in life expectancy among CF patients, which in turn was attributed to the wider use of a range of therapies, whose earlier introduction was made possible by newborn screening. Increased life expectancy has led to increased disease prevalence, and as noted, contributes to a significant increase in mean costs. From 2013, the emergence of the CFTR modulator therapies ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi), which address the underlying cause of CF in certain mutations by improving transcellular chloride transport, will have enhanced further outcomes and contributed to costs, though data on the impact is not currently available.

An examination of inpatient costs alone would give a misleading impression of “typical” CF health care costs because only a proportion of CF patients will be hospitalized. Bottom-up analyses using a prevalence-based approach of the impact of CF have been performed in a variety of countries outside the US. While some of these studies have used patients recruited through clinical trials and may therefore be subject to selection bias [12], others have used population based surveys to examine health-related quality of life (HR-QoL). The European BURQOL-RD study [13], for

example, examined child and adult costs from a societal perspective across eight European countries: Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the United Kingdom (UK). This study provides valuable insight into areas not typically examined in other studies, such as productivity losses related to absences from work or early retirement, and the costs of informal care in addition to direct medical care costs. The study found considerable variation in mean total costs between countries reflecting in part differences in GDP across disparate settings. For example, the mean total annual costs per individual with CF were €22,295 in Bulgaria and €21,144 in Hungary, costs were notably higher in other countries such as Germany (€53,256) and the UK (€48,603). Differences were evident between adults and children. The mean average total costs in Germany, France and the UK were €47,217, €36,752 and €44,583, respectively for adults and €60,412, €24,116 and €52,624, respectively for children, with different levels and patterns being apparent. Drug and hospitalization costs were typically the largest contributors to health care costs – in Germany and the UK comprising 76% and 66% of direct health care costs and 41% and 28% of total costs respectively for adults and children combined.

3 Reduced quality of life

With respect to HRQoL, the European BURQOL-RD study [13] again provides useful insights into the experiences of a

population based sample drawn from a variety of European countries. In addition to examining the quality of life among individuals with CF, they also examined that of carers using the commonly used generic instrument the EQ5D (that measures health preferences on a scale from 0 representing dead to 1 representing perfect health). In the seven countries examined (omitting Sweden due a low number of observations), the mean utility index ranged from 0.64 to 0.87 for adults with CF, from 0.65 to 0.92 for carers of children and 0.64 to 0.87 for carers of adults. They found that utility decreased with patient's age and level of dependency. Among carers, HRQoL fell as the dependency of the person they cared for increased (measured using the Barthel index). By way of comparison, the mean HRQoL across general populations of adults in 19 countries measured using the EQ5L ranged from 0.742 to 0.911 [14]. Where data are available, the mean utility index for adults with CF versus adults from the general population were: 0.783 versus 0.902 in Germany, 0.87 versus 0.915 in Spain, and 0.64 versus 0.856 in the UK. These decreases in utility clearly show the impact of the disease – especially so considering that adults with CF population are, on average, younger than the general population.

4 Scarcity, access and pricing

Health care budgets are finite, while the alternative uses for funds are essentially infinite. This gives rise to the problem of

scarcity and requires hard decisions about how to best use limited resources. As populations in most developed countries age, new and expensive technologies emerge, expectations increase regarding what constitutes a reasonable level of care and the burden of non-communicable diseases related to lifestyle choices continue to surge. Even in high-income countries this combination of pressures has caused many to question the sustainability of current arrangements for healthcare funding [15]. In all developed economies – even market-oriented health care systems such as those in the USA – the bulk of health care expenditure derives from government. Given the difficult choices around which technologies should be adopted, which needs should be met and by inference which needs should go unmet, *health technology assessment* (HTA) has been developed to help guide decision making. In essence, HTA assesses and compares alternative uses of resources in terms of costs and outcomes to establish which utilization offers the greater value for money. Outcomes are typically expressed as quality-adjusted life years (QALYs), a measure which expresses gains in years of life weighted by preferences for the quality of those life years. Costs are typically confined to those of the relevant payer for health care, most often government. Costs include direct health care costs (such as the acquisition costs of a novel therapy to slow progression of a disease) and indirect health care costs (such as the savings that might arise from avoiding disease comorbidities such as anxiety or depression). Incremental costs (the additional cost from

one alternative relative to the other) are related to incremental outcomes (the additional QALYs gained from one alternative relative to the other) in an incremental cost effectiveness ratio (ICER). If the additional cost per QALY gain is below a threshold defined to delineate “good value” from less good value for the payer concerned, the intervention is considered to have met an efficiency criterion and warrant consideration for reimbursement. Further steps are typically involved before reimbursement guidance is offered. Notably, a budget impact assessment may be required to ascertain affordability, that is, the impact a funding decision may have on health care budgets (the affordability criterion).

HTA methodology has been developed and popularized by bodies such as the National Institute for Health and Clinical Excellence (NICE) in the UK and is widely used throughout the EU. To allow for the possibility that factors other than efficiency (and affordability) may warrant consideration as part of the assessment process, a range of thresholds may be used depending on the circumstances. In practice, a range of thresholds operate within the UK, even though NICE have typically used a threshold of £20,000 to £30,000 per QALY to distinguish “good value” uses from less good value uses and others have argued for an even lower value (£13,000) [16]. Much higher thresholds have been applied, for example, for “very rare” diseases (£300,000 per QALY), for end of life care under particular circumstances (£50,000 per QALY) and for specific disease groups (notably cancer) where a separate funding stream effectively gave rise to a distinct

threshold [17]. This variation in thresholds may arise from concerns about using a single threshold for all diseases in all circumstances. Such a single threshold can be considered too stark by policymakers and the public, influenced by considerations related to the “rule of rescue” [18] or “exceptionalism” [19].

The potential for a more strategic view on the potential implications of decisions on future investments by pharmaceutical companies in R&D must also be considered.

Denying reimbursement of clinically effective therapies principally affects patients and their families, but also signals the potential profitability of investment in specific areas of medicine.

Pharmaceutical companies are for-profit organizations whose business model requires at least a reasonable return on investment. The total research and development (R&D) spend of pharmaceutical and biotechnology companies in 2015 was reported at \$141 billion, making the pharmaceutical industry the top R&D investor in the world [20]. With an estimated average success rate of 4.9% from first toxicity dose to market approval [21], investment decisions must keep in mind the high rate of failure while assessing at what price and for how long a drug can be sold to how many persons in order to cover research costs.

In this respect, pharmaceutical treatments for CF provide specific examples of a much wider issue in health care. Ivacaftor, for example, has been shown to be effective for a sub-set of CF patients with a specific gene mutation and the cost-effective-

ness has been estimated in the UK to be between £335,000 to £1.274 million per QALY [22]. There is not a specific prevalence rate that defines a “very rare” condition (though 1 in 100,000 has been used in the UK [23]). Even under the higher thresholds for such very rare conditions detailed above, ivacaftor would not have met the efficiency criteria of £300,000 per QALY used by NICE. Nevertheless, ivacaftor was approved for reimbursement in England (December 2012), Scotland (January 2013), Northern Ireland (March 2013), and Wales (May 2013) [22] albeit under agreements that saw the price paid for the drug remain confidential. Had this not been the case, suitable UK patients would have been denied access to this medication. Similar arguments were rehearsed for other CF treatments from the same manufacturer (Vertex Pharmaceuticals), and in other jurisdictions where ivacaftor has been approved for reimbursement including Ireland where researchers have noted wider use of the drug than originally anticipated [24]. In the UK, tezacaftor/ivacaftor (Symkevi) and lumacaftor/ivacaftor were both approved for reimbursement following protracted negotiations around price between the NHS and Vertex in England, Scotland and Northern Ireland (October 2019), and in Wales (November 2019). As with ivacaftor, lumacaftor/ivacaftor was approved for reimbursement despite a previous negative recommendation based on an initial price of £104,000 per patient; tezacaftor/ivacaftor was approved for reimbursement in the absence of a positive recommendation. As with ivacaftor the price negotiated with the

NHS remains subject to a confidentiality agreement between the manufacturer and the NHS.

The increasing personalized nature of therapy offers effective treatment where formerly none existed. This has challenged healthcare systems and manufacturers to create a space in which a sufficiently mutually beneficial trade can exist (while being mindful of uncertainties that exist for both parties). Mutually beneficial confidentiality agreements may help the purchaser blunt criticism for breaching commonly accepted ICER thresholds and may allow the manufacturer to exploit its monopoly position more forcefully with other purchasers. Whether society in general benefits from such an arrangement is open to question [2].

HTA methodology has offered access to new medicines for CF by informing reimbursement decisions and/or price negotiations. Other strategies have been used in similar situations for other disease areas. Similarly to some CF treatments, direct-acting anti-viral treatment of Hepatitis C virus (HCV) offers an effective treatment for distinct genotypes, but expense has deterred adoption of the medicine in some settings [25]. The so-called “Netflix model” [26] attempts to decouple R&D costs from production costs when determining the agreed price for a medicine. Rather than recouping R&D costs in the price paid per prescription, a flat fee is paid for unlimited access over a particular time period. This approach has been adopted in Australia [27] and in the summer 2019 in the states of Louisiana and Washington in the USA. It is estimated that this model could save

the Australian government \$4.92 billion over the contract lifetime compared to the traditional “per pack pricing” while securing access to care for patients [27], although these are estimates as the actual terms of the contract remain confidential.

The Netflix model will not be appropriate in all situations but may achieve superior access at lower cost under certain conditions [28]. The conditions are that all suitable patients should be identifiable, there should be clear consensus on which medicine(s) are included in the contract, cost should currently be a factor limiting access to the medicine, and budget surety should be valued by both the purchaser and manufacturer. CFTR modulator therapies meet many of these conditions, i.e. patients are identifiable via the CF patient registries, there are no other effective treatments, and cost is a barrier with new treatments potentially consuming a significant share of new drug budgets. It is difficult to imagine a situation in which budget surety is not highly valued by all parties. Other conditions that may contribute to adoption of a Netflix model include the possibility for the purchaser to spread other fixed costs over a larger number of patients, related to health promotion for example, or specialist clinics. This model could offer substantial benefits in certain circumstances even though the “very rare” nature of some CF genotypes may prevent attaining some of the advantages of the Netflix model, for example in spreading fixed costs of other initiatives more widely.

Risk sharing agreements (also known as managed entry schemes) offer another avenue to access CF therapies. This was

indeed considered in discussions around access to ivacaftor in Ireland [29] although pricing negotiations are ultimately believed to have delivered agreement. One approach to risk sharing agreements is to pay only where there is evidence of the drug having worked. From the purchasers’ perspective this both reduces financial exposure and demonstrates value to the tax payer. From the pharmaceutical companies’ perspective, this achieves market access which would otherwise have been impossible. Examples of outcome-based risk sharing agreements include ticagrelor for acute coronary syndrome, sacubitril for chronic heart failure, dulaglutide for type II diabetes and evolocumab for hyperlipidemia, oxalipatin in the treatment of colorectal cancer as well as indicators of outcome such as use of other healthcare in the case of interferon beta 1a for multiple sclerosis [30]. Given the significant uncertainty around ICER estimates for CF therapies such as ivacaftor, such outcome-based risk sharing arrangements may have advantages over the delinkage approach for the purchaser. For publicly funded health care systems, as in the UK, such arrangements have the added benefit of being able to assess the real world cost effectiveness of therapies through routine administrative data captured by the health care system. This could afford purchasers (and pharmaceutical benefit managers in private insurance-based systems) the opportunity to examine actual savings against those suggested in clinical trials where trial exclusion criteria may affect the validity of generalisations to real world situations.

5 Externalities and competition

A further, perhaps under-investigated, route to access lies in competition and the disruptive role that concerned parents can play in stimulating this. In the UK the debate and protracted negotiations around the price at which access to CFTR modulator therapies could be achieved involved two principal parties – Vertex as the monopoly seller of CFTR modulator therapies and NHS England. As the sole purchaser (monopsony), monopoly power supposedly allowed the NHS to exercise a countervailing force and extract a lower price than would otherwise prevail. However, in the UK, frustration with the pace of negotiation prompted some parents to explore alternate access routes. As reported in a leading UK newspaper the Guardian in June 2019 [31] these parents sourced a generic alternative to Orkambi (lumacaftor/ivacaftor, the CFTR therapy being negotiated at that time) manufactured in Argentina by Gador. Vertex does not hold a patent monopoly in Argentina and the drug could therefore be legally imported into the UK.

According to the report, parents were able to obtain the drug (called lucaftor), at approximately £20,000 for a year's supply, representing a 70-80% discount to the list price charged by Vertex. While still beyond the reach of most parents individually to fund this, "crowdfunding" or other charitable supports put the drug within the reach of many more families. What is interesting from the economics perspective here is the disruptive role of parents in reintroducing competition to the market. Other avenues

available to the government to exert pressure on Vertex were clearly unpalatable, such as recourse to a legal provision called "crown use" under the 1977 Patents Act, which could allow the state to override Vertex's patent in the national interest. This method was used in the 1960s to obtain access to a generic version of tetracycline and has been threatened more recently (but not used) in disputes over hepatitis C diagnostic tests and machines for treating kidney stones. Government reluctance is perhaps understandable given the potential for immediate political fallout, for example retaliation from the country where the patent holder resides (the USA for Vertex). Longer-term consequences such as the potential impact on the discovery pipeline may also have tempered government response. Current list prices and their embedded signals to encourage investors may have longer-term benefits to future generations of people with CF, but are less beneficial to the parents of a child whose condition is visibly deteriorating today. In this regard, access to pharmaceutical treatment for CF relates not just to competition but to externalities, specifically the uncompensated effects that the actions of parents today might have on other users of pharmaceutical therapies, including those of future generations. Governments and manufacturers should be conscious of these factors, given that they can subvert negotiations and give rise to unforeseeable consequences in the longer term.

6 Path dependency, the Sisyphus Syndrome

Path dependency refers to the idea that our current choices are in large part framed by the decisions we made in the past. By extension it implies that the choices we make today will in some measure help define or limit those that are made in the future. With reference to CF, the extended life expectancy made possible by new therapies such as CFTR modulators helps create a population of older CF patients that would not otherwise have arisen. The existence of this group creates new needs and opportunities for advocacy to meet those needs that would not have otherwise existed. These voices can help determine future budget allocations both in health care and in R&D. As noted, the total healthcare budget for CF is a function of the mean cost and disease prevalence. The development and adoption of new therapies into care gives rise to additional consumption and creates conditions conducive to ongoing investment in R&D in CF. Thus, akin to the mythical Greek character Sisyphus, the success helps create the conditions for ongoing endeavor. In health economics, Zweifel and Ferrari [32] used this concept in 1992 to explain the allocation of health care resources toward older people in publicly funded health care systems. While few compared to the general elderly population, CF patients can nevertheless exert a disproportionate influence on public attitudes and funding decisions through effective advocacy. This is not a problem if the result reflects the best use of society's resources. If it does not represent the best

use of funds, this disproportionate influence will challenge funders who face many competing demands for resources.

7 Quo Vadis?

As argued above, new therapies and the ability to identify suitable candidates for them have transformed the care and prospects of people with CF. Modulator therapies are a potent example of this. However, the costing strategy employed by Vertex in this instance has thrown into sharp focus questions regarding the affordability of personalized medicines, the methods used by reimbursement bodies to assess "value," and how to achieve a socially optimal rate of medical innovation.

Evaluating personalized healthcare presents a challenge for the current HTA framework. In a 2017 paper, Garrison and Towse argue that the current QALY approach does not adequately capture the "value" provided by precision medicines in reducing uncertainty, such as "value of knowing, value of hope and of value created by scientific spillover" [33]. This position was reinforced by the ISPOR Precision Medicine Special Interest Group (2018) which made recommendations regarding a wider value framework for evaluating precision medicines.

As well as requiring more evolved reimbursement models, Garrison and Towse argued that pricing models must evolve to cope with developments in physiology-based and preference-based personalised precision healthcare [33]. They

concluded that to sustain such a healthcare market, competing innovators and technology adopters must have incentives to promote long-term dynamic efficiency, and argued that to achieve a socially optimal rate of medical innovation in personalized-medicine, payers must send clear signals to suppliers regarding what they value.

This interplay between suppliers and buyers of precision medicines presents a complex marketplace, made more complex to navigate by the availability of additional new medicines. The social media backlash regarding refusal of some reimbursement bodies to pay for ivacaftor was directed at government and not the pricing decisions made by the manufacturing pharmaceutical company. Furthermore, coordinated lobbying campaigns have yielded success in many jurisdictions despite concerns over the long-term affordability of personalized-medicine for healthcare systems. Given the increasing R&D spend on precision medicines and the potential for patient benefit, it is inevitable that new HTA methodologies and reimbursement systems will emerge. Current research effort is being directed at adaptive clinical trial design, innovative decision modelling approaches, development of valuation methodologies and real-time clinical data capture.

health care systems faced with multiple competing demands on limited resources. The challenges presented by modulator therapy are replicated in other disease areas where personalized medicine also presents novel effective therapies. These challenges are helping to change how reimbursement decisions are made regarding pharmacological therapies for CF, and beyond. Patients and their advocates, drug companies, policy makers, pharmaceutical benefit managers, investors, charities and researchers will continue to adapt and shape this changing landscape in ways that, at present, are not wholly predictable. Based on observed reimbursement decisions, it is clear that current approaches to cost effectiveness have provided answers that do not reflect societies' preferences, suggesting that reimbursement approaches need to adapt. Similarly, beyond pharmacological therapies, decision models that assess outcomes in terms of longevity and quality of life will strain to capture outcomes related to screening tests that might inform choices around pregnancy or carrying a pregnancy to term. These are complex issues that go beyond the discourse of any one discipline; questions that will challenge societies for some time to come.

8 Conclusions

The CF landscape is changing. The emergence of new pharmacological therapies will improve outcomes and improve life expectancy but will also challenge

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CHAPTER 13

Improving self-management and adherence through interactions between the multidisciplinary team, the patient, and their families

Authors

Alistair Duff, Trudy Havermans, Beth Smith

Introduction

Simplifying treatment has been identified as *the* top research priority by the international CF community [1]. It is hoped that modulator therapies will help achieve this goal, but in the medium-term, the burden of care will not dramatically reduce and treatment is likely to remain time-consuming and demanding. A large, 2019 survey of CF patients and/or their carers, most of whom were from the UK/Europe, found that patients took a median of 10 treatments which took an average of 2 hours daily [2]. Adults with CF feel they are “working to stay alive,” while simultaneously attempting to shield their families from upset [3]. Parents of children and young people (CYP) with CF report constant prioritizing, often having to choose between their children’s treatment and participation in daily activities [4].

Poor treatment adherence is linked to early deterioration and high healthcare costs,

and may lead to patients feeling guilty or inadequate, or to symptoms of depression and anxiety. Adherence thus remains a key challenge for patients and teams. In simple terms, drugs do not help people who do not take them. This is a key concern given the potential for modulator therapies to significantly reduce morbidity. Early reports suggest less than optimal adherence, even for these drugs [5, 6]. Optimizing pharmaceutical care in CF in the future will therefore require a new approach from teams. This chapter is written for all members of the multidisciplinary team (MDT), and focuses on changes each member can make in the team rather than on their individual practice with patients. The chapter is organized into three parts: (i) the characterization of adherence, (ii) effective interventions, and (iii) finding and implementing solutions in day-to-day clinics.

1 The context of adherence

This section describes difficulties in assessing adherence, both academically and clinically, and is followed by a summary of the everyday context of living with CF and the main consequences of non-adherence to CF treatment.

1.1. Measuring adherence

Accurate assessment of adherence is challenging [7]; more than three quarters of pharmacists consider adherence monitoring in their own centers to be inadequate [8]. Studies often compare the administration of treatments which differ considerably (e.g. oral medication is entirely different to following physiotherapy guidelines or taking inhaled therapies). The recruitment of participants is often not clearly described (e.g. drop-outs not reported). Many studies exclude severely ill patients while others examine between- and within-group differences, including under- and over-adherent patients in the same sample. Few studies clearly define adherence, or describe the data collection procedure (e.g. providing little information on the validity and reliability of measures used). Reported rates of adherence also vary depending on the measurement modality used (e.g. self-reporting, electronic devices, diaries, proxy reports). Best practice recommendations attempt to counter-balance these limitations by endorsing multiple methods of data collection, but this does not fully mitigate the problems, hindering accurate measurement. Furthermore, the results of international, multi-center studies are

often difficult to interpret due to differences between healthcare systems, for example, differences in the costs of medicines and reimbursement systems may influence adherence. **Table 1** lists key issues affecting the assessment of adherence.

1.2. Adherence in the context of living with CF

Factors that contribute to sub-optimal adherence are rooted in the context of patients' lives. Previous ECFS books have detailed the lived-experience and context of CF during infancy, childhood, adolescence and adulthood. Living with CF means that patients have to incorporate health-related behaviors (e.g. daily treatments, avoiding smoking, attending outpatient clinics) into the context of normal developmental tasks (e.g. going to school, forming relationships, building family life). In other words, while developing emotionally, cognitively, socially, and physically, people with CF also have to become experts in health-related self-management behaviors, including adherence. This context is important when considering non-adherence issues in day-to-day life. During each developmental stage specific factors influence patients' adherence behaviors, which fluctuate from phase to phase. In infancy and childhood, parents are entirely responsible for the level of treatment adherence. This stage is followed by a transition of responsibilities, which typically occurs between mid-adolescence and young adulthood. Adolescence has traditionally been considered a period during which adherence to prescribed treatment plans decreases. However, one study found that patients in the 18–25 and 26–35 year ranges had the lowest medical posses-

sion ratio (MPR), indicating worse adherence [9]. Even then possessing medicines is not the same as actually taking them. Adults with CF face specific challenges in balancing adult life and responsibilities with optimal management. During end-stage CF, management of adherence can once again be “shared” with partners or parents, since morbidity hinders self-management.

1.3. Factors associated with non-adherence

Variables associated with adherence have been generally well described, both in clinical and in research settings (see **Table 1**, columns 3-4). These include:

- Demographic factors (i.e. sex, age): adherence and age have a statistically “concave” relationship, with highest adherence observed in the youngest and oldest age groups.
- Systemic and social factors, such as family/partner support: more support is correlated with better adherence.
- Treatment-related factors, such as complexity, taste, or time: time-consuming therapies such as physiotherapy are associated with poorer adherence.
- Individual factors, such as coping, mental health, knowledge and understanding of CF and treatment, perception of barriers, attitudes and beliefs about treatment. Key barriers include a lack of time and treatment complexity. Key attitudes that affect adherence include beliefs such as “medication is useless”, “it is not normal to take so much medication”, “it is boring” [10].

Specific gaps in knowledge have also been identified. An example is adherence to hypertonic saline, but not other medicines, was associated with disease knowledge among adolescents [11], while in a population of adults with CF partial adherence was specifically related to a lack of understanding of treatment recommendations [12].

1.4. Consequences

In clinic, patients must weigh up the necessity of treatment against the benefits of engaging in normal activities (e.g. having to choose between spending an hour on physiotherapy and inhalation therapy or joining friends going to the cinema). Most patients try to live a normal life while simultaneously managing their CF, but this does not always work out, sometimes with major consequences and costs [13] (see **Table 1**, column 5). These consequences include symptom misinterpretation (miscommunication with MDT), unnecessary symptoms (pain, exacerbations), increased morbidity (physical and mental), increased mortality, and wasting of money and time (health insurance, school/work absence). The real challenge is to determine what can be done to facilitate better adherence.

Problems with adherence		
Assessment	Incidence of non-adherence	Correlates with non-adherence
<p>Multiple methods (sources) of assessment: self-report, interviews, diaries, proxy report, pharmacy repeat prescriptions, electronic monitoring, biochemical assays</p> <ul style="list-style-type: none"> ■ Mixed groups ■ International studies difficult to compare due to differences between healthcare systems 	<ul style="list-style-type: none"> ■ Huge variability in results ■ 33% in short-term treatments ■ 8 - 95% in long-term treatments 	<ul style="list-style-type: none"> ■ Sex ■ Age ■ Mental health ■ Social support ■ Family cohesion ■ Parental supervision ■ Physician's empathy ■ Illness severity ■ Treatment-related factors ■ Illness perceptions ■ Health beliefs ■ Attitudes
Improving adherence		
Intrinsic facilitators (patient factors)	External facilitators (provider factors)	
<ul style="list-style-type: none"> ■ Optimism ■ Positive beliefs ■ Motivation ■ Responsibility ■ Meaning/value ■ Perceived confidence ■ Perception of control ■ Self-efficacy ■ Acceptance ■ Independence ■ Openness disclosure ■ Understanding 	<ul style="list-style-type: none"> ■ Parents (encouragement, practical, comfort) ■ Friends (encouragement, help prioritizing) ■ CF teams (education, timing, practicalities of organization). The provider-patient relationship is key ■ Community (school, work, society, insurance) 	

Table 1: Problems and challenges in measuring adherence to CF treatments

Problems with adherence		
	Reasons for non-adherence	Consequences of non-adherence
	<ul style="list-style-type: none"> ■ Lack of time ■ Forgetting ■ Feeling too well ■ Complexity of treatment ■ Perceived effectiveness of treatments 	<ul style="list-style-type: none"> ■ Mis-interpretation of symptoms ■ Unnecessary symptoms ■ Increased morbidity ■ Increased mortality ■ Waste of money and time ■ Burden on healthcare system ■ Health insurance costs ■ Negative impact on school, work
Improving adherence		
	External facilitators (organizational strategies)	Techniques to support/improve adherence
	<ul style="list-style-type: none"> ■ Timing ■ Integration ■ Order ■ Routine: encourage individuals to follow the same schedule and pattern every day ■ Location ■ Cluster ■ Flexibility ■ Daily pill box ■ Medication packaging (e.g. prefilled medication boxes or blister packs) ■ Medication apps ■ Synchronized medication refills 	<ul style="list-style-type: none"> ■ Open communication ■ Use teach back to confirm patient understanding ■ Create a shame-free environment and clinic culture of non-judgement around discussions of adherence ■ Promote patient participation in decision-making ■ Establish a collaborative process for problem solving ■ Management technique: Delegate – Drop – Do ■ Behavioral techniques: reminders, setting an alarm, daily schedule ■ Motivational interviewing (MI) ■ Cognitive behavioral therapy (CBT) ■ Interpersonal psychotherapy (IPT) ■ Social skills training

2 Effective interventions: the evidence

Many researchers are interested in tackling the challenge of non-adherence. This section reviews the most important intervention types, focusing on educational strategies, provision of adherence data, behavioral and motivational strategies, tailoring treatment, and modifying attributes of the healthcare system.

2.1. Educational strategies

Given the complexity of the illness, educational counselling and interventions are the most common strategies employed to improve adherence in CF. However, knowledge of the regimen alone is insufficient to ensure patient adherence. Several studies have emphasized the importance of ensuring proper technique in addition to providing education on various topics such as adherence, airway clearance, nutrition, and exercise [14,15]. In general, skills training and education to improve treatment knowledge should begin at diagnosis and be integrated into every visit by all members of the CF care team. Written instructions on the CF treatment regimen, adapted to the patient's literacy level, should also be provided at every interaction.

The results of a Cochrane review of interventions to promote participation in physical activity in CF were published in 2013 [14]. Four of the included studies used exercise education and training to promote participation in physical activity. The review concluded that there was very limited evidence that counselling and exercise education improved physical activity, and

that interventions needed to last at least 6 months in order to have any effect.

A systematic review of self-management education in CF found that although this type of intervention may improve knowledge about CF and its management, there was limited evidence of an association with positive behavioral changes, and no positive effects on clinical outcomes, including pulmonary function, weight, and nutritional intake. The authors concluded that further studies are needed to draw firm conclusions given the small number of trials of varying quality [15].

2.2. Provision of adherence data

Using past performance as a motivator for future performance has also been used to improve adherence. A small study of 15 children with CF found that feedback from electronic monitoring via a telehealth system improved adherence to nebulized treatments [16]. Another study of 39 adolescents found that frequent home pulmonary function monitoring improved medication adherence without increasing treatment burden [17]. Although there is limited evidence to suggest that adherence feedback alone can significantly improve adherence in CF, the use of a home spirometer is promising. Further studies of the growing number of technological solutions to promote optimal adherence are needed.

2.3. Behavioral and motivational strategies

Behavioral strategies include techniques such as reminders, contracting, and the use of consequences or reinforcement. A Cochrane review of randomized controlled

trials of psychological interventions in CF found the available evidence best supported psychological interventions that combined education with behavioral strategies to improve dietary intake and nutritional status in children with CF [18].

Motivational interviewing (MI) attempts to motivate patients to change their treatment-related behavior in order to improve adherence. There remains strong interest in MI for CF care, particularly since it has been shown to improve medication adherence in other chronic illness groups [19].

A CF-specific, problem-solving intervention program, CF My Way, includes education on the importance of adherence and motivation to take more responsibility for incorporating treatments into daily routines. In developing this program, the authors identified barriers to daily care, and held focus sessions with stakeholders to generate options, allowing the patient to ultimately choose relevant solutions and create a personalized treatment plan. A pilot study, delivered over 12 months to 16 adolescents and young adults, showed a post-intervention increase in MPR [20]. However, in a large randomized controlled trial in which >600 individuals with CF (aged 11–20 years) were randomly assigned to groups that received either standard care or a brief, clinic-based behavioral intervention that included education and problem solving, no changes were observed in terms of medication adherence or health outcomes, including lung function, body mass index, and health-related quality of life over 12 months [21]. Another recent study piloted a complex multi-faceted intervention that included real-time electronic

monitoring that was captured using an app, which presented adherence-related feedback with targeted interventions using behavioral principles to promote adherence and provide education. The intervention also included a manualized behavioral change session conducted during a face-to-face visit by a trained healthcare provider, followed by at least one additional review visit. The results of the pilot study revealed a 10% improvement in adherence in the intervention arm, confirming the feasibility of a full-scale randomized controlled trial [22].

2.4. Modifying attributes of the healthcare system

Multiple features of care delivery systems can impact adherence in many ways. Economic factors (e.g. medication costs), inadequate time allotment for appointments, systems with high stress and multiple demands on providers, poor continuity of care, and ineffective information sharing (e.g. between CF clinics and pharmacies, discussed later) can all negatively affect adherence. Nonetheless, interventions targeting relevant factors in the healthcare environment for individuals with CF are lacking. A multi-faceted pharmacy-based intervention study addressing access to medication and financial barriers to access reported improved adherence to tobramycin and a decrease in the rate of emergency room visits [6].

3 Finding solutions in the day-to-day clinic

Conventional interventions to improve adherence have concentrated on the individual skills of healthcare professionals. However, failures to improve medication adherence *in vivo* [21] underscore the need to identify effective strategies and, more importantly, determine when to implement them and which patients can benefit most. To be sustainable, attempts to facilitate change by individual health carers and by patients themselves, need to occur within the context of a cohesive CF team that actively supports establishing genuine partnerships with patients and their families.

3.1. Investing in relationships with patients and relatives

Most care teams have long-term relationships with patients and their relatives, and most implement holistic approaches to patient care, even though treatment is central to the consultation. In the clinic, it is of course necessary to focus discussion on symptoms, treatments, improvements and deteriorations, and treatment decisions for the following months, and to conclude the visit by establishing an optimal treatment plan. However, outside of the clinic, patients and their families do their best to minimize the impact of CF and its treatment and to lead as normal a daily life as possible. Consequently, patients may struggle to be honest due to guilt about their less than optimal adherence or a fear of disappointing their team. However, without an honest exchange it is unlikely that any barriers preventing change can actually be

addressed properly. Collaboration must be the initial aim of any consultation. This is likely to be welcomed by the patient, as the amount of interaction they want during discussions is often underestimated [23].

3.1.1. Listening actively

Ask not “*what is wrong?*” but “*what has happened?*” when talking about problematic adherence - and then listen without judgment. Good listening is not passive (i.e. staying silent, although this is a good start). Good listening is “active,” which means paying close attention to what is said, using cues (such as nods) to encourage more self-talk, and avoiding prematurely closing off the patient’s “self-talk” by offering advice or expressing judgement. Active listening helps patients become actively engaged in the consultation; listening to the content of the message and the speaker’s feelings without interrupting has a powerful impact (see **Table 2**). Throughout these conversations, it is important to avoid being oppositional. Only in rare cases are patients completely unaware of the risks associated with not taking their treatment or worried about the consequences of openly admitting poor adherence. Any sense of being pressured by health carers is likely to be met with resistance, shame, or withdrawal. Instead clinicians can convey concern. However, if a patient is “stuck,” the expression of alarm accompanied by well-intentioned instruction on “what to do” is likely to decrease rather than increase motivation [24].

3.1.2. Educating before medicating

Even when care teams think that an issue has been very well explained, people can still get the wrong idea. It is important to share knowledge of anticipated treatment effects and benefits, and to normalize how these intersect with normal psychosocial development in childhood, adolescence, and adulthood (as outlined in Section 1.2). While the efficacy of education and information remains to be established (Section 2.1), repeating information over time is helpful and important. The three-step Information Exchange technique, also known as the Elicit-Provide-Elicit cycle, seems to help patients better engage with the topic at hand and better remember the information conveyed. The process consists of the following steps: first, before providing new information, elicit what the patient already knows; second, provide new information; and third, elicit what has been retained, for example, by asking *“What do you make of that?”* [25].

3.1.3. Incorporating CF-related health-beliefs

It is crucial to understand beliefs about medicine, particularly the extent to which patients believe treatment is necessary or gives rise to concern (the “Necessity-Concern” Framework [25]). This concept has been shown to determine patients’ motivation to begin and persevere with treatment: judgements about the personal need for treatment (“necessities”) are tempered by fears of potential adverse effects (“concerns”). Parental “necessity” beliefs are significant independent predictors of child adherence to enzyme supplements

and chest physiotherapy [26]. Completing measures such as the Beliefs about Medicine Questionnaire [27] during clinic can be a useful means of initiating a conversation about patients’ and parents’ beliefs about treatment.

3.1.4. Linking life and treatment goals

Motivating patients to adhere optimally means listening to what they are doing and what they want to do in their lives. They will have hopes and ambitions, and explicitly linking these to “doing treatment” may help them achieve their goals both in the short-term (e.g. going shopping with friends, having a sleep-over, playing rugby at the weekend), and the long-term (e.g. getting a job, going to university, or having children), although this occasionally has to be tempered with acceptance of the fact that people with CF become sick despite excellent adherence. However, explicitly widening the scope of clinical consultations to align “treatment” and “life” goals and recording “personal goals” in medical records can help balance the importance of treatment and life aims to create a single set of co-created goals.

3.2. Mobilizing social support

For many people with CF, parents and partners are the main sources of practical, physical, emotional, and social support. Certainly for children and young people, “self” management is shared with parents. Parental monitoring and supervision of treatment are likely to improve adherence: greater parental supervision is likely to account for the better overall adherence seen in younger patients compared to

older children [28]. However, support from friends, whether online or face-to-face, with CF and/or non-CF peers, can be equally if not more important, particularly for teenagers [23]. Adolescents typically face the psychosocial challenge of “identity versus role confusion”; and consequently project a certain image in front of peers. This in turn creates internal pressure as they attempt to balance looking after their health and living their daily lives. However, as much

as peer-pressure is perceived negatively, teenage friendships provide encouragement, understanding, and fun, and may also help patients incorporate their care into their every-day activities (e.g. “*we will meet at the cinema after you have done your physiotherapy*”). Talking about social skills, availing of the services of youth workers or other community- or school-based staff, and welcoming friends to visit clinics and wards can help young people with CF to

OPEN-ENDED QUESTIONS

These cannot be answered with a single word or phrase. For example, rather than asking, “Do you take your medications?” a clinician might ask, “How do you get on with taking your medications?” They are useful for opening up a conversation and limit assumptions regarding a patient’s status, knowledge, or belief.

REFLECTIVE STATEMENTS

This refers to the process of reflecting back on what a patient has said. This can be simple and intuitive. For example, a clinician can effectively re-state the main content of a statement a patient has made. Even this can be a powerful incentive for a patient to say more. It demonstrates that the clinician is listening, and is a simple and effective response to a patient’s anxiety or ambivalence about changing. A more complex form of reflection is to guess at the meaning of what a patient has said. For example, a patient may talk about forgetting to take treatment and the clinician may guess that this is less about forgetting and more about prioritizing, leading them to reflect as follows: “life seems too busy just now to fit in all your treatments.” Such reflections give the clinician the opportunity to help move the conversation on to more meaningful topics, showing the patient that the clinician is not just listening but attempting to understand.

SUMMARIES

This refers to the clinician pulling together things a patient has said, and presenting them back in a brief summary. This can function both to produce novel insights and move the conversation on to a new stage (e.g. acting upon a problem that has been discussed).

Table 2: Problems and challenges in measuring adherence to CF treatments

activate their social matrix of support and, most importantly, stay “in the loop” of their friendships.

3.3. Developing organizational strategies

Motivation and organization are two key elements in achieving good concordance. Helping people with CF and their relatives to address treatment timing and scheduling, integrate treatment into daily life, use reminders and facilitators (e.g. texts, alarms, and dosette-boxes), and establish daily routines are all potentially important steps towards achieving optimal management. Treatment can be tailored to patients and their families in many ways, for example by simplifying the dosing regimen, examining their schedule and preferences, or considering changes in the route, delivery, or location of treatment.

3.3.1. Planning and monitoring

Patients decide when *they* are ready to “change”. Persuading, coaxing, even “begging” does *not* work. They will start when they are ready, and it is important that the team is also ready to help them succeed. Having a clear goal and a rational plan usually has a positive effect on treatment outcomes [29]. Although it is tempting to implement changes without preparation, planning is a crucial step. Anticipating difficulties in getting started are crucial to discuss in advance.

One way to establish goals is to make them “SMART” (Specific, Measurable, Attainable, Relevant, and Time-bound; www.smartsheet.com/blog/essential-guide-writing-smart-goals). The idea of SMART goals

has become widely-accepted, with an emphasis placed on practical goal-setting. Goals should be defined clearly, tracked with an acceptable level of certainty, realistic and relevant to the patient, and achievable within a reasonable time-frame. SMART goals can be linked to the written treatment plan. It is generally considered best to start with small, preliminary steps to increase confidence. Once goals are agreed upon, these can be written into a “change” plan, which commits the patient to change and reminds them of their reasons for wanting change. This approach helps keep the focus on what the patient will actually do, and helps them think about what could make change easier.

An important feature of a good plan is the anticipation of potential problems, which may delay or halt the progress of change, or prevent it altogether. By including these problems in the written treatment plan, they can be easily referred to in subsequent conversations.

3.3.2. Tracking adherence over time

Establishing written treatment plans as part of the consultation is useful [24]. Treatment adherence should be discussed at every visit. This is important to understand current symptoms, the effect of the prescribed treatment, and any problems the patient/family has encountered. Asking about missed treatment in the right way, in collaboration with the patient (see Section 4.1.1), is probably what every team member aspires to. A system of subjective rating by the team member and the patient, indicating whether adherence since the last visit has been “optimal”, “adequate”,

or “sub-optimal,” could potentially be implemented. It is also important to talk about barriers or a lack of facilitators that may have arisen since the last visit and to review device technique and community access to medicines when possible (see Section 4.3.3). Sometimes, introducing direct observation of treatment (e.g. by a partner or parent) can be helpful, although this should only be done with the patient’s consent. It should be explained that this information will help identify further facilitators of good treatment adherence that are specific to the individual patient and family.

3.3.3. Medication logistics

The time and effort invested in requesting, securing, and collecting medications and equipment from the CF center or local pharmacy is one aspect of treatment considered difficult and stressful by over three-quarters of people with CF and/or their relatives across Europe [2]. Reported difficulties included breakdowns in communication between “community” pharmacies and CF centers, instructions going astray, and medicines, particularly powerful antibiotics, not being supported by local family doctors. A UK-based parent focus group concurred with this view, and developed a guide to improve medicine logistics, offering patients and parents useful ways of reducing frustrations and difficulties in obtaining medicines in their communities or from their CF center [30]. Although written for the UK healthcare system, the information included in this guide is potentially useful for all teams who may already be implementing medicine logistics as part of routine care (see **Figure 1**).

3.3.4. Actively helping to automate day-to-day care

Burden and complexity are not necessarily related. For some, complex therapy may not be perceived as a burden, but for others, undertaking daily nebulizer treatment may be overwhelming. Burden is in the “eye of the beholder.” As such, it is important to understand this concept subjectively. It can be helpful to initiate discussion about establishing daily treatment routines, and opportunities to combine therapies or embed them into other activities that can be completed in a shorter, more efficient way. By anticipating changes in routines during weekends or holidays, teams can help patients to proactively manage their care when their routines change [23].

3.3.5. eHealth and telemedicine

The delivery of CF care is undergoing transformation, with teams and patients adapting to digital opportunities to interact. To date, remote and continuous tracking of patients’ health outcomes is the most exciting opportunity for CF telemedicine (see Bell *et al.* [23] for a contemporary overview). The use of developing technologies is appealing and feeds into the social context of today’s patient population. In CF, while some small-scale studies exist, (summarized in [23]) a central theme thus far is the use of mobile phone apps (which run inside a device’s operating system until it is closed) to inform, engage, and help organize patient care in a more time-efficient manner (e.g. www.mycyfapp.eu). As with any system, apps should be used sparingly. They are not a panacea to “change” behavior, but rather, useful tools for CF

- Make sure that the repeat prescription is sufficient to supply at least a month's supply of each drug (in some countries it is longer)
- Always have sufficient supplies at home (at least 2 weeks supply of medicines)
- When a medication changes, provide/ask for a printout of the updated medication list to take home and share with your family doctor
- With newly prescribed drugs, ask the prescriber how easy they are to obtain in the community/provide information on how easy they are to obtain in the community
- When a new medication has been started by the CF clinic, inform your family doctor (e.g. phone, email), and check that it has been added to your/your child's record
- Provide/request an "alert" on the provider's system (e.g. special circumstances, high doses, repeat antibiotics)
- When requesting medicines only order what you/your child needs
- Develop a relationship with your local/community pharmacy
- The CF center could liaise with your pharmacy/community provider if you have "tried everything" and are still having significant issues getting your medicines

Figure 1: Medicine logistics: points of importance for patient/parent and CF team

teams, for the right patient at the right time. To maximize the potential benefits of an app that tracks healthcare behaviors, teams should consider how it can help the patient achieve their goals. Otherwise, the effort may be perceived as intrusive; something that “pops up” in their social media at a time when they want to “escape” from CF.

3.4. Establishing a complex care pathway

With the advent of CFTR modulator therapy, the aim is that every patient is in the best condition possible before starting this type of treatment. Teams must acknowledge that this is not an easy task as it may take some time before new medicines reach all patients and frustration will discourage some. More than ever, teams must strive to provide ample education and information about new treatments. Together, teams and patients/relatives need to recognize the window of opportunity to improve health outcomes by re-calibrating goals and the treatment plan, perhaps by establishing more frequent monitoring and availing of the support of other agencies. It is essential to provide hope and motivation. Many patients and families have “heard it all before” over the past two decades, and feel that the prospects of new upcoming treatments were over-sold. Many remain skeptical but dare to hope; motivation and support to achieve optimal adherence in this group has never been more critical.

4 Conclusions: working together

Attempts to understand, measure and improve sub-optimal adherence in CF care have been ongoing for many years. Some single intervention strategies have shown short-term benefits, but for most, evidence of longer-term effectiveness is lacking. Several critical elements have been identified. First, early recognition of poor adherence through coordinated efforts involving the entire CF MDT is essential in order to implement improvements. Secondly, adherence assessment should be a continuous process that is followed-up at each clinic visit. Finally, interventions should be tailored to each individual’s barriers to adherence and their attitudes to illness and treatment, and should incorporate self-management and shared decision-making. For now, the challenge lies in integrating best practices into busy clinics. Reviews have produced a common underlying recommendation to address adherence; to genuinely work *with* CF patients and their relatives to optimize their health outcomes. CF care has entered the phase of personalized medicine which requires personalized support. Investing time in building trusting, positive relationships with patients and their relatives will form the foundation for optimal CF self-care, working on agreed goals and identifying facilitators/barriers. Such approaches are likely to pay huge dividends in the years to come.

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CHAPTER 14

Patients' priorities and the CF pharmaceutical pipeline

Authors

Nicola Rowbotham, Michele Samaja,
Alan Smyth

Introduction

Traditionally the focus of pharmaceutical research in CF (and most other conditions) has been dictated by the pharmaceutical industry and by the interests of researchers, who are mainly driven by career opportunities and funding availability. Prior to gaining marketing authorization for use, a new drug must undergo rigorous testing through adequately powered clinical trials. With a limited population of people with CF to take part in clinical trials, this can cause a bottleneck in the pipeline of new drug development. Developing drugs that are seen as important by the CF community (both lay and professional) should lead to increased trial participation and, hopefully, broader access to treatments that are of great benefit to people with CF. Medical journals generally prefer to publish "positive" results from clinical research. This leads to publication bias in the scientific literature [1]. In some cases, ineffective treatments may continue to be used in clinical practice because negative findings have not been published or because publication has been delayed.

1 What is the pharmaceutical pipeline?

A pharmaceutical pipeline describes the process of drug development. This includes the laboratory screening of large numbers of molecules for a "signal" that they may be effective, animal testing for safety and efficacy, testing in man, and finally licensing of the drug and post-marketing surveillance to monitor safety in routine practice.

2 Patient priority setting in CF

A critical step in the road to a drug development pipeline that meets the needs of patients is the process of consulting with both the patient and the clinical community to agree research priorities. There have been several recent exercises in priority setting in CF. The James Lind Alliance (JLA) Priority Setting Partnership (PSP) in CF was a global exercise that gathered treatment uncertainties and then ranked them through a series of surveys and workshops to produce a top ten list of research priorities for treatment decisions in CF [2]. The Cystic Fibrosis Foundation (CFF) in the US surveyed adults with CF, family members and clinical researchers

to prioritize a range of research topics that were felt to be under-addressed by current research [3]. The Italian Patient Centred Outcomes Research Working Group in CF (IPaCOR) produced their own research priorities for CF through a series of questionnaires and working groups with varying levels of education in research [4]. The Dutch Cystic Fibrosis Foundation (NCFS) HIT-CF programme has spent 12 years looking at “institutionalized patient participation” to align research agendas with the views of patients [5].

2.1. The James Lind Alliance (JLA) Priority Setting Partnership (PSP) in CF

The JLA is an organization that promotes PSPs in clinical research. The JLA is hosted by the UK National Institute for Health Research. The methodology brings together patients, carers and clinicians to prioritize research questions around treatment decisions [6]. The first JLA PSP in CF was carried out in 2016-17 [2]. This was a global exercise open to all who live with CF, or care for those with CF (either personally or professionally). An initial online survey collected over 1,000 research questions from the CF community. These were checked to make sure they hadn't been answered already and that the items were treatment uncertainties. Similar questions were combined, resulting in 71 questions presented back to the CF community to rank in importance. The top 20 from this second online survey were then taken forward to a workshop where the final top 10 were agreed (**Table 1**). During this process there was equal participation from lay and professional groups at all stages.

Due to the cross-infection risk with CF, adaptations (such as the use of online video conferencing) needed to be made to allow multiple people with CF to participate [7].

2.2. CF Foundation insight group

Formed in 2016, the US CFF Insight program aimed to identify a broad range of research priorities that could be answered through registry based studies [3]. Members of the US CF community were asked to submit research questions to address the community's need via an online survey. From over 400 individual questions submitted, 12 broad research topics were identified. In 2018 these 12 topics were then put to a sample panel that was drawn from their Clinical Research Advisory Board (CRAB) and Community Voice, a CFF-supported group of adults with CF and adult family members across the United States. They asked respondents to prioritize research areas that they perceived to receive less attention. They received 135 responses from members of the patient community and 19 from clinical researchers. **Table 2**, taken from their publication in the Journal of Cystic Fibrosis, compares priorities between researchers and community members [3].

2.3. Italian Patient Centred Outcomes Research Working Group in CF (IPaCOR)

The IPaCOR was established in 2013 within a collaboration between the Italian CF Scientific Society (Società Italiana Fibrosi Cistica, SIFC) and the Italian CF Patients Association (Lega Italiana Fibrosi Cistica, LIFC). It is composed of nine CF healthcare professionals (six physicians, two physio-

therapists and one biologist) and six stakeholders (three patients and three parents). In order to raise the consistency and self-awareness of the stakeholders group, a course was designed and made available to both lay and professional participants. It comprised four teaching modules (12 hours each), derived from informed discussions with a multidisciplinary clinical team. The course aimed at establishing a connection between stakeholders and the scientific community by identifying research topics which reflected the needs of CF patients and by expressing patient priorities in

scientific and programmatic terms. At the end of this course, the trained stakeholder group was asked to list priorities for CF research in orphan areas based on the needs of people with CF and on literature recommendations. This approach led to a report that highlights how the research issues priorities are perceived differently according to the stakeholders' individual knowledge of research topics and degree of training in biomedical research [4]. **Table 3**, taken from this report in the Journal of Cystic Fibrosis shows the priorities [4].

Rank	Priority
1	What are the effective ways of simplifying the treatment burden of people with CF?
2	How can we relieve gastrointestinal symptoms, such as stomach pain, bloating and nausea?
3	What is the best treatment for nontuberculous mycobacterium (including when to start and what medication)?
4	Which therapies are effective in delaying or preventing progression of lung disease in early life?
5	Is there a way of preventing CF related diabetes?
6	What effective ways of motivation, support and technologies help people with CF improve and sustain adherence to treatment?
7	Can exercise replace chest physiotherapy?
8	Which antibiotic combinations and dosing plans should be used for CF exacerbations and should antibiotic combinations be rotated?
9	Is there a way of reducing the negative effects of antibiotics e.g. resistance risk and adverse symptoms in people with CF?
10	What is the best way of eradicating <i>Pseudomonas aeruginosa</i> ?

Table 1: The top 10 research priorities identified by the CF community during the JLA PSP in CF [2]

Research topic	Weighted score ¹	
	Community Voice (n = 135)	CRAB researchers (n = 19)
Respiratory microorganism detection and treatment	8.4	10.1
Mental health	7.1	8.9
Reducing treatment burden	7.1	8.3
Gastrointestinal symptoms	6.7	8.2
CF-related diabetes	6.6	7.5
Diet and nutrition	6.5	5.5
CF-related liver disease	6.3	6.1
Exercise	6.2	4.5
Sinus disease	6.0	5.5
Lung transplantation	5.9	6.6
Alternative/holistic treatments and therapies	5.9	2.2
Pain management	5.5	5.3

Table 2: Priority rankings and weighted scores from Community Voice and CRAB researchers' surveys [3]

1. Weighted ranking score of respondents was used to rank the research topics. The weighted ranking score for each topic is a sum of all the weighted values. Reverse weighting was used such that items ranked first were given higher weight, while items ranked last were given lower weight. Community Voice members selected and ranked up to 10 of 12 possible topics to be considered a priority. The weighted score for Community Voice members reflects only those respondents who ranked the topic.

Group	SSH ¹	USH ²	TSH ³	USH ⁴	Total
n	11	26	6	141	184
Year	2013	2015	2016	2017	2013-2017
	Rank	Rank	Rank	Rank	Score
CFTR modulators	2 nd	2 nd	5 th	3 rd	20
Transplantation and immunosuppressive therapy	1 st	1 st		4 th	18
<i>Pseudomonas aeruginosa</i>	3 rd	3 rd		1 st	17
Pulmonary exacerbations			2 nd	2 nd	12
Time spent in therapy			1 st		7
<i>Burkholderia cepacia</i>	4 th			7 th	5
Physiotherapy devices		5 th		6 th	5
Psychological therapies			3 rd		5
Domiciliary therapy			4 th		4
Osteoporosis		4 th			4
Allergic bronchopulmonary aspergillosis (ABPA)	5 th				3
Rhinosinusitis			6 th		2
<i>Staphylococcus aureus</i>	6 th				2
Diabetes	7 th				1
Screening			7 th		1

Table 3: Comparison of the research priorities selected by the four groups* as ranked in the respective surveys

The score was calculated by assigning 7 points to the top rank, progressively decreasing to 1 (only the top 7 issues were considered) [4].

1. SSH = skilled stakeholder (specifically trained in biomedicine)
2. USH = unskilled untrained stakeholder (who responded to a written questionnaire in 2015)
3. TSH = trained stakeholder (completed a one year IPaCOR course)
4. USH = untrained stakeholder (who responded to an online questionnaire in 2017)

In a further ongoing study, the same group is examining how to choose a set of outcome measures to assess the validity of the results from clinical trials from the perspective of patients and stakeholders. Preliminary observations point to rather low concordance between the scoring given by health professionals and by stakeholders. Despite these limitations, this should represent an important step toward the definition of a core outcome set to address the patient-centeredness of clinical trial results.

2.4. Dutch Cystic Fibrosis Foundation

The Dutch NCFs has been working for the past 12 years to try to align its research programme with the priorities of its patients [5]. In 2007, 15 people with CF and 15 parents were asked to specify research ideas that were personally important to them. The 30 people then prioritized their top 10 research ideas and then, similarly to the JLA project, these were ranked online by almost 200 Dutch people with CF who answered the Dutch registry's invitation to participate. The top 5 were then agreed with clinicians and scientists. These topics were: insight into the basic defect, infection, inflammation, segregation policy, and psychosocial issues. This set the NCFs research agenda for 2007-2011 with several projects funded to try to address these priorities.

In 2012 the NCFs reviewed the priorities using a similar method. The priorities remained unchanged except for segregation policy being replaced by fatigue in CF. However the impact of this research agenda was subsequently judged to be disappointing as the funded projects were highly

diverse, with little promise of follow-up work, so a new approach was taken. A specific consortium of basic scientists, clinicians and patient representatives was set up who designed a research program called "HIT CF" with the aim to address the top priorities in 2012 of targeting the basic defect in people with CF, infection, and inflammation. Patients and parents of patients were involved in review of projects. This programme has brought in € 5 million of funding and resulted in many publications. The organoid technology, which is a key component of the programme, has been particularly successful. A further review of by patients and parents in 2016 resulted in the decision to now focus entirely on new therapies targeting the basic defect.

2.5. Comparing the patient priorities between these initiatives

Table 4, taken from an editorial in the Journal of Cystic Fibrosis [8], shows shared priorities across the different priority setting exercises.

It is reassuring to see similar themes evolving throughout the various research priority exercises, adding validation to their processes. However, not all of these priorities will be of interest to the pharmaceutical industry. For example, research into strategies to reduce disease burden may be more suitable for funding by patient organizations or national research funding schemes. It is important to note the differences in objectives set out for each priority setting exercise; the JLA PSP aimed to prioritize questions that could be answered by clinical research whereas the Insight CF exercise aimed to prioritize questions that could be answered through the CFF registry. The

Priority area	JLA PSP rank	CCF rank	IPaCOR rank	NCFS 2016
Treatment burden	1	3	5	
Gastrointestinal	2	4		
Exercise	7	8		
Respiratory microorganism detection/treatment	3,10	1	3,6,13	
CF related diabetes	5	5	14	
Mental health		2		
Therapies targeting basic defect			1	Only priority

Table 4: Shared research priorities across the different priority setting exercises [8]

IPaCOR prioritized research ideas from gaps that were identified in Cochrane reviews, and may be finalized through translational medicine approaches that bridge the classical “bench-to-bedside” gap. The NCFS group used a combination of focus groups and surveys to suggest topics felt to be important, and have changed these topics as the program has evolved.

3 The role of clinical trials networks in accelerating the pharmaceutical pipeline.

Clinical trial networks exist to facilitate and accelerate clinical research trials with the aim to speed up the process of bringing new medicines to patients. Examples

of these include the US CFF CF therapeutics development network (CFF-TDN) launched in 1998 and the ECFS Clinical Trials Network (ECFS-CTN) which has been active since 2008. The ECFS-CTN currently provides access to 58 large and experienced CF centres, located in 17 different countries throughout Europe. Clinical trial networks will be discussed in further detail in Chapter 15. Trial networks should work closely with the CF patient community to ensure that their priorities are aligned. They should also balance the motivations of the pharmaceutical industry and the curiosity-driven science of academic investigators against the priorities of the patient community, derived from their experience of living with CF [9].

4 Conclusions

The above-mentioned studies show that there is alignment in the research priorities of the CF community. It is important that when priorities are set, that they are not just a tick box exercise, and that the priorities develop into actual research.

Noordhoek *et al.* describe the impact that priority setting has had on the NCFS research program and the importance of a programmatic approach to project funding [5]. The CFF Insight study has a direct link within the CFF to impact on their research funding streams. The JLA CF exercise has worked hard to disseminate their priorities widely, worked closely with the UK's CF Trust and held meetings with the UK's largest research funder the National Institute for Health Research (NIHR) who have since put out funding calls focusing on the CF priorities. It is important that groups try to work collaboratively to try to answer priorities effectively and efficiently.

Co-production of research with patients and the wider CF community in all of the various stages of the research pipeline (discovery, development, clinical trials) will help ensure that patient priorities remain at the forefront of the process.

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CHAPTER 15

ECFS-CTN: shaping small gains into magic bullets

Authors

Fiona Dunlevy, Veerle Bulteel,
George Retsch-Bogart,
Silke van Koningsbruggen-Rietschel

Introduction

CFTR modulators have revolutionized the pharmacological treatment of patients and triple therapy could potentially bring disease-modifying treatment to around 90% of people with CF (pwCF). However, this does not mean that our job is done. CFTR modulators are not effective in all pwCF, and while they slow the decline in lung function they cannot be considered a cure. Furthermore, not all potentially eligible patients will have access to this highly effective treatment. There remains a need for medicines that treat the symptoms and consequences of CF. Our patients will continue to need anti-mucolytics, antibiotics, anti-inflammatories, pancreatic enzymes, and dietary supplements.

Further development of these medicines will, of course, require clinical trials. While recent trials of CFTR modulators have shown a trend for smaller populations due to increased treatment effect, trials for symptomatic treatments are likely to need larger patient populations. In addition, these

trials will be undertaken in a new therapeutic landscape, which is changing profoundly as CFTR modulators are accepted as the standard of care in more and more countries.

Clinical trial networks such as the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) are therefore more relevant than ever.

1 Why are clinical trial networks needed?

1.1. Challenges of CF trials in Europe

CF presents specific challenges to those designing and conducting clinical trials. The patient population is divided across many care sites, not all of which are experienced in conducting commercially-sponsored clinical trials. The distribution of *CFTR* mutations is varied across Europe, and even within sites. Mutation-specific medicines such as CFTR modulators require highly specific trial populations. One positive aspect is that many pwCF patients, particularly children and young adults, are clinically well with normal/near-normal lung function. Under EU regulations, all new medicines for CF must be tested in pediatric patients

as well as in adults. This requires sensitive outcome measures to detect signs of efficacy in clinically well patients. Having CF is a full-time job, and the extra burden that a clinical trial places on a patient and their family should not be underestimated. Clinical trials in CF must be optimized to carefully balance the acquisition of scientific knowledge against the burden of patient participation. There is considerable variation across Europe in standards of CF care, clinical trial resources, and patient profiles. This variation, together with language and cultural differences and a fragmented regulatory and ethics landscape, contributes to the challenges of performing multinational CF trials in Europe. Finally, there are significant regulatory and reimbursement challenges in developing medicines for CF, resulting in high competition for a limited patient pool and pressure to accelerate development to reach the clinic as quickly as possible.

1.2. Clinical trial networks

A clinical trials network is a group of skilled experienced clinical trial sites that cooperate to share knowledge and skills, and to have a stronger voice in setting and influencing the research agenda, in favor of patients.

Clinical trial networks pool resources to make improvements in all aspects of clinical trials. This approach has been compared to the methodology of marginal gains (www.trialforge.org). One of the largest clinical trials network in Europe is the European Clinical Research Infrastructure Network (ECRIN), a non-profit, inter-governmental organization that supports

investigator-led academic multinational clinical trials in Europe. Other clinical trial networks in Europe include disease-specific networks, such as the ECFS-CTN for CF. Disease-specific clinical trial networks are particularly valuable for rare diseases, where the patient population is geographically dispersed and multiple trial sites are required to recruit enough patients for clinical trials.

2 ECFS-CTN

ECFS-CTN aims to intensify clinical research in CF and to bring new medicines to patients as quickly as possible. To date, this has been achieved by focusing on commercially-sponsored clinical trials. The network was founded in 2008 as part of the EU-funded EuroCare-CF project and started operations in 2009 with 18 member sites in 8 countries [1]. The structure and conduct of ECFS-CTN is closely modelled on the example of the US-based Cystic Fibrosis Foundation (CFF) Therapeutics Development Network (TDN), founded in 1998 [2]. The TDN provided generous and invaluable guidance to facilitate the set-up and running of ECFS-CTN and remains a valuable partner today.

Since 2008, ECFS-CTN has undergone three waves of expansion, in 2012, 2016, and 2020. Today, we count 58 member sites in 17 countries, with a total patient population of 21,500 (**Figure 1**).

Over the last 10 years, we have reviewed 133 protocols and supported 79 trials, and our member sites have enrolled 3,257

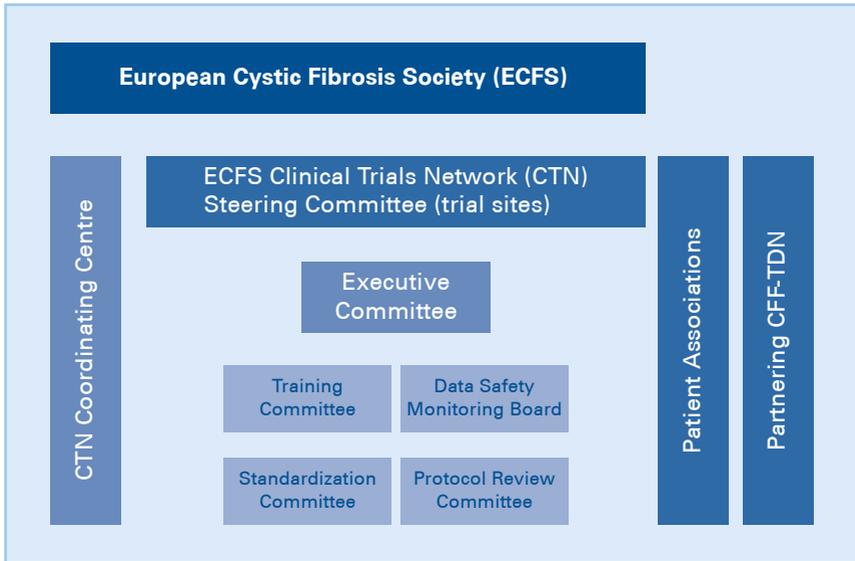


Figure 2: ECFS-CTN organizational structure

2.1. Organizational structure and meetings

ECFS-CTN **member sites** undergo a strict application process and must demonstrate adherence to CF standards of care [3], recent experience in interventional industry-sponsored CF clinical trials, and adequate infrastructure and trained staff to conduct these trials.

ECFS-CTN is governed by a **steering committee** (Sterco) and an executive committee (**Figure 2**). Further details on the operations of ECFS-CTN can be found in previously published papers [1, 4].

Sterco comprises an investigator from each member site, representatives from

European patient organizations (POs) who part-fund ECFS-CTN, and a representative from the CFF-TDN. Sterco meets twice yearly in January and June to discuss topical matters in CF clinical research and to share experiences. This forum provides an important opportunity for peer exchange and to discuss common problems and challenges facing the group. Recent discussion topics have included the emerging challenge of how sites can fairly allocate limited trial slots to patients [5]. Partnering is also an important aspect of these meetings and the regular peer exchange offered by Sterco meetings can lead to new collaborations.

Shared vision, community, and regular communication are important elements of a successful CTN [6]. Since our Steerco meetings are limited to one participant per site, we have sought to multiply the ways in which we engage our members. Recent initiatives include bi-monthly newsletters with network news as well as news items of interest related to CF and clinical trials in general. In addition, investigators and research coordinators from member sites are asked to actively participate in one of ECFS-CTN's working committees for protocol review, standardization, or training. The **executive committee**, comprising six investigators and a PO representative, meets by telephone every two weeks to develop network policies, steer actions to the different committees, discuss all clinical trials, and to decide whether reviewed protocols will be recommended to CTN sites.

These activities are supported by a coordinating center, which counts five employees including a network coordinator, administrator, project manager, quality manager, and standardization coordinator. The coordinating staff are in daily communication with the CTN director (physician) who provides expert input to resolve issues as they arise, as well as guidance for daily activities.

2.2. Increasing clinical trials capacity and infrastructure

Site infrastructure and staffing are recognized barriers to clinical trial participation [7]. An important function of a CTN is to catalogue infrastructure, research capacity, and expertise at each trial site. ECFS-CTN maintains databases of such informa-

tion and monitors the barriers preventing member sites from participating in more trials or enrolling more patients.

A 2016 survey identified research staff time as a major barrier in most sites. This led to the implementation of a three-year financial support program, generously funded by the CFF, that financially supported clinical trial staff capacity within many sites of the CTN. The entire field benefits from the increased pool of skilled CF clinical research staff. The next challenge is to promote sustainable employment and retention of that workforce.

2.3. Protocol review

Critical review of clinical trial protocols is one of our most important tasks. Protocol review allows us to implement a "quality-by-design" approach that reduces the risk of protocol errors and inefficiencies that could otherwise lead to failure of the trial or a series of costly protocol amendments to mitigate the issues. This quality-by-design approach is also advocated by the Clinical Trials Transformation Initiative (CTTI) [8].

ECFS-CTN member sites prioritize participating in trials approved by the ECFS-CTN protocol review process, which incentivizes sponsors to submit their protocols for review. The majority of industry-sponsored interventional clinical trials of CF medicines pass through our protocol review process.

Protocol review is performed by a team of three CF doctors, a research coordinator, a statistician, and two patients (or parents). They check whether the science and statistics behind the hypothesis are sound, review previous safety and dosing data, advise as to whether the proposed outcome

measures are appropriate and whether the planned study schedule and timing are logistically feasible. Patients and parents advise as to the acceptability of the burden of participation and provide their opinion on patient-reported outcomes.

Based on this review, the ECFS-CTN executive committee decides whether to sanction the protocol or to return it to the sponsor for revision. Sanctioned trials are assigned priority scores, which are communicated to CTN sites, where this information is used when deciding whether to participate in a trial or not.

Our protocol review service ensures that only high quality, logistically feasible, and scientifically sound trials are sanctioned. This process also ensures that trials likely to improve clinical care are prioritized. This helps ECFS-CTN manage the capacity of the limited patient pool. Expert scientific and medical review also identifies where additional knowledge can be gained from the trial, without adding too much extra burden on patients.

2.4. Feasibility

Identifying and selecting the right clinical trial sites is critical to successful trial conduct and the generation of high-quality data. ECFS-CTN sites are all, by definition, high quality experienced trial sites with motivated investigators and teams. Nonetheless, sponsors still need to conduct fast, accurate, feasibility enquiries to select sites with the right infrastructure, expertise, and patient profiles for the clinical trial.

ECFS-CTN offers a paid feasibility service to sponsors to survey whether member sites are interested in participating and whether

sites fulfil the needs of the trial. Our up-to-date contact list for all sites and streamlined procedures allow a high response rate and fast turnaround of feasibility questionnaires. Final site selection is performed by the sponsor, and we ask sponsors to provide constructive feedback to sites that are not selected.

2.5. Standardization and central reading

Clinical trials must produce robust data that is comparable between trials and that is acceptable to regulatory authorities. Standardization of outcome measures, techniques, and procedures is key to achieving reliable data.

The standardization committee of ECFS-CTN works to gain consensus in measuring and analyzing clinical trial outcomes in CF. Since 2009, the working groups of the standardization committee have produced 30 standard operating procedures (SOPs) and 7 peer-reviewed publications focusing on these outcome measures.

The SOPs are available to all CTN member sites and are provided to sponsors upon request. Sponsors are encouraged to use the SOPs in their protocols. Clinical trial outcome measures are further standardized via centralized expert reading centers. ECFS-CTN has established central reading centers for multiple breath washout (MBW) and nasal potential difference (NPD) measurement.

2.5.1. Centralized expert reading centers: the example of MBW

MBW with lung clearance index (LCI) is a

good example of how international collaboration standardized an experimental outcome measure into a robust regulatory-accepted clinical trial outcome. LCI is a sensitive measurement of lung function, particularly suited to measuring small changes in CF lung disease. Therefore, this technique is very useful in patients who have good lung function.

The standardization committee reviewed all the available literature on the use of LCI in patients and concluded, via a consensus-building exercise, that LCI offered a feasible and robust surrogate endpoint for lung function in children with CF and in adults with mild CF lung disease [9]. ECFS-CTN supported the establishment of a centralized core facility for LCI. This core facility trains LCI operators from other trial sites and provides an over-reading service for clinical trials. LCI has started to be integrated as a secondary outcome parameter in many clinical trials, as well as a primary outcome measure in clinical trials performed in the pediatric age group.

2.6. Quality & training

To join ECFS-CTN, sites must be experienced in conducting clinical trials in CF and must demonstrate high quality. ECFS-CTN monitors the performance of member sites by tracking the speed of clinical trial set-up activities and the numbers of patients screened, enrolled, withdrawn, and completed. We provide regular updates to sites on their performance and an annual personalized quality report that allows sites to benchmark themselves against other sites. Sites that appear to be struggling or who have lower than usual clinical trial

activity are identified, closely monitored and supported to improve.

2.7. EU projects

Collaboration with the wider research community is another way in which ECFS-CTN fulfils its goal of intensifying research in CF. ECFS-CTN has been a partner in several ongoing and completed EU-funded clinical trials (see **Table 1**).

2.8. Pediatric medicines

In 2006 the European Pediatric Regulation (EC no. 1901/2006) introduced the Pediatric Investigation Plan (PIP), which mandates that drugs developed for diseases that affect both children and adults are also adapted for and tested in children. The challenges of developing medicines for children with CF is comprehensively discussed in the 2018 ECFS “Early Years” book [10].

ECFS-CTN works to keep pediatric drug development at the top of the agenda. Our network is a voting member of the European Network of Pediatric Research at the European Medicines Agency (Enpr-EMA) (<https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema>), which aims to facilitate studies in the pediatric population, and thereby increase the availability of medicines authorized for children. We are also a specialty disease network member of the vast European Conect4children project funded by IMI2 (**Table 1**). This project seeks to “deliver high quality regulatory grade clinical trials” by improving trial design, sharing trial resources, and educating all stakeholders about pediatric clinical research.

2.9. Patient collaboration

Patient and public involvement (PPI) in clinical research is increasingly important to improve clinical trial design, conduct, and robustness. National CF POs and their umbrella organization CF Europe are essential partners in accelerating research through multiple avenues.

A PO representative is a voting member of the ECFS-CTN **executive committee** and is involved in all CTN activities. This representative also presents to the biannual Steerco assembly, reporting on relevant initiatives and activities from POs. PwCF and their parents are also active members of the protocol review committee.

ECFS-CTN works with POs to improve **communication supports** for pwCF, such as information leaflets, annual reports, and plain-language summaries of clinical trial results. Patient awareness of clinical research and education contributes to improving the culture of research at sites and can translate into greater and faster recruitment into trials, as well as increased retention.

Patient-reported outcome measures (PROMs) assess the quality of life of patients, including information such as impact on daily activities, resilience, and perceptions of the disease. Clinical trials collect this data to understand the patients' perspective on the benefits and drawbacks of the treatment under investigation. These data are also considered for reimbursement as part of the health technology assessment, which places high value on quality of life. ECFS-CTN, CF Europe and a group of expert patients are working together to develop new PROMs that can be used in

clinical trials. A youth advisory group is also being set up.

Several national POs have established **national CTNs** (France, Germany, UK, and the Netherlands). There are several tasks best undertaken by national networks, taking into account local regulations and local language. These include centralized budgeting, national trial trackers, financial and logistical support for IITs, and communication with pwCF and their families in the local language.

2.10. Registry collaboration for post-authorization studies

ECFS-CTN dovetails with the European Cystic Fibrosis Society Patient Registry (ECFSPR), especially for performing pharmacovigilance studies. This is increasingly relevant since the EMA started mandating post-marketing safety studies (PASS) and efficacy studies (PAES) and has qualified the ECFSPR (in successful collaboration with national registries) as an appropriate platform for the collection of CF data for PASS and PAES. An SOP is in place for collaborative handling of the set-up of these studies by ECFSPR and ECFS-CTN.

<p>HIT-CF project aims to bring personalized therapies to CF patients with ultra-rare <i>CFTR</i> mutations</p> <p>Role of ECFS-CTN: protocol review, feasibility, help in coordination and dissemination of project, advice</p>	<p>www.hitcf.org 1 January 2018 to 31 December 2022 Grant agreement No. 755021</p>
<p>OligoG pivotal CF project</p> <p>Clinical trial of the orphan drug OligoG CF-5/20 in CF</p> <p>Role of ECFS-CTN: protocol review, feasibility, help in coordination and dissemination of project, advice</p>	<p>www.oligogpivotalcf.eu 1 January 2018 to 31 December 2020 Grant agreement No. 755234</p>
<p>Conect4children (c4c) project</p> <p>Collaborative network for European clinical trials for children</p> <p>Role of ECFS-CTN work package for education (Europe-wide survey of training needs in pediatric clinical trials, development of GCP eLearning) Protocol review of a C4C initiated trial that will investigate the treatment of <i>Aspergillus</i> in children with CF</p>	<p>https://www.conect4children.org 1 May 2018 to 30 April 2024 Grant agreement No. 777389</p>
<p>European Reference Network (ERN) -LUNG</p> <p>ERN-LUNG is a patient-centric network of European healthcare providers and patient organizations committed to reducing morbidity and mortality from rare lung diseases through patient care, advocacy, education, research, and knowledge sharing</p> <p>Role of ECFS-CTN: providing expertise in setting-up clinical trials networks (e.g. webinar explaining the set-up and conduct of ECFS-CTN)</p>	<p>https://ern-lung.eu</p>
<p>European Network for Pediatric Research at EMA (Enpr-EMA) is a network of research, investigators, and centers with recognized expertise in performing clinical studies in children</p> <p>Role of ECFS-CTN: voting member of the coordinating group</p>	<p>https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema</p>

Table 1: European projects

2.11. Investigator-initiated clinical trials

Investigator-initiated trials (IITs) fill an important gap to answer research questions that are not addressed by industry-sponsored trials. Many CTNs fund IITs, or act as a contract research organization (CRO) to support trial conduct. ECFS-CTN does not fund clinical trials, nor can it sponsor or conduct trials. To date, the majority of trials sanctioned by ECFS-CTN have been industry-sponsored. Nevertheless, it remains a long-term goal of ECFS-CTN to support IITs. Recent work by a James Lind Alliance priority setting exercise [11] provides direction for IITs wishing to respond to research priorities defined by collaboration between pwCF and healthcare providers. National POs and government funding agencies can fund smaller IITs but the most likely funding sources for larger multinational IITs are EU-funded programs such as Horizon 2020, the upcoming Horizon Europe, and public-private partnerships such as IMI2.

A current example of how these aims can be achieved is the EU-funded HIT-CF project (Table 1). This project involves screening intestinal organoids grown from rectal tissue biopsies to measure the response to a panel of CFTR modulators. Patients whose organoids respond to a certain CFTR modulator will be invited to participate in a clinical trial of that modulator to determine whether the response observed *ex vivo* is replicated *in vivo*. This approach could lead to a label expansion of approved CFTR modulators for patients with ultra-rare mutations for whom a clinical trial would never be performed. ECFS-CTN is a consortium partner in the HIT-CF project and has mobilized as a network to support

this project, initiated and coordinated by one of our member sites.

Future IITs will rely on provision of medicines from Marketing Application Authorization (MAA) holders at affordable prices [12], which could be a challenge given the list price of recently authorized treatments. ECFS-CTN could use their combined voice to exert pressure on sponsors to sign a public memorandum promising to provide medicines for ECFS-CTN sanctioned comparative trials. As Davies *et al.* note, making this a regulatory requirement would be the most effective way to ensure the feasibility of future comparative studies [12].

2.12. Global collaboration (TDN, CanAct and beyond)

Conducting and completing clinical trials in CF has become more exciting and more challenging as more drug development programs enter the therapeutic landscape, triggering competition for patient participation, changing the standard of care as new therapies are approved, and affecting how regulators view study protocols and how healthcare systems grapple with funding decisions. The establishment of strong connections between CF CTNs occurred just as these changes unfolded. The need to review and provide necessary feedback to sponsors on study design, specifically on selection of endpoints, feasibility of study visits and procedures, sample sizes, and most of all safety monitoring, provided the motivation to coordinate protocol review processes between the CFF-TDN and ECFS-CTN and more recently CF Canada's CanACT (Cystic Fibrosis Canada Acceler-

ating Clinical Trials Network). This sends a strong message to sponsors working with all networks, while allowing individual networks to highlight key issues unique to their regions. A well-vetted process map was developed for this parallel approach, which notes key steps for communication and final decision-making by each network's highest level committee to determine study sanctioning.

Apart from keeping track of sponsors' drug development plans, we have increasingly focused on the need to develop consensus around study designs and inform regulators who approve new drug applications. This has direct relevance for protocol development and review, given the number of different regulatory agencies that companies must satisfy, and the desire to propose protocols that fulfil requirements but remain feasible, properly sized, and can be enrolled to completion.

All networks face similar issues around training research coordinators and investigators in clinical trial conduct. Sharing tools and participating in training programs with collaborative networks has been an effective way of accelerating the work, avoiding the need for each network to develop their own material afresh. Not all processes are applicable internationally, and thus customization is necessary. However, at the same time this broadens the appreciation of key differences or novel approaches by partner networks.

The extension and application of quality or process improvement principles from the CF clinical care world into CF clinical research has allowed site teams and network leadership to develop tools and

training to support team-specific improvement projects, with the goal of improving readiness for study start-up and enrolment while lessening the burden on coordinators, who may struggle to manage burdensome tasks and systems.

To make collaboration work effectively, face-to-face meetings twice yearly around the time of international conferences or steering committee meetings have proved essential to finish ongoing projects, provide feedback and consultation, share tools, and reach consensus on strategic planning, SOPs, and training workshops. These meetings are supplemented with standing monthly conference calls between network leaders to address new issues in a timely fashion.

3 Future challenges and opportunities

3.1. Trial design

As CFTR modulators become standard of care, trial designs and outcome measures will have to be revised. Continued engagement with all stakeholders, including patients and POs, trial sites, CTNs, and regulatory agencies will be needed to integrate standard of care treatments into clinical trial designs. Clinical trials of medicines for very rare mutations are discussed in a recent ECFS strategic task force publication [13]. Trials should also be designed so that they generate the data needed for reimbursement decisions, following the collaborative example set by the Hercules project for Duchenne muscular dystrophy [12]. Networks such as ECFS-CTN can

contribute to discussions on trial design and continue work to standardize sensitive outcome measures.

3.2. Patient referrals (hub and spoke)

The recent ECFS strategic taskforce made several suggestions for improving the efficacy of trial delivery. One suggestion is to reduce the number of sites opened per trial and to delegate responsibility for trial allocation / site selection to CTNs. The network would then facilitate referral of patients from “spoke” care sites to the “hub” trial sites [12]. This would require extra work and expertise at CTNs and significant engagement from sponsors and trial sites.

3.3. Re-analyzing trial data

A future avenue for IITs is the re-analysis of existing clinical trial data. In 2015, the EMA published Policy 70 to encourage disclosure and sharing of clinical trial results. Clinical study reports (CSRs) and anonymized individual patient data that are submitted as part of a MAA will now be made available for download from the EMA website once marketing authorization has been granted or refused (or when the sponsor withdraws the MAA). Policy 70 was adopted in 2015 but publication of CSRs was halted. It is not yet known when CSR publication will resume. The publication of these results will have significant implications for academic researchers who will be able to re-analyze data and compare data across trials. The high level of standardization in clinical trial outcomes in CF will help increase the robustness of inter-trial data comparisons. Access to clinical trial patient-level data will also allow researchers to probe deeper

into the safety profile of medicines. For example, an academic re-analysis of pooled safety data from seven trials of an antiobesity drug found significantly more harms than indicated via traditional safety analyses presented in the CSRs and peer reviewed publications [14].

However, the research community will need to attract and recruit data scientists, bioinformaticians, and statisticians to help mine these data. Efforts should be made to start this process and to train these people in CF now, so that the talent is in place to analyze this data once publication of results resumes at the EMA.

4 Conclusions

Networks such as ECFS-CTN bring together research teams, sponsors, and patients to achieve multiple improvements in clinical trial conduct. Aggregating multiple gains across the spectrum of clinical trial design, set-up, and conduct promotes excellence in CF clinical research in Europe and further afield. The ultimate aim of the ECFS-CTN is that these cumulative effects trickle up to intensify clinical research in CF and get new medicines to patients as quickly as possible.

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CHAPTER 16

The role of patient registries in post-marketing drug monitoring – a European perspective

Author

Lutz Næhrlich

Introduction

Obtaining marketing authorization is an important milestone, but does not mark the end of drug development. At this stage the knowledge about efficacy and safety is limited because pre-marketing phase 1-3 clinical trials investigating efficacy and safety profile are usually performed with a limited number of patients over a limited study period. Furthermore, these patients are selected according to inclusion/exclusion criteria and may not represent the whole patient population in medical practices. The limited study period does not reflect the often lifelong treatment duration, especially for cystic fibrosis (CF). Therefore the long-term efficacy and safety cannot be observed during pre-marketing phase 1-3 clinical trials, particularly when considering new drugs, or rare or very rare adverse drug reactions and interactions. For the overall assessment of a new pharmaceutical drug, post-marketing drug monitoring is needed for the whole product life to monitor safety

and to act upon identified risks, by updating information in the package leaflet, communicating risk, or changing the authorization. Another aspect is the definition of a cost-benefit ratio for pricing, which is important for public health decisions and especially access to treatment. Post-marketing drug monitoring (pharmacovigilance) is a key public health task [1].

1 How is post-marketing drug monitoring (pharmacovigilance) regulated and monitored in the European Union?

In the EU pharmacovigilance efforts are coordinated by the European Medicines Agency (EMA) and conducted by the national competent authorities/ drug agencies. The legal framework is provided in Regulation (EC) No 726/2004 with respect to EU authorized medicinal products and in Directive 2001/83/EC with respect to nationally authorized medicinal products. The guidelines on **Good Pharmacovigilance Practices (GVP)** provide key guid-

ance of the pharmacovigilance legislative covering pharmacovigilance processes and product- or population-specific considerations [2]. The **Pharmacovigilance Risk Assessment Committee (PRAC)** at the EMA is responsible for assessing and monitoring the safety of human medicines including risk-management planning and post-marketing benefit-risk assessment. Marketing authorization holders (MAH) are required to submit a risk management plan when applying for marketing authorization, which should include information on the drug's safety profile, plans how to prevent or minimize its risk, and plans for studies or activities to learn more about the safety and efficacy of the medicine. EU legislation requires national competent authorities of member states to establish national pharmacovigilance systems to collect and evaluate information on adverse reactions to medicinal products or their side effects, and to take appropriate action where necessary. Pooling resources in this way ensures consistent standards, facilitates exchange of information about drug safety and helps medicines to reach patients faster [3]. **EudraVigilance** is a single repository for such reports and is used by member states, EMA and industry. It pools information from patients, caregivers and industry reports (including data from clinical trials) [4]. Data from EudraVigilance are published online in the EMA database of suspected adverse drug reaction reports (<http://www.adrreports.eu/en/index.html>). Despite the importance of post-marketing surveillance and national obligations for MAHs and caregivers to report adverse events, **passive surveillance** remains incomplete.

In some countries, patients can report adverse reactions directly to the national authorities.

Therefore, additional active surveillance is needed, especially for orphan drugs and rare diseases, like CF. **Post-authorization safety studies (PASS)** are important **active surveillance** tools to identify, characterize and quantify safety hazards, to confirm the safety profile of a medicine, and to measure the effectiveness of risk-management measures [5]. PASS can be clinical trials or non-interventional studies and can be initiated voluntarily by the MAH, or the PRAC can oblige the MAH to conduct the PASS. For such an imposed PASS, the PRAC assesses the study protocol and the study results. The EMA publishes PASS protocols, abstracts and final reports in the "EU electronic register of post-authorization studies" register (EU PAS Register) hosted on the website of the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP), after registration of the PASS by the MAH (GVP-Module VIII (Revision 3) EMA/813938/2011) [6]. As part of the safety measures, **drug utilization studies** describe how a medical product is used in routine clinical practice in large populations (including patients not eligible for inclusion in randomized clinical trials) and the extent of off-label use. Furthermore, the EMA can oblige **post-authorization efficacy studies (PAES)** if, at the time of marketing authorization, there are concerns relating some aspects of efficacy, which can be resolved only after the medical product has been marketed.

2 The role of registries for post-marketing drug monitoring (pharmacovigilance) - the European Union perspective

Disease or product specific registries can be necessary in active surveillance to measure the safety or efficacy of drugs in clinical practice. For 392 products that received a marketing authorization in the EU between 2005 and 2013, 31 registries were requested for 30 products. Nearly two thirds of these registries were product-specific registries and one third were disease-specific [7]. The MAH is legally responsible for providing valid and reliable results. Most registries were run by the MAH, who have full control of data structures, collection and quality. However these registries often suffered delays in setup and low patient accrual [7]. Existing patient registries are not fully utilized due to the lack of sustainability, lack of harmonized protocols and governance, data structures and uncertainties about data quality. This is despite the advantage of collecting long-term data including historical controls and untreated comparator patients for a broader patient population [8]. This leads to duplication of efforts and inefficiencies in the real world. Therefore, in September 2015 the EMA launched the "Initiative for patient registries" to explore opportunities to improve and better use existing registries as a source of high-quality post-authorization data for regulatory decision-making. Key steps of this approach are dialogue with the MAH and the registry holders, definition of data collection characteristics, identification of existing data sources,

identification of the data/information to be addressed and the need for amendments to registries. The perspectives of the different stakeholders were explored in a registries workshop held in October 2016. The topics discussed included governance (especially informed consent covering PASS and data privacy), long-term sustainability, harmonized data elements, and collection and data quality parameters [9]. Between June 2017 and June 2018, disease-specific workshops were held for hemophilia, multiple sclerosis, chimeric antigen receptor T cell therapy and CF [10]. Main recommendations were agreed for all patient registries. Registries have a monitoring function for previously identified adverse events or disease-related complications, but do not systematically collect all adverse events (safety reporting). Aggregated data instead of patient-level data are sufficient for the analysis [11].

The main recommendations of the CF workshops include [10]:

- **Governance:** Improving communication between EMA, MAH and registry holders so that EMA and MAHs are aware of the data that can be collected by registries and to inform registries in advance of their data needs. Establishing a standard process for requests for registry data for Europe.
- **Informed consent:** Ensuring that all registry patients have provided informed consent broad enough for sharing summary and, if needed, pseudo-anonymized data with EMA and MAHs.

- **Data quality:** Developing data quality indicators to be applied to all national registries, including source data verification procedures. Proposing EU standards for data quality indicators and for regulatory qualification.
- **Data elements:** Existing ECFS patient registry (ECFSPR) common variables are a suitable basis for regulatory evaluations. Agreed patient report outcome measures should be included for selected evaluations.

3 What are the implications for ECFSPR?

The ECFSPR collects since 2003 demographic and clinical data from consenting people with CF in Europe, in accordance with agreed inclusion criteria and definitions. The Registry's database includes data from more than 48,000 people with CF, from 35 participating countries, and longitudinal data from 2008 to 2017. The ECFSPR created the ECFSTracker, a web-based data-collection platform to document patients directly in the database (direct data entry) or to upload data from several national registries. The main aims of this research collaboration are to measure, survey and compare aspects of CF and its treatment in participating countries, deepen our understanding of CF, provide data for epidemiologic research and facilitate public health planning. New medical treatments and their impact on CF, especially efficacy and safety, are important research questions for caregivers and patients. The ability to contribute to regulatory decisions is both

an opportunity and challenge. Following a positive workshop discussion with all stakeholders and registry representatives from all over Europe, in 2017 the ECFSPR was one of the first patient registries in Europe to request qualification of its registry as suitable for performing pharmacoepidemiology. Six questions were posed by the ECFSPR together with supporting documentation: target population and variables, safety measures collection, data collection timelines and submission to EMA, type of data submitted to EMA, data quality and completeness, and analysis plan for registry data. Specific issues were raised by the EMA and discussed with ECFSPR. The positive qualification opinion in 2018 was a milestone for the ECFSPR. The principal agreement highlighted annual datasets, limitations on known CF complications and comorbidities, and aggregated data reports by ECFS-certified statisticians instead of raw data. The positive qualification opinion emphasizes the importance of the epidemiologic groundwork of many deeply committed research collaborators across almost all countries in Europe, with ECFS support. The EMA particularly highlighted the agreement on core and annual datasets, standardized terminologies and definitions, the shared software (ECFSTracker) and the annual report [12]. These achievements are the result of a high commitment of all collaborators despite a limited budget, mainly focusing on coordination, software, and statistics. Only a few national registries, but not the ECFSPR, offer financial support for data entry so far. For the ECFSPR to contribute to pharmacovigilance and other regulatory evaluations

with high-quality data in a timely manner on a long-term basis and across Europe, the EMA qualification opinion comes with obligations and challenges for the ECFSPR [9]:

Governance structures must be prepared for a centralized data application process and for communications with MAHs and the regulator. The public should be informed about benefits and uses of patient registries.

Informed consent is essential for any data use and must be broad enough for data-sharing, considering EU General Data Protection Regulation. Audit of patient consent has been recommended.

Data quality is a crucial task for any registry. For pharmacovigilance, data quality indicators must be applied to all participating registries and centers, including source data verification. Formal accreditation of registries for supporting regulatory evaluations must be established, based on agreed EU data quality standards.

Data elements must be reviewed and adapted to achieve a suitable basis for regulatory evaluations. Patient report outcomes, an important data element, are not currently in the ECFSPR.

Data entry support at the center level is critical for success. However, stressing data quality and timelines risks putting too much pressure on the center's cooperation and commitment.

Funding is crucial for the long-term sustainability of independent and high-quality registries.

Based on these recommendations, an ECFSPR pharmacovigilance working group was established, which offers a centralized review and feasibility process for

post-marketing studies and a centralized contact point in Europe for MAHs and EMA. Furthermore, the ECFSPR has intensified the work of the ECFSPR Data Quality Group. The ECFSPR Standard Operation Procedures (SOPs) are being reviewed, including topics such as data protection. A 2-year pilot project on source data validation was started in 2018 including 30 centers from 17 direct data entry countries [13]. A dialogue with the national registries was started in 2019 to document the status of data quality programs in each country. These steps will provide a basis for further individual enhancements and regulatory qualifications. Workshops with the MAH will inform about the benefit and uses of patient registries.

These important tasks have to be handled in parallel with the daily registry routine and stress the limited personal and financial resources of the ECFSPR and collaborators. It is critical for success that these efforts are supported by upcoming cooperation and projects with MAH and EMA. There is a window of opportunity to enhance the ECFSPR to provide high-quality post-authorization data for regulatory decision-making across Europe, but it needs a resolute and cooperative action from all stakeholders.

4 Experiences of patient registries in Europe

Based on EMA requests to develop long-term safety studies in 2012, the UK Cystic Fibrosis Registry initiated a pharmacovigilance program to contribute delivering new medications to patients sooner [14]. The

EMA guidelines for PASS protocols and final reports and for PAES lead the way, and a model of collaboration with industry was established. Important components include study governance (compliance with all applicable laws), confidentiality (non-disclosure of personal data and patient level data), intellectual property (granted access to anonymized data analysis and resulting reports), stated use (only for the agreed

and stated purpose of PASS or PAES), and publication (results of scientific interest published in public domain) and funding [14]. The UK registry has been audited against Good pharmacoepidemiology practices (GPP) [15]. Based on this collaboration several studies have been performed or are ongoing in Europe (**Table 1**).

	Status	Lead investigator	Participating countries	Publications
Prospective Case-Control Safety Study of Bronchitol (inhaled mannitol) in Patients with Cystic Fibrosis from the UK CF Registry	Finalized	Siobhan Carr	UK	[16]
An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients with Cystic Fibrosis	Finalized	Jennifer Evans	UK, US, FR*, IE*	[17], [18]
Utilisation Patterns and Real-World Effects of Tezacaftor and Ivacaftor Combination Therapy (TEZ/IVA) in Patients with Cystic Fibrosis (CF)	Ongoing	Julie Bower	UK, US, D, FR*, IE*	
A Post-marketing, Observational Safety Study of Quinsair (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis	Ongoing	Nicolas Simmonds	UK, D	
An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor and Ivacaftor Combination Therapy in Patients with Cystic Fibrosis	Ongoing	Caitlin Knox	UK, US, FR*, IE*	

Table 1: Overview on CF-specific Post-Authorisation Studies based on “The European Union electronic Register of Post-Authorisation Studies (EU PAS Register)” (accessed 04.01.2020)

*Drug utilization study only.

5 Perspectives

Post-marketing drug monitoring (pharmacovigilance) is an important task for patients, caregivers, industry and regulators. Patient registries like the ECFSPR are qualified to contribute to active pharmacovigilance surveillance in Europe, however this places stress on infrastructure, governance, data quality management and financial resources. The transformation from a mainly commitment-based research collaboration to a high-quality post-authorization database for regulatory decision-making is challenging. Continuous dialogue with patients is critical. The commitment of patients, collaborating partners like national registries and individual centers, MAH and regulators is needed to build up a constructive relationship to fulfill the goals of better safety and efficacy of new treatments. Recently, the first post-marketing studies have been published, mainly from the UK and US, and the first multinational post-marketing studies for CF across multiple countries in Europe have been requested by the EMA. These studies will be the proof-of-concept for this ambitious concept. We hope that this will pave the way to a long-term sustainable and independent patient-registry database in Europe, which can be adapted to future needs and fulfill the goals to contribute to pharmacovigilance as well as epidemiology and research.

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CHAPTER 17

Interactions in patients on CFTR modulators, a case study

Author

Anna Connolly

Introduction

The development and introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies has been described as the dawn of a new therapeutic era within cystic fibrosis (CF) patient care. These medications target the basic molecular defect in specific CF mutations. Currently, the European Medicines Agency (EMA) has licensed three CFTR modulator therapies: ivacaftor monotherapy (Kalydeco), lumacaftor/ivacaftor (Orkambi), and tezacaftor/ivacaftor (Symkevi) taken in combination with ivacaftor. In October 2019, the U.S. Food and Drug Administration (FDA) approved Trikafta (elexacaftor/ivacaftor/tezacaftor), the first triple combination CFTR modulator therapy. As these agents are used chronically and regular CF treatments continue concurrently, it is important that clinicians and pharmacists are aware of the potential impact of drug-drug interactions [1].

1 CFTR modulators

1.1. Ivacaftor

Ivacaftor is a sensitive CYP3A substrate. Co-administration of ivacaftor with strong CYP3A inducers (e.g. rifampicin) is not recommended due to decreased ivacaftor exposure. Co-administration with strong CYP3A inhibitors (e.g. voriconazole) and moderate CYP3A inhibitors (e.g. fluconazole) increases ivacaftor exposure, and a dose adjustment is recommended. Grapefruit juice and Seville oranges should be avoided during treatment with ivacaftor. They may increase exposure to ivacaftor due to moderate inhibition of CYP3A. Ivacaftor may inhibit CYP2C9. Therefore, monitoring of the international normalized ratio (INR) is recommended during co-administration of warfarin with ivacaftor. Ivacaftor is a weak inhibitor of P-glycoprotein (P-gp), therefore concomitant use with P-gp substrates (e.g. digoxin) may alter the exposure of these substrates [2].

1.2. Lumacaftor/ ivacaftor

Lumacaftor is a strong inducer of CYP3A and ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. No dose adjustment is necessary when CYP3A

inhibitors (e.g. voriconazole) are initiated in patients currently taking lumacaftor/ivacaftor. However, when initiating lumacaftor/ivacaftor in patients taking strong CYP3A inhibitors (e.g. voriconazole), the dose should be adjusted. No dose adjustment is recommended when used with moderate (e.g. fluconazole) or weak CYP3A inhibitors. Co-administration of lumacaftor/ivacaftor with strong CYP3A inducers (e.g. rifampicin) is not recommended due to decreased ivacaftor exposure. The net effect of lumacaftor/ivacaftor therapy is expected to be strong CYP3A induction. Concomitant use with CYP3A substrates may decrease the exposure of these substrates (e.g. benzodiazepines). Lumacaftor/ivacaftor may decrease the exposure of hormonal contraceptives (including oral, injectable, transdermal, and implantable) which may reduce their efficacy and reliability. Concomitant use of lumacaftor/ivacaftor with P-gp substrates (e.g. digoxin) may alter the exposure of these substrates. Concomitant use of lumacaftor/ivacaftor may alter (i.e., either increase or decrease) the exposure of CYP2C8 (e.g. montelukast) and CYP2C9 substrates (e.g. warfarin), decrease the exposure of CYP2C19 substrates (e.g. omeprazole), and substantially decrease the exposure of CYP2B6 substrates (e.g. bupropion). Co-administration of lumacaftor/ivacaftor with medicinal products that are substrates for organic anion transporter (OAT) 1 and 3, and Breast Cancer Resistance Protein (BCRP) transport may increase plasma concentrations of such medicinal products [3, 4].

1.3. Tezacaftor/ ivacaftor

Generally, tezacaftor is considered to have fewer clinically significant drug-drug interactions than lumacaftor. Tezacaftor and ivacaftor are substrates of CYP3A. The concomitant use of strong CYP3A inducers (e.g. rifampicin) may reduce tezacaftor/ivacaftor serum concentration and efficacy and is therefore not recommended. Increased serum concentration of tezacaftor/ivacaftor is expected with strong CYP3A inhibitors (e.g. voriconazole) and moderate CYP3A inhibitors (e.g. fluconazole) and dose adjustments are recommended. Ivacaftor may inhibit CYP2C9 and increase exposure of CYP2C9 substrates (e.g. warfarin). Tezacaftor/ivacaftor may increase exposure of sensitive P-gp substrates (e.g. tacrolimus). Substrates of CYP1A2 (e.g. theophylline) and CYP2B6 (e.g. bupropion) may have reduced exposure when used with tezacaftor/ivacaftor. Tezacaftor/ivacaftor has been studied with an estrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the hormonal contraceptive. Tezacaftor/ivacaftor is not expected to modify the efficacy of hormonal contraceptives [5, 6]. For drugs whose dosage was increased during treatment with lumacaftor/ivacaftor (e.g. antidepressants, benzodiazepines, proton pump inhibitors, systemic corticosteroids), it is important to consider a dose reduction following transition to tezacaftor/ivacaftor. Following transition from lumacaftor/ivacaftor to tezacaftor/ivacaftor it is recommended to consider waiting two weeks before initiating certain drugs (e.g. immunosuppressants, benzodiazepines,

antifungals) due to residual lumacaftor-mediated CYP3A induction [5].

2 Patient case report

2.1. Background information

The patient is a 36-year-old female with CF, with a baseline FEV₁ of 2.1 L (70%). Her genotype is homozygous for the *CFTR* mutation F508del (p.[phe508del]/c.[1521_1523delCTT]). This patient has a background history of pancreatic insufficiency, constipation, distal intestinal obstruction syndrome (DIOS), gastroesophageal reflux disease (GORD), and multifocal aspergilloma identified on thorax CT and hemoptysis. Sputum cultures show chronic growth of *Achromobacter species* and *Pseudomonas aeruginosa*. She has a history of intermittent antifungal use to manage hemoptysis associated with aspergilloma.

2.2 Introduction of CFTR modulator therapy: lumacaftor/ ivacaftor

Lumacaftor/ivacaftor tablets are indicated for the treatment of CF in patients aged 6 years and older who are homozygous for the F508del mutation in the *CFTR* gene [3]. Treatment was commenced for this patient in March 2018.

2.2.1 Identification and management of drug-drug interactions with lumacaftor/ ivacaftor

Prior to initiation of lumacaftor/ivacaftor, a comprehensive screen for potential drug-drug interactions was completed by the

CF clinical pharmacist. The key resources used were the Orkambi Summary of Product Characteristics (SPC) [3], Lexi-comp Drug Interactions[7] and the Orkambi (lumacaftor/ivacaftor) Drug-Drug interactions quick reference guide [4].

Two potential drug-drug interactions were identified and are described below.

Lumacaftor/ ivacaftor and omeprazole:

Lumacaftor/ivacaftor may decrease the serum concentration and exposure of omeprazole (a CYP2C19 substrate). This is due to the induction of CYP3A/2C19 by lumacaftor and may result in reduced efficacy of omeprazole. Consequently, a higher dose of omeprazole may be required to obtain the desired clinical effect [3, 4, 7]. Patient management and monitoring was as follows:

- Continue current dose of omeprazole 20 mg twice daily.
- Monitor the clinical response to omeprazole and titrate up dose if required.
- Patient was advised to report any increased symptoms of GORD.

Lumacaftor/ivacaftor and itraconazole:

Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor when co-administered with a CYP3A inhibitor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours (the approved dose of ivacaftor monotherapy).

Lumacaftor/ivacaftor may decrease the exposure of itraconazole and may reduce its efficacy. This is due to the induction of CYP3A by lumacaftor. Concomitant use of lumacaftor/ivacaftor with itraconazole is not recommended but if deemed necessary, patients should be monitored closely for breakthrough fungal infections [3, 4, 7]. Patient management and monitoring was as follows:

- Commence lumacaftor/ivacaftor at the reduced dose of one tablet daily for the first week.
- Following the first week, increase to the recommended dose of two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours.
- Monitor liver function tests and itraconazole levels and titrate up dose of itraconazole if required.
- Take itraconazole level after 7 days [8]. (Steady-state plasma concentrations of lumacaftor/ ivacaftor in healthy subjects were generally reached after approximately 7 days of treatment) [3]
- Itraconazole trough level should be maintained - or be kept above 0.5 mg/L (prophylaxis) and 1 mg/L (therapeutic). Less than 0.5 mg/L is a low concentration and there may be toxicity issues at higher concentrations (>4 mg/L) [8].

2.2.2 Impact of interaction between antifungals and lumacaftor/ ivacaftor

Prior to initiation of lumacaftor/ivacaftor in March 2018, itraconazole levels were therapeutic. A trough itraconazole level of

1.29 mg/L was taken in the morning prior to lumacaftor/ivacaftor initiation. The patient was admitted into hospital in late July 2018 following an episode of frank hemoptysis (30-50 mL). The tranexamic acid dose was increased, and intravenous antibiotics were also commenced. The hemoptysis resolved. Apart from the hemoptysis, the patient reported her respiratory symptoms at baseline. A CT thorax scan revealed multifocal aspergillomas which were indicated as the likely source of bleeding.

The patient reported recurrent episodes of hemoptysis since starting lumacaftor/ivacaftor. The patient expressed that she considered stopping lumacaftor/ivacaftor as she felt her quality of life was reduced secondary to the hemoptysis. Following discussion, it was advised that treatment with lumacaftor/ivacaftor should continue as the benefits currently outweighed the risks. It was also advised to continue with itraconazole for aspergilloma management. The itraconazole level was pending on discharge from hospital.

2.2.3 Change in antifungal treatment

Following discharge, the patient's itraconazole level was reported at 0.00 mg/L. Due to undetectable itraconazole levels likely due to the interaction with lumacaftor/ivacaftor, it was decided to switch from itraconazole to voriconazole. It was acknowledged that lumacaftor/ivacaftor can also decrease the serum concentration of voriconazole due to induction of CYP3A by lumacaftor [3, 4, 7]. However, itraconazole can be poorly absorbed when given orally to persons with CF. Voriconazole has greater bioavailability (96%) [9] in comparison to

itraconazole (55%) [10]. No dose adjustment of lumacaftor/ivacaftor is recommended when antifungals, including voriconazole, are initiated in patients currently taking lumacaftor/ivacaftor [3, 4, 7]. The patient started voriconazole in September 2018 with planned monitoring of liver function tests and voriconazole levels.

2.2.4. Antifungal treatment on hold

The patient was reviewed in clinic in November 2018 while continuing lumacaftor/ivacaftor. She reported feeling well with sputum volume and color at baseline. She described an isolated episode of streaked hemoptysis two weeks prior to the clinic visit. Pulmonary function tests (PFTs) were improved, with FEV₁ of 2.26 L, compared to a baseline FEV₁ of 2.1 L. She continued voriconazole, however levels were sub-therapeutic (< 0.5 mg/L). It was decided to stop the voriconazole on a trial basis. The sub-therapeutic levels were likely due to a decreased serum concentration due to lumacaftor/ivacaftor. It was discussed that going forward, lumacaftor/ivacaftor and antifungal treatment could be alternated to gain control of symptoms of CF along with symptoms of hemoptysis and aspergilloma. The patient was advised to wean tranexamic acid. She was also advised that if she experiences hemoptysis to restart antifungal treatment and increase tranexamic acid dose.

2.2.5 Discontinued lumacaftor/ivacaftor and restarted antifungal treatment

Subsequently, hemoptysis reoccurred (1-2 teaspoons of fresh blood followed by episodes of streaking). The patient discon-

tinued lumacaftor/ivacaftor in December 2018, restarted voriconazole and increased tranexamic acid to PO 1 g BD. The hemoptysis resolved. Since stopping lumacaftor/ivacaftor the patient reported a slight increase in sputum production and some mild shortness of breath on exertion. PFTs were at baseline. It was planned to continue with voriconazole. Once therapeutic levels were obtained, the introduction of tezacaftor/ivacaftor would be considered.

2.2.6 Change in antifungal treatment

In February 2019, the patient self-discontinued voriconazole (due to sub-therapeutic levels of voriconazole <0.53 mg/L and <0.5 mg/L reported in January and February). A CFTR modulator was not used during this time. She restarted itraconazole, however levels also remained sub-therapeutic at <0.45 mg/L in April 2019. It was discussed that voriconazole would be expected to have superior absorption compared to itraconazole. Despite this, the patient was eager to continue with itraconazole. It was decided to continue with itraconazole, and the dose was titrated gradually up to 400 mg BD.

2.3. Introduction of CFTR modulator therapy: tezacaftor/ivacaftor

Tezacaftor/ivacaftor is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation [5, 6]. Treatment was started for this patient in June 2019.

Medication	Route	Dose and Frequency
Azithromycin	Oral	500 mg daily on Monday, Wednesday, Friday
Aztreonam (Cayston)	Nebulized	75 mg three times per 24 hours for 28 days (alternate months)
Budesonide & Formoterol (Symbicort) 400/12	Inhaled	One inhalation twice daily
Calcium carbonate & Colecalciferol (Calcichew D3 Forte)	Oral	One tablet twice daily
Creon 10,000 units	Oral	With meals as directed
Dornase alfa (Pulmozyme)	Nebulized	2.5 mg once daily
Folic acid	Oral	5 mg once daily
Hypertonic sodium chloride 3%	Nebulized	One nebule twice daily
Itraconazole 100 mg capsules	Oral	300 mg in the morning and 200 mg in the evening
Macrogol (Movicol) sachets	Oral	Up to 8 sachets daily
Neilmed sinus rinse	Sinus rinse	One rinse twice daily
Omeprazole	Oral	20 mg twice daily
Salbutamol nebules	Nebulized	2.5 mg twice to three times daily
Salbutamol (Ventolin) evohaler 100 mcg	Inhaled	One inhalation as required
Senna	Oral	7.5 mg - 15 mg at night as required
Tobramycin 300 mg/5 mL	Nebulized	One nebule twice daily for 28 days (alternate months)
Tranexamic acid	Oral	500 mg three times a day
Vitamin A, D, E, K (Deka plus softgel)	Oral	One capsule daily
Vitamin D (Desunin) 800 units	Oral	One tablet twice a day

Table 1: Regular prescribed medications prior to introduction of CFTR modulator therapy

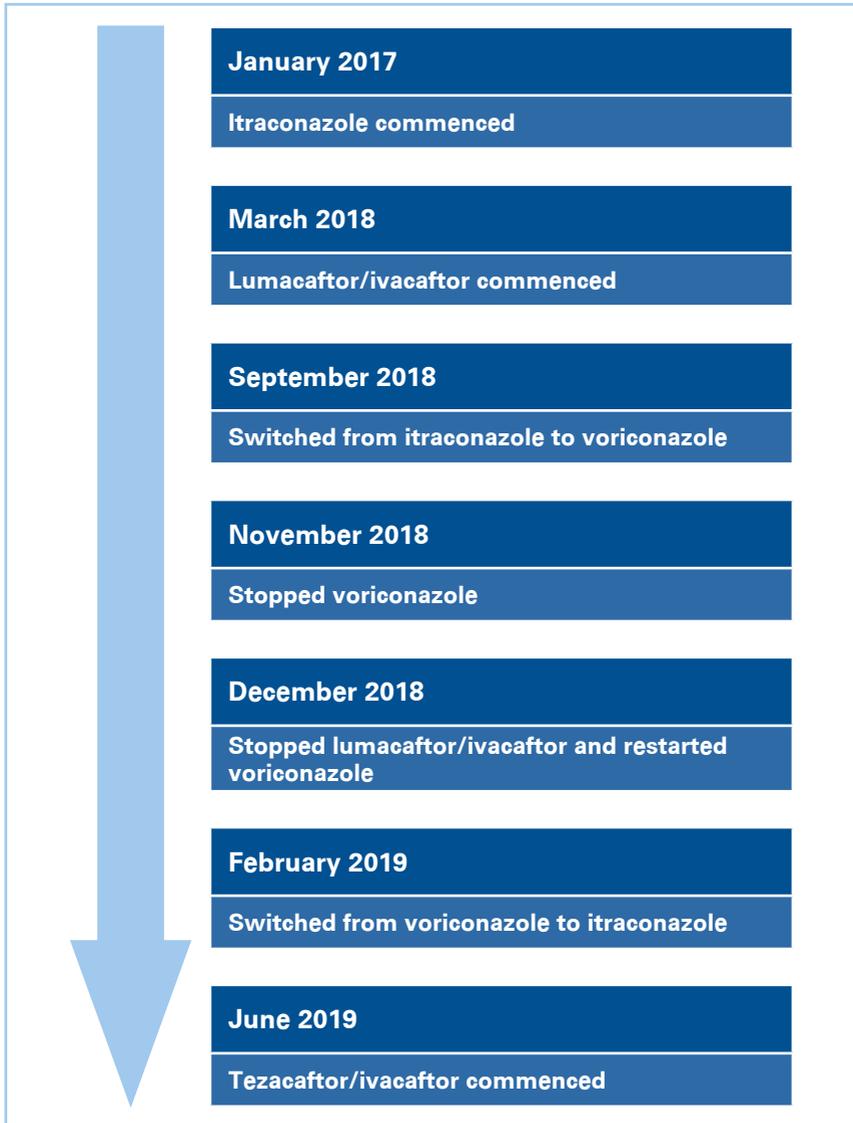


Figure 1: Timeline of antifungal and CFTR modulator therapy treatment changes

2.3.1. Identification and management of drug-drug interactions with tezacaftor/ivacaftor

Prior to initiating tezacaftor/ivacaftor, an in-depth screen for potential drug-drug interactions was completed by the CF clinical pharmacist. The key resources used were the Symkevi SPC [6], Lexicomp Drug Interactions [7], and the Symkevi+ Kalydeco initiation guide [5].

One potential drug-drug interaction was identified.

Tezacaftor/ivacaftor and itraconazole

Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (measured as AUC) by 4.0-fold and increased ivacaftor AUC by 15.6-fold. The dose of tezacaftor/ivacaftor should be adjusted when co-administered with strong CYP3A inhibitors (itraconazole), to one tezacaftor/ivacaftor tablet twice a week, taken approximately 3 to 4 days apart. The evening dose of ivacaftor should not be taken. Patient management and monitoring were as follows:

- Commence tezacaftor/ivacaftor at the reduced dose.
- Monitor liver function tests and itraconazole levels.

Usually, when transitioning patients from lumacaftor/ivacaftor to tezacaftor/ivacaftor, it is advised that the initial dose of tezacaftor/ivacaftor should be taken in the morning, approximately 12 hours after the final dose of lumacaftor/ivacaftor [5]. However, as lumacaftor/ivacaftor had been stopped in December 2018, this did not need to be considered.

2.3.2. Monitoring and patient outcomes while on tezacaftor/ivacaftor and itraconazole

Two weeks after commencing tezacaftor/ivacaftor, liver function tests (LFTs) were within the normal range and the itraconazole level was therapeutic (1.48 mg/L). One month after starting tezacaftor/ivacaftor, the patient's PFTs increased to FEV₁ of 2.36 L (80%) from a baseline FEV₁ of 2.1 L (70%). The patient reported increased energy, deeper breaths, increased appetite and an ability to clear mucous plugs more easily. The itraconazole level remained therapeutic (2.83 mg/L) with LFTs within the normal range. Currently, no further hemoptysis has been reported. It is planned to wean tranexamic acid with a view to discontinuing treatment.

3 Conclusion

This case highlights the importance of familiarity with potential drug interactions with CFTR modulator therapies and the capacity to manage these interactions appropriately. In addition to considering the impact of the drug interactions, it is essential to also consider the impact on the patient, their disease and symptoms, and overall wellbeing. Pharmaceutical care input is essential to optimize health in persons with CF. It is important to consider inter-patient pharmacokinetic and pharmacodynamic variability in addition to appreciating patient preferences in treatment. In this case, and for many persons with CF, hemoptysis is a fearful event that for many

can be associated with a decline in clinical condition and lung function. Therefore, hemoptysis management needs to be carefully balanced with the other clinical priorities of the patient. Modifying treatments on review and considering alternative options where available, can help to ensure that patient care is optimally managed.

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CHAPTER 18

CFTR modulators and pregnancy, a case study

Author

Edwin Brokaar

Introduction

Life expectancy in cystic fibrosis (CF) has increased over recent decades and more than half of patients in Western countries are now aged over 18 years. Many of these patients are well enough to consider pregnancy. In the previous few years, the proportion of CF patients using cystic fibrosis transmembrane conductance regulator (CFTR) modulators has vastly increased. As a result, the number of patients with access to CFTR modulators and who would like to become pregnant, is increasing as well. Unfortunately, information on the effects of CFTR modulators is very scarce. Yet women on CFTR modulators will become pregnant, with or without interrupting their CFTR modulators. Both options have benefits and risks that are known or can be estimated only in part. CF caregivers have a responsibility to guide their patients on how to deal with CFTR modulators and pregnancy. Here we present two young women with CF and describe the processes of deciding upon CFTR-modulating therapy during pregnancy.

1 Case presentation

Rebecca is a 27-year-old woman with CF who is homozygous for the *CFTR* mutation F508del (c.1521_1523delCTT/p.Phe508del), colonized with *Pseudomonas aeruginosa*, exocrine and endocrine pancreatic insufficiency and well-regulated CF-related diabetes (CFRD). She participated in a clinical trial with lumacaftor/ivacaftor (Orkambi) and has used lumacaftor/ivacaftor for five years. Her percent predicted (pp) forced expiratory volume in one second (FEV₁) improved from 65% to 90% during the first months on lumacaftor/ivacaftor and has remained stable during the subsequent 4.5 years. Prior to lumacaftor/ivacaftor treatment, each year she received several courses of intravenous antibiotics for pulmonary exacerbations, including tobramycin. During five years on lumacaftor/ivacaftor, her disease activity has stabilized, she has had only three pulmonary exacerbations and she was able to completely discontinue insulin treatment. At one moment during lumacaftor/ivacaftor treatment, serum creatine kinase (CK) levels rose sharply and lumacaftor/ivacaftor was discontinued temporarily. The CK increase was assessed and found not to be related to lumacaftor/

ivacaftor, which was restarted. During the interruption, Rebecca reported a decline in overall wellbeing and an increase in serum glucose levels. In October 2018, Rebecca approached the pulmonologist to discuss an anticipated pregnancy and the potential risks and benefits of lumacaftor/ivacaftor treatment during a pregnancy.

Our second patient, 26-year-old Deborah, is homozygous for the F508del mutation, is colonized with *Staphylococcus aureus* and has exocrine pancreatic insufficiency. Her ppFEV₁ gradually declined from 72% to 65% over the previous four years, but she has not had a pulmonary exacerbation during the last five years. Deborah was in the first trimester of her pregnancy when lumacaftor/ivacaftor became available. She wanted to discuss the appropriate time to start lumacaftor/ivacaftor with her consultant in relation to her pregnancy.

2 General considerations

Very little is known about lumacaftor/ivacaftor during pregnancy. The Summary of Product Characteristics (SmPC) of lumacaftor/ivacaftor recommends avoiding the medicine during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, but harmful effects on the unborn child cannot be excluded due to a lack of data. Therefore, the manufacturer states that “as a precautionary measure, it is preferable to avoid the use of lumacaftor/ivacaftor during pregnancy unless the

clinical condition of the mother requires treatment with lumacaftor/ivacaftor”. The Guidelines for the Management of Pregnancy in Women with Cystic Fibrosis state that untreated maternal medical conditions may lead to increased fetal risks [1]. These guidelines do not mention CFTR modulators specifically, as these agents were not available when the guidelines were published. The authors of a more recent literature review found no additional information and therefore, recommend avoiding CFTR modulators during pregnancy [2]. Therefore, pregnancy is not an absolute contraindication for lumacaftor/ivacaftor treatment and careful consideration is required to decide whether or not to treat a pregnant woman with CFTR modulators. Drugs may have negative effects in various stages of pregnancy, which include causing structural or functional defects, pharmacological effects on the unborn child, or an increased chance of stillbirth or early birth. With lumacaftor/ivacaftor, no such harmful effects were observed. Ivacaftor was not teratogenic when dosed at 7 and at 46 times the therapeutic human dose during the organogenesis stage of fetal development in rats and rabbits. Only at maternal toxic doses in rats did ivacaftor lead to decreased fetal body weight and structural rib defects. The pharmacological effects of lumacaftor and ivacaftor are not directly associated with DNA replication, of which harmful effects on the fetus may be expected.

Although this information suggests no direct harm of lumacaftor/ivacaftor on the unborn child, it does not exclude the occur-

rence of unknown and unexpected adverse events.

There are three possible approaches when managing the medication during pregnancy. The first is to eliminate any risk of lumacaftor/ivacaftor harming the child and refrain from use during the entire pregnancy. However, the mother's health may decline due to this approach. A compromise may be to discontinue lumacaftor/ivacaftor only at the moment pregnancy is established, as during pre-implantation stage the interaction between mother and fetus is very limited. The second approach is to continue lumacaftor/ivacaftor during the entire pregnancy. This minimizes fetal risks due to health decline of the mother, but the possible negative effects of lumacaftor/ivacaftor on the child are unknown. If a birth defect were to occur, the causality with lumacaftor/ivacaftor would still remain unclear as birth defects occur in approximately 2-4% in the general population. Finally, one may choose to discontinue lumacaftor/ivacaftor during the first trimester to minimize the chance of structural defects in the fetus that might be caused by lumacaftor/ivacaftor, but continue lumacaftor/ivacaftor during the second and third trimester to regain the benefits for the mother's health.

2.1. Individual considerations

Rebecca has shown a major and ongoing response to lumacaftor/ivacaftor therapy. Her FEV₁ at the start of lumacaftor/ivacaftor five years earlier was at the border of the recommended FEV₁ (>60%) that is necessary for a successful pregnancy according to the guidelines [2]. She improved from

unstable disease to stable disease and before lumacaftor/ivacaftor treatment, a pregnancy would not even have been considered a realistic possibility. Discontinuing lumacaftor/ivacaftor for a substantial period of time would probably lead to irreversible clinical deterioration and as a result, possible risk to a fetus. Aminoglycosides such as tobramycin that are used to treat pulmonary exacerbation are associated with ototoxic and nephrotoxic effects and ototoxicity in the fetus. Therefore, aminoglycosides should be avoided during pregnancy.

The unknown potential risks for the fetus of lumacaftor/ivacaftor and the plausible risks for both mother and child of discontinuation were discussed extensively with Rebecca, upon which she decided to continue lumacaftor/ivacaftor during the entire pregnancy with consent of the consultant pulmonologist. She was monitored closely by the pulmonologist in cooperation with the gynecologist throughout her pregnancy. Apart from a mild increase in serum glucose, the pregnancy went without complications and Rebecca gave birth to a healthy girl.

Deborah, on the other hand, had been in a relatively stable condition during the previous years and had experienced a low disease burden and her clinical condition did not require treatment with lumacaftor/ivacaftor. Introducing lumacaftor/ivacaftor in her situation would add an unnecessary potential risk to the unborn child and expose the mother to possible adverse drug reactions. Therefore, in her case the risk-benefit balance has led to the shared decision to postpone the start of lumacaftor/ivacaftor

until after birth. Starting lumacaftor/ivacaftor during pregnancy would still be possible if the clinical condition of the mother started to decline. Several times during the course of the pregnancy, the need for starting lumacaftor/ivacaftor was evaluated but rejected every time. Based on the mother's health, the use of lumacaftor/ivacaftor was not warranted at any stage during the pregnancy. Deborah too had an uncomplicated pregnancy and delivered a healthy girl.

3 Discussion

In the case of Rebecca, both the patient and the pulmonologist deemed the risk of a decline in health too high to discontinue lumacaftor/ivacaftor. This was motivated by the major benefit of lumacaftor/ivacaftor, that turned Rebecca's unstable disease into a much improved and stable condition. The patient did have some worries concerning the effects on the unborn child from her medications and lumacaftor/ivacaftor specifically. But when the detailed ultrasound scan at 20 weeks revealed no abnormalities, her concerns were eased.

The second patient, Deborah, had a FEV₁ similar to that of Rebecca before she started lumacaftor/ivacaftor. But because she had a relatively stable disease, it was chosen not to start lumacaftor/ivacaftor due to the unknown effects on the unborn child. Several case reports mention a successful pregnancy with the use of lumacaftor/ivacaftor and in a case series, all 12 pregnancies resulted in a live birth. Of these 12 pregnancies, 11 women used lumacaftor/

ivacaftor and one used tezacaftor/ivacaftor (Symkevi). In five of the 12 pregnancies CFTR modulating therapy was continued throughout the entire pregnancy. Of the seven patients who discontinued CFTR modulators, the medication had to be restarted due to pulmonary deterioration. Five out of 12 patients experienced complications during pregnancy, including three who developed gestational diabetes/CFRD [3]. Rebecca, who also had CFRD, also had an increase in serum glucose during her pregnancy.

The two cases described here illustrate that, in the absence of direct evidence for safety or harm, treatment with CFTR modulating therapy during pregnancy is a tailored decision. For both cases, the patient and consultant are content with the decision made and would do the same in an identical situation. Both patients state they were informed and counselled well by their consultant and that the advice was very important. They trusted and relied heavily on their doctor's opinion about whether or not to use lumacaftor/ivacaftor during pregnancy, as well as the assessment of the potential risks of use or non-use. This places a heavy responsibility on the shoulders of the consultant, who has to explain clearly and carefully all considerations. Patients should be informed that risks cannot be excluded and birth defects are possible – whether or not related to the use of medication. To assist clinicians, as much data as possible on CFTR-modulating therapies during pregnancy should be gathered and made accessible.

4 Acknowledgements

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CHAPTER 19

Medicines optimization in patients on NTM therapy, a case study

Author

Clare Cox

Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic pulmonary infection in patients with cystic fibrosis (CF). The most common species causing lung infection can be divided into slow growing species of the *Mycobacterium avium* complex (MAC) and rapid growing *Mycobacterium abscessus* complex (MABSC) [1, 2]. NTM can cause progressive inflammatory lung damage which is known as NTM-pulmonary disease (NTM-PD), but can also appear transiently, permanently or intermittently within the lungs without causing NTM-PD. This causes difficulties in deciding when to treat [2, 3].

Prolonged courses of multiple antibiotics are required to treat NTM-PD due to *M. abscessus*. This can be difficult to tolerate and have unpleasant side effects [3-6]. Before and throughout treatment for NTM-PD, it is important to optimize the patient's medication, by reviewing previous intolerances and concomitant medications.

This helps ensure treatment tolerability and efficacy, and may promote adherence.

Medicines optimization is defined as a person-centered approach to safe and effective medicines use, to ensure the best possible outcomes [7]. It aims to understand the patient experience, to ensure an evidence-based use of medicines and to ensure that medicines are used as safely as possible. It should be carried out routinely, to keep the patient at the center of continuous discussions. Any medication adaptations should be made in partnership with the patient, to individualize their care and improve outcomes [8].

1 Case

The CF patient is a 23-year-old female with the *CFTR* mutations F508del (c.1521_1523delCTT/p.Phe508del) and W1274X (c.3822G>A,p.Trp1274Ter). She has pancreatic insufficiency, CF related liver disease, impaired glucose tolerance, CF related gastroesophageal reflux disease, constipation and depression. She was first diagnosed with *M. abscessus*-PD in

September 2016. She had previously also cultured *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* on an intermittent basis.

Initial treatment started in October 2016 and involved followed an intravenous (IV) intensive phase regimen of amikacin, imipenem and tigecycline for 28 days, followed by a maintenance regimen of nebulized amikacin 500 mg twice daily, nebulized meropenem 250 mg twice daily, oral clofazimine 100 mg once daily, oral azithromycin 500 mg once daily and oral minocycline 100 mg twice daily. Between October 2016 and May 2019, the patient's lung function improved, and she felt better, but her NTM cultures remained positive for *M. abscessus*. Consequently, three treatment options were discussed with the patient: stop NTM treatment, augment her oral NTM regimen, or arrange a further course of IV antibiotics targeting *M. abscessus*. She opted to stop NTM treatment, as her lung function was well maintained, and she wanted to discount the antibiotic as a potential cause of ongoing bowel symptoms of bloating. The patient was started on maintenance treatment of continuous nebulized colistimethate sodium twice daily directed at *P. aeruginosa*, with no additional oral antibiotics to ensure the regimen was NTM sparing (to ensure effective microbiological surveillance for recurrence).

After coming off NTM treatment in May 2019, subsequent samples in June, July and August 2019 were smear positive and cultured *M. abscessus*. The patient was producing more sputum, was more fatigued, and was experiencing recurrent night sweats. By the end of summer 2019, the patient's lung function had declined by

200-300 mL compared to her previous baseline, with an FEV₁ of 92% and FVC of 93%.

An MRI scan in August 2019 showed marked progression of NTM, with extensive new consolidation in the lingula, right middle lobe (RML), left lower lobe (LLL) and extensive branching nodularity in the LLL, RML and upper lobes. There was also a new 1 cm thin walled cavity in the LLL, consistent with active NTM disease.

Based on the MRI findings, patient symptoms and positive microbiology, the patient agreed to be hospitalized to restart intensive phase *M. abscessus* treatment.

The patient had a history of allergy to ceftazidime (rash), meropenem (rash), and nebulized amikacin (tinnitus). The medications upon admission are presented in **Table 1**.

Upon admission (Day 1), tigecycline was started on a loading dose of 100 mg then 50 mg twice daily, with anti-emetic cover of ondansetron 8 mg IV twice daily, oral aprepitant 125 mg stat, then 80 mg once daily regularly. On Day 2 imipenem 1 g IV twice daily was added but the patient began experiencing increased nausea, which she strongly associated with the initiation of the imipenem infusion. Cyclizine 50 mg IV three times daily was added together with levomepromazine 6.25 mg po at night when needed, with a further dose of ondansetron available as needed. The nausea improved but was still troublesome, so on Day 4 the dose and frequency of imipenem was adjusted to 500 mg IV four times daily and the ondansetron was adjusted to 4 mg IV four times daily. Little improvement was seen so imipenem was stopped on Day 5 and was replaced with linezolid 600 mg IV twice daily on Day 6. We

discussed the timing of medications and ensured the antiemetics were given at least 30 minutes prior to the antibiotics to ensure maximum efficacy. Bowel habit was closely monitored due to the patient's history of constipation requiring prucalopride and as needed Laxido. She agreed to increase the dose of Laxido to three times daily with the addition of as needed Gastrografin to prevent any problems.

To counteract the decrease in calories due to her decreased appetite, the dietician arranged for supplements in the form of Fortisp compact three times daily and advised on cold food options as the patient felt that hot food was worsening her symptoms. In addition, we agreed that her long-term oral medications such as the ursodeoxycholic acid, vitamins and carbocisteine could all be paused until her symptoms were under better control.

The nausea settled and on Day 12 the patient started nebulized amikacin 500 mg once daily, oral clofazimine 100 mg once daily and oral azithromycin 500 mg once daily. During her previous treatment for *M. abscessus* the patient had developed tinnitus when on nebulized amikacin 500 mg twice daily. Following a discussion on the balance of risks, we agreed to avoid IV administration (which would be part of a usual intensive phase regimen) and to reduce the nebulized dose to once daily. Audiometry was arranged prior to starting treatment and she was aware to report any symptoms of dizziness, vertigo or tinnitus should they occur.

In the initial discussions with the patient, we had not defined the duration of the intensive phase of antibiotic treatment, with the plan to continue treatment as long as she could tolerate it. However, after a couple of weeks, the patient expressed that as an inpatient, it was becoming increasingly difficult to deal with not knowing an end date. Therefore we agreed a stop date, meaning she had 31 days of intensive phase IVs followed by the oral and nebulized maintenance treatments as an outpatient. In addition, regular and continuing appointments were set up with the CF psychologist to help her deal with this and other mental health concerns.

The rest of her hospitalization was uneventful, and she was discharged as agreed after 31 days of IV treatment, with an FEV₁ of 94% and an FVC of 96%. Sputum cultures were taken at the end of treatment that subsequently showed no mycobacterial growth.

Linezolid was converted from IV to oral administration, and the nebulized amikacin, oral clofazimine and oral azithromycin were continued along with her regular medicines. Nebulized colomycin was discontinued and we agreed to review the frequency of her mucolytic nebulizers of dornase alfa and hypertonic saline should she have trouble complying. We gave the patient a supply of oral ondansetron 4 mg three times daily to use when necessary and oral cyclizine 50 mg three times daily to use when necessary in case of any further nausea whilst on maintenance treatment, together with Gastrografin 30 mL three times daily when required for any constipation not managed by the increased dose of Macrogol. We

Medication	Route	Dose and frequency
Colistimethate sodium	nebulized	2 MU twice daily
Beclomethasone 100 mg + formoterol 6 µg (Fostair)	inhaled	2 puffs twice daily
Salbutamol 100 µg	inhaled	2 puffs when required
Carbocisteine 375 mg caps	oral	Two capsules twice daily
Dornase alfa 2.5 mg	nebulized	One nebule once daily
Sodium chloride 7%	nebulized	4 mL twice daily
DEKA Plus capsule (CF-specific multivitamin)	oral	One capsule once daily
DEKA Essential capsule	oral	One capsule once daily
Lansoprazole 30 mg capsule	oral	One capsule once daily
Prucalopride 2 mg tablet	oral	One tablet at night
Macrogol 3350 + electrolytes (Laxido)	oral	2 sachets twice daily
Creon 10,000 capsules	oral	Variable dose
Ursodeoxycholic acid 250 mg	oral	2 capsules at night
Sertraline 50 mg	oral	1 capsule each morning

Table 1: Medication on admission

also asked her to contact us should she have any problems prior to her clinic appointment in two weeks. A letter for her employer to cover the time off was provided together with an additional request they consider a phased return to work and additional breaks to enable her to more ably comply with her increased medication burden. Repeat audiometry was arranged for one month after discharge in view of the prescription of nebulized amikacin and azithromycin and her previous history. A repeat MRI was performed prior to discharge which showed some improvements in inflammation, though there were still changes consistent with NTM-PD.

2 Interactions to consider

QT prolongation can be caused by ondansetron along with maintenance azithromycin and regular sertraline. Therefore a baseline ECG was performed and repeated at the end of the intensive phase of treatment and during follow-up.

Linezolid is a reversible non-selective inhibitor of monoamine oxidase (MAOI) and there have been case reports of serotonin syndrome when administered with other selective serotonin reuptake inhibitors (SSRIs) such as sertraline. We discussed the balance of risks of concurrent use of these medicines with the patient. The patient remained on both medicines because her

dose of sertraline was relatively low and she did not feel able to discontinue it for the duration of treatment as her mood was already suffering. She was closely monitored during her inpatient stay, was made aware of the symptoms of serotonin syndrome and advised how to obtain help if symptoms appeared after discharge.

3 Monitoring requirements

Polypharmacy is a common challenge in CF. These challenges become apparent with the extensive treatment regimens required to manage *M. abscessus*-PD, and the addition of medicines to treat undesirable effects of the active treatment. The anticipation, prevention and treatment of nausea and vomiting due to tigecycline and imipenem requires a varied approach with multiple medications via multiple routes at specified times, and a close dialogue with the patient to ensure they are effective.

The use of multiple antibiotics for prolonged periods puts patients at increased risk of antibiotic-induced diarrhea and colitis, so changes in bowel habit need to be reported. Constipation also needs to be anticipated and treated. Routine blood tests of urea and electrolytes (U+E), full blood count (FBC) and liver function tests (LFTs) should be performed throughout treatment. Linezolid can cause bone marrow suppression so FBC should be monitored weekly for the first two months, then monthly if stable [2]. Patients should be counselled on the potential side effects of treatment and how they are identified and treated. This

reassures patients of the expected nature of side effects, so treatment is not discontinued prematurely. For example, linezolid can cause peripheral and optic neuropathy, clofazimine causes skin discoloration, aminoglycosides (used in both the intensive and maintenance phase of treatment) can cause ototoxicity, as can the addition of azithromycin. Thus relevant counselling and audiometry is necessary prior to, and during, treatment.

4 Discussion

Recent guidelines and consensus statements detail the multiple treatments required to tackle *M. abscessus*-PD. Intensive phase treatments for patients with clarithromycin-sensitive isolates or those with inducible macrolide resistance include amikacin, tigecycline, imipenem, oral clarithromycin or oral azithromycin for a minimum of 4 weeks, followed by maintenance treatments including nebulized amikacin and clarithromycin or azithromycin, plus 2-4 additional antibiotics (often clofazimine and linezolid).

The case above illustrates how we tailored the regimen for our patient, using a medicines optimization approach. The decision to stop the original course of treatment was made jointly, with the options fully discussed, with the appropriate safety checks and monitoring to ensure that any potential deterioration was identified and investigated promptly.

As the patient had significant gastrointestinal side effects with her first course of

M. abscessus therapy, the aim during the second course was to formulate a tolerable regimen that would allow treatment to continue for as long as possible. For this reason, the antibiotics were started in a staggered manner and the aminoglycoside regimen was modified. In addition, the anti-emetic plan was carefully constructed, reviewed daily and made in partnership with the patient, considering the severity and occurrence of her symptoms, and her wishes. Key interventions included stopping or pausing some medicines such as her regular oral medications when she was struggling taking them due to nausea, and maximizing nutrition with advice from the dietician regarding oral intake, supplements and food choices. This multidisciplinary patient-centered approach, which also included expert microbiological input, enabled the patient to get the most out of her drug therapies - an underlying principle of medicines optimization. Communication with the patient remains key to this approach, and ensures medicine use is as safe and efficacious as possible when using such complex regimens.

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