



European Cystic  
Fibrosis Society

# THE EARLY CYSTIC FIBROSIS YEARS

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## Editors

Kris De Boeck and Kevin W. Southern  
June 2018

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**Thank you to all the CF families who supplied the smiling faces for our front cover**

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[www.ecfs.eu](http://www.ecfs.eu)

ISBN xxx-x-xx-xxxxxx-x

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## PREFACE

The European Cystic Fibrosis Society (ECFS) is committed to develop reference resources and two books have already been published with success on challenging clinical areas: "Healthcare issues and challenges in adolescents with cystic fibrosis" in 2012 and "Living with cystic fibrosis" in 2015.

We are very happy to continue this tradition of writing textbooks and we have chosen to devote this third book to the early cystic fibrosis (CF) years because they represent a pivotal time in the life of a person with CF. Indeed, early diagnosis and management of CF have long been known to determine future health outcomes. This will be all the more true when breakthrough therapeutic options aiming at correcting the CFTR protein basic defect are available for very young patients.

The ECFS congratulates Kris de Boeck and Kevin Southern for the tremendous work they have done in bringing together international experts in the field to produce this excellent textbook. We hope that it will be useful and informative for caregivers specializing in the early years of the disease, but also in the later stages of the disease, and that it will help to improve CF care.

The ECFS is very pleased to offer this book "The Early Cystic Fibrosis Years" to all ECFS members.

**Isabelle Fajac**  
ECFS President

## FOREWORD

Cystic fibrosis (CF) is a complicated multi-organ disease, treated with an enormous variety of medication. On top of that, both diagnosis and treatment have a huge impact on the lives of the patients and on the lives of the caregivers. Medical treatment affects the psychosocial wellbeing of both the child and the parents; consequently, their wellbeing affects medical treatment.

When paying attention to those very important early years, we are laying the foundations for future health. Developments in understanding the disease and treating it are going very fast and are promising, yet we cannot easily underestimate the impact of the following message: "Your child has been diagnosed with CF". Life will never be the same again.

The earlier CF is diagnosed, the better. We are fortunate that newborn screening (NBS) is successfully expanding across the continent. CF Europe, representing the patients' perspective, supports this development. However once NBS is established, the work is not done. It can only be effective once we ensure high quality care, because better care improves the health and life expectancy of people with CF. This too is an ongoing process in which patient representatives and healthcare professionals join forces.

Personally I will never forget the impact the diagnosis had on us as parents, and on the upbringing of my child with CF and my other kids. We were eager to take care of our children in the best possible way. We were told that a good nutritional status is important, but our desire to control that status almost provoked an eating disorder. Understanding these kind of mechanisms is of utter importance and communication has a key role here.

This book is aimed at CF healthcare professionals, yet I feel that parents and other stakeholders may also find it very useful. I'm convinced that this textbook will lead to better guidance and care of both parents and children with CF.

**Jacqueline Noordhoek**  
President CF Europe

## INTRODUCTION

The first few years of life shape who we are, how we think and how we behave. For people and families with cystic fibrosis (CF) they are critically important to lay the foundations for future health. Early gains in these pre-school years have a profound impact on later wellbeing and quality of life.

CF is a devastating, life-shortening disease. But with an early diagnosis, linked with intensive follow-up and treatment, many of the downstream negative consequences of CF can be delayed, diminished or even prevented. A good start is essential for children with CF; not only important for the children themselves, but for the entire family.

Facilitating the early diagnosis of CF, helping the family to come to terms with the diagnosis of CF and teaching and supporting them to integrate complex treatments into a happy family life is the key task of the whole CF care team. The aim of this book is to provide a resource for healthcare professionals that will support them in this challenging task. Therefore, we invited CF experts from Europe, America and Australia to share their detailed knowledge and experience. Our aim was to achieve a book that is accessible. With the help of the authors, we feel we have achieved that goal.

We thank the many authors who contributed to this book. We thank them for the enthusiasm during the writing of their chapter and for their willingness to share their knowledge and experience so freely and openly. This book covers a wide spectrum of issues that we face in caring for pre-school infants and children. The book reflects on newborn screening and how to deal and cope with the diagnosis. A number of chapters provide clear direction on the follow-up and treatment of patients, with particular attention to good nutrition, prevention and treatment of bacterial infection and coping with the psychological impact of the disease. A chapter on unusual complications complements information on optimal treatment. We hope that CF healthcare professionals will find this book a useful reference for the day to day management of these young patients.

At a time when research into treatments of the basic defect has become so important, we also devote chapters to the current knowledge on CFTR modulator treatment in the pre-school years as well as to how research can be performed in a safe and effective manner during these “tender” years. There is much optimism in the field at the moment with the emergence of mutation specific therapies that promise to correct the basic molecular defect. These advances put into perspective the need to achieve optimal health in the “early CF years”.

Special thanks to medical writer Fiona Dunlevy for “harmonizing” the chapters as to writing style and presentation, and to Christine Dubois for logistical support. We express our gratitude to Isabelle Fajac and Jacquélien Noordhoek, representing ECFS and CF Europe for writing the forewords to this book.

Thanks to all patients and families for giving us the honor of being their caregivers. Thanks to the parents who allowed us to print the faces of their beautiful children on the cover of this book.

[Kris De Boeck and Kevin W. Southern](#)  
Editors



# CHAPTER 1

## The impact of newborn blood - spot screening on the diagnosis and well - being of pre - school children with CFF

### Authors

Anne Munck, Stéphanie Bui, Sergio Oteri, Carlo Castellani

### Introduction

Cystic fibrosis (CF) newborn bloodspot screening (NBS) is acknowledged by the global CF community as the optimal approach to an early and accurate diagnosis, and has been common practice in several countries for many years [1]. Strategies to screen for CF at birth have evolved in alignment with the gradual emergence of biochemical and genetic assays, from pioneering meconium proteins assessment in the 1970s to immunoreactive trypsinogen (IRT) measurement in the 1980s and mutation analysis in the 1990s. More recently, some strategies have included pancreatic associated protein and/or extended genetic sequencing [2].

Presently, all protocols contain multiple tiers, the first always being IRT. Due to the limited specificity of this test, further tests

are performed in IRT-positive newborns to select patients to be further investigated with sweat chloride testing. The sequence of tests following IRT is diverse, depending on the local geographic, ethnic, legal and economic situation [3]. Most national programs in Europe comply with the NBS standards of the ECFS and the ECFS NBS Working Group, with a degree of variability in sensitivity, positive predictive value and detection of infants with unclear diagnosis [2].

This paper examines NBS in CF, including the challenges and health consequences.

### 1 The impact of NBS on age at diagnosis, clinical presentation, genotype composition and prevalence of CF

A recent analysis of five national CF registries compared data on CF diagnosis among countries with NBS (France and Australia) and without NBS (Belgium, Netherlands and Sweden) [4].



The analysis concerned infants born in the years 2004 to 2011, with a similar definition of CF for all countries. Cases missed by NBS in countries with NBS programs, and cases diagnosed by pilot NBS programs in countries without a national program were excluded from the analysis. In countries with NBS, CF was diagnosed before 2 months of age (1.1 [0.7-1.6] months), increased the representation of young children in national registries compared to countries without NBS (22.7% versus 14.3%,  $p < 0.001$ ), led to early detection of children with CF and pancreatic sufficiency (19.1% versus 8.4%,  $p < 0.001$ ) and increased the proportion of children with uncertain diagnosis (12.9% versus 3.4%,  $p < 0.001$ ) [5].

The proportion of subjects carrying two CF-causing mutations (CFTR2 project [6]) is lower in countries with NBS ( $p < 0.001$ ). In the French NBS database 2002-2016, almost half of CF infants (45%) were asymptomatic with 11% presenting respiratory symptoms and 30% presenting hypotrophy [7]. In countries without NBS or carrier screening, the vast majority of cases are diagnosed thanks to the characteristic clinical signs and symptoms of CF, and the diagnosis was later at a median age of 3.6 months [1.2-12.0] ( $p < 0.001$ ).

The demographics of the CF registry changed following the introduction of CF NBS, with increased numbers of young patients, patients with pancreatic sufficiency and with unclear diagnosis. There is a need for guidance as to who should be included and analyzed in CF registries, especially if data is used to track improve-

ments in outcomes or for benchmarking.

*Key message: The CF population has changed since the advent of NBS. This should be taken into account when registry data are used for benchmarking.*

## 2 Challenges in providing high quality sweat test services

The diagnosis of CF in children who tested positive for NBS relies on sweat chloride testing as proof of CFTR dysfunction. Sweat testing for all infants with a positive NBS result is part of the recent international consensus [8]. Many newborns are reported as having CF based only on a positive NBS result, which is considered as a screening and not as a diagnostic procedure. Diagnosis should not rely upon genetic analysis, as errors can arise from Guthrie card labeling or from NBS laboratory errors including DNA misinterpretations, or detection of two *CFTR* mutations in cis (i.e. on the same chromosome) [9]. The population of children examined following positive screening is younger than the population of children examined upon presentation of CF symptoms. This raises specific technical issues around collecting an adequate sweat specimen very early in life [10]. The challenges of performing the sweat test in young children, such as small upper arms and poor hydration, could benefit from implementation of quality improvement programs [11]. Tackling these issues is important, because eventually the number of diagnoses following presentation of symptoms will equate to the cases missed by NBS, and should represent less than 5% of the CF population.

A recent study involving systematic sweat testing of over 500 children presenting respiratory symptoms and negative NBS results, led to a CF classic diagnosis in 4 cases (0.8%). All those diagnosed with CF presented with chronic cough and periodic pulmonary infections. Conversely, asthma symptoms alone did not result in any CF diagnosis, suggesting that a proper triage of systematic sweat test requests could highlight even more the impact of NBS on the use of this diagnostic test [12].

## 3 Short and long-term impact on outcome

NBS provides the opportunity, as soon as the diagnosis of CF is confirmed, to combine very early preventive and/or curative nutritional and pulmonary care with regular follow-up at CF centers [13, 14]. Even in asymptomatic or minimally symptomatic babies [14-16], nutritional support, pancreatic enzyme replacement therapy (if applicable) and physiotherapy with regular respiratory assessments will optimize nutritional status and delay the onset of pulmonary disease [13]. As a result, improved outcome with respect to growth, pulmonary disease and survival has been demonstrated in severe genotypes [15, 17, 18].

Short-term nutritional benefit has been reported since the early 2000s [19]. In a prospective study, Shoff *et al.* [20] showed that over 60% of toddlers with exocrine pancreatic insufficiency caught up the initial weight z-score at birth within 2 years of age. Recently, a multicenter study of 231 NBS

infants followed during the first year of life at 28 CF centers in the US found that suboptimal height growth remained common, despite normalization of weight [21].

Compared to people who were diagnosed following symptoms, children diagnosed via NBS had a combination of improved growth and early anti microbial interventions which delayed the progression of pulmonary disease, with better lung function at the age of 6 years [15, 22] and in subsequent years [15, 23]. Children diagnosed via NBS have also been reported to have decreased neutrophil-mediated inflammation, improved mucociliary clearance, reduced chronic bacterial colonization [15, 16, 23] when cross-infection policies are strictly applied [15], and less severe radiological damage [16, 19], in particular in children who have achieved growth recovery within 2 years of age [24]. Earlier studies showed improved survival [25] with 94% of screened children alive at age 11 in comparison with 65% when diagnosis was based on symptoms. A more recent study conducted in Australia [17] quantified the NBS survival benefit. It is important to outline that differences became apparent in the second decade and markedly so in the third decade with a 20% survival difference between cohorts at 25 years. This “lag” effect demonstrates the importance of preventive and curative management in the early CF years.

As CFTR modulators become increasingly available, the possibility of using these new therapies in infants diagnosed very early in life could maximize their effect on growth and pulmonary disease.

*Key message: NBS improves the timely implementation of nutritional and pulmonary CF care. NBS will also facilitate the prompt administration of emerging mutation specific therapies*

#### 4 An unclear diagnosis following NBS - CF Screen Positive, Inconclusive Diagnosis

An undesirable by product of NBS may be the detection of newborns whose sweat test and/or *CFTR* analysis are consistent neither with a CF diagnosis nor with a plain false positive situation. When non-mutation specific assays like scanning or sequencing are included in the NBS protocol, these inconclusive cases are more frequent. These infants are labelled “CF Screen Positive, Inconclusive Diagnosis” (CFSPID) in Europe [5] and “*CFTR*-related metabolic syndrome” (CRMS) in North America [26]. The different terms are justified by small differences in the definitions and by local health systems classification requirements. Recently, a consensus panel has reached an agreement on a common CRMS/CFSPID definition: infants with elevated IRT levels at birth and either a) sweat chloride below 30 mmol/L and two *CFTR* mutations, at least 1 of which has unclear phenotypic consequences or b) sweat chloride between 30 and 59 mmol/L and 1 or 0 *CF*-causing *CFTR* mutations. When applying this definition, mutations without functional and clinical evidence to substantiate *CF*-causing properties should not be considered [27]. The clinical evolution of these conditions is undefined, probably depending on several

individual *CFTR*- and non *CFTR*-related variables, and with a spectrum from no evidence of disease to a phenotype consistent with *CF*. Alternatively, these individuals may turn out to have a *CFTR*-related disorder which is a clinical entity associated with *CFTR* mutations but where a diagnosis of *CF* cannot be made by the current standard diagnostic criteria [28].

Long-term data on outcomes, although scarce, report good nutritional status and a frequency of respiratory cultures positive for *Pseudomonas aeruginosa* superior to that expected in healthy peers. According to different sources, between 0% and 37.8% develop pancreatic insufficiency and 3.7% to 48% are eventually diagnosed with *CF* [27].

Since it impossible to predict the individual clinical outcome, parents are advised that although their children are now healthy, there could be long term consequences and are offered clinical follow-up. The uncertainties inherent in this situation may cause anxiety about the child's health and the risk of further children with an identical *CFTR* genotype. Genetic counselling and, if necessary, extended *CFTR* genetic analysis should be made available. Children should be periodically seen in a *CF* center and their assessment may include nasal potential difference or intestinal current measurement, at least one repeat sweat test, fecal elastase measurement and sputum or pharyngeal suction cultures. Imaging can be considered according to clinical needs. A strict infection control policy is mandatory in order to limit the risk of cross-infection from children with *CF* attending the center.

It is not known for how long these children should be clinically monitored. The absence of *CF*-like symptoms by school age can be interpreted as a good prognostic factor. However, an outcome of long-term disease cannot be ruled out due to the possibility of a *CFTR*-related disorder or a mild form of *CF* emerging later in life [27].

#### 5 The psychological impact of an early diagnosis communication

The communication of a *CF* diagnosis is the culmination of a screening process that has involved many thousands of newborns, and is a pivotal moment for parents of newly diagnosed infants [1, 13]. The interconnection between parents and children is radically modified after the *CF* diagnosis, the parents' relationship balance and dynamics will no longer be the same and the disease will forever be part of the family.

Parents are generally in favor of NBS and early diagnosis and want the best opportunities for early treatment, ideally before the first symptoms appear [29]. However, the early diagnosis of a chronic progressive disease, the perspective of a heavy, life-long illness and the fear of premature death can induce concern, anxiety and depression in the parents and the whole family [30-33]. In this respect, the communication of a diagnosis and the effects that an early diagnosis can elicit in the primary parent/child relationship have long been ground for heated debate in the *CF* forum.

Denial, anger, bargaining, depression and acceptance are the usual sequential stages of reactions and the standard psychological model used to illustrate the impact of bad news, including the communication of a chronic disease. This model is not specific to *CF*, but in clinical practice a similar sequence of emotive reactions is often observed in parents after they are told of a positive screening and sweat test.

Healthcare professionals communicating the diagnosis need to be aware that the first conversations may have deep repercussions on how parents process the information and cope with the bad news. Confusion, disorientation and uncertainty experienced by parents all contribute to the challenge of conveying properly understood information [32].

A sense of hope, a positive view of the future and trust in medical care and in the multidisciplinary team depend, amongst other factors, on the first contact. Empathetic, attentive and effective communication can contribute towards acceptance of the diagnosis and elaboration of the information provided. Conversely, a technical, detached and insensitive communicative style can be experienced by parents as the traumatic beginning of their child's disease, impair their coping strategies and have a negative influence on the way they will perceive the disease and foresee the future. Specific communication capabilities and precautions are required to deliver positive and clear messages, and to verify what information and how parents have internalized. Healthcare professionals delivering an early

CF diagnosis should not rely exclusively on their common sense and past experiences, but should take full advantage of the few detailed guidelines for delivering such information.

*Key message: Appropriate communication of the CF diagnosis detected through NBS can minimize psychological harm.*

## 6 Early versus late diagnosis and the parent / child relationship

In most countries, NBS has drastically reduced the average age at CF diagnosis. An early diagnosis is good practice not only due to better clinical outcomes, but also because it reduces the stress of the pre-diagnostic period. Therefore NBS is generally associated with more confidence in medical professionals and less negative feelings. As it happens, a late diagnosis based on symptoms could be interpreted by parents as the reason for their child's unsatisfactory clinical condition and a missed opportunity for a better long-term disease control, and this may cause anxiety, guilt, anger and mistrust in health services [29].

Early diagnosis is not exempt from negative repercussions and may induce high levels of parental anxiety, depression, stress and a less effective style of communication between mother and child. Mother-infant attachment can be affected by frequent medical examinations, physiotherapy, administration of pancreatic enzymes and aerosol therapies. The parents' perception of the child's vulnerability significantly changes, possibly

leading to an overprotective behavior [34].

All these combined factors may lead to feeding problems [35]. Continuous concerns about the nutritional status of the baby may drive parents towards a constant attempt to convince their child to eat, with an escalating negative interaction between parents and child. This can result in long-term nutritional issues extending even well into adolescence or adulthood [36, 37]. On the other hand, the prompt and correct nutritional interventions which follow an early diagnosis are associated with better nutritional status and better quality of life. This in turn can lead to higher satisfaction with own body image and better quality of life in later years [38].

In a stressful situation like the communication of a CF diagnosis, parents' reactions are determined by many factors, including the infant's clinical status and social and family dynamics. Differences in coping styles and adjustment to the bad news may be independent of early or late diagnosis. Instead, these differences are probably deep-rooted at the individual psychological structure of personality and largely determined by several variables, like personal and familiar vulnerability, coping strategies and resilient capability [39].

Familiarity, flexibility, cohesiveness and good communicative patterns can have a positive influence well into adolescence and young adulthood and correlate with better psychological status and better adherence to treatments [40].

## 7 Conclusion

NBS screening for CF is now widely implemented across the globe with consequent improvements in nutritional, respiratory and survival outcomes compared with cohorts diagnosed based on symptoms. In the context of positive NBS, a sweat test is necessary for confirmation of CF. The diagnosis of CF is not always clear and individuals designated as CFSPID

may never develop CF symptoms. Nonetheless, they should be referred to a CF center to establish a plan for follow-up. Data entered into CF registries should be accurate, careful consideration of the individuals included in CF registries is important when data is used for benchmarking. Psychological issues related to NBS include contents and style of the diagnosis communication and consequences of early diagnosis on the parent/child relationship.

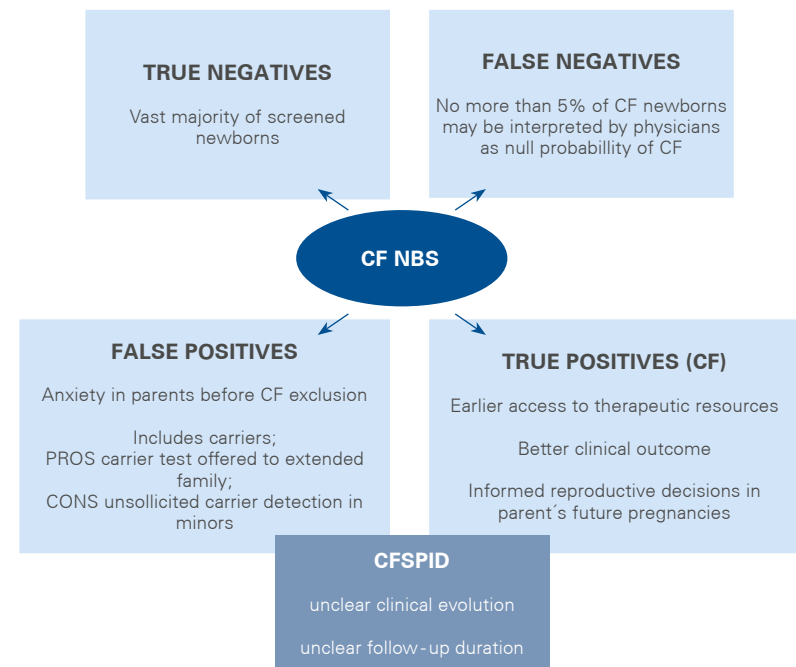


Figure 1 Possible outcomes of newborn screening

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# CHAPTER 2

## When the newborn screen for CF is positive: supporting families through the first years

### Authors

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### Introduction

The purpose of early diagnosis of cystic fibrosis (CF) via newborn screening (NBS) is to minimize morbidity and mortality. CF is best managed via surveillance and preventative treatment. Screening provides the opportunity to start this model of management before significant damage has occurred. The NBS consensus guidelines and standards of care [1] provide clear instruction on the whole screening process. Importantly, and unlike many medical guidelines, they also offer the very clear proviso: “Potential disadvantages of NBS must be recognized and their effect minimized.” Any parent who has received bad news about their child will be able to recount in detail the moment that news was imparted because it is devastating and its effects long-lasting. For this reason, it is essential that NBS for diagnosis of CF includes careful consideration and guidance on how the news of the screening result is delivered and the impact that the news will have on parents and their subsequent management of CF for their child.

### 1 “Traditional” versus “screened” diagnosis: why we need to consider the possible impacts of a newborn screening diagnosis on the emotional well-being of parents

In comparison to receiving a diagnosis at a later stage, diagnosis via NBS has the potential for causing greater psychological stress to parents. The way in which the diagnosis was “traditionally” given (and still is in some countries) leads to a very different psychological pathway for parents. In these cases, the parents often have some health concerns for their infant (or even older child) and they are likely to have made several attempts to engage health investigations. Once the diagnosis is made, there is a sense of relief and validation, they have done their job as parent and protector. This gives the opportunity for the CF team to be perceived as making an essential and positive contribution to their continued parenting role.

Conversely, diagnosis via NBS leads parents to take a different psychological pathway.

Parents have little time to observe signs of health problems, many infants are asymptomatic or have minimal symptoms. Thus, parents have no clues that their baby is anything other than fit and well until strangers appear and hit them with an unexpected and unwelcome diagnosis. The diagnosis has an immediate impact on parents' perspectives about having a different baby, one who has a serious potentially life-shortening medical condition and worse of all, an inherited condition that resulted from genes they passed onto their baby. There is scope therefore, that the diagnosis can undermine their confidence as parents and lead to a sense of guilt and failure [2]. In these circumstances, there is potential for the CF team to be perceived in a negative light and as having taken something precious from them — their hopes and dreams for a healthy child.

This chapter reviews the evidence regarding the impact of NBS and subsequent diagnosis on parents and parent-infant relationships, provides guidance on communicating a CF positive diagnosis and facilitating partnership by working with parents in the long term. Parental experience and the impact of diagnosis is illustrated by parental quotes and comments from qualitative research studies. Permission to include those quotes is supported by appropriate independent ethical consideration.

## 2 Diagnosis in the absence of symptoms

The initial stages following diagnosis involve parents processing the information received.

The diagnosis of CF via NBS presents some difficult concepts. The baby is well, looks well and appears to be thriving. Even mild absorption issues can seem similar to initial baby digestion expectations. Processing the information that the baby has a life-long medical condition for which there is no cure is difficult when juxtaposed with the healthy-looking baby before them.

The genetic inheritance of CF also poses a problem; parents wonder where these genes have originated and why they have not heard of it in their family previously. Describing recessive inheritance is difficult enough; understanding the process even harder. Though parents are informed that their child is well, and the early diagnosis enables preventative and responsive treatment, there is still a large amount of daily treatment recommended: prophylactic antibiotic, enzyme replacements, vitamins, and physiotherapy. The baby is reviewed regularly, maybe weekly, and seen in a large specialist pediatric center by a large multi-disciplinary team. On one hand parents are told not to worry, the baby is well, but on the other they are expected to deliver daily treatments and be seen by a range of healthcare specialists.

The diagnostic process intends to provide support and professional reassurance, but is in danger of producing anxiety and uncertainty. Grob [2008] described this parenting dilemma as, "Is my sick child healthy or my healthy child sick" and in doing so appropriately described the psychological uncertainty that NBS imposes on parents [3]. Grob's qualitative analysis of parental

psychological wellbeing post-NBS for CF indicated that an unsought diagnosis affects parental feelings of competence. Healthcare professionals are a frequent and imposing presence at a significant and formative stage of family life, irrespective of whether this is the first child or not. This process significantly alters the newborn period. It is therefore a responsibility of CF specialists to be aware of this effect when delivering the diagnosis and in providing ongoing care for the baby and for the wider family.

Parents experience a number of instinctive drives following the birth of a baby [4]. There is an overwhelming preoccupation with their baby, a desire to be close by and a drive to spend time gazing at the baby.

Theories suggest this preoccupation creates the "bond" which enables survival of the infant. The parents ensure the baby is fed and nurtured. The human infant is "hard-wired" to ensure its needs are met, the baby is equipped with the capacity to emit a range of noises and cries that parents find impossible to ignore. Human infants have been found to consistently prefer looking at a human face than any other stimuli [5]. The diagnosis of CF threatens the parental instinctive drive to protect their infant. When under threat, humans respond in a predictable range of ways [6]. Parental reactions to the diagnosis and the appropriate response from the healthcare provider are presented in **Table 1**.

NORMAL PARENTAL RESPONSE TO CF DIAGNOSIS	RECOMMENDED HEALTHCARE PROVIDER RESPONSE
<p><b>Shock and denial:</b> This common initial response arises from the unexpected nature of the diagnosis. Parents might search for confirmatory or refuting evidence related to the diagnosis.</p>	Remain a calm reassuring presence for parents and assist them in their search for additional information as needed.
<p><b>Strong emotional reactions:</b> Parents might feel panicky, worried and depressed. Some may report a sense of helplessness, guilt and concerns that they do not know best how to care for their child.</p>	Listen, reflect parents' feelings and offer realistic reassurance.
<p><b>Over-protective behavior:</b> Parental anxiety about the child's wellbeing can sometimes manifest as obsessive cleaning and avoidance of public places</p>	Assess the extent to which such behavior interferes with family function and the child's developmental strivings. Help parents find a balance between infection control and normative developmental opportunities.

**Table 1** Normal responses to CF diagnosis



NORMAL PARENTAL RESPONSE TO CF DIAGNOSIS	RECOMMENDED HEALTHCARE PROVIDER RESPONSE
<p><b>Expressions of anger:</b> Anger is a normal reaction to loss and can manifest as being unpleasant towards the CF team, sometimes particularly towards those associated with giving the diagnosis.</p>	Empathically listen to and reflect parents' feelings and address their concerns in a non-defensive way
<p><b>Escape, avoidance or withdrawal:</b> This less common response could involve use of alcohol or other substances. Sometimes one parent may avoid engaging in CF-related home care or not attend clinic appointments.</p>	Explore family functioning and parent coping in response to diagnosis and refer for additional mental health assessment and treatment as needed.

**Table 1** Normal responses to CF diagnosis

Diagnosis of CF via NBS demands that parents find a way to incorporate unwelcome and unsought medical information into their newly forming conceptions about their baby. In addition to wondering who their baby looks like and what they will become, they have to wonder how CF will affect their baby's future. Some parents can face and process that information more easily than others, it is best illustrated with some case examples.

*Key message: NBS leads to an unsought diagnosis that impacts parents' psychological wellbeing, sense of competence and confidence as caregivers, relationships with their children and family dynamics and functioning.*

### 2.1. Case study 1: difficulty accepting the diagnosis

Following NBS, baby Suzanne had a positive screen for CF. Following sweat test, a diagnosis of CF was communicated to her parents. The following week they were

invited to clinic to meet the team for an "education day". Suzanne's mother insisted they wouldn't accept the diagnosis, their daughter was healthy, she had no symptoms, CF was unknown in the family, therefore this must be an error.

Mum was tearful but also very angry. Dad was silent, avoided all eye contact with the pediatrician and would not engage at all, even to give his viewpoint. Mum stated that they wanted the diagnosis retracted, they could not believe the diagnosis was accurate. The parents were informed that was not possible, the child was the patient, she had a confirmed diagnosis and so there was a duty of care to Suzanne.

In this case the diagnosis was too much to bear. It had threatened the parental drives to protect their daughter from danger and resulted in shock, denial and anger in the mother and strong emotional reactions and withdrawal in the father. A natural response from the healthcare team would be to try harder to convince

the family that the diagnosis is accurate. However, recognizing how devastating the diagnosis must feel to them would be more helpful. These parents benefited from counselling to support their sense of competence as caregivers and enabled them to understand that their reaction was a natural instinctive response to protect their child.

Parental reactions are more commonly accepting of the diagnosis, but with anxiety around CF and the threat it poses.

### 2.2. Case study 2: impact of CF on parental relationship

Priya's parents were understandably upset on hearing the diagnosis; they found comfort and reassurance in conversations with experienced members of the CF multidisciplinary team. They reported over the first few months that they saw Priya first and CF second. It no longer dominated their thoughts as it had at the beginning. They had informed family and friends who offered emotional and practical support. Priya was meeting developmental milestones. Her parents had incorporated her treatments into a daily routine and there were no major concerns about her health.

At a routine clinic visit father reported concerns that his wife was overly protective of Priya but she would not make decisions about managing health risks. Instead, she looked to him to make such decisions and blamed him for failing to do so when he did not make decisions that she wanted. For example, while visiting a friend's home, they discovered one of their friend's chil-

dren had a respiratory infection and Priya's mother was worried about their daughter's exposure to the infection. When he disagreed with his wife about leaving, she later became very angry with him.

This example illustrated the impact of CF on family life in a relatively benign but unrelenting way. The CF centre team helped these parents find ways to negotiate and compromise in making decisions that would benefit their child, while supporting the couple's relationship.

### 2.3. Case study 3: "the emotional roller coaster" of a CF diagnosis over time

Six months after her CF diagnosis, Tanya was thriving physically and developmentally. Her parents felt confident in their ability to perform CF-related care and hopeful about her future. At 8 months, she developed a respiratory flu that prompted her first hospitalization. Her mother confided, "You kind of melt inside and feel like you're right back to where you were that first week when you found out."

The theory of chronic sorrow offers a useful alternative to the binary model of psychological acceptance versus denial and better explains the evolving adaptation described in the third case example [7]. Time-bound theories of grief or loss suggest that emotional responses to a traumatic life event are linear and individuals eventually reach a final state of acceptance. Thus, grief responses exhibited beyond a particular time frame are considered abnormal.

Chronic sorrow has been described as "a

normal grief response associated with an ongoing living loss that is permanent, progressive, recurring, and cyclic in nature" [8]. It is not unusual for parents of children with CF to adapt to the diagnosis by incorporating medical treatments into their daily routines while still struggling with feeling of loss. The intensity of such feelings may abate over time as they observe their child's relatively good health and normative developmental achievements. However, certain events can trigger recurrences of strong emotions. For example, when the child experiences some change in health, e.g. pulmonary exacerbation, intense feelings

of grief similar to those experienced around the time diagnosis can re-emerge. Parents have referred to this process as a kind of "emotional rollercoaster" that becomes part of their lives.

One parent shared the following description that captures this process, "You kind of melt inside and you think you're right back to where you were that first week when you found out. It doesn't happen as often as it used to, you remain positive most of the time." It is important for healthcare providers to recognize and respect individual differences in parental responses

### WE WILL NEVER FORGET

By Lisa C. Greene  
(parent of two children with CF)

We will never forget:  
The moment of diagnosis.  
The place, the sights, the sounds, the smells.  
The surreal sense of time. Is this a dream?

We will never forget:  
The shock, the disbelief, the fear.  
The anger, the tears, the shattered dreams.

And we will never forget:  
The prayers, the hugs, the helping hands.  
The kindness, the love, the hope.

to the diagnosis, on-going coping, and psychological adaptation to the CF diagnosis.

#### 2.4. Case study 4: evolving adaptation to the diagnosis of CF

Jonah has remained well since diagnosis; his parents have engaged with the CF team and report feeling supported. At Jonah's third annual review when his parents were asked about how they were managing CF, his mother reported that she had reflected on the journey she had come on since initial diagnosis.

She said that at first she felt that Jonah would stay well as long as she followed medical direction, gave treatments, and avoided infection risks. She said that she had realized that for her own psychological wellbeing she could not maintain that viewpoint in the long term as it relied too much on wishful thinking. She reported that she had to accept that CF was in her son's genes and it constantly posed risks for causing damage. She had come to view her role as continually fighting a preventative battle. Thus, she increased the treatments when required and consulted with CF experts. She also explained how the CF diagnosis helped her think about what was really important in her life - prioritizing enjoyable times with loved ones.

This attitude is more akin to the attitude held by healthcare professionals, who monitor, test and treat as a constant evolving process. Most parents are emotionally able to get to that state of acceptance.

### 3 Psychosocial implications of a CF diagnosis in the context of newborn screening

Learning that one's child has a serious health condition is a traumatic event associated with intense parental emotions that can include shock, grief, guilt, uncertainty, and loss of self-esteem [9-11]. When the father of a school-age child with CF reflected back to his child's newborn diagnosis, he described it as "the worst day of my life." Parents of infants newly diagnosed with CF report symptoms of depression, anxiety, and somatic complaints [12, 13]. A neonatal diagnosis occurs at a time when women are predisposed to postpartum depression that could be exacerbated by the diagnostic process. In one report, a mother and her spouse explained how the devastating news about their newborn's CF diagnosis within the context of maternal postpartum depression precipitated thoughts of suicide and infanticide as a way to escape the anticipated suffering of parent and child [14]. Thus, providers need to know how to recognize signs and symptoms of postpartum depression (see **Table 2**) and refer families to mental health professionals for additional evaluation and treatment.

Guidance on the delivery of diagnosis following NBS tends to focus on the chain of communication from laboratory to family but not on the communication style, locations or best recipients of the diagnosis, nor the training required for healthcare professionals to do this well [15]. There is variation within and between countries in the way in

which the NBS diagnosis is given, sometimes for good reasons such as geography. Therefore standardization of the method of delivery might not be possible, but professionals must be aware of the impact of that information. Some reported impacts from parental feedback are the request that whoever delivers the information must have an expert knowledge of CF in order to ensure that parents can have confidence in the facts provided [16, 17]. Poor communication of the diagnosis can lead to arguments and blame within couples, alterations of future plans such as further pregnancies, mistrust and lack of confidence in healthcare providers [18]. When possible, healthcare providers should also endeavor to give the positive NBS and definitive sweat testing result to both parents, thus preventing one parent from having to share devastating news and complicated genetic

information to their partner.

When mothers report significant depressive symptoms, prompt intervention is critical to improving the mother's mental health and preventing the potential negative impact of maternal depression on the parent-child relationship [19]. Additionally, some parents experience symptoms of post-traumatic stress well after the initial diagnosis [20]. Such symptoms include re-experiencing the psychological trauma of the diagnosis, negative emotional arousal, and hypervigilance of the affected child. While it is valuable to recognize and refer families with significant emotional distress, it is equally important to validate their normative grief experiences, to reflect parents' feelings, to encourage them to talk about their feelings, and to offer support.

**Five or more of the following symptoms and/or impairment in social, occupational or personal functioning constitute clinical depression.**

**Onset can be during pregnancy or after childbirth.**

- Feeling sad most of the day, nearly every day, for at least two weeks
- Sense of hopelessness
- Loss of interest in activities one normally found enjoyable
- Increase or decrease in appetite
- Increase or decrease in weight
- Sleep difficulties (too much or too little sleep)
- Restlessness or lethargy
- Fatigue or loss of energy
- Sense of worthlessness or guilt
- Difficulty concentrating or making decisions
- Thoughts of death, suicide, or harming others

**Table 2** Signs and symptoms of postpartum depression

### 3.1. The influence of the CF team

The manner in which healthcare providers inform and educate parents about the diagnosis can contribute to parents' emotional state and relationship with the care team. Providers can help families through this difficult period by recognizing that their capacity to absorb information will likely be compromised by strong emotions related to the diagnosis and by sleep deprivation typically associated with the 24 hour needs of a newborn.

Parent education about CF and their child's care needs to be tailored to meet individual family needs, rather than a one-size-fits-all approach. This means beginning the educational session by asking parents what they most want to know and establishing joint teaching goals. Then, the provider can follow each parent's lead in determining what content is addressed first and what level of detail to provide. A question (from the parent) followed by answer (by the healthcare provider) approach will help keep parents engaged without becoming too overwhelmed by the amount of information. This approach can also offer the provider insights about the meaning parents ascribe to "cystic fibrosis." It might be helpful for a member of the care team to make an agreed follow-up telephone call to the family a few days later to see how they are doing and answer additional questions that will likely have arisen in the interim.

### 3.2. The parent-child relationship

It is important for providers to appreciate the profound impact that a newborn CF diagnosis can have on the parent-child relationship. One mother eloquently stated,

"From the moment you hear that diagnosis, your relationship with that child, for better or worse, is forever changed." A diagnosis resulting from NBS comes at a time when the parent-child relationship is new, and parents are typically getting to know and falling in love with their babies.

The diagnosis forces parents to redirect their attention and energies towards learning how to administer medications and medical therapies. For some parents, particularly those who might have felt ambivalent about the pregnancy in the first place, the diagnosis of a potentially life-shortening condition could adversely affect their capacities to bond with their baby.

Even when the parent-child bond is strong, the diagnosis of CF can undermine feelings of competence. There are many ways that healthcare providers can subtly support the development of normative parent-child relationships, with just simple comments and observations. Here are some simple tips to ensure the baby is always in mind, not just CF:

- When meeting the family for the first time, smile, speak in a warm tone of voice and congratulate them on the newest member of their family. Remember that first impressions matter! Parents tend to retain vivid memories of these first encounters for decades.
- See the infant beyond the diagnosis and reflect what you see, e.g. "What a beautiful baby!" "What great head of curly hair!"
- Support parent sense of connection

with baby, e.g. “Who do you think [name of baby] looks like?” “[Baby’s name], what a [unique, lovely, great] name!”

- Notice and reflect normative infant behaviors, e.g. when baby cries loudly in response to a procedure, say something like, “S/he is certainly letting us know s/he didn’t like that.”
- Support parents’ confidence in parenting by noticing and amplifying observations of sensitive responses to the infant’s needs, e.g. when parent comfort distressed infant, “You seem to be very good at reading [baby’s name’s] cues; you know just what s/he needs.”
- Support the evolving reciprocal emotional bond between parent and child by speaking for the child, e.g. during an interview, you observe that as the parent talks, the infant gazes up at the parent and occasionally smiles. Pause and say, “I couldn’t help but notice that when you speak, [baby’s name] is completely focused on your face/voice/smile.”
- It can be helpful for parents, particularly those struggling with depressive symptoms, to know that infants are programmed to reflect the emotional expressions of their parents. Thus, infants smile in response to smiling parents; whereas sad parental faces can cause infants to become emotionally dysregulated. Providers can encourage mothers suffering from postpartum depression to smile when they look into their baby’s eyes, even if doing so does not feel genuine. Often

the infant will smile back at the parent which brings a little dose of joy to the parent, whose smile then becomes real.

*Key message: Healthcare teams can support newly diagnosed families by maintaining open communication, encouraging questions and viewing the child as a person first, the diagnosis as secondary*

### 3.3. Grappling with genetics

Upon learning about the genetic nature of the CF diagnosis, some parents may alter their future reproductive decisions [21, 22]. Many CF centers offer families genetic counselling services as a routine part of care or can refer to local genetic counselling services. Taking a non-judgmental approach to such counselling is essential in helping families make informed decisions consistent with the parents’ own beliefs and values.

Parents also report struggles with communicating complicated genetic information with extended relatives of child-bearing age [23]. Misunderstandings about the genetics of CF have been associated with family tension or “finger pointing” and inappropriate blame regarding the CF diagnosis [23]. Additionally, some parents have difficulties knowing when and how best to discuss the implications of the auto recessive genetics of CF to their children as the children approach puberty [24].

Throughout the family lifespan, genetic counselling services can assist families in making reproductive decisions, under-

standing new genetic discoveries, and explaining genetic information to family members.

## 4 Family-centered approaches to counselling and education

There is no doubt that giving parents the news that their infant has a diagnosis of CF is devastating emotionally, but it also interferes with and is counteractive to instinctive parenting drives. The CF specialist team must recognize that there is a responsibility not only to give the diagnosis well but also to provide ongoing contact, assessment and support for the parents in this newborn period. The parents need to get to a stage where CF and normality balance out.

CF teams are preoccupied with test results and medical treatments. The goals for CF teams are amongst other things, to eradicate *Pseudomonas aeruginosa* growth and to have good height and weight averages in their patients. However, parents are preoccupied with protecting, nourishing and nurturing their infant. The diagnosis of a life-long disease with no cure, daily time-consuming treatments and regular hospital appointments are all threats and unwelcome intrusions into family life. Families need to find a way of mentally processing and compartmentalizing these aspects of CF. It is clear that early surveillance and intervention produce better long-term health outcomes for CF, and that NBS is a good thing. Additionally, it has been found that for all biochemical genetic conditions that

are included in a newborn screen, parental stress is found at lower rates in parents who have received early diagnosis than those parents who have children with similar conditions that are non-screened for. Parental stress in non screened conditions results from increased child hospitalization and symptoms [25]. Therefore, CF teams need to adopt a family-centered care approach to ensure the daily management of CF is part of the medical assessment.

An unsought medical diagnosis in a well-baby that intends to keep that baby well initiates a difficult sequence of events, as outlined already. Quite possibly the largest predictor of positive parental wellbeing is having a baby that stays well. Another major predictor can be hypothesized as the parental drive to keep family life in a normal routine, despite having to include CF treatments. This can be exacerbated or ameliorated by the relationship with the CF team [26].

*Key message: Healthcare teams can support newly diagnosed families by recognizing parents as experts in knowing their children and including them as valued members of the team.*

### 4.1 . Working in partnership with the family

Receiving an unsought diagnosis necessitates a different sort of relationship with healthcare providers. Multidisciplinary care is well-established in CF, and standards of care consistently indicate the need for routine availability of psychological expertise within the team. For long-term health

conditions such as CF, it is important that family-team relationships flourish not just function. To do so, they must be grounded in mutual trust [27], and the CF team must take the time to build these relationships. Additionally, the CF team needs to provide a holistic family-centered approach to care [28]. Routine contact requires far-reaching reciprocal communication, including:

- Listening to the emotional as well as factual content of information that parents share
- Realistic hope, by letting parents know about recent research and ever-increasing longevity; offer examples of adults with CF who have families, successful careers, and life achievements
- Respectful interest in parental views of CF and how it impacts on their perception of their baby
- Empathy expressed through: tone of voice, facial expression, reflection of parents' feelings
- Reassurance that their child can have a fulfilling life
- Conversations about the likely impacts of their child growing up with CF
- Review of parental philosophy about illness and enabling a healthy self-image in their child
- Assessment and intervention if needed, for parental psychological needs
- Consideration of differing coping styles within the family
- Conversations about the role of the CF team, individual styles and preferences
- Acceptance that the CF team will be a long-term feature of their child's life

- Emotional support from the care team, e.g. at the beginning of every clinic visit ask parents how they are doing
- Focus on the lifestyle of the child beyond the diagnosis, e.g. personal interests, recent or up-coming social events

*Key message: Healthcare teams can support newly diagnosed families by establishing and nurturing true partnerships with parents.*

The introduction of a medical team into these family's lives can be an imposition and less compatible with a traditional medical model whereby the medical team holds all the knowledge and expertise, while the parents consult and accept what experts advise. In a family-centered model, healthcare providers partner with parents and the individuals with CF (when they reach school age and are mature enough to engage in the partnership) by recognizing parents' knowledge and expertise regarding their particular child with CF. Parental observations and opinions are valued and incorporated into consultations. So, parents are invited and encouraged to collaborate with the care team in developing treatment plans rather than simply to follow instructions. When symptoms are not apparent, parents may question what appears to be aggressive intervention; they might also want to explore second opinions. At other times, parents might recognize subtle changes in children that merit closer attention and require increased or new treatments. Such situations require healthcare providers to

consider parents' perspectives and develop a mutually acceptable management plan.

In short, families become engaged participants and equal partners on care teams, rather than bystanders who passively accept medical recommendations. Long-term health outcomes are better when healthcare teams include parents as partners in the health management of the child. Parents might initially report that they can feel incompetent and left out and it seems like the most important people in their infant's life are healthcare professionals, rather than them as parents.

It is essential that healthcare teams adopt attitudes and approaches that recognize parents as the experts in knowing their children, value parents' opinions, and ensure inclusion of parents in decisions about their children's care. Such partnerships can shift perspectives such that everyone (parents and providers) feels like they are part of the team. This approach has long-term impact for the accuracy of monitoring the child's health and likelihood of adherence to medical recommendations.

*Key messages:*

- *Recognize that parents will need support in creating a balance between parental roles and primary caregivers for their child, and the intrusion of CF treatments and the team into their lives; they view CF differently than you.*
- *Recognize that CF team members must maintain a benevolent, empathic attitude towards parents, e.g. "we care*

*about you (parent) as well as your child; let's work together."*

It is well-documented that at the time of diagnosis, parents need rapidly available expert information, which may or may not include access to the experts themselves [29]. Parents report wanting accurate online information, though often teams guard against internet surfing. Teams must recognize that parents will collect information from a range of sources including social media and online parent forums. The team will not be able to control the expertise that parents acquire and will not therefore be the sole sources of CF treatment guidance. The CF team will be just one source and the long-term relationship will be dependent on the team working hard on tailoring relationships to individual family styles.

Healthcare providers can support parents' quest for information by providing them lists of credible online sources and encouraging them to bring their questions about information they find to future clinic appointments for clarification. Family education begins at the time of diagnosis and continues on an on-going basis. Tips to enhance learning include the following:

- Tailor the amount and content to each family's needs
- Provide factual information that is easy to absorb; give parents a survival guide; offer additional more in-depth information over time
- Avoid medical jargon

- Refer to trustworthy information resources, in print and on the Internet
- Scaffold information—assess what parents already know and build on their understanding
- Use concrete examples
- Conduct teach-backs to assure parents' understanding
- Summarize key points
- Break down complicated information into steps
- Provide written materials or videos to augment verbal explanations
- Offer parents guidance in communicating/educating extended relatives
- Recognize parents may not retain all information shared the first time; revisit important content during subsequent clinic visits

*Key message: Healthcare teams can support newly diagnosed families by tailoring information to the parents' needs; facilitating parents' ongoing search for information.*

## 5 Helping parents cope—anticipatory guidance

*"I went into a big, almost state of denial in the hope that they were wrong... nights crying, worrying, and not knowing what to expect. And just kind of being torn between being happy that he was here... And then at the same time just being angry and resentful... Then [at times], you forget that there's anything wrong with him."*

In this section, the voice of parents is used to illustrate the emotional journey from diagnosis to the end of the first year. Parents cope with the uncertainties associated with their child's new diagnosis by gaining knowledge about the condition and related management. Some parents may also investigate alternative medicine, or seek second opinions [9, 30]. Online communities can also reduce parents' sense of isolation and confer a sense of connectedness to others with similar experiences. Knowledge and support gained from such encounters can provide parents with practical strategies in managing day-to-day challenges of caring for the child with CF while managing a household and maintaining a normative family life. As parents gain knowledge and skills, they become more confident in recognizing their child's symptoms and feel empowered to work with the CF team in addressing the child's needs. Such on-line resources have been found to assist parents in coping with chronic sorrow precipitated by developmental transitions or changes in the child's condition [31].

*Key message: Healthcare teams can support newly diagnosed families by attending to parental wellbeing and family functioning*

As parents gain knowledge and proficiency in managing their child's care, they often become strong advocates for their children by monitoring the quality of care during hospitalizations, constantly asked questions, seeking explanations, speaking up in child's best interest, and challenging medical treatment recommendations [32]. It is important for healthcare providers to understand these behaviors as normal coping mechanisms intended to protect and optimize the child's health and well-being.

Healthcare providers can become allies to parents' efforts by making additional informational resources available to families as needed, collaborating with them in developing treatment plans and co-producing strategies to enhance self-care capacities. It is therefore essential to encourage rather than discourage parental-led research. In these days of cyber-informatics, publications and data are not accessible only by qualified health professionals. Parents must be respected to have the capability to research and review data and new information. It is much better to have the approach: "Can you send me that article, so we can discuss it together?" rather than, "Don't spend time researching, just talk with us, we know best".

The first few months after the diagnosis is marked by searching for information from a variety of sources. At the same time, parents often feel overwhelmed by the

volume of information they need to absorb. One mother explained, "so much information tossed at you at one time; your brain is a sponge, but it can only hold so much." Contextual factors that help parents during this difficult time include support from family and friends, feeling satisfied with the information they had received about what to expect in the future, and being proactive about protecting child's health.

When parents meet with healthcare providers, they have opportunities to ask questions and seek/obtain clarification about misconceptions. Their interpretations of and opinions about the merit of the information will likely be affected by the provider's interpersonal style, perceived authority and expertise (CF knowledge). Thus, providers need to remain mindful of adjusting the type and amount of information that they share based on appraisals of parents' needs for information and capacities to emotionally receive the content. They also need to make themselves readily available to fill parents' information voids during the early weeks and months following the diagnosis. Healthcare professionals also have the opportunity to check other sources of information gained by parents for example when obtaining information from the Internet, parents can access sites with distressing and inaccurate content with no means to process such information.

Some parents describe a process of re-defining their child as having a health problem. One mother notes, "my perfect baby has something wrong." Another



states, *“He’s an extraordinary child and he just needs some extra care.”* To cope with this new realization, parents commonly adopt an attitude of “optimism” and “hopefulness” about their child’s future, while appreciating the present. Learning all they can about CF helps them cultivate a sense of agency that they can affect their child’s health outcomes by following the treatment regimens and protecting their child from illnesses. As parents adjust to the diagnosis, they became less preoccupied with CF and better able to embrace the joys of having a new baby.

*“We’re staying positive, I mean we’re enjoying every day... we just try to enjoy as much as we can. We’re learning just as much as anybody else, probably even more.”*

Some parents describe the diagnosis as a traumatic event that brought members of the family or the couple closer together. Some parents emphasize the importance of the couple working as a team. Parents also become educators for other family members and appreciate having opportunities for the child’s grandparents to be present during the CF team education. Sharing CF information with extended family members serves several purposes. Grandparents can help the parents inform the rest of the family. They can also support parents’ efforts to protect the child, e.g. washing hands before having contact with infant or not smoking in child’s presence. They also provide parents additional competent sources of childcare.

During the early weeks/months some

parents express ambivalent feelings about talking with other parents of children with CF. While recognizing the potential value of sharing feelings and experiences, there is also potential to learn more than newly diagnosed families are ready to know.

*“Just to talk to other people who do know and to vent a little sometimes.... Because people can get a little over helpful too, I think.”*

Once beyond the initial emotional trauma of the diagnosis, parents describe the first 6 months following the diagnosis as characterized by a mix of “ups and downs” and “good and bad days” comprised of “fun”, “exciting”, “exhilarating”, as well as “tiresome”, “overwhelming” but eventually “life as usual”. Although parents may spontaneously introduce topics about CF during conversations, they also focus much more on normative aspects of parenting and derive joy from interacting with the baby, observing sibling interactions, facilitating the infant’s acquisition of new skills, and being a family.

*“It’s fun to see [baby] grow up because he’s getting to be such a little independent person and to see the two of them [siblings] interact... That’s the joy, just watching, having your kids and knowing that they’re happy and healthy for the most part. And spending time together.”*

Parents also report normative challenges associated with having a new baby, e.g., lack of sleep and related fatigue during those early months of their child’s life. They also

talk about less predictability and control in their lives and lack of spontaneity because the baby’s needs take priority. However, these issues are counter-balanced by the infant’s responsiveness.

*“He would cry and you would get up, but then he would smile, and you take one look at him, it’s like ok. You just kind of melt and go, ‘whatever you want to do little guy.’ This is fine. You just kind of go with the flow.”*

Parents become skilled in monitoring their child for signs of respiratory illness by carefully observing the child’s respiratory sounds and differentiating between a “wet” or “dry” cough, noting the infant’s respiratory rate, presence of fever, amount of cough, wheezing, and nasal congestion. When such symptoms occurred, parents seek prompt medical attention. They also describe taking precautions by avoiding environments they believed to be detrimental to child’s health, e.g., people who smoke or public places where the infant might be exposed to infection, particularly during the flu season.

*“Just being a little more cautious with colds... when a cold starts I can’t put it off... I have to watch close to make sure, if she starts coughing, that I let her doctor know right away so she can be on antibiotics.”*

Parents engage in several strategies to cope with the added responsibilities of caring for their child with CF: developing a routine and prioritizing, enlisting help of others, talking with other parents who have an older child with CF, educating

others about CF, and consulting with the CF care team. They enlist the help of other family members and friends to help protect their child from potentially adverse exposures. They may cautiously connect with other families who have older children with CF to gain a glimpse into the future and learn what they might expect. Parents also cope by focusing on their infant’s progress, (e.g. good weight gain), normalizing child’s life, (e.g. birthday celebrations), setting expectations for child’s future, (e.g. planning for college), rationalizing that it could have been worse, (e.g. children with CF have normal cognitive and motor capacities), and making meaning of the diagnosis, (e.g. the diagnosis led to stronger family bonds). From the onset, parents set expectations for a “normal” life in which the child’s extra health needs become part of their daily routines. Being active is particularly important to many parents. Some minimize the severity of CF by comparing it to other conditions that require a wheelchair or are associated with more visible physical anomalies.

*“Overall she’s really been pretty healthy. I mean, she doesn’t really cough much, either. I mean she’s not a big cougher and her lung x-rays were normal, everything was normal.”*

*“Expect him to be a normal child. Yeah, there’s therapy and stuff, I mean there’s a couple of little things you got to do special, but, it’s nothing. Otherwise, everything else is about the same.”*

*“Number one is [I’m] happy that it’s not an exterior type defect, which could be harder.”*



Parents find comfort in social supports through the company of friends, family, and social communities. Some parents, particularly mothers, report a tendency to feel guilty when taking time for themselves or to concentrate on hobbies. Making use of family members as resources for baby-sitting offers couples opportunities to have time for themselves. Some find creative social outlets, e.g. making grocery shopping a family outing. Fathers may be more likely to use physical work or exercise as a coping strategy to deal with negative emotions. Parents may need validation from the healthcare team that time for themselves is acceptable and helpful in managing the emotional impact of the diagnosis.

By 6 months, parents are anticipating and preparing for the future. They describe searching the Internet, particularly from parent forum sites, to learn more about the potential developmental issues that children with CF might face as they get older. Parents try to prepare ways to support their children through potentially difficult issues, e.g., explaining the need for medications and physiotherapy techniques.

*"The thing I worry about is school-age when she has to take her enzymes. The hard part will be the other kids. Cause she'll be having to take pills all the time, and that natural peer pressure, that, 'What are you taking all the time. Pill popper...' I heard that could be kind of hard on some."* It is clear from parents comments that when their baby is age 6-9 months, they have reached a different phase. They have

learned the daily routine and become more familiar with the CF team, and so their enquiries and needs become more future-forward. Some CF teams have considered introducing a more formal review at this point whereby there is a "check-in" with the parents about their current and immediate term questions and concerns. For example:

- "Now you have had some time to think about CF, are there other questions/concerns that you have?"
- "How are the rest of the family?"
- "Have you considered the genetic implications further?"

By 12 months, parents describe their lives as "busy" with emotional "ups and downs." Parents retrospectively reflect that the "heart-breaking" diagnosis felt "like the world was crashing down" because they did not know what to expect. Now, they have a better understanding of the condition and feel more confident in their capacities to support their child's health-care needs. They think about the diagnosis experience much less, appreciate the benefits of NBS that led to an early diagnosis and treatment, and express much more optimism about their child's future. Given that the CF diagnosis is inextricably linked to the child's birth, the child's first birthday is often characterized as a blend of joy and loss. They derive joy from the child's good health and normative developmental progression. Part of their sense of loss comes from the looming presence of the CF diagnosis; while part comes from the normative loss of parenting a "baby," which

can be particularly poignant in parents who decide not to have more children.

*"The fun part is seeing her develop into a little person, seeing those milestones and that development and it's just been such a neat year"*

*"I was a little sad yesterday when she turned one, it's just because she's my baby. And we have decided we're not having any more children."*

Older children and young adults with CF often serve as sources of support and information for parents of infants and young children with CF. Such encounters can foster optimism about their child's future regarding personal relationships, academic success, and career. Healthcare teams also have a central role in reinforcing a sense of hopefulness about the child's future.

*"[our goals are for her to] graduate, maybe some college. For her to be carefree as a child is...she can do anything that she wants. I don't see that there's anything holding her back. Nothing."*

*"I look at it this way, I have two children [one with CF and one without] who I love and cherish. They could have different worlds and you accept that. And I try to build on it and help them to grow."*

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# CHAPTER 3

## Infants with an unclear diagnosis following newborn screening for cystic fibrosis

### Authors

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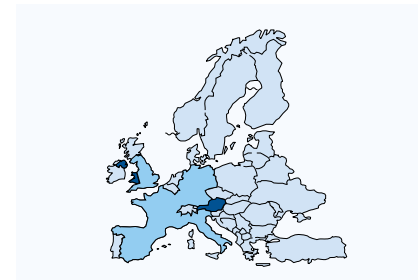
### Introduction

Newborn bloodspot screening (NBS) is a valid strategy to identify infants with cystic fibrosis (CF) and facilitate early pro-active management (see Chapter 1). Measurement of immunoreactive trypsinogen (IRT) from a dried blood spot sample remains the first step for all CF NBS programs. A variety of second step strategies are used to improve the specificity of the screen, including testing for common

mutations of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene. National and regional programs have been established in most areas with a high incidence of CF (predominately Europe, Australasia and North America) over the past 15 years (**Figure 1**). With expansion also came the recognition that NBS for CF regularly results in identification of infants with a positive NBS test, but subsequent inconclusive diagnostic testing [1, 2].

*Key message: NBS for CF results in recognition of infants with a positive screening result, but an unclear diagnosis of CF.*

CF Newborn Screening 2000



CF Newborn Screening 2018



**Figure 1** Countries with national (dark blue) and regional (light blue) newborn bloodspot screening programs for cystic fibrosis (CF) in the years 2000 and 2018.

In 2007, consensus exercises with experts and key stakeholders were undertaken in both the USA and Europe to develop case definitions and recommendations for the evaluation and management of infants with an unclear diagnosis after NBS [1-3]. These distinct exercises resulted in many consistent messages, but also in some important differences, particularly with respect to designation of infants with an unclear diagnosis.

In the United States, the expert panel recommended the term CFTR-Related Metabolic Syndrome (CRMS) to describe these infants [1]. Although not strictly a metabolic disease, the term CRMS provided a clear diagnostic designation that avoided the implication that the infant had CF. In addition, this term facilitated international coding for the condition, which is important in the US healthcare system for accessing financial support for clinic visits and care. CRMS is defined as an asymptomatic infant born with hypertrypsinogenaemia and either (1) persistently elevated sweat chloride concentrations of 30-59 mmol/L with less than two CF-causing *CFTR* mutations or (2) a normal sweat chloride but two *CFTR* mutations, of which no more than 1 is characterized as CF-causing.

In a separate exercise, the European Cystic Fibrosis Society (ECFS) Neonatal Screening Working Group proposed a different name; CF Screen Positive, Inconclusive Diagnosis (CFSPID) [2]. Originally, the word "equivocal" had been considered but "inconclusive" was selected as this is better understood by non-English speakers. CFSPID

was defined as an asymptomatic infant born with hypertrypsinogenaemia and either (1) intermediate sweat chloride concentration (30 - 59 mmol/L) and 0 or 1 *CFTR* mutations or (2) a normal sweat chloride concentration and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences. For the ECFS designation, an infant with two mutations and an intermediate sweat chloride would not be considered CFSPID, in contrast to the US CF Foundation (CFF) recommendations. A key characteristic of both designations is that these are well infants with no clinical features consistent with CF, but an abnormal CF NBS test and indeterminate diagnostic testing.

In 2015 the CFF convened an international consensus conference to update the diagnosis guidelines for CF and CRMS/CFSPID [4]. A group of experts worked on the project for over a year, including two face-to-face meetings, after which guidelines were published. As part of the consensus, a harmonized definition of CRMS/CFSPID was developed (Figure 2). It was recognized that the term CRMS may still have a role in the USA to facilitate coding and access to care, but that CFSPID may be a more easily understood term for families and healthcare professionals.

There was agreement that with better characterization of *CFTR* mutations (principally through the CFTR2 website, (<http://www.cftr2.org/>), the harmonized term would include infants with two *CFTR* mutations (if not classified as CF-causing) and an intermediate sweat chloride. A major advantage of this harmonized approach is that this

will facilitate international data collection, leading to a larger cohort to more reliably determine longer-term outcomes.

*Key message: Infants with an unclear diagnosis after a positive NBS test for CF have the official designation of CRMS/CFSPID, although in practical terms most clinicians use CFSPID in communication with families and colleagues.*

#### Harmonized definition of CRMS/CFSPID [5]

Asymptomatic infant with a positive CF NBS test

PLUS

Sweat chloride <30 mmol/L and 2 *CFTR* mutations with 0-1 CF-causing *CFTR* mutations

OR

Sweat chloride 30-59 mmol/L and <2 CF-causing *CFTR* mutations

Figure 2 Harmonized definition of CRMS/CFSPID

## 1 CRMS/CFSPID prevalence and outcomes

### 1.1. Background

As early as 2005, the detection of “diagnostic dilemmas” which would now be classified as CRMS/CFSPID was recognized to be a potential outcome of NBS for CF [6]. In France (the first national NBS program for CF), it was recognized that considerably more infants were recognized with the *CFTR* mutation, p. [Arg117His]/c. [350G>A] (legacy name, R117H) than would be expected from population studies and the genetic profile of people with CF [7]. From this study it was concluded that the vast majority of people with this genotype would not have any clinical consequence and subsequently R117H was removed from the panel of mutations used by the French in their NBS program.

*Key message: R117H is a common CFTR mutation with varying clinical consequence. R117H can occur in two forms one associated with a polyT sequence (5T), which has a negative impact on gene transcription (resulting in less CFTR protein produced). When expressed with 5T, CF diagnosis is confirmed, but when expressed with other polyT sequences (7T or 9T), protein production is normal and R117H is associated with a variable clinical consequence (for the majority, it has no clinical consequence).*

A single US center, retrospective study reported that 25% of CRMS/CFSPID infants had a respiratory culture positive for

*Pseudomonas aeruginosa*, a higher proportion than would be expected in the non-CF population [8]. One infant’s diagnosis was changed to CF after his sweat chloride concentration increased from 46 mmol/L to 73 mmol/L and his oropharyngeal culture was positive for *P. aeruginosa*. This study was the first to focus on CRMS/CFSPID outcomes and suggested that some of these infants could develop CF. However, the study design and small sample size were limitations to generalize these findings. Below we describe recent larger cohort studies from sites around the world that have provided further insight into the prevalence and outcomes of CRMS/CFSPID.

### 1.2. US CFF patient registry study

Approximately 150 accredited CF Care Centers in the USA enter patient data onto the CF Foundation Patient Registry. In 2010, CRMS was added as a diagnostic category. Between 2010-2012, 1,540 infants with CF and 309 infants with CRMS were entered into the registry (a ratio of 5:1) [9]. Compared to CF infants, CRMS infants had normal growth and nutritional indices, but some infants had 1 or more respiratory cultures positive for CF associated pathogens, such as *P. aeruginosa* (present in 10.7% of cultures) and *Stenotrophomonas maltophilia* (9.4%). A commonly reported genotype was p. [phe508del]/c. [1521\_1523delCTT] (legacy name, F508del)/R117H (7T background), which was present in 26% of the CRMS infants. Hispanic and non-white infants were present in greater proportions in the CRMS group compared to the CF group (19.1% vs. 12.5% and

11.7% vs. 6.5% respectively). The higher proportion of Hispanic infants in the CRMS group may reflect the large number of CRMS infants reported from California, which has a large Hispanic population and uses a NBS algorithm that incorporates extended gene sequencing, resulting in the detection of *CFTR* mutations of unknown clinical significance [10-13]. The increased representation by non-White infants in the CRMS group could also reflect the fact that African-American infants tend to have higher IRT levels [14], while CF itself is less common in the African-American population, leading to a higher number of false-positive NBS tests.

### 1.3. Wisconsin CF NBS study

The state of Wisconsin was one of the first states in the USA to implement NBS for CF, following a randomized clinical trial that started in 1989 [15]. They retrospectively reported their experience in a cohort of 376 patients; whom they classified into 3 groups: CF, CRMS/CFSPID, and CFTR-related disorder (CFTR-RD) [16]. Follow-up ranged from 2-20 years. The median IRT level was significantly higher in the CF group compared to the CRMS and CFTR-RD groups (171 ng/mL vs 94 ng/mL in CRMS and 106 ng/mL in CFTR-RD,  $p < 0.001$ ). None of the CRMS patients were pancreatic insufficient, whereas 83% of the CF patients were. In their study, 39% of CRMS patients had a positive respiratory culture for *P. aeruginosa*, and 70% had 1 copy of R117H on one of their alleles.

### 1.4. California CF NBS study

California has an ethnically and racially diverse population, and as a consequence, the state decided to implement a NBS algorithm that incorporated extended gene sequencing to improve the sensitivity and specificity of the test. Because of this, positive CF NBS tests are regularly associated with *CFTR* mutations of unknown or varying clinical consequence and a normal or intermediate sweat chloride. These infants were given a designation of CRMS and in the California program more CRMS cases were detected than CF cases (approximately 2:1). In the first 5 years of the program, they identified 325 CF infants and 573 CRMS infants [10]. In 20 CRMS infants (5.8%) the diagnosis was changed to CF after the development of clinical symptoms, such as failure to thrive or *P. aeruginosa* infection. Improved characterization of *CFTR* mutations may clarify the situation for many of these infants and a recommendation of the diagnostic consensus exercise is that the CFTR2 website ([cftr2.org](http://cftr2.org)) and other helpful resources, such as the French CFTR database (CFTR-France), are regularly accessed for updates on specific mutations.

### 1.5. Canada/Verona study

Investigators from 7 CF Centers in Canada and the CF Center in Verona Italy conducted a prospective, longitudinal study [17]. They identified 1-2 CFSPID subjects for every 3 CF infants. A cohort of 82 CFSPID infants was matched with 80 CF infants diagnosed through NBS and followed for the first 3 years of life. *P. aeruginosa* and *Staphylo-*

*coccus aureus* were isolated in 12% and 40% of people with CFSPID, respectively. The R117H mutation was present on at least 1 allele in 26% of the CRMS/CFSPID infants. The diagnosis of CFSPID was changed to CF in 9/82 children as a result of reclassification of their *CFTR* mutations as CF-causing and/or subsequent elevation of sweat chloride concentration above 59 mmol/L. Infants that converted from the CFSPID category to a CF diagnosis had significantly higher serial sweat chloride levels ( $p < 0.0001$ ) and serum trypsinogen ( $p < 0.01$ ) levels than did individuals who remained in the CFSPID group. The results demonstrated that sweat testing at age 2 years provided the clearest differentiation between infants who were likely to develop a positive sweat test and be reclassified as CF compared to those who were unlikely to do so.

*Key message: For infants with an intermediate sweat chloride value, repeat testing at two years of age is most likely to identify infants in whom the test will become positive.*

### 1.6. Australian study

A long-term retrospective study of CF NBS positive infants with an intermediate sweat chloride concentration (30-59 mmol/L) was conducted in New South Wales, Australia [18]. A cohort of 29 infants was followed for up to 14 years. Fourteen of the children (48%) were eventually diagnosed with CF. However, many of the infants were diagnosed as “delayed CF” based on non-specific respiratory symptoms, such as cough. In this way, the Australian physicians were differentiating between these

children and those with a more classical CF diagnosis. The longer-term designation of infants with CRMS/CFSPID who develop significant symptoms or signs consistent with CF is very challenging and discussed below.

### 1.7. Summary of CRMS/CFSPID outcome studies

**Table 1** summarizes some of the key findings from the above-cited studies. Although the studies differ in design, data reported, and duration of follow-up, some common themes are apparent. In the US, for every 5-7 CF infants identified through NBS, 1 CRMS/CFSPID infant will also be detected. This ratio will vary depending upon the geographic region, population screened and the design of the NBS algorithm. For example, in California with a program that incorporates extended gene sequencing, the number of CRMS cases identified is higher than the number of CF cases. A small proportion of CRMS/CFSPID infants will be reclassified as CF on the basis of increased sweat chloride, reclassification of their *CFTR* mutations, or the development of clinical signs consistent with CF. Again this depends on the population screened and the method used. Mutations with varying clinical consequences, e.g. R117H, are more common in CRMS/CFSPID than CF, consistent with the greater range of phenotypes associated with these mutations. The large majority of CRMS/CFSPID infants will have no significant clinical problems in the short term. Longer-term data are still limited, and we do not know what proportion will ultimately develop CF or *CFTR*-related disorder.

	Ren <i>et al.</i> [9]	Levy <i>et al.</i> [16]	Kharrazi <i>et al.</i> [10]	Groves <i>et al.</i> [18]	Ooi <i>et al.</i> [17]
<b>Study Design</b>	Prospective Cohort	Prospective Cross-sectional	Prospective Cohort	Retrospective Case Control	Prospective Case Control
<b>Location</b>	USA	Wisconsin, USA	California, USA	Australia	Multi-national
<b>Duration of Follow-Up (years)</b>	1	2-20	5	14 +	3
<b>CF</b>	1,540	300	373	225**	3,101
<b>CRMS</b>	309	57	553	29***	82
<b>CF:CRMS</b>	5:1	5.2:1	0.67:1	78:1	1.8:1
<b>Conversion of CRMS to CF (%)</b>	N/A	N/A	20 (3.7)	14 (48) <sup>†</sup>	9 (11)*
<b>Increased Sweat Chloride <math>\geq 60</math> mmol/L over time</b>	N/A	Initial <30, n=14 (27%) Initial 31-59, n=38 (73%)	22 (3.2%)	4 (14%)	3 (33%)
<b><i>P. aeruginosa</i> %</b>	10.7%	39%	N/A	78.6%	14.6%
<b><i>S. maltophilia</i> %</b>	9.4%		N/A	N/A	4.9%
<b>Pancreatic insufficiency</b>	14 (4.5%)	0	3	4 (13.8%)	0
<b>F508del/R117H</b>	26.1%	36/57 (63%) <sup>‡</sup>	N/A	4 (28.5%)	19.5%

**Table 1** Summary of Recent Studies of CRMS/CFSPID

+28% Lost to follow-up

- \* Diagnosed as CF through reclassification of a second disease-causing mutation or increased sweat Cl<sup>-</sup>
- \*\* Number of CF infants inferred based on reported annual rate of new diagnoses and timespan of study.
- \*\*\* CRMS definition was different from CRMS/CFSPID
- † Diagnosed through clinical signs and symptoms of respiratory disease or PI. Eight were diagnosed through respiratory symptoms
- ‡ R117H(7T) as their second mutation with a class 1, 2, or 3 mutation as the first



## 2 CFTR-related disorder

This is a term used to describe people with a spectrum of conditions that are thought to be associated with CFTR dysfunction, but do not fulfill the diagnostic criteria of CF [19]. The most clearly characterized is congenital bilateral absence of the vas deferens (CBAVD), but other single organ conditions such as pancreatitis and sinusitis have been implicated. There is some debate as to whether this is an appropriate term to describe people with chest symptoms, who do not have a clear diagnosis of CF. For example, some have advocated the use of this term to designate infants with CRMS/CFSPID who then develop clinical features consistent with CF, such as chronic cough or respiratory infection with *P. aeruginosa*. One could argue that this seems appropriate for a child who still lacks the phenotype to conform to a CF diagnosis, although the counter argument is that this simply transfers the family (and the child) from one uncertain clinical position to another. Clearer guidance is needed with respect to the appropriate reclassification of an infant with CRMS/CFSPID to CFTR-related disorder and hopefully with more long-term data, this will be achieved soon. In addition, these data are needed to enable quantification of the associated risk of a well child with CRMS/CFSPID developing a single organ CFTR-related disorder later in their life.

### 2.1. Case study

James is referred to a CF center for diagnostic assessment following a positive NBS

result. James is the first child of the parents and at the assessment is 21 days old, breast-feeding well and gaining weight. The NBS laboratory has reported hypertrypsinemia and two *CFTR* mutations on second tier testing. The mutations are F508del and p.[Asp1152His]/c.[3454G>C] (legacy name, D1152H). The sweat chloride is 28 mmol/L. The parents are informed that the diagnosis is CRMS/CFSPID (shortened to CFSPID) and that the outlook for James is good. He is reviewed regularly but infrequently in the clinic and remains well with another normal sweat test (26 mmol/L) at two years of age. When James is 5 his parents ask if he still needs to come to the clinic every year and what risks he has as an older boy and man with his CFSPID diagnosis. The CF clinician agrees to see him every other year and spends quite a bit of time discussing the risks for CFTR-related disorder as James matures. She outlines the risks for CBAVD and for pancreatitis and the less certain risks for sinusitis and airways disease. She explains it is difficult to quantify these risks but describes symptoms (abdominal pain/cough) and circumstances (wanting to have a family) where James may appropriately seek support and information.

## 3 Current recommendations for management of CRMS/CFSPID

### 3.1. Diagnostic evaluation

The international Diagnosis Consensus Conference made the following recommendation regarding further diagnostic evaluation [4, 5]. Based on the data from

the above studies, CRMS/CFSPID infants should undergo extended genetic analysis consisting of gene sequencing and deletion/duplication analysis to search for additional *CFTR* mutations. At least one follow-up sweat test should be performed, optimally at 2 years of age. Other electrophysiological tests of CFTR function (measurement of nasal potential difference or intestinal current measurement) may be considered in infants with an unclear diagnosis in whom extended gene testing has not been informative; these tests must be done in a validated reference center with trained staff.

### 3.2. US CFF recommendations for the follow-up of infants with CRMS/CFSPID

The US CFF convened an expert panel in 2007 to make recommendations for the evaluation, follow-up and management of CRMS/CFSPID [1]. Because of the lack of an evidence base at that time, the Delphi method was used to achieve consensus. The recommendations are summarized in **Table 2**. Some of the key features of the recommendations include evaluation and follow-up by a CF specialist, routine respiratory cultures, and genetic counseling. Diagnostic tests such as measurement of fat-soluble vitamins, which assess for clinical features of CF were recommended only if clinically indicated.

	2 months	6 months	1 and 2 years	Annually
Sweat test	X	X		
Fecal elastase	X	C	C	C
Respiratory culture*	X	X	X	X
Chest radiograph	C	C	C	C
Abdominal radiograph	C	C	C	C
Spirometry**				X
Counsel against tobacco smoke exposure	X	X	X	X
Genetic counseling	X	C	C	C

**Table 2** US CF Foundation expert panel recommendations for the evaluation and follow-up of infants with CRMS [1].

#### Abbreviations:

**X** = recommended; **C** = consider.

In addition to these recommendations, liver function tests, fat-soluble vitamin levels, and complete blood count should be considered depending upon the clinical context.

\* Only for infants with an intermediate sweat chloride in the ECFS guidance

\*\* When individuals are old enough to perform standard spirometry



### 3.3. ECFS recommendations for the follow-up of infants with CRMS/CFSPID

The ECFS also published guidelines for management of CRMS/CFSPID, again using a Delphi methodology [2, 3]. In contrast to the US recommendations, the ECFS guidance proposed different recommendations for two groups, depending on the sweat test result. Group A were infants with a normal sweat chloride concentration (<30 mmol/L) and Group B, infants with an intermediate sweat chloride concentration (30-59 mmol/L). Recommendations were more interventional for Group B infants, including more frequent follow-up (every 3 months), routine respiratory cultures, salt supplementation, and a lower threshold for initiating oral antibiotic therapy for cough. For both groups, annual review of the CFTR-2 database and repeat sweat testing at 6-12 months were recommended.

In summary, the key themes for the management of these infants are appropriate follow-up, a non-interventional approach to clinical assessment and clear communication with the families. That a significant number of these families are lost to follow-up possibly reflects the challenges of appropriate and clear communication. These families take up (and deserve) a lot of clinic time.

*Key message: US and European guidelines, developed through extensive stakeholder engagement, exist, which provide clear guidance on the evaluation and management of these infants.*

### Unresolved issues and questions

Although the 2016 international consensus exercise developed helpful recommendations for the diagnostic evaluation and follow-up of CRMS/CFSPID, a number of unresolved issues and questions remain. The contributors were unable to establish specific clinical criteria for the reclassification of CRMS/CFSPID infants as CF. Rather, they recognized that this is a complex and integrated decision made by the CF clinician that needs to take into account accumulated clinical and laboratory data [4].

Another unresolved issue is the appropriate duration of follow-up, should a child with a CRMS/CFSPID designation remain well. Although there was a general consensus that at some point, CRMS/CFSPID children may no longer need follow-up visits at the CF Center, there was no agreement regarding at what age the frequency of clinic visits could be decreased or that follow-up could even be discontinued. A key component of this is education; providing the family and ultimately the index child with appropriate information in order that they can assess their individual risk and take appropriate measures to maintain well-being. Although it is difficult to quantify precisely the risks, there is opportunity to inform the families about CFTR-related disorders and appropriate referral pathways if symptoms are apparent. For example if a young man who was identified with CRMS/CFSPID as an infant wishes to have a family, they may want to discuss with their primary care physician the potential for CBAVD.

A major unresolved issue is quantifying

the risks of long-term adverse outcomes. Patients with CFTR-related disorder, who present with single organ problems such as chronic sinusitis or chronic pancreatitis also have, by definition, inconclusive diagnostic testing for CF [19]. In many cases, mutations associated with varying clinical phenotypes, e.g. R117H, are present in these patients. It seems likely that a proportion of the CRMS/CFSPID infants of today will be the CFTR-RD adults of the future. At present we lack the long-term outcome data to accurately determine the risk of CFTR-RD in CRMS/CFSPID infants, but it would be prudent to remain vigilant for clinical features consistent with CF in CRMS/CFSPID infants, as they grow older.

## 4 Summary

As NBS for CF has become more widespread, so too has been the identification of infants with CRMS/CFSPID. Short-term outcome data suggest that the overwhelming majority of these infants remain well. However, there is a small risk of developing clinical features consistent with CF or a definitive conversion to a CF diagnosis. In addition these infants have an unquantified associated risk for developing a CFTR related disorder. Follow-up by a CF specialist is therefore warranted and communication and education are key components of this care package.

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# CHAPTER 4

## The challenge of performing a sweat test on small people

### Authors

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### Introduction

The sweat test remains a key component for establishing a diagnosis of cystic fibrosis (CF) in infants with or without a positive newborn screening (NBS) result [1, 2]. Despite this, 20% of children with a positive NBS result have no sweat test reported in the American CF Foundation (CFF) Registry, and the CF diagnosis is not documented in 10 to 24% of patients from different countries included in European CF registries [3, 4].

### 1 Why (and when) does a child with a positive NBS result need a sweat test?

In NBS programs, a sweat test provides a physiological confirmation of the screening result, or reassurance that a carrier is not a compound heterozygote with an as yet

unidentified *CFTR* mutation [5]. The detection of two mutations in the gene for the CF transmembrane conductance regulator (*CFTR*) in the context of a NBS program supports a CF diagnosis. However, false positives can happen when both mutations are located on the same allele, when the pathogenic significance of one of the mutations is unclear, or in case of a laboratory error. This emphasizes the key role of the sweat test in NBS programs [6].

The European CF Society (ECFS) Standards of Care suggest that the CF specialist team should see infants with a confirmed diagnosis after NBS by age 35 days [7]. This means that a child with a positive NBS result should ideally undergo a sweat test in the first month of life.

*Key message: Every child with a positive NBS result should have a sweat test. The “gold standard” method for a CF diagnosis following a positive NBS screening result is the measurement of sweat chloride concentration.*

## 2 How early can you do a sweat test (age, weight)?

Collecting a sufficient volume of sweat for analysis is challenging in small infants or in preterm babies, possibly because immature sweat glands are less responsive to pilocarpine stimulation. Therefore, guidelines recommend delaying sweat testing in asymptomatic newborns until the infant is more than two weeks of age and at least 36 weeks of corrected gestational age, or weighs more than 2 or 3 kg [8-10]. Children must be normally hydrated and with no significant systemic illness. The skin should be intact at the site of sweat collection. In symptomatic infants, a sweat test can be performed after 2 to 7 days of age, but with a higher probability of insufficient sweat collection. As sweat chloride is elevated in the newborn and drops over the first days of life, no sweat test should be done before 48 hours of age.

## 3 Which sweat testing devices and methods techniques are appropriate?

Since the invention of the sweat test based on the pad method by Gibson and Cooke 60 years ago [11], sweat testing has evolved to ease and improve both sweat collection (with Macroduct® and Nanoduct® systems) and assessment (e.g. by measuring sweat conductivity rather than sweat chloride) (Figure 1). Currently, it is no longer possible to purchase the equipment required to safely perform quantitative pilocarpine iontophoresis, as recommended by

Gibson and Cooke. The acquisition of new equipment will have cost implications that could impact services across Europe [12].

Compared to the classic Gibson and Cooke technique (GCT) requiring 75 mg of sweat, the capillary tube system (Macroduct® collection system) requires only 15 µL of sweat to analyze conductivity and chloride concentration [8-10, 13, 14]. The Nanoduct® sweat test is a micro-flow conductometric device, which induces and analyzes the conductivity of sweat *in situ* while attached to the subject with CF. It allows measurement of sweat conductivity with as low as 3 µL of sweat, which makes it especially suited for newborns and infants [15].

Sweat conductivity reflects the total ion content of the sweat, and while it is highly correlated with sweat chloride, values are not interchangeable [16]. Conductivity is easier to measure than chloride concentration and discriminates well between children with and without CF using both the Nanoduct® [15-17] and the Macroduct® collection system with the Sweat Check® analyzer [18]. Abnormal results for conductivity (higher than 50 mmol/L) should be confirmed by direct measurement of the chloride concentration. A recent study has provided normal values for conductivity by Nanoduct® in infants which supports this test as a suitable sweat test for NBS programs [19]. However, false negatives were reported in one study, attributed to a faulty batch of sensors.

This highlights the need for quality control for these “simplified” measurement systems. Neither the European guidelines for neonatal screening [5] nor the CFF diagnostic consensus [1] recommend sweat conductivity as a standalone diagnostic test for CF, but rather as an appropriate screen to exclude CF.

Other systems or devices such as the CF Quantum® or the Exsudose® need further validation before they can be recommended.



a) Child's arm during sweat test with a Macroduct® system.

After pilocarpine iontophoresis to stimulate sweating, the Macroduct® collection system is firmly attached to the skin of the forearm (picture). Sweat can be seen entering the tube system (blue coloured rings). Chloride analysis can be performed on as little as 15 µl sweat.



b) Child with Nanoduct® sweat test system.

After pilocarpine iontophoresis to stimulate sweating, the Nanoduct® analysing system measures sweat conductivity while attached to the child. Measuring conductivity can be performed on as little as 3 µl sweat.



c) Sweat collection using the pad method.

After pilocarpine iontophoresis to stimulate sweating, a gauze pad or a paper filter is placed on the stimulated site and covered with a plastic film. After 30 minutes, the paper or gauze is removed, and sweat is extracted by elution.

Figure 1 Commonly used sweat collection systems

## 4 What do the guidelines say?

Guidelines have been published by the CFF [9], the Association for Clinical Biochemistry and Laboratory Medicine in the UK [13], and the Australasian Association of Clinical Biochemists (AACB) [10], with only minor differences between them. A detailed standard operating procedure is available, describing the collection and measurement of the chloride concentration [14].

Trained and experienced operators should perform sweat testing according to the current guidelines. Stimulation should always be performed using pilocarpine iontophoresis.

Sweat collection is performed either by the classic pad method (filter paper or gauze) or by the capillary tube system (Macroduct®). The collection time should be at least 20 minutes but should not exceed 30 minutes. The collected volume should be  $\geq 1$  g (sweat weight)/m<sup>2</sup> (collection area)/min (sampling time).

Chloride analysis should be performed either by colorimetry/coulometry or titration with a chloridometer. The measurement of other

electrolytes (potassium, sodium) is not recommended since they are not diagnostic for CF. A sweat chloride concentration of  $\geq 60$  mmol/L strongly supports a diagnosis of CF and values between 30–59 mmol/L are considered intermediate [1]. A value below 30 mmol/L makes a diagnosis of CF very unlikely (Figure 2).

## 5 Where are the pitfalls in doing a sweat test?

Despite exhaustive guidelines about how to perform the sweat test, practical implementation is not straightforward and observed failure rates are often high [20]. The sweat test comprises three phases: stimulation of the sweat glands by iontophoresis of pilocarpine, sweat collection, and sweat analysis. All three phases are vulnerable to many sources of errors (Table 1). Strict adherence to guidelines and implementation of a quality monitoring program are essential for obtaining reliable results in a timely manner.

In the first phase, the most common pitfalls are defective iontophoresis equipment (voltage leak, poor current control) and/or damaged (desiccated) iontophoresis discs. Pilocarpine nitrate and not pilocarpine hydro-

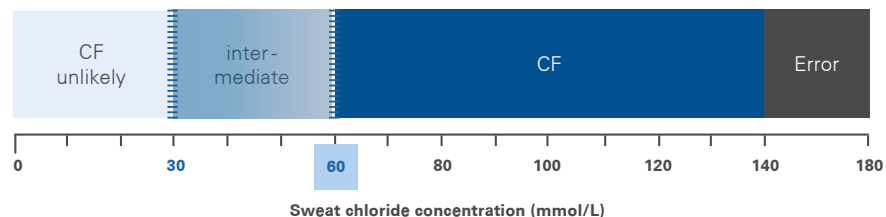


Figure 2 Interpretation of the sweat chloride concentration

chloride should be used for iontophoresis. Sweat collection is challenging in infants as they often produce small amounts of sweat. The child must be clinically stable and well hydrated. Warming of the collection site or covering the infant does not appear to increase the sweat yield. As physiologic solution or even 'sterile water' could contaminate the sample, the skin should be cleaned with distilled or deionized water. The stimulation and collection area should have the same size, and the collection area secured with a stretch bandage.

Before analysis, sweat should not be trans-

ported in the Macroduct® coil as evaporation can occur (unless it is properly sealed), just as with improperly covered gauzes or filter papers. The weight or the volume of the collected sweat is precisely measured. In case of insufficient quantity, sweat should not be pooled from different collection sites or diluted before chloride measurement. Errors in chloride titration can also occur. Measurement should be performed according to specific procedures within a certified lab, preferably affiliated to an external quality assessment program such as the UK National External Quality Assessment Scheme (UK NEQAS), the College of Amer-

### CAUSES OF FALSE POSITIVE RESULTS

Evaporation of the sweat sample
Severe malnutrition
Dehydration
Anorexia nervosa
Atopic dermatitis (eczema)
Familial hypoparathyroidism
Pseudohypoaldosteronism
Adrenal insufficiency
Glucose-6-phosphatase
Nephrogenic diabetes insipidus
Mauriac syndrome
Fucosidosis
Klinefelter's syndrome
Familial cholestatic syndrome
Treatment with topiramate

### CAUSES OF FALSE NEGATIVE RESULTS

Dilution of sweat sample
Edema
Dehydration
Hypoproteinaemia
Mineralocorticosteroid treatment
Some <i>CFTR</i> mutations, for example:
■ c.350G>A/p.Arg117His (legacy name, R117H)
■ c.1364C>A/p.Ala455Glu (legacy name, A455E)
■ c.1651G>A/p.Gly551Ser (legacy name, G551S)
■ 3849+10kbC>T

Table 1 Causes of false-negative and false-positive sweat test results

ican Pathologists (CAP) or the Royal College of Pathologists Australasia Quality Assurance Program (RCPA-QAP).

## 6 What are acceptable failure rates?

After stimulation, a sweat weight of more than 1 g/m<sup>2</sup>/min should be obtained, with sufficient weight for quantification of the chloride concentration. This means that 75 mg of sweat should be collected with a typical 2x2 inch gauze or filter paper with the GCT, or 15 mg with the Macroduct<sup>®</sup> collection system. Samples with a lower weight are labeled as “quantity not sufficient” (QNS) and should not be analyzed. Bilateral sweat testing is an option to reduce the QNS rates, but samples must not be pooled. The QNS rate is the percentage of test occasions in which no sufficient sweat sample was obtained [20]. A high QNS rate after positive neonatal screening poses clinical, psychological and economic problems. In contrast to European guidelines, North American recommendations aim for a failure rate of 10% or less for sweat tests in NBS programs [20].

Several studies have reported failure rates up to 40% for infants below three months of age [20–24]. QNS rates vary widely between centers even when the same technique is used, reflecting differences in populations tested, in the implementation of the method and/or in the experience of the operators. In one study with preterm and term infants less than 6 weeks of age, the GCT method obtained adequate amounts of sweat

(≥75 mg) in only 74% of initial attempts. The failure rate decreased with increased body weight of the infant. Failure rates were 78%, 31%, 23% and 5% in infants weighing <2 kg, 2–3 kg, 3–3.5 kg and >3.5 kg, respectively. Above 4 kg, the failure rate was close to zero [21]. The Michigan NBS program reported a failure rate of 16% in term infants and 49% in preterm infants [22]. The main predictors of insufficient sweat production were birth weight and gestational age. The authors suggest that the failure rate can be reduced by waiting until an infant reaches a corrected age of at least 39 weeks before performing a sweat test. Failure rates were similar using the Macroduct<sup>®</sup> collection system (21%) or the GCT (17%). In the Massachusetts NBS program, the percentage of QNS tests was 17% at the age of 2 weeks, 12% at 3 weeks, 8% at 4 weeks, and 5% at 5 weeks [24]. The failure rate of Nanoduct<sup>®</sup> in 3–4 weeks old healthy infants was 6%, but as high as 39% at 4 days of life [19].

There are few published studies directly comparing collection and measurement methods, especially in infants. [15, 17]. In the Minnesota NBS program, QNS rates for the Macroduct<sup>®</sup> were as low as 2%, compared to 15% for GCT [23]. In a Dutch study, Nanoduct<sup>®</sup> performed better with a failure rate of 7% compared to 22% for the Macroduct<sup>®</sup> collection system [17]. The electrodes of the Macroduct<sup>®</sup> were recently modified to obtain a better fit on the forearm of small infants. No data are available whether this change results in better QNS rates.

*Key message: The likelihood of obtaining a sufficient volume of sweat increases significantly after two weeks of age and for infants weighing more than 3 kg, but in symptomatic infants, the test should not be postponed to achieve these parameters.*

## 7 Variability of sweat tests

There are no studies specifically investigating the biological variability of sweat chloride measurements in infants. Differences between sweat chloride concentrations measured from simultaneous collections are small and without impact on the diagnostic conclusion. However sweat chloride varies over time in the same subject, with changes in the diagnostic conclusion especially in the intermediate range [25].

The median within subject variability between repeat sweat chloride tests was –2 mmol/L, but the 90% limits of repeatability ranged from –18 to +14 mmol/L. This is in accordance with the findings in CF siblings that sweat testing on different days contributes up to 14% of sweat chloride variability [26]. In adults with CF with the c.1652G>A/p.Gly551Asp (legacy name, G551D) mutation, the limits of repeatability for repeat sweat chloride measurements were ±20 mmol/L.

## 8 A presumptive diagnosis of CF when sweat tests confirmation is not possible

The interpretation of every test is dependent on the pre-test probability. In infants presenting with a positive NBS result, symptoms of CF, a positive family history or the identification of two disease causing *CFTR* mutations (defined by *CFTR2* [27]) is consistent with a high probability for CF (presumptive CF diagnosis), and treatment should not be delayed until a valid confirmatory sweat test is obtained. Sweat testing remains necessary though, to confirm the diagnosis.

In contrast, there is a low *probability* of having CF in an extreme preterm infant weighing <1 kg with heart failure, neonatal infection and multiple blood transfusions, and a positive NBS result with two mildly elevated immunoreactive trypsin (IRT) values but none of the common *CFTR* mutations. In such case, it is advised to wait and perform a sweat test when the child weighs more than 3 kg, unless the child has an ethnic background increasing the likelihood of rare *CFTR* mutations. In case of failure to thrive, a low fecal elastase (FE) can be helpful to diagnose pancreatic insufficiency associated with CF.

So far, no algorithm in current NBS guidelines explains what to do when the sweat test fails in a child with an unclear diagnosis (less than 2 disease-causing *CFTR* mutations). One can either wait until the child gains weight and repeat the sweat test, or directly proceed to an extended gene sequencing (EGS) [28]. The first approach increases



the time to definite diagnosis, increases anxiety among families and could delay appropriate treatment. The second approach risks detecting more infants with inconclusive diagnosis (CF screen positive, inconclusive diagnosis, [CFSPID]) when 2 *CFTR* mutations with variable or unknown consequences are found, and the subsequently performed sweat test reveals a normal or intermediate chloride concentration.

Measuring FE after an initial sweat test failure rather than performing EGS can keep the rate of CFSPID low and shorten the time until treatment is started [28]. Low FE is suggestive of pancreatic insufficiency associated with CF, and should trigger treatment start until a valid sweat test confirms or refutes the diagnosis. A normal FE in the first year of life does not exclude CF, as FE can fluctuate, and watery stools (particularly diarrhea) can lead to false low FE values. Therefore a valid sweat test is mandatory, even for infants with normal FE. In children with a *high suspicion of CF* (for example, positive NBS result either with a positive family history and/or 2 CF-causing mutations) and sweat test failure, it is reasonable to perform both EGS and to measure FE. In children with a *low suspicion of CF* (positive NBS result with twice elevated IRT but no CF-causing *CFTR* mutations found), it is more effective to measure FE and to perform EGS only if FE is low or sweat testing repeatedly fails.

*Key message: Failure to obtain a valid sweat test should not delay treatment in infants with a high suspicion of CF.*

## 9 Quality control issues – quality improvement programs

In practice, many deviations from guidelines are observed. High QNS rates are commonly reported. There is definitely a need for quality improvements in sweat testing infants after NBS [20]. There are many recommendations that could improve the quality of sweat testing (Table 2). First and foremost, guidelines should be carefully followed and sweat testing should be only be performed on children who are well hydrated. Equipment should be evaluated periodically and staff should develop or participate in a continuous internal and external quality improvement program (including training and external inspection). Good quality control is also required for newer collecting devices and for conductivity measurements

Despite advances in molecular genetics, the sweat test remains an essential CF diagnostic test. A recent ECFS exercise highlights the challenges of maintaining a high quality sweat test service, as NBS expands and older equipment becomes obsolete [12]. Clear operating procedures, experienced staff and quality control are essential.

*Key message: Sweat testing in infants is challenging and must be performed according to specific guidelines by experienced operators. Clear standard operating procedures and participating to quality control programs could improve the reliability of sweat testing.*

### TO IMPROVE THE QUALITY OF SWEAT COLLECTION:

- Follow the sweat test guidelines exactly
- Test only in children who are at least >2 kg and are at least 36 weeks of corrected gestational age
- Bilateral testing in each child reduces the failure rate, but samples must not be pooled
- The child should be well hydrated
- Limit the number of personnel performing sweat collection to a few well trained individuals. Each technician should perform at least one collection per week to maintain competency
- Evaluate the iontophoresis equipment for voltage leak and current control on a regular basis
- Use pilocarpine nitrate not hydrochloride for iontophoresis
- Place the positive electrode on the inner volar surface of the lower arm where there is a higher density of sweat glands
- Wrap the collection area with a stretch bandage for security
- Ensure the stimulation and collection area are the same size
- Thermal warming of the collection site does not appear to increase the sweat yield
- Do not store or transport sweat in the Macroduct® coil as evaporation can occur
- Accurately determine the amount of sweat collected either gravimetrically or volumetrically
- Participate or develop a continuous quality improvement program (training, external inspection)

**Table 2** Recommendations for quality improvement in sweat collection (adapted with permission from [21])



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# CHAPTER 5

## Nutrition in the first year of life – foundations for the future

### Authors

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### Introduction

Evidence clearly demonstrates the strong relationship between nutritional status, quality of life, respiratory health and life expectancy in cystic fibrosis (CF) [1-3]. The foundations of a good nutritional status should be formed as early as possible. For infants diagnosed through newborn screening (NBS) this should be in the first year of life. For children who did not have the benefit of NBS, nutritional status should be optimized as soon as possible after diagnosis.

Nutrition in the first year of life should focus not only on ensuring an optimal nutrition status as indicated by objective measures including weight, growth and biochemical measures of nutrition, but on laying the foundations for good lifelong eating habits which will be the cornerstone of continuing good nutritional status.

Nutritional status and eating are known to be stressful for families of children with CF. The first year of life is characterized by high rates of growth and weight gain and there are many potential CF related factors that can interfere with achieving optimum growth. Later in early childhood, children can be reluctant to try new foods and negative mealtime interactions occur [4].

The first year of life is therefore a time when families require regular, detailed and consistent nutritional advice. If successful, this advice and support will help children achieve optimum growth rates. Effective nutritional and behavioral counselling for families will enable children with CF to develop positive attitudes towards eating, an enjoyment of food and will lay the foundations for ongoing nutritional wellbeing [5]. This chapter describes how to meet the nutritional needs of infants with CF. Firstly, we outline the key aims and outcomes of nutritional intervention in **Table 1**.

To achieve normal rates of weight gain and growth in infants with normal weight at diagnosis. By 10-14 days of life birthweight should be regained. Thereafter normal rates of weight gain are:

- 200 g per week for the first 3 months of life
- 150 g per week for the second 3 months of life
- 100 g per week for the third 3 months of life
- 50-75 g per week for the fourth 3 months of life

Length should increase by 25 cm over 12 months

Head circumference should increase by 10-12 cm over 12 months

To achieve catch up weight gain in infants with faltering growth at diagnosis. Catch up weight gain is usually 10% greater than above levels so for example 300 g per week in the first 3 months of life

To attain 0 SD (50th percentile) of weight and length for a healthy same-age population by the end of the first year of life. This may not be attainable at an individual patient level but the overall aim for all infants is that weight, length and head circumference are increasing at expected rates for age.

To achieve normal plasma levels of fat soluble vitamins and normal electrolyte status

To enjoy eating a diverse, well balanced diet that meets the nutritional needs of a growing toddler with CF

**Table 1** Aims and outcomes of nutritional intervention in CF infants

## 1 Ensuring the nutritional benefits of newborn screening

The introduction and development of newborn screening (NBS) programs have contributed to proven improved outcomes for CF patients internationally. The process identifies infants with CF in the first weeks of life, often before they present with clinical signs. Whilst methods of screening vary and the practice is not yet universally established across Europe, there is agreement that NBS has major

advantages and is key to optimal care. There are financial and infrastructure barriers to its implementation for some countries. However, there is little disagreement that the practice is cost effective and that the benefits on clinical outcomes outweigh the concerns [5].

The immediate nutritional benefits of NBS include better growth in the first year. In the longer term, good nutrition ensures optimum body mass index (BMI). Longitudinal studies in Europe, Australia and the

US have conclusively demonstrated that optimum BMI is closely correlated with respiratory outcome, reduced hospital stays and life expectancy [6]. In the absence of NBS, children are generally diagnosed with CF later and more commonly exhibit the growth failure and nutritional deficiencies that were historically the early hallmarks of CF. These early nutritional impacts persist well beyond the first year of life, with negative impacts on clinical outcomes.

NBS does not itself protect against poor nutrition outcomes. Whilst infants diagnosed by NBS tend to have more normalized weight by their first birthday, length stunting remains common [7]. NBS allows dietitians and other CF healthcare professionals to take immediate and ongoing steps to ensure that nutritional outcome is maximized and negative nutritional effects are minimized.

The benefits of NBS are believed to largely arise from earlier treatment of pancreatic insufficiency (PI) together with earlier focus and emphasis on nutrition. Indeed several studies show that the nutritional improvements observed in NBS infants are irrespective of feeding choice.

*Key message: NBS for CF has a proven positive effect on short-term and long-term clinical outcomes, especially for nutrition and growth. NBS allows the swift initiation and focus of nutritional therapy. This should be a vital priority for dietitians.*

### 1.1. The nutritional status of the screened infant

In comparison with the non-screened infant the nutritional status of an NBS infant should theoretically be considerably better. It is unlikely that significant growth failure will have occurred. However, whilst appearing well, subtle nutritional deficits need to be considered and addressed. Early NBS studies demonstrated deficits in weight, length and levels fat soluble vitamins in infants at diagnosis [8, 9]. These studies remind CF teams that nutritional status can be abnormal, even in the NBS infant, and that these aspects of care will require detailed attention. Such nutritional deficits may be recoverable simply with the early treatment of PI and use of fat soluble vitamins. If nutritional deficits are significant then the advice later in this chapter on faltering growth should be followed.

More commonly the NBS infant will have a relatively normal nutritional status. The dietitian's priority should therefore be to maintain normal weight gain and growth, along with an optimal intake.

### 1.2. Achieving optimal nutritional outcomes at the end of the first year of life

The first year of human life is widely agreed to be vitally important, influencing both short and long term health. This is elevated further in the context of CF where evidence supports the benefit of good nutritional status being achieved by the end of the first year in clinical outcomes. For newly diagnosed infants, the following steps should be taken in the first year of life to ensure that key nutritional outcomes are met by

the first birthday:

- Prompt assessment of pancreatic function and introduction, education and establishment of pancreatic enzyme therapy (PERT)
- Regular anthropometric reviews and growth monitoring. Growth monitoring should be recorded and interpreted from appropriate nationality growth chart or, if these are not available, the WHO charts ([www.who.int/childgrowth/standards/en/](http://www.who.int/childgrowth/standards/en/))
- Clinic visits every 1-2 weeks until the infant is thriving, then monthly through the first year of life
- Introduction of vitamins A,D,E and K and use of sodium chloride 2 supplementation where indicated
- Timely and CF focused establishment of weaning and feeding skills

## 2 Pancreatic function and pancreatic enzyme therapy

When seeing an infant for the first time after diagnosis of CF, two considerations regarding the digestive system should be made. Firstly, what is the infant's pancreatic function? And secondly, how should this be treated? Pancreatic sufficiency (PS) and pancreatic insufficient (PI) are clinical terms describing pancreatic function. With PI, lipase output is less than 10% of normal levels and fat digestion is clearly impaired. PS means that there is sufficient residual exocrine pancreatic function to allow normal fat absorption and so PERT is not required.

*Key message: Pancreatic function should be assessed as soon as a positive CF diagnosis is made and pancreatic enzyme therapy (PERT) commenced immediately once pancreatic insufficiency is determined or heavily suspected.*

### 2.1 Determining pancreatic status and the need for PERT

To determine PI/PS and the need for PERT, the clinician should carry out the following:

- Check genotype on CFTR2 ([www.cftr2.org](http://www.cftr2.org))
- Carry out an objective assessment of pancreatic function
- Carry out a subjective assessment of malabsorption and maldigestion

#### 2.1.1 Genotype

There is a strong relationship between CF genotype and pancreatic status. People with class I–III CF mutations on both chromosomes are likely to be PI whilst those with at least one class IV–V CF mutation are more likely to be PS. However it should be noted that atypical cases have been described, including those who are homozygous for class I–III CF mutations and yet appear to be PS. Whilst there is a clearly documented relationship between genetics and pancreatic status this should not replace the need for objective and subjective assessment of pancreatic status and absorption in each individual [10].

#### 2.1.2 Objective assessment of pancreatic function

The presence of clinical signs and symptoms suggestive of maldigestion and malabsorption do not accurately determine

pancreatic function, so an objective assessment should be carried out. Tests to assess pancreatic function include the co-efficient of fat absorption, fecal pancreatic elastase 1 (FPE-1 serum trypsinogen, <sup>13</sup>C mixed-triglyceride breath test and direct pancreatic stimulation studies [11]. Many of these investigations are not routinely available in clinical practice, so are not discussed in detail.

Of the currently available tests monoclonal FPE-1 is highly predictive of PI. FPE-1 has a high degree of sensitivity and specificity, is widely available, relatively easy to perform and is not affected by exogenous PERT, so can be used to confirm PI in people with CF who have already commenced PERT. In general, FPE-1 levels under 100 µg/g stool are predictive of severe PI and the need for PERT. FPE-1 levels of 100–200 µg/g stool are associated with moderate PI. The need for PERT in such situations needs to be considered, taking into account nutritional status and abdominal symptoms. Caution is needed when interpreting FPE-1 in large volume dilute stool and in premature infants.

In addition meconium ileus is associated with PI. Infants presenting with meconium ileus and subsequently diagnosed with CF should have FPE-1 measured to confirm pancreatic status, but should be commenced on PERT as soon as oral or enteral tube feeding is established.

#### 2.1.3 Subjective assessment of malabsorption and maldigestion

A subjective assessment should not replace an objective assessment but is a useful

adjunct to decision making regarding the need for PERT, especially when genotype is unknown and objective results delayed. The factors to take into account in a subjective assessment include:

- Rate of weight gain since birth to presentation or diagnosis. If significantly less than expected, this may be indicative of malabsorption
- Timing and volumes of feed. If this is significantly greater than expected for age and body weight, this may be indicative of malabsorption and infant feeding to compensate for this
- Number of stools, quality and consistency of stools in the day. If significantly more than expected, offensive smelling stools or obvious fat in the nappy, this could indicate malabsorption
- Malabsorption profile with distended abdomen and wasted limbs
- A significant correlation between vitamin A and E deficiency and PI has been reported at the time of diagnosis but plasma levels of fat soluble vitamins may not be available at the time of diagnosis

Following the objective and subjective assessment of pancreatic function:

- PERT should be started in all infants with two *CFTR* mutations associated with PI and a confirmatory FPE-1
- PERT should be started in all infants with unknown *CFTR* mutations but with FPE-1 <100 µg/g stool, and should be considered in infants with FPE-1 between 100-200 µg/g stool
- PERT should be considered in infants and young children with clear

subjective signs of malabsorption and sub-optimal weight gain whilst awaiting objective confirmation of PS/PI

- PERT should not be commenced in infants and children with one or two *CFTR* mutations associated with PS unless there is other objective evidence of PI

## 2.2 Determining the appropriate dose of PERT for infants

A Cochrane review revealed limited evidence on the relative dosages of enzymes needed for people with different levels of severity of PI, optimum time to start treatment, and variations based on differences in meals and meal sizes [12]. Digestion requires the enzymes lipase, protease and amylase which are all produced in the GI tract, mainly in the pancreas. Amylase and protease are also secreted by the salivary glands and by the stomach (pepsin) respectively. Lipase is also produced in minute amounts in the stomach. Therefore, in people with CF and PI, digestion of dietary fat is particularly dependent on PERT.

Small cohort studies have demonstrated enhanced fat absorption when PERT is more closely titrated to fat intake. Clinical and dosing data from cohort studies and audit of clinical practice indicate doses of 500–4000 units of lipase per gram of dietary fat, with a mean requirement of 1,800 units of lipase per gram of dietary fat per day to achieve optimal absorption of fat and other nutrients in children and adults. For infants, best practice recommends a starting dose at the lower end of the dose

range seen in cohort studies followed by up-titration of the dose to achieve optimal control of malabsorption symptoms and to optimize weight gain. In a prospective multi-center study of two PERT formulations, an almost-acceptable co-efficient of fat absorption of 77–78% was achieved with doses of 992–1077 iu lipase /g fat in young children with CF [13].

The GI tract in CF is an extremely complex milieu with many factors influencing the efficacy of PERT, including the pH, motility, the microbiome and other medications. In addition dietary fat provides 50% of the energy intake of infants. This is considerably higher in relation to body weight than children and adults. Therefore infants are likely to require higher doses of PERT in relation to their size. This will be even more apparent in infants who require nutrient dense infant formulas which have an even higher fat content than breast milk or standard infant formula. For these reasons, some infants will require higher doses to control symptoms. However the CF team must remain aware that, on average, doses should not exceed 10,000 iu lipase/kg body weight per day [14]. At significantly higher doses, residual symptoms of fat malabsorption or sub-optimal weight gain should be investigated for non-CF causes, or adjunctive therapies such as proton pump inhibitors and H2 antagonists may be required.

PERT is available in a range of formulations. Of the available preparations, enteric-coated microsphere preparations are recommended. The pH-sensitive

coating protects the enzymes from inactivation by stomach acid, dissolving only when the pH exceeds 5.5 within the small bowel, thereby minimizing the possible effect of gastric pH on inactivation of PERT. Products at the lower end of the enzyme concentration range (5,000–10,000 units lipase per scoop or capsule) are preferred for infants and younger children as this enables better titration with the smaller amounts of food consumed by infants and young children.

## 2.3 Dosing and administration of PERT for infants and young children

The relationship between fat, food and PERT and the impact on digestion and absorption is fascinating to CF health-care professionals. Parents of infants and young children, however, need practical advice regarding how much PERT to give with meals, snacks and drinks and how to best give PERT.

**Table 2** presents the recommended starting doses of lipase, based on cohort studies of PERT in infants. Doses should then be titrated based on symptoms, weight gain and volumes of feed given.

Breastfeeding brings particular concerns for families regarding PERT dosing, as the volume of feed taken is totally unknown. The family should be reassured that breastmilk has excellent digestibility, naturally contains some lipase and that enzyme dose can be titrated based on symptoms and weight gain.

Once weaning begins, the amount of PERT needed with meals and snacks must be considered. Early first weaning foods include fruit, vegetables or small amounts of cereal mixed with the infant's usual milk. These weaning foods have a relatively low fat content, so can be given in small amounts without PERT.

NUTRITION MODE	RECOMMENDED NUMBER OF LIPASE UNITS
<b>Breast fed infants</b>	
Short breastfeed (<20 min)	1500-2500
Long breastfeed (>20 min)	2500-5000
<b>Infant formula</b>	
Standard (3.5 g fat per 100 ml)	1500-5000 per 50–100 ml
Nutrient dense (4-5 g fat per 100 ml)	2500-5000 per 100 ml

**Table 2** Lipase starting doses

As the weaning diet expands to include more protein and fat containing foods, most infants will need a starting dose of 2,000-5,000 units of lipase with small portions of weaning foods. Based on the typical fat content of the weaning diet towards the end of the first year of life, mealtime lipase doses of 10,000-30,000 units are typical. Most snacks at this age contain about 5-10g of fat, requiring around 5,000-10,000 lipase units. Dietary education on the fat content of foods will be needed to enable parents to make an assessment of the amount of fat in each meal and snack and therefore estimate the amount of PERT required.

Parents should be given practical information on estimating the fat content of foods and meals to enable them to adjust the doses of enzymes sufficiently, always bearing in mind that PERT is only one small part of digestion and absorption. Practitioners should avoid being overly prescriptive regarding enzyme dosing advice, as this can lead to anxiety around PERT dosing and eating. This in turn can lead to behavioral eating difficulties and heightened anxiety in the parents. Equally, the dosing of PERT is an issue which causes a great deal of anxiety for parents of infants with CF, so it is key that dietitians give practical but evidence based advice to support families.

At weaning and beyond, providing it is not impacting on weight gain, it is very helpful for parents to learn about foods that can be given without PERT. This is especially useful for snacks, given normal eating

behaviors such as nibbling at snacks, dropping food on the floor and refusing foods. This prevents parents from worrying that they have administered PERT so something must be eaten, which can lead to children being given inappropriate foods such as chocolate cake for breakfast. Snacks that can be offered without PERT are: all fruits and vegetables (except avocado), bread sticks, rice crackers and other snacks with a fat content less than 1-2 g per portion consumed providing these are not eaten in multiple amounts. For example, most toddlers can be given a biscuit containing 2 g fat without PERT, especially since some of the biscuit is likely to be on the floor rather than in their mouth. If however the child happily eats 3 of these biscuits, they will probably need PERT.

Administration of microspheres to infants can be challenging as they are not particularly easy to swallow and it seems counter intuitive to families to be trying to give their infant something such as microspheres from a spoon. Many families will correctly ask why isn't this a liquid? This question presents an ideal opportunity to explain the rationale for the microspheres. For infants aged 4 months or less the enzyme microspheres should be given orally with all feeds. The prescribed dose should be mixed with a little fruit puree or other low allergen food or a little of the infant's usual milk and given from a baby spoon. Parents should check that microspheres do not remain in the mouth post-feed especially if giving with milk. Beyond the age of 4-6 months PERT can be mixed with any soft food and given

before or during meals. The timing of PERT administration may be a factor in achieving optimal digestion and absorption, so for large volumes or longer feeds it is suggested that the total dose is split and given at the start and during the feed.

Enzyme capsules should be swallowed whole at as early an age as possible. Most children can manage this from the age of four to five years. Until then, parents should be advised to prevent their infant from chewing the microspheres. Parents should also avoid crushing the microspheres in an attempt to aid administration, as this reduces enzyme efficacy. Until a young child is able to swallow capsules, the enzyme microspheres may be mixed with a small quantity of food or liquid on a spoon and given immediately before the meal. Microspheres should not be mixed with the whole meal as this is likely to lead to the child crunching or chewing the microspheres, reducing enzyme efficacy. Another practical point to consider is that infants and young toddlers are more likely to accept sweet tastes, and the introduction of savory and bitter tastes takes more time. PERT is often given in relatively sweet foods such as fruit purees and yogurts. Given before the savory compo-

nent of the meal, the initial sweet taste of PERT can then make the savory food more difficult to accept. Would we eat our dessert before our main course? If this does seem to be a problem then it is best to mix the PERT with a non-sweet food such as pureed vegetables.

### 3 Breast feeding and formula feeding

Whether a family chooses breast feeding or infant formula feeding, the healthcare team, and dietician in particular, should ensure that the infant's intake meets the minimum macronutrient and fluid requirements. In infants with faltering growth the intake must provide 120-150% of usual requirements.

**Table 3** summarizes daily intake requirements by body weight, as recommended by European and WHO guidelines. These requirements are the absolute minimum requirements for an infant with CF, since they often need more intake to support optimum growth.

Age in months	kcalories/kg/day	Protein g/kg/day	Fluid ml/kg/day
0-3	100-110	2.0-2.5	150-180
4-6	90-100	2.0-2.5	120-180
7-12	90	1.5-2.0	100-120

**Table 3** Daily requirements for infants



### 3.1 Breast feeding

Breast feeding is internationally recognized as the best source of exclusive early nutrition and this is no different in the context of CF. Breast feeding should be encouraged in newly diagnosed infants through education, support and information [15]. Breast milk contains lipase and beneficial nutritional, immunological and growth factors and has been shown to support optimal growth in infants with CF.

Consistent with WHO guidance for all infants, exclusive or full breast-feeding should be promoted for at least 4 months (17 weeks, beginning of the 5th month of life) and exclusive or predominant breast-feeding for approximately 6 months (26 weeks, beginning of the 7th month). These same goals can be applied to infants with CF providing that optimal weight gain and growth are achieved.

Several studies and large datasets indicate that breastfed CF infants go on to have better lung function and fewer infections than formula fed infants [16]. Additionally, breastfeeding is recognized as beneficial for the mother's health.

If at the time of diagnosis, breastfeeding is established then the mother should be encouraged to continue breastfeeding. However some factors negatively influence the ability to breastfeed. Stress plays a role in breast milk production and mothers are likely to feel stressed following a new diagnosis of CF. Therefore extra care and support may be required to ensure that breastfeeding can continue. If needed, obstetric, midwifery or other relevant health-

care professionals can provide advice on the psychosocial elements of breastfeeding and pharmacological agents to aid breast milk production.

In the case of infants with meconium ileus, and depending on the level of surgical intervention required, the infant may require a short period without oral or enteral feeds. In this situation mums should be encouraged to express and store breast milk for future use. Parents should be reassured that breast feeding will be possible once the infant has recovered from the acute phase of post meconium ileus treatment, and that breastfeeding can potentially help recovery and growth of the small intestine.

*Key message: Breast feeding is the optimal exclusive nutrition for the first 4-6 months. In addition to its wide ranging health benefits, specific advantages to the child with CF are recognized.*

### 3.2 Formula feeding

For parents who choose not to breastfeed, a standard formula in adequate volumes should ensure that the nutritional requirements are met in the majority of infants with CF. Non-CF infants will generally thrive on about 150 ml/kg body weight/day standard infant formula. However infants with CF may require feeding volumes in excess of 150 ml/kg to meet their requirements for protein and energy.

If infants with CF are unable to consume the larger volumes needed to meet requirements in such situations, a nutrient dense infant formula can be advised.

Such formulae usually contain approximately 2.5 g protein and 100 calories per 100 ml compared to 1.5 g protein and 65 calories in standard infant formulas. If nutrient dense infant formulas are not available then a standard infant formula can be concentrated. Standard infant formula of 12-13% is prepared by adding 3 scoops of powder per 100 ml cooled boiled water. The formula can be concentrated to 15-20% by adding 4 scoops per 100 ml.

Maintaining the protein energy ratio of feeds at 8-12 % is important as this will help ensure optimum rate and composition of catch up weight gain (see [Table 4](#)) For this reason use of a nutrient dense formula or a concentrated standard infant formula are preferable to the addition of calorie supplements alone, as the latter will depress the protein energy ratio of the feed. [23]

With the exception of significant surgical resection for meconium ileus (see section below) or in the rare case of co-existing cow's milk protein allergy there is no indication for specialist infant formulas such as protein hydrolysates, amino acid formulas or formulas containing medium chain triglycerides in infants with CF.

	kcalories/kg	Protein(g)/kg
<b>Requirements for a 2-month old infant</b>	100-110	2.0-2.5
<b>150 ml/kg breast milk or standard infant formula</b>	98	2.25
<b>180 ml/kg breast milk or standard infant formula</b>	117	2.7
<b>200 ml/kg breast milk or standard infant formula</b>	130	3
<b>150 ml/kg nutrient dense infant formula</b>	150	3.75
<b>150 ml/kg 15% concentration standard infant formula</b>	120	2.85
<b>150 ml/kg 20% concentration standard infant formula</b>	150	3.5

**Table 4** Theoretical nutritional provision on different formulae for a 2 month old infant

## 4 Weaning

Weaning, sometimes known as complementary feeding, is the transition to solid food and liquids other than breast milk or infant formula. It should be a positive and enjoyable experience for both child and parents. Parental education is key to successful weaning and later eating habits. Weaning can be a source of anxiety and stress for families as they have to consider which foods to give, whether the infant requires a higher energy intake, how to provide this higher energy intake and how to manage PERT. Support and dietary counselling from the CF team is invaluable. As weaning progresses, parents may perceive

difficult feeding behaviors in the infant. However these are often normal, age appropriate human responses. Educating parents how to overcome difficult situations with foods is useful.

The fundamental principles of weaning, regarding why, when, what and the timing of transition with textures and tastes is the same for an infant with CF as any other infant. The overall aim is to have established a balanced varied diet high in energy and protein and key micronutrients by 12 months of age.

A 2017 European statement [17] gives clear guidance on the introduction of food into the infant's diet and is summarized in

**Figure 1.**

### Why wean?

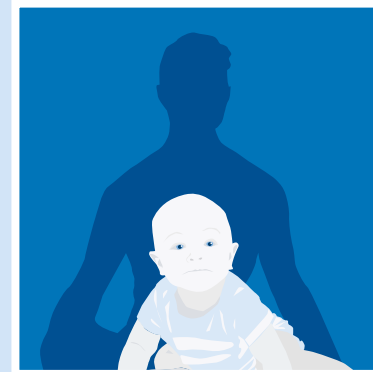
All infants reach a stage where breast milk or infant formula cannot supply sufficient nutrients to support growth. At this stage the introduction of complementary foods becomes essential to ensure the correct delivery of what is needed to support growth and provide essential micronutrients such as iron. Weaning involves the introduction of foods in a time window where infants are most conducive to developing their feeding skills. Weaning either too early or too late can have negative implications on their progress and therefore supporting the development of weaning is an essential part of the CF team.

### When and how to wean?

- Complementary foods should not be introduced before 4 months but should not be delayed beyond 6 months
- Weaning foods should always be offered from a spoon to encourage good oral feeding skills and not added to infant feeding bottles or drinks
- Practical physical signs your infant may be ready to start solid food are shown in the pictures below

**Figure 1** Introduction to food

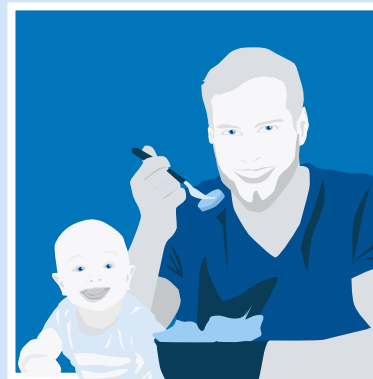
### See if your baby can...



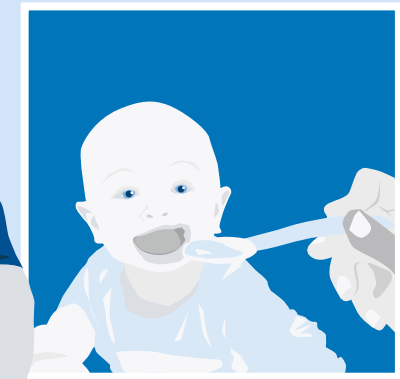
Support themselves in a seated position. Premature babies might need extra support.



Hold their head in a stable position



Show an interest in other people eating



Lean forward and open their mouth towards a spoon or food.

**Figure 1** Introduction to food

**See if your baby can...**

Put things to their mouth and make munching, up and down movements.



Your baby might show one of these signs first, but it is recommended to wait until you see a few before starting weaning.

**Which foods to include in the weaning diet?**

- Start with the introduction of weaning foods once a day and gradually increase the amount and variety of foods
- Suitable first weaning foods include pureed vegetable, fruit and baby rice
- Infants should be offered foods with a variety of flavors and textures including bitter tasting green vegetables such as broccoli and spinach
- Once the infant is taking a larger variety of first weaning foods then the introduction of protein containing foods including pulses and dairy products can begin
- Continue breast or formula feeding alongside weaning foods
- Potentially allergenic foods may be introduced any time after 4 months
- Iron is a key micronutrient for infants and young children and both breast milk and infant formula is relatively low in iron. The weaning diet should include iron-rich food including meat products, good sources of non-hem iron such as dark green vegetables and iron-fortified foods such as breakfast cereals

**Figure 1** Introduction to food

**Which foods to include in the weaning diet?**

- Due to the increased sodium requirements in CF, foods containing salt should not be restricted but parents should be given specific advice regarding salt intake

In the later stages of weaning from 9 months of age onwards parents should be educated on energy dense foods to ensure that these are included in the child's intake to maximize energy intake. Such foods include full fat dairy products, full fat margarines and spreads including nut spreads, the use of oil in cooking

**Which foods should be not be included in the weaning diet?**

There are actually very few foods that cannot be included, this is very helpful to reassure families that a varied and mixed diet is a reality. The only foods that should be avoided are:

- Honey, before the age of one year, due to the risk of infant botulism
- Whole nuts, grapes or any foods that may be a choking risk

**Figure 1** Introduction to food

Fat intake reduces throughout the first year of life. Breast milk and infant formula provide 50% of their calories from fat and as infants begin to consume a mixed diet the fat intake reduces to 30-40% of calorie intake by the end of the first year of life. In children with CF a normal to high-fat diet should be encouraged with fat providing around 40% of calories. The child should be established on family foods with a range of colors, textures and flavors. Successful weaning and introduction of foods provides a firm foundation for positive future eating habits.

Practical tips for successful weaning and establishing positive eating habits include the following:

- Take cues from the child and go at the child's pace

- Eat with your child
- Stop the meal if the child is very unhappy
- Avoid distractions
- With the exception of avocado all fruits and vegetables can be introduced without additional PERT. This gives parents the opportunity to progress with the early stages of weaning without worrying about how much PERT to give. This can be a positive first step in establishing a variety of foods
- Discourage the "more is better" approach and encourage parents to focus on positive mealtimes/quality experiences as a firm foundation for positive eating behaviors
- Encourage the child and give positive feedback to reinforce good behaviors at meals

- Encourage messy eating and messy play. Exploring food through feel and touch is an important part of learning and progressing with foods
- Ensure that all those involved in feeding the child follow the above consistently

*Key message: Weaning is an essential developmental milestone to transition infants to family foods. Positive weaning helps to lay the foundation for optimal food choices and positive feeding behaviors. This will have long-term benefits for children with CF.*

## 5 Vitamin supplementation

Biochemical evidence of fat soluble vitamin deficiency has been observed at diagnosis in newborn screening programs [18]. Many other factors can contribute to low levels of fat soluble vitamins including suboptimal PERT, inappropriate vitamin supplementation regimens, increased utilization, reduced bioavailability and reduced bowel length due bowel resection.

Poor adherence to vitamin supplementation has been shown in older people with CF as a contributory factor to fat soluble vitamin deficiency and this could also be a factor in infants and young children if parents do not adhere to the advice given regarding vitamin supplementation.

Ideally supplementation of vitamins A, D, E and K should commence once the infant's vitamin status is determined. However, enough is known about the fat soluble vitamin status of infants with CF to commence supplementation as soon as practical after diagnosis, with annual assessment of plasma levels and adjustment of the doses thereafter. Readers are referred to the many publications on vitamin status and supplementation in CF for more detailed information on this area of nutrition [15, 19].

Here we provide baseline information on suggested doses, summarized from previously published consensus statements [15, 20]. The availability of vitamin supplementation suitable for infants varies across Europe, so practitioners should consider available products and select those which best meet the below doses.

Water soluble vitamins appear to be well absorbed and although there are case reports of deficiencies, these are rare complications of CF. There is no evidence to recommend routine water soluble vitamin supplementation in infants with CF.

Vitamin A	<1500 IU
Vitamin D	400–2000 IU
Vitamin E	400–2000 IU
Vitamin K	300 µg/kg/day rounded to the nearest mg

**Table 5** Suggested daily doses of vitamins A, D, E and K for infants with CF

## 6 Sodium chloride supplementation

CF is characterized by increased losses of sodium and chloride in sweat, with the potential for sodium depletion. For infants both breast milk and standard infant formulas are relatively low in sodium. At 150-200 ml/kg infants will only receive the minimum requirement of 1.5 mmol/kg for normal infants. This is unlikely to meet the needs of infants with CF. Sodium is an important growth factor, it stimulates cell proliferation and protein synthesis and increases cell mass. Sodium chloride deprivation inhibits growth and can lead to reduced body weight and length, reduced muscle protein and reduced brain protein, RNA and lipids compared with controls [21]. A recent study confirmed a less invasive way to monitor sodium status via urine analysis, and also demonstrated sodium depletion in the study group [22].

The current consensus view is that individual assessment is needed but that most infants will benefit from an additional 1-2 mmol sodium/ kg/day.

From a practical point of view, sodium chloride solution tastes extremely salty and can cause vomiting when administered to infants. For formula fed infants, the doses required can be easily added to 1-2 feeds each day. Even if the infant doesn't complete the whole feed they will receive most of the sodium chloride. For breastfed infants administration of sodium chloride can be more difficult, but given the relatively low sodium content of breast milk (around 7 mmol per 1000 ml) it is worth persevering with this.

## 7 Faltering growth

The expectation is that CF infants should grow normally with centile positions similar to any other infant. Normal healthy growth is defined using centile positions, ideally from the WHO growth charts. The tracking of consistent and proportional centiles on these charts is good evidence of optimal growth.

### 7.1 How often should growth be measured?

Weight, length and head circumference should be measured every 1-2 weeks until a pattern of consistent proportional growth is seen on centile charts. Weight, length and head circumference should continue to be measured as standard at each clinic visit, plotted on the growth chart and the trend assessed.

### 7.2 What is faltering growth in an infant with CF?

Whilst definitions for this vary in publications the most appropriate definition is "deviation from a previously held centile."

However, a deviation from a centile over short periods of time may not be obvious in infants. Therefore the CF team should also ensure that infants are gaining weight as described earlier in this chapter.

The centile charts in **Figure 2** are examples of proportional, good growth (**2a**) and faltering growth (**2b**). The importance of optimum nutrition in infants with CF, prompt investigation into possible causes of faltering growth, and early intervention cannot be overstated.

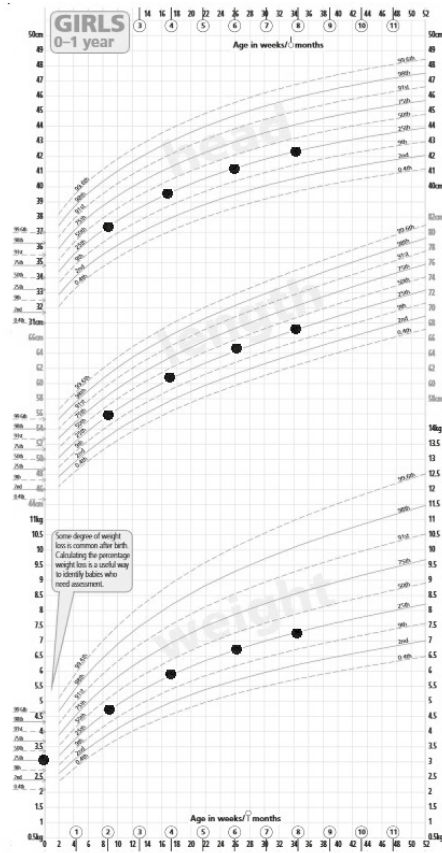
### 7.3 Investigating faltering growth in an infant with CF

To investigate food intake:

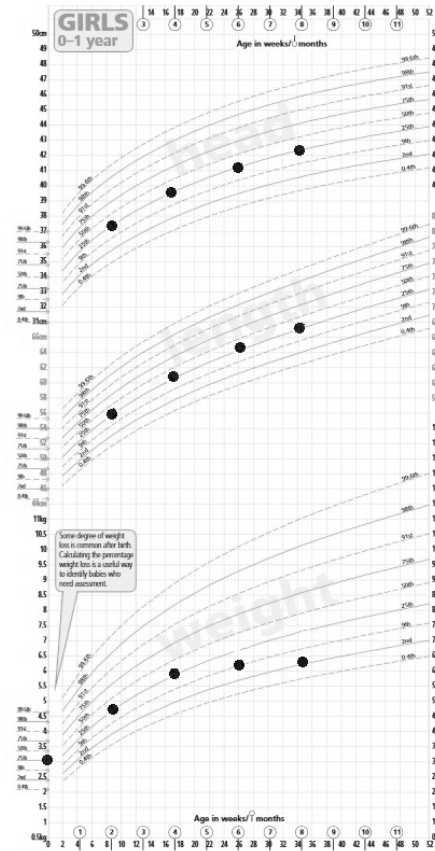
- Perform a detailed dietary history to confirm actual intake. This should include information about day and night feeds, timing and duration of breast feeds and confirmation that formula feeds are being made correctly
- If weaning has begun, perform a detailed history to assess actual intake of food, type and amount of food being consumed
- Confirm that PERT is being given correctly by all those involved in the administration. Check there is no evidence of enzymes being left lodged around the mouth

To investigate output:

- Review stool output and any subjective evidence of malabsorption such as large, loose stools, offensive smelling, obvious oil or pale color
- Review of losses from vomits/possets which may be a concern if there are frequent or large volume vomits
- Confirmation of adequate sodium status with urinary sodium assessment and calculation of fractional excretion of sodium. Reference ranges should be based on local biochemistry



**Figure 2a** Proportional centile positions and consistent centile tracking



**Figure 2b** Growth faltering across 2 centiles for weight

Other potential causes of faltering growth include:

- Presence of gastro-esophageal reflux (to be assessed and treated)
- Respiratory exacerbations
- Sodium depletion

*Key message: Growth faltering in infants with CF should be investigated and addressed without delay. Interventions to improve growth should continue until catch up to an appropriate centile position, at which time nutritional advice reverts back to normal CF advice.*

### 7.4 Interventions to manage faltering growth in the early stages

The advice below can be helpful where an infant's rate of weight gain over 4-6 weeks is less than expected.

- For breast fed infants:
  - increase frequency of feeds, consider waking for feeds at night if not naturally occurring, check that maternal diet and fluid intake is adequate
  - Seek advice from a lactation consultant in case of concerns about breast feeding technique
- For bottle fed infants: if volumes are  $\leq 150$  ml/kg, increase the volumes offered to 180-200 ml/kg/day
- Review PERT dosing, particularly in case of subjective or objective evidence of fat malabsorption. Increase dose incrementally by 2500-5000 units until symptoms resolve. If feeds or meals are longer than 30 minutes, give half the enzyme dose before the feed/meal and half during or at the end of feed/meal
- If PERT is theoretically appropriate but subjective or objective evidence of malabsorption persists, medication to increase the pH of the small intestine should be considered. This may further enhance absorption by increasing the efficacy of PERT
- If the child is over 6 months of age, focus on higher energy weaning foods. Encourage additional supplementation of diet with fats
- Optimize sodium supplementation
- Prompt investigation and treatment of gastro-esophageal reflux if demonstrated

### 7.5 Interventions to manage continuing or established faltering growth

Where there is a sustained deviation from a previously held centile or the interventions above have not corrected nutritional deficits a detailed medical review is indicated to ensure all other reasons for faltering growth are investigated and excluded.

Nutritional interventions to consider include:

- For formula fed infants advise changing to a nutrient dense infant formula or concentrate the standard infant formula as discussed earlier
- For breast fed infants advise replacing a proportion of breast feeds with a nutrient dense infant formula or a concentrated standard infant formula
- Ensure that PERT is adjusted to take account of the higher fat content of both concentrated infant formula and nutrient dense formula (4.0-5.0 g/100 ml) compared to both breast milk and standard infant formula (3.5 g/100 ml)
- If there are clear reasons why feed volumes are low (e.g. significant respiratory exacerbation) consider short term nasogastric feeding to ensure adequate volumes. This should be undertaken only in exceptional cases as it is likely to impact on establishment of good oral feeding if used inappropriately

### 7.6 What to consider when using nutrient dense formula

Use of nutrient dense formulas or concentrated standard infant formula should be reserved for infants with faltering growth or who are unable to consume sufficient volumes to support optimum growth. Their use should be the exception rather than the rule for infants with CF they are not required as a default. In the case of faltering growth neither exclusive breast feeding or standard formula can provide adequate calories or appropriate % of energy from protein to support optimal catch up (standard formula 8%, human milk 6%). When choosing an energy dense formula the WHO recommends a feed with 8.9-11.5% energy from protein for optimal gain of lean and fat mass [23].

Nutrient dense formulas or concentrated standard infant formula should be used until the infant's weight has caught up to the centile corresponding with their height or previously tracked centile. At this point the infant can be gradually transitioned back to the previous feed.

### 7.7 Support for families with a CF infant with faltering growth

Aside from the nutritional and medical interventions to manage faltering growth, the support required for families cannot be overstated. Whilst the acute aim is to swiftly restore the weight and growth, the fundamental overarching aims of the nutritional management of CF must be considered. In particular this includes reassuring families that faltering growth can be corrected and that continued establish-

ment of good eating and feeding behaviors should continue to be progressed. Failure to minimize parental anxiety can have long standing effects on the child's eating habits.

### Nutrition in infants with meconium ileus

Infants who require surgery for meconium ileus often present considerable challenges in the management of feeding and PERT [24]. Expert nutritional management of these infants is essential if they are to benefit from the same optimum nutrition as any other infant with CF. Particular challenges are to be expected in infants who require resection or stoma formation compared to those with either conservative management or primary closure following laparotomy.

If the infant has received conservative management, breast milk or standard infant formula is recommended as per previous sections.

If the infant requires stoma formation, parenteral nutrition will probably be required until oral or enteral tube feeding can be fully established and weight gain maintained. Parenteral nutrition in infants is associated with complications such as cholestasis, therefore appropriate selection of parenteral lipids and early introduction of oral or enteral feeding is required to minimize these risks.

Compared to conservative management,



the choice of feed for infants with stomas with or without resection is determined by the extent of small bowel resection, stoma position in the bowel and parental preference for breast or formula milk. Expressed breast milk has multiple benefits and should be encouraged as the first choice of feed following surgery. It is likely that actual breast feeding will not be possible in the early post-operative days and weeks as large volume feeds must be avoided to reduce stoma output. Small volume feeds are critical to establishing enteral tolerance and minimizing complications of parenteral nutrition. Mothers should be encouraged to express and freeze breast milk for future use and should be reassured that breast feeding will be possible as stoma output reduces.

There are no randomized controlled trials to determine optimal feed choice in post- meconium ileus infants with stoma. However most dietitians would agree that if breast milk is not available, hydrolyzed protein and low osmolality medium-chain triglyceride containing feeds should be used. These feeds are well absorbed and tolerated by infants who have had small bowel surgery and stoma formation.

Continuous feeding using an enteral feed pump may occasionally be needed to ensure that the feed has been completely absorbed; slowing the delivery of feed to the bowel can improve absorption. Significant small bowel resection is rare in infants with CF so this type of enteral feeding is rare.

Infants with meconium ileus may have nutritional deficit; those who are breastfed may require complimentary feeds and bottle-fed infants will require feed volumes of 180-200 ml/kg to achieve optimum weight gain and growth. If this is not achievable then the use of more concentrated hydrolyzed protein formula or nutrient dense infant formula may be indicated but this should be introduced slowly with careful monitoring of GI tolerance and with appropriate pancreatic enzyme supplementation.

Meconium ileus is associated with PI so all infants presenting with meconium ileus will require PERT when feeds are introduced, irrespective of the feed used. Infants presenting with meconium ileus who require stoma formation are at an even greater increased risk of sodium deficiency as stoma output is known to have a high sodium content so this presents an additional factor in sodium depletion.

In summary the potential nutritional problems in an infant with meconium ileus should not be underestimated. Infants with stoma require detailed attention to parenteral nutrition, gradual introduction of oral feeds and reduction of parenteral nutrition, and careful sodium and PERT management. This should ideally be managed by an expert pediatric CF dietitian.

Parents should be reassured that most infants will go on to feed normally and be well nourished, providing that nutrition in these early weeks and months is optimized until stomas are closed and the gut is once again in continuity.

## 9 Eating habits at the end of the first year of life

The expectation is that CF infants should grow normally with centile positions similar to any other infant. Normal healthy growth is defined using centile positions, ideally from the WHO growth charts. The tracking of consistent and proportional centiles on these charts is good evidence of optimal growth.

The aim of the healthcare teams in CF is to ensure that by the end of the first year of life:

- children with CF will be enjoying a well-balanced, varied diet which, if indicated, will have increased calories in simple forms using family and familiar foods
- children with CF will have given up bottles and are drinking all fluids from a cup
- families will be eating together and if additional calories are needed this can be done by making simple additions to the usual family food without impacting on the weight or fat intake of non-CF family members
- food will be in its usual place, which is a sociable and enjoyable experience and not seen as treatment

Good daily food intake by the end the first year of life is defined as consuming:

- the same foods as the rest of the family
- two good meals each day and one smaller meal
- 2-3 snacks each day which ideally are nutrient rich and not empty calories such as sweets
- 400-600 ml full fat milk
- at least 3 servings of calcium rich dairy

- foods such as milk, cheese and yogurt
- 5 age-appropriate portions of fruit and vegetables
- some fiber containing foods such as whole grain breads and cereals

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# CHAPTER 6

## Nutritional complications in the early CF years

### Authors

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### Introduction

Adequate nutrition is a cornerstone of good CF care and numerous studies have shown that survival improves with good nutritional state [1]. Several consensus documents about nutritional care in CF have been published [2].

In the CF clinic we face challenging nutritional issues at all ages. All children with CF need extra attention and more frequent follow-up. This chapter focuses on five clinical challenging situations that can occur in the first few years of life: meconium ileus and its consequences, rectal prolapse, not gaining weight, vomiting and raised liver tests.

### 1 Case study 1 - Meconium ileus

#### **A 2 day old baby vomits greenish material. After abdominal X-ray, meconium ileus is diagnosed**

Meconium ileus is often the first manifestation of CF and occurs in approximately 20% of patients diagnosed with CF. It is most commonly associated with class I-III *CFTR* mutations, specifically c1521\_1523delCTT/p.Phe508del (legacy name, F508del), c.1624G>T/p.Gly542X (legacy name, G542X), c.3846G>A/p.Trp1282X (legacy name, W1282X), c.1657C>T/p.Arg553X (legacy name, R553X,) and c.1652G>A/p.Gly551Asp (legacy name, G551D). A patient with two copies of the most common F508del mutation has a 24.9% risk of presenting with meconium ileus, a patient with F508del plus another mutation has a 16.9% risk of presenting with meconium ileus, a patient with two other *CFTR* mutations has a lower risk of 12.5% (based on 2010 US CFF registry data). Evaluation of the risk of meconium ileus in CF monozygotic and dizygotic twins also found an increased

concordance in monozygotic twins [3].

If not identified prenatally, meconium ileus most commonly presents as intestinal obstruction within hours of birth associated with initiation of feedings, which induces abdominal distention and bilious emesis. Patients can also display delayed meconium passage. In these cases the differential diagnosis includes not only CF with meconium ileus, but also conditions such as meconium plug (hard stool covered with mucus), Hirschsprung's disease, jejunoileal atresia, volvulus, and bowel perforation.

The initial workup of any newborn presenting with bowel obstruction begins with a basic abdominal film. Usually both flat and upright films are needed. In meconium ileus, abdominal films often show dilated loops of bowel with or without air-fluid levels. Air may not be present in the rectum if there is complete obstruction. Abdominal calcifications may be present if there has been a contained, or now closed, intestinal perforation. The classic "soap-bubble" sign seen when meconium mixes with swallowed air may also be observed (Figure 1). Other diagnostic imaging that may be beneficial includes barium enema which often shows microcolon due to proximal obstruction in the terminal ileum and disuse below the obstruction. A barium enema may also be beneficial in detecting malrotation by localizing the position of the cecum. A sweat chloride test can be done as early as 48 hours after delivery as long as the newborn is not edematous and is well hydrated. Otherwise genetic testing can be sought.

Medical management of simple meconium ileus has been developed around the use of hyperosmolar enemas under fluoroscopic guidance to ensure that the solution reflexes into the terminal ileum. This technique was first described in 1969 by Noblett utilizing Gastrografin® which contains diatrizoate meglumine, 0.1% polysorbate 80 (Tween 80), and 37% organically bound iodine amounting to a solution with 1940 osmol/L [4]. Gastrografin® acts as a direct solvent and shifts fluid into the bowel lumen instead of competing with the intracellular space surrounding the mucosa.

When utilizing such a hyperosmolar agent, adequate hydration (150 mL/kg/day minimum) via an intravenous line (IV) is imperative to avoid hypovolemia that can lead to shock and end-organ damage including necrotizing enterocolitis. An IV line is necessary to respond appropriately to complications such as shock or the need for emergent surgical intervention. Most commonly with Gastrografin®, a 1 in 4, or 1 in 2 dilution with water is infused under low hydrostatic pressure through a catheter under fluoroscopy through the rectum until the terminal ileum is reached. Occasionally, a newborn will require 1-2 repeated enemas every 12-24 hours. Perforation risk has been described as low as 2.7% and as high as 23%. Surgical intervention is often pursued if hyperosmolar enema is unsuccessful after two attempts. Surgery entails milking of the intestinal contents. If this fails, or if the meconium ileus is complicated by bowel perforation, an ileostomy is performed.

Noblett recommended administering 5 ml of 10% N-acetyl cysteine (NAC) via nasogastric tube every 6 hours to dissolve meconium proximal to T1, after successful delivery of a hyperosmolar enema [4]. However instilling NAC via nasogastric tube risks aspiration and chemical pneumonitis. Therefore it is now common to administer warm saline rectally every 12-24 hours for several days to encourage further evacuation of meconium. This is often followed by serial abdominal films to evaluate for the presence of remaining meconium.

Although many different solutions have been studied, Gastrografin® has consistently demonstrated the best outcomes in mouse models and in clinical use. Despite this evidence, Omnipaque™ (240 350 mOsm/kg water) and Cysto-contrast® II (400

mOsm/kg water), both less toxic and less hyperosmolar than Gastrografin®, are often used today. The rate of success of contrast enemas ranges widely from approximately 30% to 80%.

Overall in the modern era, studies show that children with CF who have meconium ileus do as well in terms of long-term outcomes of lung function, nutritional status, and infection risk as age-matched children with CF and no history of meconium ileus. However, patients with meconium ileus have a substantially increased risk of developing distal intestinal obstruction syndrome (DIOS) later in life (50% risk versus 15% risk in the general CF population).



#### MECONIUM ILEUS

- The plain abdominal films show distended loops of intestine with thickened bowel walls
- A large amount of meconium mixed with swallowed air produced the so-called "ground-glass" sign, which is typical of meconium ileus

**Figure 1** Plain abdominal radiograph in a newborn infant demonstrating "soap bubble" sign characteristic of meconium ileus.

## 2 Case 2 – Rectal prolapse

### A 2 year old child with CF strains at stool and on examination an edematous mass protruding from his anus was found.

A circumferential, full-thickness protrusion of the rectal wall through the anal orifice is termed rectal prolapse. Although the exact incidence has not been determined, it is common and self-limited in children with CF younger than 5 years, with equal incidence between genders. Various anatomical variants and medical conditions including CF predispose a child to developing rectal prolapse. El Chammas *et al.* recently reported that just under 4% of children with CF had rectal prolapse and that the most common associated factor was constipation. The prevention of constipation in these patients is very important. Patients should drink enough water, eat fibers, and use stool softeners as needed, followed by professional follow-up and adjustment of pancreatic enzymes replacement therapy (PERT). In a very small minority of patients, surgery is required if conservative management fails [5].

## 3 Case 3 – Failure to thrive

### A 4 year old boy with CF exhibits faltering growth and is crossing centiles downwards.

Advances in nutritional management have contributed to improved survival in CF over the past four decades. In the clinic we meet children with CF who are not thriving at

the expected rate and they cross centiles downwards, either in terms of weight to age or length to age or weight to length.

Failure to thrive (FTT) is often defined as a weight for age that falls below the 3rd percentile on multiple occasions or weight deceleration that crosses two major percentile lines on a growth chart. Use of any single indicator has a low positive predictive value, and a follow-up of several weight points on the growth chart is recommended to diagnose FTT. In CF Clinical Practice Guidelines it is recommended that all children reach weight for length status or a body mass index (BMI) percentile of  $\geq 50\%$  [6].

Factors of growth impairment in CF are: increased resting energy expenditure (REE), increased nutrient losses (malabsorption), decreased nutrient intake (low caloric intake) and pulmonary infections. Another factor, although unusual in this age range, is abnormal glucose metabolism (impaired glucose tolerance test [IGTT] or indeterminate glucose tolerance test [INDT], or cystic fibrosis related diabetes [CFRD]). All these factors lead to consumption of a higher level of energy and affect the body metabolism.

The first step to ensure adequate growth in a child with CF is to ensure sufficient consumption of protein (calculated to age and appropriate weight, g/kg) and calories (calculated to age and appropriate weight\*120-150% kcal/kg). If supplementation to reach the daily energy needs is needed, we recommend supplementing meals with foods from the protein group

(such as dairy, poultry, fish, egg, lentils etc.) and calories from fats (such as sesame, olive oil, peanut-butter, almond spread, cream, hard cheese etc.).

Appropriate digestion is needed along with adequate energy and protein consumption. PERT should be monitored carefully once there is evidence of intestinal malabsorption. Clinical signs include fatty or frequent stool, and poor weight gain. However pancreatic insufficiency by measurement of fecal pancreatic elastase-1 should be confirmed. This latter test appears simple and reliable with concentrations  $< 100 \mu\text{g/g}$  indicative of severe pancreatic insufficiency. Approximately 92% of infants with CF have pancreatic insufficiency by 1 year of age [7]. Adequate PERT is necessary to avoid high fecal energy losses. Enzymes are given with all foods and milk products including hydrolyzed and semi-hydrolyzed formulas containing medium chain triglyceride (MCT). The enzymes should be administered at the beginning of the meal, and sometimes in the beginning and middle of the meal if the mealtime is longer than 15-20 minutes.

The recommended initial dose of enzymes is as follows for different age groups:

- Infants: 2000-4000 lipase units per 120 ml formula or per breast-feed or 5,000 IU lipase/kg/day.
- Children  $< 4$  years: 1000 lipase units/kg body weight/meal and 500 lipase units/kg body weight/snack. Doses greater than 2500 lipase units/kg body weight/meal are not recommended.
- Older children: maximum dose recommended is 10,000 IU lipase/kg/day.

If malabsorption signs persist, the dose may be increased gradually, until symptoms have resolved and objective assessment of growth and fat absorption is positive. Enzyme dosing varies with patient age, degree of pancreatic insufficiency, amount of fat ingested, and commercial preparation. These recommended doses should be used as a starting point, and adjusted accordingly to control signs and symptoms of malnutrition and an appropriate growth rates [8].

Babies and toddlers require granules, which should be taken with fruit sauce and sometimes need lubricant or barrier cream pre-treatment to the perianal area to avoid skin irritation. For most children, meals should not last too long (around 20-30 minutes) to encourage better absorption and better eating behavior. Once solid food is introduced, enzymes should be titrated by fat intake. We begin with 10,000 lipase units for every 5 grams of fat, and adjust for best absorption. The maximum recommended dose of 10,000 IU lipase/kg/day is often exceeded in babies and very low weight toddlers.

Children with CF who have faltering growth should attend the clinic at least every 2-4 weeks until they are thriving. The clinic visit must include nude weight, length and, ideally, head circumference measurements. A personal child-based meal schedule should be tailored. Hence for some children small, frequent meals are more appropriate while for others bigger, spread out, meals will be better accepted.

Thriving is a critical issue during childhood in CF. Caregivers want the child to eat enough calories and protein, they want them to swallow the appropriate amount of enzymes, and to eat the meals in a reasonable time frame. This can lead to a lot of pressure during meal time, and to power struggles between the feeder and the child. The caregiver should be asked about the atmosphere during meals and any pressure around meal times should be discussed and counteracted. Force feeding should be detected by gently asking targeted questions and should be stopped. Feeding strategies should be creatively changed, and caloric supplementation should be increased or redeveloped, including supplement of medical nutrition formulas. In some cases of persistent malabsorption despite appropriate PERT, treatment with a proton pump inhibitor (or other antacid) may improve pancreatic enzyme activity by reducing stomach acidity.

### Supplemental feeding

If the growth rate is insufficient and all oral supplementations and feeding manipulations are insufficient for appropriate growth, we might consider enteral feeding (EF) via a nasogastric tube, percutaneous endoscopic gastrostomy (PEG) and jejunal feeding.

The CF Foundation recommends enteral tube feeding as a means to improve age dependent anthropometrics in people with CF who are unable to consume adequate calories and protein to meet growth/weight maintenance goals, despite appropriate evaluation and intervention by a multidisciplinary team [9].

The EF regimen can be implemented as night feeding in the shortest time as possible, and as tolerated by the child. Feeding can be established at a low rate and volume, and increased gradually, every week by 5-10 ml/hour until reaching the desired rate and volume. Oral enzymes can be given all at once at the beginning of the night feeding or can be split between the beginning (2/3) and end (1/3) of feeding. In a minority of cases, enzymes are administered at the beginning, middle and end of the night feeding.

An after-meal bolus of EF is another option, usually for smaller children or for those who cannot tolerate night feeding. This option can provide smaller amounts of supplementation compared to the night feeding. After the child has finished his oral meal, a bolus of formula is given by syringe or machine, as quickly as possible. An extra amount of oral enzymes should be given just before the bolus. The EF formula can be the same formula taken orally or an extensive hydrolyzed formula, as best tolerated by the child. Glucose levels monitoring are recommended with EF.

An EF regimen can be reversed by gradually reducing then stopping as the patient's growth velocity normalizes. After a period of time with exclusively oral eating and no EF, the PEG can be safely removed. If weight gain has been proven after 4-6 weeks of nasogastric tube or when the expected EF period is over 3 months, the child would benefit from placement of PEG.

### How is a PEG is inserted?

PEG placement takes approximately 15 minutes and is normally carried out under general anesthesia by a team of 2 operators: an endoscopist and an appropriately trained assistant who is responsible for skin puncture and insertion of the guide wire.

The patient is placed in the supine position, and the anterior abdominal wall is cleaned using an appropriate operative skin disinfection protocol. An endoscopic examination of the esophagus and stomach is then performed. The stomach is inflated to bring the anterior gastric wall in close contact with the abdominal wall; this helps to displace other organs such as the colon away from the gastrostomy site.

The endoscopist's assistant identifies the correct skin puncture site. The intention is to enter the stomach close to the junction of the gastric antrum and body. The site is located by using endoscopic transillumination — a bright point of light should be seen on the abdominal wall (see **Figure 1**). If a clear point of transillumination cannot be identified, the assistant should not proceed with the puncture. This difficulty strongly suggests either that the stomach is displaced up beneath the ribs or that the colon lies interposed between the stomach and the abdominal wall. The assistant applies digital compression at the proposed insertion site, and the endoscopist confirms that this is a suitable entry point in the stomach. The correct insertion point is usually mid-way between the umbilicus and the junction of the costal margin and left mid-clavicular line.

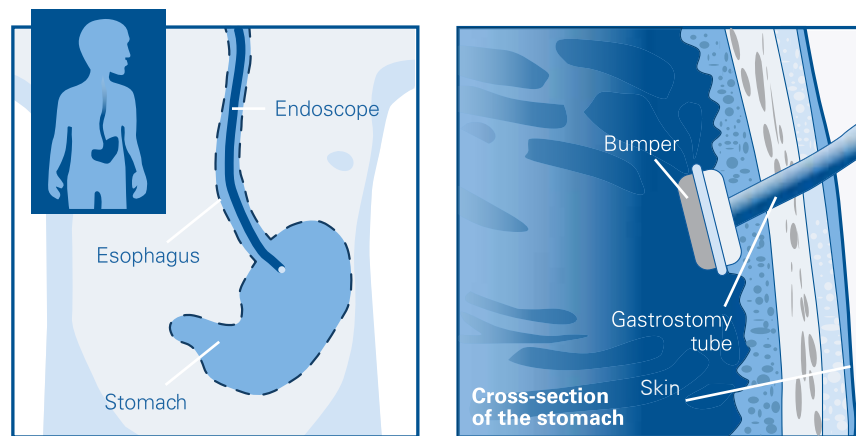
The endoscopist confirms entry of the trocar and its overlying plastic sheath inside the stomach. The trocar is withdrawn while leaving the sheath *in situ* to provide a secure track for the guide wire. The guide wire is passed through the plastic sheath, the endoscopist grasps it with the forceps, and the sheath is then withdrawn as the guide wire is slowly drawn into the stomach. The entire assembly including endoscope, forceps, and guide wire is then withdrawn.

The guide wire now passes through the abdominal puncture, into the stomach and out through the mouth. The proximal end of the guide wire is tied to a loop on the end of the gastrostomy tube. The distal end of the guide wire is gently pulled, drawing the tube and its internal bolster through the mouth, down the esophagus, into the stomach and out through the puncture site, until the internal retaining device or bumper comes to lie on the anterior gastric wall (see **Figure 2**).

Sometimes a small incision at the puncture site is needed to facilitate passage of the gastrostomy tube out through the skin. The distal end of the tube, still attached to the guide wire, is now cut off. An outer retaining device such as a disk is passed over the external tube, and this holds the tube at the abdominal wall so that it cannot slip back into the stomach. Local anesthetic is usually injected around the incision point to reduce postoperative discomfort. The tube is now cut to the desired length and the adaptor plug is inserted. A small amount of iodinated disinfectant may be applied to the

external retaining device. A dry dressing is applied to the site for removal after 24 to 48 hours. Finally, the endoscope should be reinserted to confirm that the inner retaining device is positioned correctly and to ensure that there is no bleeding.

Peristomal wound infection is one of the most common complications of PEG. The likelihood of wound infection is the result of bacterial load at the stomal site and factors relating to the patient's primary condition e.g. immunosuppression. Stomal infections may derive from the oropharyngeal flora as the PEG traverses or from the abdominal skin. In a recent prospective study on complications of PEG in 92 children, 6 infections were observed (6.5%) [10]. Current practice includes prophylactic antibiotics.



**PEG Procedure**

**Figure 2** Insertion of a percutaneous endoscopic gastrostomy (PEG)

## 4 Case 4 – Vomiting

### What to do when an infant with CF vomits /throws up?

Gastroesophageal reflux is a physiological phenomenon of effortless retrograde flow of gastric contents into the esophagus. GER is common in infants and young children and is self-limiting. GER that causes troublesome symptoms or complications like esophagitis is referred to as gastroesophageal reflux disease (GERD). The prevalence of GERD is increased in CF [11]. The pathophysiology is due to dysmotility of the lower esophageal sphincter and the pancreatic insufficiency causing decreased clearance of acid in the upper gastrointestinal tract.

There are numerous tests available to investigate a child for GERD. However history and physical examination may show that growth is within normal range and symptoms may be minimal.

Nutritional recommendations to reduce symptoms of GERD should be adjusted to the child's preferences, and generally include:

- Thickening of the food (with corn flour or a commercial thickener) or a thicker preparation of the food, especially blended foods. GERD improves as the child is weaned to solid foods.
- Giving smaller meals more frequently; less pressure will be exerted on the stomach and the overall intake will be preserved.
- Separating solids from liquids during the meal (not drinking water while eating but only a while after or a little before).

If these actions do not lead to improvement, antacid treatments (H<sub>2</sub> antagonists or proton pump inhibitors) can be prescribed. When there is doubt about the efficacy of treatment, testing using the pH probe or esophageal manometry may occur. Upper endoscopy may be performed and lower esophageal biopsies examined to assess the severity of the GERD.

In very rare cases fundoplication may be performed particularly if there is recurrent aspiration of gastric contents into the lungs affecting pulmonary function. Characteristic lung disease associated with GERD includes upper lobe or right lower lobe disease, more symptoms at night and early bronchiectasis.

## 5 Case 5 - CF related liver disease?

### A four year old with CF is found to have raised liver function tests. Could this be CF related liver disease (CFLD)?

With its frequently asymptomatic presentation and wide spectrum of manifestations, CFLD can be very difficult to diagnose in the early phases of development. This increases the risk of important aspects of this disease being ignored or minor transaminase abnormalities being over-interpreted. Screening for liver involvement should be performed by annual clinical examinations, biochemical tests and ultrasonography. The diagnosis of CFLD should be made once other causes of liver disease are excluded.

**Spectrum of hepatobiliary disease in CF**

Focal biliary cirrhosis is the classic histological CFLD lesion, reported in up to 70% of CF patients in autopsy studies, although it only progresses to multilobular cirrhosis in 5 to 10% of patients, generally by the end of the first decade of life. Given the possibility of progression to portal hypertension and related complications, multilobular cirrhosis is considered the most clinically-relevant CFLD lesion. Sclerosing cholangitis is rare in childhood but is reported in the large majority of adult patients with CFLD, even in those without clinically-apparent liver disease. Gallbladder abnormalities (notably micro- or non-functioning gallbladder and cholelithiasis) are frequent but symptomatic disease is uncommon.

Mild steatosis is detected in CF patients of all ages with a wide reported range of frequencies (10% to 70%). Although considered benign in CF and without a proven relationship to developing cirrhosis, recent data on the progression of non-alcoholic steatohepatitis to cirrhosis in children, as occurs in adults, may change this view. Hepatic congestion from right-sided heart failure may occur in older patients with advanced CF lung disease [12].

**Definition of CFLD**

According to the European definition of CFLD [13], at least two of the following conditions must be present after exclusion of steatosis: hepatomegaly and/or splenomegaly and enzyme abnormalities in at least at three consecutive determinations over 12 months, or evidence of liver disease or portal hypertension by ultrasonography.

**CFLD treatment**

The only medical therapy currently widely used for CFLD is the naturally occurring bile acid ursodeoxycholic acid (UDCA), a secretagogue stimulating canalicular and cholangiocyte bile secretion. It is used to reduce bile viscosity, and improve biliary secretion and bile acid composition, aiming to ultimately slow liver fibrosis. Anti-apoptotic and anti-inflammatory activity in the liver and bile ducts has also been reported in mouse models.

Beneficial effects on different aspects of CFLD (clinical, biochemical, imaging) have led to widespread use of UDCA, despite the lack of long term randomized controlled trials and proven long-term efficacy. A recent Cochrane review concluded that there is insufficient evidence to justify its routine use in CF [14]. A recent study refuted concerns regarding the safety of long-term high-dose UDCA administration in CF patients due to its biotransformation to the more toxic secondary bile acid lithocholic acid [15].

In the future, in consideration of the natural course of CFLD, it is critical that potential therapeutic agents are evaluated with well designed randomized clinical studies, with adequate sample size and long-term follow-up. This will ensure that the populations most likely to benefit from treatments are identified, minimizing unnecessary exposure in patients unlikely to benefit.

**6 Conclusions**

Advances in nutritional management have contributed to the improved survival in CF over the past four decades. Nutritional counselling (see Chapter 5) should be tailored personally to each child and family and should not just target growing, but also eating habits and behaviors. We should be aware of all the medical situations that may accrue to interrupt growing and eating, and give the full, appropriate treatment, to maximize growth, eating and development, for better health in childhood and adulthood.

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# CHAPTER 7

## Obtaining respiratory cultures in pre-school children with CF

### Authors

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### Introduction

Airway infection with pathogenic bacteria is a feature of cystic fibrosis (CF). Established chronic infection with *Pseudomonas aeruginosa* (*Pa*) is associated with faster decline in lung function and earlier mortality. Early detection, treatment and, where possible, eradication of *Pa* infection is vital to preserving lung function. Such pathogen surveillance requires regular respiratory sampling of children with CF. Here we discuss the different methods of obtaining respiratory samples in pre-school children, the diagnostic accuracy of each method and the relevant European and US guidelines.

### 1 The role of pathogenic bacteria in early CF lung disease and why we obtain respiratory cultures in young children

Lung disease starts early in CF with structural changes of trapped air and bronchiectasis frequently evident on imaging studies in the first year of life [1]. Airway inflammation and infection are well recognized to be associated with lung disease progression [2, 3], and airway infection with pathogenic bacteria can be detected in the first few months of life [4]. Initially, *Haemophilus influenzae* (*Hi*) and *Staphylococcus aureus* (*Sa*) are the most frequently cultured organisms. *Pa* becomes more commonly cultured over time with up to 50% of pre-school children having at least one episode of *Pa* airway infection over the first 5 years of life [5]. Initial airway infection with *Pa* can frequently be eradicated with antibiotic therapy [6]. Established chronic *Pa* infection, however, is associated with more rapid decline in lung function and earlier mortality [7-9].

Early detection of *Pa* infection and timely intervention with eradication antibiotic protocol, therefore offer an important opportunity to prevent chronic *Pa* infection. Clinical decline has also been associated with chronic infection with other organisms such as methicillin resistant *Staphylococcus aureus* (MRSA) [10] and *Burkholderia cepacia complex* (*Bcc*) [11]. While eradication treatment of *Bcc* is commonly practiced, reports remain anecdotal, with no evidence from clinical trials to help guide treatment. Eradication therapy for MRSA, however, has recently been reported in a clinical trial [12] and is likely to be adopted in the future.

Most CF specialist centers aim to collect respiratory samples at least quarterly in the outpatient setting for pathogen surveillance in young children with CF, to enhance early detection and eradication of airway infection and to avoid chronic infection. Pulmonary exacerbations in young children with CF, even when mild and community-managed, are associated with long-term decline in lung function [13]. More severe pulmonary exacerbations requiring hospitalization for intravenous therapy are associated with poorer nutritional outcomes and greater risk of structural lung disease in early life [13]. Respiratory cultures are usually collected during pulmonary exacerbations to detect new pathogenic organisms. This may provide important clinical information regarding antibiotic choices and may aid in the consideration of eradication therapies.

*Key message: Respiratory culture collection in pre-school children with CF facilitates the early detection of pathogenic organisms and can allow for prompt eradication treatment*

## 2 Different ways to obtain respiratory cultures in pre-expectorating young children

Expectorated sputum was previously the usual respiratory sample obtained for assessing airway microbiology in adults and older children with CF. Young children are generally unable to expectorate sputum spontaneously. Improvements in health outcomes in children and adults with CF mean that fewer older patients can spontaneously expectorate sputum regularly. Other methods are therefore required both for microbiological surveillance, and for diagnostic purposes at times of significant clinical change including pulmonary exacerbations.

### 2.1. Oropharyngeal cultures (cough swabs)

In non-expectorating children with CF, oropharyngeal cultures or cough swabs are usually collected and are the easiest to acquire. Oropharyngeal cultures involve swabbing the posterior oropharynx and/or tonsillar fauces. Cough swabs are collected by holding the swab in the back of the mouth without specifically touching the posterior pharynx or tonsillar fauces while the child with CF coughs into the swab. Other methods have included suctioning samples directly by passing suction tubing through the nose or mouth to the posterior

pharynx, and using saline administration to facilitate the collection of respiratory material by suction from the posterior pharynx. The optimal method of collecting oropharyngeal cultures is not known and in practice, there may be overlap of some of these methodologies.

The advantage of oropharyngeal cultures is the convenience. The sample can be collected frequently and relatively easily in the clinic environment or even in some cases by parents or healthcare professionals at home. The major disadvantages of oropharyngeal cultures relate to poor sensitivity or specificity for any individual test (see section below), although frequent collection of specimens may sufficiently aid in the detection of pathogenic organisms and reduce the potential for chronic infection.

Some organisms remain difficult to culture or identify using oropharyngeal cultures, including fungi and non-tuberculous mycobacteria (NTM), where larger volumes of respiratory material are required. While there are few data reporting other adverse consequences, procedural anxiety is not uncommon in children with CF and these types of frequent procedures could be associated with an increased risk of longer-term procedural anxiety which requires further investigation.

*Key message: Oropharyngeal swabs are most commonly used to obtain respiratory cultures as they are convenient and are not associated with any significant morbidity*

### 2.2. Induced sputum

Interest is growing in the use of induced sputum collection to obtain respiratory cultures [14]. The ECFS Clinical Trials Network (ECFS-CTN) recently published a standard operating procedure for sputum induction [15].

As for oropharyngeal cultures, there are different ways reported for induction and collection of sputum. Most protocols use a nebulizer with inhaled hypertonic saline. Methodologies vary between studies regarding nebulizer devices (usually ultrasonic or jet nebulizer), and different concentrations of hypertonic saline (4.5%-7%) [14]. In addition, the type of respiratory sample collection can vary with age, from expectoration of sputum in older patients to the use of oropharyngeal suction or cough swab in younger patients.

Induced sputum has been shown to be safe well tolerated, with minimal adverse effects [14]. The more common adverse effects reported include vomiting, bronchoconstriction, and a transient fall in the forced expiratory volume in one second (FEV<sub>1</sub>). To avoid a possible fall in FEV<sub>1</sub> due to bronchoconstriction, many protocols administer a bronchodilator such as salbutamol prior to induction with hypertonic saline.

### 2.3. Bronchoalveolar Lavage (BAL)

The gold standard methodology for collection of lower respiratory samples has been bronchoalveolar lavage (BAL). This method requires general anesthesia or significant sedation. Generally the procedure is well tolerated although adverse effects, espe-

cially fever and transient increase in cough, may be associated with the procedure [16].

BAL is invasive, making it more challenging as a method of routine collection of respiratory samples over short time frames of weeks or even months, and BAL-directed therapy does not provide longer-term cost benefit in young children with CF [17]. In addition, there are ongoing methodological issues that complicate the procedures and interpretation of results. The bacterial distribution across the lung is recognized as inhomogeneous with studies reporting differences in microbiology as well as inflammatory markers when different areas of the lung are sampled [18]. Ideally all lobes and lung segments should be sampled however this may increase the risk of adverse effects and is frequently unfeasible.

The use of BAL to direct therapy from birth through age 5 years in infants and pre-school children diagnosed with CF through newborn screening has been assessed in a randomized multicenter trial in Australia and New Zealand [5]. Infants were recruited at less than 6 months of age to either BAL-directed therapy or to standard care, managed using oropharyngeal cultures and clinical findings. There was no difference at age 5 years in the prevalence of any organisms cultured from BAL and no difference in structural or functional measures of lung disease between the groups, suggesting that BAL does not provide any clinical advantage in directing therapy or monitoring eradication of *Pa* above close monitoring using oropharyngeal cultures in the first 5 years of life.

Nevertheless, BAL remains of great importance as an investigation particularly with focal changes radiologically or if the clinical response to standard treatment approaches are unsatisfactory, or for identifying and excluding organisms such as fungi or NTM that are more difficult to culture.

*Key message: The gold standard respiratory culture collection technique is bronchoscopy with bronchoalveolar lavage, but this procedure requires anesthesia and for this reason is not used for routine pathogen surveillance at most centers*

### 3 Diagnostic accuracy of various sampling techniques

As described above, several techniques are utilized to obtain samples for respiratory cultures in pre-school children with CF. Investigators have evaluated the diagnostic accuracy of these methods, generally compared to BAL in young children. Before reviewing these studies, several caveats should be discussed. First, most studies have focused primarily on detection of *Pa*; diagnostic accuracy may differ for other organisms. Secondly, BAL is not a perfect “gold standard” itself; as noted above, regional sampling and dilutional issues may limit its accuracy. Finally, the decision to attempt to eradicate *Pa* may not necessarily be linked to the site of isolation.

#### 3.1. Diagnostic accuracy of oropharyngeal samples / cough swabs compared to concurrent BAL samples

In pre-expectorating young children, several studies have shown that oropharyngeal swabs have relatively high specificity and negative predictive value (NPV) for detecting lower airway *Pa* but only modest sensitivity and positive predictive value (PPV) (Table 1). What does this mean in the clinic? It means that a negative upper airway sample indicates that *Pa* is unlikely to be present in the lower airway (i.e., helpful for “ruling out” lower airway *Pa*), but a positive upper airway culture does not necessarily mean that *Pa* is indeed present in the lower airway (i.e., cannot “rule in” lower airway *Pa*).

Study	Age range	N	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Armstrong <i>et al.</i> 1996 [19]	1 month to 52 months	75	92%	92%	57%	96%
Rosenfeld <i>et al.</i> 1999 [20]	≤5 years	141	44%	95%	44%	95%
Jung <i>et al.</i> 2002 [21]	5 years to 21 years	38	35.7%	96.2%	83.3%	73.5%
Kidd <i>et al.</i> 2015 [22]	1 month to 5 years	99	76%	86%	42%	97%

**Table 1** Diagnostic accuracy of upper airway samples relative to BAL samples for detection of *Pseudomonas aeruginosa* in pre-school children with CF

### 3.2. Diagnostic accuracy of induced sputum samples

While not yet incorporated into routine clinical practice, induced sputum appears to be a promising non-invasive sampling method that may increase the yield of pathogens relative to upper airway cultures.

Most studies of induced sputum have been performed in cohorts composed primarily of older, expectorating people with CF [23-25]. Assessment of diagnostic accuracy in very young children is limited [14]. In small studies in pre-expectorating young children, two groups demonstrated that the yield of CF pathogens was higher from induced sputum samples than concurrent oropharyngeal samples [26, 27]. The latter study is the largest to date in this age group, with 98 paired samples from 32 people with CF. The sensitivity, specificity, PPV and NPV of oropharyngeal swabs compared to induced sputum for culturing CF pathogens were 56%, 96%, 93% and 72%, respectively. Only one study compared induced sputum to simultaneous BAL in young children with CF [28]. This small study (N=10) showed concordance between induced sputum and BAL samples in 8 of 10 cases, but larger studies are needed.

### 3.3. *Pseudomonas* serology testing for detection of new or early *Pseudomonas aeruginosa*

*Pa* serology as a diagnostic tool in CF has recently been reviewed [29]. While *Pa* antibodies in the serum correlate with isolation of *Pa* from respiratory cultures in

established *Pa* respiratory infection, the role of *Pa* serology in detecting early or new *Pa* respiratory infection is less clear. Both Douglas *et al.* [30] and Daines *et al.* [31] found poor sensitivity and specificity of *Pa* antibodies compared to isolation of *Pa* from BAL or oropharyngeal cultures, respectively. Results from these studies do not support this sampling method as a surveillance tool for identifying new or early *Pa* respiratory infection. In a retrospective, single center study, Kappler *et al.* found that *Pa* serology evaluated one year after initiation of aggressive *Pa* eradication therapy for newly isolated *Pa* had PPV and NPV of 75% and 82%, respectively, for predicting continued success of eradication 2 years hence [32]. The role of *Pa* serology in predicting the efficacy of eradication therapy deserves further evaluation.

## 4 Paranasal sinuses as a reservoir for lower airway infection

The discordance between upper airway sampling (oropharyngeal/cough swab) and lower airway respiratory culture collection (BAL) might relate to the chronic bacterial colonization seen in the paranasal sinuses of people with CF. The sinuses have been found to serve as a reservoir for CF-related pathogens to infect the lower airways. Identical *Pa* genotypes have been found in both upper and lower airway-obtained samples [33], and transplant recipients with CF have been found to be re-infected with identical pre-transplant bacterial strains that were previously identified in the sinuses [34, 35]. These observations illustrate that bacteria

harbored in the sinuses likely migrate downward, but may not always be present in the lower airways.

## 5 Respiratory culture collection guidelines for infants and pre-school children

Clinical care guidelines from the United States and Europe were created to best inform healthcare providers on evidence-based care for children and adults with CF. Within these guidelines are recommendations on obtaining respiratory cultures in pre-expectorating children (Table 2).

Organization	Oropharyngeal/ Cough Swab	Induced Sputum	Bronchoscopy and Bronchoalveolar Lavage
European Cystic Fibrosis Society (Published in 2014)	With every clinic visit (at least every 3 months)	No specific recommendations	No specific recommendations though not routinely recommended
National Health Service (U.K.) (Published in 2017)	At every clinic and inpatient encounter	Consideration to be given prior to bronchoscopy and bronchoalveolar lavage	Not routinely recommended, but indications include: <ol style="list-style-type: none"> <li>1) Need for microbiological diagnosis in pre-expectorating child</li> <li>2) To determine if <i>Pa</i> eradication was successful</li> <li>3) Child not responding to appropriate antibiotics</li> </ol>
Cystic Fibrosis Foundation (U.S.) (Published in 2000: < 2 years) (Published in 2016: 2-5 years)	At least quarterly	No specific recommendations	Not routinely recommended, but indications include: <p>For children &lt;2 years:</p> <ol style="list-style-type: none"> <li>1) Child not responding to appropriate antibiotics</li> </ol> <p>For children 2-5 years:</p> <ol style="list-style-type: none"> <li>1) Child not responding to appropriate antibiotics</li> <li>2) Infants with signs/symptoms of lung disease</li> </ol>

**Table 2** Clinical practice guidelines for obtaining respiratory cultures in pre-school children

### 5.1. European guidelines on obtaining respiratory cultures in pre-school children

The ECFS Best Practice Guidelines recommend clinic visits at least every 3 months, with respiratory culture collection performed at every clinic visit [36]. No specific culturing technique (oropharyngeal/cough swab, induced sputum, expectorated sputum, or BAL is explicitly recommended. National Health Service (NHS) guidelines from the United Kingdom recommend obtaining cough swabs at every clinic visit or inpatient encounter [37]. If a child is known to be chronically infected with a given pathogen but is otherwise asymptomatic and well, a routine cough swab may not be necessary, although these guidelines note that in clinical practice it is still frequently obtained. Indications for BAL include a need for microbiological diagnosis in a pre-expectorating child, determining if *Pa* eradication was successful following eradication therapy, and in children not responding to appropriate IV antibiotic therapy. Prior to BAL, induced sputum sampling should be attempted.

### 5.2. United States guidelines on obtaining respiratory cultures in pre-school children

For children  $\leq 5$  years of age, CF Foundation guidelines recommend routine monitoring of airway microbiology by oropharyngeal cultures at least quarterly [38, 39]. Even though induced sputum may have a greater diagnostic yield than oropharyngeal culture, it is not routinely recommended. While these guidelines acknowledge

that BAL is the only direct lower airway sampling method available, it is invasive and costly, and thus should only be considered in a child who does not respond to appropriate antibiotic therapy targeted at an oropharyngeal culture-obtained organism. In children aged  $< 2$  years, BAL may additionally be considered in infants with signs or symptoms of lung disease [38].

*Key message: Guidelines for respiratory culture collection in pre-expectorating children are available from the National Health Service in the UK, the ECFS, and the CF Foundation*

## 6 Obtaining respiratory cultures in pre-school children: future directions

In addition to utilizing 'traditional' culture-dependent methods for CF respiratory pathogen surveillance, newer culture-independent diagnostic modalities are being used in the discovery of lower airway bacterial pathogens. Real-time PCR and DNA sequencing approaches have increased the sensitivity in the detection of many respiratory pathogens, including *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and *Burkholderia species* [40, 41]. In addition, the use of molecular techniques including 16S ribosomal RNA gene sequencing in CF lung microbiome studies has enabled a broader detection of respiratory organisms [42, 43]. Studies have confirmed that the upper and lower airway microbiomes are distinctly different in measures of diver-

sity and organism relative abundance [44], and research is underway evaluating these complex relationships between organisms and how they influence CF lung disease and its progression over time. Ultimately, findings from these culture-independent methods will likely complement traditional respiratory culture collection to influence treatment strategies and improve care of children and adults with CF.

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# CHAPTER 8

## Assessing respiratory function in pre-school children with CF

### Authors

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### Introduction

The pre-school years represent a clinically challenging period of rapid lung growth and airway remodeling in individuals with cystic fibrosis (CF) while symptoms such as cough or wheeze are often absent. The prevalence of irreversible structural lung abnormalities, such as bronchiectasis, increases dramatically during these years. Interventions during the pre-school years are crucial to delay the development and minimize the progression of structural lung disease. As a result, there is a clear need for sensitive and non-invasive markers of lung disease in young children with CF that can be used in the clinic and as endpoints in interventional clinical trials. Studies measuring lung function in the pre-school years (3 to 6 years of age) may provide important insights into lung physiology and disease onset during an important developmental period. In this chapter we review three commonly reported lung function techniques for their clinical utility in pre-school children with CF: spirometry, forced oscillation technique and multiple breath washout.

### 1 Spirometry in pre-school children with CF

With spirometry, it is possible to measure expiratory flows and volumes during a forced expiratory maneuver. This is the most common technique to measure airway function, especially airflow limitation from airway obstruction until approximately the eighth bronchial generation, or to rule out restriction.

It is possible to successfully perform forced expiratory maneuvers from the age of three years in accordance with adapted pre-school guidelines for lung function assessment [1]. However, it can be difficult to obtain reliable data during forced expiratory maneuvers as these require patients to maximally and forcefully exhale their forced vital capacity (FVC) after a complete inhalation to total lung capacity (TLC). Quite often pre-school children can either exhale forcefully or completely, but not both at the same time. In these cases, it might be necessary to use alternative lung function techniques, which require only tidal breathing, as described in the sections below. While commercial equipment and technical standards documents

for spirometry are available [1-3], and normative reference data for pre-school children exist [4], cut-off values for bronchodilator responsiveness are not currently available for this age.

In contrast to later time points when it is recommended that spirometry be measured in seated people wearing nose clips, pre-school age children may perform the test while standing and even without wearing nose clips. However, their use and the position during measurement should be noted [1]. Multiple attempts may be necessary in young children to obtain at least two acceptable and reproducible spirometry measurements. The total number of necessary attempts is not limited, however exhaustion of patients during lung function measurements should be avoided. As in older patients, flow volume loops should first be analyzed for their technical quality. Due to differences in respiratory physiology between pre-school children and older patients, quality control criteria for pre-school spirometry have been published separately [2].

The primary outcomes of spirometry are FVC, the forced expiratory volume in 1 second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC, as well as the forced respiratory flows (FEF) at 25, 50, and 75% of exhaled FVC (FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>) or the so-called maximum mid expiratory flow (FEF<sub>25-75</sub>). Pre-school children may expire their entire vital capacity within 1 second and therefore the indices FEV<sub>0.75</sub> and FEV<sub>0.5</sub> (i.e. FEV during 0.75 and 0.5 seconds, respectively) have been proposed but these indices have

not yet been validated for clinical use. In addition, normative pre-school data from the Global Lung Function Initiative (GLI) are limited to the following indices: FEV<sub>0.75</sub>, FVC, FEV<sub>0.75</sub>/FVC, FEF<sub>75</sub>, and FEF<sub>25-75</sub> in addition to FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC.

The clinical utility of spirometry in pre-school CF lung disease is less clear than in later ages when FEV<sub>1</sub> is widely used as a monitoring tool and is a good predictor of health outcomes in people with moderate-severe lung disease [5]. This is most likely because FEV<sub>1</sub> is relatively insensitive to detect the onset and progression of early CF lung disease usually arising in peripheral airways. While spirometry indices are on average lower in CF compared with controls [6], there is a high degree of overlap between children with CF and healthy controls, such that many children with CF appear to have normal lung function by spirometry until adolescence. This low sensitivity hinders the use of spirometry to monitor disease on an individual level in the early years. In contrast, forced expiratory flows such as FEF<sub>75</sub> and FEF<sub>25-75</sub> may be more sensitive to detect obstruction in small airways compared with FEV<sub>1</sub>, especially in young children.

While forced expiratory flows are also generally reduced in early CF lung disease [7], high intra- and inter-patient variability limits their use in clinic surveillance and interventional studies due to the considerable overlap between health and disease. Natural variability in forced volumes measured three months apart (inter-test coef-

ficient of variation for FEV<sub>1</sub> z-score) is 17% in healthy children and 42% in CF [8]. The minimal clinically important difference for spirometry indices is unknown in the pre-school age. Clinical decision-making is however often based on intra-individual changes in FEV<sub>1</sub>, for example changes of ~13% predicted are considered relevant [9].

In summary, the restricted ability of young children to perform forced expiratory maneuvers and the high degree of overlap between health and disease limit the clinical utility of spirometry as a surveillance tool in pre-school children with CF.

	Pre-school Spirometry	Pre-school Forced Oscillation Technique	Pre-school Multiple Breath Washout
Commercial equipment	Available	Available	Available
Standard operating procedure	Available	Available	Not available*
Safe	Yes	Yes	Yes
Feasible	Limited	Feasible	Limited
Reference data	Available [4]	Available [10]	Not Available**
Intra- and inter-patient variability*	Available [8]	Available [11]	Available [8]
Discriminates between CF and health	Poor	Inconsistent	Yes
Evidence for correlation with clinical endpoints***	Limited	Limited	Available [12-15]

**Table 1** Summary of pre-school lung function techniques

\* Pre-school specific Multiple Breath Washout (MBW) guidelines are expected in 2018.

\*\* Pre-school specific nitrogen MBW normative data are expected in 2018.

\*\*\* Clinical endpoints including structural lung disease, infection status, response to therapies.

*Key messages: Lung function tests have the potential to non-invasively detect the onset and monitor progression of lung disease and the response to therapeutic interventions in young children with CF.*

*Spirometry, whilst a robust and sensitive tool in older children, has low feasibility in young children due to the cooperation and coordination required to perform forced expiratory maneuvers. In addition, forced volumes and flows are often normal in the majority of pre-school children with CF despite subclinical progression of lung disease.*

## 2 Forced oscillation technique in pre-school children with CF

The forced oscillation technique (FOT) is a lung function test that measures respiratory impedance through the application of small amplitude, high frequency pressure oscillations at the airway opening and measurement of resultant changes in pressure and flow [16]. Unlike spirometry, this technique is well suited for measurements in pre-school children as it only requires tidal breathing, minimal cooperation from the child, and the test can be completed within a short period of time. Commercial equipment, normative reference data, and bronchodilator responsiveness cut-off values validated for the pre-school age are currently available [10, 17]. The primary outcomes of the FOT include the respiratory system resistance (Rrs), which reflects airway resistance, and respiratory system reactance (Xrs), which reflects the resistance of the peripheral airways and

ventilation inhomogeneity of the lung.

The clinical utility of FOT in children with CF is unclear. Some studies have reported significantly higher Rrs and lower Xrs values in pre-school children with CF compared with healthy controls [18, 19], while others found no differences [20, 21]. Pre-school children with CF with respiratory symptoms in the past month had higher Rrs and lower Xrs than asymptomatic children [18]. A study of infants and young children with CF who underwent low frequency FOT under general anesthetic prior to the collection of BAL fluid, reported significant associations between tissue mechanics and markers of pulmonary inflammation including total cell count, neutrophil count and IL-8 [22]. However, no associations were found between FOT outcomes and pulmonary infection status.

There is limited longitudinal data comparing FOT outcomes and clinical markers of CF lung disease. A study of serial respiratory resistance and reactance measurements in pre-school children using the impulse oscillation technique reported no associations between oscillatory mechanics and upper airway infection status [21]. A multicenter, longitudinal study that monitored FOT outcomes and clinical markers in pre-school children with CF found no associations between FOT outcomes and either infection status, respiratory symptoms, or *CFTR* genotype [23].

In a large longitudinal study of 184 children with CF aged three to six years, children who had pronounced respiratory disease,

including free neutrophil elastase activity, infection with pro-inflammatory pathogens, and structural lung abnormalities on chest CT had similar FOT outcomes to those children without detectable lung disease [24]. In addition, the progression of lung disease over one year was not associated with worsening FOT outcomes. Together these studies indicate that FOT outcomes are not sensitive to monitor clinical disease status within young children with CF.

There is some data in older children with CF which suggest that FOT could be used as a tool to monitor response to treatment in children with CF. Children with CF aged between eight and 18 years hospitalized for a respiratory exacerbation showed significant improvements in Rrs and Xrs from baseline to discharge following two weeks of intravenous antibiotics treatment [25]. The pattern and magnitude of the change in FOT outcomes with treatment were similar to changes in FEV<sub>1</sub> in this cohort. FOT indices have an intra-test variability between 5-15% and inter-test variability of measurements days apart of 10% in adults, however, further data is required to determine the minimally clinically important difference [11]. Further studies are required to determine whether FOT outcomes could be used to monitor response to treatment in children too young to perform spirometry.

Conventional FOT systems measure respiratory impedance across a pseudo-randomized range of oscillation frequencies and impedance is averaged over several tidal breaths. However, new custom-made wave tube FOT systems have recently been

introduced that apply frequency oscillations to track respiratory impedance during tidal breathing and measure the flow and volume dependence of impedance within each tidal breath [26]. This technique has been shown to be more sensitive than conventional FOT to detect airway obstruction in young children with acute wheeze and asthma [27]. However, these FOT systems are currently not commercially available and there are not yet data available in young children with CF.

In summary, FOT is an appealing non-invasive, easy to perform, and widely applied pediatric lung function test. Current data suggest that FOT may be more useful to differentiate between groups rather than monitor disease progression within individuals. Novel methodology to track respiratory impedance within tidal breaths rather than averaging impedance over multiple breaths may improve the sensitivity and specificity of this technique to monitor disease within an individual and its application in young children with CF would be of interest.

*Key message: The forced oscillation technique is a feasible tidal breathing test to assess respiratory system mechanics across ages. However, respiratory impedance indices appear more useful in differentiating between health and disease rather than monitor disease progression in children with CF.*

### 3 Multiple breath washout in pre-school children with CF

The multiple breath washout technique (MBW) measures the efficiency of ventilation distribution by estimating the tidal breathing effort required to ventilate a tracer gas from the lungs [28]. The tracer gas can either be a resident gas, such as nitrogen washed out by 100% oxygen, or an inert gas, such as sulfur hexafluoride (SF<sub>6</sub>), washed out by medical or room air. Outcome measures include functional residual capacity (FRC), global indices of ventilation distribution including the lung clearance index (LCI) and moment ratios, and indices representing convection-dependent (Scond) and diffusion-convection-dependent (Sacin) ventilation inhomogeneity. Importantly, the physiology behind the Scond and Sacin indices were derived from healthy adult lung models. A significant proportion of pre-school children with CF have increased ventilation inhomogeneity despite few respiratory symptoms and normal spirometry [29]. Longitudinally, LCI deteriorates during the pre-school years in young children with CF, particularly in individuals who experience pulmonary exacerbations [8]. There is evidence to suggest that LCI is more specific than spirometry derived forced volumes in distinguishing symptoms from upper vs. lower respiratory tract infections [8]. An abnormal LCI in the pre-school years is predictive of both worse LCI and FEV<sub>1</sub> values later in life [30]. In addition, ventilation inhomogeneity in the pre-school years is associated with the presence of structural lung abnormalities on chest CT [13] and lower respiratory tract inflammation and infection [12].

Early intervention studies in pre-school children with CF are limited. Long term treatments, such as 48 weeks inhalation therapy with hypertonic (7%) saline solution, improve ventilation inhomogeneity [15]. However, short-term treatment interventions, such as hypertonic saline or intravenous antibiotics in older children with CF, have resulted in heterogeneous changes in LCI [14]. These heterogeneous responses of LCI may relate to complex dynamic changes in airway obstruction or bronchodilator response on multiple airway levels. As a result there are limited data on the minimal clinical important difference for LCI and further studies are required. The natural variability of LCI measured three months apart (inter-test coefficient of variation) is 5% (2-20%) in healthy children and 7% (0-24%) in clinically stable children with CF [8].

Technically, there are some challenges that limit the widespread use of MBW in the clinical setting. Few commercially available MBW equipment systems are validated for the use in the pre-school age range [31]. Normative data during the pre-school years are currently only available from custom-made research equipment and are not applicable to data collected using commercial devices [32]. In addition, while it is known that pure oxygen for nitrogen MBW alters breathing patterns in infants, the impact of hyperoxia on breathing pattern in pre-school children is unclear [33].

Feasibility of MBW can be low in children aged less than four years due to the requirement for stable tidal breathing and maintenance of a leak-free seal with the testing interface for multiple minutes. The use of

### 4 Future developments

facemasks in young children may improve feasibility over mouthpieces, but can add additional dead space to the system which can significantly influence LCI [34]. Recent data suggests that two high quality MBW trials may be sufficient for test acceptability, which may help to improve feasibility in young children [35]. The publication of a consensus statement for MBW testing [36] and the development of pre-school specific MBW guidelines, currently underway, will help to address these technical issues and provide guidance for users and manufacturers.

In summary, MBW is technically challenging in pre-school children but is considered a highly sensitive and reproducible physiological outcome measure in CF. The impact of MBW on clinical decision making is less established and hampered by limited reference data from available setups. The upcoming technical standards document will provide guidance for validation and application of MBW in pre-school children.

*Key message: The multiple breath washout (MBW) technique is a tidal breathing test that measures ventilation distribution, a biomarker of central and mainly peripheral airways obstruction. Feasibility depends on the experience of both children and operators. The lung clearance index (LCI) is sensitive to detect early CF lung disease in pre-school children but the lack of normative data is currently limiting its application in the clinic.*

Although spirometry is difficult in young children, training should begin during the pre-school years to ensure high quality baseline data is available by the time the child reaches school age, in order to monitor treatments for pulmonary exacerbations and track long-term disease progression into adulthood. Further development, validation, and implementation of the within-breath tracking of respiratory impedance into commercially available software may provide more sensitive endpoints from the forced oscillation technique to monitor early CF lung disease.

Current evidence suggests that the MBW technique is the most sensitive lung function test to monitor early CF lung disease in the pre-school years. Further work to generate robust normative data, validated quality control guidelines, and evidence for the influence of tracer gases and equipment-related dead space on breathing pattern and test outcomes are essential to move MBW from the research setting into clinical application.

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# CHAPTER 9

## Pulmonary radiological investigations in the pre-school child with CF

### Authors

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### Introduction

Newborn screening (NBS) for CF allows early diagnosis but routine surveillance and early detection of pulmonary damage in the young remain challenging. Multi-modality assessment of early CF lung disease is important. However, lung function testing in infants and pre-schoolers is not routinely available. Imaging in the form of chest radiography in this age group is feasible but considered insensitive for detection of early changes. Chest computerized tomography (CT) scans provide more detailed imaging but optimal CT protocols are mandatory to maximize information and minimize risk.

### 1 Evolution of structural lung disease in the pre-school child

A body of evidence from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF) and other groups demonstrates early structural damage in young children with CF diagnosed through NBS even when seemingly asymptomatic. The most prominent structural changes observed on chest CT in pre-school children are diffuse airway wall thickening and dilatation, mucous impaction and low attenuation regions (LAR) consisting of trapped air and hypoperfusion (**Figure 1**). These changes were more evident in those with greater degree of airway inflammation and infection [1, 2]. Abnormal CT findings were detected in 80% of infants who had a CT performed at median age of ~3 months, ~20% had bronchial dilatation, ~45% had bronchial wall thickening and ~65% had LAR [1].

Stick *et al.* reported an incidence of bronchial dilatation in the first year of life as 8.5%; this incidence increases with advancing age such that a prevalence of 36% was reported

by 4 years of age [2]. Longitudinal follow-up showed that most structural changes persisted when scans were repeated a year later. Radiological progression of bronchial dilatation and LAR was associated with severe *CFTR* genotype, worsening neutrophilic inflammation and pulmonary infection [3]. Results from these AREST-CF studies have provided useful insight into the early development of CF lung disease in NBS CF children and the factors associated with persistence and progression of structural lung disease.

There is still uncertainty and a paucity of knowledge regarding the natural history of these early structural changes, since longitudinal follow-up of infants in the AREST-CF studies has revealed resolution of bronchial dilatation in 25% of the scans [4]. This may partly reflect inconsistency by observers, a less sensitive CT protocol and the use of a less appropriate scoring protocol for quantifying early CT changes.

In a study of NBS CF infants at 12 months, bronchial dilatation and air trapping were reported in 26% and 42% of children respectively (London Cystic Fibrosis Collaboration NBS cohort). The changes observed on volumetric chest CT scan at this age were considered mild. There was poor inter-observer agreement and repeatability in the different CT scores [5] with the exception of air trapping using the standard Brody-II scoring system. This is a scoring system developed for school aged children with more advanced lung disease. Scoring systems are now available that are more sensitive and valid to track early CF lung disease [6, 7].

By late pre-school age, up to 50% of chil-

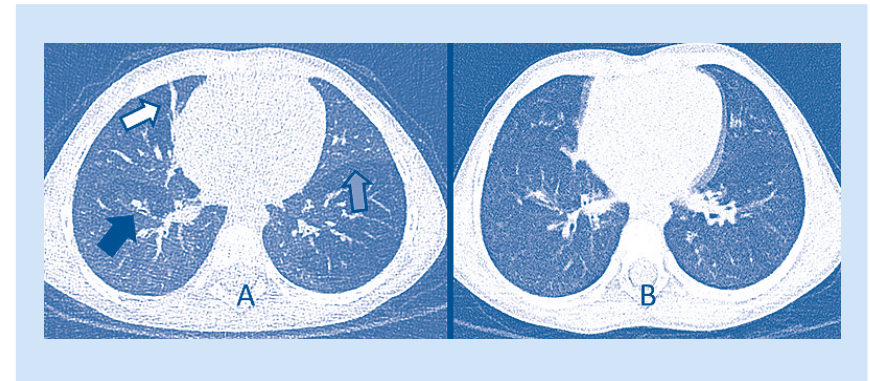
dren may have evidence of bronchiectasis [1, 8]. There is evidence that early lung disease is characterized by diffuse changes in airway dimensions and which can be considered a pre-bronchiectasis stage. More recent studies in older children with CF suggested that mucous plugging may have a significant role in the development of bronchiectasis [9]. There is limited knowledge on the natural history of LAR although likely to be reversible to an extent. There is some evidence that in older children LAR may be irreversible [10]. In summary, mild structural changes do exist in the early years with variable longitudinal course. (Figure 1)

## 2 Radiological investigations for routine surveillance and clinical trials

Radiological investigations play a role in both the routine assessment of children with CF, and may also be used as surrogate outcome measures in clinical trials.

For both these purposes, a test must satisfy several criteria [11]. The test must:

- be sensitive enough to differentiate between disease and health with plausible biological explanations
- be readily available and feasibly performed
- be accurate and reproducible
- inform specific interventions that could result in a positive change in the natural history of the disease
- have an acceptable risk benefit balance



**Figure 1** Surveillance chest CT performed at 3 and 5 years of age in the same child

CT (A) was taken at the age of 3 years using a free breathing volumetric protocol. Note the thickened airways (black arrow head), sub-atelectasis (white arrow head), contrast between low attenuation region and normal density lung (grey arrow head). Based on these findings a more aggressive treatment regimen was followed including more frequent follow up visits to the outpatient clinic, initiation of domase alfa maintenance treatment and more frequent courses of antibiotics. CT (B) was taken at the age of 5 years, using a technician guided breath hold volumetric protocol. Note that the thickened airways are still present. The sub-atelectasis has disappeared. The low attenuation regions are less prominent, although this may reflect a more inspiratory scan. Note the movement artefacts related to the heart beating. As the patient was growing and alignment of patient in the scanner was somewhat different, scrolling was needed to identify identical anatomical positions. A and B were matched based on airways near black arrow head.

In addition, for surrogate outcome measures in clinical trials, the test must be able to reliably detect a treatment effect within a useful timeframe.

Imaging scoring systems for chest radiograph (CXR) and CT have been developed to quantify pulmonary structural changes, primarily for use in research studies. Existing scoring systems for CXR and chest CT were developed previously for quanti-

fying more established CF lung disease in adults. However new scoring systems [6, 7, 12, 13] have been developed to quantify mild changes detected in young children with CF. Validation studies have established the clinical relevance of using these scoring systems and standard operating procedures have been developed to ensure optimal image acquisition for accurate interpretation. This will be discussed further in this chapter.

There is increased interest and ongoing research in exploring the use of chest magnetic resonance imaging (MRI) as a radiation free option for monitoring CF lung disease. Chest MRI can provide concurrent morphological and functional assessment of the lungs. Scoring systems and other image analysis methods are available and in development for chest MRI but more validation studies are required especially in early CF lung disease. In its current state, it is not ready for universal use in detecting the mild structural changes that are often seen in the pre-school age [14]. This imaging modality will not be discussed further in this chapter.

### 3 Chest Radiography (CXR) as a screening test for pre-school children with CF

CXR has been used widely for clinical purposes as it is readily available and can be performed quickly and easily, even in the young uncooperative child. It is a relatively cheap investigation with minimal radiation burden. Hence CXR has been recommended as routine annual investigation for CF children in the guidelines of many countries. Although CXR may be able to detect gross bronchiectasis, it is less sensitive than chest CT, hence its utility in young asymptomatic children has been questioned.

The Brasfield scoring system is the most common CXR scoring system and comprises five aspects of CF: air trapping, linear markings, nodular cystic lesions, large lesions and general severity. Scoring a CXR on each of these aspects is quick and easy [12] and it is

also a validated system that correlates with pulmonary function tests and pulmonary exacerbations.

The Wisconsin scoring system was developed to provide more detailed assessment of mild CF lung disease [15]. The scoring process is complex and can be time and labor intensive. It involves six aspects of CF lung disease: hyperinflation, peribronchial wall thickening, bronchiectasis, nodular/branching opacities, large round/ill-defined opacities and atelectasis. Each of these attributes will have different responses and the various components are weighted differently, requiring complex equations and computer spreadsheet for final score.

A study by Cleveland *et al.* showed that there was close correlation between the quick Brasfield and the time-consuming Wisconsin scoring systems, even in those less than 5 years of age i.e. pre-school ages with mild lung disease. They were equally reproducible and showed similar correlation to pulmonary function tests [16,17]

Another study by the same group showed promising results which suggested that Brasfield and Wisconsin CXR scores were as sensitive as Brody CT scores in detecting lung disease and they were both associated with future lung disease severity [18]. These CXR scoring systems can detect and monitor mild CF lung disease but in order to use the specialized Wisconsin scoring method, specially trained staff are required.

### 4 Chest CT as a screening test for pre-school children with CF

Chest CT is the validated gold standard for detecting and monitoring structural lung disease. In older children, chest CT is more sensitive than conventional spirometry for detecting lung disease [19-21]. However in pre-school children, there is limited knowledge on how lung structure varies when compared to lung function. In addition, spirometry is not often possible or reliably performed in this age group. Other methods of non-maneuver lung function such as multiple breath washout tests have been suggested as an alternative for chest CT to detect early CF lung disease but they do not necessarily identify the same group of children with structural abnormalities [22].

*Key message: Chest CT is the most sensitive imaging method to identify and monitor early structural lung abnormalities.*

#### 4.1. Bronchial dilatation

Bronchiectasis is the most important structural change in the lungs that early diagnosis and aggressive treatment for CF aims to prevent and delay. Bronchiectasis is traditionally defined as irreversible bronchial dilatation; however it is known that, in younger children at least, bronchial dilatation may be reversible. Using a sensitive method to measure airway dimensions of all visible airway artery pairs in AREST CF patients [7], diffuse airway wall thickening and widening were present early in life. Similar observations were found in the Erasmus MC CF-CT cohort of pre-school ages and these changes were risk factors

for later bronchiectasis [22]. Furthermore, in school age years, these diffuse changes became more pronounced. Established bronchiectasis is progressive with clinical importance and is a strong predictor of respiratory tract infections, chronic *Pseudomonas aeruginosa* infections and reduced lung function and quality of life [18, 23-25].

#### 4.2. Small airways disease

A prevalent finding on chest CT is the presence of small airway disease. Small airway disease is characterized by areas of hypodensity on inspiratory CT scans but is more readily observed on expiratory CT scans at functional residual capacity level as LAR [6]. In the AREST longitudinal study [26], 60% of NBS infants with CF had evidence of LAR. Although LAR may be reversible to some extent and the distribution can be variable with consecutive scans, the volume of distribution remains relatively constant with increasing age [6]. LAR is commonly seen in end stage lung disease such that LAR can take up 80% of total lung volume involvement in addition to highly prevalent irreversible bronchiectasis [10]. The pathophysiology and natural history of LAR still need to be better characterized.

### 4.3. Scanning protocol

The quality of images obtained is crucial for the interpretation of structural lung disease especially when changes are subtle and when the disease process is monitored over time. The volumetric scan protocol uses multidetector scanners to provide high resolution and continuous imaging of the entire lung (as opposed to the older method of non-contiguous, interrupted thin sections obtained in high resolution CT). Volumetric imaging allows careful slice by slice comparison with previous scans. This will enable accurate matching of airways and tracking of disease over time [27, 28]. It has been recognized in several studies that with limited slice imaging protocols, the ability of CT to detect and quantify bronchiectasis and trapped air observed over time was reduced. Bronchiectasis is best detected through volumetric inspiratory images and small airways disease is best assessed and quantified through volumetric expiratory images [29].

*Key message: How the scan is performed and assessed is critical.*

### 4.4. Controlled volume imaging

CT scans should ideally be performed at standardized inflation volumes to increase the sensitivity and reproducibility of the test to detect abnormalities [30]. This is also the case for young children, in whom small changes in inflation can lead to misleading changes in bronchial caliber. In infants this can only be achieved through general anesthesia (GA) which in itself can lead to GA related atelectasis obscuring detail, unless adequate lung recruitment maneuvers have taken place prior to scanning.

In pre-school children not undergoing GA (i.e. less than 4 years old) it is difficult to obtain images at standardized volumes. A compromise is to obtain images in a spontaneously breathing child which will be at a lung volume near functional residual capacity level with fast scanners. Older pre-school children can be trained by a respiratory technician or physiologist to perform spirometer volume controlled breathing CT scans [31]. **Table 1** summarizes practical considerations in performing chest CT in pre-school children.

For scans without sedation or anesthesia	Comments
Use fastest scanner available in the hospital	≥64 slice scanners are mostly fast enough; scan acquisitions below 0.5 seconds are possible on some machines.
Have the child trained prior to the scan by a lung function technician to identify the most feasible protocol and to put the child at ease.	Select between free breathing, breath hold during free breathing, or breath hold (usually 2-5 seconds) at total lung capacity (inspiratory) and at functional residual volume (expiratory).  A cooperative child (usually from age 5 years) may be able to perform spirometer guided CT.
Have the same lung function technician who did the training coach the child in the CT suite to execute the most feasible protocol	Use the same instructions during CT scan as during the training.
Lung function technician and CT technician to discuss procedure prior to the CT	Lung function technician tells CT technician when acquisition can start (beware of delay between pushing the start button and start of scanning).
Optimized CT protocol	Use a patient size specific radiation dose level that is as low as reasonably achievable (ALARA) to obtain images of sufficient quality (see below).
Inspiratory scan	Use lowest dose that will reliably allow evaluation of parenchyma and airways.
Expiratory scan	Use lowest dose that will reliably allow evaluation of regions of low attenuation. In general, the radiation dose for the expiratory scan can be 50% lower than for the inspiratory scan.
Free breathing scan	Adequate dose for evaluation of parenchyma, airways and regions of low attenuation. Use fast scan protocol (dose equivalent to inspiratory scan).
Use volumetric protocol for inspiratory and expiratory and free breathing scans	This allows slice per slice comparison between baseline and follow-up scans for correct differentiation between airways and arteries. It allows direct comparison at specific anatomical locations correcting for growth, lung volume and alignment related variation.
Cooperative child	Scan in supine position with arms above head.
Uncooperative young child	Have the parent with appropriate radiation shielding comforting and holding the child. Consider use of vacuum mattress to immobilize the child. For infants consider performing CT after feeding.
Pitch	In general, a pitch of 1 or slightly below 1 can be used for single x-ray source scanners and in cooperative children. In uncooperative children or others with rapid respiratory rates who are unable to reliably breath-hold, a pitch >1 can be of use to avoid artefacts due to respiratory and body motion. Ultrahigh pitch modes with pitch up to 3.2 available on some machines, with scan acquisition <0.5 seconds.
Reconstruction	Axial series should be reconstructed and stored including a slice thickness of ≤1.25 mm with 50% overlap.

**Table 1** Chest CT in pre-school children: considerations

For scans under general anesthesia (GA)	Comments
Indication	Consider when a bronchoscopy and bronchoalveolar lavage (BAL) is indicated. When CT scanner is not fast enough to acquire a chest CT with minimal respiratory or body movement artefacts.
Timing of CT	Execute CT prior to the BAL to identify the most appropriate region to execute the BAL.
Lung recruitment maneuvers	To avoid GA-atelectasis have a proper lung recruitment protocol in place before executing the CT; usually at least 4 slow inflations up to 40 cm H <sub>2</sub> O are used.
Inspiratory scan at total lung capacity	Execute scanning during breath hold at transpulmonary pressure of 25 cm H <sub>2</sub> O.
Expiratory scan at functional residual capacity	Execute scanning at transpulmonary pressure of 0 cm H <sub>2</sub> O (i.e. functional residual capacity level).
Use volumetric protocol for inspiratory and expiratory and free breathing scans	This allows slice per slice comparison between baseline and follow-up scans for correct differentiation between airways and arteries.
Reconstruction	Axial series should be reconstructed and stored including a slice thickness of $\leq 1.25$ mm with 50% overlap.

**Table 1** Chest CT in pre-school children: considerations

#### 4.5. Scanning parameters

A very important consideration of performing repeated routine surveillance chest CT is the risk of radiation associated malignancies that could arise from cumulative lifelong radiation exposure, as overall survival improves in CF patients. The serial imaging radiation risk can be reduced by using multi-slice modern CT scanners and state of the art low-dose protocol to enable images of sufficient quality to be obtained at the lowest reasonably achieved radiation doses (ALARA principle) [32].

Nonetheless, not all centers can access such machines and protocols, or personnel who are trained in performing chest CT

in young children at the lowest possible radiation dose to allow accurate interpretation. This was evident in a multicenter research study where trial centers were instructed on specific CT parameters. Even with the attendance of research fellow, radiation doses of CT scans performed varied significantly across centers [5]. The lack of standardization of CT protocol as well as old equipment contributed to the variation in radiation doses across 16 different European centers as reported by Kuo *et al.* [33].

Importantly, for a given radiation dose, the risks of radiation induced malignancy are greater at a younger age, due both to

intrinsically higher radiation sensitivity, and a longer anticipated future life expectancy during which malignancy can occur [34]. The suggested scan parameters for children are provided in **Table 2**.

*Key message: The CT protocol should be adequate to generate a diagnostic CT at the lowest possible radiation dose (ALARA principle).*

Data acquisition mode	Volumetric, helical scan technique.
Patient position	Supine with arms above the head.
CTDI <sub>vol</sub> # for inspiratory scan mGy	
1 year old	0.6
5 years old	1.0
Young adult	2.2
Field of view	As close as possible to the entirety of the lungs without cutting off the lung borders.
CTDI <sub>vol</sub> for expiratory scan	50% lower than inspiratory scan.
Tube voltage	Low enough such that the recommended CTDI <sub>vol</sub> can be reached (e.g. 80 kV).
Tube current	Adapt to recommended CTDI <sub>vol</sub> .
Pitch	<1, lower limit determined by maximum scan time allowed.
Slice thickness	Thinnest slice thickness (e.g. 1 mm).
Reconstruction increment	50% overlap (e.g. 0.5 mm with 1-mm slice thickness).
Kernel for automated analysis	Sharp reconstruction filter without under- or overshoot at edges, preferably a dedicated kernel for quantitative image analysis.
Iterative reconstruction technique	If available, iterative reconstruction techniques can be applied in addition to the requested filtered back-projection techniques.
Shielding	Breast shielding by bismuth, for example, is discouraged.

**Table 2** Suggested CT settings and parameters for young children with CF

*Taken from Kuo et al. (2016) with permission by European Respiratory Journal. In uncooperative children or others with rapid respiratory rates who are unable to reliably breath-hold, a rapid acquisition mode can be used if available (eg using ultra-high pitch or a large detector array). For some machines this allows images acquisition in less than 0.5 seconds.*

#### 4.6. Newer methods of CT scoring systems

Radiological images for detecting lung disease are mainly descriptive. Currently, CT scoring systems are used to quantify structural changes. Scoring systems should be able to detect a wide range of disease severity and to track disease longitudinally. The limitation of previous CT scoring systems has been in quantifying mild structural changes seen more frequently in infants and pre-school children with CF. The emergence of the Perth-Rotterdam Annotated Grid Morphometric Analysis scoring method (PRAGMA-CF) specially designed to provide a quantitative measure of early CT structural lung disease has shown promising results in validation studies for use in early CF lung disease [35]. Other semi-automated systems to detect bronchiectasis through artery-airway ratios and segmenting bronchial tree as well as quantifying LAR distribution and volume have been developed and validated in older children [7] and more recently in pre-schoolers [36].

Scoring methods such as PRAGMA-CF or CF-CT [1, 2] can be used but require training of the observer. The use of these scoring methods require between 15 and 30 minutes per CT scan which may not be feasibly performed in many centers for routine clinical reporting. There are currently no fully automated validated image analysis systems.

#### 4.7. Summary: CT judged against criteria as a good surveillance test

How does CT perform when measured against our earlier defined criteria for a good surveillance test?

*Sensitivity and plausibility:* CT appears to be sensitive to early lung disease in CF, much more so than clinical or lung function evaluation, or chest radiography. By directly demonstrating structural lung changes, it has high biological plausibility, although the longitudinal significance of early CT changes is only partially defined at present.

*Availability and feasibility:* CT scanners are widely available, however, equipment and staff experience vary, and performing successful low dose studies in young children is generally only feasible in specialist centers.

*Accuracy and reproducibility:* CT findings are in general accurate indicators of disease states, although milder findings may be reversible. Milder disease in younger children may have low reproducibility when assessed by human observers. Whether imaging standardization and semi-automated evaluation can overcome this limitation is to be determined.

*Influence on management:* How abnormal CT findings influence management in a young child with CF requires clarification. However, there are centers with reported experience of the clinical utility from routine surveillance CT. See Figure 1 for an example of surveillance CT in a pre-school child which resulted in a clinical intervention.

*Risk benefit balance:* Risks from radiation dose from occasional CT are not precisely quantifiable but likely to be low, especially if low dose techniques are employed.

#### 4.8. Practical recommendations for performing chest CT

Practice in CF imaging varies across specialist centers. Many major EU centers now offer biennial CT as routine surveillance from pre-school age, other centers reserve CT for addressing specific clinical questions only, such as investigation of unexplained deterioration.

Those centers which do perform routine CT must use modern equipment and low dose protocols to reduce risks to a minimum. The age at which routine scanning commences is open to question, and also varies between centers with some centers starting between one to three years of age.

Most of today's modern CT scanners (64 slice or higher) are fast enough to acquire good quality images while the child is free breathing. Ideally the child should be at ease with a lead-apron-protected parent comforting the child. In the age range between 1-3 years, a vacuum mattress can be used to immobilize the child during the scanning.

For children of 3 years and above, training of the child prior to the CT scan by a lung function technician of breath hold maneuvers should be considered [31]. The feasibility of this test depends on the character and capabilities of the child. The most

optimal approach for each child should be discussed between parents, lung function technician, and/or physician. There are also centers that routinely do an annual bronchoscopy combined with a chest CT under general anesthesia. This will allow a volume controlled protocol to acquire an inspiratory scan at total lung capacity at transpulmonary pressure of 25-30 cm H<sub>2</sub>O and an expiratory scan at functional residual capacity level at pressure of 0 cm H<sub>2</sub>O.

In centers who perform biennial CT or who do not routinely perform CT, CXR will still be most likely performed on an annual basis. Centers that do perform biennial CT scan may choose to perform limited CT protocol that includes only an ultralow dose expiratory or free breathing chest CT as an alternative to CXR on alternate years. Chest MRI is in development but for most CF centers is currently not available. In addition, other monitoring modalities such as careful physical examination, sputum cultures, multiple breath washout (MBW) are used to monitor CF lung disease in pre-school children.

*Key messages: Training of breath hold maneuvers before and coaching during the CT of cooperative children by a dedicated technician improves the quality of the CT scan and improves the diagnostic yield.*

*The use of routine CT surveillance in detecting lung disease in pre-school CF children should only be considered if there is available expertise within the specialist center; as well as appropriate medical interventions resulting from the chest CT.*



## 5 Conclusions

CF lung disease is a serious condition that starts early in life. It can be persistent and severe. Substantial lung damage can develop in the pre-school age. Hence, it is important to identify these children at an early stage with the aim to making changes to their therapy to control and prevent further disease progression. A multi-monitoring approach that includes imaging combined with frequent clinic visits, functional tests like MBW and sputum cultures is needed to guide young children safely through the treacherous first five years of life.

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# CHAPTER 10

## Pre-school airway microbiology in CF - plus ça change?

### Authors

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### Introduction

Over the last decade, molecular methods have revealed that the lower airway in people with CF hosts a microbial community, together with a “soup” of microbial and host proteins, collectively referred to as the “microbiome”. The organisms in this microbiome are termed the “microbiota” and molecular techniques have shown that this microbiota contains many organisms not previously associated with the CF airway and which vary with age [1]. Upper airway samples from infants with CF, collected monthly over the first 6 months of life, have been compared with samples from non-CF infants [2]. These studies have demonstrated a great diversity of organisms both in the babies with CF and controls. However, this work concurs with traditional microbiology in showing that *Staphylococcus aureus* is a dominant organism in infants with CF.

Young children generally do not expectorate and may not produce sputum. This presents a challenge in diagnosing lower airway infec-

tion in CF, as upper airway specimens may not reflect lower airway infection [3].

This review explores the factors influencing the respiratory microbiome in young children with CF and what we know of the clinical implications of this “new microbiology”. We will discuss how treatment of infection may improve the wellbeing and survival of individuals with CF. The increasing treatment burden, which may be particularly challenging for young children and their families, will also be discussed.

### 1 Microbiological sampling in infants and young children

Before considering the complex microbiology of the infant CF lung, it is important to understand how respiratory samples are taken in infants and young children. The most common approach is to swab the oropharynx. Older children may be persuaded to cough during the procedure (“cough swab”) and this is believed to increase the chances of collecting lower respiratory organisms. The results of

these samples, whether an organism is cultured or not, should be interpreted with caution. In pre-school children, oropharyngeal samples have been compared with simultaneous bronchoalveolar lavage, using conventional culture techniques. Results suggest that, whilst a negative culture result helps rule out infection (high negative predictive value) a positive result will over-diagnose infection (low positive predictive value). Recently, upper and lower airway organisms in CF infants have been compared, using molecular techniques, which show different (though overlapping) populations. Even within an individual infant, the concordance between upper and lower respiratory microbiota is inconsistent [4].

Current guidelines recommend that a respiratory sample should be sent for culture at every clinic visit [5], but none of the current methods of sample collection are ideal. Bronchoalveolar lavage samples the lower respiratory tract, but requires a general anesthetic in children. However, any child with a persistent wet cough in spite of treatment, and with un-informative upper respiratory samples should undergo bronchoscopy and bronchoalveolar lavage.

*Key messages: Microbiological sampling in infants and young children is challenging, therefore results of upper airway samples should be interpreted with caution.*

*A child with a persistent wet cough, where upper respiratory samples are not informative, should undergo bronchoscopy and bronchoalveolar lavage.*

## 2 Influences on the infant microbiome

The lower airway was previously thought to be sterile, except during infection. However it is now accepted that even the lower respiratory tract of healthy individuals harbors communities of bacteria and that the microbiota of people with and without lung disease differ [6]. In healthy adults, there is considerable overlap in the bacteria that comprise the lung microbiota and the oral microbiota. In contrast, the nasal microbiome is distinct from the microbiome of the lung [7].

The mother's gut flora has a strong influence on the infant's microbiota. Initially the infant gut microbiota resembles that of the mother's amniotic fluid and placenta. After the first few days of life, this changes to become aligned with the microbiota of colostrum [8]. A different pattern of infant microbiota is seen following caesarean birth but these differences disappear by the age of 6 weeks [9].

### 2.1. The role of the gut and feeding

Molecular techniques have also been used to study the relative changes in the gut and respiratory microbiota over the first two years of life in babies with CF. For almost half the families (or genera) of organisms identified, each genus appears first in the gut, closely followed by the same genus appearing in the respiratory tract [10]. This suggests that the respiratory tract may be colonized by organisms which originate in the gut. Alterations in the respiratory microbiota with changes in the infant's diet further support this. The mode of feeding

(breast vs. formula) also has a strong influence on the infant gut microbiota at 6 weeks [11].

Data from three year follow-up of CF infants provide evidence that the structure of the microbiota can influence the detection of known pathogens. Changes in both the gut (decrease in the genus *Parabacteroides*) and respiratory microbiota (increase in the genus *Salmonella*) have been reported prior to the clinical isolation of *Pseudomonas aeruginosa* from the respiratory tract [12]. These data also suggest a core microbiota, spanning the gut and respiratory tract which includes the genera: *Veillonella*, *Streptococcus*, *Bifidobacterium* and *Bacteroides* [12]. However, these data are based on oropharyngeal samples which may not reflect the lower respiratory microbiota. These data suggest that dietary interventions might be capable of shaping the respiratory microbiota in young children with CF.

### 2.2. Siblings

The environment is an important determinant of the developing microbiome in young children. This is illustrated by the microbiomes of children with CF who live together which are much more alike than the microbiomes of children who live apart. It also suggests that environment overrides genotype regarding the developing microbiome. Children with CF sharing the same environment, whether siblings or monozygotic twins, have equally similar microbiomes [14]. Siblings, with or without CF, may also act vectors of viral infection, playing an important role in exacerbations. Recently our knowledge of the bacteria that

may be present within the lungs of young children with CF has increased greatly. There are strong signals that a diverse microbiota is associated with good lung health (and vice versa) and the environmental factors that may influence this. However the mechanisms that underplay such associations are not known. It is unclear if the presence of specific genera are more or less protective (or damaging) and what indeed we may do to influence this.

## 3 Trends in infection with increasing age

Both reports based on traditional microbiological culture [15] and those using molecular diagnostic techniques [2] indicate that *S. aureus* is an important respiratory pathogen in young children with CF. In the UK, this has led to the introduction of anti-staphylococcal antibiotic prophylaxis, aiming to prevent infection with *S. aureus*.

The prevalence of respiratory organisms in pre-school children with CF varies depending on the country and the healthcare system. For example, recent US registry data [16] describe the three most prevalent organisms in pre-schoolers with CF as: *S. aureus* (around 70% of children), *Hemophilus influenzae* (30%) and *P. aeruginosa* (20%). In the UK, the latest registry report [15] lists the same top three organisms but with a notably lower prevalence of *S. aureus* (around 25%). Over time the proportion of patients with chronic *P. aeruginosa* infection increases steadily reaching 50% of patients in the late teens/early twenties.

The pattern of infection in infancy is less clear when molecular techniques are used. In older children and adults with CF the core microbiota consists of *Streptococcus*, *Prevotella*, *Rothia*, *Veillonella* and *Actinomyces* with the more commonly appreciated CF-associated infections (*Pseudomonas*, *Burkholderia*, *Stenotrophomonas* and *Achromobacter*) being less prevalent [17]. However similar studies in young children have produced surprising results with the most common genus being *Staphylococcus* followed, in decreasing prevalence, by *Streptococcus*, *Pseudomonas*, *Neisseria*, *Haemophilus*, *Gemella*, *Granicatella*, *Prevotella*, *Veillonella* and *Streptomyces* [18]. Interestingly the same study replicated the finding of studies in adults with CF whereby increasing age is associated with decreasing microbial diversity and increasing airway inflammation [18].

More recently non-tuberculous mycobacteria (NTM) have been increasingly recognized, with concern at the apparent increase in prevalence of *Mycobacterium abscessus* [19]. The prevalence of NTM appears to be low in young children but becomes more frequent at school age and beyond. Recommendations for children, in practice guidelines, are largely extrapolated from adult care. Further research in this area is required.

*Key message: The lower airway hosts a complex microbiome which is established over time and influenced by many factors*

## 4 Prevention of infection

The timely detection of infection is challenging. Asymptomatic infection is common and may result in cumulative lung damage. Respiratory infection is prevalent in the first two years of life and results in significant reductions in lung function – whether measured during infancy [20] or at school age [21]. The primary aim is to prevent infection before such damage is sustained.

The decision to treat infection in the symptomatic child is easier than the decision to treat a child without symptoms. The treatment of a child with the isolation of a known pathogen (*P. aeruginosa*, *H. influenzae*, *S. pneumoniae* and *S. aureus*) as a result of routine testing after an elective clinical encounter is also not contentious. Other isolates, such as *E. coli* and *Candida* sp. would only normally require treatment if accompanied by symptoms.

The primary routine immunization schedule for all children is equally the standard for children with CF. In addition annual influenza vaccination is recommended. Currently there is insufficient evidence to recommend the routine use of passive immunization against respiratory syncytial virus (RSV) with palivizumab for infants with CF [22]. The one randomized trial that was identified in the Cochrane review did not show a difference in outcomes between those who did, and those who did not, receive palivizumab although the number of hospital admissions in the trial overall

was very low. The reports of benefit [23] or otherwise [24–27] from non-randomized reports in terms of hospital admission, secondary infection and general health are mixed, but most units in the UK do not use routine palivizumab.

*H. influenzae* (type b) is included in the primary immunization schedule in many countries. This provides some protection for children with CF, however it is largely infection with non-typeable *H. influenzae* that is more problematic. *H. influenzae* infection is associated with pulmonary exacerbations, reduced lung function and increased lung inflammation [28].

An effective vaccine against *P. aeruginosa* would be desirable because chronic infection in young children with CF leads to deteriorating clinical status [29]. However, vaccine trials to protect against *P. aeruginosa* have so far been unsuccessful [30]. A vaccine for *S. aureus* has not progressed beyond limited animal studies [31].

Antibiotic prophylaxis with nebulized colistin and oral ciprofloxacin in young children has failed to prevent *P. aeruginosa* infection [32]. The situation with anti-staphylococcal prophylaxis is more contentious with flucloxacillin being recommended in the UK [33] for all children under 3 years of age and not being recommended in the US [34]. The Cochrane review concluded that anti-staphylococcal antibiotic prophylaxis led to fewer children having isolates of *S. aureus* [35]. Notwithstanding the practical challenge of administering an unpalatable antibiotic to babies and infants on a

daily basis, there has been some concern that prophylaxis may increase infection with *P. aeruginosa* [36]. A definitive randomized trial is in progress called CF START (ISRCTN18130649) which may provide information to better guide practice. CF START will compare infants randomly allocated to either “Prevent and Treat” (flucloxacillin) or “Detect and Treat” (antibiotics given in a more targeted manner and will report age at first growth of *P. aeruginosa*) and other important clinical outcomes.

*Key message: Prevention of infection is not currently possible, although it is possible to successfully eradicate early P. aeruginosa infection and defer chronic infection*

## 5 Exacerbations

There is no universally agreed definition of a pulmonary exacerbation in CF. Diagnosing an exacerbation in a pre-school child (an age group where viral infection is common) is challenging. In school age children, exacerbations are associated with a failure to regain lung function [37] and it is likely that exacerbations in pre-school children are also damaging.

In the Australasian bronchoalveolar lavage randomized trial, exacerbations in children younger than 5 years were defined as “any change in respiratory symptoms from baseline”. With this definition, and with considerable center to center variability in rates of reporting exacerbations, 166 children reported 2080 respiratory exacerbations

tions equating to an incidence rate of 3.66 episodes per person-year [38]. Overall 20% of the exacerbation episodes resulted in hospital admission. At age 5, lung function and the presence of bronchiectasis on CT was associated with the exacerbation rate in the first 2 years of life.

Viruses are considered to be strongly associated with a significant proportion of pulmonary exacerbations in CF. However respiratory virus detection is common, with 55% of young children attending day-care having had one or more viruses detected from routine nasopharyngeal samples [39]. Data on the incidence of viral infections in pre-school children with CF are conflicting. Some studies suggest that children with CF have more viral infection than their non-CF peers, for example human rhinovirus [40]. However, other data suggest that, although those with CF report more respiratory illness, the frequency of proven viral infection was no different to non-CF siblings [41]. In a more recent study, infants with CF were no more likely to have viruses detected from their upper airway, nor were they more likely to have symptomatic viral infection [42]. There are, however, significant associations between the annual incidence of viral infection and every measure of disease progression [41], suggesting that the normal experience of early childhood is hazardous to those with CF.

In addition it should be remembered that viral infections and bacterial infection often co-exist in children with CF and so the isolation of a virus should not offer undue reassurance that a bacterial infection is not

contributing to current symptoms. Paired viral and bacterial samples should always be taken at the onset of symptoms for which a clinical review is required.

*Key messages: Viral and bacterial infections often co-exist in young children with CF. Therefore, paired bacterial and viral samples should be taken at clinical encounters prompted by new symptoms.*

*Identifying pulmonary exacerbations at an age where upper respiratory tract infections are common is difficult, but such exacerbations are likely to be damaging.*

## 6 The first isolate of *Pseudomonas aeruginosa*

Using the Early *Pseudomonas* Infection Control (EPIC) Observational Study cohort, one of the main predictors of lower mean FEV<sub>1</sub> at age 6-7 years was *P. aeruginosa* positivity during the year of enrolment to the study [43]. Furthermore, a US CF Registry study published in 2002 reporting data from 1990, demonstrated that *P. aeruginosa* infection in those aged 1-5 years was associated with a significantly increased 8-year mortality [29].

It is hypothesized that *P. aeruginosa* changes its mode of growth from a relatively antibiotic-sensitive, motile, planktonic form to a biofilm mode of growth wherein aggregates of bacteria link together to form a matrix, while producing an exopolysaccharide alginate that surrounds the colony. Other virulence factors are produced. These mediate local changes in the host immune

system and circulation, eliminate competition by killing other bacteria in the niche and impair the diffusion of antibiotics which is needed to reach cidal concentrations [44].

Once chronic infection is established, the organism can no longer be eradicated and so treatment is aimed to reduce the bacterial burden, and long term effects of the infection. Chronic anti-pseudomonal suppressive treatment is routinely commenced in the form of daily nebulized antibiotics. Long-term azithromycin would be considered in most cases [33].

Successful eradication of early *P. aeruginosa* is important in order to defer the establishment of chronic infection – from which point eradication is no longer possible. The management of *P. aeruginosa* infection has changed significantly since the early 1990s and a consensus has been reached on the importance of eradication. The Australasian annual bronchoalveolar lavage study demonstrated that 57% of children had at least one *P. aeruginosa* infection in their first 6 years of life. It was often also the case that this infection was not heralded by symptoms, but that this could be eradicated by a two-week course of intravenous tobramycin and ticarcillin clavulanate or ceftazidime followed by 1 month of nebulized tobramycin and oral ciprofloxacin. Such eradication was associated with a reduction in airway inflammation [45].

The Cochrane review of *P. aeruginosa* eradication concluded that nebulized regimens (with or without oral antibiotics) were effective in eradicating *P. aeruginosa* [46]. The Taccetti trial demonstrated that inhaled colistin/oral ciprofloxacin was not superior to inhaled tobramycin/oral ciprofloxacin [47]. Duration of treatment was explored in the ELITE trial which showed that treatment with inhaled tobramycin for 28 days is as effective as 56 days [48]. The remaining question to be answered is which regimen is most effective and better tolerated by those requiring *P. aeruginosa* eradication – intravenous versus oral/nebulized protocols? The TORPEDO-CF trial (ISRCTN02734162) aims to answer this question, with results expected in 2018.

The widespread use of robust eradication regimens may be having an impact, with centers observing progressive decreases in prevalence of both chronic *P. aeruginosa* and mucoid *P. aeruginosa* [49, 50].

As eradication is impossible once chronic infection is established [51], and with the lack of a new antibiotic class on the horizon, approaches to increase the efficacy of existing antibiotics are being explored. These antibiotic adjuvants aim to act alongside a co-administered antibiotic to reduce the virulence and innate antibiotic resistance. This is a new area for research and currently no agents are yet ready for clinical practice [52]. A distant aspiration would be to use this adjuvant before the biofilm is established, thus preventing chronic infection altogether.

## 7 The future

As discussed, new antibiotic classes and new antimicrobial approaches are unlikely in the near future. Nevertheless the evolution of small molecule therapy [53] and *CFTR* targeted treatment in younger age groups [54, 55] may result in the phenotype of CF changing completely. In the year after ivacaftor commenced, reductions of 35% in the odds of being *P. aeruginosa* positive have been observed [56]. Primary prevention of chronic infection with *P. aeruginosa* is now conceivable. However, until this is achieved, the frequent and targeted use of antibiotics is needed, soon after the onset of symptoms. Conventional approaches have already achieved important improvements in outcomes for young children with CF. The impact of recent developments such as our increasing understanding of the microbiome and the use of *CFTR* modulators, remains to be determined.

## 8 Summary

The rate of increase in our understanding of the microbiology of the lungs and airway, in health and disease, continues to gain pace. We are beginning to understand the clinical importance of the microbiome in older children and adults with CF. The research community must make renewed efforts to understand the evolution and clinical implications of microbiome structure in young children. Due to the difficulty in acquiring respiratory tract samples from

young children and the challenges in measuring lung health, progress will be slower. In the meantime, concentrating on the regular sampling of the respiratory tract and providing prompt treatment of significant bacterial isolates has led to improvements in the health of young children and will continue to do so.

### 8.1. Illustrative case

Jay was diagnosed with CF at six weeks of age after being identified via newborn screening. He was initially well, with no significant growths from respiratory tract samples until, in mid-winter at the age of 4 months, Jay was admitted to the children's ward as a result of coryza, poor feeding and increased work of breathing. Nasopharyngeal aspirates (NPA) and a cough swab were taken at admission. RSV was identified from the NPA followed by a growth of *P. aeruginosa* from the cough swab 2 days later. Aiming to eradicate this early growth, oral ciprofloxacin and nebulized colistin were commenced and were planned for 3 weeks. However this was not tolerated due to worsening respiratory distress. Intravenous antibiotics (ceftazidime and gentamicin) were commenced and *P. aeruginosa* was successfully eradicated. It was not until the age of 5 years that Jay next had *P. aeruginosa* infection identified from sputum.

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# CHAPTER 11

## Airway clearance and activity in the pre-school years

### Authors

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### Introduction

Physiotherapy is a vital component of cystic fibrosis (CF) care, and an important part of everyday life for people with CF. Daily physiotherapy and airway clearance start upon diagnosis and can be performed by families and caregivers, under the guidance of the physiotherapist. Various techniques exist, such as modified postural drainage (MPD), assisted autogenic drainage (AAD) and positive expiratory pressure (PEP). Different techniques suit different families and the best-suited technique can change as the child grows up. Making physiotherapy and daily physical activity fun helps form good habits that will last into adulthood, to help maintain lung function and health.

### 1 Role of the physiotherapist at diagnosis

Physiotherapists are part of the multi-disciplinary team that cares for infants and toddlers with CF. Their role includes

teaching airway clearance techniques, recommending exercise, helping with inhaled treatments and treating joint, back and continence problems as they arise later in life. In some countries they may also prescribe medications.

Treatments commenced in the newborn period aim to:

- Shift the healthcare focus from reactive care to proactive care
- Improve CF care, quality of life and survival for infants and children with CF
- Provide the highest standard of personalized family centered care

Prior to newborn screening (NBS), the diagnosis of CF was primarily made based on symptomatic presentation. This presentation often included respiratory compromise and lung changes in chest radiography (this is still the case in some countries where NBS has not yet been instituted). Identifying infants with CF through newborn screening usually allows physiotherapy to be initiated prior to the manifestation of respiratory symptoms. Despite NBS, some infants may already be symptomatic at diagnosis [1].

## 2 When to commence physiotherapy

When an infant is diagnosed with CF, it is important to remember the emotional toll this has on the family. They are usually devastated by the news. Thus, it is important to give the family time to grieve over the loss of expecting a healthy child. During this time, and if the child does not have respiratory symptoms, the emphasis should be on the nutritional aspect of CF care. However physiotherapy should be started as soon as possible after diagnosis [2-4].

Physiotherapy will be an integral part of care for each person with CF throughout their life. Thus, it is important for the physiotherapist to spend time with the family, to find out how they are coping, how they think their infant is doing, discussing their lifestyle, family structure, beliefs, and how they learn. This helps the physiotherapist to engage the family in learning to care for their infant with CF and in designing a physiotherapy CF care program tailored to their needs. Children with CF (and their families) need to learn to live with the disease as a reality in their everyday life, while also leading as normal a life as possible.

## 3 The initial teaching visits with the CF family

During the initial teaching process, some clinics see the CF family daily for 2-4 days, others see the family on a weekly schedule for a month while others do the teaching all in one day. Whichever method is used will depend on the CF clinic and several other factors such as the distance the family live from clinic, time off work, or the availability of healthcare professionals. Whether the initial teaching takes place over one day or a month, the physiotherapist needs to cover the basic physiotherapy care for an infant with CF.

Physiotherapy initial teaching sessions should include [5]:

- Basic education on the anatomy and physiology of normal lungs
- Education about how CF affects the lungs, describing the role of mucus and the effect of impaired mucus clearance
- Education on the role of airway clearance throughout the life of a person with CF and an overview of some of the airway clearance techniques
- Instruction in one primary method of airway clearance – the proficiency of the caregiver in at least one method of airway clearance should be demonstrated at least one month after diagnosis
- Instruction on how to access the infant's chest; signs and symptoms to look for when their infant is getting sick
- Education on the importance of exercise and physical activity - this should fit in with the family's lifestyle

- Education on infection control with emphasis on cleaning after physiotherapy treatments, including cleaning of any physiotherapy equipment. Avoidance of hot tubs is recommended. Some CF centers also advocate avoidance of horse riding, while others allow it but not mucking out the stables, due to concerns regarding fungus and other pathogens which live in hay
- An introduction to the use of inhalations for bronchodilator, mucolytic, and antibiotic therapies. Some CF centers introduce their use at diagnosis, especially if the infant is symptomatic (see Chapter 12)

Handouts or video links can be used as additional teaching tools, providing families with materials that they can review after the initial teaching session.

## 4 Rationale for beginning physiotherapy at diagnosis

Lung disease starts early in CF. It is thought that the basic defect in ion transport leads to volume depletion of the airway surface liquid and failure of mucus to detach from submucosal gland ducts [6], both of which contribute to impaired mucociliary transport.

The clinical consequences are infection, inflammation and airway obstruction which may progress to bronchiectasis. Recent studies suggest that bronchiectasis is present in many asymptomatic infants shortly after diagnosis, and that the majority of children with CF have bronchiectasis by

five years of age [7]. Thus there has been a shift in focus to examine various treatments aimed at preventing early disease progression and minimizing lung damage before it becomes irreversible [8].

Physiotherapy is one such treatment that can be introduced soon after diagnosis, although the immediate effects may not be measurable. Airway clearance techniques aim at assisting mucociliary clearance. Since most CF infants are asymptomatic the question has arisen, "when should physiotherapy be started?"

Based on our present knowledge of CF lung disease, we know that lung disease is present in the asymptomatic CF infant and that mucociliary clearance is impaired. Thus, it is generally recommended to commence airway clearance soon after diagnosis [2-4]. In addition, starting physiotherapy upon diagnosis allows the caregiver to become attuned to the respiratory status of the infant. If the caregiver performs physiotherapy on a daily basis, they will likely be able to detect minute changes from baseline allowing for appropriate changes in care. Airway clearance techniques also become part of the infant's daily routine, which sets an important precedent as the infant grows into adulthood.

Some centers recommend monitoring babies with CF very closely and only commence airway clearance techniques as chest problems arise [5]. The majority of other centers in Europe, North America and Australia recommend airway clearance to be commenced at diagnosis.

*Key message: Airway clearance should be initiated at diagnosis.*

#### 4.1. Airway clearance techniques used in infants, toddlers and pre-schoolers

There have always been cultural and geographical influences on the choice of physiotherapy techniques. However most centers incorporate various modalities for airway clearance and exercise to offer parents and families an educated choice and an adaptable management plan.

The CF physiotherapist should work closely with the family to find the technique, or combination of techniques and exercise, that works best for them. Some techniques require no equipment, and others use a device. It is important to tailor a time-efficient treatment program that places the least possible burden on the child with CF and their family and makes adherence with the treatment possible. The caregiver must be proficient in whichever program is chosen.

There have been limited studies on the use of airway clearance techniques in infants. Most airway clearance studies have been conducted in older children and adults, the results of which have been extrapolated for use in younger children. The techniques with some evidence are MPD, PEP, AAD and postural drainage (PD) [9, 10]. CF physiotherapists should consider using these techniques to treat infants with CF. Of these techniques, none have been shown to be more effective than another. People may prefer different techniques at different times in their life.

#### 4.2. Modified postural drainage (MPD)

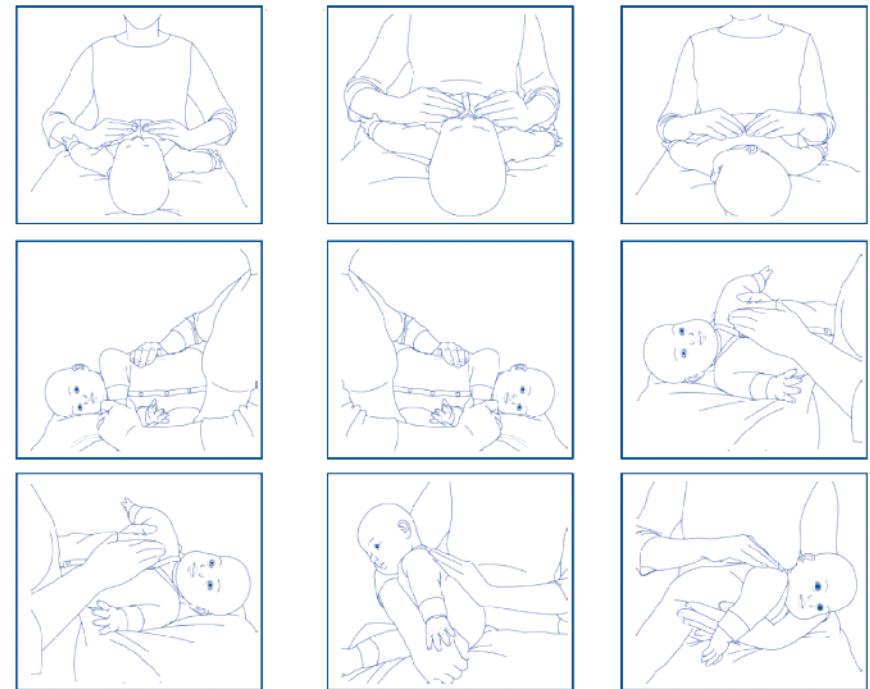
Postural drainage consists of placing the infants in various positions that utilize gravity to assist in the mobilization of secretions from a particular lung segment. Positions were modified to eliminate head-down tilt due to concerns regarding gastroesophageal reflux. More recently, it has been postulated that the changes in ventilation, which occur by placing an infant in different positions, influence the mobilization of secretions more than gravity [10]. This is one explanation for why MPD appears to be at least as effective if not more effective than PD using head-down positioning [11, 12].

The easiest way to perform treatment is to have the infant lying on a pillow on the caregiver's lap. In each position, the chest wall is percussed for 3–5 minutes, usually over a soft towel. Vibrations may also be used with percussion. If lung infection is present, more frequent and longer spells of treatment may be suggested. As the infant gets older, breathing exercises, vibrations on expiration and huffing are incorporated in the technique (Figure 1).

#### 4.3. Positive expiratory pressure (PEP)

PEP is an airway clearance technique which was developed in Denmark in the early 1980s and remains the primary method of airway clearance in Denmark for all people with CF, including infants [9, 10, 13].

PEP uses a mask with a one-way valve to which an expiratory orifice resistor is attached. A pressure manometer may be



**Figure 1** Modified postural drainage positions to target the upper, middle, lingual and lower lobes. Courtesy J. DeGuzman

inserted between the valve and the resistor. The diameter of the resistor used for treatment is determined for each individual patient with the aim of producing a steady PEP of between 10–20 cm H<sub>2</sub>O during expiration. In small infants using the smallest diameter resistor of 1.5 mm, a PEP of between 5–10 cm H<sub>2</sub>O is produced. As the infant grows, the PEP will gradually increase to reach a pressure of 10–20 cm H<sub>2</sub>O by the age of 4–5 years.

Usually, infants perform the treatment leaning in a backward “sitting” position on an arm of a parent, where the baby’s head is supported by the upper arm while the other hand holds the mask firmly on the infant’s face (Figure 2). A treatment session consists of periods of breathing with PEP (usually for 1–2 minutes with infants) followed by huffing. As infants cannot perform huffing, the caregiver may be taught to increase the expiratory airflow by interspersing PEP breathing with

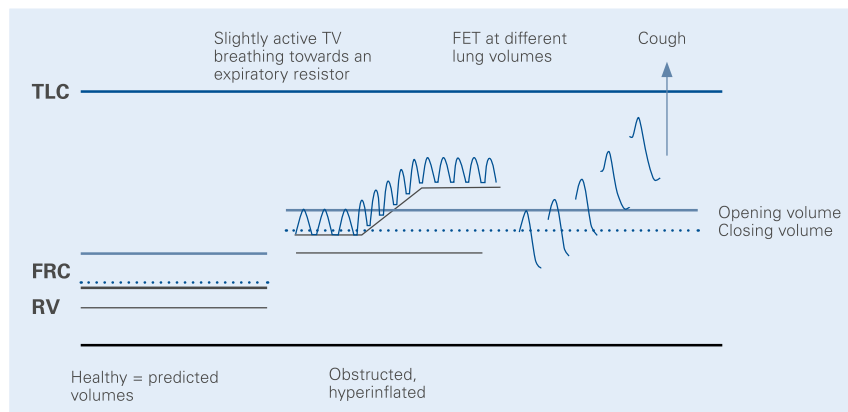
bouncing on a therapy ball while applying external pressure over the chest wall on expiration (**Figure 2**).

While breathing through a PEP mask, the functional residual capacity is tempo-

rarily increased, improving ventilation and allowing air to move behind clogged or collapsed airway [14]. The forced expiration technique increases the expiratory airflow in order to transport and evacuate the mobilized secretions (**Figure 3**).



**Figure 2** An infant being treated with BabyPEP



**Figure 3** Breathing levels during positive expiratory pressure (PEP) treatment in a patient with obstructed airways *Courtesy of L Lannefors* [9]

#### 4.4. Bubble PEP

A form of PEP called bubble PEP has been introduced in some countries for use in pre-school children. It consists of a child blowing through a tube into a jar of water creating a positive expiratory pressure and some oscillation. There have been some studies examining the depth of water required in the jar and the diameter of the tubing, with mixed results [15]. In addition, while using bubble PEP, functional residual capacity is not temporarily increased.

As there have been no long-term studies conducted on bubble PEP, caution should be taken in prescribing this as the primary airway clearance technique for pre-schoolers. However, it is a fun playful adjunct to airway clearance, especially if you add food coloring and some dishwasher soap to the jar of water.

#### 4.5. Assisted autogenic drainage (AAD)

AAD is the adaptation of autogenic drainage in infants and young children not yet capable of carrying out this technique actively themselves. AAD is carried out in a gentle and progressive way [9, 10]. Using the patient's breathing pattern and stabilizing the infant's abdominal wall to avoid paradoxical movements, the caregiver places their hands on the infant's chest wall and manually increases the expiratory flow velocity by applying over-pressure on expiration, prolonging expiration towards residual volume during an individualized number of maneuvers (**Figure 4**).

Excessive force is avoided and the number of AAD maneuvers is limited to the child's

response and tolerance. During inspiration gentle pressure is maintained on the chest wall to limit the inspiratory level and to stimulate the child to exhale slightly more than the previous breathing cycle. Feedback plays a key role, the caregivers should feel or hear the secretions move while avoiding any early or abnormal airway compression or closure. The aim is to achieve an optimal expiratory flow progressively through all generations of bronchi without causing dynamic airway collapse.

AAD can be combined with bouncing gently up-and-down on a therapy ball to relax the child and to enhance the expiratory air velocity. The child sitting upright is correctly supported, avoiding a slumped sitting position which may in turn predispose to gastroesophageal reflux (GOR) during treatment.



**Figure 4** An infant undergoing assisted autogenic drainage (AAD)

#### 4.6. Postural drainage

Historically PD with percussion was the primary method of airway clearance in infants. Up to 12 PD positions may be used but these are usually divided into 2–3 sessions per day. There has been no research into treatment length or number of PT sessions per day [13, 16].

Many side effects have been observed during PD. These include GOR, oxygen desaturation, pain and discomfort. GOR is common in normal healthy infants with a prevalence of up to 40%, however an increased incidence of 81% is observed in infants with CF [8]. For these reasons, many CF centers have reverted to using modified PD positions in infants with no head-down positioning. In 2003 Button and colleagues published a paper comparing five-year outcomes in newly diagnosed CF infants who were randomized to either postural drainage incorporating 30° head down positions or modified PD with no head-down positions. The infants randomized to modified head-down positions had significantly better FEV<sub>1</sub> and fewer changes on chest X-ray compared to the PD group [11]. This has further strengthened the argument for using modified PD positions [12].

#### 4.7. Physical activity and exercise

Activity and exercise have been shown to specifically contribute to the health of children with CF. Benefits include a slower rate of decline in FEV<sub>1</sub> [17], improved airway clearance, improved cardio-respiratory fitness [18], improved muscle mass, strength and joint mobility, improved emotional wellbeing and perceived health [19].

Working with the families from diagnosis is important to promote active lifestyle choices for the family as a whole and reduce sedentary behaviors. The early years are an important time to establish physical activity to encourage activity patterns and habits later in childhood to benefit long-term health. It is crucial at this stage that we ensure that parents have an expectation that their child will have a fully active lifestyle and not be limited in any way.

*Key message: Daily activity/ exercise should be emphasized from an early age or from diagnosis*

##### 4.7.1. Infants

Infants and toddlers need time to play and master their physical environment and cultivate fundamental movement skills for optimal development.

Newborn babies need the opportunity daily to move freely without the constraints of wraps, car seats or baby chairs for long periods. Floor based play using “tummy time” positioning or baby gym activities, which can encourage kicking, rolling and reaching for toys are some of the early activities that lay the foundations for good posture, balance and coordination.

Physical activities in infants also aim to alter ventilation distribution, alter breathing patterns, increase expiratory airflow and elicit shear forces enhancing mucociliary clearance. With regular stimulation by the parents or caregivers and the safe opportunity to explore their surroundings, core

strength will increase and the baby is able to progress through activities in sitting through to independent crawling, standing and ultimately walking. Noise during play can stimulate movement e.g. rattles, music and songs.

Both infants and toddlers can benefit from water-based activities with a parent or caregiver in a bath at home or a swimming pool, to stimulate their senses and develop muscle strength and coordination.

##### 4.7.2. Pre-schoolers

There has been a growing concern about a lack of physical activity and increased sedentary behavior among young children in general. This has led to the development of recommended physical activity guidelines for CF by an expert panel who recommend that young children with CF should perform regular, developmentally appropriate physical activity at least 60 minutes per day [20]. The amount of time spent sedentary for extended periods should be minimized (except time spent sleeping).

Activities such as running, skipping, jumping, dancing, and bouncing all contribute towards daily activity levels, as well as being fun. The more energetic the play, the more children will “huff and puff”, increasing their heart rate and respiratory rate. Riding bikes, scooters and climbing activities develop their stability and balance skills. Gross motor skills develop with activities such as throwing, catching, kicking and striking balls.

Further benefits in this age group include improving motor skills, developing social

skills, increasing self-confidence, improving communication skills and establishing good habits for being active. Young children have a natural tendency to be active in sporadic bouts which is helpful and reduces the time spent inactive over the day.

Parents and caregivers play a vital role in their children being physically active, giving them the opportunity and encouragement at every stage of development, even when their child is not naturally inclined to participate. Being an active role model, creating fun opportunities and participating as parents in games will encourage the young child to enjoy being active.

##### 4.8. Typical daily schedule

In an asymptomatic infant a daily schedule may include:

- Airway clearance 1–2 times daily, before feeds or at least 45 minutes to 1 hour after feeds. Some parents prefer shorter and more frequent sessions while others prefer longer and fewer sessions. Treatments should be spread out throughout the day, but need to fit in with the parent’s lifestyle and daily routine. Symptomatic infants may require treatment 3 times a day.
- If using modified PD, it may be performed while the infant is sleeping. As they get older it is more beneficial that they actively participate in the treatment.
- Age-appropriate play and use of different positions increase ventilation to different areas of the lung.



## 5 Who should learn to perform physiotherapy?

This will vary from country to country. Usually the physiotherapist attached to the CF center where the infant attends is responsible for the initial teaching and setting up the home program with the parents. The parents and caregivers are usually the primary providers responsible for carrying out the daily physiotherapy routine. In some European countries home care physiotherapists are able to assist with the daily physiotherapy needs of the infant or toddler. This is very beneficial to both the child and the parents, as the physiotherapist can provide further teaching with the family, and provide “hands-on” physiotherapy treatment. They can also detect early changes in the child’s respiratory status and relay this information to the CF center. If a home care physiotherapist is available, it is essential that there is strong communication between them and the CF center physiotherapist.

### 5.1. Factors influencing management.

The airway clearance technique used during infancy is usually dependent on the skill, knowledge and culture of the CF center where the infant with CF is being treated. For example, AAD requires the caregiver to have the necessary skill to manipulate the infant’s breathing pattern in a beneficial way and requires close monitoring. It is mostly used in CF centers where the physiotherapist can conduct regular home visits. Occasionally, an infant presents with air trapping and tends to breath in the inspiratory reserve volume. In

this case, AAD may be the airway clearance technique of choice as this helps normalize their breathing pattern and restore their “normal” functional residual capacity level.

In a newly diagnosed infant with CF, parents should be taught to look for signs and symptoms that the infant has increased secretions, cough, shortness of breath, increased work of breathing such as indrawing or a tracheal tug, changes in color and lethargy. With any of these signs or symptoms the CF center should be contacted for advice. This may include increasing the number of airway clearance sessions per day, or changing to another airway clearance technique and/or getting a cough swab and treatment with antibiotics.

### Case report

A 2-year-old boy with CF showed significant bronchiectasis with secretions present in the right lower lobe on CT scan. The child had been diagnosed with CF through the NBS program and had been using MPD with percussion and vibration twice a day as his primary airway clearance technique. However, the consistency and quality of physiotherapy had declined in the past 6 months as the child became more active and parents struggled to complete therapy.

The child underwent a bronchoscopy and had his mucolytics (hypertonic saline and DNase) optimized, but there was little improvement to his right lower lobe. The child was then admitted for a two-week hospitalization for intensive physiotherapy and IV antibiotics. At this time, a discussion took place as to which physiotherapy

technique would be of greatest benefit to the child. The effectiveness of MPD may have improved in hospital with the physiotherapist performing it, however the technique was not sustainable at home. AAD was trialed but similarly to MPD, the child had difficulty sitting for the duration of the therapy. Activity and exercise were discussed. The child was already very active at home, but this alone had not been sufficient to clear his secretions.

Therefore, BabyPEP was introduced in hospital and taught to the parents to use once the child returned home.

With BabyPEP, the child was able to snuggle with his parents and watch a television show during the treatment. This allowed him to complete the entire therapy session. The child adjusted to the BabyPEP very well and even lay on his left side for some of the session which helped move the secretions in the right lower lobe through the change in ventilation pattern.

Upon discharge, the child’s physiotherapy treatment was changed to BabyPEP twice a day. No CT scan was performed at discharge but chest radiograph showed an improvement in the right lower lobe which was maintained 5 weeks later upon review (Figure 5). Parents also reported increased adherence and completion of physiotherapy.



**Figure 5** Chest radiograph before and after BabyPEP treatment

*After 5 weeks of home therapy with BabyPEP, the right lower lobe showed improvement between the radiograph at discharge (on left) and the radiograph at the 5 week review after discharge (on right).*



### 5.2. Adjusting therapies as the child gets older

This is a stage of transition when the child begins to play a more active role in their treatment. Breathing exercises begin in game form and play an important role in airway clearance. Activities such as blowing bubbles, musical instruments, blow football and blow painting are just some examples which can be fun and stimulate deep breathing techniques.

Pre-schoolers from the age of 3–4 years can learn a forced expiration technique or huff, which is a forced breath out through an open mouth and is used in many airway clearance techniques. This can be initially be taught by blowing through a cardboard tube to steam up a mirror. Children from an early age often mimic coughing if asked to do so, although secretions at this stage will often be swallowed.

Bubble PEP can be used in the pre-schooler. This creative technique provides positive feedback to the child helping to maintain interest and co-operation.

As far as possible, treatment should be stimulating and should incorporate siblings in activities that are both therapeutic and fun. The trampoline is an entertaining activity which can involve friends and family.

### 5.3. Does the CFSPID infant need treatment?

Since NBS started there is a cohort of people with CF screen positive inconclusive diagnosis (CFSPID). CFSPID may

be used interchangeably with the term CF related metabolic syndrome (CRMS). The long-term outcome of children with CFSPID is unknown. Current guidelines recommend following these children with CFSPID on at least an annual basis as a few of these children will convert to a diagnosis of CF over time [21].

Children with CFSPID may not need to be taught an airway clearance technique; rather the emphasis is on activity and exercise. On the rare occasion that a child with CFSPID develops respiratory symptoms, they may need to use an airway clearance technique.

The importance of activity and exercise should be counseled to children with CFSPID and their families. All children should be encouraged to exercise as per their country's activity guidelines. Emphasizing the importance of regular exercise and activity to children with CFSPID and their families at an early age will hopefully set up good habits into adulthood.

## 6 Adherence

It is recognized that managing and promoting adherence is an essential component of care in chronic disease, where adherence to advice or medical treatment is often less than 50% [22].

Working with the family to establish a routine for treatment is important and can help influence long term adherence.

Several factors should be considered when choosing an airway clearance technique or a combination of techniques to facilitate optimal adherence to treatment, including the:

- Age and level of co-operation of the child
- Personality of child (which can show itself early in infancy)
- Level of family support and ensuring the airway clearance program is realistic and achievable

Parents whose child has been diagnosed with CF prior to 3 months of age and treatment commenced were found to have more adaptive coping styles compared to a later diagnosis [23]. The parents can develop responsive observational skills to detect early changes and learn to respond and communicate with the CF team effectively to initiate early treatment. In this way they gain confidence in their ability to assess their infant and learn to be flexible in their physiotherapy treatment approach with respect to timing and frequency.

We have found that providing parents with a range of airway clearance techniques, play and activity allows them to adapt their child's management on a daily basis. This is especially important in the older "toddler" phase, when at times it can become challenging to provide treatment for a child who has clearly decided that they don't want to do it! With these strong-minded toddlers, through patience and imagination, physiotherapy can be something that they accept and maybe even enjoy particularly if it allows some "special" time with a parent.

## 7 Ongoing support and Education

Education about the disease and its treatment starts at the time of diagnosis and is an on going process with the aim of preventing lung disease and preserving lung function. It is essential to advise and educate parents so they feel empowered to deal with changes in their child's presentation and feel confident to communicate regularly with the team in response to clinical changes.

Regular and frequent contact with the physiotherapist is paramount to help establish a good home treatment regime and address any concerns or worries that the families may have. This can be fitted into outpatient visits or during an admission to hospital. Some CF centers can arrange home visits, which are valuable, particularly around the time of diagnosis to allow anxious families to voice their concerns.

Holding group meetings for parents, sending out newsletters, keeping an updated website are all ways of providing information regarding clinical management, research updates and can provide a forum for discussion. Relatives, nursery and school staff can be educated and updated as needed to help support the child and family.

The management program should be individualized to the child's needs, lifestyle and personality as they progress through infancy, school, university, future career and family in order to optimize their quality of life throughout.

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# CHAPTER 12

## Delivery of aerosolized medicines to infants and pre-school children with cystic fibrosis

### Authors

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### Introduction

The goal of aerosol therapy is the efficient deposition of active pharmacologic agents in the respiratory tract at the anatomic location where pathology is present. Aerosolized medications have great potential utility in that they can efficiently achieve high concentrations of active drug topically while minimizing extra-pulmonary side effects associated with systemic drug administration. In CF, aerosols can be used to treat disease manifestations from the upper airway (e.g. nasal corticosteroids for nasal polyps) to the lower airways (e.g. inhaled antibiotics for *Pseudomonas aeruginosa* (*Pa*) infection).

The decision to initiate an aerosolized medication must balance the potential benefits against the increased time commitment and burden associated with this treatment modality. Poor adherence, a common problem in chronic disease management, has the additional aspect that drug delivery is dependent on operator technique.

Pre-school children and infants with CF present an especially challenging patient population in which to administer and study the effects of aerosolized medications, as there are age-specific anatomic, physiologic and cognitive differences, compared to the more-often studied older pediatric and adult populations.

This chapter will provide background on the science and technology involved in aerosol delivery, and review the evidence for aerosolized medications in the treatment of lower respiratory tract pathology in young children with CF.

### 1 Aerosol delivery and deposition

For most aerosolized medications used in the treatment of CF, a uniform deposition in the small (>16<sup>th</sup> generation) and medium (7<sup>th</sup> – 15<sup>th</sup> generation) airways is desired for optimal treatment effects. Factors intrinsic to the aerosol itself as well as factors associated with the patient and delivery system

can influence aerosol deposition and a basic understanding of aerosol science is useful when deciding which drug to use with which system in a given patient (Table 1).

An aerosol is a colloidal suspension of a liquid or solid dispersed uniformly in a carrier gas. Aerosols can be deposited in the respiratory tract via inertial impaction, gravitational sedimentation or diffusion (reviewed in [1]). The mode of deposition is influenced by particle size and velocity and the anatomic structure of the respiratory tract. Larger particles (aerosols with a mass median aerodynamic diameter [MMAD] >5 µm) as well as faster-moving particles tend to deposit in regions of the respiratory tract with turbulent airflow; thus, mostly in the upper airway or at bifurcation points in the early generations of the tracheobronchial tree. Smaller particles (MMAD <0.5-1 µm) tend to be deposited in the lower airways by diffusion, but may not have time to settle in the course of a respiratory cycle and a large proportion will therefore be exhaled. Medium sized particles (MMAD 1-5 µm) tend to deposit by gravitational dispersion and are thought to be deposited most efficiently in the small airways.

The MMAD of the aerosolized particle is determined by the mode of aerosolization and by the physicochemical properties of the drug itself. It should be noted that most aerosol medications are polydisperse colloids; that is to say that the size of the particles are not uniform. The fraction of particles in the ~1-5 µm range is referred to as the fine-particle fraction (FPF) and is generally used as a metric to describe the

proportion of particles (under ideal conditions) that has the greatest chance of being delivered to the small airways. The velocity and density of the particles also influence the mode and location of deposition, with higher velocity and denser particles tending to deposit by impaction in the upper airway.

New technologies in aerosol delivery such as the development of slow mist inhalers [2] and the use of large porous particles [3] result in less dense particles with lower linear velocities with increased lower respiratory tract deposition. These physicochemical properties of aerosols have not been extensively studied in young children, but small differences in the MMAD have been shown to have measurable differences on the efficacy of aerosolized medications in adults [4].

Age-related factors can affect the efficiency of aerosol deposition in the lower airways, as young children have more upper/central airway aerosol deposition than older children and adults (reviewed in [5]). This difference is most striking in infants and appears to be mitigated by the age of 6 years [6]. The size and geometry of the upper airways and mode of breathing change significantly in the first years of life. In school age children, oral inhalation has been shown to be the more efficient mode to deposit aerosol in the lower airways [6]. Interestingly, the opposite appears to be true in infants, with *in vitro* modeling showing significantly more upper airways deposition with the oral route than the nasal route [7]. However the exact point at which oral inhalation becomes more efficient than

nasal inhalation remains controversial. The changing size and geometry of the developing airways may also alter deposition efficiency and some controversy still surrounds the question of whether or not aerosols with lower MMADs are needed to effectively reach the small airways of infants and pre-school children [5].

Deposition location and efficiency is also impacted by characteristics of the inspiratory maneuver. Slow, deep, controlled inhalations are ideal for aerosol administration, and deviation can result in suboptimal deposition patterns. For example, crying infants and children have significantly less lower airways aerosol deposition compared to quietly breathing children [8]. This is likely influenced by the relatively short inspiratory time and high maximal inspiratory flow rates, resulting in greater inertial impaction in the upper airway.

Every attempt should be made to administer aerosolized medications to a quietly breathing child, which is challenging in infants and young children.

Strategies to maximize regular breathing strategies have been investigated in young children. Administration of the aerosol while the child is sleeping has been shown to decrease the amount of delivered drug compared to awake delivery [9]. This was likely due to lower tidal volumes and poor cooperation if the child wakes up during administration. Another strategy involved an aerosol mask with an integrated pacifier, and this was shown to provide reasonably effective intrathoracic deposition in suckling infants breathing nasally [10] (Figure 1). Even in quiet breathing however, young children are not able to coordinate large, slow breaths and thus suboptimal lower airways deposition likely ensues in this population.

	Factors leading to particle deposition in:	
	Upper airways	Lower airways
Aerosol factors	Higher velocity delivery	Lower velocity delivery
	Larger particles	Smaller particles
Patient factors	Younger children aged <6 years	Older children and adults
	Oral inhalation in infants	Oral inhalation in school aged children
	Crying infants and children	Quiet breathing (slow, deep, controlled inhalations)
	Sleeping	Awake

Table 1 Factors influencing airway particle deposition



**Figure 1** Image of a young child using a pacifier-integrated mask during a nebulization treatment.

Taken from: Amirav et al. [10]

Disease state can also effect aerosol deposition. The total deposition of aerosolized medications has been shown to be higher in adults with CF than in health, however the aerosol distribution pattern is markedly more heterogeneous with areas of little to no deposition juxtaposed with regions of increased deposition [11]. This is likely due to the combination of architectural distortion and mucus obstruction of the airways. Likely, the significant degree of heterogeneous deposition seen in adult patients is not as severe in young CF patients who have less advanced lung disease, but mucus plugging likely does impair the homogeneous distribution of aerosolized medication. Theoretically, this maldistribution

of aerosol in CF could lead to decreased effectiveness of the inhaled medication, and this is the impetus for recommending chest physiotherapy or other airway clearance techniques prior to inhaled medications. However, this practice has never been proven to be of clinical benefit.

*Key messages: Aerosol deposition in the lower airways can be affected by aerosol and patients factors.*

*Younger patients typically have more upper airways deposition, likely due to differences in coordination, cooperation and airway anatomy.*

*Lower airways deposition can be optimized by encouraging quiet, slow deep breaths and avoiding administration of an aerosol to a crying or sleeping child.*

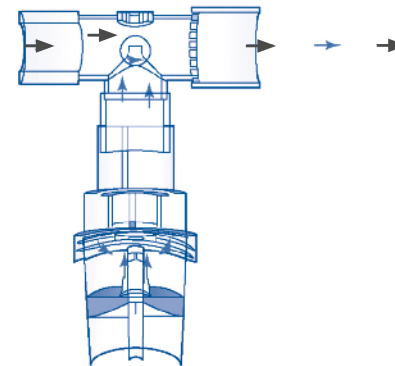
## 2 Delivery devices and patient interfaces

Aerosol medications are delivered to infants and pre-school children through liquid nebulization or pressurized metered dose inhalers (pMDIs). Dry powder inhalers (DPIs) require coordination and a high maximal inspiratory flow, which are not typically achievable by young children and will not be discussed here.

### 2.1. Nebulizers

Nebulization provides an efficient technique for the aerosolization of medications, even those which were not originally designed for this route of administration

(for example, IV solutions of antibiotics for the treatment of *Pseudomonas* infection in CF). The main methods of nebulization that are employed are jet, ultrasonic and vibrating mesh nebulization (reviewed in [12]). In jet nebulizers, the carrier gas jet is generated by passing it through a narrow orifice. The negative pressure generated by this jet allows for the entrainment and nebulization of solution, which is then either released from the device if the aerosol characteristics are favorable or recycled into the nebulizer reservoir if they are not. The characteristics of the aerosol, nebulization efficiency and rate of drug delivery can vary significantly between devices and are impacted not only by the internal configuration of the nebulizer, but also by the type of compressor and the flow rate of the carrier gas [13].



**Figure 2** Schematic of a Cirrus® nebulizer, demonstrating flow of patient-entrained air (black arrows) and the generation of aerosol from compressed gas (blue arrows) in a simple, unvented jet nebulizer.

Taken from Kendig and Wilmott [48]

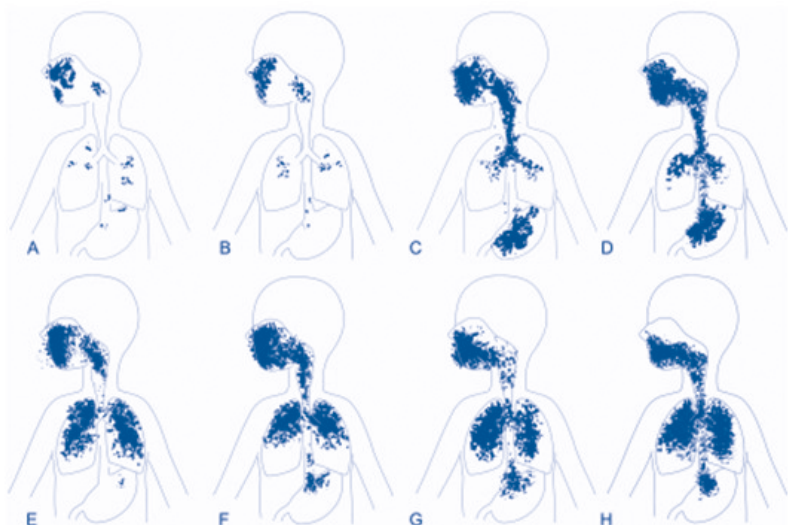
Ultrasonic nebulizers generate aerosol with ultrasonic vibration of the solution using a piezoelectric crystal; the aerosol characteristics can be controlled by modulating the frequency of the vibration. Generally, ultrasonic nebulizers generate a higher output than jet nebulizers, but tend to have a larger aerosol MMAD. In addition, the vibration of the solution can increase the temperature, inactivating biologic agents. Finally, vibrating mesh nebulizers (reviewed in [14]) extrude drug solution through a thin wafer covered with laser-drilled orifices to generate an aerosol with a more narrow MMAD distribution than jet nebulizers. Some medications have been studied and are marketed as a specific drug-device combination (e.g. aztreonam with a specific PARI® eFlow® vibrating mesh nebulizer version).

In simple, unvented nebulizers, output is constant and drug aerosolized during expiration is lost to the atmosphere. While efficiency varies, pulmonary deposition in children from unvented jet nebulizers is documented to be less than 5-10% of the total nebulizer charge [6]. This expiratory loss can be mitigated using breath-actuated or breath-enhanced nebulizers, which use the patients' inspiratory flow to either activate the nebulizer or to increase its output during inhalation. However, the inspiratory flow in young children is usually insufficient to activate the actuator, and it is therefore not commonly used in this age group.

The patient interface is also important to the efficiency of pulmonary drug delivery.

While delivery of aerosolized medications to the patient can be achieved either via a facemask or mouthpiece, because oromotor coordination and patient cooperation is variable in the pre-school age group, facemasks are typically used until school age. While pulmonary deposition in the range of 10-15% has been demonstrated with new facemask administration from a vented nebulizer, the efficiency of this deposition is highly technique-dependent and the amount of medication that is deliv-

ered can vary significantly between young children [15]. As previously discussed, crying increases inspiratory flow rate, resulting in inertial impaction of the aerosol in the pharynx. In addition, mask leak significantly diminishes pulmonary deposition, with one study showing a 10-fold decrease in pulmonary deposition with a poorly seated mask [8]. This is especially important, since young children may not tolerate use of a facemask at the start. To overcome this, parents and clinicians will



**Figure 3** Drug deposition of radiolabeled salbutamol in a young child

(A) inhaling with a pMDI/spacer through a non-tightly fitted mask, (B) inhaling with a nebulizer through a non-tightly fitting facemask, (C) inhaling with a pMDI/spacer through a tightly fitted facemask, screaming during inhalation, (D) inhaling with a nebulizer through a tightly fitted facemask, screaming during inhalation, (E, F) inhaling with a pMDI/spacer through a tightly fitted facemask, quietly breathing, (G, H) inhaling from a nebulizer through a tightly fitted facemask, quietly breathing. Taken from: Erzinger et al. [7]

often opt for “blow-by” administration of nebulized medication through an unvented nebulizer. This technique can result in significant decreases in the inspired fraction of nebulized medication [16] and is not recommended.

## 2.2. Pressurized metered-dose inhalers

pMDIs are another tool used to generate aerosolized medication for inhalation (reviewed in [17]). pMDIs use a pressurized propellant to accelerate the drug suspension (or solution) through an actuator nozzle, which will then rapidly expand (“flash”) thus generating a respirable aerosol with a reproducible MMAD distribution. However, if the pMDI is applied directly to the patient’s mouth, the size and velocity of the incompletely flashed particles exiting the actuator nozzle will result in significant inertial impaction on the posterior pharynx. However, if a valved holding chamber (VHC) is employed, the aerosol has sufficient time to completely form and its velocity is also significantly reduced, thus increasing the likelihood of pulmonary deposition (reviewed in [18]). As with nebulizer devices, mouthpiece and mask interfaces are available, and the decision which one to use is based on the developmental stage of the child; though most young children require facemask VHCs.

The convenience and portability benefits of pMDIs are making this an attractive option, but there is a rather limited list of medications (bronchodilators, anticholinergics and inhaled corticosteroids) available as a pMDI formulation for the CF population at the present time.

## 2.3. Slow Mist Inhalers

Slow mist inhaler (SMI) release the aerosol slowly (over 1-2 seconds) which decreases the coordination required to inhale the drug. The slow rate of release also decreases the initial particle velocity, thus theoretically decreasing inertial impaction in the upper airway without the need for a spacing device [2].

This device was originally developed for the adult population, but studies have been performed in the pre-school population showing that young children are capable of using this device [19]. However, as only tiotropium bromide is available in a SMI formulation for CF patients at this time, this aerosolization system is not likely to become widely applied in the pre-school CF population in the near future.

*Key messages: Most aerosol medications available for the pre-school CF population are delivered either by nebulizer or pressurized metered dose inhaler (pMDI).*

*pMDIs should always be used with valved holding chambers to optimize lower airways deposition.*

*In most pre-school patients, a tight-fitting facemask should be used to administer aerosolized medication. A loose-fitting mask or “blow-by” administration of aerosol medication can result in very poor lower airways deposition.*



**Case study**

An asymptomatic 2-year-old girl with CF who is currently prescribed only enzyme replacement therapy and ADEK vitamin supplementation has new growth of *Pa* on an oropharyngeal swab in the clinic. The decision is made to treat with inhaled tobramycin, given the strong evidence for microbiological eradication in the age group [20], and she is prescribed 300 mg twice-daily inhalation of TOBI solution, administered via nebulization for 28 days. In considering the mode of administration, you recommend a constant output or breath-enhanced nebulizer, since this young patient's inspiratory flow is likely insufficient to activate a breath-actuated nebulizer. A tight-fitting mask interface is recommended for this child, since she isn't able to coordinate a mouthpiece. Also, the parents will attempt to ensure quiet, deep breathing with the administration and are informed that administration of the medication while the child is crying significantly decreases lower airways deposition of the drug. Given the frequent occurrence of bronchospasm observed with administration of inhaled tobramycin, premedication with an inhaled beta-2-agonist, administered via pMDI (mask interface) with a valved holding chamber, is also prescribed. The TOBI is discontinued after 28 days. The girl remains asymptomatic and a repeat oropharyngeal culture taken one week after discontinuing the antibiotics shows only usual pharyngeal flora. Routine microbiological surveillance is resumed.

Two years later, the same child has developed a chronic wet cough. Oropharyngeal

and bronchoalveolar lavage microbiology has shown only methicillin-sensitive *Staphylococcus aureus* and the cough has not resolved despite oral and intravenous antibiotics. Given the clinical situation of new chronic symptoms, you offer the choice of once daily dornase alfa or twice daily hypertonic saline to parents. In this case, the child was treated with once daily dornase alfa. At follow-up, the cough had significantly improved.

### 3 Evidence for the use of aerosolized medications for pre-school CF

There is very little evidence for the optimal timing of treatment initiation and sequencing of these drugs in these patients who are often asymptomatic with no or very mild clinical signs of pulmonary disease. For pre-school children with protracted symptoms or evidence of decline in objective pre-school pulmonary function testing, the first line of therapy is investigation for and treatment of a new lower respiratory tract infection, rather starting a new chronic nebulized therapy. However, since CF lung disease is clearly present even early in life [21], there is a reasonable impetus for understanding the role of early aerosolized therapy in this group. In this section, we will review the evidence for the main aerosolized medications used in young children with CF: hypertonic saline, inhaled antimicrobials, dornase alfa, bronchodilators, anticholinergics and inhaled corticosteroids.

**3.1. Hypertonic saline**

Hypertonic saline (HTS; 7% NaCl w/v) is thought to function by hydrating the airway surface liquid and mucus of the lower airways, thus facilitating mucociliary clearance. In older children (over 5 years) and adults, HTS has been shown to decrease the rate of pulmonary exacerbations, while having a modest benefit on FEV<sub>1</sub> [22]. However, when this drug was investigated in 321 children aged 4-60 months, there was no difference in the rate of pulmonary exacerbations. However, in a small subgroup analysis of 45 children who underwent infant pulmonary function testing, there was a small (+38 mL) improvement seen in the forced expiratory volume in 0.5 s (FEV<sub>0.5</sub>) outcome measure [23]. The authors hypothesized that this increase in FEV<sub>0.5</sub> could reflect a true improvement in pulmonary physiology in this group, but that the spirometric outcomes measures used in the study may not have been sensitive enough to detect a robust treatment effect.

This hypothesis was supported by a single-center sub-study that had used the lung clearance index (LCI) as an investigative outcome measure and showed a significant treatment effect of HTS in this single center pilot study [24]. This finding was the impetus for the ongoing Saline Hypertonic in Pre-schoolers (SHIP) study ([www.clinicaltrials.gov/ct2/show/NCT02378467](http://www.clinicaltrials.gov/ct2/show/NCT02378467)) that uses LCI as the primary outcome measure and speaks to the importance of sensitive outcome measures in future clinical trials investigating the efficacy of aerosol medications in CF pre-schoolers.

*Key message: Hypertonic saline has been shown to decrease LCI in pre-schoolers, but there is no impact on exacerbation frequency – this may reflect the inability of traditional outcome measures to adequately detect treatment effects in the pre-school population*

**3.2. Dornase Alfa**

Dornase alfa (recombinant human DNase) is a mucolytic drug that functions by catalyzing the hydrolysis of extracellular DNA within the airway mucus, thus decreasing mucus viscosity and facilitating mucociliary clearance. There is no evidence to support its use in children under the age of five years, however there is strong evidence in adults and children over five years of age that has been extrapolated to this younger population. In a landmark randomized controlled trial (RCT) of 968 adults and children over five years old, dornase alfa was shown to increase FEV<sub>1</sub> by approximately 6 % and decrease pulmonary exacerbations by one third [25]. These data were replicated in another large RCT of 474 children aged 5-11, with an increase in FEV<sub>1</sub> and decrease in exacerbation frequency. It is important to note that, similar to HTS, improvements in LCI in children with preserved spirometry have been shown [26]. This suggests that there may be benefit to using this medication in children with earlier lung disease, even in the face of normal classical pulmonary function tests and no clinical symptoms.

To date, no published controlled studies have investigated the efficacy of dornase alfa in younger children, though one RCT

of 24 infants (mean age 42 weeks) that was published in abstract form, showed no difference in infant pulmonary function testing or chest CT outcomes [27]. Despite this, there is biological plausibility for the utility of this drug in the under 5-year old population, with high levels of extracellular DNA reported in the airways of asymptomatic CF patients under 2 years of age [28]. In addition, administration of this drug seems well tolerated and feasible; in an analysis of a large registry database, dornase alfa has been shown to be well tolerated in children aged 3 months to 5 years [29]. Given the results of trials in older children, especially those showing physiologic improvement in children with no evidence of lung disease on spirometry, it is reasonable to assume that some young children may benefit from this therapy. Further study is required to help determine which young CF patients might benefit most from this therapy.

### 3.3. Inhaled antimicrobials

Inhaled antimicrobial therapy is used for the treatment of new or chronic *Pa* infection in patients CF. There are more controlled trial data involving this class of drugs in young children than in hypertonic saline or dornase alfa. With respect to chronic *Pa* infection, two studies from the 1990s were the first placebo-controlled RCTs to demonstrate the efficacy of an inhaled antimicrobial in CF, although the practice had been in place for years in some CF centers (especially in Europe).

First, in a double-blind, crossover of 71

young adult patients with chronic *Pa* infection, 600 mg of preservative-free study tobramycin inhalation solution (TIS) was shown to increase FEV<sub>1</sub> by 4.3% and decrease *Pa* sputum density at 28 days [30]. Second, in a study of 520 older children (≥6 years) and adults who were chronically infected with *Pa*, an intermittent (alternating 28 days on and off) regimen of inhaled TIS was shown to increase FEV<sub>1</sub> by 10% after 20 weeks and to decrease the rate of exacerbation hospitalization by 26% [31].

In a placebo-controlled trial of 21 children under six years of age with new or intermediate *Pa* growth (growth up to 12 months prior to study initiation), treatment with a 28 day course of 300 mg BID of TIS resulted in a 100% microbiological clearance rate based on bronchoalveolar lavage (BAL) sampling [20]. However, the post-treatment BAL sampling was done 24h after discontinuation of the TIS at a time when there was still detectable tobramycin in the airways, which may have overestimated the success rate. In ongoing post-treatment monitoring 28 days after completion of therapy, 2/8 patients on TIS had positive oropharyngeal swab cultures for *Pa*, however this was still significantly lower than 9/13 patients in the placebo group.

The two other antibiotics commonly used for chronic *Pa* infection are colistin and aztreonam lysine, both of which have been investigated in trials in older children or adults. Colistin has never been compared with placebo, but was shown to be inferior to tobramycin in terms of pulmonary function gains after 4 weeks of treatment [32].

Aztreonam has been shown to increase FEV<sub>1</sub> and quality of life scores as well as the time to rescue antibiotic therapy compared to placebo in patients over 7 years of age on frequent TIS therapy. There have been no studies on the utility of these antibiotics in young children with chronic *Pa* infection over 12 months in duration and there are very few children who would meet these criteria.

Studies into the eradication of *Pa* in patients who show first-time growth in respiratory cultures have also been done, again with most evidence around the utility of TIS. More young children are included in these trials, again likely because first-incidence of *Pa* growth is more common in this group, compared to chronic growth.

In the first placebo-controlled study of *Pa* eradication in 22 children, 12 months of twice daily-inhaled tobramycin (80 mg of the intravenous solution) resulted in a higher rate of *Pa* clearance in the treated group [33]. The dosing regimen of TIS was refined in a later study of 88 patients over the age of 6 months (37 patients were under 6 years of age), which showed that 28 or 56 days of twice daily TIS (300 mg preservative free solution) therapy results in equally high rates of microbiological clearance (93% and 66% at 1 month and 2 years after the 28 day therapy respectively) [34]. A later study also showed that there is no benefit to adding oral ciprofloxacin to this eradication protocol in children aged 1-12 years [35].

Recently published data from an RCT in children under 6 years of age ([www.clinicaltrials.gov/ct2/show/NCT01082367](http://www.clinicaltrials.gov/ct2/show/NCT01082367)) show similar rates of clearance with 28 days of TIS, but also identify the importance of timely identification and treatment initiation on the rate of pathogen clearance. 3 weeks of nebulized colistin (with adjuvant oral ciprofloxacin) was also shown to be effective at achieving microbiological clearance in children aged 2-18 at 23 months, when compared to no treatment [36]. Finally, an open-label study investigating three times daily inhaled aztreonam showed comparable rates of eradication (~75% 4 weeks post treatment and ~50% 28 weeks post treatment) in children 3 months to 18 years of age and did not vary across age groups.

Overall, the evidence for inhaled antibiotics for the treatment of new *Pa* growth in young children with CF is quite strong, and its utility in chronic infection can likely be inferred. It is interesting to note that tobramycin serum levels measured after administration in pre-schoolers has been shown to be highly variable [15]. This goes to show that the delivery of aerosol medication can be unpredictable, especially in this age group, and medications with wide therapeutic indices are likely better suited to this delivery mode in younger children.

*Key message: There is strong evidence for the use of inhaled antibiotics for the treatment of Pseudomonas aeruginosa infections in the pre-school population*

### 3.4. Bronchodilators

The evidence for bronchodilators (either beta-2-agonists or anticholinergics) is limited in CF in general, and mostly based on biologic rationale. CF lung disease is characterized by progressive airways obstruction, which respiratory physicians tend to treat with bronchodilator medications and the vast majority of pre-school CF patients are prescribed beta-2-agonists [37]. Indeed, there is some support to this practice, as bronchodilator responsiveness and bronchial hyperreactivity have been documented with varying prevalence in older children with CF, and children with CF also often have an overlapping diagnosis of asthma [38]. Whether this co-diagnosis is truly correct and whether chronic treatment with bronchodilators has any effect on the disease process is unclear. In fact, there is also a theoretical possibility that diseased airways whose patency is maintained by bronchomotor tone could collapse with the administration of beta-agonist administration [39], but this theoretical risk has never borne out in clinical studies.

Other biologically plausible indications for beta-agonist administration include the prevention of secondary bronchospasm induced by other inhaled medications, to increase the efficiency of airway clearance techniques, to increase ciliary activity/mucociliary clearance (independent of bronchodilation) (reviewed in [40]) or even increase the activity of *CFTR* [41]. However, there is little clinical evidence to support the common use of this medication in CF.

Studies investigating the use of short acting beta-2-agonist (SABA) in CF have been reviewed recently [42]. There have only been 2 trials with follow-up periods longer than 2 weeks, and neither has shown significant changes in spirometric or clinical outcomes. There are no clinical trials specifically addressing the use of SABA in young children with CF.

Inhaled anticholinergic drugs have more recently been investigated in the pediatric CF population. On pooled analysis, one combination phase II/III trial of 807 patients (23 under 5 years, 238 between 5-11 years) showed a significant treatment difference in the primary endpoint, FEV<sub>1</sub> area under the curve from 0-4 hours of 2.62%. However there was no change in the frequency of pulmonary exacerbations or quality of life [43]. Subgroup analysis of this study suggested that older patients ( $\geq 12$  years) and those with lower baseline pulmonary function were more likely to derive benefit, which suggests that pre-school patients are not likely the ideal candidates for this medication.

Ultimately, the evidence for the long-term utility of the use of an aerosolized bronchodilator is lacking in the CF literature in general, and in the pre-school CF literature specifically. Trial administration of an aerosolized bronchodilator (SABAs) to pre-school children who are symptomatic of bronchospasm (i.e. wheezy to auscultation) is reasonable, as is pre medication for children who have shown signs of bronchospasm with other inhaled medication (e.g. HTS). Routine administration

of SABAs to all young children with CF, however, while commonly practiced, is not supported by the literature and is not recommended [44].

### 3.5. Inhaled corticosteroids

While the biological rationale of direct reduction of endobronchial inflammation is appealing, there is minimal evidence to support the routine use of inhaled corticosteroids (ICS) in CF, let alone pre-school CF [45], though one large registry review did report a lower rate of pulmonary function decline in children on inhaled fluticasone [46]. However, this treatment is not without risks, and in addition to the well-documented impact on linear growth, there are some concerns that chronic inhaled steroid use could increase rates of acquisition of lower airways pathogens such as *Pa* in CF patients [47]. Currently, American CF Foundation guidelines recommend against routine inhaled corticosteroids in the pre-school population due to a lack of evidence for its efficacy [44]. Despite this recommendation, the most recent registry data show that 16% of American pre-school CF patients under 3 years of age and 31% of American CF patients between 3 and 5 years of age are prescribed an ICS. Similar to the discussion above regarding SABA use, the “CF asthma” crossover phenotype [38] is clinically very difficult to manage and this is even more pronounced in the pre-school years when spirometry isn't available to help guide. However, due to the lack of evidence of any effect of ICS administration in this population, clinicians should weigh the potential risks and benefits before starting a medication that has

a non-trivial side-effect profile. Certainly, routine prescription of ICS to asymptomatic pre-school patients is to be avoided.

*Key message: There is minimal evidence for the universal administrations of bronchodilators or inhaled corticosteroids in the pre-school population, despite their widespread use for infections in the pre-school population*

## 4 Conclusions

As is the case with most diseases, the medical literature supporting specific practices of aerosolized medications in the pre-school age range is limited in CF. However, there is growing interest in quantifying the response to these therapies in young children, since there is clear evidence that lung disease is present in CF patients well before the onset of clinical symptoms or deterioration in classical spirometry. The strongest evidence for the use of aerosolized medications in this population is for the use of inhaled tobramycin for the treatment of new *Pa* infections. The use of HTS to improve hydration of airway surface liquid and mucociliary clearance appears to have a physiologic impact (though the clinical impact is less clear), though a large trial is currently underway to investigate this further. The ideal time to start HTS or mucolytics such as dornase alfa remains unclear in the pre-school CF population. With respect to the most commonly prescribed medication in CF, SABAs, there

is little evidence supporting its routine use, especially in the pre-school population. Finally, there is no evidence to support the routine use of ICS in this population, and their prescription should be avoided unless there is a clear indication for their use.

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# CHAPTER 13

## Understanding and working with challenging behaviors and fears in pre-school children with cystic fibrosis

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### Introduction

This chapter will focus on living with cystic fibrosis (CF) during the early years, the challenges for parents and families, and the important supportive role of the CF team. It is divided into four parts. The first part looks at coming to terms with the diagnosis over time and integrating CF into the family. The second part considers the impact of medical procedures on the child and ways to support both child and family. The third part describes normal developmental topics in young children and how these may interact with CF and treatment. The final part describes specific worries that families may have about the future, and how these may interfere with childrearing.

### 1

#### Coming to terms with CF

Over the years, parents go on a journey from being a “novice” to a “parent expert” in the CF of their child. Recent research has shown that more than half of parents (20/38) had never heard of CF prior to their child’s diagnosis [1]. Parents enter a world of medical terms, which can be difficult to pronounce, never mind understood. The translation of CF into their daily life and what to tell others is a difficult job. A mother once said:

*“Sometimes I try to avoid certain people, because I don’t know what to tell them and I don’t want to break down in tears.”*

Retrospectively, some parents recall that they used a standard sentence to tell other people about CF, others report sharing an extended version, and some parents choose not to disclose CF. There is no standard or correct way to share infor-



mation about CF, but it is important that parents feel secure in the choices that they make.

Coming to terms with the diagnosis, is the beginning of an ongoing learning process for parents [2]. Over time, parents may desire to know more information and have new questions about their child's CF. Besides getting information from CF specialists, one of the resources almost all parents consult is the internet [1, 3]. This source of information may allow parents to become more actively involved in decision making about their child's treatment [1]. However, one should be aware that being informed is not necessarily equal to being knowledgeable or understanding the information correctly. Misinformation can also create stress and potential conflict between parents and professionals [3]. The internet is a useful resource when parents feel they have a better understanding of CF and its effects on their lives [3]. The CF team have an important role to play in supporting the knowledge and understanding of families about CF.

Parents also often worry about which symptoms are part of their child's CF, or which belong to a normal childhood illness. Through the years, and with feedback from the CF team, parents learn to distinguish the different symptoms and become increasingly confident and competent in knowing when to act and what to do.

### 1.1. Medicalization of childrearing

CF is a progressive chronic disease, with a high level of necessary daily treatment,

regardless of age or disease severity, and an unpredictable disease course. Accordingly, it is understandable that when providing CF care for their child, parents may at times experience feelings of anxiety, depression, or helplessness. Some healthcare professionals advise that parents stringently adhere to their child's treatment regimen, necessary hygiene protocols, and are aware of exposure to bacteria. This advice can put pressure on parents and often they report feeling responsible for prevention of infections, in particular *Pseudomonas aeruginosa*, which can lead to further anxiety [4].

*"I will not allow people in the house when they have a slight cold"*

*"I will not allow my child to play in a sand pit"*

Some parents become slightly obsessed with prevention of infections, taking unnecessary precautions to avoid contact with bacteria. Such behavior can impact unduly on a patient's childhood and their own well-being [4]. For example when children with CF are not only kept away from stagnant water in ditches or jacuzzis, but are also restricted from swimming in a chlorinated pool. Of course, as for healthy children, it is important to teach the child to wash their hands appropriately, after toilet use and before eating.

CF teams should provide evidence-based recommendations about infection prevention and encourage parents to ask questions about the dos and don'ts. This

supports families to strike an appropriate balance between healthy behaviors and living a full life with CF.

### 1.2. Coping

How parents deal with bad news, stressful situations, and caring for their child with CF, is influenced by a multitude of factors, including their coping styles. The literature on coping in CF describes a continuum of coping styles from active-monitoring-optimistic styles, to passive-avoidance-repressive styles [5]. Active coping strategies include seeking information or support, and monitoring a child's illness symptoms [5-7]. Passive coping strategies include denying certain aspects of the illness, distraction, or self-blame [5, 7].

Active coping styles are positively related to quality of life in CF, whereas more passive coping styles have a negative influence on adherence and parental mental health [5, 7]. For example, when parents avoid thinking about CF or other stressor, or engage in behaviors such as eating or drinking. These may help parents to cope in the short term, but are unlikely to be helpful in the long term. The CF team can help parents find more positive coping strategies, for example by encouraging them to ask questions during visits, to talk to others, and make sense of complex emotions and cognitions about CF. Exploring coping styles and intervening when necessary can improve both parental and child health outcomes. This makes it an important task for the CF team.

*Key message: Exploring and providing help in coping styles is a crucial task and aims at prevention of future problems.*

## 2 Medical procedures and investigations: how to help children and parents cope with painful procedures or investigations

According to the European standards of care, there are some inevitable medical procedures that children with CF experience as part of their care. Some of these procedures occur daily, such as inhalation, taking pills and doing chest physiotherapy, others regularly, such as throat swabs, and finally some occur at more distant intervals, such as taking blood samples, or placing an intravenous line. The setting and conditions under which such invasive interventions are performed influence levels of perceived distress. Early childhood experiences of traumatic procedures can have long-term effects on quality of life, as well as adherence to therapy in later life [8, 9].

*Key message: Invasive medical procedures are part of CF and topical anesthetics should be used to avoid a first negative experience.*

## 2.1. Venipuncture

Regular needle procedures such as venipuncture for routine control of disease, or the insertion of an intravenous line for antibiotic treatment, are inevitable in CF, and they are a major cause of child and parental distress [10].

### 2.1.1. Patients' perspective

Children usually regard venipuncture as being the most feared procedure of medical care in hospital or clinic. Depending on their age and gender, most of them can tolerate the procedure using a range of strategies, such as distraction, taking control, or crying. However, some children are unable to do this and exhibit high levels of fear, pain and behavioral distress. Typically, this results in difficulties in needle insertion and can lead to situations in which three or more adults must hold the child down, causing incredible distress to all involved. It cannot be denied that needles and venipuncture are not benign stimuli for children, but unpleasant sensory and emotional experiences.

There are several pharmacological and non pharmacological approaches to help children manage during such procedures. Over the last 25 years very good results have been obtained with topical anesthetics, for example EMLA® [11]. Despite this convincing evidence, there are still many clinics where topical anesthetics are not integrated into clinical routine as an essential part of venipuncture in children. In addition, reports on complementary adjuvant methods, such as cooling spray, lavender essence inhalation, and medical

clowning or clinic clowns, as a distraction [12], suggest they could be helpful. From a child's perspective, it is our obligation to use these methods when needed.

*"I cried because they wanted to have my blood. Mummy was allowed to come and then I saw this bubble machine and they let me play with it and it was ok."*

### 2.1.2. Parents' perspective

For many parents, visiting the hospital with their child can be an anxiety provoking experience. There are strong correlations between parental anxiety and child distress during venipuncture, yet most parents prefer to be present during venipuncture, and almost all children perceive this as helpful. The benefits of parents being present during the procedure and taking active roles, have been repeatedly shown [13]. Interestingly, parents who are taught explicit distraction and comforting techniques and encouraged to use them during venipuncture, found the techniques useful and agreed more with their child's care than parents who were present but not taught such strategies [14].

Of note, parental reassurance is also sometimes correlated with higher levels of child's distress. In a video assisted study, children noticed levels of fear in the faces of their parents more often in those using reassurance, rather than in those employing distraction techniques [15]. Parents should be informed how they can support their child and in doing this not undermining healthcare providers (e.g. by saying "what a bad nurse"). Parental support is impor-

tant to embed helpful coping strategies for future years.

### 2.1.3. Perspective of healthcare professionals

Undertaking invasive and potentially painful procedures is also distressing for healthcare professionals, particularly those caring for children with chronic conditions. Interestingly, healthcare professionals' behavior, more than parents' behavior influences distress and coping in children during venipuncture [16]. From research in pediatric oncology it is well documented that nurses spontaneously focus on utilizing simple psychological interventions such as education, emotional support, active or passive distraction, or participatory approaches during their practice [17]. The role of a familiar CF nurse in comforting a child undergoing a frightening procedure cannot be appreciated enough.

## 2.2. Needle phobia

Needle phobia must be differentiated from the quite usual fear or anxiety, which is a normal reaction of a child experiencing an invasive procedure. This is especially the case for toddlers and pre-school children, to whom the purpose and necessity of the intervention cannot yet be explained or understood, and accordingly a level of anxiety is a normal reaction. However, following a very distressing experience some children may develop an actual phobia, which can make necessary tests impossible. Some clinics report the use of inhaled nitrous oxide for sedation [18], or nasal or rectal application of medicines.

Since needle-phobia can have a negative influence in the long-term course of disease, and has an important impact on health behavior in adolescence and adulthood, prevention of negative experiences with unmanaged distress should always be our primary goal [8, 9]. Severe needle phobia and anxiety is a serious condition. In children under 5 years of age, this should be treated with psychological interventions such as behavioral therapy [19]. In addition, CF teams should take every opportunity to undertake routine assessment bloods whilst the infant/child is under general anesthetic, for example if they need a bronchoscopy or another procedure.

## 2.3. Throat swabs

Although not as painful as venipuncture, regular throat swabs are as distressing for some children. In a large proportion of children, this procedure can stimulate a gagging/retching reflex, and occasional vomiting. Children with previous bad experiences, perhaps because they were forced to open their mouth, often refuse this procedure, which again results in suboptimal disease management. Children endeavor to escape from the doctor, lash out at parents and staff, attempt to gain control by delaying the procedure, and so on. These children might develop a phobia, as described in the venipuncture paragraph above. For these children, behavioral therapy has also been shown to be effective.

In summary, painful and discomfiting procedures are inevitable in caring for CF. Since subsequent reactions of a child are often determined by early experiences, it

is important to pay attention to the setting: look for a quiet and familiar space, let familiar nurses and doctors perform the interventions (or support others), and allow the parents to be with their child (even if they feel anxious). For venipuncture, the use of local anesthetics (i.e. EMLA®) has shown to be very helpful. Advising the parents on how best to support their child to cope with these procedures is important. This helps not only the child but also makes parents feel more involved and fulfilled. From the age of three years old, children find it important to remain in control. Let them tell you where to put the needle, or when to do the throat swab (as long as it happens in an adequate time frame). They might give the command by counting and they will feel very proud!

*Key message: A familiar setting and the presence of parents, using strategies as distraction and reassurance, may reduce venipuncture distress and prevent long-term effects on health behavior.*

### 3 The terrible twos and CF

During the developmental stage between infancy and pre-school, one often uses the term “*terrible twos*”, because children regularly oppose things that grown-ups would like them to do. This is the stage of refusing to eat certain food, go to bed, or get dressed. Temper tantrums, including spells of breath-holding for some children, are often reasons for conflict between a child and parents, jeopardizing early attach-

ment. In CF, these behaviors can pose a threat to adherence to treatment.

In this section, the focus lies on three developmental aspects during the early years of life that specifically define this period, namely: 1) increasing mobility, 2) language development and 3) greater self-awareness. The specific challenges for families with CF and adherence to treatment will be illustrated with quotes from families.

*Key message: During the early years, children go through several normal developmental stages, including increased mobility, self-awareness and the acquisition of language. Families need information and education about these normal developmental processes in relation to CF.*

#### 3.1. Increasing mobility

As an infant starts to crawl and walk everyone is happy and proud! However, the child’s subsequent exploring behavior is not always appreciated by any parent who wishes to protect their child and ensure a secure and safe environment. In CF, this is particularly acute as parents are concerned with protection against germs and bacteria, as described in Section 1.1. Parental and child temperament, personality, past experiences, and family dynamics, determine the duration or intensity of parent-child interactions [20]. For a family with CF, the increased mobility in the early years of life poses many challenges, for example for physiotherapy or at meal times [21-23].

*“Our toddler does not want to sit down to have dinner, he wants to run around!”*

*“Taking time for physiotherapy interferes with playing in the garden with her new ball”*

In this example both physio and playing are important for a child with CF, but most will agree that actively playing outside is preferred over percussion in front of the television. Yet, adherence to therapy is very important for most young parents and they feel responsible. Some say they feel “judged” at the outpatient clinic because the health of their child results partly from the quality of their therapy. These parents dread the weighing scale, which they perceive will show how well they cared for their child (or not).

Many parents establish a routine of preparing their children by saying “...you can play now, for another five minutes, then we are going to do your nebulizer” or “...dinner is ready in ten minutes so toilet and washing hands in five minutes”. These routine child rearing techniques are important and normal for any child, but for children with CF they must include elements of the CF therapy. In a way, this will become their norm over time. However, when a child has no CF symptoms, parents may get tired of forever “forcing” their child to sit still and do their treatments, or feel sorry for their child to stop them play.

*“He has got CF, the poor thing...let him play and enjoy life...after all, he is not coughing now, so skipping the nebulizer for once cannot be a real problem...”*

In addition, information in newspapers or online about the danger of taking too many

antibiotics do not only misinform parents, but can also wrongfully support them in their decision to skip treatments.

Parents may be anxious to talk openly with professionals about their occasional non-adherence due to difficulties in child rearing. Similarly, the CF team may doubt treatment adherence, but concerned to address this for fear of undermining their relationship with the parent. No simple solution is available, although open communication is probably the best way forward, through empathy and understanding.

#### 3.2. Language

A second developmental acquisition during the early years is language. Verbal communication gives a child a new skill, they can experiment with words and actions and in doing so further understand the world and their place in the world. This language skill provides new ways of communicating with parents about physical and emotional needs, wants or desires, but also about demands and rules. The limited vocabulary of the pre-schooler rapidly expands into two and three word sentences. The suitability of words is not yet fully established, causing some misunderstandings, and the learning process may affect the relationship between parents and child. For example, in CF, many things must be done in the morning before going to school or work.

*“I do not want to eat! I can go to school without eating, I am not hungry!”*

*“I do not want to do my neb (nebulizer)!”*  
A child saying, “I don’t want!” and thus

using words to express his needs or wishes can cause worrying conflict [21]. To overcome this, parents can try to translate the child's "no", into underlying emotions, so the child feels the parent understands him.

*"I know you do not like this, but we will do it together."*

The ability of parents to translate words into feelings will depend on parents' own upbringings and their learnt skills to do so. Distraction, rewards and incentives are also good ways to help a child overcome their frustration with words and wants:

*"I understand you do not want to do your nebulizer, but we can watch TV together, you nebulize and it will be done in no time!"*

As seen in the section on mobility, with the newly acquired verbal skills it is important to establish a routine that includes ample room for conversation and (hopefully) less room for argument.

### 3.3. "Sense of self" or increased self-awareness

A third developmental realization during the early years, with important neurobiological and psychological changes, is the increase in self-awareness. The sense of "me" is an awareness of oneself in a world. During the early years, the people and things around a child are there to satisfy him/her. One can hear a child say: "Tom wants this new car, I mean me, myself, I want this car". This sense of self is important as it will guide a child towards who s/he wants to be, what s/he wants to do and with whom.

Over time we observe how a child perceives him/herself in relation to other people, and s/he starts to compare him/herself with others. In CF, we see a gradual awareness of the self and of "being different" from siblings or peers, which may cause emotions such as anger, anxiety or worry (see next part), but also a sense of pride:

*"See how well I can jump on the trampoline!"*

*"I can breathe really well and make the biggest bubbles"*

However, a 4 or 5 year old may also say the following:

*"I hate coughing all the time..."*

*"When can I stop taking pills like the other children?"*

*"I do not feel sick, so why do I have to go to the hospital?"*

*"Sis said I will die if I do not take my pills... is this true?"*

This is the start of defining the self as a person with CF. The challenge lies in helping the child with this definition. S/he is not CF, but a person with CF and with good self-care and support from family and the team, this person can lead a meaningful and valued life with CF.

Many parents dread these questions and worries, also because they fear rebellion against therapy [24]. CF teams can prepare parents by regularly informing them about normal developmental stages and topics that may emerge relating to CF.

The important achievements of increased mobility, language and self-awareness make this developmental stage one of growing independence, of taking initiatives, and exploration of the world. The worries about the picky eating, the battles over nebulizers or the concern about bugs in the sandpit are normal. Prevention through information and education is crucial because this developmental stage is an important foundation for later development stages.

## 4 Worries about the future and how these interfere with common sense childrearing?

The final section focuses on worries in children with CF and their families during the pre-school years. Between the ages of 3 and 5, a child's life expands to outside of the home environment, to the world of nursery and pre-school as described in the previous section. It may be the first time that parents are entrusting the primary caregiver role of their child to an adult outside of the family unit. As seen in Section 3, this transition may be accompanied by CF specific concerns, such as whether their child will be exposed to other children's coughs and colds, the nursery's cleanliness, and staff's adherence to the medication routine.

*Key message: CF is a "family diagnosis": the ongoing process of adjustment and adaptation of a family to CF can impact on adherence to CF treatments as well as a child's mental and physical well being. There is an important role for the CF team in supporting parents to find a healthy balance nurturing their child with CF in medicalization and hygiene, and in living a normal life.*

### 4.1. Sharing the diagnosis with children

For children with CF, learning about their diagnosis and treatment regimen signifies the start of a lifelong relationship with their condition. Accordingly, is it important that children receive accurate and age appropriate information, even during these early years. It can be challenging for families to decide what, when, and how to tell children with CF, and their siblings, about the condition. Pesle *et al.* (2016) found that for the 26 parents in their study, the ideal mean age to tell a child they had CF was 3.7 years, although age of disclosure ranged from infancy up to 8 years [25]. The study also found that some parents over-estimated their child's knowledge of CF and their understanding of the reason for hospital appointments.

### 4.2. Pre-school children's understanding of their health

A young child's ability to understand illness and health conditions is related to their cognitive development. Three to 5-year-old children are egocentric in their thinking and focused on the here and now. An understanding of illness causality may be developing, but they are prone to magical thinking, for example believing "I got a

cough because I did not say thank you.” Pre-school aged children are likely to conceptualize CF as a single symptom, rather than a multifaceted condition, and are unlikely to be able to fully grasp the invisible aspects of the condition. With an increasing self-awareness at approximately 4 years of age children start to become more curious about CF, but struggle to comprehend the permanence of a chronic health condition, asking questions such as “will I still have to do physio when I’m older?”

Past research has found that over half of 4 to 6 year old children knew they are born with CF, but most did not know what their different treatments were for, and none of the children knew that their lungs and pancreas were affected [26]. While this is developmentally normative, it highlights gaps in pre-schoolers’ understanding. There is a role for the CF team in supporting parents to talk to pre-schoolers about CF, the areas of the body affected, how they got CF, the role of daily treatments in keeping the body healthy, and a rationale for medical procedures. We know that parents sharing small pieces of information, regularly and repeatedly, supports children’s knowledge and understanding to develop in an age appropriate way.

#### 4.3. The impact on siblings

A common parental concern centers around the impact of caring for a child with CF on their healthy siblings. Historically, the negative psychosocial impact of chronic health conditions on siblings (especially in oncology) has been documented in terms of reduced parental attention, lower

levels of social contact with peers outside of school, as well as poorer psychological well-being.

Conversely, more recent research documents that healthy siblings of a child with CF report a good quality of life, above that of their peers who do not have a sibling with a chronic health condition [27]. This study also found that the negative aspects of CF are more likely to be perceived by siblings when their sibling with CF is older than them, had experienced a hospital admission, or had *P. aeruginosa* infection. When a sibling attends clinic or visits the ward, it is important that healthcare professionals engage with them and provide positive feedback, for example, thanking them for being kind and supportive. In conclusion, it is important that siblings’ well-being and quality of life are considered as part of holistic CF care.

#### 4.4. Parental mental health

Throughout the pre-school years, parents and families continue in their adjustment and adaptation to the emotional, practical and social aspects of CF. It is well established that parents of pre-school children with CF report elevated levels of anxiety and depression, above the rates seen in the general population [24, 28]. International guidelines recommend regular screening and clinical assessment of parental mental health difficulties, such as anxiety and depression, and subsequent psychological intervention [29].

In pediatric CF clinics, parents are often not used to being asked about their own psycho-

logical well-being, and while an invitation to do so is often welcome, it can initially feel unnerving. It is important for psychosocial professionals to strike a balance when reviewing parental mental health, not pathologizing the normal process of adjustment and adaptation to that of having a child with a chronic and life-limiting health condition. CF is often considered to be a “family diagnosis”: the ongoing process of family adjustment and adaptation to CF can impact on adherence to treatments as well as a child’s mental and physical well-being. There is an important role for the CF team in reviewing and supporting parental adjustment and well-being.

#### 4.5. Family planning and the future

Having a child with CF has been shown to influence the subsequent reproductive choices of parents. In a sample of 124 mothers, 67% choose not to have a second child with CF either by deciding against further pregnancies, or using pre-natal screening and selective termination [30]. Reproductive decision making has been shown to be influenced by the number of children already in the family, however, not by the perceived current and future health of the child with CF, perceptions of increase emotional, practical and financial burden or future treatment advances.

The introduction of non-invasive prenatal diagnostic testing is likely to impact on family planning decisions, and it has been suggested that uptake may increase with women valuing the opportunity for safe and early testing. It is also important for the CF team to be aware of their own personal

feelings about reproductive choices, and to ensure they do not impose their views or values on the families they are working with. Facilitating a referral to an independent genetic counselor can be helpful in supporting a family to make a decision that is right for them. In addition, healthcare professionals must respect that parents’ attitudes and choices in relation to prenatal diagnosis, termination of pregnancy, use of reproductive technologies and desired family size, change over time [31].

*Key message: A supportive and non-judgmental approach from the CF team, and access to genetic counseling is invaluable to families when they are making reproductive decisions for the future.*

#### Case example

Sarah lives with her husband, Jack, and her 4 and a half-year-old daughter Sophie. Sophie was diagnosed with CF at 3 weeks old via NBS. Sarah and Jack have learned to live with CF and have established a treatment routine. Thus far, CF care has been easy, apart from some temper tantrums at the age of 2 and a half-years, during which Sophie refused her physiotherapy. Outpatient clinics generally go well, and with the right distraction Sophie has learned to cope with blood tests. In her last clinic she was prepared for her first CT scan and she did very well, earning a diploma! Sarah is currently 38 weeks pregnant with her second child (Ella), who was conceived via IVF and does not have CF. Jack and

Sarah have prepared Sophie well for the arrival of her baby sister and she is excited.

When baby Ella is born, Sophie initially enjoyed playing with Ella and helping her parents with her care. After a few weeks, Sophie started to ask the following questions; “Ella forgot her creon?” and “why has Ella not done her physio today?”. Sarah and Jack are not sure how to answer these questions and so they use distraction techniques to avoid the questions. Sophie becomes a little withdrawn and her parents think she is worried about Ella. Sarah is also feeling worried and guilty about the situation. Sophie decides that if her sister does not take creon, she no longer needs to either, and she becomes reluctant to swallow her capsules.

The family have made an appointment to meet with the team psychologist to discuss Sophie’s treatment adherence, and how to respond to her questions in an age appropriate way. The psychologist encourages parents to be open and honest with Sophie about CF; to explain that Ella does not have CF and does not need to take creon with her milk. However, Ella has to do other things to keep healthy, such as drink milk and sleep lots. Sophie may benefit from age appropriate information about how CF affects her body and what creon does. In the short term the use of an incentive may support creon adherence. The psychologist also offers parents a session to explore their own feelings about CF, and previous barriers to talking with Sophie about CF.

## 5 Conclusion

In this chapter, we have highlighted themes that are important in caring for children with CF during their early years. We have reviewed a child’s developmental, parental interactions and team support (also see **Table 1**). The chapter has focused on the typical processes and challenges that families and CF teams encounter. Of course, there are significant individual differences in patients, their families, their experiences and their needs. The CF team should adapt their care to the needs of individual families. They can provide age appropriate information, support and encourage adaptive coping styles, support children and parents during medical procedures, and address concerns about normal development or CF specific worries.

It was beyond the scope of the chapter to discuss the additional needs of children with comorbid difficulties besides CF; for instance autism or attention deficit, or the impact of major life events that young families may experience, such post-natal depression, divorce, job loss, moving house, etc. The day-to-day practice of caring for and working together with a young family with CF is diverse and challenging, but most of all, a gratifying job

Behavior	Age	Impact on CF care	What can parents do	How might the CF team support
Increased mobility	1 year plus	Refusing to stay still for physio or nebulizers.	Establishing a daily treatment routine with naturally occurring incentives.	Education about normal development Sharing age appropriate behavioral strategies.
Increase in language skills – saying no	14 months plus	Refusing to swallow creon	Routine Use of immediate incentives to reinforce cooperation.	Sharing age appropriate behavioral strategies
Increased fussy eating behavior	2.5 years	Refusing to eat certain foods or eating small portions of food	Set mealtimes with clear expectations of behavior	Sharing age appropriate behavioral strategies.
Fear or anxiety about medical procedures, e.g. blood tests, cough swaps	2 years plus	Distressed by procedures, difficult for medical staff to monitor CF, deliver treatment	Parents to be present and model coping behavior.	Training parents to use behavioral strategies.
Increasing curiosity about CF and treatments	4 and 5 years	Parents sometimes are unsure about what to say to children	Talking to children honestly and openly sharing about CF and their treatments. What is CF? What parts of the body are affected? How do people get CF? etc.	Supporting parents and families to share age appropriate information with children with CF and their siblings

**Table 1** Early years development, possible impact on CF care and support from the CF team.



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# CHAPTER 14

## A spoonful of sugar helps the medicine go down; palatability and acceptability of medicines for small children with CF

### Authors

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### Introduction

Many medicines are used in the management of cystic fibrosis (CF). This chapter explores the types of medicines used, explains why they are used and provides some tips to minimize the burden of delivering medicines to small children with CF.

Important therapies used in the management of CF include agents for the prevention and treatment of infection and bronchodilators and mucolytics for the respiratory system. In addition, pancreatic enzyme replacement therapy (PERT) and vitamin supplementation are often required to counter the malabsorption that results from pancreatic insufficiency. The absorption of many drugs can be adversely affected by the malabsorption that characterizes CF.

When administering medicines to children, dose is often calculated based on the child's body weight or height, and doses change as the child grows. Many of these calculations are extrapolated from adult data where it is assumed that the anatomy and physiology of the child maps directly to the adult. Caution is advised in people with CF where absorptive pathways are altered as part of the disease. In addition, some medicines, including antibiotics, are excreted more quickly by the kidneys of people with CF requiring a larger dose (and sometimes more frequent dosing).

It is important to monitor young children with CF to ensure that the dose is appropriate. In particular, higher doses of antimicrobials will be required in order to achieve therapeutic effect when compared to people without CF. Medicines are used to treat many aspects of CF. It is likely that your child will require many different medicines and the treatment timetable can be quite challenging. Some parents/carers create a medicine tracker

for their child to provide a reminder of what medicines are required, together with the dose and the time of administration. This is usually in the form of a weekly planner and there are many templates available online. One example that provides a print version and an app is <http://www.mymedschedule.com/>.

It is widely recognized that age-appropriate medicines for children have been overlooked for many years due to the limited market-size of the population. Babies, infants and children require flexible dosage forms. For infants and pre-school children liquid medicines and suspensions have been the most popular option. Liquid medicines are convenient for dose accuracy and can easily be handled by parent/carers, but are often associated with poor palatability. Masking the taste of a liquid medicine is challenging and in some cases the strategy for taste masking can impact negatively on the effectiveness of the medicine, by disrupting absorption.

In 2007, European and US regulatory agencies decided that the development of any new drug must be accompanied by a plan to develop a paediatric formulation. Any new medicine developed after 2007 is required to have a plan to demonstrate that it is acceptable to the target population. This means that more appropriate medicines should be available for children. Medicines available prior to 2007 are unlikely to change as there is little commercial incentive to the manufacturers to develop a pediatric formulation.

Medicines are supplied as a range of products, which may include tablets, capsules, oral liquids, inhalers, nasal sprays and nebulized medicines. This chapter explores some of these medicines and the challenges associated with them. Specific advice on managing poorly palatable medicines is provided in the following section.

## 1 Challenges of medicines administration and strategies to overcome the challenges in small children

### 1.1. Oral medicines

Many medicines are given orally as this is the easiest route for the child and the parent/carer. However, there are many issues associated with unpalatable oral liquids (e.g. antibiotics), tablets that are too large to swallow and the large quantity of capsules (e.g. PERT) that are sometimes required in CF.

Oral medicine treatment regimens can vary. The duration of treatment can range from a few days to much longer. It may be necessary to take the medicine either with food or on an empty stomach, and the timing of each dose can vary. It is important that the healthcare team provides clear advice on the timing of doses.

In the case of unpalatable liquid medicines, parent/carers may consider providing the child with a drink or snack immediately after dosing to remove the taste as quickly as possible. Often cold foods can help minimize the impact of poor taste so chilled

snacks or iced water can offer benefits.

Medicines are flavored in an attempt to conceal the bad taste of the drug component, however flavors can also contribute to an overall sensation of poor taste themselves. Different brands of medicines can have different flavors and it may be that a child prefers one brand over another. There is a drive to remove sugar from medicines to reduce the incidence of dental caries, and sugar-free products will taste different to those that contain sugar. Floxapen™, a sugar containing flucloxacillin was withdrawn from the market as part of the drive to remove sugar-containing medicines. This withdrawal was frustrating for families in the UK, where this antibiotic is widely prescribed for prophylaxis. Parents reported that the Floxapen™ brand had superior palatability compared to other brands. The CF population is particularly vulnerable to specific formulations being discontinued for commercial reasons and policymakers and regulatory agencies should take an active role in preventing this.

If the medicine is to be given on an empty stomach, but a child requires a snack to remove the taste of the medicine, it is advisable to the smallest amount of food possible to prevent the possibility of reducing the activity of the drug. Co-administration with food leads to a slower gastric emptying time that can delay the onset of action of an orally administered drug. There is also a risk of the drug binding to the food components so that overall absorption is reduced. This is particularly important for antibiotics dosed with milk, as the calcium

within the milk can chelate the drug and prevent absorption. Apple purée (apple sauce) is often recommended to take with medicines to improve palatability although this may not always be readily available. In all incidences consult with a pharmacist to ensure that the use of food is appropriate with a particular medication.

Strategies that parent/carers can consider to help administer poor tasting medicine include:

- Consider alternative brands as they may use a different flavoring system or sweeteners, which may be better for certain patients. The same brand is not always available due to the procurement processes within a pharmacy so ensure that where relevant the brand is prescribed (if permitted).
- Consider changing from a liquid to a solid if you think that the child is old enough, as this can also minimize the taste. A useful technique is to practice using sugar free sweets. Encourage the child to place the sweet on their tongue and swallow it with a full glass of water. It is important not to push this onto the child as all are different. Some children can do this at three years old but some sixteen year old teenagers still struggle. Positive support is crucial.
- Use an oral syringe. Directing a liquid to the back of the mouth so that it avoids the tongue minimizes the contact with the taste buds and can improve acceptance.
- Encourage parent/carers to have a positive attitude with the medi-

cines, so that giving medicines is not stressful or confrontational. Experience suggests that with time all infants will tolerate even the least palatable formulation. This is not always easy and parents often find it helpful to talk to their CF team to talk about this and get reassurance that they are doing the right thing.

- Consider rewards and encouragement. This is not practical for every dose due to the high burden of medicines but perhaps a weekly reward for taking medicines is practical using a wall chart with stickers for younger children.

Specific oral medicines that can be problematic include:

- Antibiotic suspension: some brands are available that better mask the metallic taste of the medication. Discuss this with your pharmacist or healthcare team to see if they are aware of any differences in brands for your local region. Using a more concentrated formulation will reduce the volume required for a small infant.
- Salt solution is a vital part of most patients' regime but is quite poorly tolerated due to taste. It can be added to a bottle when feeding a baby and to a small amount of juice for older infants/children. An early transition to tablet form helps, as it completely masks the taste. For some infants administering a salt solution can be very challenging and in these cases, oral rehydration therapy may provide good salt supplementation during hot weather.

- Vitamin preparations are required for children with CF. Pancreatic insufficiency associated with CF can affect the absorption of fat soluble vitamins, particularly vitamins A, D, E and K. The recommended daily dosing of vitamins to a child with CF is higher than to a healthy child due to poor absorption.

- Multivitamin preparations specifically designed for people with CF are becoming available and can include more than one vitamin (for example, ADEKs). ADEKs use water-mixable forms of fat-soluble vitamins to improve their absorption. The preparation usually also includes vitamin C and B complex, and other vitamins plus zinc to supplement dietary intake. The type of vitamins given and their dosage, however, are defined according to a patient's age and stage of the disease. The use of a combination vitamin product can result in a lower tablet burden for the patient which offers obvious benefits. ADEK-plus formulation is a chewable tablet making it appropriate for younger patients. These CF specific preparations can provide an excellent option for infants and small children, but are relatively expensive.

#### Case study – Taking enzymes (Antonia Hug)

"Although they are a bit foggy, my memories of taking medicine with each meal as a toddler are still present today. Administering my enzymes demanded a high degree of creativity from my parents

as they were constantly trying to find easy-to-consume foods such as yogurt, soft pudding or mash to hide the granules in. I was diagnosed with cystic fibrosis at four months old.

Thus, taking tablets has always been a part of my conscious experience. Another memory is the patience with which my parents and grandparents approached daily meals, attempting to make them more attractive to me by using my favorite ingredients since food often triggered episodes of severe stomach ache. This makes it hard to come up with a one-fits-all solution to administering enzymes to small children with cystic fibrosis except:

- be patient,
- find soft foods that are both easy to consume and liked by your child,
- hide the granules somewhere where your little one will forget they exist.

When switching to the position of parents of CF babies and toddlers, however, the savior seems to have a name: "applesauce." Praised as the solution for small CF patients refusing to take capsules, tablets and all the other constant companions for the most part of their future lives, applesauce supposedly makes it easier for them to take the enzymes because of the texture and taste. Even better, apple purée is acidic which helps the enzymes get to the small intestines intact. But this savior is not tailored to everyone. There have been reports of children preferring ketchup, applesauce laced with colorful baking chocolate sprinkles or mashed potatoes. Take the time to experiment, and once you find something your little CF person likes I

would recommend going for it. In my case it was vanilla yogurt - and this preference has stuck with me up until today, although I no longer find it necessary to hide my enzymes in it!"

#### 1.2. Inhaled medicines

Drugs can be directly delivered to the lungs via an inhaler device which administers the drug as a powder or fine dispersion of powder. Alternatively a solution can be nebulized which changes the drug into an aerosol before it is inhaled.

If a drug is to be given with an inhaler, parents/carers should closely follow the instructions provided by the healthcare team. Many of the medications delivered by a traditional metered-dose inhaler (MDI) are similar to those used in asthma. Not all CF patients will need these therapies and will be guided by clinical presentation after examination by their consultant.

Bronchodilator drugs are commonly administered via an inhaler. The inhaler is typically a hand-held small aerosol that is activated by the patient. These must be used with a spacer device to prevent the medicine collecting in the mouth and throat, as it needs to reach the lungs to have the greatest effect. Inhaled bronchodilators usually begin to work within 20 minutes, and the beneficial effect can last for four to six hours.

The healthcare team will provide training on correct inhaler technique. No matter how old the person with CF, a spacer should always be used with a MDI (traditional style inhaler).

The below steps are for a generic spacer as there are many on the market. The healthcare team will provide for specific instructions for the relevant device:

- 1) Shake the inhaler device
- 2) Place the inhaler device into the spacer
- 3) If using a mask place it over the nose and mouth of the child. This does not need to be a tight seal as this will cause discomfort to the child
  - a. Put one puff into the spacer
  - b. Allow the child to breathe at a normal rate and depth for around 30 seconds
  - c. If having a further puff, return to step 1 and repeat
- 4) If not using mask, place spacer mouth piece into the child's mouth, ensuring teeth are not obstructing the flow
  - a. Put one puff into the spacer
  - b. Allow the child to take 5 steady breaths
  - c. If having a further puff, return to step 1 and repeat
- 5) If using a steroid inhaler make sure to rinse child's mouth out

### 1.3. Nebulized medicines

Many types of medications can be delivered by a nebulizer. These include antimicrobials, hypertonic saline and mucolytics such as dornase alfa.

Many antimicrobials used for the treatment of acute infections or chronic persistent infections can have side effects. Of particular concern is the chronic use of

aminoglycosides for *Pseudomonas* or *Mycobacteria* infections. Multiple courses of intravenous therapy can lead to accumulation in the inner ear leading to hearing disturbances as well as possible renal damage. Giving these medications via the nebulized route can help reduce this risk.

There have been many advances in nebulizer devices over the past 10 years. Traditional compressor type devices that require up to an hour to deliver the medications are being replaced by smart adaptive aerosol delivery devices such as the iNeb™. With correct technique they can deliver the dose within minutes. This, in combination with only delivering medication at appropriate points in inhalation, leads to better overall deposition in the lungs and increases treatment compliance.

Young children, especially babies will not be able to use these smart breath actuated devices. Using traditional compressors with face masks presents additional challenges, however it is the only option. It is important that the mask is not forced onto the child as this can be upsetting for the infant and can lead to non-compliance later in life. Allowing the infant to become familiar with having a mask on at first can help introduce them to the concept of nebulizers. Once familiar with wearing a mask, airflow can be introduced and then medication can be added. It can take weeks of practice before both the child and parent are comfortable with this, so it is vital to remain positive and encourage them to continue.

Mucolytics are drugs that act to thin the

mucus in the airways to make it easier to cough it out of the lungs. These medicines are inhaled directly into the lungs to have their best effect. This is usually done via a nebulizer which converts the medicine into fine droplets so that it can reach deeper into the lungs for the greatest effect. Parent/carers may not notice a dramatic response to mucolytic therapy and need to be encouraged that this is an investment in longterm well-being to improve adherence with treatment.

In the UK, dornase alfa (brand name: Pulmozyme®) is a commonly used mucolytic for children with CF. It is usually given once each day at least an hour before physiotherapy although some children may only require this every other day, depending on the assessment of their CF team. Most parent/carers try to have a routine to provide the medicine at the same time each day. Developing habits is a key to achieving good treatment adherence. If a dose is missed it is important not to administer a double dose on the next scheduled administration.

### 1.4. Intravenous medicines

Intravenous (IV) medicines are liquid solutions delivered directly into the blood through a small tube attached to a needle that feeds directly into the blood stream. These are usually administered by medical professionals in hospital and sometimes at home, occasionally by the parent/carer with clear guidance and preparation.

With current standards of care, many infants with CF may not need any IV antibi-

otic treatment in their pre-school years. For those that require IV treatment a longline may facilitate treatment and extreme care must be taken to avoid toxicity. If aminoglycosides are required, it is essential that tobramycin is used once daily.

## 2 What is good adherence?

It is recognized that the burden for those living with CF is high. Despite parent/carers' best efforts to adhere to the medical regime there will always be cases where complete adherence is not possible. There will be occasions when doses are missed. Even in a hospital setting not all patients receive every dose of medicine. In fact adherence over 80% of all doses is considered a success. It is important that the healthcare team work in partnership with the parent/carers to support them in an open and transparent manner; to develop a regimen that is achievable and possible in a busy family.

Good adherence is directly related to positive health outcomes. Having a routine often helps adherence as treatment becomes part of the daily routine. It often takes some time to work out what works best for each child and family, particularly when therapies change. Healthcare workers should be aware that busy mornings are challenging, and that weekends and holidays disrupt daily routines and therefore may not be associated with improved adherence.

It is recognized that challenges will arise as a child develops. Often as a child reaches 2

years of age they begin to resist therapies or there are noticeable changes in behavior that can affect compliance. Each child is different and there are strategies that may work with some children to help in adherence. It is important to encourage parents to persist with medicines yet not feel too disheartened when a child refuses medicines. Complete adherence is a challenge.

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### 3 Conclusions

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The CF care team and parent/carers need to work together closely to ensure that infants and small children receive the most appropriate therapy as consistently as possible.

There are new incentives to develop age-appropriate medicines for children and any new medicines have to be demonstrated to be acceptable to children. This change in regulations means that future medicines will likely be developed to be more palatable to both children and their parent/carers. There is a move away from liquids where taste is an issue, both in masking the bitter taste of the drug and providing a flavor that is liked by children around the world, to tasteless medicines. These tasteless medicines are likely to be provided as sprinkles, granules or mini tablets that are small enough for children to swallow without a risk of choking or aspiration. There is also scope to dose them with whatever food your child wants on that particular day providing a better chance of adherence.

However, until these new medicines arrive it is important to support parent/carers in appropriate administration of medicines.

### References

Advice on taking a range of medicines can be found on the Medicines for Children website <http://www.medicinesforchildren.org.uk/>

Specific advice on taking foul tasting antibiotic flucloxacillin can be found here <https://www.cysticfibrosis.org.uk/the-work-we-do/research/research-areas/improving-palatability-of-flucloxacillin>

# CHAPTER 15

## Unusual complications in the pre-school child with CF

### Authors

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### Introduction

This chapter aims to highlight unusual complications in the pre-school child with CF. Some complications are directly related to CF. These CF-related complications may be the first manifestation of CF in this age group and should trigger physicians to perform a sweat test and genetic analysis. Some unusual complications in pre-schoolers with CF are therapy-induced and should be monitored when certain treatments are administered. Finally, pre-schoolers with CF can also develop disease that is not directly related to CF, but rather to their age. Viral infections increase the risk of colonization with *Staphylococcus aureus* and gram-negative bacteria and should be avoided if possible. Recommendations about immunization programs and other preventive strategies are highlighted below.

### 1 CF-related complications in the pre-school child with CF

#### 1.1. Pseudo-Bartter and salt-loss syndromes

##### 1.1.1. Pathophysiology and presentation

Pseudo-Bartter syndrome is an unusual complication in CF resulting from excessive electrolyte loss via sweat, often combined with gastro-intestinal loss due to recurrent vomiting or diarrhea [1-5]. Electrolyte and fluid depletion, especially low serum sodium, activates the renin-angiotensin system (RAS), leading to secondary hyperaldosteronism, which is the most important driving force in this feature. High aldosterone stimulates electrolyte-exchangers in the renal tubuli, resulting in potassium secretion and reabsorption of water, sodium, chloride and bicarbonate. This leads to hypochloremic, hypokalemic metabolic alkalosis [1-3].

Urinary chloride in pseudo-Bartter syndrome is low, in contrast to Bartter syndrome, where urinary chloride is elevated due to renal loss. This CF-related



complication is mostly seen in young children under the age of 2.5 years and is often found before CF is diagnosed [1-5]. Diagnosing pseudo-Bartter in a pre-schooler should be an alerting sign for underlying CF. Even after CF has been diagnosed, pseudo-Bartter syndrome frequently tends to reoccur [1-3, 5]. In infants with CF, pseudo-Bartter has been described with a prevalence of 20%. However, it is also reported in children above 4 years of age and even in adolescents and adults [4].

Presentation of pseudo-Bartter syndrome can be subacute or chronic; with the chronic presentation often being inconspicuous [1, 5]. Hyponatremia tends to be more pronounced in a subacute presentation [1]. An acute infection often triggers this salt loss syndrome [5]. Besides, heat exposure and excessive sweating can also be the initiating factor [6].

On physical examination clinical signs of dehydration are clinically less evident in salt-depleted patients with CF compared to control subjects [1]. Regardless activation of the renin-angiotensin-aldosterone system, an increased blood pressure is rarely seen [1, 5].

### 1.1.2. How to diagnose?

Laboratory testing shows hyponatremia ( $\leq 134$  mmol/L), hypochloremia ( $\leq 100$  mmol/L), hypokalemia ( $\leq 3.4$  mmol/L) and/or alkalosis (bicarbonatremia  $\geq 27$  mmol/L) [1]. Sometimes an elevated urea and creatinine can be found (prerenal acute kidney injury). Renin and aldosterone are often elevated [1,2]. Urinary testing shows

reduced chloride and sodium excretion, which suggests a non-renal cause of electrolyte loss [2].

Apart from pseudo-Bartter syndrome in case of excessive sweat loss, differential diagnosis of hypochloremic alkalosis includes Bartter syndrome, diuretic use, primary hyperaldosteronism and persistent vomiting (pyloric stenosis).

If isolated hyponatremia is seen, differential diagnosis should be made with syndrome of inappropriate antidiuretic hormone secretion (SIADH)[1].

### 1.1.3. How to treat?

In chronic and inconspicuous presentation of pseudo-Bartter syndrome, daily oral salt supplementation is needed. In subacute presentation of pseudo-Bartter syndrome, parenteral fluid and electrolyte replacement is required, using solutions rich in sodium, chloride and potassium [1]. Contributing factors such as infection should be identified and treated.

### 1.1.4. How to avoid?

The salt content of a normal diet and of breast milk or formula feeding is insufficient for children with CF. Sodium chloride supplements of 3 mmol/kg/day are recommended, and should be increased to 5-6 mmol/kg/d in circumstances of excessive heat exposure (hot climate, sports activity) [1]. Pseudo-Bartter syndrome still can occur in CF patients, regardless of sufficient daily salt intake.

Regular screening for serum hypoelectrolytemia is advised. Screening for low urinary chloride and/or sodium can be helpful, especially in patients with an increased risk.

### 1.1.5. Possible complications of salt-losing syndromes

If pseudo-Bartter syndrome is missed, serious complications of electrolyte disturbances can manifest as seizures, tetany, hypoventilation, decreased cardiac output, cardiac arrhythmias and even death [4].  $\text{CO}_2$  retention might be linked not only to lung disease but also to hyperbicarbonatemia [1].

Persistent sodium chloride depletion may cause failure to thrive and should be considered in the assessment of failure to thrive in pre-schoolers [1, 7]. Some authors suggest that electrolyte abnormalities in CF may further worsen the density and the viscosity of the mucus secretions, thereby increasing the risk of recurrent chest infections [1].

*Key message: Salt supplements are essential in infants and toddlers with CF, since the usual infant diet contains too little salt. Salt supplements cannot completely prevent pseudo-Bartter syndrome in CF.*

## 1.2. Cholestasis in the pre-school child

### 1.2.1. Pathophysiology and presentation

No specific CFTR mutations have been associated with the presence and severity of CF liver disease (CFLD). However, recently, a novel CFTR mutation, c.3871G>T, presenting with cholestasis that initially clinically resembled biliary atresia was described [8]. Another case

report suggests an association with R117H 5T [9].

In the hepatobiliary system, CFTR is expressed exclusively in cholangiocytes. It is thought that the primary chloride channel defect results in dehydrated, inspissated secretions that plug and obstruct the intrahepatic bile ducts, initiating progressive periportal fibrosis. Retention of toxic bile acids induces production of excess collagen, leading to the peribiliary fibrogenesis. In most cases the progression from focal to multilobular biliary cirrhosis takes many years. However, in some patients there is a rapid progression to multilobular cirrhosis with portal hypertension and, rarely, liver failure. Most patients will not develop multilobular cirrhosis.

Neonatal cholestasis is the earliest manifestation of liver involvement in CF. It is a rare complication, accounting for 0.6-0.7 % of all neonatal cholestasis [10, 11]. It usually occurs in the first 3 weeks of life and can be complete or incomplete. Complete cholestasis can be mistaken for biliary atresia [12, 13]. These observations suggest that prolonged jaundice, at least in some patients, is due mainly to obstruction of the extrahepatic bile ducts by thick bile, and it is probable that this leads to intrahepatic bile stasis. CFLD remains the third most common cause of death in people with CF [14].

About 50% of cases with neonatal cholestasis in CF co-occur with meconium ileus and parenteral nutrition. The outcome of CF patients presenting with neonatal chol-

estasis varies widely from full recovery within the first months of life in the majority of cases to occasional cases of early onset liver failure and death [11]. The co-occurrence of meconium ileus appears not to be associated with the development of CFLD.

Beside neonatal cholestasis, later cholestasis may occur secondary to treatment with antibiotics such as flucloxacillin, amoxicillin-clavulanate or erythromycin as in non-CF subjects [15]. There are no data supporting CF subjects being more prone to drug induced cholestasis than non-CF subjects.

*Key messages: Neonatal cholestasis is the earliest manifestation of liver involvement in CF. Onset of CFLD is usually in early childhood.*

*The true incidence and prevalence of CFLD is difficult to assess since there is no single, reliable diagnostic test.*

### 1.2.2. How to diagnose?

In the neonatal cholestasis presentation of CF, total and direct bilirubin are elevated, hepatomegaly may be present and stools have decreased pigments, leading to occasional confusion with the diagnosis of biliary atresia. In all infants with prolonged conjugated jaundice cystic fibrosis must be excluded. Clinical examination for hepatomegaly, the most common clinical presentation of CFLD, should be performed regularly. Upper abdominal ultrasound and blood liver function tests should form part of the annual assessment.

### 1.2.3. How to treat?

The only available therapeutic approach to potentially delay progression of CFLD is administration of ursodeoxycholic acid (UDCA) although it has not been convincingly demonstrated to change the natural course of the disease, especially outcomes such as death or need for liver transplantation [16]. UDCA is a nontoxic exogenous, hydrophilic bile acid which possesses choleric, hepatoprotective and immunomodulatory properties. Treatment with UDCA aims at improving biliary secretion in terms of bile viscosity and bile acid composition. Beneficial effects on liver biochemistry, hepatic excretory function, liver histology, and essential fatty acid status have been reported.

A daily dose of 20 mg/kg UDCA is initially recommended [14]. However, studies have shown that the most efficient dose of UDCA is 20–30 mg/kg body weight/day – higher than the doses used in other liver diseases. It is given in two or three divided doses and initiated as soon as the diagnosis of CFLD is made. It is well tolerated. Evaluation of indices of cholestasis and cytolysis should be performed 3 and 6 months from initiation of therapy to test for the efficacy of UDCA and the dose should be increased if necessary. The main side effect is diarrhea, in which case reducing the dose generally is sufficient. Surgical intervention is sometimes indicated for neonatal cholestasis i.e. rinsing sludge from the extrahepatic biliary tree by flushing the bile ducts with saline.

### 1.2.4. How to avoid?

To date there is no specific way to avoid neonatal cholestasis or other manifestations of CFLD. In the future, effective treatment of CFLD should combine repair of the basic defect and reduction of inflammation.

## 1.3. Renal calculi in the pre-school child

### 1.3.1. Pathophysiology and presentation

There is a higher prevalence of nephrocalcinosis and urolithiasis in CF patients, compared to age-adjusted controls [17, 18]. This feature is mostly found in adolescents and young adults with CF, but can also occur in pre-school children.

Analysis of these calculi reveal calcium oxalate stones in most of the cases. However, the pathophysiology of this stone formation is still under debate. Chemical analysis of urine in CF patients (with or without calculi) shows often hypercalciuria, hyperoxaluria, hyperuricuria, hyperphosphaturia and hypocitraturia, where plasma levels tend to show a lower phosphatemia and a higher uricemia.

Different pathophysiology theories are described and assume that the mechanism of stone formation is multifactorial [17, 18]:

- **Hyperoxaluria**, due to higher intestinal oxalate absorption, is present in 20-70% of CF patients. Two reasons for this feature are hypothesized. First, malabsorption in CF leads to a higher amount of free fatty acids in the gut. Calcium preferably binds to these lipids instead of oxalate, leaving more 'free oxalate' in the gut, favoring

more absorption. Another hypothesis is the absence of *Oxalobacter formigenes* in the intestinal flora of CF patients, as a result of prolonged antibiotic use. These gram negative anaerobic bacteria degrade oxalate. In the absence of these organisms a higher intestinal uptake of oxalate can be the initiating step towards oxaluria.

- **Hyperuricuria**, which is also often seen in CF patients, facilitates the formation of calcium oxalate stones. A combination of high protein intake, high doses of pancreatic enzymes (containing purin) and increased endogenous production of uric acid in CF patients is suggested to be the underlying mechanism.
- Urinary citrate inhibits renal calcium stone formation. **Hypocitraturia** is common in CF patients, however the exact mechanism is unclear.
- Calcium homeostasis in CF patients is altered if vitamin D deficiency is present, leading to **hypocalciuria**, which is protective of renal calculi. Infrequently, CF patients have hypercalciuria, which can contribute to the risk of renal stone formation, if other risk factors are also present. This may be the case in Vitamin D intoxication, as described later in this chapter. Apart from an iatrogenic cause, the underlying mechanism of hypercalciuria is unknown [8]. A theoretical mechanism may be the use of antibiotics such as ceftazidime and co-trimoxazole, provoking a proximal tubulopathy with hyperphosphaturia, activating parathyroid hormone, and

thus leading to hypercalciuria.

- The association of **CFTR mutations** in the kidney and nephrocalcinosis is not clear, but may play an additional role [17].
- **Low urine volume** due to excessive sweat loss and intestinal fluid loss, combined with less oral fluid intake, could also be a contributing factor.

In 50% of cases urolithiasis presents with abdominal or colic pain, often accompanied by hematuria [18]. In pre-school children with CF the occurrence of renal calculi is rare, but not negligible. The first presenting sign is often a urinary tract infection. The risk of reoccurrence of renal calculi is 10% in the first year [18].

### 1.3.2. How to diagnose?

Diagnosis is based on anamnesis and physical examination. In pre-school children the presenting sign can be a urinary tract infection, with or without classical symptoms of dysuria or fever.

A urinary sedimentation can show hematuria and chemical analysis of the urine can reveal the above mentioned chemical abnormalities, predictive of stone formation. Medical imaging with echography, abdominal radiography or CT-scan can confirm the diagnosis. Since all CF-related calculi are radiopaque, abdominal radiography can be used in follow-up.

In order to analyze the composition of renal calculi, all urine should be collected in a filter. In children with renal calculi an underlying disease should be ruled out, as most calculi reveal an underlying metabolic

pathology. If calcium-oxalate stones are found, CF should be suspected.

### 1.3.3. How to treat?

Non-steroidal anti-inflammatory drugs can be used as a conservative treatment for renal calculi [18]. In some cases, calculi should be taken out with endoscopy or extracorporeal shock wave lithotripsy (ESWL).

### 1.3.4. 3.4 How to avoid?

Good hydration is the basis of prevention of renal calculi. In subjects with an increased risk, exogenous sodium-intake should be limited, as well as the use of oxalate-containing food (spinach, rhubarb, nuts, tea, strawberry, grains). Supplements of citrate can be an option if hypocitraturia is present. In hypercalciuria, thiazidediuretics can be considered.

*Key message: Renal calculi are rare in pre-schoolers with CF, but do occur more frequently than in non-CF children.*

## 2 Therapy- related complications in the pre-school child with CF

### 2.1. Vitamin A and D intoxication

#### 2.1.1. Background

In most countries fat-soluble vitamins are prescribed as commercial available, fixed multi-vitamin formula (containing 800 IU Vitamin D, 9000 IU Vitamin A, 50 IU Vitamin E and 500 µg Vitamin K per tablet in case of Aquadeks®). However, these commercial products are not available nor reimbursed

in all countries. Additionally, their standard dosage does not permit personal-based supplementation. The use of pharmaceutical preparation of these vitamins overcomes this issue. Improper preparation or use of these vitamins can however result in life-threatening conditions. Vitamin intoxication in CF is mostly due to an over-dosage of supplements and often this is the case after improper preparation of over-the-counter supplements. Vitamin supplementation is further discussed in Chapter 5.

### 2.1.2. Hypervitaminosis D and Vitamin D intoxication

Hypervitaminosis D is considered when serum vitamin D levels exceed 100 ng/ml or 250 nmol/L [19]. Serum vitamin D levels above 150 ng/ml or 375 nmol/L are associated with Vitamin D intoxication [19]. Clinical presentation of Vitamin D intoxication is the result of hypercalcemia, such as poor appetite, weight loss, vomiting, abdominal pain, constipation, polyuria and polydipsia. In severe cases life-threatening dehydration and cardiac failure can be seen [20].

Diagnosis of Vitamin D intoxication should be made if very high serum levels of 25(OH) Vitamin D, low PTH values, hypercalcemia with normal or high phosphorus levels and normal or low alkaline phosphatase are seen. Urinary calcium/creatinine ratios are usually elevated. In case of chronic Vitamin D intoxication calcium storage can occur in the kidney, resulting in nephrocalcinosis, which can be detected with ultrasound [21].

Treatment of Vitamin D intoxication consists of immediate removal of the exogenous source. Administration of intravenous saline solution is the first line treatment, to establish a good hydration state, to increase the glomerular filtration rate and to enable calcium excretion. Loop diuretics can be added to increase calcium excretion. Glucocorticoids may be helpful in case of persistent symptoms of hypercalcemia, to reduce the production and activity of 1,25(OH)<sub>2</sub>Vitamin D, subsequently reducing intestinal calcium absorption. Bisphosphonates can also successfully reduce serum calcium levels, but should be used with caution, as severe side effects can be seen [22].

### 2.1.3. Hypervitaminosis A and Vitamin A intoxication

In contrast to Vitamin D intoxication, fewer cases of Vitamin A intoxication are described in literature. Intoxication with vitamin A supplements result in skin lesions (desquamation, fissures and extreme dry skin), fatigue, myalgia, arthralgia, blurred vision, anorexia with nausea and vomiting. In the presence of headache pseudotumor cerebri should be suspected, resulting in serious sequelae if diagnosis of Vitamin A intoxication is missed [23]. Chronic hypervitaminosis A can lead to liver fibrosis and decreased bone mineral density. Not only increased doses of exogenous supplements can cause Vitamin A intoxication. In case of advanced liver disease a reduction in retinol binding protein can lead to vitamin A intoxication if regular doses of Vitamin A are added. In these cases Vitamin A supplements should be reduced [7].

Treatment of vitamin A intoxication starts with elimination of the exogenous source. Rehydration and analgesia can help as supportive therapy. In case of an increased intracranial pressure, acetazolamide is required [23].

Despite removal of the exogenous source of fat-soluble vitamins, these lipophilic vitamins can be stored in fat tissue, prolonging their effects of toxicity even for several months. Regular control of serum levels, especially of vitamin A and D, is advised in pre-schoolers (and older patients) who take pharmaceutical prepared supplements.

*Key message: Fat soluble vitamins can cause intoxications with irreversible complications and should be monitored.*

## 2.2. Cushing syndrome induced by inhaled steroids in combination with Cyp3A4-interacting therapy

### 2.2.1. Pathophysiology

Iatrogenic Cushing's syndrome is a well-known complication of prolonged treatment with systemic corticosteroids. Iatrogenic Cushing's syndrome induced by inhaled, intranasal and skin applied steroids is less common. In normal circumstances, inhaled steroids enter the systemic circulation through bronchial absorption. This proportion of corticosteroids is mainly metabolized by cytochrome P450 of the liver, namely by Cyp3A4, consequently reducing its systemic effect.

Concomitant administration of Cyp3A4-inhibitors decreases steroid degradation

by the liver and results in an increased systemic corticosteroid circulation, favoring the development of iatrogenic Cushing's syndrome.

Case reports of rapid developing Cushing's syndrome in CF-patients receiving CYP3A4 inhibiting drugs and inhaled or topical steroids have been published [24, 25]. The most common interactions are seen with anti-fungal medication as itraconazole, fluconazole and voriconazole, macrolides as clarithromycin (not as azithromycin that has no CYP3A4 inhibiting function) and rifampicin all being Cyp3A4-inhibitors.

Patients with underlying liver disease are even more prone to develop Cushing's syndrome in case of co-administration of the aforementioned drugs with inhaled corticosteroids [26].

*Key message: Adrenal suppression can be seen in children treated with normal doses of inhaled steroids when concomitant therapy includes CYP3A4-inhibitors.*

### 2.2.2. How to diagnose?

Cushing's syndrome is often characterized by a rapid weight gain, moon face, increased blood pressure and sometimes an impaired glucose tolerance with polyuria and polydipsia. However, adrenal suppression can present unnoticed with only subtle stunting.

Diagnosis of an iatrogenic Cushing's syndrome is confirmed if morning serum free cortisol values are low (often immeasurable), in combination with low adrenocor-

ticotropic hormone (ACTH) and dehydroepiandrosterone sulfate (DEAS-S), confirming a complete suppression of the hypothalamic-pituitary-adrenal axis.

Physicians should be aware of this possible complication with combination therapy of CYP3A4 inhibitors with inhaled or nasal corticoids.

### 2.2.3. How to treat?

To prevent an Addison's crisis hydrocortisone should be administered at a normal physiological dose of 10-15 mg/m<sup>2</sup>/24 h (divided in 3 doses), while the exogenous source of corticosteroids should be stopped if possible. In case of stress situations (fever, vomiting, acute illness, trauma) hydrocortisone should be increased up to a 3-fold dose. Monitoring of morning free cortisol and ACTH should help the physician to decide if hydrocortisone maintenance therapy can be stopped. Often this lasts for several months, even with a rapid onset of Cushing's syndrome. An ACTH test should be performed in order to decide if stress-doses of hydrocortisone may be stopped.

### 2.2.4. How to avoid?

While combining treatment with a CYP3A4inhibitor and inhaled or intranasal steroids, dose adaptation of inhaled corticosteroids is advised in order to prevent Cushing's syndrome.

Underlying liver disease or an individual sensitivity in the cytochrome system may explain why only some patients develop these adverse events. Awareness of these possible side effects, while monitoring

morning free cortisol and ACTH is advised.

*Key messages: Medication interactions may become an increasing problem to deal with in CF, especially with the advent of new treatments such as CFTR modulators.*

*Be aware of Cushing's syndrome when inhaled or intranasal corticoids are combined with CYP3a4 inhibitors as:*

- *Azoles: fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole*
- *Isoniazid*
- *Macrolides: clarithromycin, erythromycin*
- *Grapefruit juice*

*Of note: ivacaftor is a weak Cyp3A4 inhibitor, Lumacaftor is a Cyp3A4 enhancer.*

## 2.3. Acute renal failure induced by aminoglycosides (gentamycin)

### 2.3.1. Background and pathophysiology

Frequent antibiotic use in CF starts from an early age. Antibiotics can be administered via the inhalation, oral, intravenous or intranasal routes. Different administration routes are often combined to achieve a response to respiratory exacerbations or to achieve the eradication of a CF pathogen as *Pseudomonas aeruginosa*. Despite the advantages of these strategies, side effects such as acute renal failure (ARF) or acute renal injury have been reported. Case reports of ARF with oral ciprofloxacin [27], inhaled tobramycin [28], IV aminoglycosides [29] have been published in the late nineties and early 2000s.

A nationwide survey of ARF in the UK CF

population by Bertenshaw *et al.* demonstrated an incidence risk of ARF between 4.6 and 10.5 cases/10,000 CF patients/year, approximately 100-fold higher than in children without CF. Of note, six of the 24 cases described in this survey were pre-schoolers aged from 0.4 to 4.4 years. The authors of the survey concluded that the use of IV aminoglycosides, particularly gentamycin, had an important role in the development of ARF in the CF population [30].

Subsequently, a case-control study was conducted by Smyth and colleagues to determine risk factors for ARF in the CF-population [31]. Their overall conclusion was that CF patients who receive IV gentamycin, and not tobramycin, are at increased risk in developing ARF. The chance of ARF increased 24-fold with the presence of any of the underlying risk factors: having CF-related diabetes (CFRD), dehydration, congenital or acquired renal impairment or the use of other nephrotoxic drugs (NSAID, ciclosporin etc.) [31].

These findings resulted in a policy to avoid treatment of CF-patients with IV gentamycin, regardless of its good effect on gram negative bacteria and low cost. Tobramycin has a lower nephrotoxic potential than gentamycin and is now considered as a first choice aminoglycoside for IV treatment [32, 33]. Moreover, the TOPIC study has shown an equivalent efficacy of a once daily dose, compared to a thrice daily dose, therefore significantly decreasing the possibility of nephrotoxic side effects in children [34].

Aminoglycosides are bacteriostatic; they

bind to bacterial ribosomes, interfering with normal bacterial protein synthesis. Human mitochondrial ribosomes have structural similarity with bacterial ribosomes, making the mitochondrial function prone to aminoglycoside-associated toxicity [33]. Renal excretion of aminoglycosides occurs by free filtration by the glomerulus, with a re-uptake in the proximal tubule. The subsequent increased concentration of the aminoglycoside in the proximal tubule cells interferes with normal mitochondrial function and results in aminoglycoside-induced ARF, which is typically non-oliguric and characterized by damage of the proximal tubule [33, 35].

### 2.3.2. How to diagnose?

Aminoglycoside renal toxicity targets the proximal tubule and is nonoliguric. Therefore, diagnosis should be made on laboratory measures and not on fluid balance. The study of Smyth *et al.* defined ARF as raised plasma creatinine above the upper limit for age [31]. Downes and colleagues define ARF according to the KDIGO-criteria (Kidney Disease-Improving Global Outcomes), i.e. "1/ a rise in serum creatinin by  $\geq 0.3$  mg/dL within 48 hours or 2/ an increase of serum creatinine  $\geq 1.5$  times baseline, defined as the lowest value obtained within 3 months prior to and following admission, with a value of at least 0.6 mg/dL or higher" [35].

In clinical practice, serum creatinine levels should be monitored before the first dose (baseline) and during treatment with aminoglycosides.

### 2.3.3. How to treat?

Rapid recognition of ARF is the first step of treatment. Aminoglycosides (especially IV, but also inhaled) should be stopped. Underlying risk factors, as dehydration should be treated. Concomitant possible nephrotoxic medication (NSAID, furosemide) should be interrupted.

In the survey study of Bertenshaw *et al.* 54% of the cases (adults and children) required dialysis [30]. Most patients (92%) recovered completely from ARF.

### 2.3.4. How to avoid?

If IV aminoglycosides must be given, the following preventive measures should be taken in order to minimize the risk of ARF: [32-35]

- Use tobramycin instead of gentamycin
- Only use once-daily dosing regimens
- Avoid long term treatment, as this could result in dose-accumulation and subsequent toxicity
- Monitor serum creatinine levels closely: at baseline, during therapy and at the end of treatment
- Monitor serum drug levels closely. Values around the upper limit have been associated with an increased risk of ARF and a high through level is toxic. In case of inhaled therapy with aminoglycosides, consider also drug monitoring if available
- Ensure good hydration, since dehydration is often associated with ARF. Children with CF are more vulnerable for ARF in warm weather. Pre-drug hydration can avoid ARF.

- Avoid concomitant use of other potentially nephrotoxic medications:
  - Ibuprofen
  - Vancomycin
  - Colistin
  - Furosemide
  - Ciprofloxacin
  - TMP/SMX [35]
- Be aware of risk factors as pre-existing renal disease, CFRD, low serum-albumin levels, sepsis.

*Key message: Aminoglycosides intravenously should be administered with caution. Gentamycin should be avoided to prevent acute renal failure. Close monitoring of risk factors, renal function and drug monitoring is advisable in case of aminoglycoside treatment.*

## 3 Age-related complications in the pre-school child with CF

The pre-school child with CF should not only be seen as a child with a chronic disease that needs special care and treatment. The pre-school child with CF is also a child with normal childhood issues that should be addressed by the CF team. Just as pre-school without CF, they may develop allergies and eczema, that should be recognized apart from CF-related symptoms and treated as such. In this part we try to highlight some classical issues/complications that are common in the pre-school aged children, apart from their CF-disease.

Although bacteria have historically been considered to play a major role in CF airway da-

mage, a strong impact of respiratory viral infections is also now recognized. Human rhinovirus is the most commonly encountered respiratory viral pathogen in CF although adenovirus, bocavirus, coronavirus, influenza, parainfluenza, metapneumovirus and respiratory syncytial virus are all also responsible for infections in this population. Emerging evidence confirms that respiratory viruses are associated with deterioration of pulmonary function and exacerbation and facilitation of bacterial colonization in CF patients [36].

Viruses may have an impact on bacterial adherence, immune response and on interaction with biofilms. Furthermore, animal studies have shown that CF mice carrying the most frequent *CFTR* mutation in humans, p. [phe508del]/c. [1521\_1523delCTT] (legacy name F508del) have increased morbidity and mortality following infection with a common human enterovirus. F508del mice had impaired viral clearance, a slower type I interferon response and delayed production of virus neutralizing antibodies [37]. Inefficient viral clearance in the F508del mice mirrors the prolonged duration of respiratory virus infections observed in people with CF. CF patients do not seem to suffer more frequently from viral infections than their healthy counterparts, but they are at a greater risk of lower airway involvement and symptoms tend to persist for longer.

The most predominant viruses are rhinoviruses, significantly associated with CF exacerbation, and influenza virus. Molecular techniques, especially multiplex polymerase chain reaction (PCR), help to diag-

nose viral infections, and the coming rise of metagenomics will extend knowledge of viral populations in the complex ecosystem of CF airways. Prophylaxis and vaccination are currently available only for respiratory syncytial virus (RSV) and influenza, but antiviral molecules are being tested to improve CF patients' care [36].

Viral detection is equally frequent in infants with CF compared to healthy controls, and symptomatic viral detections occur even less often in infants with CF. In pediatric CF populations, respiratory viruses are identified at between 23 % and 64% of pulmonary exacerbations, while samples taken during clinical stability are positive for viruses between 13% and 53% of cases [38].

*Key message: Pre-school children with CF can suffer from common 'pre-school' problems as allergies and respiratory viral infections.*

### 3.1. Respiratory syncytial virus (RSV)

#### 3.1.1. Additional risk of RSV in the young child with CF

Experimental reports have implicated RSV in facilitating lung disease in CF caused by *P. aeruginosa*. RSV infection has been shown to increase adherence of *P. aeruginosa* to epithelial mono-layers *in vitro* by up to 16-fold, and to increase colonization in lung homogenates 2000-fold, and to impact lung function changes in mice.

CF may be associated with an increased vulnerability to severe RSV lower respira-

tory tract infection (LRTI). Studies indicate that children with underlying medical conditions and RSV LRTI are admitted to hospital for longer periods of time, have a higher requirement for oxygen therapy, and more often require hospitalization in pediatric intensive care units than previously healthy children with RSV LRTI. This is also true for children with CF [39]. However, in the first year of life, prevalence of viral detection is not more frequent in infants with CF compared with healthy children. Infants with CF presented less often with respiratory symptoms if a virus was present which might be due to interplay of different factors such as local epithelial properties and immunological mechanisms [40].

#### 3.1.2. How to diagnose?

Real-time reverse transcriptase PCR (rRT-PCR) is currently the usual clinical laboratory test to detect RSV.

#### 3.1.3. How to avoid?

Outbreaks of RSV often occur between late fall and early spring. It is critical that babies and children with CF avoid infection with RSV by limiting exposure and by good hand hygiene.

A systematic literature review identified only one randomized study assessing the use of palivizumab in infants with CF. The overall incidence of adverse events was similar in palivizumab and placebo groups and there were no clinically meaningful differences in outcomes at 12-months follow up. The literature review stated that the strength of the current evidence

(only one included randomized study, with limited data) is "insufficient to allow conclusions about the efficacy and safety of palivizumab prophylaxis in children with CF" [41]. A 2017 systemic review concluded that palivizumab may have a potential role in reducing RSV hospitalization in children less than 2 years with CF but that additional research is warranted [42]. Thus there are no general recommendations for palivizumab in CF. However palivizumab should be considered for infants with CF less than one year of age with concomitant risk factors [43].

#### 3.1.4. How to treat?

Treatment of RSV infection is mainly supportive, and modalities such as bronchodilators, epinephrine, corticosteroids, hypertonic saline, and antibiotics are generally not useful. Evidence supports using supplemental oxygen to maintain adequate oxygen saturation. The other mainstay of therapy is intravenous or nasogastric administration of fluids for infants who cannot maintain their hydration status with oral fluid intake [44].

### 3.2. Influenza virus

#### 3.2.1. The additional risk of influenza in CF

Influenza viruses, in particular, have been shown to be involved in pulmonary exacerbations [45].

#### 3.2.2. How to diagnose?

Nasal aspirates or swabs are the most appropriate samples to be taken, rather than sputum or throat swabs. Several



methods to diagnose influenza are available and physicians should follow local guidelines.

### 3.2.3. How to avoid ?

In Canada both the live-attenuated intranasal influenza vaccine (LAIV) and the injectable intramuscular vaccine are recommended for children and adolescents with CF. LAIV continues to be recommended for use in children in the UK, Finland and Canada, as studies conducted in these countries demonstrate an overall protective effect of LAIV in children and adolescents. Results from a study by Boikos *et al.* 2017 support the safety of LAIV in patients with CF between the ages of 2–19 years [46].

### 3.2.4. How to treat?

Antiviral agents are important in managing influenza infection and include the neuraminidase inhibitors zanamivir and oseltamivir. These drugs can limit the infection and prevent the spread of the virus.

A literature review however was unable to identify any randomized controlled studies or quasi-randomized controlled studies on the efficacy of neuraminidase inhibitors for the treatment of influenza infection in people with CF [47]. The absence of high level evidence for the effectiveness of these interventions emphasizes the need for well-designed, adequately powered, randomized controlled clinical studies.

## 3.3. Chickenpox (varicella) in CF

### 3.3.1. The additional risk of chickenpox and CF

TJ David states in his review on CF 1990 that “deterioration in respiratory function after chicken pox has led us to use intravenous acyclovir 10 mg/kg/dose, three times daily for five days, starting at the onset of the rash”. This was based on a paper by NE Macdonald *et al.* 1987 [48] stating that varicella zoster virus (VZV) infection can result in significant morbidity in patients with CF. The risk of severe pulmonary complications rises with age. This is of greater concern in patients receiving systemic corticosteroids.

The risk factors for severe varicella in neonates generally are 1) the first month of life, and 2) early delivery (<28 week of gestation) since transplacental transfer of immunoglobulin G (IgG) antibodies occurs after this time.

### 3.3.2. How to diagnose?

The disease is usually diagnosed based on the presenting symptom. In unusual cases it may be confirmed by PCR testing of the blister fluid or scabs. Testing for antibodies may be done to determine if a person is immunized or is not immune. This is especially relevant when a child is to be put on a waiting list for lung transplantation to know whether vaccination is needed or not. People usually only get chickenpox once.

### 3.3.3. How to avoid ?

Chickenpox is an airborne disease making it difficult to avoid.

Routine immunization of children is recommended in many countries. Immunization within three days of exposure may improve outcomes in children. Some countries require the varicella vaccination or an exemption before entering elementary school. A second dose is recommended five years after the initial immunization. There is no Cochrane review on CF and varicella vaccination. Varicella immunization has been recommended for children with CF, at a young age if it is not within the routine immunization of the country or at any age if they have no clear history of having had varicella. More guidance can be found in Malfroot *et al.* [49].

### 3.3.4. How to treat?

Treatment of varicella in children with CF does not differ from that in healthy children, unless they fall in the high risk category because of age or concomitant disease.

## 3.4. Classical immunization programs should not be forgotten.

Immunization is today one of the safest, most cost-effective, and powerful means of preventing deaths and improving lives. Most countries have an immunization program for children including diphtheria, tetanus, pertussis (DTP vaccine), measles, mumps, rubella (MMR) and poliomyelitis. Some also include varicella, Pneumococcus and *Haemophilus influenzae type b* and hepatitis B.

According to a recent Cochrane report no randomized controlled trials were identified to draw conclusions on the efficacy of routine pneumococcal immunization in people with CF in reducing their morbidity or mortality. As many countries now include pneumococcal immunization in their routine childhood vaccination schedule it is unlikely that future randomized controlled trials will be initiated [50]. There is no Cochrane report on conjugate vaccines for preventing *Haemophilus influenzae type b* infections (Hib) in CF. However a Cochrane review in children in general [51] concluded that Hib vaccine is safe and effective.

For patients with CF, immunization against hepatitis A and B should be included in the immunization program. Hepatitis B virus (HBV) antibody titers should be assessed in patients with CF associated liver disease (CFALD) with a history of vaccination, particularly in those who received HBV vaccines in infancy or who are malnourished [52]. HBV antibody protection can be enhanced through vaccine boosters. Regarding BCG vaccination there are gaps in knowledge as how the CF patient will respond to immunization. Tuberculosis is rare in CF possibly due to a selective advantage of CF carriership [53]. However, due to obvious diagnostic difficulties and the fact that occult tuberculosis can be reactivated after transplantation immunization in accord with established local practice seems logical [49]. Vaccine against *P. aeruginosa* cannot be recommended [54].



An investigation of immunization coverage in the Paris region found that immunization rates were inadequate for both mandatory childhood vaccines and for the additional vaccines recommended children with CF [55]. This shows the importance of regularly assessing the coverage of both routine and specific immunization programs.

Children with CF should follow national immunization programs without delay to obtain optimal vaccination coverage.

*Key message: Normal immunization programs should not be postponed. Additional immunization such as vaccination against influenza, hepatitis and chick-enpox are strongly advised.*

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# CHAPTER 16

## Safe ethical clinical trials in pre-school children with CF – more than just a token

### Authors

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### Introduction

There is a huge discrepancy between the pediatric disease burden and the clinical research effort and funding devoted to pediatric populations [1].

Optimal medical care must be based on evidence-based intervention. There are, however, significant deficits in our current knowledge about the safety and efficacy of many drugs in children, since most data are derived from studies in adults [2, 3]. In fact, children have been described as “therapeutic orphans” due to the lack of appropriate studies in their age group [4, 5]. As a result, about one third of outpatient medications prescribed to children are unapproved by regulatory authorities or “off-label” [6]. As many as 79% of hospitalized children are treated with off-label

drugs [7]. To our knowledge, such data has not been published for children with cystic fibrosis (CF) and it is likely that the situation is even worse. Indeed, data are scarce for pre-school children with CF, despite their high medication use.

So the question is, how can we improve knowledge about the appropriate use of treatments in children with CF while exposing the minimum number of children to the smallest possible risk in research?

*Key message: Clinical trials in pre-school children are needed to develop safe and effective treatments for this age group.*

## 1 What is the current EU regulation on clinical trials in children?

Historically, the protection of children in research was achieved by excluding them from clinical trials. This has resulted in a lack of properly evaluated medications for children. The need for pediatric drug trials became obvious and eventually led to a paradigm shift, with the establishment of the Pediatric Regulation (EC no.1901/2006) in the EU [8]. The current legislation not only requires mandatory research by the pharmaceutical industry but also provides guidelines to improve the quality of pediatric research [8]. The main aim of this regulation is to decrease the evidence gap in pediatric drug prescriptions by mandating high quality research down to the pediatric age group for all drugs under development. This pediatric regulation contains three major initiatives: the adoption of incentives for industry, the implementation of a mandatory Pediatric Investigation Plan (PIP) considering all age ranges and the creation of a Pediatric Committee [9].

The regulation requires that pharmaceutical companies researching new drugs, new formulations of drugs, new indications or new routes of administration for adults integrate similar research for the pediatric population in their development plan [8]. Waivers are given when the condition studied does not exist in the pediatric age. The regulation also intends to stimulate research into the safety and efficacy of drugs that are already used in children without much supportive data. If successful studies on pediatric indi-

cations and formulations are carried out in line with the PIP, the applicant receives a Pediatric Use Marketing Authorization (PUMA) approval with 10-year market exclusivity [9].

In theory, the EU Pediatric Regulation is a fantastic initiative to boost pediatric drug trials. In practice, however, several hurdles remain. For example, PIP waivers are granted if the adult indication under investigation does not exist in children, even if the drug's mechanism of action could be relevant to other pediatric indications [10]. Of 28 new oncology drugs with a potentially relevant mechanism of action in pediatric malignancies, 50% obtained a waiver for a PIP because the adult condition under study does not occur in children. Also, priorities for drug research in children have been proposed repeatedly, but the field cannot progress if this is not matched with the necessary funding [11]. Today, pediatric research is seen as an integral part of the drug development process. However, a planned update of the PIP process will likely further bridge the pediatric evidence gap.

*Key message: A regulatory paradigm change in pediatric medicine: from protecting children against clinical research to protecting children through clinical research!*

## 2 Examples of networks for pediatric research

### 2.1 European Network of Pediatric Research at the European Medicines Agency (Enpr-EMA)

The European Medicines Agency (EMA) has established the European Network of Pediatric Research to encourage collaboration between academic and industry members from within and outside the EU, to link existing working groups to build up scientific and administrative competence and to define consistent and transparent quality standards as well as strategies to resolve major challenges.

### 2.2 Agencies to improve child-focused clinical trials (RESPECT, WHO, iCAN)

The EU initiative named "Relating Expectations and needs to the Participation and Empowerment of Children in Clinical Trials (RESPECT)" focused on parent and child involvement in pediatric research. This initiative highlighted the need to solicit the child's perspective during all stages of pediatric drug development [8].

The World Health Organization (WHO) campaign "Make medicine child size/Better medicines for children" adopted in 2007 is an example of efforts at an international level to raise awareness among politicians, pharmaceutical companies, researchers, healthcare professionals and the public.

Children's Advisory Network (iCAN) is a world-wide consortium of children's advisory groups to provide a voice for children and families in pediatric medicine through

interactive and collaborative forums [12].

### 2.3 CF-specific clinical trials networks

The field of CF has several disease specific networks, such as the Cystic Fibrosis Foundation Therapeutics Development Network (CFF-TDN) in the USA and the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN). To our knowledge the AREST-CF (Australian Respiratory Early Surveillance Team for Cystic Fibrosis) is the only program dedicated entirely to children with CF. AREST-CF run a unique program aimed at children under the age of 7 years, called the Early Surveillance Program. After observational studies had proved that extensive damage already occurs at pre-school age, the team embarked on an interventional study in CF infants and pre-schoolers to assess whether azithromycin can prevent structural lung changes (ClinicalTrials.gov Identifier NCT01270074, study ongoing).

*Key message: Pediatric networks are of great importance to promote research in children and to provide a voice for children.*

## 3 What is so different about trials during the early CF years?

Children are a unique population with developmental and physiological characteristics, distinct from adults. As trial participants children have special needs because of their vulnerability, their apprehension for medical procedures and their developmental peculiarities. Teams involved in research with children must respect children's autonomy and

individuality. They must consider the fundamental biological differences between adults and children in physiology, pathology, pharmacokinetics, and pharmacodynamics [13]. In pharmacokinetics, there are differences in metabolic pathways, organic functions, and metabolic rates. In pharmacodynamics, differences exist in receptor functions, effector systems, and homeostatic mechanisms. Possible side effects from drugs are influenced by growth and development. The drug doses needed depend on body weight or surface area [8]. These differences imply that mere extrapolation from adult data into the child population is inappropriate [8]. Furthermore, childhood has several ages and stages. Studies must be performed in all relevant age groups such as newborns, infants and toddlers, pre-school children, school age children and adolescents.

For these reasons, it is essential to study drug dose, safety and efficacy in children. Only then can children benefit from safe and appropriate access to new and existing therapeutics.

### 3.1 Dose calculation

Drug pharmacokinetics vary hugely according to age. After studies in adults, pharmacokinetic studies should be conducted in adolescents to establish baseline characteristics and subsequently in lower age groups to progressively establish pharmacokinetics in smaller children. Additionally, there must be a strong rationale to justify the final dose selection in very young children.

Young children have a different body composition as compared to adults. Therefore drug absorption, distribution, metabolism and elimination in children can differ substantially from that in adults. Genetic polymorphisms contribute to the variability in drug response and metabolism. Many genes have increased expression in early life compared to adulthood. Conversely, many drug-metabolizing enzymes and pathways are less developed in children. For comprehensive reviews on pharmacokinetics in children compared to adults we refer to Matalova [14] and Batchelor [15].

### 3.2 Safety

The risk of side-effects is increased in children as compared to adults, because many if not all their organs are relatively immature. Extra caution must be paid to newborns who have immature hepatic and renal clearance as well as an immature blood-brain-barrier. The possibility of effects on the psychosocial development of the child is real. Safety parameters must therefore be adjusted, and a longer follow-up period compared to adults is advised.

### 3.2 Challenges for formulating medicines

Typically, formulations developed during the adult program do not consider age-appropriate formulations. Palatability and patient acceptance are important factors when developing a drug for children. The key challenge with pediatric oral formulations is to produce dosage forms that can be adapted to body weight and contain taste-masking properties without toxic excipients. The

palatability of oral drugs should ideally be tested under various circumstances since taste perceptions can be altered, by infection for example [16]. The development of inhalable treatments should include testing of inhalation devices and techniques adapted to each age group

### 3.3 Minimizing invasiveness

Most children fear doctors, needles and invasive tests. More effort is required to limit the number of blood draws and the amount of blood to be drawn. This can be achieved by micro assays, studying salivary drug concentrations and sparse sampling supplemented with a Bayesian forecasting approach [17].

For periodic sampling, placement of an intravenous line may be indicated. Sedation under nitrous oxide may be needed for certain procedures.

Examinations need to be performed at the child's pace (easy does it) and hence more time and personnel are required for research in pre-school children compared to research in adults.

### 3.4 Participant recruitment

Recruitment is one of the most challenging aspects of pediatric clinical trials. This may in part be due to historical reasons. Parents are insufficiently aware of the lack of evidence for specific treatments in children. Awareness of the importance of research in children must grow, and general information about safe and meaningful research in children must be promoted.

Recruitment is difficult if few children meet the trial's inclusion criteria as well as protocol requirements. However, this can be amended by involving all relevant partners (pediatricians, parents, children) in the design of the protocol. It is essential to incorporating the view of children and parents, as they are the most important stakeholders. When informing families about a specific study, the trial must be explained in detail to both parents (for consent) and where possible to the children (for assent) in an age-appropriate manner.

Young parents have busy lives. Recruitment can be improved by providing appropriate incentives and compensation for time and income lost due to participation. The parental investment goes beyond travel costs. Disruption of school and age-related activities should be avoided or kept to a minimum (see also Section 8 on ethics).

Effective communication considering different cultures and customs is crucial and should continue throughout the whole trial period, not only with the parents but also with the child [8].

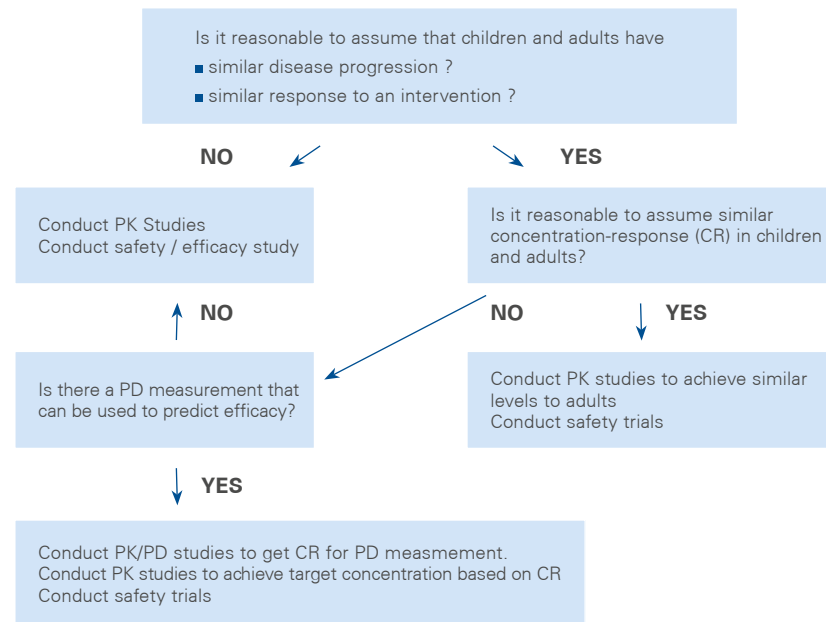
*Key message: Children are not small adults!*

## 4 Is proof of efficacy needed or only proof of safety?

Providing proof of efficacy of a treatment in children is preferred to just finding the correct drug dose and providing proof of safety. Indeed drug approval implies finding the right balance between benefit and potential harm.

A useful paradigm to determine which studies are needed in children when efficacy and safety have been proven in adults or older age group is presented in **Figure 1**, adapted from [18].

The response to the questions in the algorithm can differ according to the type of treatment studied e.g. CFTR modulators, mucolytic drugs, anti-inflammatory drugs or antibiotics. In CF, respiratory disease progression depends on parameters such as age, genotype and nutritional status. Hence the relative benefit may differ according to disease state. In young, usually stable, children a longer observation time is needed to measure a benefit or to document a lesser decline in health during drug treatment.



**Figure 1** Algorithm to determine which studies to perform in children

## 5 How to assess efficacy in pre-school children with CF?

### 5.1 Clinical outcome measures

*Nutritional status* (height, weight, body mass index) is easy to obtain and interpret. It is an important outcome but a large proportion of pre-school children, especially when diagnosed after newborn screening, will have a normal baseline nutritional status.

In pre-school children, *pulmonary exacerbations* are mainly driven by viral infections. Their frequency in CF does not really differ from that in healthy children. Therefore, this outcome has not proven useful in pre-school trials [20].

*Quality of life* scores like the parental version of CFQ-R questionnaire also suffer from a ceiling effect in many pre-school children.

### 5.2 Surrogate outcomes and biomarkers

*Infant lung function tests* are feasible but rather invasive, require sedation and have limited availability.

*Lung clearance index* (LCI) is a promising biomarker moving towards surrogate outcome status as its clinimetric properties are increasingly being mapped and as its track record in clinical trials increases [21]. In pre-school children with CF, LCI is already abnormal at age 3 years and increases further during pre-school age. LCI drops during episodes of cough but not when only nasal symptoms are present; as such LCI outperforms FEV<sub>0.5</sub> as an outcome parameter [22].

Whether a pharmacodynamic test can predict clinical benefit, will again differ according to the intervention studied e.g. a drop in sweat chloride concentration is an acceptable biomarker to predict clinical benefit from CFTR modulators. In pre-school children with CF, particularly in those with rare *CFTR* mutations, drug response *ex vivo* in intestinal organoids can be used as biomarker. Easy to use, non-invasive and fast responding biomarkers are not available for interventions other than CFTR modulators.

As mentioned, separate safety studies in pre-school children are always needed and longer follow-up periods are mandatory.

Studies should preferably start as a randomized controlled trial with an open-label extension period as soon as efficacy has been proven. Even for safety monitoring, an initial placebo-controlled period may be the best option in pre-school children with CF. The ivacaftor trial in pre-school children taught us this lesson [19]. Because of the open-label design, it is at present unclear whether the intermittently raised liver function tests recorded during the trial were due to ivacaftor treatment or whether these elevations occurred at a frequency that would normally be seen in pre-school children with CF and were only recognized because of the frequent testing during the KIWI study.



*Lung imaging*, either by chest CT or by chest MRI is mainly of use in studies with longer durations.

When measures of CFTR function are needed, *sweat chloride concentration* is very feasible and available. Also feasible but less available are intestinal current measurements and forskolin induced swelling assays in intestinal organoids. The latter can be used to predict treatment benefit *ex vivo*.

Bronchoalveolar lavage is feasible but invasive; biomarkers like neutrophil elastase can be useful to study anti-inflammatory or anti-infective therapies [23]. Bacterial cultures of the airway are feasible, but the variable disease progression and complex natural history of CF lung disease make this outcome only of use for very specific indications such as e.g. eradication of *Pseudomonas aeruginosa*.

*Key messages: The improved outcome of pre-school children with CF requires longer timelines to prove the efficacy of a new intervention.*

*Lung clearance index has great potential as outcome measure for clinical trials in the pre-school age.*

## 6 What motivates parents and children to participate in clinical trials?

Understanding the motivations for research participation may help healthcare professionals better tailor the process of recruitment and informed consent to the perspec-

tive of parents and children.

A systematic review examined the motivations of children and their parents to participate in drug research [24]. **Table 1** presents the most frequently mentioned factors that motivate and discourage children and parents to participate in clinical trials.

## 7 From what age on?

Children are vulnerable, at risk for exploitation and must be accorded special protection during clinical research. Since performing clinical trials in children is a precarious undertaking, special attention needs to be given to the informed consent process.

For most pre-school research, the focus of consent and information will remain with the parent or legal guardian. However, children who are capable of forming their views have a right to express those views in any proceedings affecting themselves directly (United Nations Convention on the Rights of the Child). Pediatricians must find a proper balance between protecting the children's interests when they are not fully capable to do so themselves and respecting their autonomy when they are. However, little is known about children's capabilities to meaningfully decide on research participation. In a study in children 6 years of age and older, the determining factors for children's competence to consent to clinical research were explored. Age explained most of the vari-

	Motivating factors	Discouraging factors
For children	<ul style="list-style-type: none"> <li>■ personal health benefit</li> <li>■ altruism</li> <li>■ increasing comfort</li> <li>■ positive relationship to researcher</li> <li>■ positive influence of family/friends</li> <li>■ financial reimbursement</li> <li>■ increasing knowledge</li> <li>■ curiosity</li> <li>■ felt as the "only option"</li> </ul>	<ul style="list-style-type: none"> <li>■ burden and disruption of daily life</li> <li>■ feeling like a "guinea pig"</li> <li>■ fear of risk</li> </ul>
For parents	<ul style="list-style-type: none"> <li>■ health benefit for their child</li> <li>■ altruism</li> <li>■ trust in research</li> <li>■ positive relationship to researcher</li> </ul>	<ul style="list-style-type: none"> <li>■ fear of risk</li> <li>■ distrust in research</li> <li>■ logistical aspects</li> <li>■ disruption of daily life</li> </ul>

**Table 1** Factors influencing decision to participate in clinical trials

ance in competence to consent, followed by intelligence. Experience with disease did not affect competence, nor did other variables such as gender, socio-economic status, ethnicity or parental competence judgement [25]. Therefore, information to children about the reason for the research and the risks involved should be adapted to their age and intellectual capacity. Then, in addition to obtaining parental permission, researchers must solicit the child's assent which has been described as "affirmative agreement to participation in research".

The Ethics Committees in different countries determine whether assent will be

required and from what age. EnprEMA compiled the legal age of consent and mandatory or suggested age ranges for assent in different European countries [2]. In the following countries, the legal age for consent is under 18 years: Ireland, the Netherlands and United Kingdom (16 years), Finland (15 years). The recommended age for taking assent in children is lowest in Belgium and France (4 years onwards). Almost all countries apply assent forms according to age ranges.

The assent process must be age and developmentally appropriate. It should be an empowering and respectful experience for

the child. It is reasonable to include information about their condition, about what will happen and what to expect and then asking them whether they would like to participate [9]. Although assent needs no written form or signature, several investigators and Ethic Committees (EC) prefer written documentation. The operation of assent has been left to the decision of the ECs leading to huge variability in practices [26].

*Key message: In practice, for most pre-school research the focus of consent and information will remain with the parent or legal guardian. However age appropriate information should be given to the child from the youngest possible age.*

#### Ethical issues in pediatric clinical research

- Research objectives and underlying scientific rationale (strong or weak)?\*
- Patient representatives' involvement in research conception?
- Is participation of minors necessary?
- What are the standard-of-care alternatives to participation? Prospects of direct benefit?
- Measures taken to minimize risks and burden tied to participation (design optimization)?
- Non-inclusion criteria backed on scientifically sound reasons?\*
- Other settings considered (e.g., alternative design, staged consent, off-trial access, etc.)?\*
- Post-trial access or benefit-sharing considered? Return of research results?\*

#### Legal and ethical consistency

- Adequate international or multi-center cooperation (optimum study and sample sizing)?\*
- Compliance with national or regional (e.g., European) law?
- Interference between study settings and child or parents' interests?
- Connate legal aspects (e.g., data custodianship, patenting, etc.)?
- Overall ethical justification (compliance with general principles, e.g., dignity)?
- Ad hoc ethical justification (e.g., commensurability to child's medical experience)?
- Adequate study management and monitoring?\*
- Appropriate study investigators' training in research ethics and communication?\*

**Table 2** Considerations for research in pre-school children with CF

### 8 Ethics in trials in young children and how ECFS-CTN can help?

The systematic review about research in pediatric oncology by Dupont *et al.* [27] provides a reference conceptual framework composed of 46 ethical issues relevant to research in children. This same framework on research ethics, legal and ethical consistency, professionalism and consent can be used for reflection about research in pre-school children with CF. From this long list, presented in **Table 2**, we highlight a few items (\*) that are of particular relevance for CF and that have not yet been discussed in this chapter.

#### Professionalism

- Proper scientific conduct and prevention of conflict of interests or roles (caregiver and researcher)?
- Multidisciplinary team meeting and consensus about commensurability and equipoise between participation or alternatives in an individual child's situation?
- Participation compatible with individual child's interests?
- Opportunity to offer participation to the family (e.g., linguistic or psychological factors)?
- Opportunity of off-trial access to drug (if available)?
- Prevention of professional biases (e.g., inducement, over motivation, or under-motivation, etc.)? \*
- Adequate understanding of a family's needs and values?
- Assessment of a family's understanding and expectations (optimism or pessimism)?

#### Consent

- Appropriate consent settings and timing (e.g., differing timepoints within the treatment protocol when consent to randomization is asked for)?
- Quality of information (content, means, and adaptation to family's needs)?
- Enough time for pedagogy and discussions with parents and child?
- Child involved in the decision making? (According to age, maturity, and their needs or trajectory)?
- Did the family carefully consider all alternative options?
- Does the child agree to participate?
- All measures taken to secure family consensus (dispute prevention and resolution)?

**Table 2** Considerations for research in pre-school children with CF  
\*Item of particular relevance for CF discussed in Section 8

Optimal trial design and appropriate study planning and management to avoid futile research is part of trial ethics. ECFS-CTN aims to improve the clinical trial protocol via protocol review, so that it approaches the standards listed in this research ethics section as much as possible. Of course, for commercial trials the opinion of the regulatory authorities such as the EMA must be taken into account and may influence the final protocol. Still, ECFS-CTN can voice their worries if futile or unfeasible research is proposed as part of a PIP.

Given the high cost associated with most new treatments in CF, there is a real ethical concern that benefit-sharing, return of research results and post-trial access to treatment may not be achieved for all populations after the clinical trial. Allowing participants in a successful clinical trial to continue treatment until it becomes commercially available is important but does not cover all needs. Increasingly we, the academic research community, must ask ourselves how we can combat this inequity in access to treatments. The only

certainty we have at present is that costs drop after the patent expires.

Many clinical trials require a high number of patients to adequately answer the research question posed. Hence multi-center or multinational trials are needed for most studies. In the past many trials, especially investigator-initiated trials (IITs), had a low sample size and therefore inconclusive results [28]. This must be improved. Since research in CF research is often funded by national patient organizations, ethical study management should include an audit to determine whether sponsored research was conclusive and whether study reports were published.

Training days for research personnel in ECFS-CTN sites foster skills in research ethics. Certification of study personnel for distinct outcome parameters of clinical trials ensure high-quality study conduct.

There is considerable variability amongst ECFS-CTN sites in the percentage of the patient cohort included in clinical trials. This has many causes including access to clinical trials, study personnel, space, time, research communication and organization within the team. The level of motivation of the clinical team to educate patients and families about clinical research could also be a factor. For example, certain centers discuss every clinical trial with all subjects who meet study inclusion criteria; in other centers the investigator decides for the patients by approaching certain patients only. There is also no guidance as to what compensation can be considered enticement without coercion [29].

Institutional review boards approve very different financial compensations for the same phase 3 trial, going from travel only to food plus travel plus an inconvenience fee and compensation for time lost. It also seems appropriate that children are not forgotten. The proposal of the authors is to compensate parents for costs of parking plus travel, food, lodging and time lost, and to similarly compensate the child for time lost and inconvenience. The rate proposed corresponds to the standard minimal wage per hour for a survey, then 1.5 times and 2 times that amount for non-invasive and invasive studies respectively [29].

*Key messages: Pediatric clinical research should be performed WITH and FOR children, not in children!*

*An ethical study is a scientifically sound study with appropriate study management.*

## 9 Conclusion

Performing clinical trials in pre-school children is the only way to develop safe and effective treatments for this age group. Children are vulnerable and therefore research in children requires extra precautions in an adapted environment.

Clinical trial networks improve expertise in research methodology and research ethics. They are a stepping stone for discussions with patient/parent groups, health authorities and pharmaceutical companies.

Children are not small adults. Performing clinical trials in pre-school children requires knowledge about pharmacokinetics (what does the body do to the drug) and pharmacodynamics (what does the drug do to the body) in this young age group. Consent from parents and assent from children (as young as possible) are a very critical part of research ethics. Children must be treated with respect and patience. Clinical trial design must be adapted to their age. Longer timelines may be needed for safety and efficacy assessments. Invasive procedures must be kept to a strict minimum. Even in young children, a blinded study period will usually be superior to an open-label safety study only.

Parents and children will be motivated to participate in clinical research if they experience the proper commitment, expertise and time from clinical research teams.

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# CHAPTER 17

## Mutation specific therapies for pre-school children with CF

### Authors

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### Introduction

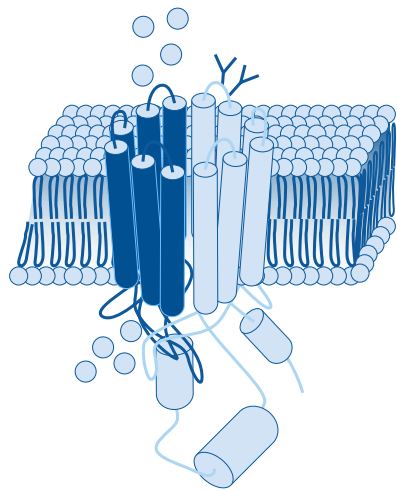
There are currently more than 2,000 different mutations identified in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. A better understanding of their consequences has led to the development of novel, mutation-targeted strategies correcting the underlying basic defect [1]. This contrasts dramatically with the symptom-directed treatment used for many decades. Although many molecular-based therapies are currently under investigation, most have only been studied in older children and adults. Few interventional studies have been performed in the pre-school CF population, and there are no data on treatment effects in the first year of life. This chapter summarizes the state of play of modulator therapy for older patients, current clinical trials in pre-school

children and potential development in infants. We outline the potential benefits of early modulator therapy in infants and pre-school children.

### 1 *CFTR* mutation classification

The *CFTR* protein is a cyclic adenosine monophosphate (cAMP) regulated ion channel found in the apical membrane of epithelial cells throughout the body (**Figure 1**). Normal *CFTR* secretes chloride and bicarbonate in airway, intestinal, pancreatic and sweat gland epithelia and exerts regulatory effects on other proteins such as the epithelial sodium channel (ENaC). The loss of *CFTR* function in cells where it is normally expressed impacts on many cellular processes. Crucially, respiratory epithelial surfaces become dehydrated, which impairs mucociliary clearance of inhaled pathogens [2]; there may also be direct effects on bacterial killing related

to pH abnormalities [3]. These processes combine to result in early infection, inflammation, mucus accumulation and over time,



**Figure 1** Schematic cystic fibrosis transmembrane conductance regulator structure

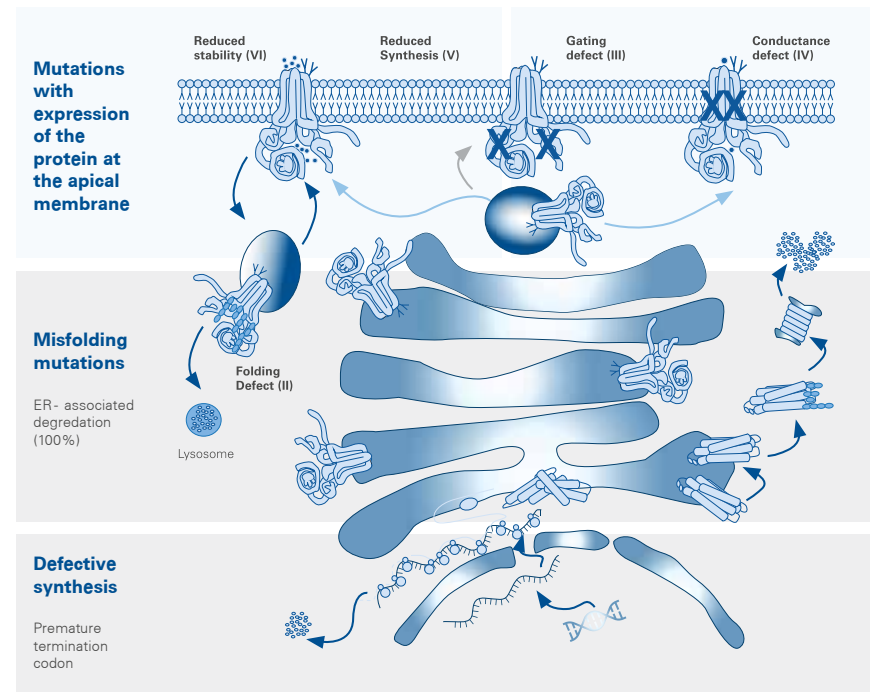
bronchiectasis and fibrosis.

Expanding knowledge of the biology of CFTR protein and the effects of specific *CFTR* mutations has allowed identification of potential targets for mutation-specific treatments. The treatment paradigm is shifting from management of the downstream consequences of CFTR dysfunction to targeting the basic underlying defect [1].

Mutations in CFTR have conventionally been grouped into five classes (see **Table 1**), but more recently a sixth class has been described. In Class 1 mutations, a

nonsense mutation or premature stop codon results in an unstable mRNA and absence of CFTR protein production. The ideal model for modulator therapies for this class of mutation would target the defect by promoting read-through strategies allowing normal translation processes. Class 2 mutations lead to misfolding of the protein, meaning that the CFTR protein cannot be trafficked to the cell surface and more rapid degradation of the synthesized protein. The most common CF-causing allele, p.[phe508del]/c.[1521\_1523delCTT] (legacy name, F508del), is an example of a class 2 defect. Modulator therapies in this group aim to restore protein folding and counteract its degradation so that more CFTR can reach the cell surface. Class 3 are gating mutations, whereby CFTR is assembled and correctly located at the cell surface membrane, but the abnormal channel does not open in response to intracellular signals.

Class 3 mutations can be improved by drugs potentiating the gating of the channel; indeed the use of modulator therapies in patients with gating mutations provided the first proof of principle of clinical efficacy of CFTR modulation. Class 4 mutations demonstrate reduced ion conductance and class 5 are splicing mutations resulting in reduced amounts of CFTR protein being produced. Like class 3 mutations, class 4 and 5 mutations may be targeted by drugs which potentiate the gating of the channel. Class 6 mutations, are associated with an unstable CFTR protein with a shortened half-life.



**Figure 2** Biogenesis of CFTR, according to the classes of mutations (I to VI)

Class	Type	Example	Functional Consequence on CFTR Protein	Therapeutic Potential
1	Nonsense	p.Trp1282X/c.3846G>A (legacy name, W1282X)	Little to no functional protein produced	Read-through agents
2	Misfolding	p.phe508del/c.1521_1523delCTT (legacy name, F508del)	Protein degradation, and little trafficking to cell surface	Correctors
3	Gating	p.Gly551Asp/c.1652G>A, (legacy name, G551D)	Abnormal channel opening	Potentiators
4	Conductance	p.Arg117His/c.350G>A (legacy name, R117H)	Reduced ion conductance of channel	Potentiators
5	Splicing	2789+5G -> A	Reduced amount of normal protein produced	Potentiators

**Table 1** Summary of *CFTR* mutation classes

Class 1, 2 and 3 mutations are associated with typical, severe, multiorgan disease. In contrast, class 4 and 5 mutations may result in sufficient CFTR protein quantity or function at the cell surface such that they can produce some residual CFTR activity. Such mutations can therefore be described as residual function mutations and may result in a milder phenotype. Examples include the class 4 mutation p.Arg117His/c.350G>A (legacy name, R117H).

It must be pointed out that these classes are not mutually exclusive and a mutation can combine two defects e.g. the common F508del mutation which has both class 2 and class 3 properties. There is a move towards using a simpler classification structure. An example of such a classification might be the “theratype” approach which characterizes mutations by their response to particular modulator therapies [4].

*Key message: Increased understanding of CFTR biology has led to the development of mutation specific therapies.*

## 2 How healthy are pre-school children with CF today?

Many countries now have new-born scree-ning programs, and even in those which do not, diagnosis is most commonly made within the first year of life. Symptomatic preventive treatments, such as physiotherapy, nutrition and antibiotics have improved outcomes for patients. Much of the time pre-school children are asymptomatic or have only subtle symptoms.

However, research studies on infants, toddlers and pre-school children reveal that, with sensitive tools, significant CF lung disease can be detected early in life. The two most prominent early respiratory surveillance studies are the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) and the London Cystic Fibrosis Collaboration (LCFC). AREST CF identified that babies with CF have reduced forced expiratory volume in 1 second (FEV<sub>1</sub>) compared to healthy infants. Bronchial obstruction and pulmonary distension as well as ventilation inhomogeneity are present as early as 3 months of age. The LCFC cohorts demonstrated significantly smaller deficits in lung function at 1 year than previously described but identified that babies with early abnormalities of lung function were at higher risk of continued abnormalities of lung function at 1 year of age [5]. AREST CF also reported focal areas of bronchiectasis, mucus plugging and air trapping on CT scans in children who did not present any respiratory symptoms. Progression of structural lung damage and pulmonary function decline were associated with bronchoalveolar lavage evidence of neutrophilic inflammation and pulmonary infection with *Staphylococcus aureus* or *Pseudomonas aeruginosa* in the lower airways [6].

Implementation of therapies targeting CFTR at birth, before the onset of significant damage, could therefore provide a critical window for disease modification to prevent pulmonary disease initiation. This contrasts with the paradigm highlighted in older patients that such therapies may slow down

the disease progression. As discussed later in the chapter, there may be a similar window of opportunity for extra-pulmonary complications. Of course, balanced against this wish for early prevention is the need to consider long term safety in the young child which cannot simply be inferred from trials in older populations due to maturational and drug absorption differences between age groups.

*Key message: Although with conventional therapies young children with CF enjoy good health, there is an urgent need for disease modifying therapies to prevent early, difficult to detect pulmonary and extra-pulmonary disease.*

## 3 CFTR modulators

### 3.1. Ivacaftor (trade name; Kalydeco®)

Ivacaftor is a potentiator drug marketed as Kalydeco®. Two pivotal trials of this drug in patients with the class 3 gating mutation G551D, STRIVE and ENVISION, provided the first proof of principle for clinical efficacy of CFTR modulation. Ivacaftor significantly reduced sweat chloride, a biomarker of CFTR activity, in some cases into the normal non-CF range. In older children and adults, it led to substantial improvements in lung function, weight, pulmonary exacerbation rates and quality of life scores (CFQ-R) [7-9]. Side effects include disturbance in liver function tests (LFTs, transaminases), which in rare cases necessitate stopping treatment. This phenomenon was observed more frequently in

younger children [10], although the natural history of LFT fluctuations in this age group is poorly understood. Preclinical data suggested that fetuses of animals dosed with ivacaftor developed cataracts. Detailed ophthalmological evaluation has been undertaken in clinical trials, and the occurrence of sporadic lens opacities has been reported in human studies although causation has been unclear. The studies leading to the licensing and reimbursement of ivacaftor for adults and subsequently children are described below.

#### 3.1.1. STRIVE and ENVISION - ivacaftor in G551D

STRIVE assessed the safety and efficacy of ivacaftor in patients over 12 years [7] whilst ENVISION [8] assessed the same parameters in children aged 6-11 years. In both studies, patients with G551D and a second CF-causing allele were treated for 48 weeks with ivacaftor or placebo. Both studies met their primary and secondary endpoints. Patients in STRIVE had a 10.8% improvement in absolute percent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) from baseline. Excitingly, even the younger population in ENVISION with higher baseline FEV<sub>1</sub> demonstrated an improvement in ppFEV<sub>1</sub> of 12.8%. The improvement occurred rapidly and was sustained through to week 48. Patients in the treatment group also demonstrated improved weight gain and a significant drop in sweat chloride. The older cohort had improved respiratory symptom scores on the CFQ-R and decreased risk of pulmonary exacerbation. The fact that any changes seen in respiratory symptoms were non-significant in the



children underscores their relatively better health and perhaps a lack of sensitivity of the CFQ-R in younger patients.

### 3.1.2. KONNECTION - ivacaftor for non-G551D gating mutations

In 2014, following the KONNECTION study [9] the license for ivacaftor was extended to include 8 further class 3 gating mutations including c.1646G>A/p.Ser549Asn (legacy name, S549N), and c.1651G>A/ p.Gly551Ser (legacy name, G551S). KONNECTION demonstrated an improvement in lung function, BMI, sweat chloride and CFQ-R, and did not uncover new safety concerns. Sub-analysis of the group demonstrated that the presumed gating mutation c.2908G>C/ p.Gly970Arg (legacy name, G970R) showed minimal sweat chloride response and little change in clinical parameters. Therefore, G970R was not included in the extended license. We now know G970R is not a gating mutation, but causes alternative splicing.

### 3.1.3. Ivacaftor in non-gating mutations, KONDUCT - ivacaftor in R117H

*In vitro* testing in Fisher rat thyroid (FRT) cells transfected with different CFTR mutations demonstrated significant activity of ivacaftor in several mutant forms of CFTR protein that result in functional CFTR at the cell surface [11]. This was the case for R117H, a class 4 mutation. This supported the KONDUCT clinical trial which assessed the efficacy and safety of ivacaftor in patients over 6 years with R117H and another CF-causing allele [12]. The results are complex to interpret,

partially due to the variable clinical presentation associated with the R117H mutation [13]. Ivacaftor significantly improved sweat chloride and CFQ-R scores in all age groups. Improvements in FEV<sub>1</sub> were more modest than those seen in patients with class 3 mutations, and only reached significance in adults, perhaps due to more established disease in these patients. No new safety concerns were identified. As a result, the drug was licensed in Europe for adults over the age of 18 years only, and reimbursement is variable across different geographical regions.

### 3.1.4. KIWI and KLIMB - ivacaftor in the pre-school population

KIWI was a pivotal study informing regulatory approval for ivacaftor in the pre-school population. This open-label study enrolled 34 children with a gating mutation on one allele (predominantly G551D) to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ivacaftor in 2-5 year olds weighing over 8 kg [10]. The study confirmed the appropriate dosing regime, PKs revealing exposures similar to those observed in adults. At week 24 sweat chloride had changed from baseline by a mean of -46.9 mmol/L ( $p < 0.0001$ ). Weight Z score changed by 0.2 ( $p < 0.0001$ ) and BMI Z score by 0.4 ( $p < 0.0001$ ) suggesting improved nutritional status.

Fecal elastase increased by a mean of 99.8 µg/g ( $p = 0.0009$ ) reflecting improved pancreatic function; this was the first time such a marker of pancreatic exocrine function had been included in a trial protocol. These results challenge the

notion that early pancreatic damage is fixed and irreversible. It was not possible to measure the effect on lung function due an expectation of minimal detectable changes on pre-treatment spirometry and difficulties obtaining spirometry in this age group. The majority of side effects and safety concerns were comparable to those observed in older patients. The 2-5 year olds demonstrated raised transaminases, in 15% to 8 times the upper limit of normal. All of these children had mild elevations at trial entry, and the LFTs normalized on holding or discontinuing ivacaftor. However, the effect of ivacaftor on the immature liver may be more pronounced than in older patients. KLIMB was an 84-week extension phase of KIWI. This showed the improvements in nutritional status and sweat chloride were maintained throughout the treatment period and no additional safety concerns were uncovered, though abnormalities of LFTs were again noted, and led to study discontinuation in 3 patients [14].

*Key message: LFTs should be closely monitored when starting patients on ivacaftor and this is particularly important in the pre-school child.*

### 3.1.5. The 123, ARRIVAL and ARRIVAL-EXT - ivacaftor trials in the pre-school population

In May 2016, a trial opened to assess the safety and efficacy of ivacaftor in 3-5 year olds with gating mutations and to examine the impact of long-term treatment on the course of CF disease progression. There

was an aim to enroll 50 children to this phase 3b, 2-part, randomized, double blind, placebo-controlled crossover study with a long-term open-label extension. However, shortly after the study opened, local reimbursement decisions made ivacaftor available through clinic in many regions and ongoing recruitment was deemed practicably and ethically unsustainable. The trial was closed early on this basis in August 2017. At the time of writing, analysis of the outcomes, particularly of the early cross over phase in which lung clearance index (LCI) was performed, are awaited.

ARRIVAL is an ongoing phase 3, 2-part, open-label study to evaluate the safety, PK and PD of ivacaftor in patients less than 24 months of age with gating mutations. Children are being enrolled in cohorts, starting with the older children and decreasing age once interim safety data have been assessed. Children as young as three months are currently being enrolled.

ARRIVAL-EXT is open-label trial to assess the longer-term effects and safety of ivacaftor in children under two with gating defects which, at the time of writing, has just started enrolling.

These data are being reviewed by regulatory authorities to decide if a license is appropriate in this age group.

### 3.1.6. Ivacaftor - longer-term data

Most of the long-term data examining the effects of ivacaftor come from PERSIST, a 96 week open-label extension of STRIVE

and ENVISION (i.e. G551D patients over 6 years). Ivacaftor was well tolerated during this time, with less than 1% of patients stopping treatment due to side effects or adverse events. The improvements in lung function, weight, respiratory scores and reduction in pulmonary exacerbations observed in the parent studies were sustained until the end of the study period [15].

Because ivacaftor is now considered a standard of care for patients with the named mutations, further randomized controlled trials of this drug are unlikely to be conducted in this population. Therefore, to answer new questions and identify emerging trends, data must be collected from observational studies and registries. Patients on ivacaftor have been shown to have a slower long-term rate of decline in

lung function compared to the expected rate of decline and sustained improvements in nutritional outcome measures reflecting disease modulation [16]. This highlights the importance of registry data collection in understanding disease and treatments.

### 3.1.7. Ivacaftor - licensing and reimbursement

At the time of writing, ivacaftor is licensed in America, Europe, Canada and Australia for patients aged 2 years and older with one of 9 class 3 gating mutations. Additionally, it is licensed in the EU for patients aged 18 and over with the R117H mutation. The FDA have approved its use in patients over 2 years old with the R117H mutation and a number of other residual function mutations such as c.200C>T/ p.Pro67Leu (legacy name, P67L) based partly on data

Study	Mutation	Age	Design	Length (weeks)	End Points Met?
STRIVE	G551D	12+	Placebo-controlled	48	Yes
ENVISION2	G551D	6-11	Placebo-controlled	48	Yes
PERSIST	G551D	6+	Open-label extension	96	Yes
KONNECTION	Gating	6+	Placebo-controlled, cross-over	24	Yes
KONDUCT	R117H	6+	Placebo-controlled	24	Some
KIWI	Gating	2-5	Open-label	24	Yes
KLIMB	Gating	2-5	Open-label	84	Yes

**Table 2** The clinical trial program for ivacaftor

from *in vitro* studies [17]. Patient groups were influential in the licensing and reimbursement of this high cost drug. However, despite a marketing license, local reimbursement is still not available in some regions. This highlights global inequalities in access to treatments for CF. Licensing and subsequent reimbursement decisions for ivacaftor in the pre-school population were based on randomized controlled trials (RCTs) showing efficacy in older children and safety data from 2-5 year old children in open-label trials. These data combined with the consensus that early intervention improves outcomes supported the initial application for approval without any RCTs in this age group.

### 3.2. Ivacaftor-lumacaftor combination therapy (trade name; Orkambi®)

The class 2 misfolding mutation, F508del, is a high priority for developing mutation specific therapy as it is globally by far the most common, accounting for ~70% of all CF alleles. Lumacaftor is a “corrector” molecule which allows trafficking of the protein to the cell surface. In early clinical trials, lumacaftor monotherapy did not unveil any safety concerns and exhibited a modest, dose-dependent change in sweat chloride. However, it did not lead to clinically significant changes in lung function or other parameters [18]. The important fact that mutated F508del-CFTR protein can be potentiated if it reaches its correct location at the plasma membrane [1] supported a dual therapy approach using lumacaftor and ivacaftor (lum/iva). This combination therapy is marketed as Orkambi®.

### 3.2.1. TRAFFIC and TRANSPORT - Lum/iva for people with CF who are homozygous for F508del

TRAFFIC and TRANSPORT were large phase 3 studies assessing the safety and efficacy of lum/iva in patients over 12 years old homozygous for F508del [19]. In both studies, subjects received lum/iva or placebo for 24 weeks. Both studies demonstrated a significant improvement in the primary outcome measures with mean absolute improvement in FEV<sub>1</sub> between active treatment and placebo ranging from 2.6 to 4.0 percentage points (p<0.001). There was a statistically significant weight gain and reduction in pulmonary exacerbations in the lum/iva group and fewer hospitalizations. There were no major safety concerns, and no increased frequency of serious adverse events in the treatment group, though patients in the treatment arm were more likely to discontinue dosing. Increases in blood pressure and chest tightness/bronchospasm were associated with lum/iva.

### 3.3. Lum/iva for 6-11 year olds, who are homozygous for F508del

An open-label phase 3 trial was conducted to evaluate the safety, tolerability, pharmacodynamics, and efficacy of lum/iva combination therapy in this younger age group. 58 patients aged 6-11 years with CF who were homozygous for F508del were enrolled. The study showed a statistically significant improvement in the airway function measure, LCI, but not in standard spirometry. Improvements were also reported in sweat chloride (p<0.0001), body mass index (Z score

+0.15 p<0.0001) and quality of life scores (CFQ-R scores; +5.4 p<0.01). The trial did not reveal any new safety concerns within this younger age group [20]. A subsequent placebo-controlled trial supported these findings, and has been used to apply for EMA licensing [21].

### 3.3.1. Lum/iva for pre-school children who are homozygous for F508del

A clinical trial of children aged 2-5 years homozygous for the F508del mutation has recently completed, and results are awaited (clinicaltrials.gov NCT02797132).

### 3.3.2. Lum/iva for pwCF who are F508del compound heterozygotes

Phase 2 trials of lum/iva did not demonstrate any significant improvement in sweat chloride or lung function for patients with one copy of F508del and one class 1 mutation [18] and trials ceased for this group. Currently, the next generation molecules described later in the chapter provide the most potential for this group of patients.

### 3.3.3. Lum/iva: longer-term data

The PROGRESS study assessed the long-term safety and efficacy of lum/iva in patients aged 12 years or older. Patients from TRAFFIC or TRANSPORT studies were dosed with open-label lum/iva for 96-weeks. No new safety concerns were identified during this time. The study showed that patients on lum/iva had a slower decline in lung function over the study period compared to the rate of decline anticipated from registry data of patients not on lum/iva [22]. Patients

not on lum/iva had an average decline of 2.29% (-2.56 to -2.03) in lung function each year, and patients on lum/iva had an average decline of 1.33% (-1.80 to -0.85) each year. However, these conclusions must be considered with the caveats around comparison with such a control group. There is an ongoing 96-week open-label extension phase in children age 6-11 years.

As lum/iva becomes available to patients across the globe, registry data may provide further understanding of its long-term effects and perhaps influence local reimbursement decisions.

### 3.4. Lumacaftor/ivacaftor - licensing and reimbursement

Improvements seen with lum/iva in F508del homozygotes were not as marked as those seen in ivacaftor responsive mutations and reimbursement for lum/iva remains limited. In 2015, the FDA and EMA approved its use in patients aged 12 years and above and homozygous for F508del, however reimbursement has only been agreed upon in the USA, Canada, France and Germany. In 2016, the FDA extended the license to include patients aged 6-11 years, and the EMA decision is pending. It is likely that reimbursement for pre-school children, homozygous for F508del, will be variable.

Study	Mutation	Age	Design	Length (weeks)	End Points Met?
TRAFFIC	F508del homozygous	12+	Placebo-controlled	24 weeks	yes
TRANSPORT	F508del homozygous	12+	Placebo-controlled	24 weeks	yes
PROGRESS	F508del homozygous	12+	Open-label extension	96 weeks	yes
	F508del homozygous	6-11	Open-Label	24 weeks	yes
Vx15-809-109	F508del homozygous	6-11	Placebo-controlled	24 weeks	yes

**Table 3** Main studies investigating lumacaftor/ivacaftor combination for people with CF

## 4 Lessons learned from the ataluren clinical trials program

Ataluren is a drug produced by PTC Therapeutics which, *in vitro* was demonstrated to promote read-through at the ribosome, facilitating normal protein synthesis [23].

Several phase 2 studies in CF patients with class 1 mutations suggested that ataluren improved CFTR dependent chloride transport measured by nasal potential difference (NPD), and led to detectable CFTR protein in the nasal epithelium [24-26]. A phase 3 trial ran between 2009 and 2011. This large scale, randomized, placebo-controlled trial enrolled patients over 6 years of age with at least one class 1 mutation. The primary endpoint was change in FEV<sub>1</sub> at week 48. The study failed to show statistically significant improvements in primary or most secondary outcomes. However, *post hoc* analysis showed that those patients who were not taking chronic inhaled amino-

glycoside antibiotics such as tobramycin demonstrated an improvement in FEV<sub>1</sub> of around 5% and a reduced pulmonary exacerbation rate [27]. Competitive inhibition was proposed as a plausible explanation for this phenomenon as aminoglycosides and ataluren both act on the ribosome. PTC initiated a further placebo-controlled trial in patients not receiving inhaled aminoglycosides, and submitted a licensing application.

Unfortunately, the trial failed to meet its primary or secondary outcomes and PTC has since halted its CF research program. Important lessons for researchers to take from the experience include the need to be cautious with *post hoc* subgroup analysis and ensuring that phase 3 studies are robustly designed. In particular studies should be appropriately powered to detect a clinically significant difference in outcome measures that are meaningful to patients with CF.

As around 15% of CF patients have at least 1 nonsense mutation, new compounds able to induce read-through are eagerly awaited and are currently being explored by a small number of other companies and academic groups.

## 5 Other potential mutation specific therapies

Though the advent of CFTR modulators has improved CF care for some, their use is still limited by reimbursement in many areas and the fact that not all mutations have a modulator available. There are several additional compounds in preclinical and clinical trials. Details of such trials can be found on websites such as <http://www.cftr.info/clinical-trials/>. A few of the mutation specific therapies currently in development are outlined below. So far, these trials are being conducted in adult patients.

The corrector molecule, tezacaftor, combined with ivacaftor (tez/iva) promises possibilities for patients in the near future. The efficacy of this combination was assessed in F508del homozygous patients aged 12+ (the EVOLVE study) and in patients with residual function mutations (the EXPAND study). There was a FEV<sub>1</sub> rise of 4.0% in EVOLVE and 6.8% in EXPAND with improvements in multiple secondary endpoints [28, 29]. Trials in patients with class 1 mutations were terminated early based on lack of efficacy. A fourth trial in patients with gating mutations has failed its primary outcome according to a recent

Vertex press release. There is an ongoing 96-week open-label extension for homozygous patients and those with residual function mutations. Trials will commence soon in school-aged children.

Vertex is also undertaking an extensive 'next generation' program to develop a triple combination therapy. *In vitro* experiments demonstrated that the combination of a second corrector used in combination with tez/iva, produces additive effects on processing and trafficking. Data press released [30] and presented as a conference abstract, although not yet peer-reviewed and published, suggest promise, even for patients with only one copy of F508del and a previously non-rescuable mutation (such as a nonsense mutation). Such combination strategies could be a major step forward for patients with class 1 mutations, who currently have no modulator therapies available. To date trials are early stage (phase 2) and limited to older patients.

Early conference data suggest the Galapagos potentiator GLPG1837 is well tolerated [31] and may have a similar effect as ivacaftor on FEV<sub>1</sub> for patients with gating mutations [32]. GLPG2451 is another potentiator in early evaluation [33]. ALBA-TROSS evaluated GLPG2222, a corrector molecule, in adults with a gating mutation already on ivacaftor therapy to ascertain if the combination offered advantage over ivacaftor monotherapy and to establish the appropriate GLPG2222 dose. Results are anticipated, and may lay the foundations for a phase 3 trial and a program to develop triple combination therapy.

Flatley Discovery Lab's FDL169 is a corrector molecule for use in patients who are F508del homozygous. A phase 1b, randomized, placebo-controlled study to assess its safety, PK and PD in patients with CF homozygous for F508del has just opened.

QR-010 (ProQR) is an RNA-based oligonucleotide designed to bind specifically to the defective CFTR mRNA and to restore the function of the CFTR protein. A proof of concept study in homozygous and compound heterozygous patients and a phase 1b trial of QR-010 in homozygous patients have been completed. Early data suggest that the drug is safe and well tolerated in single nebulized doses. In homozygous patients, topical application has a statistically significant effect on NPDs [34]. Other RNA editing based therapies such as antisense oligonucleotides for splicing mutations are being studied by different academic groups.

One anticipated barrier to enrolment for trials with novel corrector/modulator compounds was reluctance to stop current modulators for a washout or randomized period. In fact, many of these trials recruited extremely quickly; but this issue will become an increasing challenge for future trial design and implementation.

## 6 Gene therapy and stem cell therapy for CF

Due to the monogenic inheritance pattern of CF, gene therapy seems an exciting target. The UK CF Gene Therapy Consortium (GTC) recently completed a phase 2b clinical trial with liposomal vectors in older children and adults which demonstrated stabilization of FEV<sub>1</sub> over the course of a year [35]. The GTC is currently pursuing a potentially more efficacious technology using pseudo typed lentivirus and many groups worldwide are exploring gene editing techniques. Adult stem cells are multi potent, long lived cell lines which have the potential to give rise to terminally differentiated daughter cells. Adult stem cells from bone marrow, referred to as mesenchymal or marrow stromal stem cells (MSCs) have been shown *in vitro* to possess the capacity of differentiating into airway epithelia. CFTR-corrected MSCs are able to secrete chloride in response to cAMP agonist stimulation [36]. In the future, this and similar findings may give rise to a therapeutic opportunity.

## 7 Implications of new-born screening for mutation specific therapies

Through screening programs, babies as young as a few weeks are routinely being diagnosed with CF and identified as having mutations amenable to modulation therapies. Currently, none of these molecules have been tested for safety in such small babies and none are licensed. However, since early treatment with standard therapies in CF improves outcomes in early and later life, it seems reasonable to hypothesize that early administration of modulator therapies in this critical window may also impact on health for these babies. The current ARRIVAL study plans to enroll a cohort as young as three months old in this open-label ivacaftor trial. The development, licensing and reimbursement of novel modulator therapies in this age group will be an interesting area to watch as it will pose a number of ethical and trial design conundrums.

## 8 What are the benefits of early therapy in infants and pre-school children?

### 8.1. Respiratory disease prevention

The pathophysiology of early CF lung disease is caused by ineffective mucociliary clearance and defective innate defense which allows bacterial infection to become persistent in bronchial secretions despite aggressive antibiotic treatment [37]. This induces an exaggerated and prolonged inflammatory response in the

CF lung. This cardinal feature is the major driver for pulmonary disease progression and contributes to irreversible lung damage [38]. Early acquisition of pathogenic bacteria and subsequent chronic infection are associated with increased morbidity and mortality [39].

Therefore, it can be postulated that initiating a CFTR-targeted therapy at the earliest point before the onset of this pathogenic cascade and presence of structural, functional, or inflammatory disease may be more effective than treating the child once this vicious circle has been initiated. Indeed, eradication of initial bacterial infection and reversal of the pro-inflammatory pathways is a major goal. It is known that CFTR modulation is associated with restoration of mucociliary clearance, presumably because of increased airway surface liquid hydration due to restored CFTR mediated chloride secretion. Inhibiting airway dehydration would therefore target the cornerstone of disease initiation. This would of course be most efficient when initiated at the earliest opportunity before substantial mucus accumulation in the airways has occurred.

### 8.2. Pancreatic function

The majority of patients with CF also have severe pancreatic insufficiency (PI) as a result of decreased secretion of pancreatic bicarbonate and fluid, obstruction of the pancreatic ducts and subsequent autodigestion of the pancreas ultimately resulting in severe reduction of pancreatic enzyme secretion [40]. It has long been thought that this damage was already irreversible

at birth. However, as described above, studies in young children treated with ivacaftor showed increased fecal elastase levels as early as 1 month after treatment initiation [10]. Ivacaftor improves proximal small intestinal pH profile in patients with the G551D *CFTR* mutation and induces contemporaneous weight gain. These data provide evidence that pancreatic exocrine function might also be improved, even to normal ranges in some children whose pancreatic damage is not extensive [41].

With regard to CF related diabetes (CFRD), abnormal insulin regulation has been detected in pre-school children and in the animal model of the new-born ferret suggesting that the defect in CFTR impacts per se on insulin secretion by beta cells [42]. Therefore, drugs that correct CFTR function may improve glucose tolerance in CF. In childhood, dysregulated insulin secretion may be sub-clinical whilst beta-cell mass is largely intact. As islets are lost over time due to exocrine fibrosis and continuous pancreatic inflammation, the impact of abnormal CFTR function becomes more critical. Therefore, preserving an intact “biobank” of beta cells by CFTR modulation might help to delay or even prevent diabetes in CF patients. This beneficial effect has been recently supported by a small pilot study which enrolled a 6 year old child [43].

*Key message: Contrary to previous assumptions, trials of ivacaftor in pre-school children suggest that pancreatic function may be recovered in this age group.*

### 8.3. Other Organs

Although no data are as yet available, it could be hypothesized that CFTR modulator therapy might also be beneficial for other complications present in early CF such as intestinal and biliary obstruction (the latter being a precursor of hepatic cirrhosis) the upper airway complications such as sinusitis and nasal polyps and bone disease.

## 9 Conclusion

The substantial progress in novel modulator therapies over the past few years has raised hopes of improving CF disease which were unthinkable in the past. One of the most important challenges is the early initiation of CFTR modulator therapies before any irreversible damage occurs. However, shifting the treatment paradigm to primary prevention of CF disease requires better characterization of the relevant biomarkers and clinical trials outcomes. In particular safety outcomes need to be carefully observed and recorded. This will require close collaboration between clinical centers, patient/parent organizations, registries and clinical trials networks.

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