



**European Cystic
Fibrosis Society**

Living longer with Cystic Fibrosis

Editors

Dominique Hubert · Nicholas Simmonds

June 2015



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ACKNOWLEDGEMENTS

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PREFACE

Living longer with Cystic Fibrosis, the title in itself is already a reason to celebrate. Indeed, in developed countries the number of adults with CF now outnumber the children with CF.

Many thanks go to Dominique Hubert and Nicholas Simmonds for putting this entire book together. They did a great job in defining the necessary book chapters. They then identified the necessary contributors and motivated them to not only provide an overview of the evidence base in the literature but to also share their personal experience with the readers. The final result has become a highly interesting and easy-to-read book.

We hope that this book will help to attract more adult care physicians to the field of CF. With the continuously increasing number of adults with Cystic Fibrosis in every country, there is great need for training young internal medicine specialists in the complex care of adults with Cystic Fibrosis.

ECFS is very pleased to offer this book “Living longer with Cystic Fibrosis” to all ECFS members.



Kris De Boeck MD PhD
ECFS President

INTRODUCTION

The demographics of Cystic Fibrosis (CF) have changed considerably over the last few decades with median survival of around 40 years of age in most developed countries. It is no longer a disease exclusively of childhood as the number of adults living with CF outnumber children in many regions. While this should be celebrated it is also important to recognise that with this improvement in survival comes a new set of challenges for patients and their caregivers. That is why, after the first book published in 2012 on “Healthcare Issues and Challenges in Adolescents with Cystic Fibrosis”, ECFS decided to publish a book dealing with adult issues “Living Longer with Cystic Fibrosis”.

Our ambition was to cover a wide range of healthcare issues relevant to adults and an ageing adult population, in order to provide all members of the CF team with a resource to consult when considering some of the difficult issues that occur when people with CF grow older. We also wanted to provide some insight into the emerging issues so that healthcare services can keep pace and provide effective services in the future.

We thank all the authors from many different countries who worked together to achieve a comprehensive review of the main issues in adults, and who shared their experiences. We also thank the adult patients who have contributed to this book by providing invaluable insight into what it is like to live with CF as an adult.

Dominique Hubert and Nicholas Simmonds

CHAPTER 1

Changing epidemiology: new challenges in CF

Authors

Nicholas Simmonds, Barry Plant

Introduction

In the seven decades since cystic fibrosis (CF) was first described, considerable changes in both CF disease course and survival of patients have been seen. Improvements in our understanding of the natural history of CF, as well as progress in diagnosis and treatment have resulted in the majority of patients now reaching adulthood and enjoying many of the employment, social and personal achievements that their healthy peers take for granted. While these changes should be celebrated, we also need to acknowledge the challenges of an ageing patient population, and ensure that we keep pace with the issues of increased healthcare burden, increased disease complexity in the face of comorbidities associated with getting older, and the emerging antibiotic and infection challenges. This chapter discusses these new challenges and suggests approaches to future disease management in an adult CF population.

1 The changing demographics

Since the first description of CF as a distinct disease entity by the pathologist Dorothy Andersen in 1938, the demographic characteristics of the patient population have changed beyond recognition [1]. At that time, the diagnosis was devastating, with more than 70% of children dying within the first year of life, usually from meconium ileus, severe malnutrition and/or respiratory failure. The disease was originally termed ‘cystic fibrosis of the pancreas’, as pancreatic destruction was considered to be the primary defect and the respiratory manifestations were thought to be a secondary complication of malabsorption. Since then, our understanding of the pathophysiology and underlying disease mechanisms have improved considerably; however, the ultimate aim of a cure has yet to be realized. Thankfully, death in childhood is now rare and life expectancy has improved steadily (**Fig. 1**) [2].

In the USA, the median survival rose from 14 years in 1968 to 20 years in the mid 1970s [4]. Median predicted survival in many developed countries is now over

40 years of age, but it has only been in the last 30 years that reaching adulthood has become a realistic prospect for the majority of individuals. We are now in an era where the number of adults with CF will soon exceed the number of children [2]. In registries where adulthood is defined as at least 16 years of age, rather than 18 years, this has already occurred; for example, 57.6% of all CF patients in the UK 2012 annual data report were classified as adult [5].

The introduction of national and multinational registries, which collect large volumes of clinical data, has been instrumental in improving our understanding of CF and the changing demographics. The US CF Foundation Patient Registry (CFFPR) contains the data of nearly 30,000 patients and has been running for decades. For the year 2012, the US registry reported that 49.1%

of the population were adults (≥ 18 years), with an age range from birth to 82 years and a median age of 17.7 years (mean 19.8 years) [3]. The European Cystic Fibrosis Society Patient Registry (ECFSPR) is more contemporary but now contains the records of over 32,000 patients across 22 European countries spanning a diverse sociodemographic and cultural spectrum [6]. Overall, the European data are very similar to the US data: 49.3% of patients were reported as adults (≥ 18 years), with a wide age range from birth to 80.1 years and a median age of 17.8 years (mean 19.5 years) (Fig. 2).

In some European countries the proportion of adult patients is particularly high, such as in Denmark where at least 56% of CF patients are adults (≥ 18 years). Approximately 20% of the European registry popu-

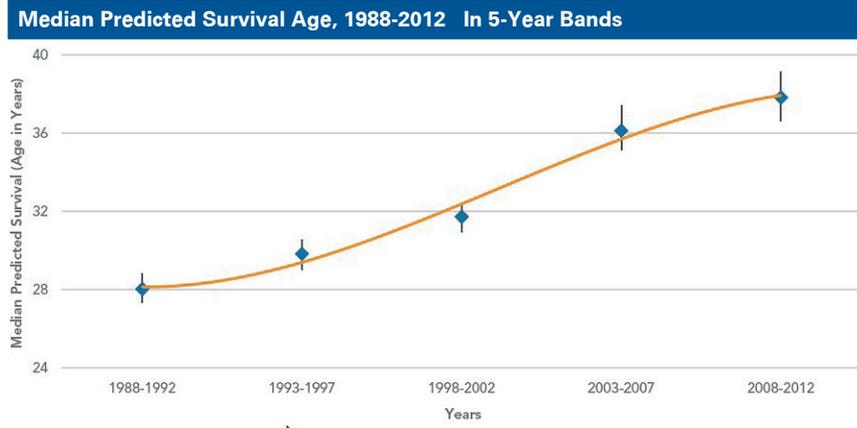
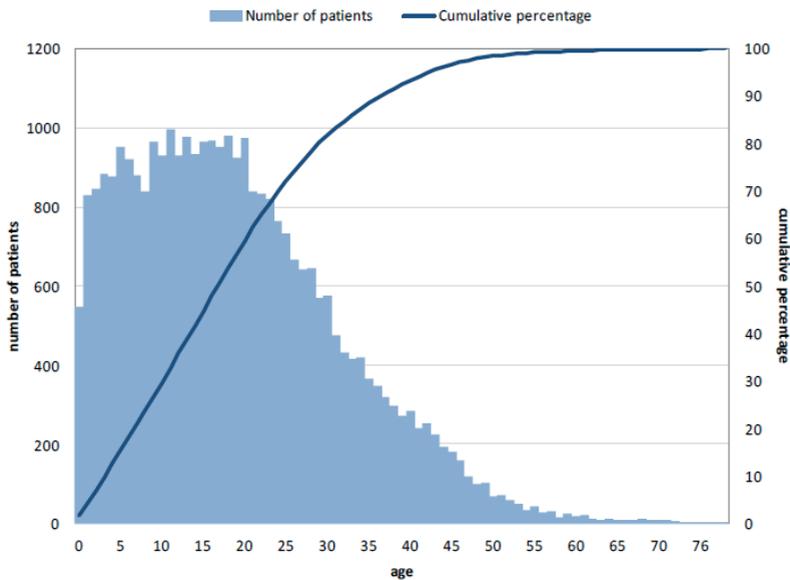


Fig. 1 Cystic fibrosis patients under care at CF Foundation-accredited care centers in the United States, who consented to have their data entered in 2012 - Median predicted survival, 1986–2012 (using 5-year bands on the x-axis to reduce year-to-year variability). (Reproduced with permission from Cystic Fibrosis Foundation [3].)

lation is aged over 30 years and 6% are over 40 years. However, there is significant variation between sociodemographic regions, presumably reflecting issues such as access to care, delayed diagnosis, resources and health policies. A cross-sectional analysis of the ECFSPR highlighted this by reporting some important demographic differences across Europe [7]. The median age of patients from European Union (EU) countries was 4.9 years higher than non-EU countries, and the proportion of patients aged at least 40 years was also higher for

EU countries (5% vs. 2%). Importantly, when demographic indicators of EU countries were modelled on non-EU countries, it was estimated that their CF population would rise by 84%, underlining the startling potential impact that sociodemographic factors can have on survival. In the UK, it has been estimated that the adult CF population will grow by approximately 145 patients per annum [8]. As this equates to a moderately sized adult clinic, this has important implications, not only to the patient, but also to future healthcare provision and staff training.



Each blue vertical bar represents the number of patients of that age alive in 2010. The cumulative percentage (blue line, right vertical axis) describes how many patients (as a percentage) are below a certain age (e.g. 50% of the patients are less than 18 years of age).

Fig. 2 Cross-sectional data of patient age in Europe, 2010. (Reproduced with permission from European Cystic Fibrosis Society [6].)

2 Why are CF patients living longer?

The reason for the steady improvement in median survival with an increasing adult population is the result of a multitude of factors. These can be broadly classified into genetic and non-genetic factors, which include environmental (e.g. pathogens, sex, tobacco smoke exposure and climate), healthcare-related (e.g. access to specialist clinics, infection control measures and adherence) and socioeconomic factors. Consequently, some determinants of survival are more amenable to modification than others; for example, treatment-related factors are easier to control than those related to climate. Since 1938, key scientific advances, including the identification of hypertonic sweat in the 1950s and the discovery of the CF gene (cystic fibrosis transmembrane conductance regulator [*CFTR*]) in 1989, have been instrumental in improving our understanding of CF pathophysiology [9–11]. However, even before these events, important improvements in care occurred as a result of careful clinical observation and a systematic approach to treating disease complications (e.g. infection and nutritional deficiency). Poor nutrition, the acquisition of pathogens such as *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*, undertreated CF-related diabetes, and female sex are well established factors associated with worse outcomes in CF [12–15].

Key treatment milestones over the years have included the introduction of intensive antibiotic regimens, pancreatic enzymes and the optimization of nutrition, effective

airway clearance, lung transplantation, anti-inflammatory drugs, drugs that enhance sputum clearance (e.g. dornase alfa) and, more recently, the introduction of mutation-specific protein-modulating drugs [16–19]. These, combined with the multifaceted approach to CF care delivered by a specialist multidisciplinary team (MDT), have been the principal factors leading to patients living longer, and are a model for the management of other chronic diseases [20].

When the *CFTR* gene was first discovered, it was thought that some of the CF survival variability would be explained by different mutations; however, the correlation of genotype with phenotype has been shown repeatedly to be poor, with the exception of pancreatic status (e.g. sufficiency vs. insufficiency) [21]. *CFTR* mutations can be divided into six classes according to their effect on *CFTR* function. Classes I to III are usually associated with more severe disease. Typically, a patient carrying one of these mutations on each CF allele is diagnosed early (i.e. aged <1 year) and has pancreatic insufficiency [22,23]. Patients with at least one class IV to VI mutation are often diagnosed later, are pancreatic sufficient, and therefore have better nutrition [24,25]. Some mutations associated with preservation of *CFTR* function manifest as milder lung disease, but for the vast majority of other mutations this does not hold true, and variability may exist between two individuals with the same genotype [22]. Putative mechanisms to explain this include numerous infectious, nutritional, and environmental influences, although none is likely to fully explain the differences [26]. Non-*CFTR* mutations or polymor-

phisms – termed ‘gene modifiers’ – probably contribute to this situation but, to date, only a limited number of modifiers have been identified [27–29].

Improvements in the diagnosis of CF have also contributed to the increase in survival. Even for patients with atypical features, the better understanding of underlying disease mechanisms and the development of more sensitive diagnostic tools, such as gene sequencing, have resulted in improved diagnosis. In the vast majority of cases, the diagnosis is straightforward and is confirmed if an individual has at least one phenotypic feature (e.g. widespread bronchiectasis), evidence of abnormal *CFTR* function (e.g. by sweat test), and/or two recognized *CFTR* mutations [30,31]. However, because CF disease expression is highly variable, reaching a diagnosis is not always straightforward, and this is particularly the case for adults presenting for the first time. These patients can be a diagnostic challenge as they may have an equivocal (or normal) sweat chloride and only one (or even no) identifiable *CFTR* mutation on first-line genotyping [25]. They are usually pancreatic sufficient and their disease is often termed ‘non-classic’ or ‘atypical’ CF. They may present with extrapulmonary features and, consequently, are sometimes first seen in a clinical setting outside of respiratory medicine, such as men with azoospermia in fertility clinics. For this reason, the diagnosis is often delayed (sometimes by many years), which may cause frustration and anxiety. As newborn screening is now practiced routinely in many countries, the rate of delayed diagnosis will decline significantly in years to come. However, it

will be replaced by a new set of challenges associated with identifying patients who are asymptomatic and could remain so for many years. The effects of this on patients with non-classic CF who may have a lower risk of developing extensive disease are wide ranging, and include the healthcare ‘burden’ of investigations, clinic visits, and treatments, as well as the psychological burden on patients and their families. However, if ultimately patients have better health and their survival rate is improved, as suggested in studies of classic CF [32], then newborn screening will be justified. The next 40 years will provide critical information on this debate.

The result of improved survival is an increasingly ageing CF population. Reports of patients aged over 40 years highlight their characteristics and potential reasons for longevity [33–35]. While a higher proportion than in the general CF population are categorized as non-classic CF, the studies highlight that many patients with classic disease are also living into their 40s and beyond [35,36]. An international study of 366 patients aged over 40 years reported that 68% were pancreatic insufficient and 33% were homozygous for the mutation *F508del* [33]. The subset of patients from the USA and UK had a higher proportion of patients with classic disease, with 81% reported to be pancreatic insufficient and 44% having the homozygous *F508del* genotype. Overall, the factors pertaining to improved survival in general, as discussed above (e.g. improved nutrition and delayed *P. aeruginosa* acquisition) [34], are likely to be the most important determinants of longevity, but other factors, which are

difficult to quantify – such as exercise and education, may also be important.

As patients grow older their needs are likely to evolve and services will need to adapt to accommodate this. These issues and some of the challenges in satisfying these changing needs are discussed below.

3 The challenges of longer life expectancy

3.1. Treatment burden

Improved survival increases the treatment burden, which is an evolving new challenge for patients, their healthcare teams, and care funders. With an ever increasing number of drugs prescribed, adherence issues are likely to remain an ongoing and important issue. For example, inhaled therapies have been an integral part of CF airway management for many years [37–39], and there are now multiple different drugs that are delivered via this route (e.g. antibiotics and mucolytics). However, their benefit outside the arena of clinical trials is based on the assumption of ‘real-world’ adequate adherence. A UK group compared patient self-reported, physician-reported and actual adherence to treatment using electronic monitoring via an I-Neb nebulizer system [40], and showed that median actual adherence as recorded by the I-Neb downloads was only 36% compared with 80% for self-reported adherence. Recent refill data from another study demonstrated that those with high adherence to nebulized antibiotics had a significant reduction in hospitalizations

compared with those with lower adherence, demonstrating a real-world benefit [41]. However, the time commitment associated with adequate adherence is considerable: in a recent US study, the mean time spent on therapies per day (excluding cleaning) was 108 minutes when patients adhered to their prescriptions [42].

For the patient, the challenge is to adhere to these treatments in order to maximize their chance of a good health outcome. Healthcare providers and practitioners need to support this effort and, where possible, change to delivery systems and formulations (e.g. dry powder) that minimize treatment time and hence patient burden. The rapid delivery systems [39,43,44] offer new promise, and emerging real-world data show evidence for the link between sustained adherence and effectiveness [45]. The new challenge for patients with CF and their healthcare teams is to sustain this effort in an environment where some patients may be relatively less symptomatic.

3.2. Restoration of *CFTR* function

Restoration of *CFTR* function targets the underlying cause of CF rather than the consequences and remains the ‘Holy Grail’ of CF therapy. Until recently, this was a research aspiration [46,47]. However, the emergence of personalized pharmacological *CFTR* potentiators and correctors [16,48,49], based on *CFTR* genotype, offers exciting new possibilities for all patients with CF.

Ivacaftor is a new class of drug (*CFTR* modulator), which has recently been licensed in many jurisdictions for the treatment of patients with CF who are aged 6 years

and older and who have at least one copy of the 'gating' mutation *G551D* [16,48] or one of eight other non-*G551D* gating mutations [50]. In a large, 48-week, randomized controlled trial conducted in patients with CF aged 12 years and older with at least one copy of the *G551D* mutation, a 10.6% mean absolute improvement in forced expiratory volume in 1 second (FEV₁) % predicted was observed [16]. Similar findings have since been demonstrated in other cohorts [48,50]. Worldwide, this will benefit approximately 5% of the CF community, with an estimated 2000 patients aged ≥6 years carrying at least one copy of the *G551D* mutation and 400 patients aged ≥6 years with at least one non-*G551D* gating mutation. In this cohort, the challenge of maintaining sustained clinical efficacy, safety and effectiveness is crucial. Recent clinical trial data demonstrated a sustained effect up to 144 weeks [51], and real-world multicentre data have also shown sustained benefits [52–54].

Moving forward, challenges remain. For example, the concept of 'de-escalating' other therapies would be very well received by patients and caregivers alike but currently the effect of this is unknown. Drug–drug interaction is an important emerging area, as co-administration of ivacaftor with strong inhibitors or inducers of CYP3A significantly increases or reduces ivacaftor exposure, respectively [55]. For patients without these gating mutations, the personalized approach has yet to be realized, and important questions remain amid conflicting results [49,56]. How healthcare providers measure and manage patient expectations of these treatments is also a key consideration.

3.3. Drug resistance and emerging infections

Antibiotic resistance rates are increasing in adult populations [33,35], and associated toxicity, intolerances and/or allergy are increasing challenges for healthcare teams [57,58]. In addition, many chronic treatments were previously studied in a manner or at a time that did not assess the effect of adding these therapies to existing treatments, and the potential for drug–drug interactions is not well understood [17,59]. The assumption is that additional therapies will have additional benefits. However, a recent retrospective study highlighting the potential interaction between nebulized tobramycin and oral azithromycin showed a reduction in effectiveness, and raises important questions for the future [60]. More work is needed in this area.

Disease complexity is changing in CF. As a result of the delay in progression of many of the clinical manifestations of CF, patients are encountering problems at different or later periods in their lives. Aggressive strategies to eradicate *P. aeruginosa* have delayed the time to chronic infection, and increasing numbers of young adults make the transition from paediatric care with no *P. aeruginosa* infection. It is important that adult patients and their healthcare providers continue to monitor for the acquisition of new pathogens and commence eradication protocols in a timely fashion [61]. However, an independent working CF adult is not the same as a dependent child, with potentially different supports, objectives and commitments. Further work to determine the best or most appropriate eradication, moni-

toring and treatment approaches in this expanding adult population are a future priority. Although this 'Pseudomonas-free' cohort is an important achievement, antibiotic resistance [33,35] and the emergence of other pathogens, including the increase in prevalence of non-tuberculous mycobacteria infection and in particular *Mycobacterium abscessus* [62,63], are important challenges. The consequences of current antibiotic practice will need to be monitored continually [64]. Recent data suggest the potential for person-to-person spread of some strains of *M. abscessus*, highlighting the importance of continued evaluation and re-assessment of segregation practices for healthcare providers [65,66].

3.4. Extrapulmonary complications

Extrapulmonary manifestations of CF are an increasing challenge (Fig. 3), as morbidities of ageing are superimposed on 'traditional' CF complications, adding to the complexity of treatment needs [67]. These issues are discussed in greater detail in later chapters but an overview of their associated challenges is presented below.

Prevalence rates for many extrapulmonary complications increase with age. For example, CF-related diabetes (CFRD) occurs in 27–52% of adults over 40 years of age [33,35,69]. CFRD is associated with worse outcomes [70–73] and, critically, it is an independent predictor of mortality [74–76]. Microvascular complications (nephropathy and neuropathy) can occur (usually after

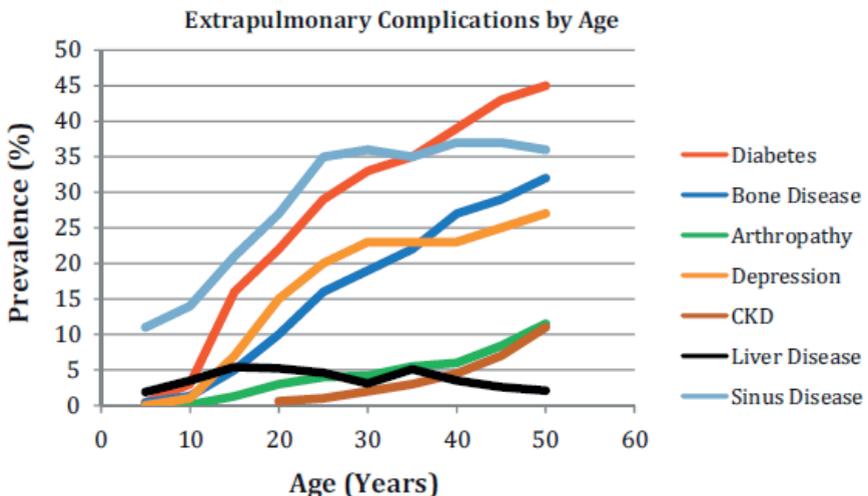


Fig. 3 Prevalence of extrapulmonary complications by age adapted from the CFFPR (US data). (Reproduced with permission from Elsevier. [68].)

10 years from the onset of CFRD) and, although rare, there are increasing reports of macrovascular complications, all of which have the potential to increase with an ageing CF population [77].

CF-associated liver disease (CFLD) is a difficult topic. While data exist suggesting that *de novo* CFLD does not develop in adults without prior evidence of disease [78], there is increasing evidence supporting an association between CFLD and an increased risk of mortality [79–81]. Chronic kidney disease (CKD) increases with age and is reported predominantly in adults [82,83]. The risk of CKD doubles with every additional 10 years of age. Patients with CKD also typically have poorer pulmonary function [84].

The prevalence of osteoporosis in CF increases with age (Fig. 3), although, interestingly, the prevalence appears to be decreasing over time for the CF population as a whole. As there is also a higher incidence of osteoporotic fractures in CF patients compared with healthy controls, screening and early treatment of osteoporosis are important [85].

The risk of malignancy in 'healthy' populations increases with age [86]. CF studies have employed the use of the standardized incidence ratio (SIR), which is the ratio of observed compared with expected cancers in a cohort, extrapolated from general population data. Current data demonstrate a significant increase in gastrointestinal cancer risk in CF (SIR 3.5) [87]. Our understanding of the relationship with age is evolving. Original 10-year data suggested an increased risk of digestive cancers with increasing age; however, follow-up pooled

20-year results reported that the SIR does not differ significantly in different adult age groups (although over 60% of all observed gastrointestinal cancers were reported in patients over 40 years of age).

As a consequence, the decision of when and how to investigate possible bowel pathology presents a complex clinical dilemma [88]. Currently there are conflicting data on whether CF confers an increased risk of non-gastrointestinal cancers [89–91]. Anxiety and depression occur in 9–30% of CF patients, and are more common in adults than in children with the disease [92,93]. Individuals with anxiety and/or depression are more likely to have a high perceived increased burden of illness, poor adherence and high healthcare utilization [94]. In addition, anxiety and depression have been shown to correlate with pulmonary function and pulmonary exacerbation frequency [92,93]. Thus, this highlights the need for improved early identification and management strategies for psychological illnesses.

3.5. Other challenges

There are a number of other important but diverse challenges that patients may face as they live longer. These range from transplantation challenges to social issues. These will be discussed in greater detail in later chapters but a brief outline is provided here.

The point at which a patient should be referred for lung transplantation needs to be analysed and revised regularly to take account of the expanding therapeutic options available before this stage is reached. Although predictive modelling of survival is useful, it needs to be dynamic [95,96]. Traditional thinking was heavily

influenced by a critical paper from over 20 years ago, which reported a median survival of 2 years in patients with FEV₁ <30% predicted [97]. Since then, in the modern treatment era, another single-centre study has shown a radical increase in survival from 13 months to 5.3 years [98] in this cohort. Equally, over this time span, there has been an increase in antibiotic resistance [33,35], renal disease [82], and the emergence of novel pathogens [62] in end-stage disease, which pose separate problems for the transplant services. Thus, further survivorship modelling is now required to establish the optimal window for transplant referral [67].

Parenthood, with appropriate careful interdisciplinary planning, care and close team work between the obstetric, fertility and CF teams, for both women and men, is not an uncommon or unrealistic expectation for many adults with CF [99]. For women, medium-term outcomes based on disease progression do not appear to be adversely affected by pregnancy [100]. However, a recent study highlighted more illness-related visits, pulmonary exacerbations, and a decrease in some domains of quality of life, presumably reflecting the impact of the physical and emotional challenges of early motherhood on disease self-management [101]. New challenges for patients and healthcare teams will include the desire for a second or third child, and pregnancy after lung transplantation [102]. Increasing employment is an important result of patients living longer, and although the positive effects of employment are difficult to quantify, it is likely to contribute to wellbeing for many. The negative health

outcome consequences of unemployment, including societal isolation and poverty, are well documented in other chronic diseases [103–105]. Registry data from 2011 suggest that approximately one-third of all adults are in full-time employment and many others are in part-time work [99,106].

Healthcare modelling needs to consider the fact that future clinics will be treating an increasing number of adults, and more distinct disease cohorts may emerge. For example, this could include not only the classic and non-classic phenotypes but also the emergence of CF disease that behaves clinically like non-CF bronchiectasis in the era of mutation-specific therapies. Models of care provision, the best management of disease complications, and the expectations of patients and healthcare teams may all differ. Important debates on maintaining standards will be necessary as patient numbers increase. The optimal size of a clinic is unknown but needs to be balanced between clinical experience and personalized continuity within an MDT. Embracing benchmarking models [107,108] and continued development and utilization of international consensus-driven standards of care are critical to achieving optimal patient care [109–111].

Finally, in the treatment of CF there is an increasing need to manage cost-effectiveness issues for the funder. Such analyses should include complex health technology assessment approaches, which evaluate comparative treatment effectiveness (novel and established). Total costs should include not only direct healthcare costs, but also the cost of lost productivity by both patients and family caregivers [112].

4 Conclusion

CF treatment and care are changing rapidly and have resulted in improved patient survival. The burden of care and disease complexity are increasing, and new treatment modalities may augment or potentially indirectly contribute to this burden. A dynamic and open-minded approach moving forward is critical. These issues are explored in greater detail in the forthcoming chapters.

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CHAPTER 2

The increasing complexity of CF-related problems: Pulmonary complications

Authors

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Introduction

Major improvements in cystic fibrosis (CF) care over past decades have steadily increased survival. Nonetheless, the natural history of CF lung disease is still characterized by a progression to end-stage disease, and respiratory failure is the first cause of death, followed by liver disease and complications after lung transplantation [1]. This chapter presents the different complications of CF lung disease and describes the management possibilities for progressive respiratory insufficiency.

1 Pneumothorax

Approximately 3.4% of all people with CF will present with pneumothorax at some point in their lives, the annual incidence being 0.64% or 1/167 patients per year [2]. For patients who have previously presented a first episode, the risk of recurrence is very high (50%–90%), and in these cases a pneumothorax on the contralateral side is frequently observed (46%). Most pneumothoraces occur in adults (72.4%), which probably reflects a more severe lung involvement [2]. The possible risk factors for pneumothorax are thought to be chronic infections with *Pseudomonas aeruginosa*, *Burkholderia cepacia* or *Aspergillus*, forced expiratory volume in 1 second (FEV₁) <30% predicted, tube feeding, pancreatic insufficiency, allergic broncho-pulmonary aspergillosis (ABPA), massive haemoptysis, inhalation of dornase alfa or tobramycin, and compromised social status [2].

1.1. Diagnosis

Pneumothorax should be considered as a differential diagnosis in patients experiencing new chest pain and/or increased

dyspnoea. The first step for diagnosis is a postero-anterior chest X-ray. However, in some cases, only chest computed tomography (CT) scan can provide a definitive diagnosis [3].

1.2. Management

Management differs according to size (small vs. large) and frequency (first vs. recurrent) of the pneumothorax [4]. Patients with small pneumothoraces, who are in a clinical stable condition, may be closely observed in the outpatient setting with a follow-up chest X-ray after 24 hours [4]. A patient with a large pneumothorax should always be admitted to the hospital. A chest tube should be inserted in cases of large pneumothorax, clinical unstable patients or in patients with increasing pneumothorax on follow-up chest X-ray.

There are no randomized, controlled trials that systematically evaluate the evidence for the correct management of recurrent or persistent pneumothorax [5]. Pleurodesis is an option, with the aim of achieving symphysis between parietal and visceral pleura. Thoracoscopic pleurodesis (talc poudrage, pleural abrasion, partial pleurectomy) is generally preferred over instillation of a sclerosing agent through a chest tube [4]. In addition, surgical procedures including video-assisted thoracoscopy surgery and/or thoracotomy can be performed for treatment of blebs and bullae by stapling and mechanical abrasion of the parietal pleura [4]. The need for future lung transplantation has to be taken into account, as pleurodesis is considered to be a relative contraindication to lung transplantation [6,7].

Further supportive measures consist of

checking that airway clearance techniques and aerosolized medications are optimal, and adding oral or intravenous antibiotics and noninvasive ventilation (NIV) if necessary [4]. Airway clearance techniques that create positive expiratory pressures and intrapulmonary percussion should be withheld in patients with pneumothorax; other airway clearance measures should be continued. Aerosolized medications should be continued unless there is a significant increase in coughing with a risk of deterioration. Coughing remains a very important tool for the drainage of sputum, especially in patients who are immobilized with a chest tube. Some aerosolized medications can be suspended on an individual patient basis.

For a small pneumothorax, there is normally no need to add systemic antibiotic treatment. In large pneumothoraces with a fistula, systemic antibiotics should be given in order to minimize the risk of pleural infection. NIV may become necessary in large pneumothoraces because of increased carbon dioxide retention in severely ill patients with advanced lung disease; on the other hand, NIV has the potential to negatively impact on the healing of the fistula. Very precise monitoring of the patient in these circumstances (sometimes in the intensive care unit [ICU]) is, therefore, mandatory [4].

If pneumothorax causes a life-threatening complication, management decisions should always be taken by a team of specialists (thoracic surgeons and pulmonologists). The mortality rate during a first episode of pneumothorax is estimated to be 6%–14% [2].

In the first 2 weeks after resolution of a pneumothorax, it is recommended not to fly, lift heavy weights or perform spirometry [4].

2 Haemoptysis

Haemoptysis is a common complication, occurring in approximately 9% of people with CF at some point in their lives. Minor haemoptysis is reported in up to 60% of adults with CF. Massive haemoptysis (>240 mL in a 24-hour period) or recurrent bleeding (>100 mL/day over several days) is fortunately less common, occurring in less than 1% of all CF cases. However, it can become instantly life-threatening as a result of asphyxiation and/or circulatory collapse.

2.1. Management

Minor haemoptysis very often requires no specific treatment. Persistent minor haemoptysis, however, may indicate a pulmonary exacerbation. Airway clearance manoeuvres and aerosolized medications, which may irritate the bronchial tree, should be adapted to the clinical situation, and tranexamic acid and oral or intravenous antibiotics should be added to treatment [4]. The available evidence indicates that tranexamic acid may reduce both the duration and volume of bleeding with a low risk of short-term thromboembolic complications [8]. Beta blockade may be considered in patients with recurrent minor haemoptysis who are resistant to conservative therapy, with no apparent adverse effect on lung function and an acceptable safety profile [9]. Measures to detect coagulation defects should be implemented in order to enable timely correction.

Massive haemoptysis is more frequently seen in older patients and in those with more severe disease, but it may also occur

in patients with minor functional impairment who already show abnormal bronchial vessels [10]. Supportive measures for CF patients presenting massive haemoptysis include admission, oxygen, fluid resuscitation, correction of thrombocytopenia and coagulopathy (fresh frozen plasma). Airway clearance and aerosolized medications are suspended in the immediate period after a massive haemoptysis. Patients who do not respond to the initial medical treatment should undergo bronchial artery embolization (BAE) [4]. Endobronchial tamponade and selective or double-lumen intubation may need to be considered to control bleeding while awaiting BAE. Intubation should be avoided and reserved for unstable patients with airway compromise [11].

CT [12] or bronchoscopy is used in some centres in order to localize the bleeding site and prepare for BAE. However, the general consensus is that there is insufficient evidence that these investigations are helpful and performing them may delay treatment [4]. BAE will control the bleeding in the vast majority of cases [13]. BAE should be performed by an experienced interventional radiologist, as the bronchial circulation has many variants, non-bronchial systemic arteries may supply the bleeding site, and spinal arteries arising from the bronchial circulation are common. Minor complications are frequent and include chest pain. Major complications are rare but may be catastrophic, resulting from embolization of a systemic artery [14]. Recurrence rates tend to be high (new supplies, recanalization of the occluded arteries) (20%–40%), and some patients experience multiple recurrences; fortunately, BAE can

be repeated [15]. In refractory cases, the successful use of recombinant activated factor VII has been described [16]; surgery is a last resort [17].

Despite an accrued mortality rate in patients with pneumothorax or massive haemoptysis, these patients should be admitted to the ICU and intubated promptly, should this be required, as approximately 60% survive to hospital discharge [18].

3 Allergic broncho-pulmonary aspergillosis

Allergic broncho-pulmonary aspergillosis (ABPA) is an immuno-allergic disease triggered by inhalation of *Aspergillus* spores in susceptible and genetically predisposed individuals, such as people with asthma or CF [19,20]. It is characterized by a strong T-helper-2 cellular response and an intense humoral response resulting in the production of polyclonal IgE as well as *Aspergillus*-specific IgE, IgG and IgA antibodies [20].

Retrospective data from older epidemiological studies reported a prevalence of ABPA in CF of 2%–14% [21,22]. However, the true prevalence is difficult to establish because of the substantial overlap with classical CF respiratory disease. The lack of accepted uniform diagnostic criteria and screening programmes, assessment during asymptomatic intervals, variability in laboratory techniques and expertise, as well as under-recognition of the disease by clinicians further blur the picture. It is very likely that even nowadays a substantial number of ABPA cases among people with CF go unrecognized.

3.1. Diagnosis

The diagnosis of ABPA is based on a combination of clinical findings and proof of immunological reactivity to *Aspergillus* spp. [20]. The CF community still relies mainly on the consensus criteria issued by the Cystic Fibrosis Foundation in 2003 [23]. Classical ABPA in CF is defined by:

- a (sub-)acute clinical deterioration not attributable to another aetiology
- total serum IgE >1000 IU/mL in steroid-free patients
- positive immediate cutaneous hypersensitivity to *Aspergillus* antigens (Ags) or elevated *A. fumigatus*-specific IgE levels
- precipitating or IgG antibodies against *A. fumigatus* in serum, and
- new radiological abnormalities, which have not cleared with physiotherapy and antibiotic treatment.

Clinically, ABPA is indistinguishable from classical CF respiratory disease. Expectoration of mucus plugs may raise a suspicion. Fever, malaise and loss of weight may be non-specific symptoms. ABPA should be suspected in CF patients presenting acute pulmonary exacerbations who are poorly responsive to intravenous antibiotics. The clinical stages of acute phase, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic lung disease described in non-CF patients are not directly applicable to CF patients; however, it is important to be aware that tapering off oral corticosteroids after the acute phase may be difficult in some patients, that flare-ups exist and that some patients will progress to a corticosteroid-dependent stage. Imaging techniques play a pivotal role in the

diagnosis and monitoring of ABPA. Central bronchiectasis with normal tapering of the distal bronchi is the hallmark of the disease in non-CF patients [24]. Fleeting infiltrates, lobar/segmental collapse in different areas of the lung caused by mucoid impactions, and high-attenuation mucus on high-resolution chest CT – a pathognomonic feature – can also be seen in CF patients.

Sputum culture is neither sensitive nor specific for the diagnosis of ABPA.

The immunological reactivity against *Aspergillus* antigens is ascertained by a variety of parameters, of which total serum IgE, total serum *A. fumigatus*-specific IgE and skin prick testing with recombinant *A. fumigatus* (rAspf) antigens are the most discriminative. Patients with active disease have elevated total serum IgE levels. In CF, a total serum IgE >500 IU/mL can be considered diagnostic, but cases with even lower total serum IgE have been described [23]. *A. fumigatus*-specific IgE levels may also help to differentiate patients with associated ABPA from those without associated ABPA [25]. In a skin-prick study, CF patients with ABPA reacted to at least one of two rAspf antigens in contrast to patients without ABPA [26]. Serial determination of total serum IgE level and total serum *A. fumigatus*-specific IgE is also very useful for the monitoring of 'ABPA flares' [25]. The biological diagnosis of ABPA may be improved by combining different markers [27].

3.2. Management

Identification of potential environmental sources, asthma control, swift detection, treatment of exacerbations and prevention of further lung damage are the main treat-

ment goals. Pharmacological interventions include systemic corticosteroids, antifungal drugs and anti-IgE antibodies.

Oral corticosteroids remain, unfortunately, the cornerstone of therapy because of their potent anti-inflammatory properties. In asthma patients, the most widely used dosing schedule is prednisolone 0.5 mg/kg/day for 2 weeks, followed by a conversion to alternate-day dosing and a slow taper over 3–6 months. In CF patients, there is no uniform dosing protocol; in some reports, a higher initial dose of prednisone of 1–2 mg/kg/day has been administered [23]. Clinical and biological responses are monitored; a decline in total serum IgE level >35% signals remission. After discontinuation of oral steroids, patients are monitored for clinical and biological quiescence. Monthly intravenous pulse therapy has been used with the aim of limiting side-effects [28,29] and managing relapses [28] or in cases of life-threatening exacerbations [28,30]. In CF patients with steroid-dependent ABPA, alternate-day dosing seems indicated to reduce side-effects.

Inhaled corticosteroids alone only achieve asthma control, but are not a treatment for ABPA according to expert opinion [31].

The role of antifungal drugs in the treatment of ABPA remains controversial. They are frequently combined with oral corticosteroids. It is speculated that they reduce the fungal burden, limit the inflammatory response and, thus, provide a steroid-sparing effect; however, no randomized, controlled trials have been conducted to date [32]. In practice, antifungal drugs – and especially itraconazole – is frequently administered at a dose of 5 mg/kg/day for 3–6 months [23].

Itraconazole has limited oral bioavailability and only approximately 50% of CF patients achieve therapeutic blood levels [33]. Sub-therapeutic levels carry the risk of both therapeutic failure and development of resistance. Itraconazole may have substantial side-effects (e.g. photosensitivity, hepatotoxicity), and also causes relevant drug–drug interactions [34]. As a potent inhibitor of CYP3A4, it may significantly decrease metabolic clearance of oral, but also of inhaled, corticosteroids. Indeed, the ‘steroid-sparing’ effect could well be due to inhibition of corticosteroid metabolism [34]. Iatrogenic Cushing’s syndrome and/or adrenal insufficiency have been reported in CF patients treated concomitantly, and for extended periods, with azoles and inhaled corticosteroids. The second-generation azoles – voriconazole and posaconazole – have also been used in CF patients with ABPA. Pharmacokinetic, drug–drug interaction and side-effect issues are similar to those observed with itraconazole. Omalizumab, a monoclonal antibody against IgE, has been used in CF patients suffering from ABPA, either in addition or as an alternative to oral corticosteroids and antifungals. The reported results were overall encouraging, with improvement in symptoms, pulmonary function, hospitalization and exacerbation rates, and – most important of all – reduction or even discontinuation of oral corticosteroids. However, anti-IgE antibodies are not efficient in all patients, and failures are prone to be under-reported [35]. Results of an exploratory, randomized study to assess the efficacy of omalizumab in CF patients with ABPA are awaited; until then, the routine use of omalizumab is not recommended [36].

Other therapeutic approaches include nebulized amphotericin B to treat acute ABPA or maintain remission. Dry-powder formulations of itraconazole also hold promise.

4 Progressive respiratory insufficiency

Respiratory insufficiency is a major problem and complication in CF patients. Acute and chronic pulmonary infections and inflammation lead to progressive lung damage, bronchiectasis, and fibrosis [37]. Hypoxaemia occurs as a result of these changes. Hypoxaemia is defined as a partial pressure of oxygen in the blood of a person breathing room air of less than 60 mmHg or as a transcutaneous oxygen saturation of <90%. The development of hypoxaemia may result in pulmonary hypertension, which is associated with worse outcome [38,39]. Several medical resources have been developed over the past decades, and many have become established in the therapy of CF patients who have pulmonary or ventilatory failure. It starts with oxygen supplementation followed by NIV. Newer possibilities are extracorporeal lung assist (ECLA) and extracorporeal membrane oxygenation (ECMO), which are normally used as a bridge to lung transplantation.

4.1. Management

In most CF patients, short-term oxygen therapy becomes necessary for the first time during night, exacerbation, or exercise. Short-term therapy switches to long-term therapy when oxygen is needed at

rest. In a Cochrane review, the outcome of short- and long-term oxygen therapy in CF patients was evaluated [40]. Interestingly, long-term supplementation of oxygen showed no significant effect on survival, lung, or cardiac death, but improved regular attendance at school and work. Supplementation during sleep showed an improvement in oxygen saturation but with the disadvantage of mild hypercapnia [40]. In these patients the qualitative sleep parameters did not change significantly. During exercise, oxygen therapy improved the oxygen saturation and the duration of exercise significantly. Unfortunately, oxygen supplementation during exercise resulted in a mild elevation of blood carbon dioxide level [40].

Whereas hypoxaemia in CF has its origin in lung damage and reduced oxygen consumption, a longer-lasting hypercapnia in addition to hypoxaemia is a sign of respiratory failure and signals a further step toward end-stage disease. At this point, NIV should be discussed between the CF team members [41]. The pressure support ventilation modus with bi-level positive airway pressure is the recommended and favoured setting for NIV in CF patients [41,42], but pressure controlled ventilation and continuous positive airway pressure may be adequate for some patients and clinical situations [41,43]. Pressure support ventilation is distinguished from other ventilator modes by its ability to vary the inspiration time breath by breath, permitting close matching to the patient's spontaneous breathing patterns. In addition, inspiratory duration can be influenced by a sensitive patient-initiated

trigger signalling the delivery of inspiratory pressure support, and by reduction of the inspiratory flow causing the ventilator to cycle into expiration [42].

For patient comfort, most clinicians use nasal interfaces for NIV in CF patients. With nasal masks, the patient is able to cough and expectorate without interrupting the ventilation, which is one of the most important advantages. When starting NIV, there are two possible approaches: start with a low inspiratory pressure (8–10 cm H₂O) and titrate upward as tolerated by the patient, or start with a higher inspiratory pressure (20 cm H₂O) and adjust downward [44].

In acute situations, invasive mechanical ventilation may be indicated but the prognosis in this situation is very poor. In a study by Efrati et al., a mortality rate of 94% was found among patients admitted to the ICU who were receiving treatment with mechanical ventilation for acute respiratory failure or during the period awaiting lung transplantation compared with 30% in the patient group receiving NIV [45]. But there is a difference between patients who are transferred to the ICU. Transfer for reversible pulmonary and extrapulmonary complications can be managed appropriately in the ICU setting. For example, endotracheal intubation because of haemoptysis and pneumothorax have a good prognosis [18]. As many CF patients receive NIV as a bridge to lung transplantation, clinicians are asked to think about the perspective of the patient if NIV is failing. Different procedures should be discussed with the patient and their family, as well as with colleagues in the ICU. The perspective given to the

patient depends on the procedures that are available in the ICU. In centres where lung transplantations are performed, invasive mechanical ventilation, ECLA and ECMO are routinely available; but this should be a rescue indication because only a limited time should be spent on extracorporeal devices. Currently, awake ECMO with spontaneous breathing represents a novel and promising bridging strategy [46,47]. Patients are able to cough and expectorate alone or with the help of physiotherapists, and to perform active movements with their legs and arms to stabilize muscle function and strength. As this is a rescue therapy and only available in experienced centres, a new allocation system should be developed for lung transplantation whereby patients with CF receive an organ before they reach the stage of terminal respiratory failure and the need for ECLA. In conclusion, a wide range of possibilities exists for progressive respiratory failure in CF patients, including oxygen therapy, NIV, mechanical ventilation, ECLA and ECMO. The prerequisite for the use of these devices is an established 'standard operating procedure' within the CF team, and including the ICU and the transplant centre in the management of end-stage CF lung disease.

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CHAPTER 3

The increasing complexity of CF-related problems: Emerging infections, non-tuberculous mycobacteria and fungal pathogens

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Introduction

Disease complexity is changing in cystic fibrosis (CF) as the life expectancy of the patient population increases. In addition to the classical pulmonary infections with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, other pathogens – including non-tuberculous mycobacteria and fungi – have emerged as important factors affecting disease course. This chapter describes these emerging pathogens infecting the CF lung and discusses the challenges they present to clinicians and patients.

1 Emerging infections

The unique subset of microbes that commonly infect the lower respiratory tract of individuals with CF has evolved over time. When CF was initially recognized as a distinct disease entity in 1938, it was linked primarily to *S. aureus* pulmonary infections [1,2]. After penicillin became available, children with CF and staphylococcal infections were, for the first time, given effective antimicrobial agents, with dramatic clinical responses [3]. During the 1950s and 1960s, *P. aeruginosa* became recognized as an important CF pathogen [4]. *Burkholderia cepacia* complex organisms, previously referred to as *Pseudomonas cepacia*, emerged in the 1970s, and were associated with rapid declines in pulmonary function and increased mortality [5]. Through the years, dramatic improvements in life expectancy in CF have been realized, but this longevity has been accompanied by the recognition of an increasingly broad

and esoteric group of microbes that infect the CF airways, changing the epidemiology of respiratory tract infection in CF patients [6,7]. In addition to the development of multiresistance in common CF pathogens such as *P. aeruginosa*, several newer, inherently resistant, Gram-negative species are becoming more common, including *Stenotrophomonas maltophilia*, *Achromobacter (Alcaligenes) xylosoxidans*, certain *Ralstonia* species, and those within the new genus *Pandoraea*. Many of these pathogens are closely related and have similar phenotypes, making accurate laboratory identification challenging. While some of these organisms are clearly harmful [8,9], the roles of others in the pathogenesis of CF lung disease is still uncertain.

1.1. *Burkholderia cepacia* complex

When the genus *Burkholderia* was named in 1992, it was composed of seven species. Since then, further taxonomic studies have identified numerous additional *Burkholderia* species [10]. The genus currently consists of more than 60 species, most of which are found in the natural environment and are not pathogenic for healthy individuals. Several species, however, are capable of causing chronic and often severe respiratory tract infections in people with CF [11,12].

The prevalence (2010 and 2012) of chronic *Burkholderia* infection is reported to vary between 0 and 13% in the CF population attending various CF centres [13,14]. In approximately 20% of CF patients infected with *Burkholderia*, the organism causes a fatal illness called the 'cepacia syndrome'. In this syndrome, the patients contract

respiratory infections, with rapid decline in pulmonary function and frequent bacteraemia, a highly unusual finding in patients with CF. The species within this complex that is believed to be primarily responsible for the cepacia syndrome is *B. cenocepacia*, although both *B. multivorans* and *B. dolosa* have also been associated with the syndrome [6,15]. *B. cenocepacia* or *B. multivorans* are recovered from 80% of the *B. cepacia* complex infections seen in patients with CF [6]. All of these clones can be spread from person to person, although many patients have unique clones, which are likely to have been acquired from their environment [16–19]. The recognition of epidemic spread, and the increased mortality rates associated with the epidemic strains, have led to the policy of strict segregation in clinical units since the 1990s [20,21].

Because *B. cepacia* and *B. multivorans* are associated with accelerated lung function decline and high mortality, and are often panresistant to antimicrobials, lung transplantation used to be considered a life-saving therapy for those CF patients infected with these bacteria. It was subsequently observed that CF patients with chronic *B. cenocepacia* infection had a higher mortality after lung transplantation than CF transplant patients who were infected with other bacteria. Sepsis with positive blood cultures has been reported in the early post-transplant period in some patients infected with *B. cenocepacia* [22,23]. As a result, most centres no longer offer lung transplantation to patients with CF who are infected with *B. cenocepacia*.

Treatment of chronic *Burkholderia* infec-

tion is difficult because of a high level of antibiotic resistance. Multidrug antibiotic treatment in combination with immunosuppressive agents has been proposed [24]. In recent studies, a combination of inhaled amiloride and tobramycin failed to eradicate *B. dolosa* [25], and the efficacy of inhalation with aztreonam in treating these microorganisms could not be demonstrated [26]. *B. cepacia* complex infections present a significant challenge for CF clinicians and patients. The problem of how to manage and treat these infections becomes more important as the CF population ages. There is a clear need for clinical trials to assess the effectiveness of different antibiotic regimens in CF patients infected with organisms of the *B. cepacia* complex [27].

1.2. *Achromobacter xylosoxidans*

Achromobacter xylosoxidans is an aquatic, Gram-negative bacillus that is a pathogen in immunocompromised hosts. Like *Burkholderia* and *Stenotrophomonas* species, it is difficult to correctly identify and it suffers from a confusing nomenclature. Currently the prevalence of *A. xylosoxidans* in CF ranges from 2% to 11% [13] and it appears to be increasing [28,29]. Cross-infection between *Achromobacter*-infected and non-infected CF patients has been reported [30–35]. *Achromobacter* species are characterized by multidrug resistance even at the time of first acquisition, and development of further antibiotic resistances is common during the course of chronic infection [36–38].

The clinical relevance of *Achromobacter* infection has been difficult to prove [33], but association with acute exacerbations

has been reported [39]. Chronic infection with *A. xylosoxidans* has been associated with higher concentrations of proinflammatory cytokines, similar to levels seen in patients who are chronically infected with *Burkholderia* or *P. aeruginosa*, suggesting that the organism does elicit an inflammatory response [40]. Only a few studies, with conflicting results, have been published on the effect of chronic infection with *A. xylosoxidans* on the course of CF lung disease [31,41].

There are, however, some case reports that have described patients with rapid decline in lung function and deterioration of clinical status after contracting chronic *A. xylosoxidans* infection [42,43]. Marked genetic relationships were found between strains isolated from the same patients at different times, as well as a correlation between the genetic profiles of *A. xylosoxidans* strains and clinical course of CF lung disease, and the ability of *A. xylosoxidans* strains to establish a persistent infection [42].

1.3. *Stenotrophomonas maltophilia*

S. maltophilia is an aerobic, Gram-negative rod, which was first isolated in 1943 and called *Bacterium bookeri*. It was formally classified as *Pseudomonas maltophilia* in 1961, renamed *Xanthomonas maltophilia* after further taxonomic analysis in 1981, and finally reclassified as *S. maltophilia* in 1993. The prevalence of *S. maltophilia* varies from 3% to 20% [14]. This variability in prevalence may reflect differences in ability to identify the organism in different clinical laboratories. It is unclear whether *S. maltophilia* simply colonizes the lungs of

people with CF without adverse effect or causes true infection leading to pulmonary inflammation and clinical deterioration. The use of steroids or antipseudomonal agents, including quinolone antibiotics and inhaled aminoglycosides, has been implicated as a risk factor for *S. maltophilia* acquisition [44,45]. When investigating the effect of chronic *S. maltophilia* on lung function and clinical status in CF patients, the results were contradictory: patients with chronic *S. maltophilia* infection were found to have lower levels of lung function and higher risk of pulmonary exacerbations compared with controls without chronic *S. maltophilia* infection [46,47], but no negative clinical effect based on the development of chronic *S. maltophilia* infection has been demonstrated [48,49].

1.4. Other microbes

Several other organisms have occasionally been identified from the respiratory secretions of CF patients. Some are environmental bacteria that rarely cause human infections, while others are components of the normal human flora.

1.4.1. *Pandoraea apista*

Pandoraea is a recently described genus of environmental Gram-negative bacilli. The species most often linked to CF is *P. apista*, although other species have also been cultured from CF patients [50]. There is limited information on the clinical significance of *Pandoraea* infection in CF patients, but this bacterium has been associated with chronic infection, patient-to-patient spread, and rapid pulmonary deterioration [51–53].

1.4.2. *Inquilinus limosus*

The genus *Inquilinus* was described in 2002 after a comprehensive taxonomic evaluation of CF sputum isolates [54]. This organism is capable of chronic persistence in the airways of CF patients and may assume a mucoid phenotype. In one study of sputum samples from children and adults with CF, the incidence of *I. limosus* was 4.9% in adults and 1.2% in children [55]. The clinical significance of this bacterium is unclear, but in one report, new acquisition of *I. limosus* was associated with worsening respiratory status in one patient [55,56].

1.4.3. *Ralstonia* spp.

Another group of Gram-negative bacilli occasionally isolated from individuals with CF belong to the genus *Ralstonia* [54,57]. Again, identification of these bacteria can be problematic, but new molecular approaches show promise of being more satisfactory [55]. The clinical significance of *Ralstonia* bacteria in CF is unclear.

1.4.4. Anaerobic bacteria

Oxygen tension is low in CF airway secretions [58,59], suggesting a niche suitable for the growth of anaerobic bacteria, and several reports have indicated that anaerobic bacteria do indeed reside in CF airways [60]. Organisms typically believed to belong to the normal microflora of the oropharynx (*Prevotella*, *Veillonella*, and the *Streptococcus anginosus* group), are all found in the respiratory tract of patients with CF [61]. The microbial communities are remarkably stable, even in the face of repeated courses of antimicrobial therapy [61–63]. Anaerobes identified from sputum

by sequencing have been associated with less inflammation and higher lung function compared with *Pseudomonas* at early exacerbation [63]. Novel therapeutic approaches aimed at modulating airway bacterial communities are needed and may lead to improved treatment of CF lung disease [64,65].

1.5. Conclusion

The improvement in life expectancy of CF patients has resulted in increasing complexity of their respiratory disease with the emergence of new pathogens. The principles of treatment are very similar to those used for *P. aeruginosa*. The importance of clinical response to antibiotics must be stressed, independently of the antibiotic susceptibility [66].

2 Non-tuberculous mycobacteria

There is growing recognition of the clinical importance of non-tuberculous mycobacteria (NTM) in CF. Prevalence studies have shown that *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* complex account for 95% of NTM found. NTM are ubiquitous environmental organisms, and are classified into 'slow' and 'rapid' growers. *M. avium* is a slow-growing NTM. Rapid growers (in <7 days), include *M. abscessus* and *M. chelonae*, referred to as the *M. abscessus* complex, which comprises *M. abscessus sensu stricto*, *M. abscessus* subgroup *massiliense*, and *M. abscessus* subgroup *bolletii* [67]. Human-

to-human transmission of NTM has traditionally been considered unlikely; the same isolates found on different patients in a centre could occur by indirect transmission via the environment. There are no standard recommendations for the frequency of NTM monitoring, but it would be beneficial to check for these organisms at each visit, especially in adolescents and adults.

2.1. Prevalence

In 2003, the first multicentre, prevalence study of CF patients in the United States found that the prevalence of NTM in sputum was 13% [68,69]. In 2010, the prevalence was about 11% in a single-centre study in North Carolina [70].

In Europe, single-centre studies have found variable NTM prevalence, from 13.3% in Germany to 5% (in adult CF) in a recent prevalence study in the United Kingdom [71]. In France, a multicentre study reported a prevalence of 6.6%, with *M. abscessus* being identified as the most common pathogen [72]. As surveillance has increased simultaneously with expanding laboratory techniques, it is difficult to assess whether data reflect an increasing prevalence or an improved capacity to recover NTM.

2.2. Clinical course

It is often difficult to determine whether isolation of NTM reflects colonization or a disease that requires an antibiotic treatment. In 2007, The American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) revised the guidelines for diagnostic criteria of NTM lung disease [73]. Criteria consist of clinical symptoms, and nodular or cavitary opacities

on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules. Microbiological criteria are positive culture results from two separate sputum samples, or from at least one bronchial wash or lavage.

In CF, clinical symptoms such as increased sputum production, weight loss, fever, night sweats or worsening lung function might be due to bacterial exacerbation or allergic broncho-pulmonary aspergillosis. When these clinical symptoms appear despite intravenous antibiotic courses or aspergillosis treatment, NTM may be the causative agent of these symptoms and should be considered in a diagnosis.

Establishing a relationship between chronic NTM and clinical severity is complicated by the many factors that influence respiratory deterioration in CF. In a database of 1216 CF patients and 536 NTM isolates, the group with chronic NTM infection, particularly with chronic infection with *M. abscessus*, had a higher rate of annual decline (in percent predicted forced expiratory volume in 1 second [FEV₁]) than a control group adjusted for FEV₁, age, sex, chronic *Pseudomonas* infection, nutritional failure, CF-related diabetes and allergic broncho-pulmonary aspergillosis (ABPA) [70].

2.3. Risk factors

A French case-control study found that *M. avium* and *M. abscessus* target different CF populations: MAC-positive patients were significantly older at NTM diagnosis than *M. abscessus*-positive patients (23 vs. 17 years), with 75% of the MAC-colonized patients being more than 16 years old. Receiving at least one intravenous antibi-

otic course in the year before inclusion in the study and the isolation of *Aspergillus* sp. were risk factors associated with *M. abscessus*. However, ABPA was not a significant factor for *M. abscessus* [74]. In a database of 1216 CF patients and 536 NTM isolates, a higher prevalence of *S. maltophilia* and *Aspergillus fumigatus* was found in the group of NTM-colonized patients [70]. Another recent case-control study, in 30 patients with *M. abscessus* disease fulfilling ATS criteria [73], found no positive association between *M. abscessus* lung disease and the use of inhaled therapies (antibiotics, rhDnase or steroids), or low-dose azithromycin in the 4 years preceding *M. abscessus* isolation [75]. In a retrospective study, on 12 patients with NTM-positive culture, six patients met the ATS criteria for NTM pulmonary disease. These patients were all pancreatic insufficient, and six had received prolonged systemic steroid treatment [76]. However, systemic steroid therapy was not shown to be a risk factor in a large USA prevalence study [68].

Data on the long-term use of azithromycin as an anti-inflammatory agent for CF are controversial. An *in vitro* study found that azithromycin blocked autophagosomal clearance by preventing lysosomal acidification. This alkalization of autophagosome impaired intracellular killing of mycobacteria and increased chronic infection with NTM in a mouse model [77]. In a French study, no positive association was found between *M. abscessus* lung disease and the use of low-dose azithromycin in the 4 years preceding isolation of *M. abscessus* [75]. In a large US cohort from the CF Patient Registry, 191

patients with NTM-positive culture in 2011 and not in 2010 were compared with 5212 controls with NTM-negative culture in 2010 and 2011. Among adolescents and adults, patients with the greatest number of years on chronic azithromycin were less likely to develop NTM [78]. Azithromycin may be even more effective in preventing NTM infections among patients without a prior NTM diagnosis.

2.4. Treatment

After an NTM lung infection is established, eradication is difficult, and three or more drugs are required against NTM to prevent the development of drug resistance.

Treatment for NTM can be long. The ATS statement recommends a treatment time of at least 12 months after the sputum culture becomes negative (Table 1). There is poor correlation between *in vitro* susceptibilities and *in vivo* efficacy, except for macrolides [78,79].

2.5. Transplantation

The view that NTM, especially *M. abscessus*, constitutes an absolute contraindication for lung transplantation is being modified. Two recent retrospective studies did not find an increase in mortality. The first, a Danish study, reported on 52 patients who underwent lung transplanta-

MYCOBACTERIUM SPECIES	DRUG REGIMEN
<i>Mycobacterium avium</i> complex	<ol style="list-style-type: none"> 1. Clarithromycin 15–30 mg/kg/d (max. 1 g) or azithromycin 250–500 mg/d 2. Rifampicin 10 mg/kg/d (max. 600 mg) 3. Ethambutol 15 mg/kg/d
<i>Mycobacterium abscessus</i>	<ol style="list-style-type: none"> 1. Azithromycin 250–500 mg/d 2. Cefoxitin IV 200 mg/kg/d (max. 12 g) 3. Amikacin IV 10–15 mg/kg/d or 25 mg/kg three times a week <p>Alternative agents:</p> <ul style="list-style-type: none"> Imipenem IV 1 to 2 g/d Tigecycline IV 50 mg/d Linezolid 300–600 mg/d Inhaled amikacin (diluted in 3 mL normal saline) 250–500 mg twice a day

Table 1 Recommended drug regimens for common non-tuberculous mycobacteria [79]

tion between 1994 and 2011. Among them, 11 were colonized with *M. abscessus*, nine of whom fulfilled the ATS criteria; five patients had an active infection. There were some postoperative complications (e.g. deep tissue infection, sternal abscess) but no deaths were linked to the *M. abscessus* infections [80]. The second study was a retrospective study of 13 patients who were infected with *M. abscessus* according to ATS criteria. All patients received a combination of antibiotics (cefoxitin, clarithromycin and amikacin) at least 6 weeks after lung transplantation. No deaths due to *M. abscessus* infection were reported [81]. While aggressive treatment before and after lung transplantation is recommended, eradication prior to transplantation is often difficult, and lung transplantation with favourable survival is possible in patients with *M. abscessus* infection.

3 Fungal infections

Whether fungi in the CF lung are 'bystanders' or should be considered true pathogens has been debated [82]. Filamentous fungi may contribute to the local inflammatory response, and therefore to the progressive deterioration of lung function [83]. With the increasing complexity of treatment, including antibiotic treatment and perhaps, not least, inhaled antibiotics, attention to fungal infections and evidence of the clinical impact has increased.

Fungal colonization in the CF patient is frequent and is dominated by *A. fumigatus*

[84–86]. Up to 40% of CF patients are colonized with *Aspergillus* [87]. ABPA is the best described entity, but other *Aspergillus* lung infections include *Aspergillus* bronchitis [88], less frequently invasive pulmonary aspergillosis and occasionally aspergilloma. The contribution of *Aspergillus* to CF lung disease outside ABPA remains less clear. Recent work has shown that *Aspergillus* sensitization and/or airway infection is associated with worse FEV₁ in CF [89].

Aspergillus bronchitis presents with cough, increased sputum production, decline in lung function and lack of response to antibacterial antibiotics. Some patients have an increase in IgE, and have been considered to be at an early stage of ABPA [88]. These patients may have specific *Aspergillus* IgE and IgG, but do not meet the criteria for ABPA [90]. Radiological findings such as infiltrates, atelectasis and bronchiectasis are seen. The recommended treatment is generally azoles [88].

Invasive pulmonary aspergillosis is mainly seen in CF patients with lung transplant. It occurs diffusely in the lung, where the bronchial wall is invaded by *Aspergillus*, causing lung infiltrates, pneumonia or lung abscesses. The diagnosis is supplementary based on findings such as haemoptysis, growth of *Aspergillus* in sputum or bronchoalveolar lavage fluid, positive galactomannan in bronchoalveolar lavage fluid (>1 ng/mL) [91,92], and positive *Aspergillus* IgG. The symptoms include cough, dyspnoea, fever, haemoptysis, decline in lung function, and chest pain, despite antibiotic treatment. The treatment usually includes intravenous antifungal treatment

followed by oral azoles. In some cases antifungal inhalation therapy may be added. In rare cases, growth of *Aspergillus* in a pre-existing cavity is seen, and may result in an aspergilloma [93].

In addition to *Aspergillus* spp., the most frequent fungal pathogens recovered from respiratory specimens of CF patients are *Scedosporium* spp. [84–86,94] and *Exophiala dermatitidis* [84–86]. *Geosmithia argillacea* may occasionally be seen [84]. *Trichosporon* spp. may potentially be associated with severe exacerbations in CF patients [95].

The clinical impact of fungal infections has been described within a wide range. *E. dermatitidis* may trigger antibody production and cause significant airway infection in patients with CF [96]. It has been reported that there is no association between sensitization against *Scedosporium apiospermum* complex and poorer lung function in CF [97]. A case of more severe pulmonary infection with *S. apiospermum* in an adolescent with CF was however effectively treated with nebulized voriconazole [98]. A serious decline over 2 years from a lung function (FEV₁) above 50% to requiring transplantation with the main pathogen on sputum culture throughout that period being *S. apiospermum* has been described [99]. *Candida* spp. are the most commonly isolated yeasts in CF [85]. However, the definitive role of *Candida* remains unclear [100]. *Aspergillus*, but not *Candida*, sensitization has been associated with greater lung function decline and pulmonary exacerbations [101].

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CHAPTER 4

The increasing complexity of CF-related problems: CF-related diabetes and bone disease

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Introduction

Significant improvements in the management of the respiratory complications of cystic fibrosis (CF) have meant that extrapulmonary complications are becoming more prevalent. It has become increasingly important to manage these other complications as they can cause burdensome symptoms, and affect quality of life and, in some instances, survival. This chapter focuses on two such areas – CF-related diabetes (CFRD) and CF-related bone disease. Both have mixed aetiologies, including a direct impact from abnormal cystic fibrosis transmembrane conductance regulator (*CFTR*) function and indirect influences, such as drug-related complications (e.g. corticosteroid usage).

1 CF-related diabetes

CFRD is the most common extrapulmonary CF-related complication, and is associated with significant morbidity and mortality [1]. This section discusses the epidemiology, pathophysiology and management of CFRD with particular focus on some of the more controversial areas, such as screening and treatment.

1.1. Epidemiology of CFRD

Although a scattering of case reports have described CFRD in very young children with CF, established diabetes in the first decade of life is rare. CFRD prevalence increases with age, affecting approximately 2% of children, 19% of adolescents and 50% of adults in the USA [2], and 22% and 52% of European adolescents (<18 years) and adults (>40 years), respectively [3]. Similarly, in adult CF patients (>20 years) who were followed for 5 years, CFRD prevalence increased from 25% to 53% [4]. In

the UK, the prevalence of CFRD among adults is approximately 30%, with impaired glucose tolerance confirmed in half of the patients [5].

Annual CFRD incidence is also age dependent up to the fourth decade, with reported rates of 1–2% in children (<10 years) and 6–7% in adults (30–40 years) [6]. CFRD risk is independently associated with *CFTR* mutation class (*CFTR* class I and II), impaired pulmonary and hepatic function, corticosteroid therapy, pancreatic enzyme supplementation, and female sex, although the basis for this sexual dimorphism remains unclear [6–8].

1.2. Pathophysiology of CFRD

CFRD is a distinct entity from type 1 and type 2 diabetes mellitus, but shares common clinical and pathophysiological features with both. Abnormal *CFTR* function causes impaired secretion of chloride, bicarbonate and fluid into pancreaticobiliary ducts, resulting in the production of viscid secretions, and ensuing pancreatic ductal injury and impaired blood flow within pancreatic tissue. Subsequent ischaemic damage to the exocrine pancreas followed by fibrosis and fatty infiltration leads to progressive destruction and deterioration of endocrine β -cell function and, ultimately, to insulin deficiency. Post-mortem studies have not consistently identified a correlation between the extent of β -cell loss and CFRD. In addition to reduced β -cell number, increased islet amyloid deposition and induction of endoplasmic reticulum stress have been proposed to contribute to CFRD pathogenesis [9,10]. Unlike type 1 diabetes, however, there is little evidence to suggest

that β -cell damage in CFRD is immunologically mediated or modified by autoimmune susceptibility genes [11,12].

Defective insulin secretion is a well recognized but poorly understood pathological feature of CFRD that has been identified in young CF patients with otherwise normal glucose tolerance prior to developing CFRD [13–15]. While fasting insulin and C-peptide levels in plasma may be normal, first-phase insulin secretion is impaired, delaying and attenuating release of insulin in response to an oral glucose load [16,17]. Recent data suggest that impaired insulin secretion may result directly from the *CFTR* defect, as treatment with ivacaftor, a *CFTR* potentiator, improved first-phase insulin secretion in a small study of subjects with the *G551D* *CFTR* mutation [18].

Defective secretion of incretin hormones, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), has also been implicated in the blunted insulin response to oral glucose. GLP-1 and GIP are secreted from enteroendocrine L cells in response to the content of fat and carbohydrate in the intestinal lumen. These hormones are important determinants of postprandial glycaemia through their ability to stimulate insulin secretion. Interestingly, CF patients have low postprandial stimulation of GLP-1 and GIP release, an effect that can improve with pancreatic enzyme supplementation [19].

The contribution of insulin resistance to CFRD pathogenesis is variable, and is influenced, primarily, by the underlying clinical state, with active infection, inflammation, decreased pulmonary function and concurrent therapy with corticosteroids all known

to reduce insulin sensitivity. Generally, studies have demonstrated that mild peripheral insulin resistance occurs in CFRD, with insulin sensitivity preserved in CF patients without diabetes [20]. Although once rare, the incidence of obesity is increasing in the CF population, and increased fat mass may become an important determinant of glucose tolerance in CF patients in the future [21].

1.3. Clinical presentation and complications

CFRD develops insidiously; many patients remain asymptomatic, and only a minority of individuals present with overt hyperglycaemic symptoms such as polyuria or polydipsia. More commonly, osmotic symptoms are exacerbated by situations that increase peripheral insulin resistance including acute pulmonary infection, use of glucocorticoids, use of immunosuppressants following transplantation, or consuming large amounts of carbohydrate [4]. Other patients present following reported hypoglycaemia hours after eating, reflecting delayed insulin secretion [22]. Although insulin deficiency is the primary defect in CFRD, unlike those with type 1 diabetes, diabetic ketoacidosis is uncommon, which probably reflects partial preservation of basal insulin secretion from β -cells.

CF patients who present with symptomatic hyperglycaemia are more likely to have progressive decline in body mass index (BMI) and pulmonary function prior to diagnosis than those diagnosed with CFRD through routine surveillance [23]. Similarly, studies of continuous glucose monitoring systems have found that greater

daily glucose excursions are associated with larger declines in lung function and nutritional status [24]. Recent data from murine models suggest that hyperglycaemia impedes pulmonary bacterial clearance in *CFTR*-deficient mice and promotes ongoing infection [25]. In humans with CF, clinical deterioration in lung function and BMI is seen up to 4 years before even subtle defects in glucose homeostasis are detected [26,27]. This 'pre-diabetic phase' has been proposed to result from progressive β -cell failure and relative insulinopaenia, and reinforces the importance of anabolic actions of insulin in CF, and the detrimental impact of insulin deficiency on glucose metabolism, nutritional status and clinical outcomes in these patients [27].

Diabetic microvascular complications have been described in CFRD and are related to duration of diabetes and glycaemic control, with the presence of fasting hyperglycaemia being of particular importance. In one series, Schwarzenberg et al. found that no patients with CFRD without fasting hyperglycaemia had evidence of retinopathy or nephropathy, whereas 14% and 16% of subjects with fasting hyperglycaemia and diabetes for greater than 10 years had microalbuminuria and retinopathy, respectively [28]. Rates of autonomic neuropathy or gastropathy were not related to fasting hyperglycaemia and were similar to those reported for patients with type 1 diabetes. In view of these findings, it has been recommended that annual screening for microvascular complications begins in CFRD patients with fasting hyperglycaemia of 5 years' duration. In contrast to type 1 and type 2 diabetes, macrovascular

complications, including ischaemic heart disease and cerebrovascular disease, are currently uncommon in CFRD. However, with increasing life expectancy and rates of obesity and hypertension, macrovascular complications are likely to become more prevalent in this patient population, and ongoing clinical vigilance is advised.

Further related to complications, patients with CFRD die earlier than CF patients without diabetes. Although patients with CFRD have more concurrent problems than patients without diabetes, the increased risk of death associated with CFRD is independent of other CF-related complications [1]. Hyperglycaemia, *per se*, has been associated with death [29].

1.4. Screening and diagnosis

Given the insidious and, often, clinically silent onset of CFRD, and the association of CFRD with negative clinical outcomes, including pulmonary function, nutritional status and mortality, regular screening for diabetes in CF is justified, particularly considering the simplicity of diagnostic tests. Unlike other forms of diabetes, however, the glycated haemoglobin (HbA_{1c}) test is not yet a recommended screening tool for CFRD because of uncertainties related to low sensitivity [30]. Similarly, reliance of fasting hyperglycaemia alone to diagnose CFRD will fail to identify 50% of cases compared with one-third for type 2 diabetes [30,31]. While continuous glucose monitoring appears promising as a valid and sensitive method for detecting abnormal glucose homeostasis, it is not a currently recommended screening method because of a lack of long-term clinical outcome data associated with this tool [30].

In contrast, several longitudinal studies have demonstrated a correlation between the standard 2-hour oral glucose tolerance test (OGTT) with CF-outcomes, and therefore this method is recognized as the gold standard screening investigation for CFRD [30,32]. Testing blood glucose 1 hour after a glucose load may be the most sensitive test, but efficacy of treatment based on this result alone is not known [32].

Recent consensus guidelines recommend that annual screening for CFRD begin by age 10 years in all CF patients [30]. Increased screening is also advocated for specific situations where patients are at increased risk of developing hyperglycaemia, including pregnancy (guidance recommends an OGTT pre-conception, at the end of the 1st and 2nd trimesters, and 6–12 weeks post-partum), inter-current illness requiring systemic antibiotics and/or glucocorticoids (fasting and 2-hour post-prandial glucose monitoring for 48 hours), continuous enteral feeding (regular self blood glucose monitoring), and prior to organ transplantation [30].

Current diagnostic criteria for CFRD are the same as for type 1 or type 2 diabetes (Table 1), although there is a call for defining CFRD at the point where pulmonary damage occurs [30,32]. Until this time, a diagnosis of CFRD is based on established criteria including fasting hyperglycaemia (>7.0 mmol/L), 2-hour OGTT glucose >11.1 mmol/L, random blood glucose >11.1 mmol/L in the presence of classic symptoms (polyuria and polydipsia), and finally, HbA_{1c} >6.5%, but as noted, a value of <6.5% does not exclude CFRD. Few CF patients have normal glucose tolerance, and 'indeterminate glucose tolerance' is a

recognized entity for those patients with normal fasting and 2-hour glucose levels but whose glucose level exceeds 11.1 mmol/L during OGTT. Impaired fasting glucose (5.6–6.9 mmol/L) may be present in some patients. While the prognostic significance of impaired or indeterminate glucose tolerance in adults is unclear, in children they are associated with an increased risk of early-onset CFRD [33]; thus, these patients should be monitored closely.

1.5. Treatment

Insulin insufficiency is a hallmark of CFRD and insulin treatment is the only recommended pharmacological therapy [30]. As with other types of diabetes, CFRD in concert with fasting hyperglycaemia is managed with standard basal-bolus insulin regimens, consisting of either multiple daily

subcutaneous insulin injections or continuous subcutaneous insulin delivery via an insulin pump. In adults with CFRD without fasting hyperglycaemia, pre-meal insulin therapy is advocated and improves BMI [34]. Whether CF patients with 'indeterminate' or 'impaired' glucose tolerance benefit from insulin therapy remains the subject of ongoing clinical investigation, although it is widely practiced.

Increased resting energy expenditure and nutrient malabsorption from pancreatic exocrine insufficiency characterize CF; thus, meeting the dietary and nutritional needs is an integral part of CF management. Unlike type 2 diabetes mellitus, restricting the caloric intake is not an option for most patients with CFRD because they expend high levels of energy and require a high caloric intake to promote weight gain and

CATEGORY	FASTING GLUCOSE (mmol/L)	mid-OGTT GLUCOSE (mmol/L)	2-HOUR GLUCOSE (mmol/L)
Normal glucose tolerance	<5.6	<11.1	<7.8
Impaired fasting glucose	5.6–6.9	<11.1	<7.8
Impaired glucose tolerance	<7.0	<11.1	7.8–11.0
Indeterminate glucose tolerance	<7.0	>11.1	<7.8
CFRD* without fasting hyperglycaemia	<7.0	N/A	>11.1
CFRD* with fasting hyperglycaemia	≥7.0	N/A	>11.1

*CFRD, cystic fibrosis-related diabetes; N/A, not applicable.

Table 1 Diagnostic glucose categories as determined by a 2-hour oral glucose tolerance test.

growth. Some patients require nocturnal nasogastric or gastrostomy feeding to meet nutritional requirements, and may need overnight insulin cover with isophane or a long-acting insulin analogue to prevent nocturnal hyperglycaemia. In general, clinicians should tailor insulin regimens and doses to meet individual requirements, taking into account the patient's current clinical state.

Randomized controlled trials in CFRD of glucose lowering *per se*, and of specific glucose-lowering agents, are few, and currently available data do not support the use of oral hypoglycaemic agents over insulin in the management of CFRD [30]. A recent Cochrane review found only two randomized controlled trials comparing insulin treatment with oral hypoglycaemic agents [35]. Following on from an earlier study [36], Moran et al., with specific reference to effects on body weight, randomized patients to insulin injection, repaglinide tablets, or placebo tablets. Results showed that compared with placebo and repaglinide over 12 months, insulin modestly improved body weight whereas repaglinide, when compared with the other treatment arms, did not. Neither insulin nor repaglinide significantly improved HbA_{1c}, which notably was not the primary endpoint [34].

Given the role of peripheral insulin resistance in the pathogenesis of CFRD, inclusion of insulin-sensitizing agents in the CFRD armamentarium seems logical. To date, however, there are insufficient data to support the use of these medicines in CFRD, and concerns have been raised regarding side-effects for use in CF patients; these include gastrointestinal disturbance (metformin), malabsorption of carbohydrates (acarbose), lactic

acidosis (metformin), osteoporosis (thiazolidinediones), liver dysfunction (thiazolidinediones), weight loss (sodium-glucose co-transporter-2 inhibitors), respiratory infections (dipeptidyl peptidase-4 inhibitors), and inhibition of *CFTR* function (sulfonylureas). Non-insulin injectables, such as GLP-1 agonists, are also associated with gastrointestinal symptoms and weight loss. Whereas some patients with CFRD are treated successfully with oral agents, current guidelines recommend that patients with CFRD should be treated only with insulin.

1.6. Conclusions

Improvement in survival of patients with CF has led to an increasing prevalence of CFRD. Epidemiological studies, for the most part, support screening, early diagnosis, intervention and continued efforts to improve glycaemic control. Yet, few randomized controlled studies exist to guide screening and treatment. A greater understanding of the pathogenesis and consequences of CFRD will provide opportunities for improved medical management and clinical care for CF patients with and without diabetes, with the goal of minimizing complications and prolonging life.

2 CF-related bone disease

The prevalence of CF-related bone disease and its associated complications increases with age. This section discusses the risk factors, complications and treatment strategies for CF-related bone disease.

2.1. Bone loss and reduced bone mass

According to the World Health Organization criteria, osteopaenia and osteoporosis are defined, for adults only, as the decrease of bone mineral density (BMD) of at least 1 standard deviation (SD) or 2.5 SDs, respectively, below the mean BMD of healthy young adults of the same sex (aged 25–30 years – the age at which the lifetime peak of bone mass is reached). This is technically expressed as a BMD T-score that is ≤ -1.0 and ≥ -2.5 (osteopaenia) or ≤ -2.5 (osteoporosis) [37]. A different definition is necessary for children and adolescents, as their skeletons are still developing and growing (for further details see ref [38]).

In recent years, regular evaluation of bone mass has been increasingly recommended and performed in both adults and young CF patients (up to the age of 30 years). Minimizing the risk of fractures, with their consequences of reduced mobility and increased risk of pulmonary infections, is now considered very important. The pathogenesis of bone involvement in CF is very complex and involves several different mechanisms: intestinal malabsorption, malnutrition, vitamin D and K deficiency, pulmonary complications (chronic infections, systemic inflammation, respiratory failure), reduced physical activity, reduced levels of insulin-like growth hormone factor 1, hypogonadism, delayed puberty, and steroid treatment. All these factors can be involved, even at an early age. The impact of *CFTR* mutations on bone has been investigated in both animals and humans. Three studies observed decreased bone formation and increased bone resorption in *CFTR*-null mice, with severe trabecular

and cortical osteopaenia [39–41]. Excluding other possible causes of bone loss (e.g. malnutrition, pulmonary infections), these animal models demonstrated that loss of *CFTR* function has a direct effect on bone.

CFTR expression has been demonstrated in human bone cells (osteoblasts, osteoclasts, osteocytes) [42]. In patients with CF, an increase in pro-inflammatory and pro-resorptive cytokines has been observed during pulmonary infections, with a consequent increase in osteoclast number and activity until antibiotic therapy is started [43]. In cultures of human osteoblasts, inhibition of *CFTR* channel function induced a significant decrease in osteoprotegerin secretion and an increase in prostaglandin E_2 secretion, with increased bone resorption [44]. The possible impact of specific gene mutations on bone has also been investigated, but the results are still inconclusive, and studies on larger CF populations are required. In a study of 88 adults with CF, the *F508del* mutation was found to be associated with reduced BMD [45]. In another study of 136 young patients, those who were homozygous for functional class I and functional class II (including *F508del*) mutations of the *CFTR* gene showed a marked decrease in BMD, whereas those who were heterozygous for either class I or class II mutations had a lesser decrease [46]. Another study did not find any direct association between the *F508del* mutation and low BMD [47].

Pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF- α) or interleukin 6 (IL-6), are already known to have a direct role in bone loss in other chronic inflammatory diseases, such as asthma and rheu-

matoid arthritis, and increased production of these cytokines has also been observed in pulmonary infections and chronic inflammation in CF [43,48]. In particular, Shead et al. observed a positive correlation between osteoclast number and serum TNF- α , a positive correlation between the resorption area and IL-6, and a negative correlation between osteoclast number and osteoprotegerin [43].

2.2. Bone density and fractures

Osteopaenia, osteoporosis and fractures have been reported in many studies of adults with CF, with bone loss starting at an earlier age than in healthy individuals [49–54]. A recent meta-analysis of 12 studies of bone disease in adult patients (1055 in total), reported a pooled prevalence of 38% for osteopenia, 23.5% for osteoporosis, 14% for radiologically demonstrated vertebral fractures, and 19.7% for non-vertebral fractures [55]. In a study of young women (16–34 years) and men (25–45 years) affected by CF, the fracture rates (at any site) were twice as high as in the general population [51]. The most common fracture sites in CF patients are ribs and vertebrae (especially thoracic), with fracture rates reported to be as much as 10-fold (ribs) and 100-fold (vertebrae) higher than in the general population [54].

Data on BMD in children, adolescents and young patients are less consistent than the data for adults [56–59]. Some authors have found reduced BMD in prepubertal children [46], but others have reported normal or almost normal values during childhood, with progressive BMD reduction during adolescence [58,59]. In a study of 136 young

patients (age 3–24 years), BMD (measured by dual-energy X-ray absorptiometry and corrected for body size) was normal in 34%, moderately decreased in 32%, and markedly decreased (Z-score <–2) in 34% [46]. The available data on fractures in children and adolescents with CF are scant and inconclusive, and most studies do not report fractures, with the exception of studies in adolescent females [56–58,60,61]. Differences in age, pubertal status, degree of preserved respiratory function and disease severity in the studied populations may explain the conflicting results. Some studies on children and adolescents with CF demonstrated the importance of nutritional status for bone health. BMD was correlated with weight (nutritional parameter) and lung function, and the rate of calcium deposition in bone was significantly associated with increased calcium absorption and serum leptin concentrations [62–64].

Several studies in adults and small samples of children have reported that forced expiratory volume in 1 second (FEV₁) is the main determinant of bone density [46,47,60,65]. Adequate pulmonary function seems to be essential for bone health in CF. With respiratory impairment, physical activity is reduced, appetite is lost, muscle tissue is wasted, chronic inflammation deranges the bone remodelling processes, and in addition, patients may need higher doses of glucocorticosteroids – all factors that lead directly to loss of bone mass.

2.3. Prevention and treatment

Careful evaluation of bone status is an essential aspect of the optimal management of both young and adult CF patients.

Prevention, early recognition, and adequate treatment of bone metabolism derangements are now possible and must be pursued. However, notwithstanding the current awareness of the problem and agreement on the principles [54,66], there are still few randomized controlled studies. Nutritional aspects are of primary importance, and dietary counselling is recommended in order to ensure correct calcium and vitamin D intake and to help maintain muscle mass. There are only a few short-term studies on calcium and vitamin D supplementation [67,68], and a Cochrane review concluded that there is “no evidence of benefit or harm” from vitamin D [69]. According to a recent study, high doses of vitamin D (50,000 IU daily) may be required in people with CF, but the efficacy and safety of such doses could not be established from the short duration of treatment (28 days) and follow-up (6 months) [70]. Vitamin K is also important for normal bone metabolism, and supplementation has been considered in young CF patients [71]. For all of these aspects, however, longitudinal studies on large cohorts of CF patients are needed to develop recommendations on dose, schedule and duration of treatment.

Physical activity is another basic component of bone loss prevention. No controlled trials have been carried out, but there are reasons to expect that physical exercise can improve bone mineral accrual and reduce bone loss in CF [72], and it has been reported that CF patients with better exercise capacity (assessed by cardiopulmonary exercise and the 6-minute walking test) have higher BMD values [73].

Hormonal replacement treatment may be indicated in carefully selected cases [66]. Growth hormone treatment has shown positive effects on height, weight, lean mass, bone mineral content and quality of life, and the benefits persisted after withdrawal [74]. Sex hormone treatment is still controversial but may be useful in the presence of delayed puberty [66].

A vitally important goal of CF management is the reduction of fracture risk. Fractures have a relevant negative impact on the patients’ quality of life and even survival, because of reduced mobility, chronic pain, and a significantly increased risk of pulmonary infections. Vertebral and rib fractures are particularly ominous, because they directly hamper respiratory function, facilitate infection exacerbations [51,54], and are, above all, a serious impediment to respiratory physiotherapy and lung transplantation. Such aspects should be strongly emphasized because, until relatively recently, even high-risk patients – including candidates for lung transplantation – have been rarely investigated for bone fragility [75]. Special attention must always be paid to glucocorticoid therapy, as it has well-known negative effects on bone and calcium metabolism. Long-term glucocorticoid treatment increases the risk of fractures even in young patients, and the minimum effective dose must be used.

Regarding bone-active drugs, both oral and intravenous bisphosphonates have been successfully used in adults with fragility fractures or significant BMD reduction, in particular patients starting long-term treatment with systemic glucocorticoids or awaiting lung transplantation [48,54,66].

A recent review of seven randomized controlled trials of bisphosphonate use for 6 months or more in adults with CF (237 patients in total) concluded that these drugs significantly improved BMD, although further studies are required to evaluate their effects on fracture risk [76]. Bisphosphonates have rarely been used in children and adolescents with CF because of the unknown long-term risks. In accordance with the recommendations of the European Cystic Fibrosis Society [66], they should be used only in the presence of fragility fractures (mainly vertebral fractures). A recent multicentre randomized, placebo-controlled trial of 171 young patients (aged 5–30 years) demonstrated the efficacy and safety of oral alendronate in improving BMD [77].

2.4. Conclusions

The prevalence of CF-related bone disease is increasing as survival continues to improve. There are many associated risk factors, and early interventional strategies are important. Data on the optimal drugs for established osteoporosis are currently limited; therefore, more robust clinical trials are needed to establish the long-term safety of bisphosphonates and their efficacy on the reduction of fracture risk. This is particularly relevant for an ageing CF population as bisphosphonates may be indicated over many years.

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CHAPTER 5

Increasing prevalence of other medical problems

Authors

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Introduction

Ageing adult patients with cystic fibrosis (CF) are facing increased pulmonary (see chapter 2) and metabolic (e.g. diabetes and bone disease, see chapter 4) complications, but many other medical problems may also occur. This chapter discusses the most common ones, namely arthropathy, gastrointestinal problems, risk of cancer, cardiovascular disease and vascular access.

1 Arthropathy

The most common and well-described forms of arthropathy are hypertrophic pulmonary osteoarthropathy and CF-related arthropathy [1].

1.1. Hypertrophic pulmonary osteoarthropathy

The classical clubbing of the fingers and toes in patients with CF is considered to be a form of hypertrophic pulmonary osteoarthropathy (HPO) and is mostly painless. Apart from this classic clubbing, HPO usually involves the distal ends of the long bones of the long extremities (wrists, ankles, knees). HPO in CF presents with pain in the distal ends of the long bones and is often symmetrical. Radiographically, there is evident periosteal elevation, due to periosteal proliferation, and nuclear bone imaging may be of help in establishing the diagnosis.

HPO is, not surprisingly, usually associated with more severe lung disease and may increase during infectious exacerbations. When radiographic evidence is included in the definition, the prevalence of HPO in CF is about 5% and increases with age, with a median age of onset in early adulthood

[2]. Treatment of HPO consists of optimal management of pulmonary infections and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as biphosphonates [3]. To date, no studies have been conducted on the management of HPO [4].

1.2. CF-related arthropathy

CF-related arthropathy (CFA) is slightly more common compared with HPO. In contrast to HPO, the onset occurs somewhat earlier in life, and is usually not associated with the severity of lung disease or infectious exacerbations [1]. CFA presents itself with recurrent episodes of joint pain, swelling, tenderness and limitations of movement. Symptoms develop over 12–24 hours, and most episodes are limited to a few days. CFA may occur in one or more joints and may, in some cases, mimic rheumatoid arthritis. There may also be fever and skin involvement. Unlike HPO, radiological examinations do not reveal any abnormalities. Case reports of arthropathy, mimicking CFA, in patients with CF following quinolone therapy have been published, although tendinopathy is a more common complication of quinolone therapy [5]. Treatment of attacks of CFA is targeted to the relief of symptoms, as there is no association with the severity of lung disease or infectious exacerbations. Acute attacks may resolve spontaneously within several days, but NSAIDs and bed rest may suppress symptoms. In more chronic forms of CFA, other interventions, including systemic and local steroids and disease modifying anti-rheumatic drugs, have been used. However, studies on the optimal treatment of CFA are lacking [4].

2 Gastrointestinal complications in adults

2.1. Distal intestinal obstruction syndrome

Distal intestinal obstruction syndrome (DIOS) is one of the most frequent complications in adult patients with CF (35.5/1000 patient years) [6]. It is characterized by the accumulation of viscid faecal material within the bowel lumen combined with sticky mucoid intestinal content adherent to the intestinal wall of the terminal ileum and caecum. Risk factors for developing DIOS are: severe cystic fibrosis transmembrane conductance regulator (*CFTR*) genotype (Classes I-III), pancreatic insufficiency, dehydration, poorly controlled fat malabsorption, a history of meconium ileus and/or prior DIOS, post-organ transplantation, and CF-related diabetes.

Patients usually present with acute or persistent pain in the right lower abdominal quadrant. A palpable mass in the ileocecal region is often present at physical examination, but the most reliable diagnostic intervention is ultrasound. This intervention can distinguish DIOS from other complications [7]. Prior abdominal surgery can result in atypical presentation (including unusual site of maximal pain). Rapid diagnosis is of utmost importance in order to prevent complete intestinal obstruction.

Treatment of DIOS [8] differs between clinics and countries. In incomplete obstruction, the combination of oral rehydration in combination with stool softeners (Klean-Prep, Movicolon; Norgine, Amsterdam, The Netherlands) are successful in most patients. Alternatively, sodium meglumine

diatrizoate (Gastrografin™; Bayer Health-Care AG, Berlin, Germany) can be used orally or by nasogastric tube. In patients with complete obstruction, a more aggressive approach is needed, including complete lavage using a nasogastric tube. However when vomiting occurs, enemas, including Gastrografin, can be helpful if the enema contents can access the terminal ileum. Colonoscopy by an experienced gastroenterologist may be useful in rare cases.

2.2. Development of exocrine pancreatic insufficiency in previous sufficient patients

Exocrine pancreatic insufficiency is present in 85%–90% of all paediatric patients with CF. Using the diagnosis and understanding of ‘mild’ disease and its relation with class IV and V mutations, the number of CF adults with pancreatic insufficiency is lower. However, pancreatic sufficiency is not a ‘static’ condition. Over the years the exocrine function of the pancreas may deteriorate and patients may slowly develop pancreatic insufficiency [9]. Therefore, in pancreatic-sufficient CF patients who develop fat intolerance, have unexplained weight loss or newly diagnosed glucose intolerance or CF-related diabetes, the diagnosis of pancreatic insufficiency should be considered.

Diagnoses of pancreatic insufficiency can be made by measuring pancreatic elastase-1 (EL-1 – a specific human protease synthesized by the acinar cells) in a stool sample. Values of less than 200 µg/g stool may direct to the diagnosis of pancreatic insufficiency.

2.3. Pancreatitis – acute, chronic and recurrent

In patients with CF, pancreatitis occurs mainly during adolescence and young adulthood. It is much more common among patients who are pancreatic sufficient but may occur among patients with pancreatic insufficiency [10]. Acute pancreatitis can be the first manifestation of CF and has been reported in patients carrying a wide range of mutations [11,12]. It may resolve but can also lead to chronic or recurrent pancreatitis [12]. Although symptoms mimic the symptoms of non-CF pancreatitis, the course of this complication is often less severe.

Diagnosis is made by clinical symptoms and elevated serum lipase. The latter is often less elevated compared with non-CF patients because of the limited capacity of the pancreas to produce amylase in CF. Treatment includes absence of oral intake of food, intravenous fluid resuscitation and analgesia. In patients with recurrent or chronic pancreatitis, treatment with a high-fluid and salt-based diet, and high-dose proton-pump inhibitors in combination with pancreatic enzymes may lead to a decrease in symptoms, as they may allow the pancreas to ‘rest’.

2.4. Gallbladder disease

Gallbladder abnormalities are frequently observed in patients with CF. Gallbladder stones and a shrunken (or microgallbladder) have been observed in up to 25% of patients either by ultrasound, magnetic resonance imaging (MRI) or even at autopsy [13–15]. However, only a minority of CF patients (1%–4%) develop sympto-

matic gallbladder disease [14,16]. Cholelithiasis is more prevalent in CF patients compared with healthy individuals and is thought to be due to several causes, including cholesterol hypersaturation of abnormal viscid bile and biliary stasis. As gallstones in CF are radiolucent, plain abdominal radiography is seldom diagnostic and therefore ultrasound or MRI are the diagnostic procedures of choice.

Patients with CF may present with biliary colic, though complications such as cholecystitis, cholangitis or obstructive jaundice are rare [16]. Treatment of cholelithiasis with ursodeoxycholic acid has been studied and has been shown to be ineffective [17]. Therefore, a laparoscopic procedure is preferred in order to prevent open surgery, especially in patients with more severe lung disease [18].

2.5. Chronic CF-related liver disease

Cirrhosis and complicating portal hypertension usually develop in late childhood or during adolescence and complicate CF in 5%–10% of adult patients [19,20]. Most of the clinical consequences relate to complications of portal hypertension, in particular gastrointestinal varices and features of hypersplenism. Although these conditions are usually diagnosed in childhood, occasionally cases can be recognized in adult life. The role of ursodeoxycholic acid in older patients is unproven [21], despite its frequent use. Progressive liver disease may require consideration for orthotopic liver transplantation, which may even extend to multiorgan (lung, heart–lung) transplantation [22].

3 Cancer

There is an increased risk of gastrointestinal malignancies in people with CF, particularly of the oesophagogastric region, small intestine, colon and biliary tree [23,24].

After numerous case reports suggested increased rates of colonic malignancy in patients with CF, Neglia et al. reported increased rates of colonic malignancy in two patient cohorts, one from Europe (1992) and one from North America (1985–1992) [25,26]. Cancer risk is often estimated by calculating the standardized incidence ratio (SIR), which is a measure of relative risk, and is defined as the ratio between the number of cancers observed to the number of cancers expected. A recent Registry analysis provided data to support the earlier studies using a 20-year observation period [24]. The risk of colon cancer increased (SIR = 6.2; 95% confidence interval [CI] 4.2 to 9.0). Several important findings of this study were: no increased risk in rectal cancer; an apparent greater risk for males than females; the increased risk was seen clearly in the older adult population (>30 years) than the 20–29-year-old age group; and a marked increase in risk of bowel cancer post-transplantation (SIR = 30.1; 95% CI 15.8 to 52.2). In order to compare this increased risk with other populations at risk of bowel cancer, the SIR for an individual with a first-degree family history of colonic cancer is 2.2 (95% CI 2.1 to 2.4), and for an individual with a sibling with colonic cancer the SIR is 2.0 (95% CI 1.8 to 2.3) [27].

There is an increased risk of oesophageal, gastric and small-intestine malignancy in CF. However, rare cancers in a small population (e.g. the adult CF population) where risk can appear high (large SIR) may support increased risk but yet affect only a very small number of individuals because the incidence of such a cancer is rare [28]. Evidence of increased rates of hepatobiliary malignancy in patients with CF is less certain despite published case reports of hepatocellular and pancreatic cancer; however, most evidence supports an increased risk of cholangiocarcinoma [24]. For rates of non-gastrointestinal cancers in patients who have not undergone organ transplantation, the overall cancer risk in CF patients was similar to the background risk [24].

Notably, the study demonstrated that patients with CF have an increased risk of testicular cancer and lymphoid leukaemia, and a decreased risk of malignant melanoma compared with the general population [24]. In addition to those described above, studies have clearly shown specific cancers in patients with CF who have undergone transplantation, including cutaneous malignancy, gynaecological cancer (in women), and post-transplant lymphoproliferative disorder [29–32].

In a single-centre study, significant increases in radiation exposure were found as a result of diagnostic imaging during a 17-year period from the early 1990s. This may be important as patients live longer and have increased lifetime exposure to radiation [33].

3.1. Screening for gastrointestinal malignancy

Screening for bowel cancers in the general population reduces the incidence and mortality of colorectal cancer [34]. Several tests are available to identify and allow subsequent removal of pre-cancerous lesions (polyps) and early occult cancers, including stool-based tests (e.g. faecal occult blood tests), structural examinations (e.g. colonoscopy, sigmoidoscopy) or imaging (e.g. barium enemas or computed tomography colonography) [35].

The role of screening for colorectal cancer in CF is unproven, and false-positive faecal-based tests can occur in patients as a result of small-volume haemoptysis. Specifically, the role of colonoscopy screening is also unproven; however, in some centres, all patients over the age of 40 years are offered this procedure, as are younger patients who are being considered for transplantation. The role of screening is likely to become more of an issue as the age of patients undergoing transplantation increases [36,37]. Adequate bowel preparation before colonoscopy can be a challenging issue and may require the institution of CF-specific preparation procedures (i.e. more intense bowel preparation), as bowel clearance has been reported to be inadequate [28].

Patients with persistent and unexplained upper gastrointestinal symptoms should be investigated with upper gastrointestinal endoscopy. Any patient with Barrett's oesophagus should be screened for oesophageal adenocarcinoma according to local gastroenterologist advice. Regular examination of the abdomen is advised in

adults with CF liver disease [19], supported by annual liver function tests and coagulation profiles [20]. An annual ultrasound scan and alpha-fetoprotein is also recommended in patients with cirrhosis to screen for hepatocellular cancer [38].

4 Cardiovascular disease

Pulmonary disease remains the major cause of death and morbidity in patients with CF [39]. Cor pulmonale occurs in the terminal phase of the disease; however, features of pulmonary hypertension may be detected in up to 25% of patients with severe disease [40]. Consistent results on the impact of pulmonary hypertension on survival prior to transplantation have been reported recently [40,41]. Abnormalities in the structure and function of the right ventricle are frequently seen in patients with advanced lung disease and may be present at early stages of the disease, though the clinical significance remains uncertain [42,43]. Diastolic left ventricular abnormalities have also been reported in patients with severe lung disease [44].

CF-related diabetes of long duration (particularly in those with poor glycaemic control) can result in microvascular complications [45]. To date, macrovascular complications, including coronary artery disease, have been reported infrequently; however this may emerge in the future, along with enhanced longevity. Recent registry data confirm improvements in the nutritional status of adults with CF and even in some worrying signs of obesity! As an example,

the median body mass index of males with CF over 30 years is approaching the upper limit of the healthy weight range (20–25 kg/m²) [46].

Recently, evidence of hyperlipidaemia in the adult CF population has been documented. Raised blood lipids were noted in 24% of pancreatic-insufficient and 43% of pancreatic-sufficient patients, and were more likely in those who were overweight or obese [47]. Importantly, with increasing age, total cholesterol and low-density lipoprotein cholesterol have been found to increase [48]. The role of screening is unproven and requires prospective study, although it would be warranted in older people with CF (e.g. >40 years) who have other conventional risk factors for vascular disease (e.g. family history, smoking, obesity, hypertension).

Cardiovascular complications including coronary artery disease have been associated with chronic obstructive pulmonary disease, even allowing for smoking history [49]. This may be due to vascular complications of a chronic systemic inflammatory state, which is also a feature of patients with CF who have chronic bacterial infection and bronchiectasis. Indices of increased vascular wall stiffness have been reported in adults with CF and may herald the emergence of vascular diseases in long-term survivors [50,51]. In a study of adults with CF, patients had an increased augmentation index (which has been shown to be a measure of vascular stiffness) compared with age-matched controls. Furthermore, the investigators demonstrated that augmentation index increased with age and was higher in patients with CF-related

diabetes [50]. The implications of these recent findings as the CF population ages are unclear. However, post-transplantation vascular complications may emerge as a common complication of long-term survivors when chronic renal insufficiency is common and hypertension can complicate immunosuppressive therapy.

5 Vascular access

Repeated courses of intravenous antibiotics for patients with CF can potentially lead to poor vascular access. Peripherally inserted central catheters (PICC) and midline catheters are commonly used for adults with CF, though more permanent vascular access devices may be required (e.g. portacath device) [52]. These can be complicated by infection, line fracture, loss of skin integrity and thrombosis [53,54]. The recognition of venous insufficiency can be obvious or, in some patients, clinically silent. Recently, several case series reported superior vena cava obstruction [55,56]. Management of a thrombosis complicating a PICC line or portacath is also complex, and requires careful assessment of the risk of extension and/or embolization of the thrombus and the haemorrhagic risks associated with anticoagulation or antiplatelet therapies. Ideally, a long-term vascular access device should be removed in the event of a thrombotic complication; it does raise new dilemmas as where to place and what type of device should be used for future vascular access [56]. Indeed, the need to consider unusual approaches to vascular access may

occur in some patients with central venous occlusions, and these include inferior vena cava portacaths placed in the femoral venous system, and even arteriovenous fistulae. The exclusion of hypercoagulable states is important in patients who develop venous thrombosis. The exact role of assessment for thrombophilia prior to insertion of a long-term vascular access device is uncertain, though assessment is advocated by some [57–59].

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CHAPTER 6

Complications of treatment

Authors

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Introduction

Over the years, an increasing number of therapies have become available to treat the complications of cystic fibrosis (CF), including drugs that are frequently given in high doses over prolonged periods and outside normal licensed indications. As survival improves, individuals with CF will increasingly have repeated exposure to these often toxic medications, adding to the potential to develop treatment-related complications as the individual with CF grows older.

Drugs used to treat CF can be broadly divided into the following categories: antimicrobials, anti-inflammatory agents, bronchodilators, digestive and nutritional agents, and those aimed at aiding mucus clearance. A new and rapidly evolving therapeutic area is the group entitled 'mutation-specific' or 'gene-modulator' drugs. This chapter reviews the potential for complications in each of these drug groups, focusing on CF-specific complications rather than elaborating on the side-effects and/or complications typically seen in all patients.

1 Antimicrobial agents used in CF

Antibiotic therapy is the cornerstone of CF treatment, as most individuals succumb to respiratory failure caused by repeated and difficult infections (pulmonary exacerbations), which often only respond to prolonged courses of intravenous (IV) therapy. Treatment is complicated by the fact that CF individuals process drugs differently; they have a higher volume of distribution [1] and faster excretion rates [2] than non-CF patients, meaning that IV drugs often need to be administered in higher doses and for prolonged periods, increasing the potential for side-effects.

All antibiotics have known side-effects, which include allergic reactions, but they can also result in idiosyncratic and unpredictable reactions (**Table 1**). The potential for allergic reaction to a specific antibiotic drug increases with repeated dosing, and over time some individuals become intolerant to most classes of antibiotic, making treatment problematic. Hypersensitivity reactions are most commonly seen with beta-lactam antibiotics given intravenously, and desensitization has only limited success [3]. However, the same antibiotic can often be given by another route (e.g.

inhalational) without intolerance [4]. Some antibiotics have direct toxic effects, which can result in irreversible organ damage if used in the long term. These largely belong to the aminoglycoside group.

1.1. Aminoglycosides

Aminoglycosides are powerful bactericidal antibiotics that are commonly used in the treatment of Gram-negative infections. Many are highly effective against *Pseudomonas aeruginosa*, are relatively cheap

DRUG	SIDE-EFFECTS
Aminoglycosides	Nephrotoxicity, ototoxicity
Ceftazidime	Rash, hypersensitivity reactions, headache, gastrointestinal upset
Aztreonam	Rash, blood dyscrasias, hepatitis, cholestasis, gastrointestinal upset
Meropenem	Skin reactions, blood dyscrasias, headache, gastrointestinal upset
Colomycin	Neurotoxicity, visual disturbances, vasomotor instability, nephrotoxicity
Teicoplanin	Gastrointestinal upset, hypersensitivity reactions
Flucloxacillin	Rash, cholestasis, gastrointestinal upset
Vancomycin	Nephrotoxicity, ototoxicity, blood dyscrasias
Cefotaxime	Gastrointestinal upset, headache, allergic reactions, blood dyscrasias
Ticarcillin	Rash, hepatitis, cholestasis, gastrointestinal upset
Fosfomycin	Electrolyte disturbance
Amoxicillin + clavulanic acid	Gastrointestinal upset, cholestasis, rash
Piperacillin + tazobactam	Hypersensitivity reactions, rash, gastrointestinal upset, blood dyscrasias

Table 1 Common side-effects of intravenous antibiotics used in CF

compared with other classes of antibiotics and are widely used in CF. They are lipid and water-soluble molecules that are not absorbed well through the gut, but following IV administration have a rapid compartmental distribution and achieve peak serum levels within 30 minutes. Activity is related to peak levels and the 'post-antibiotic' effect (a continuing bactericidal action when the drug is no longer detectable). However, as CF patients have accelerated renal clearance and modified pharmacokinetics [1], high doses of IV aminoglycosides need to be administered (up to 10 mg/kg body weight per day) to achieve therapeutic concentrations, which increases the potential for side-effects. To reduce this risk, serum drug level monitoring should always be performed with aminoglycosides therapy.

1.1.1. Renal toxicity

Aminoglycosides do not bind well to plasma proteins and are eliminated through the kidney via glomerular filtration. Up to 15% of the filtered dose is reabsorbed by the proximal tubule through a saturable mechanism, which, once exceeded, results in the disruption of lysosomal function by binding to brush border membranes with subsequent cellular apoptosis. Aminoglycoside-induced nephrotoxicity is a dose-limiting feature and, unfortunately, toxic levels are close to the therapeutic range. They can cause acute kidney injury. Although episodes rarely occur with inhaled therapy [5], they are relatively commonly associated with IV delivery [6,7]. Their repeated use is also associated with chronic renal insufficiency, as nephron numbers are genetically

determined (the human average is 1 million per kidney) and damaged nephrons cannot regenerate (nephrogenesis is completed by 36 weeks of gestation). Studies have shown a correlation between lifetime aminoglycoside use and deteriorating renal function [6]. Routine 3-monthly IV anti-pseudomonal antibiotic therapy, including an aminoglycoside, in an attempt to maintain lung function and prevent pulmonary exacerbations has been commonly practised in the past, particularly in paediatric care. This increased the lifetime exposure to these toxic drugs and ran the risk of exacerbating the development of resistance patterns [8]. With patients surviving for longer the practice is highly questionable, especially as it has not been definitively shown to confer an additional benefit compared with a more reactive approach (i.e. treatment only when a pulmonary exacerbation occurs) [9], and may be associated with higher mortality [10].

Toxicity varies between aminoglycosides. For example, gentamicin, previously commonly used in paediatric CF practice, is more nephrotoxic than other aminoglycosides. Its structure (two amino sugars joined to a hexose nucleus) reduces its absorbability, and its subsequent accumulation potentiates tubular necrosis and ultimately renal dysfunction [11]. It should not be used in CF patients, for whom tobramycin is preferred.

Strategies to reduce the nephrotoxic effects of aminoglycosides include altered dosing schedules and/or the concomitant use of reno-protective agents. As regards dosing, increasing the dosing interval reduces basal serum aminoglycoside levels

and the accumulation of the drug within the kidney, while theoretically still allowing the high peak serum levels and post-antibiotic effect to potentiate bacterial killing [12]. Less-frequent daily dosing has been shown to be as efficacious as thrice-daily dosing [13], with less acute kidney injury in children (based on urinary markers) in one study [14]. As regards reno-protection, agents that compete for the renal binding sites may reduce the toxic effects of IV aminoglycosides. One such drug is fosfomycin (1,2-epoxy-propyl-phosphonic acid), which is well tolerated by CF patients [15] but not yet widely used in many CF centres, and also has the added benefit of possessing effective anti-pseudomonal properties. An early study showed that it reduced acute kidney injury when used concomitantly with IV tobramycin in the treatment of CF exacerbations [16].

1.1.2. Vestibulocochlear toxicity

Aminoglycosides are taken up by most cell types within the inner ear, and can cause both vestibular and cochlear damage. The exact mechanism remains unknown, but is probably related to an oxidative process. Significant serum levels are associated with IV therapy, although rare vestibular [17] and transient cochlear (tinnitus) [18] complications have been reported with inhaled preparations. With IV dosing, acute vestibular effects (vertigo) are related to high peak levels; for this reason, IV boluses need to be given over several minutes. Cochlear damage occurs more slowly and insidiously, and is irreversible, resulting first in high frequency hearing loss. Although the incidence is unclear, high-frequency audi-

ometry and distortion product otoacoustic emissions measurement in children has suggested up to 21% may be affected [19], but other studies have not found an effect [20]. There may also be a genetic susceptibility to ototoxicity in some individuals, independent of their CF status [21]. As CF patients grow older, this is an area that requires greater monitoring, as the precise incidence in large adult populations is unknown.

1.2. Colomycin

Colomycin is a cationic cyclic polypeptide (sometimes known as polymixin E). It is bactericidal to many Gram-negative pathogens, including *P. aeruginosa*, and exhibits low levels of bacterial resistance as its killing action is predominantly physiochemical. It is commonly used in inhaled form in the suppression of chronic pseudomonal infection in CF, where systemic absorption is very low and side-effects are limited to acute intolerance in the airway. It is available for IV use as colomycin sulphomethate, which it is mainly excreted through the kidney. Early studies using large doses (up to 26 megaunits [MU] daily) demonstrated significant renal and neurotoxic side-effects [22,23], but it is now used in much lower doses in CF (up to 6 MU daily), where acute side-effects are usually transient [24]. However, it may potentiate the nephrotoxic effect of IV aminoglycosides, and therefore combination therapy should be used with caution.

1.3. Inhaled antibiotics

The focus of the chapter thus far has been on the treatment of pulmonary exacerbations

tions with IV antibiotics. However, inhaled (nebulized) antibiotics have been the mainstay of treatment of chronic *P. aeruginosa* infection in CF for decades, with good evidence of their efficacy [18]. Early introduction of long-term anti-pseudomonal inhalation therapy decreases the requirement for IV antibiotic treatment overall and should therefore reduce IV drug (particularly aminoglycoside) toxicity [25]. There are also some early data to suggest they may be useful in the treatment of acute exacerbations [26]. As the drug concentration in the sputum is considerably higher than with IV delivery, this approach has appeal, especially as there is minimal systemic absorption and therefore less propensity to cause renal dysfunction.

One of the major disadvantages of nebulized therapy, however, is the slow delivery time and other practical issues (e.g. equipment cleaning), which can significantly affect adherence. Dry powder preparations of the antipseudomonal antibiotics colomycin and tobramycin are now available. They have the advantage of ease of use compared with nebulized antibiotics, and have been shown to improve adherence [27]. Side-effects are limited to local airway irritation, and this form of delivery will be increasingly used as other antibiotics in development become available.

2 Anti-inflammatory agents

2.1. Steroids

The anti-inflammatory effect of corticosteroids has been widely studied for CF lung

disease [28]. Despite sufficient evidence supporting the hypothesis that steroids slow down the progression of inflammatory lung disease, their long-term use has remained limited because of side-effects (e.g. osteoporosis, growth restriction, diabetes [29,30]). Most recommendations and guidelines advise against their use [25,31] except for specific indications, such as allergic bronchopulmonary aspergillosis (ABPA).

2.2. Nonsteroidal anti-inflammatory drugs

The use of ibuprofen as a nonsteroidal anti-inflammatory drug (NSAID) has been shown to slow down pulmonary function decline in children [32], and its use is recommended by the Cystic Fibrosis Foundation for children (6–17 years of age) with a forced expiratory volume in 1 second greater than 60% predicted [31]. The most recent European Cystic Fibrosis Society best care recommendations concluded that ibuprofen should only be used in conjunction with specific monitoring [25]. However, it has not been widely used because of perceived concerns about side-effects, although complications even with high dosages were not significant [33]. Importantly, both the beneficial and adverse effects are unknown in adults, which is particularly important as adults in general have a high prevalence of complications relating to the use of NSAIDs (e.g. gastrointestinal and renal side-effects).

2.3. Azithromycin

Azithromycin has been shown to be beneficial in CF patients, probably as a result of a combined effect on infection and inflam-

mation. In patients who are chronically infected with *P. aeruginosa*, maintenance therapy with low-dose azithromycin has been shown to improve pulmonary function and reduce pulmonary exacerbations [34], and is recommended as the standard of care [25]. Even in the absence of *P. aeruginosa* infection, a positive effect on reduction of exacerbations has been observed [35], although pulmonary function tests remained unchanged. Concerns remain regarding durability of the effect and induction of resistance of other bacteria, but these have not been fully substantiated by clinical evidence to date [36].

3 Drugs to treat mucus/aid sputum clearance

As hyperviscous mucus secretions significantly contribute to CF lung disease, agents that treat this and/or aid sputum clearance are an integral component of CF therapy. Nebulized dornase alfa (DNase) has been available for over 20 years and, to date, no specific age-related or treatment duration-related complications have developed. Other therapies, such as nebulized hypertonic saline and inhaled mannitol, are more recent developments.

3.1. DNase

Dornase alfa has proven mucolytic and anti-inflammatory effects and improves lung function in CF patients. It is generally well tolerated, is not associated with a significant number of treatment-related long-term complications, and is safe in both children and adults [37].

3.2. Osmotic agents – hypertonic saline and mannitol

Airways in CF are dehydrated and therefore inhalation of hypertonic products increases the water in the airway surface liquid layer resulting in better mucociliary clearance. Hypertonic saline (7%) [38] and mannitol [39] have been shown to be effective and are widely used because of their efficacy and also partly because of their low treatment cost. Both agents are available for inhalation, but should be used only after pretreatment with a bronchodilator as they can act as bronchial irritants. Initial tolerability testing is necessary [25].

4 Other drugs

4.1. Bronchodilators

Bronchodilators of all types are regularly used in CF patients, although little evidence is available concerning their therapeutic or prognostic value [40]. No CF-specific long-term complications have been reported. New data are emerging, which suggest that muscarinic agents such as tiotropium may be beneficial [41].

4.2. Digestive and nutritional agents

Pancreatic enzymes are used in high dosages in pancreatic insufficient patients. Extremely high dosages may be associated with fibrosing colonopathy, a rare but dramatic clinical situation not amenable to simple dose reduction [42]. This can be prevented by not exceeding 10,000 lipase units/kg/day total enzyme dose [43]. Distal intestinal obstruction syndrome – a condi-

tion caused by inspissated faeculent matter partially or completely obstructing the gut – can complicate a patient with inappropriate dosing [44]. Other nutritional aspects of care include fat-soluble vitamin (A, D, E and K) supplementation; these are all very well tolerated with no specific long-term complications recognized. Probably the most widely recognized issue is underdosing due to poor adherence, which is an issue that spans all age groups.

5 New therapies and emerging issues

5.1. Mutation-specific therapies

The long-term complications of this new group of therapies cannot yet be fully described. Ivacaftor is the first, and currently only, drug in this group to be licensed. It has safety and efficacy data up to 144 weeks for patients carrying at least one *G551D* mutation, suggesting sustained efficacy and good tolerability up to this point [45]. Monitoring of serum hepatic enzymes is recommended at 1 month after the start of treatment with ivacaftor, and every 3 months during the first year, and then once a year thereafter.

5.2. Emerging issues

Few data are available concerning drug–drug interactions specific to the CF population, although the high doses of some therapies used may be associated with an increased risk of complications. The general philosophy in CF has always been to add a new therapy onto existing therapies. Positive or negative interactions are

not always possible to predict, although the synergistic effect of some antibiotics is an example of when additional drugs are beneficial. However, there are some emerging examples of where this philosophy may be beginning to have an adverse effect. For example, a recent retrospective study highlighted the potential interaction between nebulized tobramycin and oral azithromycin, showing a reduction in effectiveness [46]. A further example is the increasing use of triazoles to treat fungal disease. Triazoles are known to interact with inhaled corticosteroids and potentially cause adrenal insufficiency; therefore, with widespread inhaled corticosteroid use, this complication may become more prevalent [47,48]. Finally, although the new era of mutation-specific therapy holds great promise, early *in vitro* data suggest important drug–drug interactions may exist with long-term treatment. Data from primary human respiratory epithelia have shown that chronic ivacaftor treatment abrogates the effect of lumacaftor (a mutation-specific therapy under investigation) in *F508del* homozygous cultures [49]. This study and other preclinical evidence demonstrate that long-term treatment with combination mutation-specific therapies may have unexpected and unpredictable results [50].

6 Conclusions

The treatment armamentarium for CF has expanded vastly over the past few decades, resulting in significantly improved survival. This positive effect has brought

with it a new set of challenges, including an increased frequency of drug-related complications, drug–drug interactions and treatment burden. In the era of mutation-specific therapy, there may be a real opportunity to reduce treatment burden and challenge the philosophy of adding on more therapies; however, this point has not yet been reached. In the meantime, judicious use of the current therapies available and careful monitoring for drug-related side-effects will continue to remain a priority.

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CHAPTER 7

End-of-life care for CF patients

Authors

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Introduction

Pulmonary involvement in cystic fibrosis (CF) is the most common cause of morbidity and mortality in people affected by the disease. Symptoms such as dyspnoea, anxiety, cough and pain commonly reduce quality of life, and patients experience repeated acute exacerbations with variable and sometimes only partial recovery despite intensive treatment. For some patients, lung transplantation offers hope of improved survival and quality of life, but this hope is subject to organ availability, receptor eligibility and post-transplantation complications. As a result of these issues, accurate temporal prognostication in CF remains challenging, and most patients will die of their disease in the hospital setting. The unpredictability of future outcomes can be associated with psychological distress, anxiety and depression, which in turn add to the complexity of supportive care provision. This chapter describes the issues associated with providing effective end-of-life care for CF patients, and discusses the multidisciplinary approach required to meet the physical and psychological needs of patients and their families at this difficult stage.

1 A model for end-of-life care

An integrated model of care that aims to maintain the current physical condition for those waiting for donor organs while also offering maximal benefit from palliative care options could improve end-of-life care for patients, families and the healthcare team. Palliative care planning is particularly important in CF because predicting a time of death is extremely difficult. The patient and family should receive realistic information about health status and further options of care. Providing therapies that result in clinical improvement does not preclude a separate strategy aimed at alleviating unpleasant symptoms. The main symptoms requiring medical management in the terminal phase of the disease are dyspnoea, pain, anxiety and confusion. CF patients and their families may benefit from the continuity, multidisciplinary care, and the focus on symptom control and emotional support that are the hallmarks of a good palliative care approach. A model that maximizes patient-determined quality of life, provides a communication strategy, and addresses the complex physical and psychological issues, but is still flexible to incorporate individual differences, is required.

2 Integrated palliative care in CF

The treatment of CF has changed dramatically over the past 50 years, with increasing life expectancy and decreasing burden of disease. There has been a shift in perception from what was previously known as a universally fatal disease, to a chronic debilitating illness, and the preparation for end-of-life or palliative care now requires a more considered approach [1–3]. While recognizing this shift, it has to be acknowledged that CF is still a life-limiting, non-curable illness. Most patients with CF experience a progressive deterioration of lung function at a variable rate of decline, associated with recurrent episodes of exacerbations, which are treated with antibiotics, and complications. Treatments for CF are aimed at disease modification (slowing or halting progression of disease), purely at palliation with improvement of symptoms and quality of life, or the treatment may consist of a combination of both approaches. Despite an intensive daily therapy regimen, there is a considerable symptom burden, and the clinical course is prolonged, variable and unpredictable [4,5]. The very nature of CF as an illness, with its recurrent cycles of infection–treatment–improvement, means that it is often difficult to define ‘end stage’. In CF care, the provision of oxygen, intravenous antibiotics and physiotherapy are continued right up to the patient’s final days. Although unlikely to combat infection at this late stage, medications and antibiotics may continue to be administered to improve sputum expectoration, which is one of the most debilitating aspects of the illness.

2.1. When to initiate palliative care

In CF patients with end-stage lung disease, lung transplantation represents a viable option. However, it must be acknowledged that not all patients are eligible for transplantation, and organ availability remains an issue, and may preclude patients from receiving a transplant in due time. Patients on the lung transplant waiting list are seriously ill with a high level of symptoms and risk of succumbing to CF, but at the same time they are hoping for a rescue transplant that dramatically alters the course of their disease. In those CF patients who receive a transplant organ, life expectancy is limited by the occurrence of chronic rejection, cancer and other complications [6,7].

These factors create a hybrid situation of intensive management and potential indeterminate prolongation of life, balanced with palliative care and preparation for possible death. As a result, for most patients with CF, the simplistic categorization as to whether the patient is in ‘active treatment’ or ‘palliative’ care seems inappropriate. This difficulty in establishing a terminal phase of CF, the continued active treatment until the time of death, and the possibility of non-invasive or invasive mechanical ventilation as a bridge to transplantation may act as barriers to introduce palliative care for symptom control and support. When the patient is being considered for transplantation, it can be difficult to address end-of-life issues, as the psychological approach of the patient, family and medical team is one of ‘fighting on’ in the hope of transplantation rather than ‘bringing life peacefully to a close’.

Studies have reported that few patients with CF are given the chance to opt for palliative care and most patients with CF die in hospital [8–10]. The unpredictable course of CF creates challenges to the appropriate timing of discussions on the goals of care. A report on the experience of palliative care treatment by the Adult CF Centre in Newcastle, UK, reviewed 41 deaths over a 10-year period. The transition to palliative care was gradual for the 35 patients who declined or were unsuitable for transplantation. It was found that the discussion of potential transplantation provided an opportunity to discuss palliative care and end-of-life issues. Although 46% of the patients reviewed participated in a long-term palliative care programme, 37% had an abrupt change from active to palliative therapy in the last 2 days of life, which reflects the sudden physical deterioration associated with the disease. This study noted that an inadequate level of palliative care in the final stages of the disease could lead to patient discomfort, and add to the distress and bereavement of family and other patients with CF. The study concluded that there are challenges in introducing the concept of palliative care when a patient is awaiting lung transplantation [11]. Do-not-resuscitate orders are often not written until the final few days of life. Many patients continue to receive disease-modifying therapies up until the last 24 hours of life [12]. Although many disease-specific therapies can be administered in the home setting, most CF patients die in hospital [13].

A survey of advance care plans of adults with CF in the US reported that 79% felt comfortable talking to their clinician about

the care they would want if they became too ill to make decisions for themselves; however, only 28% of their CF clinicians had asked them about their wishes. The study recommended that efforts to improve clinician communications with CF adults about advance care planning are required to ensure that such a discussion becomes an integral component of adult CF care [14]. Qualitative interviews identified similar themes regarding lack of information and the challenge of maintaining hope while planning for death. Hope and a positive psychological frame were essential to coping; however, this was a hindrance to the acquisition of information. Denial as a coping strategy resulted in a lack of preparation for declining health [15].

The introduction of end-of-life discussions should not be regarded as a negative view of CF or a failure of the CF team [16]. Robinson et al. reported that the introduction of palliative care for people with CF assists the management of difficult treatments and support planning for complex decisions, and they concluded that it is possible to use a palliative approach to manage and control symptoms while retaining the optimistic strategy required for clinical improvement [2]. In another study, many patients and families viewed transplantation and palliative care as being mutually exclusive, but the qualitative interviews suggested that the CF team believed in a dual model, where both forms of care are negotiated concurrently, although they reported feeling the tension between providing maximum comfort to patients and maintaining hope of transplantation [15].

2.2. Care strategies

In an integrated model of care provision, palliative care should be applied at an earlier stage of the disease, and specific disease-modifying treatments and palliative care may run in parallel. Palliative care can be integrated with ongoing therapies at an earlier stage of the disease. Providing therapies that result in clinical improvement does not preclude a separate strategy aimed at obtaining objective control of symptoms [2,3,9,17–20].

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their families facing problems associated with a life-threatening illness, and prevention and relief of suffering should be provided by means of early identification, accurate assessment, and treatment of pain and alleviation of other problems, including physical, psychosocial and spiritual issues [18].

At a time of disease progression, the CF team is often focussed on a decline in lung function and oxygenation, prompting intensification of treatments. The terminal phase of the disease is usually heralded by increasingly frequent and severe exacerbations, breathlessness and dependence on oxygen therapy, increased difficulty expectorating sputum, chest pain and discomfort. At a time of disease progression, the patient and family should receive realistic information about health status and further options of care. An anticipatory planning of the end-of-life phase and a discussion of the patient's wishes will result in an acknowledgement of advanced disease, a risk of dying and an outline of potential

treatments, but also in a recognition of a limit to what can be achieved. It may also be helpful to have a specific assessment of physical symptoms such as breathlessness, cough, pain, fatigue and secretions, as well as the emotional impact of these symptoms, coping strategies, and fears and concerns for the future. Early management planning in the terminal phase of the disease not only allows the patient and family to prepare for the possible moment of death, but also provides time for important decisions to be made such as putting affairs in order and planning a funeral.

Much of the palliative supportive care can be provided by the CF team as general palliative care, but the palliative care team can also provide advice and support, and can see patients with specialist needs or when lung transplantation is being considered. Key elements of palliative care include the relief of symptoms and distress using a combination of drug therapies and additional measures. However, a team approach is required to address the needs of patients and their families, the enhancement of life, the mitigation of suffering, and the recognition of dying as a normal process of bringing life to a natural end. A flexible approach is needed to meet individual patient needs. Terminal care should be organized in the place chosen by the patient and their family (hospital, hospice where possible, or home). Terminal care should not end with the death of a patient; psychological and spiritual support should also be offered to the bereaved families.

As well as providing physical care, staff must be able to contain their own distress in order to help patients and their families

face key fears about death, dying and identity. The limited research available within CF care indicates that staff can experience considerable distress when providing specific end-of-life care [16,19], and that CF care providers are increasingly recognizing the need to provide good-quality end-of-life care for their patients [19].

3 Palliation of symptoms in CF

Treatment options for patients with advanced lung disease should be maximized by optimizing all relevant aspects of care. For example, airway clearance techniques should be adapted to the patient's needs and circumstances, and aerobic exercise should be performed whenever possible. Nebulized rhDNase can be used even in severely ill patients, and a trial of nebulized hypertonic saline may have additional benefits. In patients with *Pseudomonas aeruginosa*, maintenance of inhaled antibiotics is standard care, although treatment options include monthly or alternate monthly nebulizations, often with two different antibiotics. Acute exacerbation of chronic bacterial infections should be treated promptly with at least two different antimicrobial agents. In very sick patients with CF, the optimal duration of treatment is unknown, but might well be beyond the empirical 14–21 days. Respiratory complications, such as pneumothorax and massive haemoptysis, need adequate intervention and may prompt consideration for lung transplantation.

The main symptoms requiring particular medical management in the terminal phase of the disease are breathlessness, pain and anxiety (**Table 1**) [20].

Breathlessness is a dominant symptom that can be treated by a combination of drug therapies, such as opiates and benzodiazepines, and non-drug therapies, such as nursing in an upright posture, use of a cool air fan, breathing control measures and reassurance [21–23]. Morphine and its derivatives can be administered via a variety of routes suitable to patient needs (oral, transdermal, sublingual, subcutaneous or intravenous). Morphine can also be nebulized, although the effectiveness of drug absorption varies between patients. Retrospective studies have shown that patients can tolerate levels of opiate sufficient to manage dyspnoea without respiratory depression, and intravenous morphine <5 mg per hour has been reported to control dyspnoea in the majority of patients with CF [24]. Opiate medication (opioids) may be combined with benzodiazepines, antidepressants and antiemetics, according to the individual needs of the patient. Palliative sedation is the monitored use of medications to relieve refractory and unendurable symptoms, by inducing varied degrees of unconsciousness; the aim of palliative sedation is to control suffering, not to hasten death.

Breathlessness is frequently linked to anxiety in a vicious circle, and cognitive behavioural therapy techniques or anxiolytics can be useful [25]. Oxygen is indicated for hypoxia, but is not beneficial to patients who are breathless without hypoxia [26].

BREATHLESSNESS

- Drug treatment
 - Morphine (immediate release) 2.5–10 mg 4-hourly PO as needed or morphine (modified release) 10 mg daily PO (in children 0.2 mg/kg 4-hourly plus 0.1–0.2 mg/kg/h as needed PO)
 - Lorazepam 500 µg SL 6-hourly
- End of life
 - Morphine 2.5–5 mg SC as needed or 10–40 mg/24 h in continuous SC/IV infusion, titrated to effect
(in children 10 µg/kg/h plus 10 µg/kg bolus every 5–10 min SC/IV titrated to effect)
 - Midazolam 2.5–5 mg SC as needed or 10–30 mg/24 h in continuous SC/IV infusion, titrated to effect
(in children 0.1–0.3 mg/kg 4-hourly SC or 1 µg/kg/min plus 1 µg/kg every 15 min in continuous SC/IV infusion, titrated to effect)
- Additional measures
 - Oxygen if hypoxic
 - Pulmonary rehabilitation
 - Supportive equipment (e.g. wheelchair or stair-lift).
 - Distraction
 - Reassurance
 - Cool air fan
 - Cognitive behavioural therapy

COUGH

- Codeine phosphate 15 mg 6-hourly as needed PO
- Morphine (immediate release) 2.5–10 mg 4-hourly as needed PO or morphine (modified release) 10–20 mg daily PO

Table 1 Palliation of symptoms using drug therapies (some drug treatments for common symptoms are outlined, with safe starting doses that require titration to achieve best possible symptom relief with least possible adverse effects) and additional measures

SECRETIIONS

- Clearance
 - Nebulized 0.9–7% saline 6-hourly
 - Sputum clearance physiotherapy
 - Non-invasive ventilation during physiotherapy
- Suppression
 - Hyoscine hydrobromide patch 1 mg 72-hourly transdermal
- End of life – death rattle
 - Hyoscine hydrobromide 250–500 µg 4-hourly as needed SC or 1–2.5 mg/24 h continuous SC/IV infusion (in children 5–10 µg/kg 8-hourly SC, titrated to effect)
 - Glycopyrronium 200 µg 4-hourly as needed SC/IV or 0.6–1.2 mg/24 h in continuous SC/IV infusion (in children 5–10 µg/kg 8-hourly SC/IV, titrated to effect)
 - Alternatively, atropine 0.25–0.75 mg 4 hourly SC/IV or hyoscine butylbromide 20 mg 4 hourly SC/IV, could be considered

ANXIETY

- Lorazepam 500 µg 6-hourly SL as needed
- Midazolam 2.5 mg SC as needed or CSCI
- Reassurance
- Distraction
- Cognitive behavioural therapy

HAEMOPTYSIS

- Tranexamic acid 1 g 8-hourly PO
- Bronchial artery embolization

*PO, orally; SL, sublingually; SC, subcutaneously; IV, intravenously; CSCI, continuous subcutaneous infusion.

As reduced exercise capacity is an inherent feature of severe lung disease with associated breathlessness, patients are likely to need additional support in coping with daily activities.

A non-productive cough may be helped by opiates [27,28]. Patients with terminal lung disease due to CF may have difficulty expectorating sputum and have a particular fear of 'choking to death'. Hyoscine is useful in drying secretions at the end-of-life stage [29].

In the final phase of the disease, it is uncommon to intubate and ventilate individuals, unless as a bridge to lung transplantation. However, intermittent non-invasive ventilation may be considered for symptom relief and as an aid to chest physiotherapy. Before commencing this form of therapy, counselling is important for both the patient and their family as they need to understand that it is not being used to prolong the process of dying but to help with symptoms such as breathlessness and clearing secretions.

In the terminal phase of the disease, additional psychological, spiritual and social support is mandatory.

4 Impact of lung transplantation on end-of-life care

End-of-life care for CF has changed, reflecting the wider adoption of lung transplantation as a rescue therapy for end-stage CF lung disease [3,30,31]. For patients on the lung transplantation list, the goal is to keep the patient as well as possible until potential donor organs can be found. As a

consequence, it may be difficult to address end-of-life issues as the psychological approach of the patient, family and medical team is one of 'fighting on' in the hope of transplantation rather than 'bringing life peacefully to a close'. When the patient is being considered for transplantation, non-invasive positive pressure ventilation (NIPPV), extracorporeal CO₂ removal by means of extracorporeal membrane oxygenation (ECMO), and/or invasive mechanical ventilation have a role for hypercapnic respiratory failure or as a bridge to lung transplant. More aggressive interventions such as intensive care, enteral feeding, and indwelling catheters are also seen as appropriate.

Prior to the widespread availability of lung transplantation, intensive care for CF patients was generally considered futile because it could not reverse the underlying lung disease and was associated with high mortality rates. Neither physicians nor patients wanted the patient to be transferred to the intensive care unit (ICU) if death on the ventilator was the likely outcome. More recently, ICU outcomes have improved, particularly for patients requiring ECMO or NIPPV [32–39], and it appears that the consensus against the use of aggressive care at the end of life in CF may be eroding. A French survey on the use of NIPPV in 4416 patients with CF showed that it was used as a first-line treatment for severe hypercapnic respiratory exacerbation and for stable diurnal hypercapnia, especially when associated with sleep disturbances. The surveyed centres reported a number of expected benefits from NIPPV, but few of those benefits have been formally proven [36,37]. In other patients, these techniques

can be used in the short term as a moderately effective therapy for dyspnoea or to facilitate sputum expectoration during physiotherapy, although they require a period of adaptation. Conversely, the use of these ventilation methods may complicate end-of-life care, and may appear for those patients to be only marginally less 'invasive' than endotracheal intubation. The issue of withdrawal of NIPPV may be just as difficult as withdrawal of a ventilator.

In the context of improved overall survival and the availability of lung transplantation, several studies have reassessed the indications for intensive care in CF. Patients with acute respiratory failure due to an acute reversible condition (haemoptysis, pneumothorax or antibiotic allergy) have been reported as having a better 1-year survival, indicating that ICU treatment, including invasive ventilation, may be both appropriate and effective for those patients [10,38–45]. Survival is poorer among patients with acute-on-chronic respiratory failure without any identifiable triggering event necessitating invasive ventilation, but in a study by Sood et al., 55% survived to ICU discharge, 40% underwent lung transplantation and 33% were alive 1 year later [10]. Several groups have reported similar transplant outcomes in ventilated CF patients compared with non-ventilated candidates [41] when ventilation was used as a bridge to lung transplantation.

Despite these promising results, clinicians and patients should consider very carefully the decision to use non-invasive or invasive ventilation, as end-of-life care for patients with CF may be made more difficult in the ICU setting, in that the withdrawal of venti-

latory support will be the common mode of death. In a sense, these methods may introduce an unsettling sort of 'choice' into the decisions surrounding terminal care. Many patients with CF have grown up with a certain image of how their last weeks and days will be spent, and the introduction of these newer methods of ventilation is likely to challenge the expectations of both patients and caregivers.

Two single-centres studies have focused specifically on the effect of lung transplantation on end-of-life care. In a study by Dellon et al. [31], patients on the lung transplant list were more likely to die in the ICU, more likely to remain intubated on the last day of life, and more likely to have the discussion about terminal care delayed. This means that patients were unable to participate in any decision-making plans. A similar study by Ford and Flume [30] found that patients on the transplant list were more likely to die in the ICU receiving assisted ventilation. Ford and Flume argued that the provision of more aggressive care to those awaiting a transplant is appropriate, but surmised that clinicians are opting for aggressive care without considering the realistic odds of survival to transplantation. There appears to be reluctance on the part of CF clinicians to discuss advance care planning, even though adults with CF may wish to do so. A more comprehensive understanding of the factors that promote or hinder effective decision making about lung transplantation and a more detailed directive on the use of medical interventions as death approaches should help clinicians to support patients and families through this complex set of decisions.

Use of invasive positive pressure ventilation should always involve clear discussions around therapeutic options and goals of care.

5 Psychological aspects

Palliation involves a different type of patient care and means that clinicians must be conscious that they are changing the direction of therapy, which in turn, will change the way in which the patient has lived with the disease. Palliation is not universally used in CF and may often be introduced late in the disease. Good communication between the CF team, the patient and the family is paramount during all aspects of the terminal stages. The CF team must take into account the level of understanding, the concern, and the fear of the unknown felt by both the patient and their family when discussing any treatment changes, and should be prepared to answer questions and re-discuss issues throughout this time. Following a decision to introduce palliative therapy, the CF team must carefully discuss the options with the patient and their family. Treatment choices must allow for continued good communication between the patient and their family. It is also important to provide support to friends and family around issues of visiting and staying with the patient.

It is important for the CF team to understand the possibilities and limitations of the care they are able to provide [11,46,47]. The CF team, the patient and the family must work in partnership when planning end-of-life care, including providing comfort

and the use of analgesia and anxiolytics. Bereavement support for friends and family often starts before death and continues afterwards. Provision should be made for support to be offered whenever necessary. Attention to all these points can assist in creating a communication pathway with the patients and their family so that their needs can be met fully. Families who have been bereaved will continue to struggle with their loss; however, if they feel that they were fully involved in the process, and that they received ongoing and appropriate support and understanding, then the bereavement process can become easier.

6 Conclusion

Although therapeutic innovations may continue to enhance survival and quality of life in CF, many patients, families and physicians will still have to confront the premature mortality that accompanies the essentially fatal diagnosis of CF. Even in a period of advancing survival, compassionate and skillful end-of-life care will remain an essential part of comprehensive care for patients and their families, and will require specialist skills and good cooperation between the CF and palliative care teams.

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CHAPTER 8

Occupational and social issues

Authors

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Introduction

Being an adult with cystic fibrosis (CF) is both an achievement and a challenge [1]. Today, most adults with CF achieve normal social and vocational development into adulthood and, like healthy people, have to balance their lives around different occupational and social issues (Fig. 1). This real-life balancing act is driven by a strong wish to successfully integrate CF into their desired lifestyle and their aspiration to be considered as 'normal' and not 'different' [2]. This chapter examines the social aspects of living with CF as an adult, focussing on work, family, and the financial challenges of life with the disease.

1 Working life for adults with CF

After having reconciled education and CF, with more or less difficulty, during childhood, adolescence and early adulthood, adults with CF can aspire to enter the workforce. This raises new challenges for them and their caregivers.

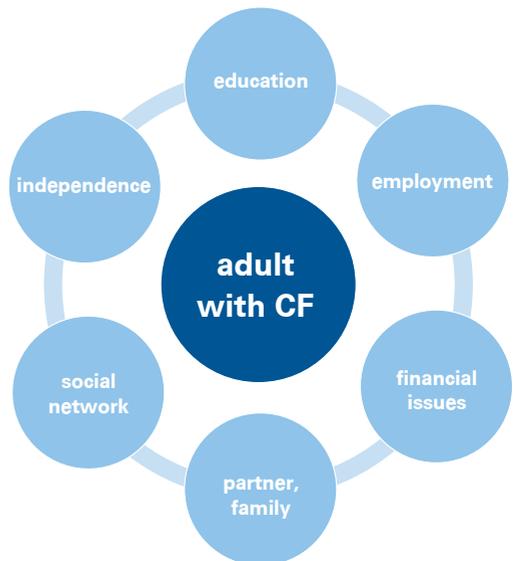


Fig. 1 The adult with CF: occupational and social issues.

However, as for other people with a chronic disease, they may be limited in their ability to achieve full participation in the workforce. The occupational issues faced by adults with CF, such as career choice and work disability, have recently gained interest among researchers, probably reflecting the improved survival rates and the growing adult CF population. Studies aimed at understanding the factors associated with work for people with CF have examined the level and nature of work participation, and results have been useful in highlighting the difficulties encountered. However, many of these studies have been conducted in single centres, and therefore results may not be generalizable to the rest of the adult CF population.

1.1. Employment rates and types of employment

The high level of employment among CF adults is well documented. Studies have reported employment rates mostly in the range of 60–70% at the time of the surveys [3–8], with a very significant proportion of interviewees (>90% in some surveys) reporting ‘any history of labour force participation’ [4–8]. In particular, the return-to-work rates for lung transplant recipients seems encouraging, although evidence is still sparse [7,9,10].

The job profiles for people with CF appear to be quite particular. Compared with the general population, significantly higher proportions of CF adults follow non-manual occupations; 70–80% had white-collar occupations that were sedentary or light physical jobs [3–5,7,11]. These

occupations were mainly in skilled categories that required a good educational background [7,11], and several studies have reported that people with CF have a higher educational attainment than the general population [7,11]. In addition, a survey stated that individuals who worked prior to but not at the time of the evaluation held a substantially higher percentage of unskilled jobs (31%) than those who were working at the time of evaluation (6%) [11].

The recourse to part-time work is usual, and occurs in 30–50% of workers with CF [4,6–8]. This option could help to maintain employment despite declining health and growing care needs [7].

1.2. Factors related to employment

Identifying the characteristics of adults with CF who are working compared with those who are not is seen as key to guiding the way to employment for people with CF. The literature on factors associated with employment is conflicting; however, the discrepancy is probably due to methodological issues (e.g. studies not using the same statistical analyses or the same variables, or lack of statistical power associated with small sample sizes), rather than a lack of consensus. Nevertheless, some broad patterns have emerged.

1.2.1. Clinical status

The hypothesis that employment is associated with clinical status seems credible. Forced expiratory volume in 1 second is the clinical parameter most frequently tested in studies, and it has been associated with work status in some studies

[4,7,12,13] but not in others [5,6]. The overall evidence is that increased severity of disease is associated with a greater risk of disability.

1.2.2. Educational attainment

People with poor educational attainment are usually particularly vulnerable to precarious career trajectories. This is especially true for those with CF. Good qualifications enhance employment prospects independent of disease severity [3,5,7,8].

1.2.3. Social deprivation

One study reported that the greater the social deprivation, the lower the employment chances [13]. This was not unexpected. Interestingly though, social deprivation appeared to amplify the negative impact of poor clinical status on employment [13].

1.2.4. Quality of life

The association between employment and some psychological factors has been investigated. It has been shown that health-related quality of life was associated with work status. People with CF who were working had better quality of life indices, such as health perception, role perception, physical functioning, social functioning and disease mastery, which were independent of clinical parameters of disease severity [6,8]. It was not possible to determine from these cross-sectional studies whether those who were not working reported lower quality of life because they were unable to work or whether those with lower quality of life were less able to

work. However, it is possible that being in employment may increase perceptions of quality of life. This discussion of causality also applies to the finding that CF adults who were working had lower depression scores compared with those not working [5].

1.3. Barriers to employment

In the studies of employment in people with CF, about 70% of those who did not work stated ill health as the reason [3,4,7,8,13]. In addition, of those who were in employment, a large majority felt that CF prevented them from having a career [7], at least half thought that CF resulted in limitations in their job [7], and about a quarter reported having changed specific job duties because of CF or of having to make workstation adjustments [6–8]. Challenges to employment for people with CF include activity limitations, the need to take time off for care and/or treatment, financial issues, the risk of a worsening health due to occupational hazards, and concerns about disclosure of the disease. CF is a multi-organ disease that can affect functional abilities, primarily lung function. The exercise capacity of adults with CF is often reduced, therefore preventing them from taking physically demanding jobs. Job characteristics must be in accordance with the disease severity. An additional challenge is the progressive nature of the disease; a job may suit an individual with CF at a given point in time but may become unsuitable as disease progresses. This emphasizes the need to consider the work environment as well as the profession. Patients with CF should seek careers

that allow some flexibility, for example by making workstation adjustments, changing contract arrangements and hours, or relocating to another job. Such considerations are also important given that management of CF is time-consuming and can be a significant burden. In addition to the time spent each day on treatment, most CF people in employment need to miss work days for appointments or hospitalizations [7,8], which can cause service disruption [7]. There is a risk that patients might delay or avoid treatments because of anxiety about disrupting their professional duties.

Sick leave or the need to work only part-time hours may also negatively affect income (see *Financial issues* below). Overall, up to a third of people with CF who were interviewed in studies reported having to take a cut in pay because of their disease [6–8].

As mentioned above, health status can be a barrier to employment, but there is also the problem of potential deleterious effects of work on health. Indeed, some occupational exposures could be harmful to workers with CF and should be avoided. Thus, a study reported that people with CF had been warned to avoid the following activities (in descending order of frequency of warning): healthcare work, physical work, work involving contact with children, work involving exposure to dust or fumes, outdoor work, work involving contact with animals, hairdressing, and work in green spaces [7]. Most of these activities could expose the individual to respiratory pathogens or irritants that may alter lung function. Finally, a person with CF who is working or seeking a job will necessarily face the decision of whether or not to disclose their

disease to their employer and colleagues. Data on the frequency of disclosure in the workplace vary widely across studies [3,7,14,15]. There is no universal recommendation for this issue; it depends on individual situations and on the context, such as specific regulations that exist in some countries to protect workers with disability. People who have a more severe disease may be more likely to disclose the information [15], probably because they face more difficulties in reconciling work and CF, and may need occupational adjustments to pursue a career. It seems that the effect of disclosure on professional relationships is rarely negative [15].

1.4. Recommendations on occupational issues

If a growing proportion of adults with CF take part in the world of work, the difficulties they face must be acknowledged. Vocational guidance could be provided to adults with CF who are interested in learning more about employment and how it can be integrated into their CF lifestyle [16]. Indeed, half of adults report that CF affected their choice of occupation or career [4,6,8]. However, only a minority of them discussed their career choice with their physician [4,6,14], and it is rare for patients to receive formal career counselling [4,6,8,14].

In practice, educational and vocational guidance and counselling should be developed in paediatric and adult CF centres. For the adults with CF who fail to maintain employment, vocational rehabilitation guidance should be planned. National policies should support CF people in work, for example by paying them compensation when they

are working part-time, or by encouraging employers to make their workplace flexible. Research in the field of employment in CF adults should be reinforced. In this regard, the 'medicalization of employment' in research to date has been criticized, and there are calls to explore this topic from a social model perspective instead [17].

2 Social issue for adults with CF

2.1. The transition to adulthood

With most adolescents now reaching maturity, many CF clinics have developed specialized transition programmes to prepare young people for adult life with CF [18]. This is important because the social role of an adult with CF is different from the role of an adolescent. An adult with CF encounters issues that are part of the normal adult social role, including independence, self-care, the possibility of further or higher education, finding a job, intimate relationships, forming a family, and building a home. For chronically ill adults, Higham et al. [19] summarized five important overarching themes: living with unpredictable health, and fear of death and dying; hopes for normality; hopes for a normal relationship and/or marriage; hopes for having children; and hopes for a normal work life [19].

2.2. Social relationships

An important aspect of the adult role is social relationships, principally of (intimate) partners, family, friends and colleagues. Both the quantity and the quality of these relationships affect mental health, health

behaviour, physical health and mortality risk [20]. The impact of CF symptoms and treatment on this social role is extensive. For example, in clinic, patients often talk about their worries about finding a partner, and they reveal that they feel that forming and maintaining an intimate relationship is a challenge. Worries about disclosing the diagnosis, the first kiss (the fear of coughing up sputa), and the worry of rejection because of CF, are often talked about.

"I liked her a lot and I knew she liked me, but I was afraid she would not want me because of my CF. We got together and talked a lot and I was afraid of mentioning CF yet still I felt I had to talk about it. Not talking about it felt a little bit like lying. Turned out she already knew! It was such a relief!"
(25-year-old man)

Patients' relationships with family (e.g. parents and siblings) are often strong, and CF is often mentioned as a binding factor. Many adults are, to a certain extent, reliant on their parents or siblings, be it financially, emotionally or medically. For example, some patients cannot afford their own home and have to continue to live with their parents. Others live with their parents because of their physical limitations and needs. Finally, friendships and colleagues are, for many patients, a significant contributor to their wellbeing [21]. These relationships provide the adult with the feeling of leading a normal life and thus having a normal adult role. When health deteriorates, patients may need to withdraw from their social life and

work activities. Withdrawing from work means fewer social contacts and patients often report that they feel useless. They have lost their role in society, and this has implications for their feelings of self-esteem and self-worth. For this reason, patients may delay the cessation of working activities, thereby potentially risking their health [21]. There is also a group of patients who seem to lead a more isolated life, who do not (look for) work and who live in a small social circle. Little is known about this group, but observations in clinic seem to indicate that CF has taken a major place in these people's lives, which seems to prevent them from reaching an adult role.

2.3. Having children

A central part of adult life is the desire to live independently and to form a household. For some adult patients this may include having children. The decision-making process involved in starting a family is often long and full of doubts, which may pose a burden on the partner relationship. Patients regularly express their concerns about the remarks and judgements that family and friends and even members of the CF team might make about the potential risk of having and taking care of a baby.

Once the decision to have a child is made, the adult has to fulfil another role – becoming a parent (with CF). There is little information in the literature about the impact of raising a child on the psychosocial wellbeing of a patient and their family, or about the impact of raising a child on CF and treatment [22]. Talks with patients reveal that they worry about their ability to raise a child, about whether they will live long

enough to see their child grow up, or how the child will feel about having a parent with CF. Despite these considerations, most patients are happy with the decision they have made once they have a child. With regard to the physical impact of caring for a child, Colpaert [22] interviewed 28 parents with CF and found that caring for a child resulted in less time for self-care and CF treatment, which may have implications on lung function and life expectancy, and this can also be a burden on the partner relationship [22]. Nevertheless, Colpaert also found that having a child gave extra meaning to life, which is often a motivational factor to adhere to treatment and, above all, is an adult role many patients aspire to.

3 Financial issues

3.1. Financial independence

As mentioned above, one of the goals in adults with CF is to live independently, but this requires financial resources. Most patients who have a full-time job are able to rent a place to live. Buying is more complicated because of the problems of obtaining a mortgage and life insurance (see below). When patients cannot work full-time because of health reasons, which is common in CF [8], it is often not possible to live independently without the financial support of parents or a spouse/partner. When CF progresses and health deteriorates, patients may have to reduce their working hours or stop work altogether. As well as the impact on their social relationships, this decision also has implications on

their financial independence. When patients stop working, their financial situation often becomes complicated by the many pitfalls in social security. Benefits and disability allowances differ from country to country and are likely to change frequently during the adult life of the patient.

'I worked full-time for 18 years. Because of my CF I had to take sick leave and was made redundant. I had to choose between finding another part-time job which meant earning a lot less or going on benefits, which compared to the salary in part-time work meant a little bit more money. I want to work because this makes me feel worthwhile, but my financial situation makes it hard to choose.'

(34-year-old man)

3.2. Administration

The administrative challenges for patients with CF are complex and differ from country to country. Administrative tasks include medical paperwork, such as keeping track of prescriptions and appointments, applying for social benefits and other financial support, paying hospital bills, and health insurance issues. In some countries, people with a disability may be able to get help paying their utility bills. Overall, administration in CF is complicated, and many patients need help in completing these tasks to ensure that they keep on top of their treatment and receive the financial support that they are entitled to.

3.3. Insurance

Obtaining a basic package of insurance is a normal part of adult life. However, for people with a chronic illness, some types of insur-

ance are difficult to obtain. For example, in most countries it is almost impossible for adults with CF to obtain a loan, a mortgage or life insurance. Many insurance companies exclude life-threatening diseases from their mortgage policies. This means that, for most adults with CF, buying a house is only possible with the help of a spouse or parents.

'I wanted to buy a house and so I went to the bank for a mortgage and life insurance. To obtain a life insurance as part of the loan I needed to complete a medical questionnaire. They asked me whether I had medical problems. I was not sure whether to disclose about my CF... I did not want to lie, but I knew that CF would probably exclude me. I wondered whether I could state that I had mild CF.... It was all very confronting and difficult. I never got the life insurance, because of my CF.'

(34-year-old woman)

Social health legislation is complicated and for most patients it is difficult to see the wood for the trees. The often rapidly changing regulations make things even more puzzling, and, again, many patients require help with this part of their life.

4 Summary

Recent years have seen a growing interest in the occupational and social life of the adult with CF. Many adults work, and studies have shown that these adults often have higher

educational attainment and do non-manual work. With deteriorating illness, those who do manual work have to stop working because of CF sooner than those who do non-manual work. Most studies show that working is associated with illness severity, lung function and exercise capacity. Other correlates are qualifications and social deprivation, with the latter being negatively associated with work. Barriers to working are ill health, time-consuming treatment and particular work environments. In addition, disclosure about the illness prevents some people with CF from starting work as they do not want to be confronted with rejection because of their disease. Social relationships and fulfilling a social role are other important aspects of life for adults with CF. The extent to which a patient can fulfill these adult roles reflects the extent to which the individual can lead as normal life as possible. Social relationships in adulthood include partners, own children, family, friends and colleagues. Illness severity has a strong impact on the quality and quantity of social relationships. In addition, disclosure about the illness in personal relationships is an important issue. The financial position of a patient affects the extent to which an adult with CF perceives their level of 'normality'. Some can obtain financial independence, but many are partly dependent on their partner or family, for both housing as well as day-to-day living. Illness severity and disease trajectory are often associated with changes in the financial situation of the patient. Insurance and mortgage availability are important issues, and are often complicated by rapidly changing regulations that exclude chronically ill patients from obtaining financial services compared

with their healthy peers.

In conclusion, the provision of good educational and vocational support and guidance, as well as vocational rehabilitation, is an important task for the CF team. The social and financial life of adult patients is often complicated by their disease, its severity and treatment. For many, the aim is to fulfil their social aspirations in a similar way to their healthy peers, but most are well aware that CF will affect their ability to achieve this and that coping strategies will be required throughout their adult life.

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CHAPTER 9

Patients becoming parents: Reproduction and pregnancy

Authors

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Introduction

During the past 20 years, there has been a dramatic change in the epidemiology of cystic fibrosis (CF) in European and North American countries due to an improvement in overall survival. This has resulted in an increasing number of adult patients, which is now equal to or more than the number of paediatric patients in many registries, depending on the definition of 'adult' [1–3]. Moreover, many adult patients have very good social and occupational integration, and many of them are living with a partner. These conditions have led to an increasing number of people with CF considering parenthood. The increase in number of pregnancies has been noticed in most worldwide CF registries (e.g. 211 pregnancies in the US CF Foundation 2011 report and 61 in the French registry in 2011) [1,3]. In cases of infertility, assisted reproduction techniques can be employed to facilitate pregnancy. Assisted reproduction is also proposed for men with CF, nearly all of whom have congenital bilateral absence of vas deferens.

The method has been used for many years with an increasing rate of success in specialist centres [4].

The question of reproduction and pregnancy is therefore an important issue for the CF team. This chapter discusses fertility issues in men and women with CF, including the importance of genetic counselling, assisted reproduction (almost always necessary for men and sometimes for women), and the ethical issues surrounding parenthood and assisted reproduction, especially in patients with severe disease. The care and management of pregnancy in women with CF are also discussed.

1 Fertility issues

1.1. Fertility in women

Despite an anatomically normal reproductive tract, many women with CF have reduced fertility. The global fertility rate in CF woman remains debated. Anovulatory cycles are one of the causes of infertility, and are sometimes, but not always, due to poor nutrition and lung function. The isolation of the cystic fibrosis transmembrane conduct-

ance regulator (CFTR) protein in the hypothalamus may suggest a central dysregulation inducing *CFTR*-related abnormalities in ovulation [5]. *CFTR* is also present in the whole genital tract (Fallopian tubes, endometrium and cervical mucosa). Therefore, altered hydroelectrolytic contents of uterine secretions and abnormal viscosity of cervical mucus may induce both obstruction of the cervix and impairment of sperm capacitation [6]. Despite these various causes of fertility impairment, many women with CF are able to conceive spontaneously, and it is strongly recommended that they receive safe and efficient contraceptive advice [7].

Assessment of fertility is indicated if pregnancy does not occur naturally. Assisted reproduction was required in 34% of 222 French CF pregnancies [8] compared with 5.6% in the general population. The method used depends on the suspected cause of infertility. It may be an artificial intrauterine insemination using the partner's sperm, sometimes associated with ovarian stimulation and *in vitro* fertilization [7].

1.2. Fertility in men

Infertility in men with CF was first described in 1968 and affects at least 97% of men with the disease [9]. Men with CF are azoospermic, secondary to congenital bilateral absence of the vas deferens. In addition, the seminal vesicles display various abnormalities such as aplasia or hypoplasia, and the body and tail of the epididymis are absent or malformed. The head of the epididymis has a different embryological origin and is usually not affected. The testes may be atrophic or normal. These abnormalities are related to mutations in the *CFTR* gene. CFTR protein

is present in the epididymis and vas deferens, and deficiencies in the protein lead to dehydrated secretions and obstruction in the genital tract during male foetal development [9,10].

The CFTR protein may also play a critical role in spermatogenesis or sperm maturation. Histological examination of testicular biopsies in men with CF has indicated abnormalities in spermatogenesis, including a low rate of mature spermatids, maturation arrest or malformed late spermatids [10]. These abnormalities could be expected in the presence of chronic illness or malnutrition but they may also be another expression of the CFTR protein abnormality in the spermatozoa. However, the *in vitro* fertilization rate of oocytes with CF spermatids appears to be equivalent to the rates in non-CF individuals [10].

Only a few investigations are necessary to confirm infertility in men with CF. Diagnosis is supported by semen analysis showing azoospermia, low ejaculate volume (<1.0 mL) and acidic pH. Clinical examination is usually sufficient to confirm absence of the vas deferens. Scrotal exploration or transrectal ultrasound may also be used. The serum hormone profile (follicle stimulating hormone, luteinizing hormone, testosterone) indicates that men with CF have normal spermatogenesis [9,10].

Obstructive azoospermia cannot be corrected by surgery. The alternatives for men with CF are adoption, sperm donation to the partner, and sperm aspiration coupled with intra-cytoplasmic sperm injection (ICSI). Collection of semen is obtained either from the epididymis by percutaneous or microsurgical aspiration or by testicular extraction.

The sperm is then separated and cryopreserved for subsequent use. Following induction of ovulation in the female partner, the oocytes are harvested under ultrasound guidance and ICSI can be performed. An appropriate number of embryos is then transferred to the uterus after fertilization [9]. There are few reported data in the literature on the results of these techniques in CF patients. The pregnancy rate has been reported to be 63% with ICSI, and approximately 50% of these pregnancies resulted in a live-born child [4,11]. These results are good compared with those of ICSI in non-CF men with congenital bilateral absence of the vas deferens (pregnancy rate between 20% and 53%) [11]. There is limited information about the rate of paternity in CF patients in the different CF registries (e.g. 48 men in a French survey in 2003 [12]).

Information on infertility is often issued at the time of adolescence, but studies have shown that few patients were aware of fertility treatment [13]. Information about treatment options and their results should be widely disseminated in order to ensure that patients have all the information they need to make a decision about parenthood [10,13].

2 Counselling

2.1. Genetic counselling

Patients with CF who wish to be a parent should be informed of the risk of having a child with the disease. Their child will be a carrier at least, and if the partner of the CF man or woman is also a carrier, the risk

of having a child with the disease is 50%. Genotyping of the partner should therefore be offered ahead of pregnancy or an assisted-reproduction programme.

If the screening for the partner is negative, the risk of a child being born with CF is very small – approximately 1 in 400 – which accounts for possible unrecognized mutations [13]. If the partner is a carrier, the couple has the option of undergoing prenatal or pre-implantation genetic diagnosis to minimize the risk of having a child with CF. Alternative measures are adoption or use of donor sperm.

The genetic counselling should be performed in advance of any pre-pregnancy procedures, and should involve explanation of the various options so that the couple can make an informed and reasoned decision.

2.2. General counselling and ethical issues

Counselling regarding their own health and long-term issues is also relevant for CF patients desiring a child. The effects of the disease process, potential impacts on family life and the prospect of an earlier death should be discussed with the patient and their partner. Lung transplantation should not be forgotten, and survival rates post-transplantation may need to be included in the discussion. These discussions are particularly important when assisted reproduction or adoption is being considered. The CF patients and partners should discuss all of these issues with both the CF team and the fertility specialists, and in turn, the teams should be prepared to address these considerations with the patients and their partner.

3 Pregnancy in CF

The evidence base for the management of a pregnancy in women with CF is limited. Several reports and database analyses have been published since the first published case in 1960 [14] and the first series of 10 cases in 1966 [15–22]. Guidelines for the management of pregnancy within a multidisciplinary approach were published in 2008 [23].

3.1. Prognostic factors and outcomes

Recent studies have demonstrated a successful outcome of pregnancy in women with CF, with no short- or long-term effect on pulmonary or nutritional outcomes [21,24]. This success is probably the result of efforts to optimize pre-conception care together with close monitoring and treatment of pulmonary exacerbations and nutritional status. Two cohort studies from national registries concluded that CF women who become pregnant were initially healthier than controls [18,25].

The mean rate of miscarriage has been reported to be 4.6%, and preterm delivery was frequent (24.3%) [16]. Maternal perinatal death was estimated at 7.9%, and 13.6% died within 2 years of giving birth. However, more recent studies have shown better results [24,26]. Reduced forced expiratory volume in 1 second (FEV_1) and low body mass index are, of course, predictors of foetal complications, and some authors have suggested that patients with an FEV_1 lower than 50–60% of predicted values should avoid pregnancy. Other publications have confirmed an increased risk of preterm delivery but the same long-term survival rate,

even for women with poor lung function and an FEV_1 lower than 40% [17,27]. It is therefore difficult to use an absolute threshold level of FEV_1 as a cut-off for possible pregnancy. A stable state, good compliance to treatment and a good response to antibiotic treatment seem to be equally important conditions for a good outcome. Pulmonary hypertension remains a contraindication. Reports have suggested poor outcome with rapid decline in lung function in pregnant women infected with *Burkholderia cepacia* [23,28]. There is currently no clear consensus about decisions concerning these patients.

A poor nutritional status, usually associated with a more severe disease, is also considered as a relative contraindication for pregnancy [23].

Maternal diabetes leads to increased rates of spontaneous abortion, preterm birth and congenital malformation in the general population [29]. In more recent studies, diabetes did not appear to be associated with worse survival for pregnant women with CF [18]. Tight glucose control is recommended. In women without diabetes before pregnancy, a prevalence of 14% gestational diabetes has been reported, and glucose tolerance testing is recommended during pregnancy [27].

There are few reports of pregnancy in CF women with liver disease or cirrhosis.

3.2. Planning a pregnancy

Planning a pregnancy is important for a better outcome. Planning should incorporate all aspects, and ideally should be discussed and planned very early between the CF team and the couple in order to allow time for genetic counselling and the consideration of psychosocial issues, professional adapta-

tion for those who work, and the impact of a young child in their life. It is essential to explain the influence of pregnancy on CF course and of CF on pregnancy, and to describe the treatment and monitoring required during pregnancy.

Pregnancy should be planned when the woman with CF is in a stable disease state and after optimization of all aspects of CF care, including airway clearance, inhaled treatment, and nutritional status. In women with diabetes mellitus, insulin is the recommended treatment in order to optimize blood glucose control before pregnancy.

A checklist to expand the process of care before, during and after pregnancy has been proposed [23].

3.3. Medication

The pre-pregnancy period should be used to review the medications that are permitted and contraindicated during pregnancy. The medical regimens for patients with CF include the use of pancreatic enzymes, vitamins, inhaled, oral or intravenous antibiotics, and mucolytic and anti-inflammatory medications such as azithromycin (but not ibuprofen). Anti-pseudomonal beta-lactam antibiotics are safe to use during pregnancy and are the drugs of choice to treat pulmonary exacerbations. Intravenous aminoglycosides can cause foetal ototoxicity and nephrotoxicity, although intravenous tobramycin at the recommended dosage regimen has not been reported to induce renal or hearing impairment in the new-born. However, it is usually recommended to avoid intravenous aminoglycosides during the first trimester [23]. The benefit of the use of inhaled tobramycin to treat exacerbations

remains to be demonstrated. Preserving the health and wellbeing of the mother should be essential in the decision about medication use in CF during pregnancy, particularly for the management of pulmonary exacerbations. Fortunately, many of these medications have been largely used with no safety issues. Permitted and contraindicated medications have been detailed in recent reports [6,23,30].

3.4. Monitoring

Pregnant patients are regularly and closely monitored to ensure good compliance with treatment, particularly physiotherapy, lung function tests, early diagnosis of bronchial exacerbation, nutritional status, blood glucose levels in case of diabetes, and screening for gestational diabetes. Hospital admission may be recommended for the treatment of acute exacerbations or in cases of poor weight gain and the need for nutritional support. The recommended energy requirements for pregnancy vary from 2000 to 3000 kcal/day, and patients with poor nutrition prior to conception may need to increase their energy intake. It is important to control pancreatic insufficiency and malabsorption, as well as chronic infection as this increases energy loss. Supplemental enteral feeding is sometimes necessary, but the route of delivery (nasogastric tube or gastrostomy) is sometimes difficult during pregnancy. Moreover, as pregnancy progresses, uterine enlargement induces increased intragastric pressure, which aggravates gastro-oesophageal reflux. In some difficult cases, parenteral feeding can be considered, with some success in reported cases [31].

3.5 Obstetric care

It is also very important to work closely with an obstetric team that is experienced in the management of women with high-risk pregnancies [23]. Many women will carry their baby to full term. In this case, vaginal delivery is preferable to Caesarean section, which is associated with wound pain and anaesthesia, placing the patient at risk of developing retained secretions and atelectasis. However, for women with poorer lung function in the latter stages of pregnancy, the optimal timing of delivery should be decided jointly by the obstetrician and the CF physician after considering carefully the risk–benefit of foetal prematurity against maternal health. In both vaginal delivery and Caesarean section, epidural analgesia or epidural anaesthesia allows control of post-partum pain and maintenance of efficient chest physiotherapy.

Breast milk from a mother with CF has normal electrolyte and protein levels, which, theoretically, allows breastfeeding. However, breastfeeding requires increased maternal caloric intake and therefore women with poor nutritional status may be advised against this feeding method. Attention to good and continued adherence to chest physiotherapy and usual medications is important in the post-partum period.

3.6. Pregnancy following lung transplantation

Successful pregnancies following transplantation of solid organs such as kidneys, liver and heart have been reported, with no increased risk for new-borns. However, chronic rejection remains a significant challenge after lung transplantation [32,33].

A recent report identified 19 cases of pregnancy in women following lung transplantation; the rate of pregnancy success to birth was only 42%, and the incidence of complications was high [32]. Therefore, CF women with lung transplants should receive counselling, and should be advised of the high risk of rejection and associated mortality.

4 Conclusion

Many young women and men with CF now have the health and the opportunity to become parents. The CF team has an important role to play by providing comprehensive information, counsel and guidance to aid an informed decision. Management of patients, before, during and after pregnancy should occur in the setting of a multi-disciplinary CF team in partnership with physicians of reproductive therapies and/or obstetric care for high-risk pregnancies.

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CHAPTER 10

Psychological issues: Dealing with increasing disability

Authors

Araxie Matossian, Helen Solas

Introduction

Continued improvements in the diagnosis, treatment and management of cystic fibrosis (CF) have led to a significantly better life expectancy for people with the disease. Despite this medical progress, CF remains a progressive, gradual and lethal illness characterized by both visible and concealed physical symptoms. The high treatment burden increases the difficulty patients experience in balancing education, family, work and other adult responsibilities [1]. The adult with CF faces the challenges of the natural human life cycle, which is characterized by the alternations of building, maintaining and changing life structures [2]. The challenges may be hard at times and can affect a patient's wellbeing [3]. Psychological symptoms such as anxiety and depression or demotivation have been reported [4,5]. This chapter describes the different modalities of psychological adaptation and the coping mechanisms used by patients suffering from chronic disease. In addition, Engels' paradigm of the bio-psycho-social

model [6], which gives more insight into the complex interrelations between a patient's different life dimensions and a patient's care and treatment is discussed in the context of adults with CF. There are several dimensions that can be used to understand what is important in an adult patient's life. These dimensions include: illness as the suffering of body and mind; CF within the context of the family history; and the adult patient and the healthcare provider. A fourth important dimension is the interrelation with the social environment (see Chapter 8 *Occupational and social issues*). Chronic illness appears as 'the painful point of intersection' between these different bio-psycho-social factors [7].

1 Individual differences in adaptation to illness

According to Cohen and Lazarus [8], psycho-social adaptation to illness is determined by the patient's subjective perception of their illness. A perception of personal control seems to be one factor that promotes good adaptation. Three concepts related to perception of control are locus of control

[9], learned helplessness [10], and self-efficacy [11].

Locus of control refers to a person's belief about how much power one has over events in one's life: Do I control my life or does something else control it? People with an internal locus of control will perceive outcomes and events as a result of their own behaviour. People with an external locus of control will perceive similar outcomes as a result of external factors such as fate or coincidence. Internal and external loci of control represent two ends of a continuum, and most people lie somewhere between the two extremes [9].

In Seligman's study of learned helplessness, animals were repeatedly exposed to electric shock that they could not escape from. Eventually the animals stopped trying to avoid the stimulus. When the situation changed and they were able to escape, they did not take any action. They had developed learned helplessness – a lack of confidence that anything could be done to help them. The same behaviour, the tendency to give up in situations in which one is not really helpless, has been observed in people [10].

Self-efficacy is to believe in your own capabilities to execute the planning and actions required to reach a goal. In other words, the individual's own belief in coping in a given situation. Behaviour is largely controlled by the individual expectation or how one will perform. People with high self-efficacy, those who believe they can perform well, are more likely to view difficult tasks as something to be mastered rather than something to be avoided. People who believe they can deal effec-

tively with stressors are not perturbed by them. If, however, they believe they cannot control the aversive circumstances, they distress themselves and impair their level of functioning [11].

External locus of control and learned helplessness are overlapping concepts. Seligman claimed that depressed patients suffer from a lack of personal control or from learned helplessness [5]. People with perceived low self-efficacy suffer from negative emotions such as anxiety and stress, and have higher resistance to treatment [11,12]. Depression has negative effects on treatment adherence, family function and health-related quality of life [13]. High self-efficacy in patients with chronic diseases is related to better physical, social and emotional quality of life [14,15].

2 Coping with chronic illness

Coping can be described as the process people go through when dealing with stressful events in their everyday life. Coping strategies are aimed at reducing distress related to illness and treatment in order to maintain a subjective wellbeing. Coping includes a range of emotional regulating strategies, thought processes and behaviours. There are individual differences in how people respond to stressful events. Adults with CF are faced with additional demands and increasing disability. How they cope may have relevance to their quality of life. Lazarus and Folkman [16] stated that it is not the situation itself that is stressful but

the individual's interpretation of it. They classify coping as problem-focused coping and emotion-focused coping. Problem-focused coping is aimed at reducing or eliminating the stressor. This involves strategies such as seeking information, generating alternative solutions, weighing the cost and benefit, and learning new skills. Emotion-focus coping is directed toward regulating one's emotional distress. This way of coping is more likely when nothing can be done to change what causes the stress. Emotion-focused strategies involve avoidance, accepting responsibility, exercising self-control and positive reappraisal.

Zimmer-Gembeck and Skinner [17] constructed a framework of the development of coping from infancy to adulthood. The four most common ways of coping are support-seeking, problem-solving, distraction and escape. Support-seeking includes seeking emotional support from friends and family, and seeking information and advice from health professionals and others. Problem-solving is a cognitive activity to master a problem. It includes strategies such as planning, list making and reflection. Distraction can be a cognitive or behavioural activity, or both. It involves keeping busy with activities, thinking about something fun, or thinking about something else in order to try to forget the stressor. Escape includes leaving the stressful environment or avoiding direct action.

Coping strategies can be cognitive or behavioural, and several are employed at the same time. Coping is used to master a problem but it does not necessarily mean that one has mastered the problem. Active coping such as problem-focused, problem-solving

and support-seeking strategies are more often associated with positive functioning and better health compared with the more passive or avoidance strategies [18,19]. Research on coping with CF has found similar results. Optimistic acceptance was associated with a higher health-related quality of life, and distraction (behavioural avoidance) was associated with poorer quality of life [20]. Higher levels of active coping and lower levels of disengagement were associated with better psychological quality of life in patients awaiting lung transplantation. Active coping was also associated with lower levels of stress, depression and anxiety compared with disengagement [21]. Regarding adherence, optimistic acceptance and hopefulness were associated with greater adherence to treatment. Patients who were non-adherent used avoidance strategies to a greater extent than those who were adherent [22].

Health professionals need to explore how each patient adapts and copes with their CF disease. It is important to identify the person's challenges within the context of their current life phase. Efforts to modify a patient's adaptation and coping strategies during routine clinic visits may lead to improved quality of life.

3 Illness as the suffering of body and mind

Since their diagnosis, adults with CF, compared with healthy adults, cannot "forget their own body." The body of an adult patient with CF simply does not "work in silence and secretly" [23]. CF and

treatment are an everyday struggle with (or against) an illness that makes daily living difficult.

“Ever since I was a child, every time I go to the toilet, I am reminded of the fact that I have a serious illness”
(22-year-old man)

CF and treatment causes patients to suffer inside their bodies, but also in relation to their environments.

“What affects me the most is the sad and compassionate look in their eyes when I cough”
(21-year-old woman)

With deteriorating health, many ‘normal’ aspirations of fulfilment in adult life are affected.

“When I was offered the opportunity of a job abroad I did not dare to leave the country because my health was deteriorating and I knew transplantation was near”
(49-year-old man, post-transplantation)

Patients are constantly and dynamically shifting between periods of being sorely afflicted by their CF and periods of suppressing it from their consciousness (awareness). These changing, antagonistic attitudes are most probably important and necessary in order for patients to try to balance the management of their disease and to achieve as normal a life as possible [24]. This approach to living with CF is vital because otherwise emotions, such as worry, anger, anxiety or frustration, would

overwhelm the patient.

Growing older with CF also means coping with new diagnoses and more medications. At the onset of new symptoms, a patient is required to specifically attend to his/her illness, which brings the illness to the fore [25]. Illness can become something burdensome, and can completely preoccupy the patient. Depending on their circumstances and personality, a patient will react on a continuum between denial, avoidance and accurate concern. An avoidance coping style has been described as maladaptive [26]. However, avoidance and denial may enable a patient to adapt to CF and feel more in control. A degree of denial is associated with increased self-esteem, less psychological distress, and may enhance quality of life [20]. Living an adult life with CF is an ongoing, ever-changing process between the perception of being well and the perception of being sick.

An important theme in the context of CF as an illness of body and mind is the challenge of adherence to treatment. Adhering to increased treatments, while trying to lead as normal a life as possible, is a real challenge. Adherence fluctuates over time, with periods where adherence to treatment is easy for the individual and periods where this is more difficult. For example, when an adult is changing jobs and disclosure about the illness has not been made, medicines will have to be taken in secret, and taking time for physiotherapy or resting is more difficult. Adults have to make choices about their adult role and this will inevitably affect their adherence decisions. In a way, this is normal behaviour for all humans: adherence to any important decision is difficult to us

all – 80% of New Year’s resolutions are not kept! [27].

In CF, much research has been conducted on why, when and how patients adhere to treatments, or not. Important factors are personality, age, gender, illness severity, knowledge, perceptions, emotions, attitudes and beliefs, barriers and socio-economic issues [28–30].

4 CF within the context of the family history

Adults with CF bear their own ‘history’. This is the story of their childhood in a family that has had to face, adapt, cope, institute care, and integrate CF into the family’s interactive functioning. A person’s childhood context influences their attitudes toward life and illness, and consequently shapes their coping styles and resilience, but also their vulnerability.

“My brother died from CF when I was 16, my sister died from CF when I was 22. My mother always told me I was different, even though I had the same mutation. This comment of my mum’s made me what I am today, determined to survive”
(49-year-old man, post-transplantation)

Within the family context, CF can be considered as both a short- and a long-term threat. CF causes stress and pain to the whole family and can negatively affect attachment, leading to fears of separation and loss [31]. During adulthood with CF, deterioration of health further affects a patient’s relationship with their family, both their family of

origin and their present family if they have one. CF may disturb the patient’s ability to take on normal everyday tasks, thereby modifying their role and responsibilities within the family.

“How can I remain her desirable partner?”
(32-year-old man)

“My husband has to do all the housekeeping and take care of our child and me”
(35-year-old woman)

In addition, the way both the patient and the family feel about and cope with health deterioration is important. Worsening disease often arouses different emotions, which will inevitably disturb the normal family balance. For example, a patient may conceal information about their situation or treatment in order to avoid the family’s reaction of suffering and fear. This secrecy is necessary in order to prevent strong emotions for both the patient and the family.

“I did not mention being listed for transplantation to my mum for a long period of time because that would bring back memories of when my sister died”
(25-year-old man)

Patients share with their family certain life values, responsibilities and roles. Patients have a family history, which includes their own personal family myths. Exploring a family’s (early and actual) functioning and its interactions may aid the understanding of the patients reactions to their worsening medical situation and their representations of their CF. In addition, this will aid

the understanding of the patients' personal beliefs and perceptions of their CF as well as the decisions they make.

5 The adult patient and the healthcare provider

An important part of the adult patient's life is interacting with the CF team. This interaction contains an inter-subjective relationship between a patient and members of the CF team. The patient and the healthcare provider continually influence one another, and through this relationship they build up a 'therapeutic treatment process'. Patient and caregivers evolve together. This means that both are involved in the treatment process by actively thinking and participating in it or, in contrast, by neglecting it [23]. The interactions between the adult patient and the healthcare provider will strongly influence the quality of the CF treatment process, but also the wellbeing of the patient (and the healthcare provider).

During adult life, the patient and the healthcare provider face deterioration and end-of-life issues [32–34]. The way a caregiver defines the aim of interventions at this stage of suffering and pain will influence the way they care for each patient. In addition, a caregiver has to cope with the way a patient views the care plan. For example, the time at which the patient and the caregiver adapt to the change in health status may be different. Some patients need time to accept and adapt to their new situation. They may feel uncertain and anxious about new required treatments

[35]. Even though patients may expect new situations throughout their lives, it is still difficult to imagine themselves living them.

"It took me a very long time to accept I had diabetes. I ate everything that contained sugar! I went on like that for about 3 years. My physician could not cope with my behaviour and blamed me for not looking after myself. But I just was not ready yet!"
(23-year-old woman)

"I was 19 years old when the doctor told me I needed a transplant. I was horrified, I did not feel that bad. Transplantation was for older patients...."
(25-year-old woman)

Adult patients, again and again, have to manage and recover from severe pulmonary exacerbations and cope with a gradual deterioration in functional capacities. They have to continually adapt and try to lead a normal life. Being successful or feeling successful in doing this may strengthen their beliefs of being indestructible or invincible. Even though patients know that deterioration is inevitable, they continue to hope that end of life or discussions about transplantation are far away. For this reason, these discussions are often difficult to initiate.

"I was worried, but still believed I would be ok.... then the doctor started to talk about transplantation. I was shocked, I was not ready for that. Maybe in a year's time!"
(19-year-old woman)

Patients and families know the facts, but actually hearing the verdict is always a shock. Relating to this is the fact that talking about end-of-life palliative care in the context of hope for transplantation remains difficult throughout [36], as they appear to be mutually exclusive [37].

6 Conclusion

Adults with CF face deteriorating health, which is determined by both biological and psychosocial factors. The patient, their family and members of the CF team are intertwined and evolve in continuous interaction within the context of the illness and the gradual deterioration. CF and treatment are important modulators of the extent to which an adult can fulfil their adult role, in continuous interaction with the environment, including family and caregivers. The emotional wellbeing of the adult patient fluctuates over time and interacts with the severity of CF, with a patient's personality and social role, with their coping style and with the (medical) social support systems.

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PATIENT TESTIMONIES

1 Patient testimony 1

59-year-old man

I am a 59-year-old man with CF, and I receive follow-up care from the Cochin Hospital CF Centre in Paris.

When I was 6 (in 1960), my parents were informed that I had CF after my siblings and I took a sweat test. Today, I know it is linked to an F508del mutation. There were seven children in the family and four of us had CF. My parents were clever enough to ensure there was no difference in education between the children with CF and the others, and everybody was on the same low-fat diet.

I was rather frail and dreamy, and my childhood and adolescence were marked by learning difficulties (due to dyslexia) and stomach pains. I learned my own limitations. As a student, my parents gave me a lot of autonomy and let me study in another city; they even allowed me to travel far from home in the summer. I was lucky enough to be encouraged to choose an education that matched my interests: visual arts.

Thanks to a grant from Canada, I had the opportunity to follow a Masters degree in Fine Arts in Toronto. There, for the first time, I met pulmonologists who specialized in CF.

As a student, I used to have small jobs in the summer and then I started working as a teacher in visual arts. It allowed me to both develop my personal creativity in visual arts and build a professional network in the field. In 1991, I was appointed as a teacher in a National Advanced Arts School where I could give all my lessons on a 2-day timetable. I like the job as it gives me the opportunity to debate on Art with a lot of different people.

For almost 20 years I did not inform the school administration or my colleagues of my disease, which, in my view, was part of my private life. The health problems did not happen all at once; I was aware that they could become serious, as I lost an older brother in 1974 and a younger brother in 1996. The awareness of my weaknesses and limitations played an important role in my life choices (e.g. lifestyle, place to live).

The disease is part of me but does not define me. It is important to accept and cope with the difficulties and the current disabilities but it is not everything; it is also vital to find an area in which one can think and act within one's own limitations.

I met my wife 16 years ago. This is an amazing story: she had just had a baby girl, but the biological father had not legally recognized her. I was really happy and proud that a woman responsible for a child trusted me. I adopted her daughter a year after our wedding. Being in a stable relationship and sharing daily life with her is wonderful; seeing my daughter growing is a chance. Being in charge of a family and knowing how fragile I am myself is a source of anxiety at times. I need to accept this – not to forget the situation but also not to put all emphasis on it. Having a family is also a source of vital energy; I do not think I would consider transplantation in the same way without my family. Also, my youngest sister underwent a transplant 10 years ago and is in good health, which is a source of encouragement.

For years I could only talk about my disease with people with whom I had a strong emotional relationship. I only informed my superior authorities about my condition a few years ago, around 2009. I then needed to explain the disease in more details when I asked for (and eventually obtained) a work transfer, which had become necessary because of my increasingly disabling condition (following an exacerbation caused by the flu in 2012, I need oxygen supply during the night and after prolonged effort).

Now, things are changing and my level of autonomy is decreasing. Taking care of myself is more and more time-consuming, and the disease impacts on several aspects of my life. Therefore, I discuss and explain the situation whenever it is possible or necessary. Thanks to the everyday support of my wife, I can still be professionally active, teaching 2 days a week and keeping an artistic practice, though less intensive. As for the medical appointments, drugs, nebulized therapy, physiotherapy – I still manage on my own.

It is a learning curve to accept what I cannot do anymore and to choose activities that take my limitations into account. I still look to the future waiting for a transplant (I have been on the waiting list since the beginning of 2015). Thanks to this perspective I can project myself into the future for a decade, which is actually the timeframe I have always had in mind since I was 20.

2 Patient testimony 2

28-year-old woman

I have been living with CF for 28 years; I was diagnosed at the age of 8. My life has had its ups and downs until I started taking Kalydeco. At this point my condition had started to seriously affect my everyday life, my job and my future. I was down to 21% of FEV₁ on my worst days and was dealing with more IV courses than before, as well as several episodes of pneumothorax, which was a new addition to my problems.

I am not lying when I say that I was asking myself how the rest of my life would be and wondered whether I would need a lung transplant soon.

I had been discussing the Kalydeco clinical trial with my doctor for months before I received it, and even though the information was very positive it had always been an "IF" situation that seemed too good to be true. As a CF patient, I have never allowed myself to let my emotions cloud my mission to survive; Kalydeco was a way out that I didn't dare to hope too much for in case of disappointment.

I have now been taking Kalydeco for over 2 years and it couldn't have arrived at a better time. It has really changed my life drastically. The effects of this new drug were very impressive during the first month – my lung capacity increased to 34% on my best days, which by itself produced a huge improvement in my everyday life. Everything else naturally followed this improvement: I am less tired, I gained weight, I am less infected, my digestive system is more normal, and more.

It took a while for me to realize what was happening. There is a phase where you feel like you are walking on water, where you feel like you can do anything; it's a very good feeling. Then there's the phase where you wonder when it's all going to end, when you are going to get sick again. I did get sick a few times after starting Kalydeco, but nothing compared to how I was before. I have not needed an IV course for over 2 years! I haven't missed

more than 2 days of work at a time in 2 years. I feel that I can fight off a 'cold' almost like a normal person.

Today, I know that I will always have CF, and my lungs will never function at full capacity ever again, but I do feel like my life perspectives have changed. I now feel that this illness can be controlled and that patients with CF can now live a normal life with CF. I never saw myself living past 40-years-old – if I was lucky; I thought that by the time I was 30, I would be in a wheelchair with oxygen or going through lung transplantation that may or may not fail. I always feared not being able to have a family of my own, or to live long enough to see my children grow up to be adults. I didn't see myself as having much of a career because I was starting to reach a level that was becoming too demanding for me. I also feared that travelling would become an issue for me too; being Franco-American, it is important for me to be able to visit my family and friends in the USA, and my health was starting to compromise that as well.

All of these things are now a possibility for me. I am confident that I can live a long enough life, that I can handle having children of my own, one way or another, and my career has finally picked up in a way that I know I am capable of assuming intellectually. The little things in life that used to be a struggle – like walking up and down stairs, like having a sports activity, like being able to see my friends during the week until late at night – are not hard anymore and make me so happy.

Kalydeco represents extraordinary progress in the treatment of CF. It has changed the lives of a small percentage of CF patients but seems to have opened so many doors to more treatments for all CF patients.

Kalydeco has given me even more hope and strength to continue fighting this illness, and the results speak for themselves.

3 Patient testimony 3

54-year-old woman

My name is Sylvie, I am 54-years-old, and I have CF. I was diagnosed at the age of 10. My early childhood was difficult for my parents as I had a lot of medical issues. I never felt unhappy, even when I was in hospital. I am the second of a family of five children, and my parents were thus very busy but they could always find some time to come and visit. I kept myself busy by drawing or doing crafts.

I grew up surrounded by the love of my family. My paediatrician told my parents: "Let her do as much as she wants to; when she doesn't have the strength to keep on, she will stop." Even at school, I had to take part in the physical exercise classes, but the teachers knew it was not a whim when I had to stop. I wanted to do what the others were doing and, even better, to show I was able to – to show I was 'normal' despite the fever or the sinus drainage device I had to wear. I am convinced this helped me to build unusual strength and energy.

My grandmother used to say: "There is always a worse situation than the one we live in. We have to enjoy what we have." I made it my motto and I live life to the full, which I am regularly criticized for, as I do not allow myself time to rest.

I managed through childhood and teenage years, and then became pregnant. The extent of the disease then revealed itself. I was losing weight and the doctors were quite pessimistic. My gynaecologist contacted 11 hospitals to find one willing and able to take care of me and I felt like a poisoned chalice. Thirty years ago there were a lot of risks associated with a CF patient having a baby. A paediatrician even said to my mother that I was about to give birth to a 'monster', and until 5 months of pregnancy they suggested termination. I really wanted to have my baby, and it became the objective of my life, despite all the difficulties. I ended up at the Clamart maternity and gave birth to a little daughter. I had lost 12 kg, but my baby weighed 3 kg and was in good health, and for the first 4 months I was even able to breastfeed her. I then had to take high-dose antibiotics because I had partially lost my lung capacity. But I was happy because, despite CF, I was a mother. Myriam was alive and so was I. My daughter grew up with the help of my family. I was not sure I would be able to see her growing up and so gave her all the love I had and also stepped aside to help her create a unique relationship with her godmother 'in case' the worst happened to me. We experienced thousands of beautiful things together and enjoyed

as much as we could. When I had to stay in hospital, I used to do crafts and send them to her.

From the time I arrived at the Cochin Hospital, I have been able to benefit from home IV. This was a major improvement for the whole family. It was not easy at the start as I needed assistance, but I wanted more freedom and gradually managed some medical care on my own. The medical team saw that I was able to manage, and I became more and more autonomous over the years.

My daughter was older when I divorced and decided to take a new direction in life. I had several health issues over the years (gallbladder removal, carcinomas of the skin) but all experiences are worth living as they make one stronger. When I met my husband in 2004 my daughter had already left home to live her own life with her boyfriend. Dancing became a new passion for me. I was living a dream I had always thought impossible with CF. The cough scared a lot of dancers at first but they rapidly got used to it.

Following a lung function decrease, I have needed constant oxygen supply since 2007. I use my creativity to customize my device with colours that match my clothes.

2008 was a great year, as both my daughter and I got married, and I became a grandmother, which is a dream for all CF patients. My granddaughter is now 6, and I am happy to have her at home every 2 weeks and during the school holidays. She

is used to the inhaled treatments (for my 'shoot' as I used to say), physiotherapy, IVs. For her, all of this seems to be perfectly normal, just like it was for her mother who, of course, is now working in the medical sector.

Even though there are still a lot of unknowns linked to my condition and despite disaster being predicted several times, I am still very positive about my life. If you can be followed up by a good medical team and be surrounded by nice people who let you live your life, you can develop many more assets than most people in good health. I think that CF patients do enjoy every single moment of their lives and become stronger through difficulties.

I want to thank the doctors who help us on this long road. CF gave me strengths that are hard for other people to believe. I am getting older but I hope my strength will last for a long time as there are still plenty of happy moments to live!

4 Patient testimony 4

52-year-old woman

Thankfully, my lung function was reasonably stable for as long as I can remember. However, in April 2010, aged 47, I suffered a severe bleed in the lungs, probably as a consequence of the shortage of vitamin K in the UK. I was feeling a little below par despite changes made to my medication. In October, after returning to the

UK from China, I became ill with terrible chest pains. In 2011, I was hospitalized and put on oxygen for the first time, as well as IV steroids and bronchodilators. Thus, my decline in health commenced, with my lung function dropping from 60% to 55% FEV₁. After discharge from hospital, I 'failed' my walking test during my annual review (i.e. my oxygen levels would fall from 94%/95% to below 90%) and, for the first time, I needed oxygen if I wanted to fly anywhere.

By the summer of 2012, I was in hospital again, even back in the same room! In clinic, they had started treatment for CF-related diabetes. After a flu vaccination in the October, I was again showing worsening symptoms of chest infection exacerbation, low-level fever, headaches, nausea, loss of appetite and weight loss. A repeated cycle of oral antibiotics and several changes to my medication failed to help, and the rapid return of these symptoms led to more and more time off work. I had the full support and sympathy of my boss as, until then, I had had a very good attendance record for over 20 years. By May 2013, despite feeling unwell and my lung function being down to 53%, my husband and I went on a fabulous cruise around Japan to celebrate our 50th birthdays. I caught a nasty cold on holiday and on return to the UK I was back in hospital for more IVs and further changes in medication. My lung function dipped to 50%. This was the first time I was prescribed oxygen for exercise, and it took tremendous courage to walk in public and go the gym with an oxygen tank. At first I sobbed, but then I decided to buy

*some CFT-shirts and take the opportunity to raise awareness. But this time I was out of hospital for less than 4 weeks before my oxygen levels suddenly dropped to 86%; my lung function had dropped to 30%. I commenced night-time ventilation to help get rid of the build-up of CO₂ in the blood. This was a big shock. I was having nightmares and feeling panicky at the thought of being dependent on oxygen 24/7. Sputum cultures showed I was growing a new bug called non-tuberculous mycobacteria *Mycobacterium avium* complex (NTM MAC), so I was started on three oral antibiotics for 12–18 months, even though it was eradicated quite quickly.*

During my 7-week hospital stay, the infection did not respond to various IV antibiotics, but my lung function finally improved to 33%. I was allowed home but not before my husband and I had the 'transplant chat' with the consultant and one of the specialist nurses. It was all handled so well. In all my CF life, I had considered myself as one of the 'well ones' and never thought I would be a double-lung transplant candidate. However, the possibility of a transplant gave me a great deal of hope. I didn't like the alternative very much! Realising I was in lung failure was strangely a relief – the uncertainty of my future was a bit more clear and it provided the answer to my continued poor health over the past few years.

After 6 months' sick leave from work, I was entitled to invalidity benefit from my employer's insurer, amounting to 70% of my salary indefinitely. I am so grateful

to retain my financial independence and to not have to go through the demeaning and increasingly strict testing procedure for state benefits. Since 2013, I have also been entitled to take early retirement if I can afford to do so. I do hope to take the pension I worked hard for all those years, and am so glad I don't have to continue working for a state pension for which many people living longer with CF may not survive to receive.

The wait for an initial consultation with the transplant team was 3 months, for the inpatient assessment another 3 months, and another 3 months to resolve several outstanding issues. Because of my rapid decline and the long wait for a transplant – around 2 years on average – it was agreed to list me for the lung transplant at the end of March 2014.

I am fortunate not to have any antibody or other complications. Around the same time, I stopped using the TOBI Podhaler as I noticed it made me more breathless. Since then, my lung function has very slowly improved to 45% and I no longer feel ill all the time. However, it was confirmed at Harefield that I still have severe lung disease and still need a transplant. I have received two calls for transplant already, but the donor lungs were not good enough for transplantation to proceed. I am so grateful I don't feel desperately ill – the wait and disappointment at another false alarm is so much more bearable for my family and me.

The future after a transplant is still very uncertain, but CF people are used to taking lots of medications. Now that I am

stable and keeping up the strict regimen of treatment and exercise I have been blessed with the best chance of getting through such a massive operation.

In the meantime efforts to increase the supply of organs need more urgent attention for those like my friend for whom time has run out. There is not even a link to the opt-in online register on my GP website. What about voter registration, adding a section about donor registration? Ascertaining everyone's opinion is surely better than opt-out/opt-in!

