Healthcare issues and challenges in adolescents with cystic fibrosis

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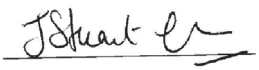
PREFACE

Cystic Fibrosis is a disease where parents, patients and clinical team members have to overcome many barriers to ensure optimal treatment is available for individual patients. Adolescence is perhaps one of the most challenging times for people with cystic fibrosis and is in general an under-researched area in the field. The European Cystic Fibrosis Society has commissioned Carlo Castellani and Harry Heijerman to bring together a high quality team of experts in this area to contribute to this monograph. Our ambition was to cover a range of healthcare issues relevant to young adults in order to provide cystic fibrosis teams and others associated with cystic fibrosis care with a resource to consult when considering some of the difficult issues during adolescence.

Our contributing authors have accepted this challenge with enthusiasm and have produced a series of chapters of excellent quality.

We hope that this book will be a useful manual for cystic fibrosis teams. We also anticipate that families and young people with cystic fibrosis will find this book of value. The ECFS thanks the editors and the authors for the effort they have put into this publication and we look forward to further monographs on challenging areas in cystic fibrosis.



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CHAPTER 1

Healthcare issues and challenges in adolescence

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1 Introduction

Adolescence has long been recognised as challenging to adults. Indeed, Socrates is reported to have written in 450 BC that, *"Our youth love luxury. They have bad manners and contempt for authority. They show disrespect for their elders and love idle chatter in place of exercise. Children are now tyrants not the servants of the household. They contradict their parents, chatter before company, gobble up their food and tyrannize their teachers."* In contemporary society, adolescence is commonly viewed as a period of turmoil, with seemingly little understanding of what makes adolescents tick. Indeed, adolescence continues to be viewed as a highly challenging period for parents and for communities – as well as for healthcare professionals.

However, although adolescence is certainly a time of increased health risk, it is also now recognised as being a time of developmental opportunity. How young people negotiate adolescence, in terms of how well they make the transition to adult roles and responsibilities, is now recognised as one of the most significant determinants of future health and well-being in

adulthood – both in those with and those without chronic health conditions [1].

The health issues experienced by adolescents with chronic conditions are reported to be "linked to the illness they suffer from, to adolescence in general, and to psychosocial problems generated by the interaction between the illness, the adolescent and his immediate environment" [2]. Given the widespread lack of undergraduate and postgraduate training in adolescent health and the fact that so many of the health issues experienced by adolescents are emerging issues, it is not surprising that many healthcare professionals report that managing the complexity and range of health concerns in adolescents is more difficult than in other age groups [3].

This introductory chapter sets out to explore the changing shape of contemporary adolescence, to provide a framework for understanding adolescent development, and to explore the impact of adolescence on chronic disease and *vice versa*. In doing so, it sets the stage for subsequent chapters, which describe more specifically the complexity of cystic fibrosis (CF) in adolescence.

2 The changing shape of adolescence

The term 'adolescence' is derived from the Latin *adolescere*, meaning to grow up. The onset of adolescence has typically been defined by the physical changes that accompany the complex sequence of hormonal maturation known as puberty. Rather than physical maturation, the end of adolescence has typically been characterised by a series of transitions into adult social roles and responsibilities, such as completion of education, commencement of paid employment, and getting married and having children. Previously, these social endpoints occurred within a relatively short time frame which, in most parts of the world, extended from the late teens to the early twenties and were fairly consistent with the achievement of the age of legal majority.

Despite the widespread belief that 18 years is when adolescents gain adult legal rights and responsibilities, even in law, there is no single definition of adulthood [1]. Rather, in most parts of the world, a collection of laws describe different ages that denote adulthood. In relation to health, these include laws related to the age of consent, the minimum age that young people can legally drive and buy alcohol, and the age at which young people are considered to be capable of making important decisions that affect their health.

Until recently, there was general acceptance that adolescence was encapsulated within the second decade of life. However, the shape of adolescence has changed [1]. Downward shifts in the age of onset of puberty and upward shifts in the age of achievement of the social transitions that historically marked adulthood mean that, as previously defined, adolescence now continues for much longer. This extended length of adolescence is consistent with a new understanding of cognitive maturation, which is now recognised to extend to at least the mid-twenties.

What is less clear now is when adolescence ends – and what we call it. This is largely because the social role transitions of this period are much more fluid than previously. Past generations experienced fairly linear role transitions; stereotypically, young people completed their education, entered a short period of further education or vocational training (commonly defined by gender), and then 'settled down' to get married and parent children. In contrast, contemporary young people now complete secondary education, following which (or indeed during) they may take a 'gap' year characterised by work and/or travel, and then enter a period dominated by post secondary training. This period of training might be undertaken on a full-time or part-time basis and might be accompanied by full-time or part-time work. After a couple of years in the workplace, young people not uncommonly commence a period of further study, which may herald a significant career change for both men and women. Young people now generally stay at home for longer, and having moved out of home, not uncommonly return to the family home for extended periods, especially when financially challenged. Sexual intimacy commonly starts before they leave home and continues despite returning home. In many European countries, first marriage is now undertaken a decade later than 50 years ago, and marriage no longer signifies that children will follow. Indeed, having children now occurs regularly before marriage, whether one has a stable partner or not.

About 25 years ago, the United Nations and the World Health Organization defined 'adolescence' as 10–19 years, 'youth' as 15–24 years, and 'young people' as 10–24 years. Despite these definitions, there is little consistency in the literature about whether young people are referred to as 'adolescents', 'youth', or 'adolescents and young adults'. Regardless of what it is called, it is increasingly apparent that rather than 10–19 years, the period from 10 to 24 years better captures the physical, cognitive and social changes embodied by the term adolescence.

There has similarly been little consistency in the age ranges in research studies, whether they purport to study primarily adolescents or to include adolescents in studies of younger children or adults. There are good reasons to use different age cut-off points according to the specific research question. For example, a study of patterns of specialist healthcare use in adolescents might choose to report data in relation to the age that paediatric specialist healthcare services commonly cease, which could be anywhere between about 12 and 21 years, depending on where the study is conducted. More commonly, a variety of age cut-off points are used without adequate justification. Thus, studies of children may range from 0–12 years, 0–14 years, 5–14 years or 3–19 years. Studies of adults might extend from 15–35 years, 17–45 years or 19–64 years. Arguably, the widespread use of age ranges that have little relevance physiologically or bear little relation to other transitions (e.g. education, welfare) has been a mechanism that has inadvertently made invisible the dynamic burden of disease across the adolescent years. By contrast, the recent use of the 5-year age range that

differentiates early adolescence (10–14 years), mid-adolescence (15–19 years) and late adolescence or early adulthood (20–24 years) has presented a highly nuanced picture of the changing health profile across adolescence [4–6].

3 Adolescent development: maturing bodies and brains

Adolescence is a period of marked physical, cognitive and social maturation that builds on the developmental opportunities of earlier childhood [1]. Puberty is accompanied by profound yet paradoxical consequences for health. On the one hand, puberty propels the individual into dimorphic physical maturation with peaks in strength and fitness. Yet puberty is also accompanied by a rise in emotional and behavioural problems with long-lasting effects. Health problems that commonly emerge following puberty include major affective and anxiety disorders, eating disorders, deliberate self-harm, tobacco and substance use, psychotic states and functional somatic disorders. These health-related behaviours and mental health states are strongly associated with pubertal stage rather than chronological age [7]. This has given rise to a view of puberty as a sensitive period, in which there is heightened sensitivity to social and environmental influences that become manifest as mental and behavioural disorders. The interest in puberty as a sensitive period relates particularly to how these patterns of response might become biologically embedded or 'hard wired' and thus more resistant to later interventions, as well as to how interventions at this critical time may alter this trajectory.

Despite the variability of adolescent development by age, it can be useful pedagogically to separate the 10–24-year-old age span into early adolescence (10–14 years), mid-adolescence (15–19 years) and late adolescence or early adulthood (20–24 years). Table 1 describes some of the major aspects of adolescent development within the domains of physical, cognitive and psychosocial maturation.

Recent advances in brain imaging technology have contributed to new understandings of adolescent development [8,9]. In contrast to earlier beliefs that the brain was fully formed by the end of childhood, there is now evidence that adolescence is a period of profound brain growth and maturation. Brain connections and signalling mechanisms selectively change during adolescence and early adulthood, with opportunities for brain remodelling in response to social and behavioural influences.

One of the regions of the brain that undergoes the most protracted development in humans is the prefrontal cortex. This is the site of executive control functions including planning, emotional regulation, decision making, multi-tasking and self-awareness. The prefrontal cortex starts to develop very early in life. Its development continues throughout adolescence until at least the third decade [8], which may explain the steady improvement in self-control from childhood through to adulthood. In contrast, there is evidence that the limbic system, which governs reward processing, appetite and pleasure seeking,

develops earlier in adolescence than the prefrontal cortex. The greatest disparity in maturation of these systems is during early to mid-adolescence. One explanation for heightened risk taking at this time is that a developmental imbalance favours behaviours driven by emotion and rewards over more rational decision making [9,10].

Recent data suggest that adolescents engage in 'risky' behaviours despite knowledge of the risks [11]. They also appear to be more influenced than adults by exciting or stressful situations when making decisions, so called 'hot cognitions', especially in the presence of peers. This behaviour is consistent with the notion of sensation seeking (i.e. the willingness to take risks to attain novel, varied and stimulating experiences), which appears to be an important mediator in the engagement of health-risk behaviours. Such behaviour typically increases between 10 and 15 years of age in a pattern that suggests pubertal influence [11,12].

4 Health-related behaviours and states: social context matters

Many health-related behaviours and states that contribute to the burden of non-communicable diseases in adults have their onset during adolescence. For example, over 90% of adult smokers start smoking tobacco during their adolescent years, problematic substance use commonly commences in adolescence, and a range of other behaviours such as unsafe sex, violence and other antisocial behaviours typically start during adolescence [1]. Similarly, adolescence is the peak age of onset for many psychiatric disorders; over 75% of adults with a mental health disorder first experience the problem during adolescence [13].

Rather than blaming adolescents for unhealthy decisions, it can be helpful to understand that social disadvantage and negative experiences during infancy and early childhood can interfere with the achievement of normative developmental milestones in later childhood. These can lead to a cascade of effects in adolescence where bullying and peer rejection can result in school disengagement, orientation to more antisocial peers and early uptake of health-risk behaviours including tobacco, alcohol and other drug use, together with a greater likelihood of mental disorders [14]. A single set of risk and protective factors influence different health-related behaviours during adolescence, which results in clustering of several risk behaviours within individuals.

In addition to the effects from earlier childhood, what happens during adolescence itself also matters. For example, a socially disadvantaged adolescent who has gone through primary school with a chronic disease enters secondary school with a greater risk of poor health and life outcomes in adulthood. However, their path through adolescence will be modified by their individual strengths and vulnerabilities such as intelligence, personality, social skills and sexual orientation, as well as their experience of risk and protective factors that cluster within an individual's family, school or community [15]. These adolescent-specific experiences mean that

for the same set of social disadvantages from earlier childhood, one adolescent might engage in multiple health-risk behaviours while another follows a more healthy trajectory through adolescence. Schooling is particularly important for adolescents, as beyond the benefits of educational achievement, schools provide an important opportunity for pro-social engagement that can promote healthy peer relationships, emotional control and, ultimately, good health [16].

Adolescence is a sensitive time for social learning through imitating behaviour, especially that of peers. Young people's ubiquitous engagement with social media has changed the very notion of the peer group, expanding it from one's local school or community to a global scale. In addition to changing the speed at which socio-cultural norms can now be influenced [17], new media has also arguably contributed to the rise of what were previously less common attitudes or behaviours, such as self-harm and suicide, binge eating and even school shootings. The possible benefits of using new social media for health gain are still only starting to be explored.

5 Chronic health conditions in adolescence

There has been a dramatic reduction in childhood mortality from acute infectious diseases over the past 50 years. In concert with this has been an increase in the prevalence of children with special healthcare needs from childhood through adolescence [18,19]. As a result of medical and technical improvements, children with previously fatal childhood conditions (e.g. CF, chronic heart disease, chronic renal disease, spina bifida and cancer) are more likely to survive into adolescence, with many of them carrying heavy demands due to the complexity of treatment regimens [3]. In addition, there has been a true increase in the incidence of many other chronic conditions, including food allergy and anaphylaxis, a range of autoimmune disorders, obesity and type 1 and type 2 diabetes, as well as various behavioural and mental disorders [3].

A large disease-specific literature describes the impact of specific disorders on adolescents and their families in terms of adjustment and coping, co-morbid depression and anxiety, and health-risk behaviours. A problem with this approach is the lack of appreciation of the overall prevalence of chronic conditions in this age group, which occur in about 10–15% of adolescents [3,18,19]. More widely, there has been a failure to study how the relative impact of particular groups of conditions differentially affects adolescents. One exception is a study of the relationship between medically attended chronic conditions and functionally defined disability, which demonstrated that functional disability was most common in children with learning-behavioural conditions (88%), followed by neuro-developmental conditions (61%) and physical conditions (32%) [20]. Experience from peer support groups highlights the extent that issues are shared by young people with different chronic diseases [21], with obvious implications for clinical services.

6 The impact of chronic health conditions on adolescent development

Adolescence can be a challenging time without the additional problems of a chronic health condition. Although many adolescents with chronic conditions are highly resilient, they commonly face more difficulties negotiating normative developmental tasks compared with their healthy peers.

6.1. Effects on physical development

Short stature and delayed puberty are common sequelae of severe chronic disease and/or its treatment. Underweight can be associated with a range of conditions, such as CF, but obesity is more commonly experienced as a result of conditions that limit physical activity, such as disability, or of treatment with corticosteroids. Visible signs of illness and its treatment, such as surgical scars, the physical 'bumps' from indwelling intravenous access, or simply having to take medication in front of peers can create significant physical differences for chronically ill young people that set them apart at a time when looking the same as one's peers is a very important aspect of 'fitting in'. Sensitivity about physical differences can contribute to concerns about body image and contribute to poor self-esteem and reduced social confidence.

6.2. Effects on cognitive development

Some chronic conditions can affect cognitive development in adolescence. The resulting problems of inattention and learning difficulties can result in reduced educational achievement. Difficulty with learning can also be experienced by young people with chronic conditions as a result of school absenteeism secondary to poor health, frequent medical appointments or extended periods of hospitalisation. Reduced expectations of the young person by their parents, teachers and clinicians can further undermine educational performance.

6.3. Effects on psychosocial development

The demands of a chronic condition and its management generally increase a young person's dependence on their family at the very time when healthy young people are starting to individuate and are developing greater autonomy. Parents' efforts to closely monitor their teenager's health regimens and activities, though understandable in the context of a severe chronic condition, can further inhibit an adolescent's opportunities to move beyond the family and thus reduce their capacity to make sensible decisions as they move towards greater independence.

Many young people with chronic illness describe feeling excluded from their peer group. Having a chronic disease can also result in fewer opportunities to socialise with peers at school and at recreational and sporting activities, which further contributes to social isolation. Adolescents with chronic conditions are twice as likely to experience poor emotional well-being compared with their healthy peers, and they generally experience more everyday stresses. The lack of social, educational and vocational opportunities for those with poor physical health can cause additional distress. Although many young people with chronic conditions do cope remarkably well, anxiety and depressive symptoms can

masquerade as poor adherence with treatment, behaviour problems, declining school performance, social withdrawal and school refusal, and substance misuse.

7 The impact of adolescent development on chronic health conditions

Adolescence itself can reciprocally affect chronic illness and its management, with puberty having a major influence. For example, physically caring for a young person with a severe physical disability can become more difficult as a result of the pubertal growth spurt, simply due to greater weight and size, and the challenges of sexuality and menstrual management are generally greater for carers of adolescents with intellectual disability. Control of diabetes across the pubertal years is more challenging due to the effects of growth hormone on insulin resistance. Lung function commonly deteriorates in adolescents with CF following puberty, especially in girls. As a result of changes to renal and hepatic metabolism during puberty, more care is required in monitoring medications.

Maturing cognitive capacities in early adolescence can result in new anxieties from chronic conditions, whether in terms of newfound sensitivity about long-standing physical differences, or the challenging implications that accompany more mature understanding of the life-limiting nature of conditions such as CF. This is commonly a feature of early adolescence.

However, despite these new insights, adolescents are not greatly influenced by concerns about the future consequences of current behaviour, such as smoking or poor adherence to treatment. Together with the concept of invulnerability (i.e. that bad consequences happen only to others), adherence to treatment can become more problematic at this time. Young people's desire to fit in may prevent them from adhering to their treatment regimen; in most circumstances, peer engagement will be prioritised over disease control (e.g. taking medication), especially at school.

Although it is often assumed that adolescents with chronic conditions are less likely to participate in health-risk behaviours such as smoking and drinking, there is no evidence to support this; indeed, they are at least as likely to engage in health-risk behaviours as their healthy peers [22]. In the context of their underlying chronic disorder, many suffer from a 'double whammy' due to the higher attributable risk from these behaviours [23]. For example, smoking can worsen the health outcomes of young people with asthma, CF and diabetes; late-night parties and alcohol binges can complicate the management of adolescents with epilepsy; and dieting, irregular meal times and consumption of high-energy fast food make diabetes more difficult to control.

8 Consulting with adolescents

Whereas most child health education is targeted at parents, health education for adolescents requires specific engagement with the young people themselves. Consulting with adolescents alone for part

of the consultation provides many different opportunities. First, it signals to parents that adolescents are growing up and need to acquire the skills to consult alone with clinicians. This is an equally important signal for adolescents to appreciate – even if they cannot acknowledge it at the time. Second, it provides a safe space for adolescents to ask questions about any aspect of the disease and its management, however 'dumb' they think the question might be. Third, consulting alone provides the mechanism for confidentiality that is an essential requirement for adolescents to engage honestly and openly with healthcare professionals around more sensitive aspects of their health such as poor adherence, substance misuse, sexuality and emotional well-being [24].

Consulting with adolescents does not imply a diminished role for parents at this time, although this is commonly how parents perceive it [25]. Parents continue to provide crucial support for their children throughout adolescence. They certainly continue to provide essential information to the healthcare team. However, it does signal that adolescents are no longer regarded as young children, that they face a different set of health issues as they mature, and that it is the responsibility of healthcare professionals to ensure that holistic healthcare is appropriately provided in order to ensure that the best possible health and developmental outcomes can be achieved.

Arguably, healthcare systems have yet to become sufficiently oriented to the health issues and developmental challenges of adolescents. Using the framework of 'Adolescent Friendly Health Services', the World Health Organization has urged healthcare systems to respond to the leading barriers experienced by young people in accessing healthcare services [26]. Beyond CF-specific expertise, clinicians require the attitudes, knowledge and skills to provide 'adolescent friendly' healthcare to young people. This includes: knowledge of adolescent development and the changing burden of disease across the adolescent and young adult years; knowledge of the medico-legal context of working with young people and their families; skills to take a psychosocial history, provide anticipatory guidance and basic counselling; knowledge of when, where and how to refer young people with more significant concerns, such as persistent depression; and skills to build up the capability of young people to better look after their health as they mature.

A key challenge for child-focused clinicians who provide healthcare to adolescents is the need to gradually shift their focus of engagement and communication from the parents to the young person themselves while maintaining communication with the parent. A key challenge for adult-focused clinicians is to appreciate that despite their physical maturation, many adolescents and young adults are still maturing emotionally and cognitively and can still benefit from their parents being engaged with their healthcare in ways that are respectful of the young person.

This might sound complicated. However, adolescents are in a strong position to tell you what they need. If in doubt, just ask them.

Table 1
Developmental characteristics of adolescence and young adulthood [1].

	Physical development	Cognitive development	Social and emotional development
Early adolescence (~10–14 years)	Puberty: growth of body hair, increased perspiration and oil production in hair and skin; great physical growth (both height and weight); breast and hip development and onset of menstruation (girls); growth in testicles and penis, wet dreams, and deepening of voice (boys).	Growth in capacity for abstract thought; mostly interested in present with little thought about the future; expansion of and increased importance placed on intellectual interests; deepening of moral thinking.	Struggle with sense of identity; feel awkward about themselves and their body; worry about being normal; realise their parents are not perfect; have heightened conflict with parents; become increasingly influenced by peer group; have a raised desire for independence; return to childish behaviour when stressed; are prone to mood swings; test rules and limits; become more private; have a growing interest in sex.
Mid-adolescence (~15–19 years)	Physical growth slows for girls but continues for boys.	Continued growth in capacity for abstract thought; increased capacity for setting goals; interest in moral reasoning; think about the meaning of life.	Have intense self-involvement, alternating between high expectations and poor self-identity; continue to adjust to changing body; worry about being normal; tend to distance themselves from their parents; have a continued drive for independence; are driven to make friends and have a greater reliance on them (popularity can be an important issue); have a heightened capacity for emotional regulation; experience feelings of love and passion; have increasing interest in sex.
Late adolescence or early adulthood (~20–24 years)	Young women are typically fully developed physically; young men continue to gain height, weight, muscle mass, and body hair.	Ability to think ideas through from beginning to end; ability to delay gratification; examination of inner experiences; increased concerns for the future; continued interest in moral reasoning.	Have a firmer sense of identity, including sexual identity; have increased emotional stability, concern for others, and independence and self-reliance; still place importance on peer relationships; develop more serious relationships; regain some interest in social and cultural traditions.

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CHAPTER 2

Epidemiology of cystic fibrosis lung disease progression in adolescence

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1 Introduction

Physiological and emotional changes that challenge all adolescents can be accompanied by accelerated progression of lung disease in the adolescent with cystic fibrosis (CF), leading to irreversible morbidity and increased risk of mortality. In this chapter, the epidemiology of lung disease progression in adolescents with CF and the physical and psychosocial factors that may influence this process will be reviewed. The published literature on the epidemiology of adolescent CF lung disease is currently dominated by studies of North American populations that are followed in the US CF Foundation (CFF) Patient Registry [1] and the Epidemiologic Study of Cystic Fibrosis (ESCF) [2]. There is reason to believe, however, that adolescent CF experiences and outcomes vary to some degree from country to country as a result of differences in genetic backgrounds, healthcare delivery systems, clinician practice patterns, available treatments and cultural behaviours among adolescents, peers and families. A comprehensive analysis of the epidemiology of adolescents with CF would

ideally include comparisons across all countries with adolescent CF populations. Whenever possible, epidemiological data from as many different countries as possible will be included in this review.

2 Assessing pulmonary disease progression by spirometry

Today, more than 80% of CF deaths result directly or indirectly from loss of pulmonary function [1], although only a small fraction of these deaths occur among adolescents. In 2010, 7.4% of all patient deaths reported in the 2010 US CFF Patient Registry occurred among patients 12–17 years old, comprising only 0.63% of the 12–17-year-old US CF population [1]. Despite the relative rarity of death in the adolescent CF population, there is an increased probability of irreversible loss of lung function during adolescence [3] that increases the subsequent risk of mortality [4].

When characterising CF lung disease, there has been a traditional emphasis on spirometry, and in particular forced expiratory volume in 1 sec (FEV_1) and the fraction of FEV_1 present compared with a reference population (FEV_1% predicted) [5]. As FEV_1% predicted is lost, lung disease stage advances and predicted 2-year survival decreases [4]. It is important to note, however, that inflammation-induced lung damage precedes the ability to detect functional loss by spirometry. Air trapping, bronchial wall thickening, and bronchiectasis can be detected in infants with CF by high-resolution computed tomography [6–9] and chest X-ray [10]. Similarly, ventilation inhomogeneity can be discerned well before spirometric changes [11–13]. Unfortunately, there are relatively few published data describing the epidemiology and progression of early structural or ventilation changes in the CF lung, whereas spirometric data are widely available. Although Rosenthal [14] has suggested that the reliance by the clinical community on FEV_1 as an indicator of CF health status is questionable, the measure remains an influential driver of patient management, including (but not limited to) defining lung disease stage [5] and disease aggressiveness phenotype [5,15], supporting the diagnosis of pulmonary exacerbation [16], evaluating response to exacerbation management [17–22] and demonstrating treatment efficacy in controlled CF clinical trials [23–28]. Several different normative equations have been employed to estimate the fraction of FEV_1 an individual retains compared with a reference population of the same sex, height and age (FEV_1% predicted) [29]. In this chapter, unless otherwise stated, FEV_1% predicted values will be determined using the reference equations of Wang et al. [30] for females up to age 15 years and males up to age 17 years, with the reference equation of Hankinson et al. [31] for older individuals.

3 Variability of lung disease progression

Not surprisingly, individuals with CF who die at younger ages experience greater average rates of FEV_1 loss over their lifetimes compared with those who die at older ages [32]. However, rates of FEV_1 decline

are not constant across all ages [3,33]. Only a minority of children with CF experience substantial FEV_1 loss by the age of 6 years. For example, 91.0% of 3456 children in an ESCF study had an FEV_1 ≥70% predicted at age 6 years, with 83.3% having an FEV_1 ≥80% predicted and 68.1% with an FEV_1 ≥90% predicted [34]. Unfortunately, mean rates of FEV_1 decline increase as children get older, with an ESCF analysis of children 6–18 years of age identifying FEV_1 decline rates of 1.12% predicted/year for 6–8-year olds (n=1811; p=0.369), 2.39% predicted/year for 9–12-year olds (n=1696; p=0.0060) and 2.34% predicted/year for 13–17-year olds (n=1359; p=0.042) [3].

4 FEV_1% predicted versus age

Individuals with CF advance through progressive stages of lung disease. However, CF lung disease progression is heterogeneous, with the age at which an individual reaches a given lung disease stage providing an indication of the relative aggressiveness of his or her lung disease phenotype [5]. Heterogeneity of CF lung disease stage (as FEV_1% predicted) within the adolescent population suggests that individual FEV_1 decline rates vary broadly prior to adolescence (Fig. 1).

Changes in FEV_1 distributions observed in successively older adolescent groups in Fig. 1 are consistent with lung disease progression continuing during adolescence. For example, 37.7% of 12- and 13-year-olds followed in the US CFF Patient Registry had a best recorded FEV_1 ≥100% predicted in 2010 compared with 30.8% of 14- and 15-year-olds and only 20.9% of 16- and 17-year-olds (Fig. 1). Similarly, 12.2% of the youngest adolescents had a best FEV_1 <70% predicted in 2010, whereas 18.4% of 14- and 15-year-olds and 26.7% of 16- and 17-year-olds found themselves in the same situation. However tempting it is to employ such cross-sectional data to infer lung disease progression, they are inadequate to estimate rates of FEV_1 decline from year to year. Accurate estimation of decline rates during adolescence requires longitudinal analyses of the same population over time to avoid bias introduced by demographic differences between age groups as well as patients entering or leaving the population due to new diagnoses, relocations or deaths.

5 Lung disease aggressiveness phenotypes

In 2006, Schluchter et al. divided homozygotes for the most common *CFTR* mutation, F508del, from the US CFF Patient Registry into quartiles by FEV_1% predicted at each age to create a topographical map of age versus FEV_1 in order to identify F508del homozygotes with the most and least aggressive CF lung disease phenotypes [15]. These investigators demonstrated that ~95% of patients identified as having a 'mild' or 'severe' phenotype based on mapping (Fig. 2A) remained in their respective phenotypic zones during subsequent years [15]. The potential utility of disease aggressiveness phenotypes in the management of the entire CF population has been

reviewed [5]. Interestingly, adolescents with CF who are under 15 years of age and have relatively high FEV_1% predicted prove difficult to categorise using the aggressiveness phenotype algorithm (Fig. 2A), as their disease progression 'fate' has yet to be fully realised. For these individuals, the extent to which their FEV_1 is preserved or lost during adolescence determines whether their disease phenotype will ultimately be categorised as 'mild' or 'intermediate' in aggressiveness (Fig. 2B).

6 Risk factors for adolescent pulmonary function decline

As noted previously, cross-sectional analyses of adolescent CF populations (Fig. 1) suggest substantial heterogeneity in lung disease progression. To identify risk factors associated with variability in lung disease progression in children with CF, Konstan et al. identified 11 demographic or clinical parameters (of the 28 initially studied) that exhibited significant univariate associations with rate of FEV_1 decline in any of three age groups: 6–8 years, 9–12 years and 13–17 years [3]. These 11 parameters were incorporated into a multivariate model to predict rates of FEV_1 decline over 5–6 years. The parameters retained included: clinical presentations (sex, sputum production, crackles, wheeze and sinusitis); objective measures (FEV_1% predicted, culture history for *Pseudomonas aeruginosa*, weight-for-age [WFA] percentile, and liver function test [LFT] results); and intervention histories (treatment with intravenous [IV] antibiotics for pulmonary exacerbation and prescription of pancreatic enzyme supplements) [3]. Seven of these parameters were found to be statistically significant with respect to predicting rate of FEV_1 decline in adolescents aged 13–17 years: baseline FEV_1% predicted ($p<0.001$), sex ($p=0.002$), WFA percentile ($p=0.021$), sputum production ($p=0.003$), crackles ($p=0.010$), past IV antibiotic treatments for exacerbation ($p<0.001$) and pancreatic enzyme use ($p=0.041$). Parameter estimates and their 95% confidence intervals from this model are shown in Fig. 3.

Using Fig. 3, an individual's future rate of FEV_1 decline is estimated by summing his or her parameter status estimates. For example, the estimated future rate of FEV_1 change for a 13-year-old boy with an FEV_1 of 95% predicted, a WFA in the 55th percentile and no *P. aeruginosa* infection, sputum production, crackles, wheeze, sinusitis, prior year history of exacerbation treated with IV antibiotics or elevated LFT, but who requires pancreatic enzyme supplements would be (–2.34) + (–0.37) + (–0.3) + (0.13) + (–0.41) + (0.33) + (0.18) + (–0.04) + (0.0) + (0.42) + (0.02) + (–0.04) = –2.42% predicted/year.

With this method, the effects of differences in a single parameter on the rate of lung function decline can be assessed, all other parameters being equal. For example, overall adolescent male FEV_1 decline rates are predicted to be 0.61% predicted/year greater than female decline rates (Fig. 3). This result may seem counterintuitive given previous reports of more aggressive CF lung disease progression among females compared with males [35], but the contribution of other parameter estimates may offset

these differences, and FEV_1 decline rate calculations for individuals require summation of all parameter estimates.

7 Lung disease progression: nature versus nurture?

Some parameters captured in the rate of FEV_1 decline modelling (Fig. 3) suggest underlying biological factors that are markers for lung disease and are for the most part beyond the influence of clinicians. Sputum production and crackles suggest exaggerated airway inflammation and obstruction, and it is not surprising that these symptoms are associated with more rapid FEV_1 decline. Similarly, some individuals with CF carrying at least one 'mild' *CFTR* mutation are pancreatic sufficient and do not require pancreatic enzyme supplementation [36,37]. These individuals also enjoy a relatively greater overall survival compared with those with two 'severe' *CFTR* mutations [38,39]. In this context, it is not surprising that rates of FEV_1 decline are higher in individuals prescribed pancreatic enzyme supplements than in those not prescribed supplements.

Relationships between FEV_1 decline rates and other parameters may be more complicated than they first appear. For example, an association between history of pulmonary exacerbation and future FEV_1 decline makes intuitive sense, as it has recently been suggested that a substantial portion of patients with CF treated for pulmonary exacerbation fail to recover associated FEV_1 loss [20]. However, by sheer numbers, more pulmonary exacerbations in North America are treated with inhaled and/or oral antibiotics than with IV antibiotics [40], and thus a clinician's decision to choose IV antibiotics to treat an exacerbation may include a subjective assessment of his or her patient's disease status and risk of progression, as well as an objective assessment of exacerbation severity.

Finally, relationships between some parameters and FEV_1 decline rates seem counterintuitive and inexplicable in strictly biological terms, and these may provide insight into variations in standards of care. For example, it is difficult to rationalise a biophysical relationship between the presence of wheeze and a reduced FEV_1 decline rate (a relationship that was observed to be statistically significant in younger children and nearly so in adolescents [3]). However, if one postulates that the presence of wheeze may increase the rigour of pulmonary management and/or treatment adherence, then wheeze can be viewed as an indirect marker of better pulmonary care and it would make sense for it to be associated with better FEV_1 outcomes. The most striking example of a counterintuitive relationship between a parameter's status and estimated future rate of FEV_1 decline can be found with FEV_1% predicted itself, where greater baseline lung function is associated with greater future decline. Understanding that patients with the very lowest FEV_1% predicted values have little room for further lung function decline (i.e. there is a basement effect), there is no biological basis from which to conclude that the very highest lung function levels should cause accelerated FEV_1 decline.

However, it has been documented that CF clinicians can be more hesitant to prescribe chronic pulmonary therapies to healthier adolescents [41,42] and also that healthier patients can be less motivated to adhere to prescribed therapies [43]. Furthermore, it has been shown that the responsibility for adherence shifts more and more towards the adolescent and away from their parents/caregivers, creating a potential for reduced adherence [44]. Viewed in this context, better lung function may be a marker for less rigorous management/adherence and in turn a marker for increased risk of FEV_1 decline. Interestingly, this phenomenon appears to extend beyond adolescence and into young adulthood, where higher FEV_1 values have also been associated with a greater risk of near-term lung function decline [45].

Evidence that clinician and patient behaviours affect adolescent lung disease progression is largely indirect, but substantial. First, at least three chronic CF pulmonary therapies have been shown to reduce mean rates of FEV_1 decline: high-dose ibuprofen [46–48], inhaled corticosteroids [49], and dornase alfa [50]. It follows that a clinician's decision to prescribe or not prescribe such therapies has the potential to impact future FEV_1 decline, as does a patient's decision to be adherent to these therapies or not. Second, the tendency to prescribe chronic pulmonary therapies has been shown to be heavily influenced by lung disease stage, with the proportion of patients prescribed therapies increasing with decreasing FEV_1% predicted [41,42]. If clinicians are less inclined to prescribe therapies that reduce the rate of lung function decline in patients with better lung function [41,42], it is perhaps not surprising that these patients are at relatively greater risk of FEV_1 decline.

Additional evidence that clinical practice may play a role in adolescent lung disease progression can be found in comparisons of FEV_1 distribution among adolescents from different countries, where practice patterns presumably differ to some extent (Fig. 4). Although simple in premise, such comparisons must be tempered by recognition of the potential for bias introduced by differing patient genetic backgrounds, CF diagnostic methods, and death rates. Perhaps more importantly, such comparisons are complicated by fundamental differences in CF registry data collection across geographical regions that can be challenging to transcend [51]. Beyond the obvious problem of comparing data collected in different (but proximal) years (Fig. 4), it should be noted that regional registries do not employ a uniform standard for calculating FEV_1% predicted; the UK CF Registry data in Fig. 4 are calculated using the normative equations of Knudson et al. [52], whereas data from the other regions are calculated using the equations of Wang [30] and Hankinson [31]. Furthermore, assigning a single pulmonary function value for each patient in a given year is, in itself, a somewhat arbitrary practice, and varies by region. For the most part, data in Fig. 4 employ the 'best recorded' FEV_1% predicted that year, with exceptions being data contributed to the ECFS Registry by France (N=898), which reported the final FEV_1 measure of the year, and Germany (N=950), which reported the FEV_1 closest to the patient's birthday. Finally, the UK CF Registry records pulmonary function from an 'annual encounter'.

Given the many caveats associated with demographic comparisons across geographical areas [51], Fig. 4 does suggest that there is geographical variability in CF lung health in adolescents, and it is not unreasonable to conclude that how children with CF have been managed in these regions has at least partially contributed to these differences.

A final indication that differences in patient management can influence adolescent lung disease progression can be found in a comparison of US adolescent lung disease distributions between 1995 and 2010. Again, cross-sectional comparisons of different adolescent CF populations of the same age may be prone to bias due to an inability to account for demographic differences. Recognising these caveats, the percentage of 12- and 13-year-olds in the US CFF Patient Registry with an FEV_1 ≥100% predicted increased from 22.4% to 37.7% between 1995 and 2010, while the percentage of 16- and 17-year-olds with FEV_1 ≥100% predicted nearly doubled from 11.4% to 20.9% over the same time period (Fig. 5).

Incremental improvements in the pulmonary health of adolescent CF populations are remarkably consistent between 1995 and 2010 and coincide with a decrease in signs and symptoms of respiratory disease in adolescents [53]. Perhaps not coincidentally, a steady increase in the use of chronic pulmonary therapies within the adolescent ESCF population also occurred between 1995 and 2005, with prescriptions for inhaled antibiotics increasing from 8.0% to 50.0%, prescriptions for inhaled corticosteroids increasing from 18.1% to 53.5%, and prescriptions for dornase alfa increasing from 57.5% to 76.0% (Fig. 6) [42]. Increased use of chronic pulmonary therapies over this time period are notable because they occurred in a population with improving lung function [53] against the trend that prescription of these therapies is lower in patients with higher FEV_1% predicted than in those with lower FEV_1 values [41,42]. Observed increases in pulmonary health in the US adolescent CF population are likely also related to the remarkable improvements in the nutritional status, growth and stature of younger children with CF that has been achieved in recent decades [1].

8 Conclusions

Inexorable lung function loss and premature death are characteristic of a majority of individuals with CF. However, mean rates at which lung function is lost are not constant across an individual's lifetime or between individuals of the same age. Progressive damage to CF airways can begin early in life, but the most common measure of lung disease in CF, FEV_1% predicted, is only modestly affected in early childhood. Mean rates of FEV_1 decline increase as children with CF get older. By adolescence, overall rates of FEV_1 decline are roughly double what they had been when individuals were 6–8 years of age. Despite an overall increase in the rate of lung disease progression at the population level immediately prior to and during adolescence, individual rates of FEV_1 decline can vary widely, creating a distribution of lung disease stages at a given age.

Although adolescence is characterised by an increased risk of CF lung disease progression, remarkable improvement in the pulmonary health of adolescents with CF has been realised over recent decades. Circumstantial evidence that clinician and patient behaviour can have a substantial impact on lung disease progression (e.g. through more rigorous use of chronic pulmonary therapies) suggests that the potential for further improvement in the pulmonary health of adolescents with CF remains.

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Figure 1

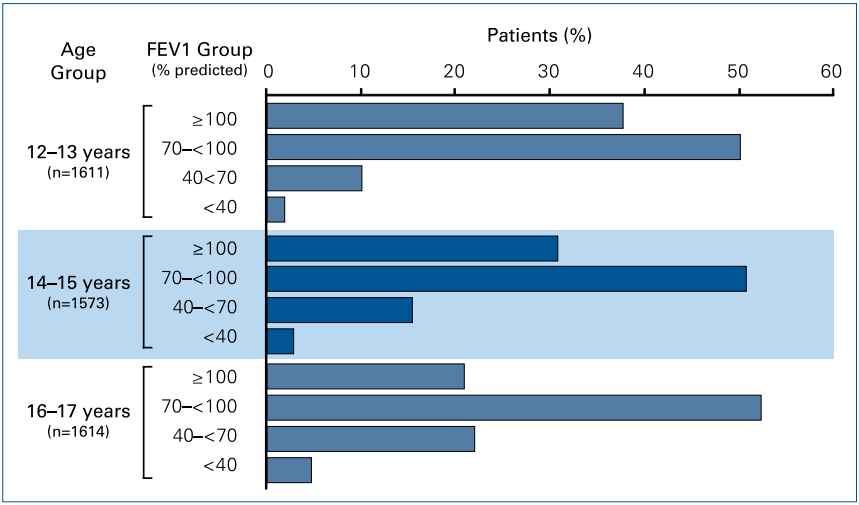

Fig. 1. Heterogeneity of FEV_1% predicted among US adolescents with cystic fibrosis (CF). Distributions of adolescents followed in the 2010 CF Foundation Patient Registry [1] stratified by their best recorded FEV_1% predicted in 2010 for different age groups. Patients were assigned to age groups based upon their age on their 2010 birthday, and the percentages shown total 100% within each age group.

Figure 2

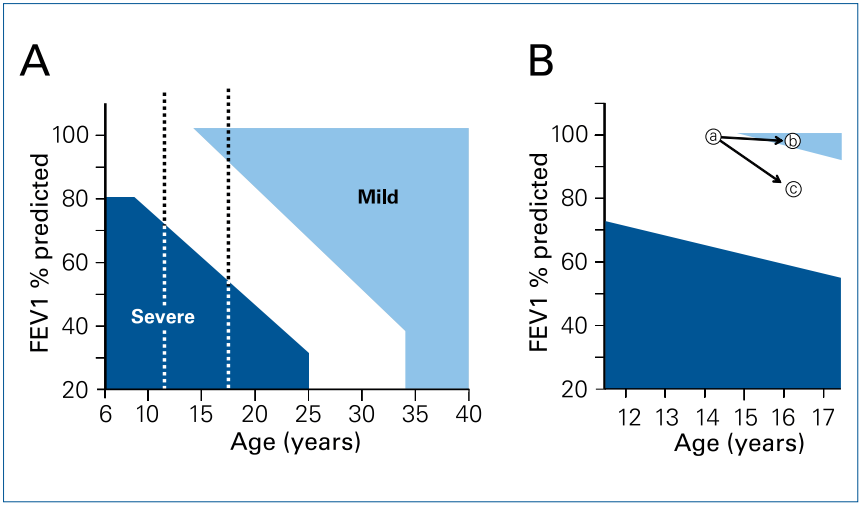

Fig. 2. Topographical mapping of cystic fibrosis (CF) lung disease phenotypes. Panel A: disease aggressiveness phenotype map adapted from Konstan et al. [5]. Patients with a 'severe' lung disease phenotype (black zone) are at greater risk for mortality at a younger age, whereas those with a 'mild' disease phenotype (grey zone) are more likely to survive to older ages. The adolescent CF population is found between the vertical dotted lines. Panel B: disease aggressiveness among CF adolescents 12–17 years of age. The disease aggressiveness phenotype of a 14-year old with an FEV_1 of 100% of his or her predicted value (circle 'a') is uncertain and dependent on rate of FEV_1 decline over the subsequent 2 years (circles 'b' versus 'c'). Adapted from Journal of Cystic Fibrosis, Volume 8S, Konstan MW, Wagener JS, VanDevanter DR, Characterizing aggressiveness and predicting future progression of CF lung disease, pages 8S:S15-S19, copyright 2009, with permission from Elsevier.

Figure 3

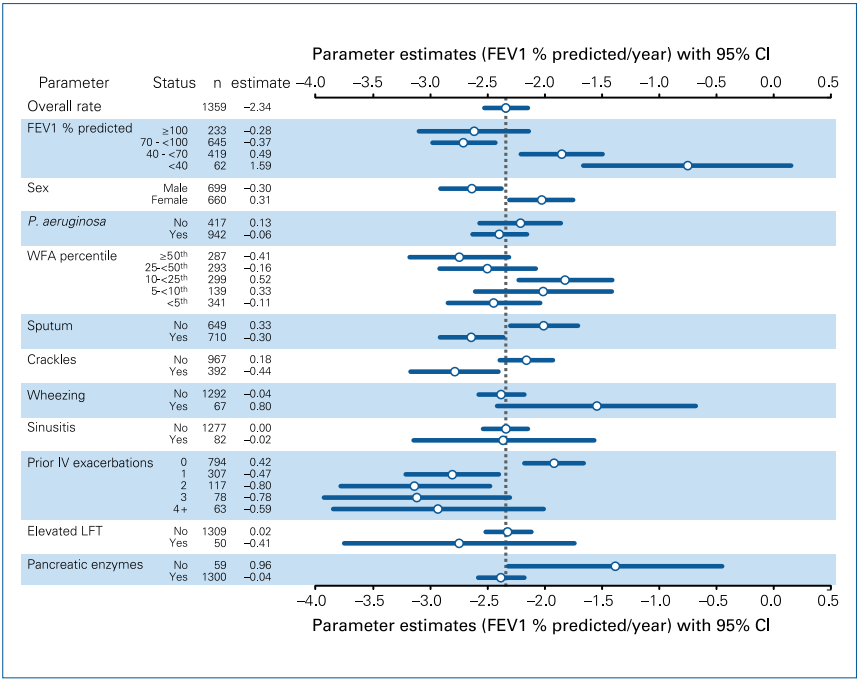

Fig. 3. Multivariate modelling of FEV_1 decline rates in adolescents with cystic fibrosis (CF) aged 13–17 years [3]. Parameters are shown in the left column. n = number of patients included in the model with a given parameter value. Bars are 95% confidence intervals (CI). Dotted vertical line is the overall estimate for rate of FEV_1 decline for the population (2.34% predicted/year). LFT = liver function tests; WFA = weight for age. Adapted from Journal of Pediatrics, Volume 151 Number 2, Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, Stokes DC, Wohl MB, Wagener JS, Regelmann WE, Johnson CA, Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis, pages 134–139, copyright 2007 with permission from Elsevier.

Figure 4

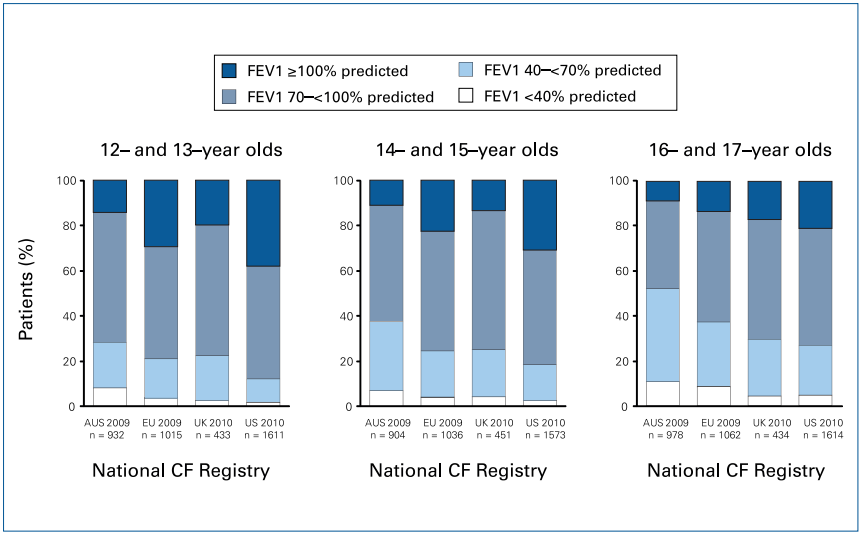

Fig. 4. Distribution of lung function in adolescents with cystic fibrosis (CF) by age and geographical location. Stacked bars show the proportions of adolescents with CF of a given age group within different lung function ranges (as FEV_1% predicted) by geographical region. Aus 2009, patients followed in the Australian CF Registry in 2009; EU 2009, patients followed in the European CF Society Registry in 2009 from Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Moldova, Portugal, Serbia, Slovenia, Spain, Sweden, Switzerland and The Netherlands; UK 2010, patients followed in the United Kingdom CF Registry in 2010; US 2010, patients followed in the US CF Foundation Patient Registry in 2010.

Figure 5

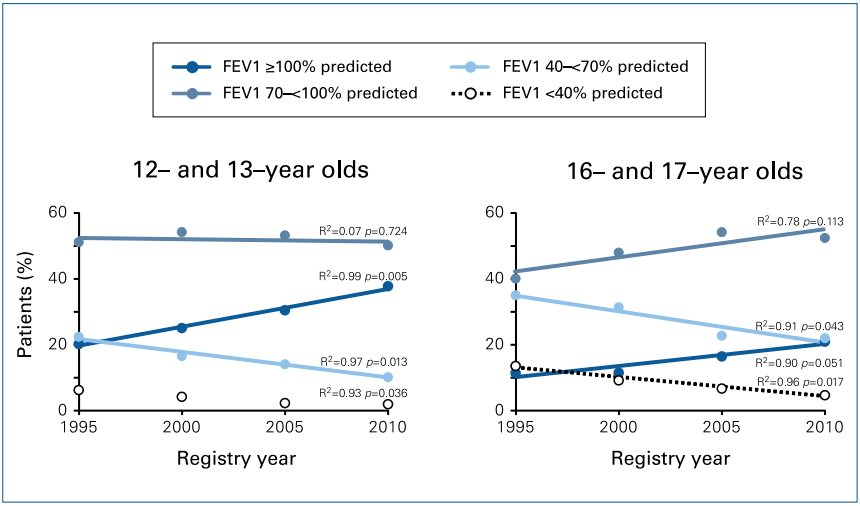

Fig. 5. Changes in FEV_1 distribution among adolescents in the US Cystic Fibrosis Foundation Patient Registry, 1995–2010. Left panel: FEV_1% predicted distributions among 12- and 13-year-old patients. Right panel: FEV_1% predicted distributions among 16- and 17-year-old patients. Lines represent simple linear regressions of proportions of patients in each FEV_1 category versus time, for which correlation coefficients (R^2) and *p*-values are provided.

Figure 6

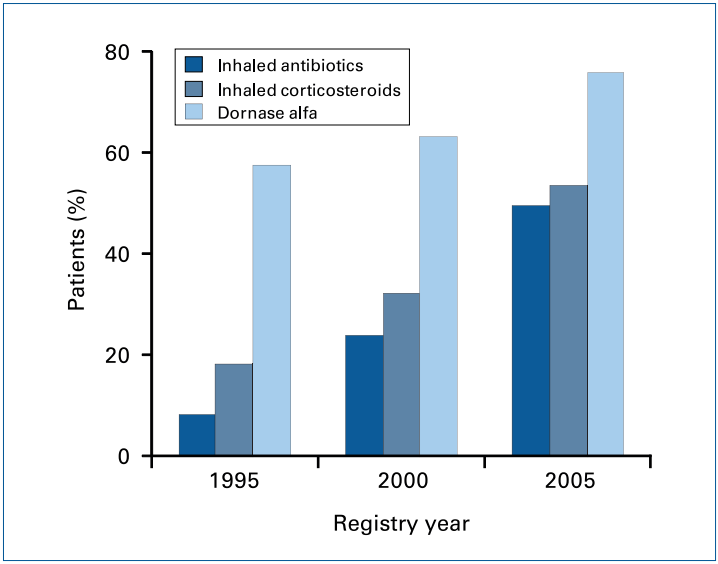

Fig. 6. Prescriptions of inhaled antibiotics, inhaled corticosteroids, and dornase alfa among patients aged 13–17 years followed in the Epidemiologic Study of Cystic Fibrosis Registry for the years 1995, 2000 and 2005 [42].

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CHAPTER 3

Transition from the paediatric to the adult cystic fibrosis centre

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1 Introduction

Due to early diagnosis, improved treatment modalities and centralised care, life expectancy for people with cystic fibrosis (CF) has increased significantly over recent decades [1]. Childhood is less characterised by disease and decline in lung function, and the majority of young people with CF are likely to reach adulthood. This results in a significant and increasing shift from paediatric to adult care for individuals with CF. This process of transition is a major step for the adolescent and their parents. Therefore, assistance and guidance are needed in order to optimise the outcome of this major change in treatment environment.

In most clinics, preparation for the transfer of individuals to the adult CF clinic currently starts at about the age of 16 years. There is an increasing awareness, however, that preparation for transition should start at an earlier age, even from birth. The process of transition should be started by the paediatric clinic, preferably in close collaboration with the adult clinic. After the actual transfer, the process of

collaboration should continue in order to ensure continuity of care.

Cultural differences between the paediatric and adult services have to be negotiated in order to ensure a smooth transition both for the young person and their parents. Both services should aim to impose minimum emotional and physical disruption so that the young person is confident and assured that the change will not be a step backwards. Transition is best supported by implementation of a protocol that is developed by paediatric and adult services according to existing guidelines.

This chapter will discuss the meaning of transition in general, the key players in the transition of individuals with CF from paediatric to adult care, and the challenges faced by patients, parents and healthcare professionals.

2 The transition process

The definition of transition is the transfer from one stage of life, or physical or mental condition or from one social role to another, which temporarily disrupts normal life and requires a period of adjustment [1,2]. Transition involves people's responses during a process of change in order to master and regulate that change. It occurs over time and leads to adaptation. It is an ongoing process, not a solitary event.

Schumacher and Meleis [3] distinguished four types of transition.

- Developmental transition: changes in life stages of a human being; it is a normal biological process, for example from teenager to adolescent.
- Situation-related transition: changes in social status, for example within a family the changing roles between parents and children.
- Transitions in health and sickness: movement to a different stage of a chronic illness, for example declining lung function in CF.
- Organisational transition: change from provided care to demand-driven care; centralisation of care.

All four types of change are involved in the transition from paediatric to adult care. The key players in this shift of care will each undergo their own transition process in order to negotiate the challenges they encounter.

2.1. Factors that may influence the transition process

In order to properly assist people moving through the transition process of paediatric to adult care, it is essential that healthcare providers understand the factors that may influence the process [3,4] These include the expectations of individuals, their families and healthcare professionals and the level and type of support available from family and wider social networks. In addition, the level of knowledge and understanding of the chronic illness by the patient and family, as well as by all healthcare professionals involved in the care of the individual patient will affect their capacity to respond to the changes associated with increasing age and the movement to adult care. The availability of resources to support emotional and physical well-being are also important.

3 Key players in the transition from paediatric to adult CF care

The key players involved in the transition from paediatric CF care to adult care are the individual with CF, their parents and the paediatric and adult healthcare services.

3.1. The individual with CF

All children undergo several developmental changes, both physical and emotional, in a relatively short period of time. These developmental steps are:

- 0–3 years: feeling safe and bonded with their parents is very important
- 3–6 years: the child can make the distinction between themselves and their parents, develops a will of their own and pushes the boundaries
- 6–10 years: the child learns how to associate with children of their own age, develops self-esteem, wants to be independent but still relies on their parents.

According to a World Health Organization definition, adolescents are young people aged between 10 and 19 years [5]. Individuals start developing their own identity during adolescence and will undergo bodily changes and become aware of their own sexuality. They will look to the future and the role they will play in it. They will face choices about education, career, relationships and family planning. Having CF can make these choices more difficult, due to an increasing awareness of limited life expectancy and interruption of a natural progression to self-sufficiency, particularly in sensitive areas such as physical disability and sexual awareness [2]. Developing their own identity is a huge challenge, particularly in the context of care, which they have to accept from parents on the one side and healthcare professionals on the other. At this stage of their life they do not want to be any different from their peers, and feelings of isolation, insecurity and inadequacy may be expressed as anger against themselves, their family and their caregivers [2]. This can have a negative influence on their development to independence.

Adolescents with CF face the challenge of disease at one of the most vulnerable stages of their lives. To have an open attitude and communicate equally with their parents and caregivers is not an easy task; at this stage of life, they have interests other than CF and CF-related therapy. It is important that they feel supported by their family and caregivers in making their own decisions and are encouraged to correct or change decisions if they have made an oversight, regardless of their behaviour. Adolescents with CF want to be treated like adults and their parents and healthcare professionals have to be aware of this need and respond accordingly.

3.2. Parents

Parents form an important constant for their child as they make the transition to adult care. Over the years parents have played an important role in providing the CF care for their child.

After initially receiving the news that their child had CF, parents also had to go through a transition process. Not only did they have to defy the emotional aspects

but they also needed to adjust to their role as health caregiver. Different emotions can influence this process: fear for the future, guilt, uncertainty, grief, anger and denial are a few of them. It is important for parents to recognise these emotions at an early stage and strive to prevent them from becoming extreme so that they do not have a negative influence on their relationship with their child and complicate the path to self-sufficiency and self-management.

The transition from child care to adult care is a logical step for the adolescent with CF. The individual wants to be more independent and to take life into their own hands. For parents this is an emotional step; before, they were responsible for their child's care and now gradually they have to transfer it to their child and the adult healthcare professionals. This can cause fear for loss of continuity of care and control of their child's health. Therefore, the transition process should involve the parents and include the provision of adequate parental support and guidance. What they have to let go, their child has to take over. The responsibility they feel towards compliance of care of their child and the fear of decline can be a discouraging factor in their pivotal role in the transition process. This is an understandable fear and can be difficult for parents to overcome. For them it is a challenge not to overrule a decision that their child makes if the decision does not correspond with their own; instead they need to support their child in a positive way and teach them to make their own decisions, accept the consequences and adjust to the outcome if necessary. Parents must lovingly accompany their child to a life in the adult world as it really is, even if it is not always what they wished for or expected [2].

3.3. Paediatric care team

The preparation of individuals with CF for the transition to adult care is carried out mainly by paediatric healthcare professionals [6]. In fact, the process of transition starts as soon as the diagnosis of CF is made, and in the case of neonatal screening this will be very early. Parents and child will enter the healthcare service from the very beginning. They need optimal guidance and support from the paediatric healthcare professionals in order to establish an optimal relationship with mutual respect towards each other [2]. Parents must learn to trust their own judgement and ability to give their child the right care. They must be able to build up a normal relationship with their child and not a relationship that is based on fear and concern. The way a child responds to a chronic condition is closely dependent on the reaction of the parents and siblings. The experiences of patients and their parents during paediatric care affects their perception of the whole transition period [7].

The challenge for the paediatric healthcare professionals, therefore, is to respectfully guide both parents and children and to provide age-appropriate care. Paediatric healthcare professionals are trained to treat according to growth and development of the child. However, guiding parents in their learning process in administering care and in building up a good relationship with their child requires the additional skills of communication and empathy, as well as particular knowledge and an investment of time.

Parents and child can develop a strong bond with the professional paediatric health caregivers. It is important that the healthcare professional is aware of the fact that it is a professional relationship that will end [8]. It is mandatory that healthcare professionals have a positive attitude towards the adult care system so that parents and child can face the transition process with confidence [2]. When the child becomes an adolescent, parents have to step aside and let their child gradually take over and the paediatric team need to make a positive contribution to this transfer process.

A protocol that is approved by all concerning parties may be a helpful tool. It can work as a guideline and can be useful during evaluation of the service and in monitoring the development of child and parents.

Establishing optimal collaboration and contact with adult care hospitals is important, not only to streamline the working methods but also to keep each other informed and to share experiences. Adult care is more experienced in educational issues, career planning and also in family planning. Paediatric healthcare can benefit from this experience and staff can inform parents and their child according to the latest developments in adult care. They can also share protocols where appropriate.

For the adult healthcare professionals, meeting the adolescent with CF in the paediatric setting and participating in the outpatient clinic can be helpful in becoming familiar with the individual and their family. It is a way of initiating communication in a familiar setting. The adult healthcare professional can also benefit from the experience of the paediatric care centre in supporting adolescents and use this when addressing the young adult in the adult care setting.

An important role is set aside for the CF nurse consultant/CF coordinator [4,8,9]. Nurses working alongside people can help them to identify changes imposed by illness and seek new possibilities from disruptive experiences [4]. The tasks for the CF nurse can include:

- keeping close contact with parents and their child
- being the binding factor between healthcare providers in child and adult care by communicating with their fellow CF nurse consultants/CF coordinator
- being involved in the transition process from the start and supporting parents and child/adolescents in their rites of passage
- ensuring that the professional health caregivers involved all work with the same methods where possible and according to the same protocols and guidelines
- communicating with the lead physician
- coordinating the joint paediatric and adult outpatient clinic and introducing the adolescent and their parents to adult care
- being available for questions
- advising the adolescent and their parents in their choice of hospital
- building bridges where differences in culture exist between paediatric and adult centres
- being the familiar face during the transition process.

3.4. Adult care team

Healthcare systems have responded to increasing numbers of adults with CF. As a result centralisation of care and multidisciplinary teams for adults with CF have been established in most countries [1].

Adolescents around the age of 18 years and sometimes younger, will transfer to an adult care system, which must respond appropriately to their needs [1]. The adult healthcare professionals cannot treat the adolescent as a full-grown adult yet, but have to offer developmental-appropriate healthcare as a continuum from paediatric care.

It is a challenge to manage this sequence in a structured way due to the differences between paediatric and adult care. Choosing one physician who is responsible for the overall care is important. This key physician will be the healthcare professional with whom the young adult will communicate during their visits to the outpatient clinic. Usually, in adult care, this key physician is the pulmonologist. The CF nurse/CF coordinator in adult care can again play an important role in coordinating the many aspects of care concerning CF. They can make the first visit to the adult centre a personal experience and make the young adult and their parents feel at ease. The CF nurse can also ensure that comprehensive referral information from the paediatric centre is received by the adult centre well before the first appointment so that the adult team can gain a proper insight into the specific details of care and the complications related to CF [1].

Despite a better physical and emotional start to life for the individual with CF, the burden of care remains high and will, in most cases, increase with age. Adult care will be more focused on the prevention and treatment of progression of illness. Complications of CF become more frequent and include CF-related diabetes, metabolic bone disease, multi-resistant pulmonary pathogens, multiple drug allergies and toxicities, liver and kidney failure, and the psychosocial consequences of living with a chronic disease. Achieving successful pregnancy for women and infertility treatment for men has become possible, so managing a family in the setting of a chronic illness such as CF has become a reality and occurs with increasing frequency [1,2]. Consequently, more subspecialties are now involved in CF care. It is important they these subspecialists are educated in CF care and realise that one problem never stands alone but involves many aspects. Multidisciplinary communication between specialists becomes essential for the young adult who needs to receive the same message and attitude regarding treatment; this is particularly important for young adults who are still inexperienced in communicating directly with specialists without the presence of their parents. If messages regarding the healthcare plan differ, the individual may start to feel insecure and vulnerable, which can undermine their confidence both in the system and in their own management of CF. Some specialist can be affronted by a young adolescent who wants to discuss everything and has a clear view of what they want. Both situations require communication skills, time and patience, which is not always available. The specialist must realise that the young adult may have more underlying emotional disturbances than is immediately obvious [2]. Good communication is a challenge for both.

Treatment of young adults with CF in an adult hospital requires certain resources. Segregation policy for example advises single rooms with bathroom facilities. Access to the Internet becomes essential, as patients spend most of the day in their room. House rules need to be discussed with patients as they attempt to stretch their boundaries. Nursing staff need experience and communication skills to deal with this kind of behaviour, as well as an understanding of CF; knowledge of the transition process and factors that affect it are mandatory.

4 European guidelines for transition to adult care

In 2005, a consensus committee appointed by the European Cystic Fibrosis Society developed standards of care for patients with CF, including guidelines on transitional care from paediatric to adult services [10]. The key points are as follows.

- Transition to adult care should take place during emerging adulthood, 16–19 years of age.
- The age of transition should be flexible but completed by 19 years of age.
- Transfer may be occasionally delayed or accelerated for psychosocial or medical reasons, for example transplantation or developmental delay.
- The idea of transition to adult care should be introduced soon after diagnosis. All patients and their parents should have the opportunity to meet the adult team prior to transfer.
- There should be flexibility in the details of transition.
- A written joint policy should be developed between adult centres and referring paediatric clinics.
- A joint clinic between the teams from the age of 15–19 years is a valuable transitional arrangement. A transfer report including details of diagnosis and subsequent care from all key team members and issues of special importance to the patient and parents should be provided.

5 Model for a transition protocol

A transition protocol can provide a structure for the delivery of CF care. Such a tool should be developmentally appropriate and comprehensive for both paediatric and adult multidisciplinary teams. The main goal of a transition protocol for care of individuals with CF is to facilitate the development of a system that ensures continuation in the areas of learning to cope with change, providing health and care information, supporting family and social networks, and encouraging the mastering of self-management.

5.1. Key elements for paediatric services

Within the transition protocol there will be elements of focus for the paediatric healthcare team that encompass their partnership with the young person, their parents and the adult healthcare team.

- Guide parents and their child in learning practical and theoretical skills related to CF.
- Monitor the coping strategies that parents and child adopt and discuss these with them when necessary.

- Stimulate and guide parents to gradually hand over the responsibility of care to their child.
- Guide the adolescent in taking charge of their routine treatment, managing problems and learning independence.
- Address the general healthcare concerns of individuals, including lifestyle issues (alcohol, drugs, nutrition and physical activity) as well as sexual health, fertility and reproduction, and guidance around capacity for ongoing education and employment.
- Accompany the adolescent on visits to the paediatrician without their parents.
- Support and advise parents and child on their choice of adult hospital.
- Pay attention to differences in working methods regarding flushing a port or changing a button at home or administering antibiotics intravenously.
- Introduce parents and child to the adult clinic.

5.2. Key elements for the adult service

Within the adult CF care centre, the following key elements should be considered in the transition protocol.

- Keep up practical and theoretical skills concerning CF and teach new ones.
- Be attentive to changed responsibilities; less involvement of the parents and more responsibility from the adolescent for their own healthcare and therapy.
- Remain attentive for differences in working methods regarding flushing a port or changing a button or administering antibiotics intravenously.
- Keep addressing general healthcare concerns, including lifestyle issues (alcohol, drugs, nutrition and physical activity) as well as sexual health, fertility and reproduction, and guidance around capacity for ongoing education and employment.
- Keep supporting self-care.

Well before the actual transfer, a written referral report should be sent to the adult professional healthcare team. The main elements of this report should include case history, complications, hospital admissions, treatment, complications of treatment, current medication, operations and possible complications, and the psychosocial development of the patient.

6 Summary

Adolescents prefer technically competent healthcare providers who are honest and trustworthy and attend to their needs. As they gradually outgrow the paediatric environment they desire staff attitudes to become less childish and more age-appropriate, and welcome being treated as an equal partner in care. Healthcare professionals should enquire as to preferences and adjust their communication style accordingly.

Everyone involved has a role in this transition process. It is a challenge for all key players to constantly adjust to the ongoing developments and stay amenable to new changes; it is a personal transition process.

Not all child or adult healthcare services will have the necessary support systems recommended by existing guidelines.

However, the most important element is communication and the ability to listen to the patient, which is possible for everyone involved in this transition process.

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CHAPTER 4

Growth, damage and repair in the cystic fibrosis lung

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1 Normal lung growth

1.1. Prenatal development

Prenatal development of the complex systems of branching airways and gas-exchanging alveoli is conventionally divided into four phases [1].

- Embryonic (weeks 0–6): during this period of organogenesis, the lung appears as a ventral bud of the oesophagus. Lobar and segmental portions of columnar epithelium form as the developing airway.
- Pseudoglandular (weeks 6–16): subsegmental branching begins, driven by mesenchymal signals; all conducting airways and vascular structures are completely formed by the end of this period. Epithelial cellular differentiation begins proximally and spreads distally during this phase; mucous glands begin to appear and cartilage and smooth muscle are laid down in the airway walls.
- Canalicular (weeks 16–24): the characteristic feature of this phase is the development of the pulmonary parenchyma, which will differentiate into alveoli, and the parallel increase in

capillary structures. Epithelium transforms from a cuboidal appearance into flatter structures in close contact with these small vessels. In contrast to airway development, alveolar formation starts peripherally via endothelial-derived growth factors and signals and progresses proximally; recognisable type I and II pneumocytes are present by 20 weeks, although surfactant production does not begin until later in gestation. By the end of this period, the gas-exchanging alveolar structures are thin walled, providing an effective blood–gas exchange unit, and surfactant is beginning to be produced onto the epithelial surface.

- Saccular (weeks 24–term): this is the period during which alveoli ducts and sacs form, vessel numbers increase dramatically and the surface area of the lung increases significantly. Surfactant production increases to facilitate *ex utero* survival.

To date, most of the available evidence would suggest that these mechanisms are well preserved and normal in a foetus with cystic fibrosis (CF). Post-mortem specimens from several decades ago showed a degree of obstruction of submucosal glands or dilatation of the submucosal gland acini [2–4] but otherwise largely normal lung morphology; other studies have failed to find even this abnormality [5]. Intriguing studies of transient, intra-amniotic CF transmembrane conductance regulator (CFTR) gene therapy to mice with CF raised the hypothesis that CFTR was an important regulator of lung differentiation antenatally and permanently reversed the lethal gut phenotype [6], although these results were not recapitulated in a later study using similar techniques [7].

1.2. Postnatal development

Airway number and branching pattern is completely formed by term but the peripheral airways are short and the parenchyma contains numerous transitory ducts and saccules. The majority of alveolarisation, whereby these structures grow into numerous fully formed alveoli, is now known to occur postnatally. This was initially considered to be complete within the first 2 years of life although some work from the 1960s suggested that this might continue until around the age of 8 years [8]. Recently, Narayanan et al. used a hyperpolarised helium-based magnetic resonance imaging technique to study alveolarisation beyond this age [9]. Their study provides the first evidence that this process does not stop in early life, rather it continues through adolescence into early adulthood. These data make a focus on early lung disease in CF even more critical, if potentially irreversible damage is occurring during a time of, as yet incomplete lung growth.

2 Mechanisms of damage and insult in the CF airway

2.1. Infection and exacerbations of lung disease

The basis of CF airways pathophysiology is abnormal ion transport at the epithelial surface that leads to a low volume of periciliary liquid (PCL), dehydrated overlying

mucus and impaired mucociliary clearance (MCC) [10]. However, *in vivo,* lack of normal CFTR *per se* may be insufficient to reduce MCC. In a culture model exposed to phasic motion designed to mimic the *in vivo* lung, high levels of adenosine triphosphate (ATP) were present in the PCL, which corrected ion transport and thereby maintained PCL height and MCC [11]. This study implicated the requirement for a 'second hit', in this case in the form of a viral infection, which raised ATPases and disrupted this well-maintained balance. As it is impossible for any child to avoid such infections, it follows that MCC likely becomes abnormal at some stage between birth and full maturity of the lungs. The relative frequency of bacterial infections and the tenacious mucus produced by some young children would certainly support this notion.

By mid-childhood to adolescence, and despite modern, aggressive eradication strategies, most children with CF will have experienced lower-airway bacterial infections and in a significant proportion of them infection will have become chronic. The commonest organism is *Pseudomonas aeruginosa,* although chronic infection with *Staphylococcus aureus* and emerging Gram-negative pathogens such as *Stenotrophomonas maltophilia* and *Achromobacter Xylosoxidans* are not infrequent [12]. Whereas in early childhood atypical mycobacteria are rare, they become more common with increasing age, *Mycobacterium abscessus* being the organism with the greatest potential for adverse clinical consequences and the most challenging to treat. In part, the increasing prevalence of these organisms, along with fungal species such as *Aspergillus fumigatus*, seems to relate to the cumulative antibiotic burden these young patients have received, although other factors are also likely to be relevant. Increasing focus on molecular tools to study the entire 'microbiome', rather than just selective culture of organisms, has led to the realisation that there are numerous species present in the CF airway [13,14]; which of these are most relevant clinically and whether any of them could actually be beneficial remains to be determined.

With regard to *P. aeruginosa* in particular, much is now understood about how this bacterium adapts to the CF lung and establishes a chronic existence [15]. Alginate is synthesised as a result of spontaneous mutations in the *Muc A* gene, leading to a mucoid phenotype. A mechanism of quorum sensing, whereby soluble molecules such as acylhomoserine lactones diffuse freely across bacterial cell walls, their concentration thereby an indicator of bacterial density, triggers formation of biofilms within which bacteria are protected both from host defences and from antibiotics. Bacteria within biofilms are metabolically inactive, dividing very slowly, a state in which antibiotics, even if present in the surrounding environment, would be inefficient. On top of this chronic state of infection, patients experience 'exacerbations' of their symptoms (increased cough, sputum production, change in sputum consistency or colour, breathlessness, wheeze and less commonly, fever) with accompanying reduction in lung function [16]. The cause(s) of these exacerbations are incompletely understood. Viruses have been implicated [17] and may be more important in childhood than adulthood. Most of the evidence is against a new pathogen or massive

increase in bacterial load in the majority of cases. Possible alternative explanations include a subtle change in relative bacterial proportions within the microbiome, changes in the phenotype and secreted exoproducts of the resident bacteria, or even host-related switches in inflammatory responses. Whatever the underlying cause, such exacerbations are far from benign, being strongly implicated in the long-term decline in lung function [18] and indeed in approximately 25% of patients, leading to acute drops in lung function that fail to return to baseline [19,20].

2.2. Airway inflammation

CF inflammation is dominated by large numbers of neutrophils influxing the airway lumen. Although there is some evidence from xenograft models that mutations in *CFTR* may *per se* be pro-inflammatory [21], the majority of evidence from clinical studies [22] and more recently from the CF porcine model [23] points, in my opinion, to inflammation as a secondary phenomenon. The trigger may be viral, bacterial or fungal infections, or perhaps even inhalation of particulate matter in polluted air. The epithelium and resident macrophages produce a variety of pro-inflammatory mediators that are chemoattractant for neutrophils. Interestingly, even when corrected for the number of pathogens present, levels of neutrophils and related mediators are higher in the lower airway of patients with CF than in children with lower-airway bacterial infection without CF [24]. Several mechanisms have been proposed for this including increased ligation of pathogen-associated molecular patterns with their pattern-recognition receptors [25], higher levels of activation of calcium-dependent signalling [26] and overload of the endoplasmic reticulum with misprocessed CFTR [27].

For an inflammatory response to be most useful to the host, it needs to both initiate and halt appropriately. In the latter regard, the CF response appears deficient. IL-10, one of the major anti-inflammatory cytokines, is low in the CF airway [28], and levels of lipoxins, which are major mediators of inflammatory resolution, have also been shown to be low [29]. Several studies support the concept of delayed apoptosis in CF neutrophils [30]. These and other mechanisms may explain the persistent inflammation seen in the airways of apparently uninfected CF cases. Although interpreted by some as supporting the primary inflammation hypothesis, I would suggest that it is equally likely that these mechanisms have achieved bacterial killing but normal removal from the airway is delayed by impaired apoptosis or failure of anti-inflammatory switch mechanisms.

Once in the airway, the job of a neutrophil is to aid in the eradication of infecting organisms, a mechanism that works well in non-CF hosts with lower-airway infections. This mechanism may be fully effective in early CF and may successfully eradicate organisms, particularly when aided by prompt recognition of infection and targeted administration of antibiotics. However, at later stages of disease, and certainly by adolescence, the presence of chronic infection despite significant neutrophilia implies that host defence mechanisms are now incompletely effective. There are some data suggesting that,

as white blood cells express CFTR, their function is inherently abnormal in CF; work from murine models undergoing bone marrow transplants supports this (as do a number of clinical studies) [31]. In addition, once significant inflammation is present, neutrophil-derived proteases cleave receptors involved in bacterial clearance off the surface of neighbouring neutrophils, rendering them inactive [32]. Thus, at the early stages of disease, the host defence/inflammatory response may be reasonably well preserved, but at later stages, adolescence and beyond, it may be starting to suffer from its own over-exuberance. This is clinically significant because in addition to failing to perform its primary function, the inflammatory response leads to high local levels of enzymes such as neutrophil elastase, matrix metalloproteinases and cathepsins [33]. These impair the function of newly recruited inflammatory cells but are also likely to be the prime cause of the airway wall destruction that translates into radiologically evident bronchiectasis and leads, ultimately, to a shortened life expectancy.

2.3. Airway wall remodelling and destruction

The lungs from patients who have died of CF or which have been removed prior to transplantation (these days thankfully few of them adolescents) are characterised by massive bronchial dilatation, airway wall thickening, mucus gland obstruction and underlying fibrosis. The relatively slow time course over which this happens, transforming what was a healthy respiratory tract at birth, and the limited tools available, make studying this process difficult. It has been shown using bronchoscopic lavage and endobronchial biopsy that remodelling begins even in childhood, with thickening of the reticular basement membrane, increased quantity of smooth muscle and raised levels of glycosaminoglycans indicative of tissue breakdown [34,35]. Other groups have reported increased levels of such breakdown products, such as desmosine, in the urine [36]. Some of these processes seem to relate directly to lumenal inflammation, but others appear uncoupled, suggesting a parallel process; the fact that the inflammatory infiltrate in the airway wall itself is largely comprised of T-cells [37], including the newly-described Th17 phenotype [38], may relate to this and merits further exploration.

3 Normal mechanisms of lung repair

As the vast majority of CF pathology occurs in the airways rather than the alveolar region, this section focuses on the former with regard to repair mechanisms.

3.1. Cell migration

Following an insult to the airway that results in a breach of epithelial integrity, a combination of cell spreading and migration initiates the repair process. Cell migration is a complex process, which can be divided into five stages [39,40].

- Morphological polarisation: progenitor cells close to the wound edge acquire directionality towards the wound; this is important in the formation of cellular protrusions, lamellipodia and filopodia. It is likely triggered in part by the lack of

contact between cells or between cell and extracellular matrix at the wound edge, and in part by a wide array of secreted signalling molecules and growth factors.

- Membrane extension: polymerisation of actin results in cellular protrusions on the leading edge of the cell. The Rho/Rac family of signalling molecules is closely implicated in these processes.
- Formation of adhesions: the plasma membrane of these protrusions attaches firmly to the substratum via transient adhesion complexes comprising receptors, kinases and structural molecules.
- Traction and contractile forces: traction on these protrusions and myosin contraction allows the cell to move forward. The signalling molecules involved likely overlap with those involved in membrane extension by regulating phosphorylation of the myosin light chain.
- Breaking of adhesions: breaking of adhesions at the rear of the cell allows forward movement to be completed; this occurs via a number of proteolytic enzymes.

Epithelial cells can undergo these processes collectively, maintaining contact with their neighbours via junctional complexes and thereby moving as a sheet rather than as isolated cells. Spreading to cover the denuded area is thereby efficient and rapid.

3.2. Proliferation

Once cell migration has taken place (the first 12–24 hours), these cells proliferate and differentiate to restore structure and function of the airway; this process can take days or weeks, and may completely fail to resolve if the insult persists. Basal cells in the proximal airways and Clara cells more distally have the ability to differentiate into superficial ciliated epithelial cells and repopulate damaged or completely denuded areas [41]. There is some recent evidence suggesting that, contrary to all previous assumptions, ciliated epithelial cells themselves can act as progenitors, likely by de-differentiating into basal-like cells. Putative progenitor cells have also been indentified in proximal submucosal glands [42] and in neuroepithelial bodies at the bronchiolar level [43]. More distally in the alveolus, type II cells are progenitors of type I cells [44]. Migration to the lungs and subsequent differentiation into alveolar cells has been described of bone marrow stem cells [45], although it is less clear whether this happens to any great extent in the conducting airways, the major site of pathology in CF.

3.3. The role of the extracellular matrix and growth and repair factors

The extracellular matrix is critically important in cell migration, secreting molecules such as fibronectin, which are chemotactic for bronchial epithelial cells. Matrix metalloproteinase-9 accumulates at the leading edge of the migrating epithelium [46] and its activation by the extracellular matrix is essential in effective wound repair as is the molecule urokinase-type plasminogen activator [47]. A large number of soluble, epithelial-derived factors have also been implicated including epithelial growth factor, keratinocyte growth

factor, hepatocyte growth factor, the trefoil factor family of peptides, insulin-like growth factor, transforming growth factor β, cytokines and inflammatory mediators [39].

4 The impact of CFTR Dysfunction on lung repair

There is some evidence to suggest that CFTR is involved in respiratory epithelial wound repair and that these mechanisms may therefore be impaired in CF. Hajj et al. used an immunodeficient murine xenograft model to study repair processes in tracheal implants and observed significant differences between wild-type and CF epithelia; the latter proliferated at a greater rate, but then differentiated more slowly, leading to an abnormally deep, hyperplastic epithelium [48]. Data in this paper, along with others from this group, showed that the expression of pro-inflammatory cytokines and matrix metalloproteinases were also increased in the repairing CF airways. Somewhat in contrast, Trinh et al. reported normal rates of proliferation but reduced migration in CF epithelia; they identified this as being related to defects in signalling between epithelial growth factor and its receptor coupled with reduced potassium channel function [49]. Schiller et al. reported that CF cells or those treated with the chemical CFTR inhibitor, $CFTR_{inh}$-172, or suppression of *CFTR* expression with RNA silencing, demonstrated significantly slowed wound repair in a cell culture model [50]. This mechanism occurred via reduced protrusion of lamellipodia on the leading edge of the migrating cells and was linked to chloride ion transport. More recently, similar results have been reported by Trinh et al. with well-matched cell lines; wound repair of Phe508del CF cells could be significantly improved with the Vertex corrector agent, VRT-325 [51]. Taken together, these results do suggest a primary defect in airway epithelial repair in CF, which is likely further compounded by the inflammation present *in vivo*.

5 The effect of bacterial superinfection on the healing epithelium

Denuded epithelium may present an attractive niche for microorganisms; such areas will lack the normal mucociliary clearance mechanisms and be rich in molecules such as fibronectin to which many bacteria bind. In addition, repairing, migrating epithelial cells have been shown to have increased numbers of asialylated glycolipids, which are receptors for a number of bacteria such as *S. aureus* and *P. aeruginosa* [25]. This may in part explain the common finding of a positive bacterial culture after a severe viral infection and post-influenza bacterial pneumonias. Repair may be slowed by certain bacterial exoproducts such as proteases, which disrupt the tightly balanced adhesion/release mechanisms of wound repair.

6 Why is adolescence an issue?

Adolescence is a unique time in development: rapid increases in linear growth,

pubertal hormonal changes, psychological adjustment and potentially detrimental behavioural patterns are virtually universal. In the context of CF, the impact of the latter may be severe (e.g. smoking or non-adherence to treatment). In addition, there is an increasing risk of new complications such as diabetes mellitus, which further impact respiratory health.

6.1. Physiological issues

For several decades, CF clinicians and researchers have observed that adult females appear to be at a clinical disadvantage compared with their male counterparts in terms of prevalence of chronic infection, lung function and survival [52,53]. This is less clear or absent in childhood [54], although paediatricians know to fear the adolescent girl doing 'badly' as often this is the prelude to a precipitous decline. Recent data linking the female sex hormone, oestrogen, with patterns of bacterial growth and exacerbation may shed some light on the basis for this. Chotirmall et al. demonstrated that the mucoid switch in *P. aeruginosa* could be triggered by growth in a medium supplemented with oestrogens but not in a medium with testosterone [55]. Female patients were more likely than males to be chronically infected with a mucoid strain of the organism and were significantly more likely to present with an infective exacerbation during the follicular phase of their menstrual cycle, when levels of oestrogen were at their highest. This was not seen in females on the oral contraceptive pill, findings that may lead to a future clinical trial.

Diabetes mellitus is relatively rare in young children but by adulthood it affects about a third of individuals with CF [56]. Many of these new cases appear during adolescence for reasons that are unclear but seem to relate to the threshold having been reached in the number of beta cells, which provide sufficient insulin for adequate glycaemic control. Glucose is secreted onto the airway in the presence of hyperglycaemia and may be a substrate for bacterial growth [57], which may account for the increased prevalence of severe pneumonias and influenza in patients with diabetes. During the years before a clear-cut diabetic diagnosis is reached, patients commonly display not only poor growth and nutrition but also a greater decline in lung function. A diagnosis of CF-related diabetes, even when adequately treated, carries an adverse prognosis.

6.2. Behavioural and adherence issues

Normal adolescence is a time for a young person to develop independence, a process that includes challenging boundaries and making their own decisions. Young people who have gone through childhood with CF, with its combined psychological burdens (differences from peers, awareness of life-shortening nature) and practical burdens (treatments, clinic visits, hospital admissions), may be at increased risk of teenage rebellion. Unfortunately, the impact of 'normal' adolescent behaviours may be significantly greater for these individuals. Non-adherence to time-consuming therapies will adversely affect respiratory status, and smoking, perhaps even more so. In

teenage girls in particular, a desire to be thin [58] can in some cases lead to non-adherence with pancreatic enzyme preparations and ignoring dietary advice; as there is a close link between nutrition and lung health, this can have significant negative consequences.

Transition to adult services can be a stressful time for both the young person and their parents; carefully structured programmes likely reduce stress and increase satisfaction levels [59]; in many cases, being seen by an adult team and treated as an independent adult is often a stimulus for the adolescent to adopt a more responsible attitude to adherence.

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CHAPTER 5

Cystic fibrosis-associated liver disease in adolescence

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1 Introduction

Cystic fibrosis (CF) is a complex monogenic disease caused by mutations in both of the CF transmembrane conductance regulator (*CFTR*) alleles. It can present with a wide range of phenotypes due, in part, to the modifying effects of non-CFTR factors (genetic and/or environmental). The high morbidity and mortality associated with CF is predominantly due to pulmonary complications. However, advances in nutritional and pulmonary care have increased life expectancy and consequently brought to light the increasing importance of other organs affected by CF, including the liver. The adolescent period represents an important milestone in relation to whether an individual with CF is likely to develop clinically significant consequences of CF-associated liver disease (CFLD).

2 Spectrum of hepatobiliary disease in CF

CFLD is the third leading cause of death in CF, and accounts for 3–5% of overall mortality [1]. As with other organ systems

affected by CF (e.g. sinopulmonary tract), there is a wide spectrum of hepatobiliary manifestations, reflecting the complex interactions between *CFTR* mutations and other factors. However, the majority of hepatobiliary manifestations are not clinically significant.

The true prevalence of CFLD and its various manifestations remain unclear for several reasons: 1) there is no universally accepted definition for CFLD; 2) the majority of patients with CFLD are asymptomatic, including those with cirrhosis and portal hypertension; and 3) there is a lack of highly sensitive and specific non-invasive tests for CFLD.

Focal biliary cirrhosis, the hallmark hepatic lesion in CF, is characterised by progressive focal periportal fibrosis secondary to biliary obstruction (Fig. 1). In a minority of patients (5–7%), the clinically 'silent' focal biliary cirrhosis progresses to multi-lobular biliary cirrhosis [2,3]. Despite the presence of cirrhosis, liver failure is rare in the paediatric/adolescent population. However, hepatic steatosis (prevalence of 20–60%) commonly leads to clinical attention in the form of hepatomegaly, abnormal liver biochemistry and abnormal ultrasound [4].

Extrahepatic abnormalities of the biliary tree may also be present [4]. Up to 10% of patients develop gallstones, 5–20% develop a non-functioning microgallbladder, and 3–20% develop an obstructed distended gallbladder. Uncommonly, changes that resemble primary sclerosing cholangitis on imaging, such as beading and stricturing of bile ducts, have also been reported [5].

3 Definitions

Although a universally accepted definition for CFLD is lacking [3], it is important to distinguish between clinically and non-clinically significant CFLD. Thus, for the purposes of this discussion, clinically significant or severe CFLD is defined as cirrhosis with portal hypertension in the absence of another cause for liver disease.

4 Pathogenesis

The CFTR protein functions as a cyclic adenosine monophosphate-dependent chloride channel, bicarbonate channel, and as a modulator of other ion channels. The manifestations of CF generally arise from ductal and glandular obstruction due to an inability to hydrate macromolecules within ductal lumens. Within the hepatobiliary system, CFTR is expressed in intrahepatic and extrahepatic cholangiocytes (including the gallbladder) but not in hepatocytes [4]. CFTR plays a role in the cholangiocyte transport system. Hence, CFTR dysfunction causes retention of toxic bile acids, which leads to increased expression of fibrogenic and pro-inflammatory cytokines, hepatic stellate cell activation and eventual peribiliary fibrogenesis [6,7]. The ongoing inflammation may lead to recruitment of other inflammatory cells, which further generates cytokines that are responsible for hepatic stellate cell recruitment and activation. This vicious cycle of fibrogenesis, which leads to multi-lobular cirrhosis, only occurs in a minority of patients.

5 Genetics

Severe CFLD is associated with functionally severe *CFTR* mutations (e.g. Classes I–III). Thus, in the vast majority of cases, patients with severe CFLD are pancreatic insufficient [3]. To date, only the *SERPINA1* (α1-antitrypsin) Z allele has been convincingly demonstrated to be a genetic risk factor for developing severe CFLD; the odds ratio for association with severe CFLD is high at ~5 [3].

6 Diagnostics of severe CFLD

6.1. Clinical features

The diagnosis of severe CFLD can usually be established by the time a child reaches adolescence. In the largest cohort of carefully defined patients with severe CFLD [2,3], 90% of patients with CFLD were diagnosed by 20 years of age, with a mean age at diagnosis of 10–11 years. Less than 3% of patients were diagnosed after the age of 30 years. It is plausible that those diagnosed in adulthood had unrecognised severe CFLD during childhood/adolescence. Severe CFLD was more common in males with an earlier age of CFLD diagnosis (males 8.5 years, females 10.5 years; p=0.007).

Liver disease in individuals with CF is often subclinical, even in severe CFLD. A common clinical finding is hepatomegaly, which is often due to steatosis. The liver span should be measured by percussion as the liver edge may extend below the costal margin due to lung hyperinflation. Isolated hepatomegaly is common and occurs in 6–30% of CF cases, but is rarely associated with clinical consequences. Conversely, a hard or multi-lobulated liver suggests cirrhosis, and detection of splenomegaly suggests portal hypertension. Signs of chronic liver disease (palmar erythema or spider naevi), malnutrition and fat-soluble vitamin deficiency should be sought.

6.2. Blood tests

Abnormalities in liver biochemical tests, such as elevations in alanine aminotransferase, aspartate aminotransferase or gamma-glutamyl transferase are common. However, biochemical tests are poorly predictive of severe CLFD [3,8]. Indeed, up to 25% of CF cases have abnormal liver biochemistry in the absence of overt histological evidence of hepatobiliary fibrosis [2]. In addition, a complete blood count, coagulation profile and fat-soluble vitamin levels should be measured. Thrombocytopenia due to hypersplenism is seen in portal hypertension, and the international normalised ratio (INR) provides a measure of hepatic synthetic function. Elevations in INR may be due to vitamin K deficiency rather than hepatic dysfunction, and a trial of vitamin K supplementation is recommended.

6.3. Abdominal ultrasound

An abdominal ultrasound scan with Doppler measurements of the portal venous flow may be helpful for detecting severe CFLD. Specifically, findings of nodularity and splenomegaly are reliable markers of severe CFLD [9]. However, a normal ultrasound

does not exclude severe CFLD. Increased echogenicity is a non-specific feature common to both steatosis and fibrosis. Furthermore, ultrasound has poor predictivity for the future development of severe CFLD [8].

6.4. Liver biopsy

Liver biopsy remains the gold standard in the diagnosis of established cirrhosis. Furthermore, liver fibrosis on biopsy has been reported, retrospectively, to be the only modality that predicts the development of severe CFLD [8]. However, due to the focal and patchy distribution of early CFLD, the severity of disease may be underestimated in a liver biopsy. Indeed, a recent study reported that liver fibrosis would have been missed in 22.5% of cases if single- rather than dual-pass biopsies had been performed [8]. Prospective studies are needed to validate its importance as a predictive marker and justify its role in clinical practice in view of the associated risks. Liver biopsy usually requires general anaesthesia and is associated with rare but serious complications including bleeding, biliary peritonitis and visceral perforation (~2%) [10].

6.5. Non-invasive markers of hepatic fibrosis

In light of the limitations of the aforementioned tests, there is great interest in alternative non-invasive tools to detect fibrosis. Transient elastography has been proposed for use in the detection of liver fibrosis in a variety of chronic liver diseases. However, transient elastography has not been validated in the paediatric and CF population, and there are no paediatric reference ranges.

6.6. Exclusion of other liver diseases

In the presence of abnormal liver biochemistry and/or other abnormalities, CFLD should not be simply assumed to be the underlying cause. Other conditions should be considered as they may be associated with significant morbidity and mortality if left untreated (Table 1).

7 Management of severe CFLD

7.1. General principles

There is currently no specific therapy for the treatment or prevention of severe CFLD. The management of CFLD requires a multidisciplinary team consisting of a gastroenterologist, dietician/nutritionist, and surgeon experienced in hepatobiliary surgery. The general principles of management of CFLD are similar to those for other chronic liver diseases. Irrespective of whether severe CFLD is present, follow-up is important and should include careful abdominal examination at each clinic visit and annual screening using blood tests and imaging. An annual review by a gastroenterologist is highly recommended (Fig. 2). Follow-up by a non-paediatric gastroenterologist following transition to adult care is mandatory, particularly in patients with established severe CFLD.

8 Prophylactic therapy

8.1. General measures

As there is no specific preventative therapy

for severe CFLD, general measures to prevent non-CF-related liver injury should be taken. Avoidance of hepatotoxic insults (e.g. drugs and alcohol in adolescence) and vaccination against hepatitis A, hepatitis B and varicella zoster viruses should be considered. Identification of other co-factors (e.g. obesity) is also important.

8.2. Treatment with ursodeoxycholic acid

The role of ursodeoxycholic acid (UDCA) in the treatment and prevention of severe CFLD is controversial [11]. Treatment with UDCA has been associated with liver biochemical improvement in CFLD [12–14]. However, liver biochemistry is a poor marker of severity and progression of liver disease, and progression can occur in the presence of normal liver biochemical markers [3,8,15–17]. A systematic review identified 10 placebo-controlled trials assessing UDCA for at least 3 months and included three studies for detailed assessment (n=118; age range 4–28 years) [18]. Although biochemical improvements were noted, clinically relevant outcomes of portal hypertension, liver failure, liver transplantation or survival were not reported in any of these studies. Overall, the review concluded that there were insufficient data to support the use of UDCA in CFLD.

Outside of this systematic review, one study reported repeat liver biopsy findings with UDCA treatment [17]. In this small, uncontrolled 2-year study, UDCA resulted in biochemical and histological improvements in the seven patients who underwent repeat liver biopsies. Inflammatory changes and bile ductular proliferation both improved. The clinical significance of these findings is unclear in view of the study limitations.

Most studies that have assessed UDCA have considered its role in the treatment of established severe CFLD. A potentially more beneficial objective is the prevention of severe CFLD. One Italian study assessed the preventative role of UDCA in CFLD [19]. This non-randomised retrospective study included 26 children with CF and a history of meconium ileus. One subgroup (n=14) were started on UDCA prior to their second birthday in the absence of signs of CFLD (early group). A second subgroup (n=12) received UDCA only when signs of CFLD were noted on follow-up appointments. Over the 9-year period of observation, none of the early group developed CFLD. In contrast, 33% (4/12) of the children in the second group developed features of CFLD by the end of the review period. A large, prospective and randomised controlled study using a more stringent definition of severe CFLD is needed to confirm these preliminary findings.

In addition, previous recommendations for the use of UDCA were made on the basis of lack of harm and potential benefit in CFLD, due to the reported benefits of UDCA in other liver diseases. However, the role of UDCA therapy in conditions for which the treatment was previously recommended, such as primary sclerosing cholangitis and primary biliary cirrhosis, has recently been called into question [20,21]. Of particular concern are the outcomes from a randomised double-blind placebo-controlled trial of high-dose UDCA (28–30 mg/kg/day) in primary sclerosing

cholangitis [20]. This study was prematurely terminated because of an increased risk of death and liver transplantation in the UDCA treatment arm compared with the placebo arm, despite improvement in liver biochemical abnormalities with UDCA. In short, there is currently no evidence to support the use of UDCA in the treatment or prevention of severe CFLD. Well-conducted studies are much needed.

There are other potential roles for UDCA in CFLD. UDCA is helpful for pruritus although various other agents including antihistamines, cholestyramine, rifampicin and naltrexone may also be helpful. UDCA has been reported to be unhelpful for cholelithiasis in CF [22].

9 Nutritional therapy

Optimisation of nutrition and hence of growth and pulmonary status, is a key aspect of the overall management of CF. In severe CFLD, there should be emphasis on fat-soluble vitamins and consideration of medium-chain triglyceride supplementation. Restriction of protein and sodium intake is unnecessary in compensated severe CFLD.

10 Portal hypertension

In the majority of cases, the morbidity and mortality from severe CFLD is related to the complications arising from portal hypertension. Oesophageal varices and portal hypertensive gastropathy may be asymptomatic or present with life-threatening gastrointestinal bleeding. In the presence of significant splenomegaly, avoidance of contact sports is recommended.

10.1. Endoscopic variceal ligation

There are currently no clear evidence-based recommendations to prevent variceal bleeding in CF. Treatment options include β-blockers, endoscopic variceal ligation and surgery. There are also special considerations in patients with CF. The use of β-blockers is a relative contraindication in CF due to the risk of bronchial reactivity. Repeated general anaesthesia for endoscopy is associated with a risk of pulmonary complications.

The optimal timing of endoscopic variceal ligation is unclear – either before or after first bleed (i.e. primary versus secondary). Endoscopic assessment of oesophageal varices should be considered when clinical, haematological (e.g. thrombocytopenia) or radiological features of portal hypertension are present. In a recent study, platelet count $<115 \times 10^9$/L was associated with high negative and positive predictivity for identifying varices endoscopically [23]. Regular surveillance (every 6–12 months) is reasonable thereafter if oesophageal varices are present.

10.2. Surgery/shunt

The use of transjugular intrahepatic portosystemic shunt or porto-systemic shunts has been reported in small case series of children with severe CFLD for treatment of portal hypertension and/or as a bridge to liver transplantation [24,25]. Partial or

total splenectomy can be considered as additional options for the management of medically unstable portal hypertension [26]. Splenic embolisation has also been reported as an alternative [27].

10.3. Liver transplantation

In the situation of liver failure, intractable variceal bleeding or porto-pulmonary syndrome, liver transplantation is indicated [28]. Decompensated liver failure (ascites, jaundice, coagulopathy unresponsive to vitamin K, hepato-pulmonary syndrome or encephalopathy) is uncommon but nonetheless associated with poor prognosis.

In a questionnaire-based survey of European paediatric CF centres [29], the main indications for transplantation in 57 cases were liver failure (69%), hypersplenism (57%), poor nutrition (47%) and oesophageal bleeding (27%). Overall 89% of the group were noted to have varices pre-transplant and 42% had suffered at least one bleed.

The outcomes of 148 children with CFLD from the United Network for Organ Sharing were recently reported [30]. These children were <14 years old (mean age 11.7 years) and almost two thirds were male. The majority (n=143) of this group underwent isolated liver transplantation, with just five children having combined lung–liver transplantation. The 5-year survival rate for these children was 85.8%. Although this survival rate was less than that following transplantation for other indications, there was a significant advantage for the transplant children with CFLD compared with a control group of children with CFLD who remained on the waiting list (i.e. without transplant). In addition, the 5-year survival rate for this group of children with CFLD was greater than in a smaller group of adults (72.7%). Transplantation in combination with other organs, such as liver–lung, liver–heart–lung, liver–pancreas and liver–small bowel has been reported with promising survival data to date [31,32].

The optimal timing of transplantation for CFLD remains unclear, but improving long-term outcomes have strengthened the rationale. A scoring system was proposed to support the timing for transplantation but the tool had a particular bias towards variceal bleeding [33]. Given improvements in endoscopic management of varices and changes in transplantation management, this scoring system requires updating. Nonetheless, it has become clear that earlier transplantation when indicated (liver failure and/or intractable portal hypertension) leads to better outcomes compared with delayed transplantation [30]. Mortality is also strongly dependent upon respiratory function [29] and nutrition. However, improvement in nutrition is evident post-transplantation, whereas benefit in respiratory function is variable [29,34,35].

11 Future research

Greater insights into underlying molecular mechanisms are required. The complex interactions between modifying genetic and environmental factors that influence CFLD manifestations and severity remain to be determined. Although there is no specific therapy available for the treatment

or prevention of severe CFLD, there are exciting advances in therapies aimed at improving CFTR [36].

12 Conclusions

The diagnosis of severe CFLD can be made, in the majority of cases, before adulthood. The absence of severe CFLD by the end of adolescence makes it very unlikely that an individual will develop clinically significant complications of CFLD in adulthood. Regular screening and monitoring are important. The management of severe CFLD requires a multidisciplinary approach, with particular focus on prophylactic measures, nutritional therapy and management of portal hypertension. Liver transplantation in carefully selected patients (hepatocellular dysfunction and/or intractable complications of portal hypertension) is associated with satisfactory and improving outcomes. We hope greater understanding in the pathogenesis of severe CFLD will translate into effective preventative and therapeutic measures.

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Table 1
Liver diseases other than cystic fibrosis-associated liver diseases in adolescents.

Condition	Initial investigations
Wilson disease	Serum copper and ceruloplasmin
Autoimmune hepatitis	IgG and anti-nuclear, anti-smooth muscle and anti-liver kidney microsomal antibodies
Coeliac disease	IgA and anti-tissue transglutaminase, anti-endomysial and anti-gliadin antibodies
Viral hepatitis	Serology for hepatitis-A, -B and -C viruses, cytomegalovirus, Epstein–Barr virus (testing for other viruses depends on clinical context)

Figure 1

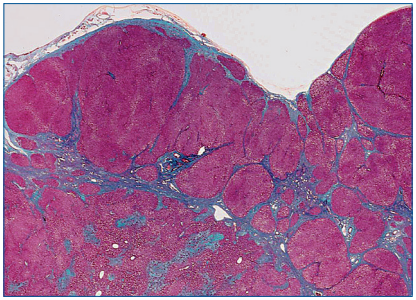

Fig. 1A

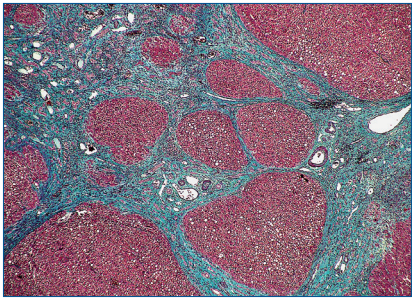

Fig. 1B

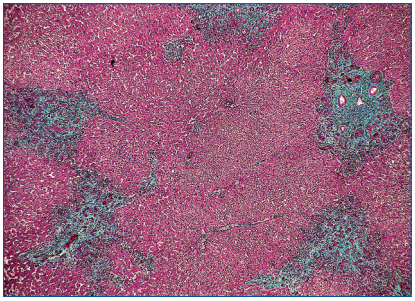

Fig. 1C

Fig. 1. Liver explant of a 13-year-old male with cystic fibrosis. (Fig. 1A) Low-power overview showing macronodular liver capsule. Underlying liver shows variation in stage of fibrosis from periportal fibrosis to complete cirrhosis. (Fig. 1B) Closer view (original magnification x100) showing focal biliary cirrhosis, with fibrous septae linking portal areas, and surrounding regenerative nodules of hepatocytes. Expanded portal areas show bile ductular proliferation secondary to biliary obstruction. (Fig. 1C) Closer view (original magnification x100) showing an earlier stage of fibrosis, not yet cirrhotic. There is fibrous portal expansion, with periportal fibrous septa, and occasional portal–portal bridges, without regenerative nodules. Masson trichrome stain: red = hepatocytes, green = collagen. Courtesy of Dr Amanda Charlton, Children's Hospital at Westmead (Sydney, Australia).

Figure 2

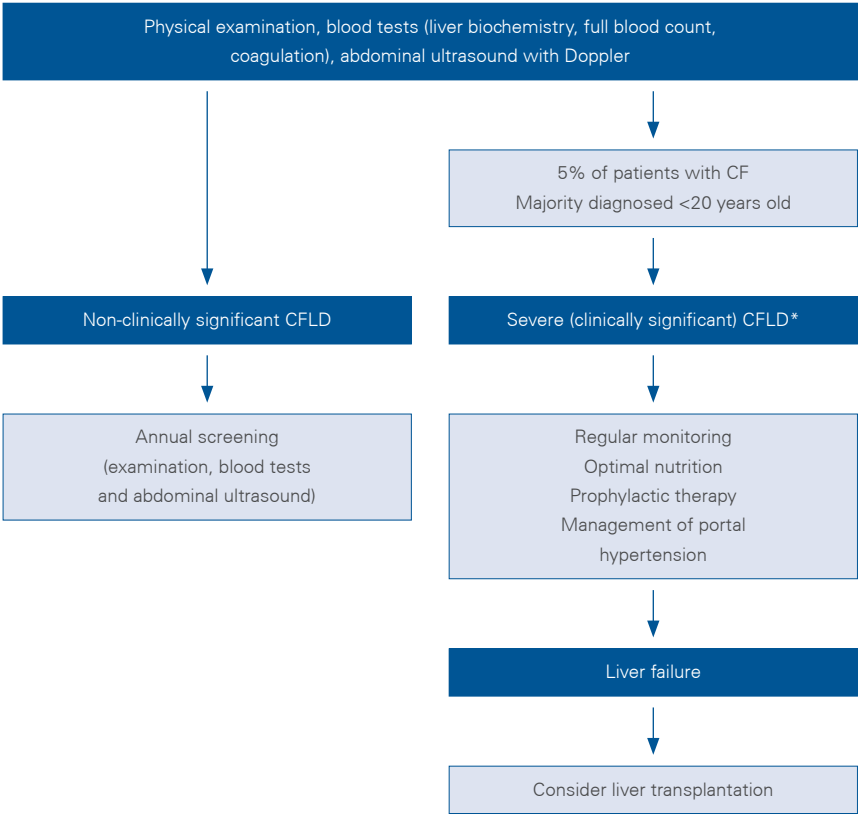

Fig. 2. Overview of the management of cystic fibrosis-associated liver disease (CFLD). * Cirrhosis and portal hypertension

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CHAPTER 6

Treatment adherence in adolescents with cystic fibrosis

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1 Introduction

The management of cystic fibrosis (CF) is aimed at reducing symptoms of the disease, improving nutrition and growth and maintaining lung function. Considerable progress has been made in the development of medications to treat the symptoms of CF, including airway clearance, inhaled antibiotics, oral medications and increased calorie intake. Recently, the first disease-modifying drug, VX770, was approved and is available for a small subgroup of the population; it is taken once daily [1]. Despite major advances in the diagnosis and treatment of CF, management of this disease continues to be arduous and disruptive, requiring 2–4 hours per day depending on disease severity [2]. The complexity of this regimen makes adherence particularly challenging.

For younger children, parents are primarily responsible for organising and assisting with treatments. In adolescence, however, there is a shift toward greater independence and autonomy. Although adolescence is generally a turbulent period, teens with CF face additional challenges related to worsening health, more frequent hospitalisation and greater responsibility for

managing their disease. This often leads to worse adherence [3,4]. In this chapter, the critical aspects of adherence for teens with CF are reviewed including rates, predictors and consequences. Approaches to measuring adherence are also discussed together with new intervention strategies for this age group.

2 Rates of adherence

Adherence is defined as the degree to which a patient actively participates in his/her prescribed treatment regimen [5]. Rates of adherence for adolescents with chronic illnesses vary widely depending on the disease, complexity of the regimen and method of assessment [6,7]. Across illnesses and age groups, studies have suggested that, on average, rates of adherence are below 50% [8,9]. Across diseases, previous studies have indicated that adherence is better for simpler treatments, including small pills administered once daily, compared with more complex treatments such as dietary modifications, airway clearance, glucose monitoring and nebulised medications [10,11].

Similar rates of adherence have been found in CF. In a European study of adults with CF, objective data derived from pharmacy refill histories and electronic monitors showed that adherence ranged from 67% for oral antibiotics to 31–53% for inhaled antibiotics, 53–79% for mucolytic agents and 41–72% for hypertonic saline [12]. Comparable rates of adherence (median rate of 36%) were found in adults in the UK using the I-Neb delivery system (Philips Respironics, Chichester, UK) [13]. Using pharmacy refill data, Eakin et al. reported a composite adherence rate of 62% for key pulmonary medications (i.e. azithromycin, dornase alfa, inhaled tobramycin and hypertonic saline) in individuals aged from 6 years through adulthood [14]. McNamara et al. reported that in children who were colonised with *Pseudomonas aeruginosa*, monthly adherence to nebulised antibiotics ranged from 60% to 70% over 1 year [15]. In one of the few studies examining adolescents' adherence to multiple treatments, Modi et al. reported adherence rates ranging from 22% to 71% on objective measures [16].

3 Predictors of adherence

The reasons for poor adherence are multifaceted, including patient and family factors, disease variables and complexity of the treatment regimen (Table 1) [7,8]. Factors associated with poor patient adherence include increasing age, lower socioeconomic status, patient and caregiver mental health issues, family conflict and denial of illness [10,17,18]. In children, for example, depressive symptoms were associated with lower rates of adherence to airway clearance after controlling for demographic variables [19]. Symptoms of depression are also common among caregivers and have been associated with worse adherence to pancreatic enzymes, resulting in a failure to gain weight at the next clinic visit [20]. In contrast, symptoms of anxiety tend to have

a curvilinear association with adherence, with both high and low levels of anxiety exerting a negative effect. Accordingly, the most adherent patients show moderate levels of anxiety, as opposed to anxiety that is minimal or severe [21]. Conversely, there are several factors that appear to positively affect adherence, such as family cohesion, social support, perception of control over one's life, and physician empathy [22,23].

4 Consequences of poor adherence

Poor adherence has several consequences for both the individual and the healthcare system. Low rates of adherence clearly affect adolescent health outcomes, leading to increased morbidity, more frequent hospitalisation, and earlier mortality [3]. As patients spend more time in the hospital, they spend less time at school or with friends and family, which directly reduces their health-related quality of life [24,25].

The consequences of poor adherence are not restricted to the adolescent's health but also include higher healthcare costs, clinical decision making and interpretation of clinical trials of new medications [26,27]. Several studies have shown that poor adherence across chronic conditions is associated with higher healthcare costs and wasted resources [26,28,29]. Recent estimates suggest that lack of adherence costs the US healthcare system approximately $300 billion each year, including $100 billion for increased hospital admissions [30]. In patients with CF, Briesacher et al. found that better adherence to tobramycin inhaled solution was associated with fewer pulmonary exacerbations and a decreased risk of hospitalisation, thus leading to lower healthcare costs [31]. For patients who appear to not respond to current therapies but who are actually non-adherent, physicians may increase the dose or prescribe new medications. This increases medical costs and can lead to overdosing. Finally, poor adherence can potentially bias the results of clinical trials by either underestimating or overestimating the drug's effectiveness [28]. Most clinical trials assess patient adherence using indirect methods, such as vial and canister counts, which can be easily manipulated. Alternative methods include using electronic monitors, drug concentration levels, or daily phone diaries [32].

5 Measuring adherence

Assessment of adherence is extremely complex, given the number of treatments prescribed for CF and the various methods of treatment delivery (e.g. pills, nebulisers, Acapella [Smith's Medical, St Paul, Minnesota, USA]). Measures of adherence include self-report, daily phone diaries, electronic monitors and prescription refill histories, each with its own strengths and weaknesses. Self-report measures ask patients directly about their adherence behaviours. Unfortunately, reliance on self-report consistently produces inflated estimates relative to other measures, largely due to social desirability and recall bias [16]. Patients often want to 'please' their medical team and also have difficulty remembering

how often they do their treatments [13]. Although self-reported adherence is less accurate than more objective measures, questionnaires such as the Treatment Adherence Questionnaire (TAQ-CF) are useful tools to stimulate self-reflection and conversation [6]. After completion, adolescents have commented that they were unaware of how poor their adherence was until they had completed the form.

Diary measures, a different type of self-report, tend to be less vulnerable to social desirability and recall bias [16]. For example, the Daily Phone Diary (DPD) utilises a cued recall procedure to gather information about patients' activities over the previous 24 hours [33]. The DPD elicits the type of activity, duration, the presence of others and a mood rating for activities lasting 5 minutes or longer. Thus, the DPD is an unobtrusive measure of adherence, which yields more accurate information. Another strength of this approach is its short recall window (past 24 hours), which reduces the potential for forgetting. However, the DPD is time-consuming to administer, yields complex data for analysis and may be limited in its use for younger children [16]. The DPD has been judged a 'well-established' measure in several reviews of evidence-based assessment [32].

Electronic monitoring offers more objective and less time-intensive methods for measuring adherence. Currently these devices are available for bottled medications (medication event monitoring system [MEMS] caps), metered-dose inhalers (MDIs), and nebulisers, and have demonstrated large discrepancies between self-reported adherence, provider estimates and actual use, highlighting their accuracy and utility. In one study, adolescents reported 99% adherence to aerosolised medications, whereas electronic monitors revealed adherence rates of 53% [16]. Newer technologies, such as the I-Neb adaptive aerosol delivery system (Philips Respironics), store the date, time, duration and dose of each inhaled medication. In a study of adult patients with CF in the UK, I-Neb data over 3 months indicated a median adherence rate of 36% (range 7–109%) compared with 80% reported by patients and 50–60% by the multidisciplinary team members [13]. In all cases, healthcare providers overestimated their patients' adherence. Thus, providers do not have accurate perceptions of adherence and are often unaware of the challenges their patients face.

As technology is refined, electronic monitors may become the 'gold standard' for measuring adherence [7,16,32], particularly if they provide useful, easily accessible information that can facilitate patient–provider communication. However, it should be noted that electronic monitors are expensive, often malfunction and are not available for all CF treatments (e.g. boosting calories, airway clearance) [16,32].

Finally, prescription refill histories are another useful way to measure adherence. Information on medication type, dose and date of refill can be obtained from pharmacy databases and compared with the patient's prescribed treatment plan to calculate a medication possession ratio (MPR) [14]. The MPR captures the amount of medication possessed by the patient relative to the amount he/she was prescribed in a specific

time frame. However, it does not capture whether the medication was taken, nor does it account for medication dispensed in clinic or inpatient settings [16]. Although an indirect measure, MPRs have been shown to correlate with other measures of adherence and to predict pulmonary exacerbations in patients with CF aged from 6 years and throughout adulthood [14]. MPRs are also useful for identifying patients who fail to refill their prescriptions [16].

Adherence to nutritional recommendations, airway clearance and exercise regimens is more difficult to assess than other CF treatments. Accelerometers may be used to measure daily activity. Additionally, daily phone diaries offer the advantage of unobtrusively measuring exercise and snack adherence.

In summary, each method of measurement has its own strengths and limitations, indicating that a multi-method approach is necessary to increase precision. Self-report measures are useful to stimulate discussion and self-reflection, whereas daily phone diaries, electronic monitoring and prescription refill histories provide more accurate information. Importantly, measuring rates of adherence does not capture the barriers that contribute to poor adherence, such as forgetting, time management and side-effects.

6 Barriers to adherence

At the individual level, each patient and family has a unique set of barriers that make it more difficult to adhere to the CF treatment regimen. Common patient barriers include time management, forgetting and lack of knowledge of disease management. An Adherence Barriers Questionnaire (ABQ) has been developed for adolescents and young adults with CF that can be used to identify the key barriers for each component of the regimen. For example, parents and teens with CF have gaps in their understanding of CF care – particularly nutritional recommendations, such as boosting calories [10]. In a recent study, 92% of parents were unaware that fat has more calories than carbohydrates, and these gaps negatively affected both the parents' and patients' ability to follow nutritional recommendations.

Assessment of adolescents' Knowledge of Disease Management (KDM) [34] provides a snapshot of what they understand about the CF regimen, allowing providers to identify and remediate gaps in knowledge. For example, an adolescent who believes enzymes should be taken after meals is unintentionally taking his/her enzymes at the wrong time, leading to difficulties with weight gain and growth. The KDM measure has been developed for children, adolescents and parents to assess knowledge in four domains: Lung Health, Nutrition, Treatment, and General Health. Scores are generated to create individual profiles of each respondent's strengths and weaknesses across these scales (Fig. 1). These scores can then be given to various members of the CF team to correct misconceptions and misinformation. The KDM demonstrates good convergent validity with physical health indicators and observed skills [35,36] and is currently being translated into Hebrew, Portuguese (Brazil), German and Dutch.

With respect to treatment characteristics, adolescents may face barriers due to side-effects, such as bad taste (e.g. tobramycin), coughing fits and gagging (e.g. hypertonic saline) or chest pain (e.g. vest). In addition, factors related to the healthcare system, such as the high cost of drugs and equipment, and limited access to medical care, make adherence challenging and should be discussed openly with patients.

Whether a patient's barriers arise from individual, treatment or healthcare system factors, collaborative patient–provider communication is critical to prevent and address poor adherence. For example, one study found that physicians and parents disagreed on 17% of the child's prescribed treatments [10]. This discrepancy may arise from inadequate assessment of the patients' understanding of his/her treatments or because of poor recall of medical recommendations. A written Prescribed Treatment Plan (PTP) [10,32], which specifies frequency, dose and duration is a useful tool for ensuring that patients understand what has been prescribed, and may ultimately improve adherence. Furthermore, providers should openly discuss patients' lifestyles and schedules, cost of treatments, and other barriers that may hinder adherence before prescribing or changing the treatment plan. The KDM and PTP are available free of charge from http://www.psy.miami.edu/ksa_measures/.

7 Adherence interventions

Currently, interventions fall into three major types: 1) broad-based psycho-educational; 2) healthcare system changes that improve efficiency (quality improvement) and communication; and 3) behavioural approaches that focus on increasing motivation and changing patient behaviour (problem solving, behavioural contracting) [7,37]. Successful interventions maximise the strengths of these three approaches by integrating them in a tailored interactive way.

Psycho-educational interventions typically provide verbal, written or computer-based information about symptoms, the importance of adherence and skills training (correct use of a metered dose inhaler). However, numerous studies in the chronic illness literature indicate that education alone is not sufficient to create behaviour change [27,37,38]. In fact, adolescents with the poorest adherence often know the most about their treatments; they have been lectured enough times to know exactly what they should be doing! Educational approaches are especially limited when they are not tailored to the individual's knowledge deficits and fail to address the patient's specific barriers [10].

Organisational interventions aim to create a consumer-friendly environment by altering how treatments are prescribed, monitored and modified. For example, a CF centre may strive to simplify regimens, provide written treatment plans and monitor patient adherence more closely. The PTP described above, minimises misunderstandings between patient and physician and creates a physical record of the treatment plan that families can refer to on an ongoing basis. In terms of medication monitoring, at the Schneider Children's Medical Center of Israel, a pulmonologist

is able to access pharmacy refill histories on patients with CF immediately to identify problems with adherence. These strategies promote discussion between patients and providers, thereby enhancing collaboration and clinical decision making. In fact, a recent study in children with CF found that electronic monitoring of nebulised medications facilitated patient–provider discussions about the causes of poor adherence, prompting individualised alterations to the regimen [15].

Finally, behavioural approaches utilise techniques to promote behaviour change, such as reward systems, problem solving and contracting. Little evidence exists to support the benefits of behaviour modification strategies such as token economies and reinforcement for complex treatment regimens [39]. Such strategies are overly simplistic, fail to take into account the specific underlying barriers contributing to poor adherence (e.g. cannot find the time, unwanted side-effects) and produce short-lived effects that are difficult to maintain [40,41].

Alternatively, there is a great deal of evidence to support the efficacy of brief behavioural interventions, such as problem solving [37,42]. This approach engages the adolescent and parent in a session to identify barriers to adherence and then brainstorm possible solutions [11,43]. This interactive approach increases adolescent motivation and acknowledges that teens and families are the true experts in managing their disease. For example, an adolescent who forgets to take enzymes regularly needs a different solution from an adolescent who is embarrassed to take enzymes in front of others.

Motivational interviewing (MI) is another behavioural strategy that enhances motivation and derives the goals directly from the patient. This intervention focuses on eliciting the desire to change from the patient rather than the provider, emphasising a 'bottom up' rather than a 'top down' approach [44]. Thus, change is most likely to occur and be maintained when the desire to change is expressed by the patient. MI is useful in addressing resistance, by accepting patient ambivalence and collaborating to set goals that are most valued by the patient. Accordingly, MI may be particularly effective with adolescents, who are striving for independence and autonomy [3]. Although a comprehensive description of MI is beyond the scope of this chapter, Duff and Latchford provide an excellent overview of MI and its applications to CF. A manual of MI techniques is available online as a free download (http://www.cfww.org/docs/pub/edition12/12_motivational.pdf) [44].

7.1. Technology-based interventions

Technology offers unique opportunities to disseminate a wide variety of interventions, including those described above. For example, text messaging is an affordable, adolescent-friendly method for sending information and treatment reminders to increase adherence [45]. A more comprehensive approach to improving adherence is offered by internet-based health interventions, which incorporate education and problem solving to enhance self-management [46]. Adolescents, who typically have extensive experience with computers, find such programs appealing and easy to use.

A randomised controlled trial is currently underway to examine how a CF-specific social networking site for teens affects knowledge, adherence, social support and health-related quality of life [47]. The website (www.cffone.com), includes live chat, educational resources and customised calendars for treatment reminders. The site is accessed through a web-enabled cell phone and is designed to be multi-modal, interactive and integrated with an individual's habitual cell phone use.

7.2. A clinic-based adherence intervention model

Another potentially powerful way to address adherence is to integrate it into standard medical care. Patients with CF are seen on a regular basis by their healthcare teams, typically quarterly, and thus, an effective intervention could capitalise on the interactions that are occurring regularly and on the relationships that have been established. Recently, Quittner et al. have developed a clinic-based intervention to improve adherence – I Change Adherence And Raise Expectations (iCARE) – which is delivered by members of the multidisciplinary CF team using the model described below [34]. iCARE builds on the strengths of the educational, organisational and behavioural approaches to adherence that are evidence based.

7.3. Interactive Model of Personalized And Collaborative Treatment-Adherence (IMPACT-Adherence)

This model consists of five components: 1) assessment and remediation of knowledge of disease management (e.g. which foods have the most calories); 2) *in vivo* evaluation of patients' treatment skills (e.g. "show me how you use your Acapella"); 3) provision of the PTP; 4) assessment of individual barriers (i.e. ABQ); and 5) a brief, behavioural, problem-solving session resolving their barriers (Fig. 2). The first two components are completed annually, generating scores that can be used to remediate gaps in knowledge and skills deficits across the year by different members of the multidisciplinary team. The remaining three components are completed at each clinic visit. Initially, the patient completes the ABQ to facilitate the problem-solving session. Next, the adolescent, parent and healthcare provider collaborate in a 10–15-minute problem-solving session to identify barriers to adherence (e.g. forgetting, busy schedule, side-effects), brainstorm solutions and vote on a solution that everyone thinks is 'worth trying'. The final step is to write the agreed solution on the PTP, which documents the current treatment regimen, and for all three participants to sign this as a behavioural contract.

This intervention model differs in several substantive ways from adherence programmes tested in the past. First, it is a patient-centered approach, allowing the adolescent or young adult to choose the treatment that he/she wants to work on, which may not be the treatment chosen by the CF team. The adolescent also leads the problem-solving session, writing the solutions that are generated by the triad (adolescent, parent, provider), which ensures his/her engagement and attention during the session. The triad votes on each solution (+ or –) and only a solution that gets plus votes from all is considered; the adolescent

then chooses which of these solutions he/she wants to try. This process enhances the adolescent's perception of control. Second, this intervention is personalised in two ways. The knowledge and skills measures yield a profile of that individual teen's strengths and weaknesses in these domains, which guides the teaching and remediation performed by the providers at each clinic visit. In addition, the barrier and solutions reflect the teen's specific values and lifestyle (e.g. making time for music lessons). Finally, this intervention is collaborative. It involves the patient, family and provider in a 'team' effort to improve adherence, and models positive communication as solutions are discussed.

8 Conclusions

Despite groundbreaking advances in the development of effective medications for CF [1], adherence remains the most significant challenge for our patients. The CF regimen stands out as the most complex and time-intensive regimen relative to other chronic conditions, with rates of adherence at or below 50%. Poor adherence significantly limits treatment efficacy, leading to substantial morbidity, earlier mortality and higher healthcare costs. The most promising avenue for treating adherence is to integrate personalised interventions into the clinics where our patients have received their care, have developed relationships with providers, and where they feel comfortable generating collaborative solutions to overcome this problem.

Table 1
Factors influencing medication adherence in adolescents.

Patient/family factors	Disease-related factors	Regimen-oriented factors
Demographics ■ Age ■ Sex ■ Socioeconomic status ■ Race ■ Knowledge **Developmental** ■ Transition to independence ■ Cognitive limitations ■ Inadequate supervision **Psychiatric co-morbidity** ■ Depression and anxiety ■ Attention deficit hyperactivity disorder ■ Patient and family adjustment and coping ■ Parent–child conflict	■ Disease progression ■ Genotype-phenotype relationships ■ Course of treatment ■ Disease severity ■ Daily symptoms	■ Regimen complexity ■ Patient treatment burden ■ Under- or overdosing ■ Inadequate follow-up with CF team ■ Perceived efficacy ■ Treatment side-effects ■ Duration and frequency of device use

Figure 1

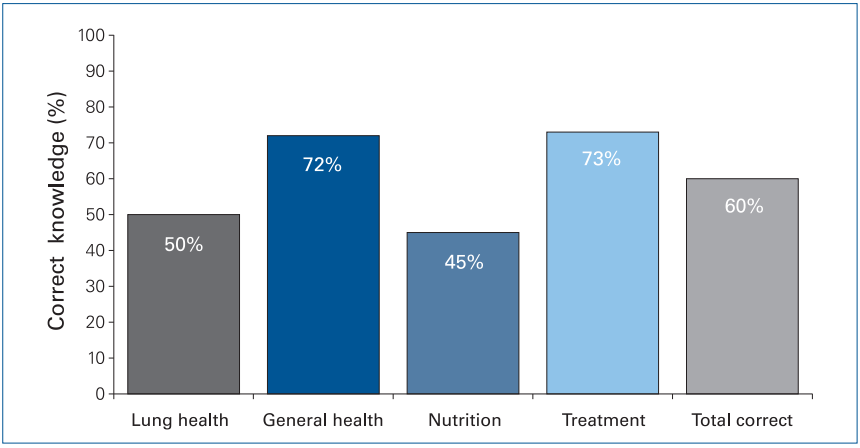

Fig. 1 Sample individual profile for an adolescent who completed the Knowledge of Disease Management (KDM) measure.

Figure 2

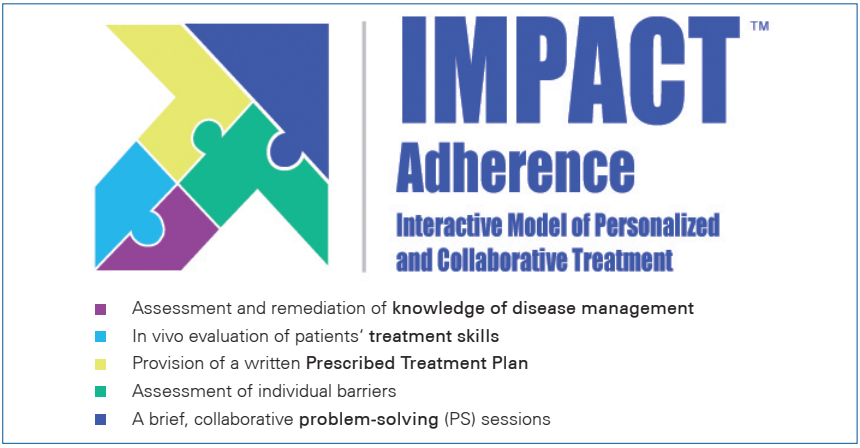

Fig. 2 Five components of the Interactive Model of Personalized and Collaborative Treatment (IMPACT) – Adherence.

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CHAPTER 7

Nutrition and eating problems in adolescents with cystic fibrosis

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1 Introduction

The widely acknowledged improvement in life expectancy in individuals with cystic fibrosis (CF) has been largely attributed to enhanced clinical interventions, including a greater emphasis on adequate nutritional status. CF requires high energy requirements and a dietary target between 120% and 150% of the recommended dietary requirement, 35–40% of which should be provided by fat.

Achieving these dietary recommendations is challenging. Observation studies have demonstrated that children of school age who have CF do not have the same appreciation of the need to maintain/gain weight as their parents, whose typical strategies to encourage eating are not only ineffective but may have a negative impact on family functioning [1]. Adhering to nutritional recommendations may be even more difficult during adolescence, which is a time of physical and psychosocial changes, experimentation and risk-taking behaviour.

2 Nutrient requirements in adolescence

The massive growth that occurs during adolescence demands more energy and nutrients [2] than any other period of the life cycle [3]. These needs parallel the rate of growth, with demands at the peak of the growth spurt up to twice as high as those in the remaining period of adolescence [4].

Prior to puberty, such needs are similar for boys and girls, but afterwards body composition and biological changes (e.g. menarche) emerge and affect sex-specific nutrient requirements [2]. Failure to consume an adequate diet can result in delayed sexual maturation and can arrest or slow down linear growth [2].

In healthy adolescents the dietary reference intakes (DRIs) developed by the Food and Nutrition Board of the Institute of Medicine provide quantitative estimates of nutrient intakes for planning and assessing diets [5–8]. The DRIs replace and expand upon the recommended dietary allowances (RDAs). The DRIs contain four categories of recommendations for nutrient reference values (Table 1), and provide the best estimate of nutrient requirements for adolescents (Table 2).

In adolescents with CF, the definition of energy needs is much more challenging. Individual variables include differences in maldigestion and subsequent malabsorption [9], pulmonary exacerbations [10], lung function [11], fat-free mass [12], sex [8], pubertal status [13], *CFTR* and modifier genotype [8,14], age [15] and medical complications such as liver disease or CF-related diabetes. Daily calorie recommendations provided by CF scientific societies range from 120% to 150% of the recommended level for healthy individuals [16,17]. In order to achieve the recommended energy goal, individuals with CF require a higher fat intake (35–40% of energy) [18]. Formulae to calculate the energy needs of children and adolescents with mild-to-moderate CF are available [19], including one from the Cystic Fibrosis Foundation Nutrition Consensus Report that incorporates levels of activity, pulmonary function and degree of malabsorption [20]. Such formulae may be used as a starting point to calculate energy needs, but energy intake should then be adjusted based on gain in weight and height, velocity of weight and height gain, and fat stores [15,17].

3 Nutrition monitoring

3.1. Anthropometric measurements

Accurate measurements of weight (in kilograms) and height (in meters) should be made at every scheduled physical examination [21]. These values should be charted in order to assess sequential growth and changes in nutritional status and to allow comparison with reference values [21]. Values should be expressed either as percentiles, as percentage of the normal values for age or as standard deviation or Z scores. Percentage weight for height, weight for age and height for age are often used when expressing nutritional status of children, though their reliability has been questioned [22]. In addition, body mass index (BMI) percentile charts should be

used for children and adolescents aged <18 years, in order to give a more accurate interpretation of nutritional status, especially in the individual with stunted growth [21].

3.2. Formal dietary assessment

A recorded diet diary should be collected and a dietetic interview should be conducted annually. The latter should incorporate a review of nutritional intake, enzyme intake (dose, timing and method of administration, titration based on fat intake), vitamin and mineral supplements, oral and enteral supplemental formulae, herbal and alternative therapies [23].

3.3. Assessment of pancreatic status and intestinal absorption

In pancreatic-insufficient patients, the adequacy of intestinal fat digestion should be undertaken annually or more frequently if clinically indicated [24,25]. Plasma levels of the fat-soluble vitamins A, D and E should be measured annually. An assessment of vitamin K status is obtained by measuring the prothrombin time.

3.4. Assessment of pubertal stage

Assessment of pubertal stage should be standardized and performed annually from 10 years of age. Pubertal delay is well documented in undernourished but also in well-nourished female adolescents with CF [26].

3.5. Estimation of skeletal age

Estimation of skeletal age should be part of the assessment of any child with stunted growth or pubertal delay. Surprisingly, the delay in skeletal maturation is modest in most individuals with CF and seems to increase with age, as pulmonary problems become more severe [23].

3.6. Bone mineral density and body composition

Bone mineral density and body composition should be evaluated by dual-energy X-ray absorptiometry (DEXA) scans as part of the nutritional assessment in all individuals with CF after 10 years of age [27,28].

4 Understanding eating habits in adolescents with CF

During adolescent years, people with CF, like their peers, begin to explore alternative or 'adult' health behaviour, including food choices and weight and size models. In relation to weight and eating behaviour, adolescents with CF inhabit two worlds – the non-CF world where weight loss is deemed good and the CF world where weight gain is prized [29]. Exploring these different perspectives may be useful when approaching and treating this challenging issue.

4.1. Food choices of adolescents

The project HELENA [30] (Healthy Lifestyle in Europe by Nutrition in Adolescence) provides data on knowledge and attitudes towards nutrition, physical activity and at-risk eating behaviour collected from a sample of European adolescents. Adolescents are aware and knowledgeable about nutrition and healthy eating issues but find it difficult to carry them out. They indicate a multitude of factors that can influence their food choices and preferences, including

availability, convenience, cost, influence of peers, parents, hunger, and health concern. However, one of the most important determinants of alimental choices is the adolescent's food preferences. Taste, in particular, plays an important role: generally speaking adolescents won't eat what they don't like.

4.2. Common eating behaviour

A similar study [31] described the diet and common eating behaviour of school-age children and adolescents in the USA. Results of the study revealed that nutrition guidelines were often not met, and the minimum number of servings of the five major food groups (grains, vegetables, fruits, dairy, meat/meat substitutes) recommended by the USDA Food Guide Pyramid were consumed by less than 5% of youths [32]. None of the girls in either age group (9–13, 14–18 years) and only 2% of 9–13-year-old boys and 5% of 14–18-year-old boys met the recommendations.

As a group, adolescents tend to snack (accounting for 25–33% of daily energy intake), miss meals (34% of females and 28% of males aged 14–18 years; breakfast is the most common meal skipped), eat away from home, consume fast foods, and start on 'diets', especially females (Table 3) [33].

Adolescents' perceptions of food and eating were identified using focus group interviews [34]. Many adolescents feel that healthy eating is not a primary concern during the teenage years: the quality of their diet is a reflection of this lack of concern. In general, they know what they should and should not be eating, but they identify some barriers, such as lack of time ("we have too many other pressures on us"), inconvenience of healthy eating ("more difficult to prepare"), lack of self-discipline (many adolescents felt that they did not have adequate self-discipline to eat healthy foods) and lack of sense of urgency ("I'll worry about it later on in my life"). Many teenagers have an overriding orientation toward the present and little concern about the future in terms of their own health, and do not perceive much urgency to change their behaviour as "the future is so ephemeral": long-term benefits of good health and eating practices do not outweigh the short-term advantages of certain unhealthy activities [34].

4.3. Non-traditional eating patterns

Adolescence is a time of experimentation and idealism. Because food is charged with symbolic meaning, it may be used as a means to establish individualism and express one's identity and uniqueness. Food choices convey strong messages about the individual to friends, family and the outside world. Eating patterns such as vegetarianism may be adopted as a way of exploring new roles and lifestyles, testing adult restrictions, or becoming interested in global or environmental issues. Many of the activities, which according to teenagers themselves are unhealthy, such as smoking, drinking and drugs, are inextricably intertwined with age-appropriate developmental issues of identity, self-concept, friendship, independence and authority. Thus, to give up what we call 'junk-food' would mean to give up much more than healthy eating habits.

4.4. How much and what are adolescents with CF consuming?

Little is known about this age group. A case–control study examined differences in nutritional parameters and intakes in 58 children and adolescents (5–16 years), divided into three age groups (5–8 years, 9–12 years and 13–16 years). The results showed that energy intakes increased with age and were higher in CF groups than in control groups. Weight gain and growth was normal between 9 and 12 years but declined from 13 to 16 years. Fat intakes of participants aged 13–16 years was greater than in healthy peers, but only 29% achieved the 40% of energy from fat. A wide degree of variation in energy intake (44–163% of estimated average requirement) and wide confidence intervals suggest a greater polarisation of nutrient intakes in participants aged 13–16 years [35].

5 Identification and management of eating disorders in children and adolescents

Incidence and prevalence of eating disorders in children and adolescents have been increasing over recent years [36]. During the past decade the prevalence of obesity in children and adolescents has also increased dramatically, together with further emphasis on dieting and weight loss among children and adolescents [37,38]. The epidemiology of eating disorders has gradually changed towards increasing prevalence and younger ages in males and minority populations in the USA and also in countries where eating disorders used to be less common [39]. It is estimated that 0.5–1% of adolescent girls in the USA have anorexia nervosa and 1–4% binge eat. Males are less affected, accounting for 5–10% of all cases of eating disorders.

A big issue is that a large number of people with eating disorders do not meet the strict criteria for diagnosis of anorexia nervosa or binge eating as stated by the Diagnostic and Statistical Manual of Mental Disorders (DSM) edition IV [40] and are labelled as having 'partial syndromes' or 'eating disorders not otherwise specified'. The next edition of the DSM [41–43] should take into account the fact that compared with adults children have limited verbal capacities, fewer abstracting abilities, less awareness of emotions and less ability to inhibit their behaviour. For example, fear of weight gain, distortion in body image and denial demand levels of cognitive sophistication that continue to evolve throughout adolescence [44].

Furthermore, a number of eating disturbances seen in childhood and early adolescence do not fit within the 'eating disorders' DSM diagnostic categories, and may therefore be underestimated. The four most common among these are Selective Eating/Picky Eating (highly limited range of foods and extreme refusal to try new foods), Food Phobia, Food Avoidance Emotional Disorder, and Pervasive Refusal Syndrome [45].

6 Perceived body image, body satisfaction and eating behaviour in CF

In theoretical models, a disturbed self-image and body image are often considered

the core psychopathology of eating disorders [46]. Similarly to other severe, chronic, somatic diseases, CF is characterised by a number of symptoms and circumstances that predispose the individual to a conflictual experience of one's body (e.g. growth problems, cough, abdominal pain, maldigestion, recurrent infections). Developing a positive self-image and body image in the presence of these problems is a major challenge as individuals grow into adults [47,48]. Body image perceptions of individuals with CF reflect prevailing cultural mores, such as the relative unacceptability of 'fatness' in women and the 'muscular' body in males.

6.1. Sex differences

Young women with CF tend to overestimate their weight while young men with CF tend to underestimate it: in a very underweight group, 29% of women but only 11% of men saw themselves as normal or overweight [49]. Girls with CF (10–21 years) reported significantly more illness-related worries, including emotional strains, greater treatment discouragement, lower self-esteem and lower adherence to some aspects of CF treatment (coughing, eating high-fat foods, taking medication/pills) [50].

6.2. Eating problems in adolescents with CF

Adolescents with CF experience many of the risk factors that have been documented in the eating disorders literature (pressure to eat during their childhood [51], low self-esteem [52], and life stressors including the experience of bereavement [53]). This poses the question of whether young people with CF are prone to develop eating disorders that contribute to malnutrition, and several studies have attempted to address this question.

According to DSM IV diagnostic criteria, as a group, individuals with CF do not show the core features of anorexia nervosa [29,46,54,55]. There are however some anedoctal reports of anorexia nervosa. Goldbloom [56] described a case of fulminant anorexia nervosa in a woman with cystic fibrosis. In addition to this being the first extensively documented case, the report speculates on reasons for an association between CF and eating disorders and indicates how failure to diagnose eating disorders can complicate medical treatment. Gilchrist and Lenney [57] described a 15-year-old girl with CF and distorted body image and anorexia; despite being underweight she aimed at losing a further 6 kg to become a 'size zero'.

Within the group of atypical eating disorders, an uncontrolled 3-year study by Pumariega et al. [54] identified 13/108 adolescents with CF (10 female, 3 male; 12–21 years) with an atypical eating disorder characterised by marked weight loss, food avoidance, amenorrhoea, and body image and body function distortions in the context of either normal gastrointestinal function or adequate pancreatic enzyme replacement therapy. They also demonstrated significant depressive symptoms associated with eating disorders.

When rigorous diagnostic criteria are used, formal eating disorders such as anorexia or bulimia do not appear to be prevalent [29,58,59]. However, subclinical levels of eating disturbance appear to

be elevated compared with the general population, with 53% of the adolescents with CF reporting disturbed eating attitudes ('restraint' was the most common) compared with 10–47% of adolescents in the general population. Fear of weight gain and feeling of fatness were evident in up to 15% of a study sample, with one participant describing a misuse of pancreatic enzymes and another describing binge-eating behaviour over a 2-month period, both for reasons connected with body shape and/or weight. Body shape and weight played significant roles in the self-evaluation of up to 36% and 53%, respectively, of the total population under study [29].

Another study [60] focused on the impact of nutritional interventions on patients' perceptions and behaviours concerning body image and eating habits. Although all patients, especially in the intervention group, received more pressure to eat, only a minority reported disordered eating. Excessive dieting was reported by enteral tube feeders (11%), patients taking oral caloric supplements (6%), CF controls (17%) and healthy controls (36%).

With regard to overweight and obesity, a UK study [61] including 1869 individuals with CF (0–18 years) reported an 18% incidence of overweight and 2.4% incidence of obesity. The observed prevalence of overweight in CF in 2002 was comparable to the prevalence of overweight in the general population 20 years before. The authors concluded that changes in lifestyle (less activity) and in eating patterns in the general population could have influenced the BMI status of the CF population.

7 Interventions

Regular and clear assessment of individual attitudes towards eating, shape and weight may be a useful initial step in identifying those at risk of eating disturbances. Screening questions about eating patterns and body image should be asked to all pre-teens and adolescents. The *Bright Futures* guidelines provide examples for addressing this issue with adolescents of different ages [62]. Any evidence of excessive weight concern, inappropriate dieting, or a pattern of weight loss requires further attention, as does primary or secondary amenorrhoea or failure to achieve appropriate increases in weight or height in growing children. Most adolescent girls express concerns about being overweight and many may diet inappropriately: most of these girls do not have an eating disorder. On the other hand, simple denials by the adolescent do not exclude the possibility of such a disorder. Collateral information from parents may help to identify abnormal eating attitudes or behaviours. Frequent self-weighing among adolescents has been associated with lower body satisfaction: adolescents should not be encouraged to engage in frequent self-weighing [63].

Assessment of the 'barriers' to nutritional recommendations perceived by the adolescent, as well as of their attitudes, beliefs and behaviour facilitates the appropriate knowledge and skills to perform the treatments correctly. Identifying 'meal-skipping', which is particularly common in adolescence, and understanding the

correlates of meal-skipping behaviours is important for planning adequate nutrition interventions. Educating adolescents to assess and interpret unhealthy eating behaviour in significant others (e.g. mother, friends) may be a useful nutrition promotion strategy [64].

Adolescents need a food culture based on 'foods to eat' rather than 'foods to avoid', and to understand suitable weight-control measures. Effective and age-tailored nutrition messages are of the greatest importance in adolescents. Leverton [65] pointed out that often teenagers are given the message that good nutrition means "eating what you don't like because it is good for you". Rather, they should learn to "eat well because it will help you in what you want to do and become". Teenagers are present-oriented and tend not to be concerned about how their eating will affect them in later years. However, they are concerned about having lots of energy, achieving and maintaining a healthy weight and physical appearance, doing well in school, and optimising their sports performance. While adolescents need to be aware of the long-term risks related to an inappropriate diet and of the long-term benefits of healthy eating, focusing on short-term or immediate benefits will have more appeal to them.

Finally, specific psychosocial intervention should be provided if an eating disturbance/disorder is suspected.

8 Conclusions

Nutrition continues to be a challenge in the care of individuals with CF. In the past, the goal was to provide adequate calories to improve survival. Nowadays the focus has shifted to optimisation of nutrient intake in order to promote normal growth and nutritional status and to avoid overt and subtle nutrient deficiencies [66].

Evidence to support well-defined nutrition recommendations is available [16,17,21,23]. The use of enteral supplements to increase overall energy and protein intake has produced conflicting results [67,68]. More efforts are needed to address these concerns [25]. When close attention is dedicated to individual energy needs and nutritional status, under-nutrition can be prevented or promptly treated. In the vast majority of patients, normal weight and nutrition can be attained through the rational use of a normal high-energy diet.

It has been repeatedly shown that behavioural intervention combined with nutrition education produce clinically and statistically significant increases in daily energy intake and weight [69,70].This kind of intervention is more efficacious than standard care for children aged 4–12 years [71]. It has also been shown that adoption of a standardised approach to nutritional assessment and treatment leads to significant improvements in nutritional outcomes of individuals with CF aged 2–22 years [72]. In the same experience, when behavioural concerns were identified by the care team, a paediatric psychologist evaluated the family and looked for specific barriers that could negatively impact the child's adherence to behavioural and nutritional interventions. Patients and families received recommendations focused on behavioural modification and individualised nutritional education.

Table 1
Dietary reference intake categories of recommendations for nutrient reference values.

■ Recommended dietary allowance (RDA)
The average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97–98%) healthy individuals in an age- and sex-specific group.
■ Adequate intake (AI)
A recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group of healthy people that are assumed to be adequate – used when an RDA cannot be determined.
■ Tolerable upper intake level (UL)
The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.
■ Estimated average requirement (EAR)
A daily nutrient intake value that is estimated to meet the requirement of half of the healthy individuals within an age and sex group – used to determine dietary adequacy of populations but not for individuals.

Table 2
Recommended Dietary Allowance (blue rows) and Adequate Intake recommendations for adolescents [5–8].

	Recommended intake for adolescents					
	Females			Males		
	9–13 years	14–18 years	19–30 years	9–13 years	14–18 years	19–30 years
Energy (kcals/day)	2071	2368	2403	2279	3152	3067
Carbohydrate (g/day)	130	130	130	130	130	130
Total fibre (g/day)	26	28	25	31	38	38
N-6 polyunsaturated fat (g/day)	10	11	12	12	16	17
N-3 polyunsaturated fat (g/day)	1.0	1.1	1.1	1.2	1.6	1.6
Protein (g/day)	34	46	46	34	52	56
Vitamins						
A (µg/day)	600	700	700	600	900	900
C (µg/day)	45	65	75	45	75	90
D (µg/day)	5	5	5	5	5	5
E (µg/day)	11	15	15	11	15	15
K (µg/day)	60	75	90	60	75	120
Thiamin (mg/day)	0.9	1.0	1.1	0.9	1.2	1.2
Riboflavin (mg/day)	0.9	1.0	1.1	0.9	1.3	1.3
Niacin (mg/day)	12	14	14	12	16	16
Vitamin B6 (mg/day)	1.0	1.2	1.3	1.0	1.3	1.3
Folate (µg/day)	300	400	400	300	400	400
Vitamin B12 (µg/day)	1.8	2.4	2.4	1.8	2.4	2.4
Pantothenic acid (µg/day)	4	5	5	4	5	5
Biotin (µg/day)	20	25	30	20	25	30
Choline (mg/day)	375	400	425	375	550	550

RDAs and AIs may both be used as goals for individual intake.

Table 3
High school students in grades 9–12 (N=15,349) engaged in dieting and weight loss behaviours [33].

	Females (%)	Males (%)
Dieted to lose weight	59.4	26.1
Fasted to lose weight	18.8	6.4
Took diet pills, powders or liquid	10.9	4.4
Took laxatives or vomited	7.5	2.2

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CHAPTER 8

Sexual and reproductive issues in adolescents with cystic fibrosis

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1 Sexual and reproductive issues in adolescents

Adolescence is a period in human life that is characterised by transition and dynamic development, with changes occurring in every aspect of personal life in a complex interaction between biological, physical, psychosocial and cultural factors. Adolescence is a time of exploration, gaining independence from parents and adults in general, establishing relationships with peers of both sexes and making choices that will shape identity and future health. During adolescence, health behaviours are established and continue throughout adult life.

Adolescence is a time of emotional progress and onset of sexual behaviour. Sexuality involves many of the developmental tasks that young people have to face: asserting gender identity, reassessing body image in the face of change, building self-esteem, testing sexual role and pursuing exploratory behaviours [1]. The development of adolescent sexuality is a complex phenomenon, the success of which contributes significantly to the adjustment to adulthood. Importantly, adolescent

sexual experience is often motivated by circumstances and pressure (e.g. external pressure from peers and media) rather than by mature decision making; the onset of sexual relationships occurs at an earlier age and risk-taking behaviour is reflected by the high rates of sexually transmitted infections (STIs), unwanted pregnancy and the use of emergency contraception [2].

Adolescents are often unaware of these risks and have unmet educational needs with regard to sexual health, although they find it hard to voice these concerns. Consequently, comprehensive sexual education plays a central role for youth in both promoting safer sexual activity and delaying its onset.

Sexual health also means reproductive health. By providing the appropriate educational support we may offer young people the way to reach and preserve both.

2 Sexual and reproductive issues in adolescents with CF

Improvements in the treatment and management of cystic fibrosis (CF) have resulted in a progressive increase in life expectancy for individuals with the disease. Nowadays, adolescents with CF enjoy better physical health and can expect to live longer. Consequently, sexual and reproductive health (SRH) issues are increasingly relevant for both individuals and their families. Young adults with CF may expect to have a normal sexual life and to experience parenthood [3,4].

All adolescents find aspects of sexuality confusing, embarrassing or worrying, but those with chronic disease face additional stresses that may affect their psychosexual health [5,6]. SRH issues are often poorly communicated or even ignored when dealing with young people with a chronic progressive disease, as both cure and care by healthcare professionals are focused on stabilising the disease and on survival [7,8].

Adolescents with CF do engage in sexual behaviour and they are exposed to the same risks of STIs and unplanned pregnancy as other teens [7,9,10]. However, in contrast to healthy peers, they have to face unique challenges that can potentially impact on their sexual health: delayed puberty, concerns about appearing physically different, lack of sufficient information and knowledge about sexual development in CF, fertility issues (infertility in males), genetic transmission, health implication for pregnancy, morbidity and reduced life expectancy, dependent and overprotective relationships with parents [11].

Addressing SRH issues means pursuing the perspective of a satisfactory quality of life with the intention of avoiding further anxiety, stressful situations and isolation that could increase the burden of daily care and concerns for health. Unfortunately, information is frequently given too late, when frustration is a common mood in both teens with CF and their parents. This may be due to uneasiness felt by adolescents and healthcare providers when talking about sexuality and to insufficient skills of healthcare professionals in dealing with SRH issues [12,13]. Moreover, there are no formal guidelines for CF care providers with regard to the most appropriate timing and content of SRH discussions, although several recommendations have been published [10].

2.1. Puberty

The timing of puberty drives psychological and social development. In fact, many adolescents with CF have problems with their body image because of the delayed pubertal growth spurt, and the awareness of looking different from their peers may lead to a stressful period of low self-esteem.

Both females and males with CF experience a delay in the onset of puberty compared with healthy peers, with a mean delay of 2 years in females and 1.5 years in males [14]. The aetiology of this phenomenon appears to be complex and multi-factorial. Data suggest a correlation with malnutrition as well as with lung disease severity, although this delay still exists despite intensive treatment leading to good clinical and nutritional status [15,16].

Johannesson et al. suggested a direct role of the mutated *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, resulting in impairment in the secretion of gonadotropin-releasing hormone and subsequent delay in attaining pubertal levels of sexual hormones [15,17]. The clinical observation of a correlation between menarche in CF and *CFTR* mutations has recently been confirmed [16] and is also supported by a mouse model of CF, in which F508del homozygote animals showed delayed onset of puberty [18].

Another theory correlates the delay in puberty to increased resting energy expenditure, which may be higher in females with CF compared with both control females and males with the disease [19]. This hypothesis is not supported by recent observations that resting energy expenditure in females with CF might be independent of menarchal status [20].

2.2. Physical components in females

Although females with CF have an anatomically normal reproductive tract and normal sexual function, several sites within the female reproductive tract are affected by the defective CFTR protein [3,9]. It has been speculated that altered CFTR expression in the hypothalamus may result in an abnormal secretion of gonadotropin-releasing hormone, which in turn leads to dysregulation of the neuroendocrine hormonal secretion and delayed sexual maturation [21]. Furthermore, as most of the female reproductive tract is lined by epithelial cells, impaired CFTR function may possibly modify genital tract secretions [9].

Oestrogen levels may also influence CF disease and may be involved in transepithelial ion transport, thus explaining the observed catamenial changes of both respiratory symptoms and lung function reported by females with CF who are of childbearing age [22].

A minority of women with CF have reduced fertility or infertility. This could be related to the rheological characteristics of the cervical mucus, which may lack the increase of water content that usually follows oestrogen stimulation during ovulation [23]. In addition, a change in uterine bicarbonate secretion could interfere with the ability of sperm to fertilise the oocyte [24]. Other possible causes of decreased fertility in females with CF could be poor nutritional status, and severe lung function impairment, high levels of systemic inflammation and long-term steroid therapy inducing ovulatory disturbance.

In spite of all this, more and more women with CF are getting pregnant and it has been

shown that women with good and stable CF disease are likely to have successful pregnancies and deliver healthy babies [3].

Other relevant issues are the vulnerability to vulvovaginal candidiasis related to antibiotic treatment and urinary stress incontinence, which may appear even at a young age [9].

2.3. Physical components in males

The male genital tract appears to be more sensitive to CFTR malfunction than any other organ involved in CF [25]. Almost all males with CF are infertile because of the abnormal development of the mesonephric portion of the reproductive tract. Bilateral obstruction or absence of the vas deferens causes azoospermia, while atrophy or absence of the seminal vesicles is responsible for the low ejaculate volume [26].

Despite these abnormalities, which cannot be corrected surgically and are not related to general clinical status, men with CF can have normal sexual relationships [27]. Assisted reproductive techniques employing microsurgical aspiration of sperm from epididymis or testis and in vitro fertilisation of oocyte with intracytoplasmatic sperm injection have been repeatedly and successfully used in men with CF [28], despite a possible role of the CFTR protein in spermatogenesis or sperm maturation [29].

3 Informing adolescents about CF-related sexual and reproductive issues

Healthcare providers need to recognise that SRH is a delicate topic for many adolescents, with only a small proportion coming forward with questions and concerns. Parents are key players in this information/education process, but their knowledge is often incomplete and frequently inaccurate. The responsibility for initiating and conducting SRH education should therefore lie with healthcare professionals [10].

Information and proactive discussions on how CF may affect physical, emotional and interpersonal development should be initiated early and tailored to the developmental age of the adolescent. An open, individualised and non-judgemental patient–doctor dialogue is recommended, as well as emotional support and readiness to discuss new issues as they arise. The capabilities, knowledge, wishes and rights of the adolescent must be carefully considered, and confidentiality and privacy should be assured (Table 1).

3.1. Content of the information

The quality and quantity of the information about SRH issues may differ greatly depending on the sex of the individual and also on the CF centre and country of residence. Frequently, information for teens and parents is incomplete [10]. Insufficient or incorrect information may lead to misconception and misinterpretation, for example with confusion between male infertility and impotence or the belief that infertility means that men do not need to use condoms, thus increasing the risk of STIs [8,30].

Issues to be discussed include: the experience of adolescence with a chronic condition (puberty delay, poor self-image, risk-taking behaviour), sex-specific reproductive

physiopathology in CF, behavioural aspects of sexuality in CF, contraception in CF, hope for future parenting, possibility of reproductive and fertility assistance, and the genetic implications of CF (Table 2) [10].

3.2. Preferred source of information

Individuals with CF identify their CF healthcare providers as an important source of information, especially in adolescence. Although male teens report they first heard about SRH issues from a variety of sources [8], they seem to favour discussions with both CF clinic staff and parents and would rather not be informed about infertility by other patients or friends [8,30].

Female teens also report the need to discuss SRH issues with the CF team [12,31], but they often feel that CF healthcare providers' knowledge about contraceptive choices is not up to date, underlining the need for a gynaecologist trained in CF issues to be part of the multidisciplinary CF team [32].

Teens also value parents as an important source of information. Unfortunately, published experiences suggest that frequently parents are not appropriately and correctly informed: only 23% of parents understand the issues connected with female fertility and 44% believe that males with CF have normal fertility [31]. However, 95% of parents wish to be the first people to inform their child on such issues or ask to be involved in the education process [12,31]. Written up-to-date information may be useful in dealing with SRH issues of CF adolescents [12,30,31,33].

3.3. Timing of information

The most appropriate age for discussion of SRH varies. For male adolescents with CF the most appropriate age to discuss infertility and propose semen analysis is still debated, as is the need and timing of education follow-up. Male reaction to learning about infertility varies with age: those who were informed at a younger age were less likely to have a negative reaction at the time than those informed at an older age but, as expected, the former report a change in relevance over time, especially when fatherhood is planned [8]. Semen analysis should be discussed and offered throughout adolescence and young adulthood, taking into account the maturity and developmental stage of the individual.

Information to parents should be provided as early as possible and at least within the first 2 years from diagnosis [10]. The majority of parents express a need for more information when their child is around the age of 10 years, in order to feel confident that their child can properly understand and process the information [12,34]. Parents tend to discuss issues with their sons at an earlier age than CF doctors would initiate such discussions (13.2 years versus 17.2 years) [8].

Early discussion with adolescents is indicated in the paediatric setting [35]; later on, in adulthood, reproductive options must be extensively discussed once again. Sawyer et al. found that males were rarely informed by healthcare professionals about infertility before the age of 15 years [8]. Other studies report that the majority of males find it appropriate to be informed earlier than is currently done, preferably during the early teens [13,33,35].

An anticipated proactive discussion on SRH is suggested with both parents and teens but this kind of education/information is a dynamic process, and counselling on these issues has to be renewed over time. Most healthcare professionals consider 13–14 years the best age to discuss infertility issues with male patients [34]. Similarly, female adolescents with CF suggest that the best age to approach sexual health issues is between 13 and 14 years [12,27]. Parents believe that discussion should begin at about the age of 12 years; in addition, mothers recommended that healthcare providers begin discussions with parents when their daughters are round 9 years old (average 9.4 years) [12,31].

4 Contraception in CF

The choice of contraception in adolescents with CF must consider many aspects, not only related to the young age but also to health-related issues, including pharmacological interactions. The correct use of barrier contraceptives should always be encouraged to reduce the risks of contracting STIs.

There is no particular contraceptive method that is either contraindicated or recommended for females with CF. Each method needs to be weighed up against CF manifestations in the individual. Conditions such as diabetes, liver disease, gallstones, pulmonary hypertension and osteoporosis must be taken into account in choosing the contraceptive strategy. A permanent central venous access and cigarette smoking increase the thromboembolic risk related to hormonal contraception. Malabsorption of oral contraceptives does not seem to represent a major concern [36,37].

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Table 1
Provision of education on sexual and reproductive health issues in adolescents with cystic fibrosis.

- Proactive and anticipated discussion with adolescents (importance of parents)
- Positive and supporting approach, tailored to the individuals developmental age
- Emotional support
- Discussion routinely repeated in follow-up
- Open dialogue and non-judgemental approach
- Comprehensive approach in education about safe sex (information on risky sexual behaviours and information on contraception)
- Duty of confidentiality

Table 2
Key points for information and educational support on sexual and reproductive health issues for adolescents with cystic fibrosis.

Males should be:	Females should be:
■ Informed that in most cases (95–98%) males with CF are infertile (unable to conceive spontaneously without a fertility medical intervention because ejaculatory fluid does not contain spermatozoa)	■ Informed that they are likely to be fertile
■ Informed that they do not or will not have erectile dysfunction and that CF does not interfere with sexual activity	■ Offered contraceptive choices that are suitable for adolescence
■ Informed about low ejaculate volume	■ Advised to use condoms to prevent sexually transmitted infections
■ Informed that spermatogenesis is likely to be normal	■ Educated, monitored and treated for vaginal yeast infections
■ Offered semen analyis	■ Evaluated and eventually treated for urinary incontinence
■ Advised to use condoms to prevent sexually transmitted infections (even if they are infertile)	■ Offered hope for future pregnancy
■ Educated, monitored and treated for genital yeast infections	■ Advised about the importance of a planned pregnancy (importance of lung function, optimal control and stability of the disease, possible negative effects of drugs used to treat CF on foetal health and development)
■ Offered hope for future fatherhood	■ Informed that genetic counselling is available and recommended
■ Informed that genetic counselling is available and recommended	

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CHAPTER 9

The social life of adolescents with cystic fibrosis

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1 Introduction

The current adolescent cohort of people with cystic fibrosis (CF) will have been diagnosed in an era of general optimism about effective treatment and life expectancy, and many adolescents with CF immerse themselves in the same daily pursuits as their friends who do not have the disease. The prospect of improved health outcomes and quality of life may change the adolescent's viewpoint from one of illness and treatment to one of optimism for leading a life similar to that of their healthy peers. With this in mind, routine self-management of CF can be seen as worthwhile.

However, adolescence is a risky period when, despite increased strength and the reduced susceptibility to disease, morbidity and mortality rocket to the highest rates in the natural lifespan of individuals with CF. In addition, the rapid neurological development in adolescent brains contributes to a level of self-awareness approaching that of an adult, but self-control and the ability to inhibit certain behaviours remain poor with potentially detrimental effects [1].

In this chapter, the challenges of CF in adolescence are explored by looking

at adolescents' attitudes to health, their management of treatment, their use of social networks, and their education and future work opportunities. New technological developments in CF and CF treatment and their appeal to adolescents with CF are also discussed.

2 Health

Adolescence is a stage of rapid growth, with psychological as well as physiological changes. This period of development may be the first time the young person with CF experiences a negative impact on their health status as a direct result of having CF [2]. It is often during the teenage years that the adolescent experiences reduced health gains despite treatment efforts remaining the same or even being increased.

The severity of the medical condition and the complexity of daily treatments have been found to correlate with poorer psychological outcomes [3]. Young people with a chronic health condition are more likely than their healthy peers to be at risk of infantilisation and of adopting a sick role as a personal identifier [4]. Yet, the assumption that all teenagers with CF will be negatively affected by their diagnosis must be avoided. Modi et al. [5] found that rates of depression in adolescents and young people with CF are relatively low. Like their healthy peers, adolescents with CF experience ups and downs as they move through their teenage years. They struggle with self-esteem and body image, strive for independence, search for their identity and at times suffer from immense self-doubt. This turmoil is normal and part of growing up to become a balanced young adult. However, it is well documented that having CF may compromise typical developmental processes [6]. Keeping this in mind, it is not surprising to find poorer adherence to treatment, especially during adolescence, which is the result of a complex behavioural response and not simply a stance of non-compliance.

The adolescent brain is not fully formed in terms of executive function, and the skills of organisation and planning are variable [3]. An immature ability to inhibit certain behaviours and to emotionally self-regulate means that consequential thinking is poor. Teenagers are natural risk takers, a behaviour that is not concordant with self-management of CF treatment. Treatment management in CF requires an understanding of and a commitment to prevention of future health deterioration and is dependent on the personal belief that the treatment is necessary and beneficial [7]. Given the teenager's predisposition to behave according to immediate impact, their inability to plan for the future and at times their concept of the self as invincible, it is inevitable that the long-term concept of 'prevention' will be a poor motivator for treatment adherence.

Attitudes to health are variable and continue to develop during the adolescent years, with rapid neurological development of the brain to achieve adult maturity. Barriers to effective treatment management have been identified, such as accidentally or intentionally forgetting to take medication or no perceived benefit of medication. This illustrates the adolescent's typical attitude to life, which is a 'live life for now'

attitude characterised by immediate rather than deferred gratification. George et al. [8] found that clinic visits, social support and perceived health improvement facilitated treatment management. For adolescents it seems that a focus on how treatment goals can impact more immediately in terms of social integration and acceptance may be most likely to succeed [9].

Like their healthy peers, adolescents with CF will experiment and may engage in what may be considered risky behaviours. In a study of young adults with CF, 83% drank alcohol (with 13% drinking more than recommended amounts), 46% had tried smoking (3% continued to smoke regularly), 35% had tried illicit drugs and 40% had engaged in unprotected sex. Interestingly, these researchers found that the group with CF engaged in lower rates of risky behaviour than the healthy group with the exception of unprotected sex [10]. It is unclear exactly why young people with CF pursue fewer risky activities. It may be that parents are preventing them by protecting or restricting their activities. It may also be related to the fact that adolescents with CF have a 'career in health care' making them more aware of the value of a healthy body and the need to care for one's body compared with healthy peers.

3 Home treatments

In the earlier stages of childhood, parents bear the burden of diagnosis, converse with the healthcare team on treatment decisions and take all responsibility for treatment management in the home. In the adolescent years, teenagers themselves are gradually more capable of feeling and reporting their own symptoms and understanding the impact of CF.

Parents of young people with CF face the same issues as those with healthy adolescents, but it is usually the adolescents themselves who drive the separation and individuation process. A teenager with CF may at times be emotionally demanding and cause frustration regarding their attitude to illness, understanding of treatment, failure to assume an adult role and dependency on parents or professionals. Teenagers may perceive the healthcare professionals in the same category as all adults including parents, and may question their ideas, arguments and opinions as part of a necessary developmental shift towards individuation. This can produce battles with parents and professionals over symptom reporting, treatment decisions, freedom, trust and responsibility.

Research on the impact of home on the well-being of the adolescent with a chronic condition has produced conflicting results; however, reports in CF suggest that family can be a great source of support [11]. For example, parents' optimistic attributions to the psychosocial adjustment of their child to CF are associated with fewer adolescent internalising and externalising problems [12]. Parents play a key role in supporting their adolescent child both through the transition into adulthood and the competent management of their own health condition. They can provide an invaluable contribution to this process by giving non-clinical practical

support, acting as trouble-shooters in times of health crisis, working in partnership for ongoing health management and by being there as a protector. Adolescents want their parents to be educated about how to handle adolescents with CF and thereby prepare them for adult life [13]. Parental anxiety and over-involvement are not helpful [14].

Given the challenges faced by parents in managing adolescents with CF it is important to understand what prevents poor outcome in the general population. Studies have shown that families in which communication and bonding with adult figures is good are less likely to produce teenagers who engage in risky behaviours [15]. Parents who supervise and are involved in their adolescent's activities are providing a safe environment for their teenagers to explore opportunities [15].

4 Social world and networks

One of the strongest inherent drives in an individual with CF, from the unconscious developmental acquisition of skills to the conscious psychological self-awareness in adolescence, is to lead as typical a life as possible. The way in which adolescents with CF measure themselves against what they consider to be typical is to compare themselves with their peers. Herzer et al. [16] studied the supports and strains identified by adolescents with CF and diabetes. Parental strain was recorded when parents were either over-protective or rejecting. Peer support buffered parental strain but parental support could not buffer friendship strain. The implication is that friends are an invaluable protective factor, and promoting social connectedness in adolescents with CF is important. Quality of life, self-concept and emotional well-being are improved in social relationships. It has been the case that parents have felt the need to over-protect their adolescents with CF. It makes rational sense that parents who have put in effort to maintain good health status in their child will be worried about transferring responsibility for treatment management to their child during the uncertain stage of adolescence. Parents may well be worried about the negative influence of peers and the potential for bullying when the diagnosis is disclosed. However, bullying in CF is rare compared with teenagers with behavioural or mental health problems [17].

Some young people with CF may experience difficulty in developing social relationships, possibly due to a fear of exposing the diagnosis and treatment. The general acceptance of segregated clinics for people with CF as a means of infection control has affected the feasibility of a natural source of social support. The use of no-contact social network websites offers the opportunity to overcome this difficulty. The evaluation of social networking websites as a means of support is sporadic but those that have been reported indicate some benefits in enabling an individual to construct a public profile, generate a list of others with whom they share a connection and access a wider range of people with similar interests than would otherwise be possible [18]. Irrespective of any value specific to CF, it is the case that more than 90% of teenagers

and young people regularly access social network sites and at the very least this supports connections and possibly also friendships.

Young people with CF experience similar concerns and desires as their contemporaries without CF. Friendships and social networks improve resilience and well-being [19]. Most people with CF achieve ordinary social and vocational development into adulthood irrespective of lung function. A favourable mental health status is important to maintain a good quality of life [20]. Health professionals and parents of adolescents with CF can inadvertently create a life experience where procedures, medicines, hospital admissions and lifestyle restrictions are imposed by others. Adolescents with CF can feel a sense of loss of control and it is important that the healthcare teams and parents provide opportunities for the inclusion of adolescents in decision making [21]. For adolescents with CF to do well in life, a primary goal is to maintain a sense of normality and this requires an affiliation with their social network.

5 Work and education

Improved health outcomes and better life expectancy have led to a situation in which nearly half of the CF population is over the age of 18 years [22]. Decades ago, there was little time nor reason for youngsters with CF to have a plan about their future education or career. Nowadays, most will have a plan but CF and CF treatment play a central role in adolescent education and career planning. Research has shown that accepting the limitations imposed by chronic disease and readjusting life goals may have a positive effect upon well-being in adolescents with CF [23].

Adolescents with CF often experience more school absence compared with their healthy peers. Grieve et al. [24] strongly advised informing school staff about CF and treatment so that school can provide an educational environment in which students with CF can optimise their cognitive potential. It is mainly about understanding what can facilitate the management of the disease: for example, students must be permitted to use the bathroom without having to ask, to carry their own medication and administer it themselves, to be excused from physical education classes during periods of illness exacerbation, to use the lift (if available) rather than the stairs. Stimulating self-efficacy in adolescents is important because this has a positive influence on academic performance and career trajectories. In addition, high self-efficacy is related to fewer depressive symptoms [24].

Even though many adolescents with CF can have similar employment opportunities to their healthy peers, several issues have to be addressed that are specific to CF. The day-to-day treatment demands, the regular respiratory infections, regular intravenous treatments (in or outside the hospital) and the high calorific diet may make it harder to find an appropriate job. In addition, when applying for a job, the person with CF needs to consider disclosure of the diagnosis. Most adolescents with CF choose to disclose the diagnosis when applying for a job [22];

however, anecdotal feedback indicates that this may lead to not being offered the job.

Employment rates vary between countries, from 10% to 41%. Most individuals with CF feel that employment does not interfere with their daily treatment routine [25]. However, little is known about whether daily treatment routines interfere with employment, which for optimal CF care is an important issue, or even whether treatments reduce the chances of being employed in the first place.

As mentioned above, getting a job and participating as a skilled adult in society are achievable goals, and adolescents with CF can, more than ever before, reach out to new challenges both in education and in job opportunities. Selecting an occupation has become a crucial topic just as it is for healthy teens. This is a major challenge for CF teams, as recent research has shown that adolescents with CF receive very little guidance on preparing themselves for a professional career [25].

6 New technologies and their contribution to care

The use of new technologies is appealing and 'trendy' and links in with the social world of today's adolescent population. Most patients and families are to some extent familiar with telehealth, which refers to remote healthcare services using telecommunication technologies [26]. For example, at home they utilise medical devices (e.g. spirometer, pulse oximeter), e-mail consultations, text reminders, telephone, e-diaries, mobile texting, Internet (e.g. websites such as the European Centres of Reference Network for Cystic Fibrosis [ECORN-CF], patient websites), and pharmacy video training. Another potential use of telehealth in CF may be the provision of physical activity or exercise programmes [27].

In CF and other chronic illnesses, studies on telehealth have been predominantly small and short feasibility trials using a wide age range of patients, limited disease variability and often poorly defined outcome measures [27,28]. Nevertheless, the availability and use of new technologies in adolescents with chronic illnesses is increasing [29] and has led to an immense growth of web-based and mobile information and communication technologies [30]. However, the literature shows that attempts to utilise telemonitoring in the care of individuals with chronic disease have failed because insufficient attention has been paid to understanding patient and clinical needs or the complex clinical realities of the disease [28].

6.1. Clinical outcome and assessment of patients

Hardisty et al. [28] interviewed a panel of experts about what they considered to be the most important aim of telehealth and their response was "to monitor and improve clinical outcome". Patients themselves stated that they hoped it would add to their health and well-being. Monitoring symptoms and making objective measures (spirometry and nebuliser compliance) via telehealth are definitely feasible for patients with CF [27]. It seems possible to use telemonitoring to identify trigger points

for intervention and also potentially to prevent the need for aggressive treatment, including hospitalisation [31,32]. Nevertheless, several problems remain. First, common technological problems need to be addressed, such as the time lag in audio feed and disrupted connections [32,33]. There is also a need for clear criteria (e.g. what constitutes an exacerbation) in order to use new technologies reliably and more insight is needed into the usual daily variation in symptoms of CF [27].

6.2. Adolescents and new technologies

Adolescent patients are willing to adopt and use telehealth technology [27,34]. This is no surprise because most of them use their computers on a daily basis as a communication tool and generally for interacting online with friends with CF. Young patients report little concern about their clinical data being transmitted electronically and they are generally comfortable using the necessary equipment [35]. This is in contrast to reports from older patients with chronic obstructive pulmonary disease and heart failure who expressed a distrust of technology and a lack of computer literacy [28].

For patients and their families, the main advantage of telemedicine is probably convenience and efficiency (e.g. electronic documents, appointments via e-mail, psychological support via e-mail, video conferencing). The use of electronic imaging of data can help in teaching an individual about their current health status, for example lung function trends. A further advantage of telehealth is the option of reduced travel. The use of mobile applications to improve self-management was feasible in a geographically dispersed CF population [35], indicating that time and costs may be reduced by conducting a telemedicine consultation based in a local hospital and connecting to the individual's CF centre.

An example of how telehealth can be implemented is the use of electronic personal health record (PHR) systems. PHRs are often created in parallel to electronic medical record (EMR) systems and support patient-centred healthcare by making medical records and other relevant information accessible to patients and by improving their access to knowledge for self-management [36]. As part of a transfer programme to adult care, adolescent patients can become familiar with their PHRs. Even though most PHRs are easy to use, the actual use by patients is still small [36]. Reasons for this low use may be the poor set-up of many systems, but more importantly the lack of patient participation in their development. Adolescent and young adult patients are the ideal group to be involved in the development of PHRs and other new technologies.

6.3. Adherence

Adherence to treatment regimens is a major problem in CF, especially during adolescence [37,38]. Recent studies have used new technologies to assess adherence [39,40,41]; however, Jarad and Sund [32] found that adherence to telemonitoring itself was also poor in individuals with CF (≥12 years). Research is needed to better understand what motivates adolescents to use different modes of telehealth [36]. For now, telemonitoring is likely to be most helpful for selected

adherent patients at times of clinical deterioration and frequent exacerbations [32].

6.4. Challenges relating to access, confidentiality and costs of new technologies

New technologies are widely available in some countries but less so in others. Many patients around the world do not have regular access to the Internet, mobile phones or personal computers. In addition to lack of access, little is known about the cost benefit of using new technologies [27], though the use of telehealth-enabled nebulisers may save costs [34]. Introducing new technologies is expensive and little is known about fees or the problem of invoicing for use of e-healthcare. Hospitals need to make large investments to implement technologies and also to maintain the systems [33]. Finally, the use of new technologies raises concerns about patient confidentiality, especially when used by adolescents who are under the age of legal majority. Even though young patients are not concerned about their data being transmitted, this should be a matter of concern for healthcare professionals

In summary, most adolescent patients will use and understand new technologies. Most are happy to use e-mail, mobile phones, appliances, websites and any other kind of technology, simply because they already do so on a day-to-day basis. Some issues need consideration in future e-health research and in setting up new systems. First, adolescents and young adult patients need to be involved in the development of programmes. Secondly, more input and ideas are needed from physicians with respect to how telehealth can be incorporated into their clinical CF care programmes. Intervention by technology is often highly complex and requires training for both healthcare professionals and patients. Adherence to telehealth and telemonitoring by physicians, CF teams and patients needs to be explored, and common technical problems need to be addressed; cost–benefit issues also need to be studied. Finally, one of the key factors for the success of new technologies in CF healthcare will be patient satisfaction in using them [33]. It is evident that patient health-related quality of life and satisfaction are essential outcomes when investigating the use of new technologies in CF.

7 Challenges in caring for adolescents with CF

The adolescent years are eventful, often unpredictable, certainly hectic and possibly the most important years in a young person's life, simply because the adolescent years embody the crucial stage between childhood and adulthood. For adolescents with CF this is no different and individuals face the same challenges as their healthy peers. However, while the adolescent is busy growing into a typical young adult, CF also demands care and attention.

With the improvement in CF healthcare, adolescents of today are able, more than ever before, to have an optimistic outlook on their adult years. Their educational and job opportunities have improved and many adolescents with CF finish their secondary education. During the adolescent years, however, self-awareness develops and the

adolescent with CF will be increasingly aware of the restrictions imposed by CF. CF treatment is time consuming, often boring and, particularly through the eyes of the adolescent, a hindrance to participation in typical teenage social activities, which for the adolescent with CF is the ultimate goal.

During the adolescent years the human brain is developing to adult levels of executive functioning and acquiring skills of organisation and planning. It is these skills that are needed to ensure optimal care in CF. Parents and CF teams will have to be patient, understanding and optimistic that the adolescent will develop sufficient adult skills to look after themselves properly in order to self-manage their CF.

Clinical practice and the literature show that social interactions are highly beneficial during adolescence. Support from family and from peers, both those with CF and those without, is essential for healthy social development during the teenage years. It is not surprising that Internet social network websites play a major role in the lives of all adolescents, whether or not they have CF.

New technological developments have potential in the care of patients with CF, especially in adolescents who are familiar with the use of technology in their everyday lives. It is important to include young patients in the development of such technologies and to encourage adolescents to use them as a method of self-management. Adolescents with CF are the patients that connect the older CF generation with the children born today and together with healthcare professionals they can play an important role in shaping the treatment strategies of the future. In return, we need to face their personal challenges with them as they travel through the difficult period of adolescence.

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