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The Prognosis of Cystic Fibrosis – A Clinician's Perspective

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1. Introduction

Looking at the prognosis of Cystic Fibrosis (CF) from the clinician's point of view is very relevant. Median predicted survival age of CF increased from 6 months when the disease was first described (1938) to 12 years in 1970 and over 35 years in 2010 in the United States of America (Davis, 2006). Three types of factors weigh on this prognosis, which is conditioned by lung disease: factors linked to the quality of care management, to genetics and to the environment. It has been estimated from studies in twins and siblings that the relative influence of the latter two is roughly equivalent. Though pollution may have increased in certain areas, and lighter forms of CF are now being detected by neonatal screening and in clinics where nasal potential measurements are widely available, their impact is limited and can not account for the spectacular changes in life expectancy. Thus, this improvement is due essentially to a better care management. Quality of care is the main determinant of CF prognosis.

The question of prognosis is almost invariably the very first that parents of a newly diagnosed CF infant will ask their physician, whose task to answer in a sensitive and sensible fashion is by no means easy. This question is also at the heart of daily concerns of the clinician, who has to take its determinants into consideration not so much in view of their fascinating underlying mechanisms (e.g. modifier genes) but rather to the extent they can give grip to improved care.

2. How to express CF prognosis? Median predicted survival: Facts, limitations and hopes

CF is a serious disease, which reduces life expectancy. Parents have often already found on the internet the associated 'Median predicted survival', which is the estimated duration of time until 50% of a given population dies. This given number of years has the effect of a guillotine and haunts their thoughts. For CF patients in 2008, it was 37.4 years in the US (CFF Registry, 2008), 38.8 years in the UK (UK CF Registry, 2008) and 46.6 in Canada (44.8 years after excluding adult diagnoses) (Canadian CFF, 2008). However, for a number of methodological issues, it is difficult to compare results of national registries. Evaluating cohorts on the basis of the presence or absence of pancreatic insufficiency was recently suggested as a way to help to overcome some of the current limitations (Buzzetti *et al.*, 2009).

Limiting the analysis to patients homozygous for the *F508del* mutation could be even 'cleaner' (Zelin *et al.*, 2010; Lebecque *et al.*, 2010). It is important to note that over the past 60 years, median predicted survival has actually increased in a continuous fashion by almost 6 years every decade (Davis, 2006). Part of this improvement is probably linked to the increased detection of milder forms of the disease. As proposed for the comparison of registries, it would be interesting to study the data of only those patients homozygous for the *F508del* mutation. For four reasons developed below, this brutal landmark has limited value in an individual patient.

2.1 Cohort effects

Cohort survival curves consistently show that survival continues to improve with each successive birth cohort over the decades. However, this effect is not taken into account by current survival curves. As a result, advice based on the latter could be unduly pessimistic. This has led authors to model the trend observed in cohort survival curves and to extrapolate a median survival for recent cohorts. Accordingly, a median life expectancy of the order of 40 years was predicted for newborns in 1990 in the UK (Elborn *et al.*, 1991). This proved to be realistic and updated extrapolation for the birth cohort of the year 2000 predicts a median survival of 50 years (Dodge *et al.*, 2007). Recent work has further validated this approach (Jackson *et al.*, 2011).

2.2 Wide heterogeneity of the disease

Median predicted survival does not take into account the vast heterogeneity of CF. Yet the latter has long been recognized, even amongst patients homozygous for the *F508del* mutation (Kerem *et al.*, 1990; Johanssen *et al.*, 1991). When diagnosing a new patient carrying 2 CF-causing mutations, this variability renders precise individual prognosis almost always impossible.

2.3 Quality of life

The raw median predicted survival rate says nothing about quality of life. In CF, pulmonary function is often used as a surrogate for survival, with FEV_1 remaining the single most useful parameter (Kerem *et al.*, 1992). Though insensitive to early stages of the disease, spirometry is widely available, inexpensive, non-invasive and very reproducible. It can usually be performed from the age of 5 and upwards. FEV_1 has the advantage of reflecting pulmonary involvement, thereby conditioning prognosis, throughout the whole course of the disease. The rate of FEV_1 decline might be an even stronger surrogate for survival (Liou *et al.*, 2001; Schluchter *et al.*, 2002; Rosenbluth *et al.*, 2004).

Quality of life is at least as important as its length. For every human being, it is largely conditioned by how an individual handles the careful balance of renunciations, and accepts these. Its precise and fine perception inevitably escapes all questionnaires. Specific tools developed over the past 20 years cannot presume to its assessment but can help discern the impact of new treatment modalities and are increasingly being used in this context (Abbott *et al.*, 2011). This also implies that, given the choice between equally efficient treatments, the least invasive treatment and follow-up modalities are to be favoured (Wainwright *et al.*, 2011). Under close supervision and for adequately selected patients, home intravenous

antibiotic treatment is a less disruptive alternative to hospital admissions. Though fatigue can be worse for home participants, home treatment has been associated to improvement in quality of life (Balaquer *et al*., 2008). At all stages of this complex long-term disease, a holistic approach of the care management of both the patient and his family is essential (Bush *et al*., 2006; Cohen-Cymberknoh *et al*., 2011).

2.4 Hope for a curative treatment

Predicting survival of a disease based on the past and present data bypasses the possibility of discovering a cure. Despite all prognostic improvements linked to progress in follow-up and symptomatic treatment of CF, it remains imperative to discover a cure for respiratory disease of CF, for at least 3 reasons: i) current treatment is increasingly cumbersome, 'devouring' about 2 hours every day on average; ii) the cost of CF treatment is constantly rising, leading to fears that there may be increasing limitations as to its availability, even in richer countries; iii) some patients still experience a much more rapid FEV1 decline. The approach favoured today is that of the search for pharmacological agents capable of circumventing the consequences of genetic anomalies as determined by CFTR gene class mutations (Amaral, 2011; Rogan *et al*., 2011). The principle is to interrupt 'the source' of the cascade of events that leads from an ionic transport anomaly in the respiratory epithelium to lung destruction. Treatment tailored to the type of mutation appears today reasonably within reach (Accurso *et al*., 2010). Should this eventuality become a reality, the prognosis of patients still free of significant pulmonary lesions would be radically transformed.

3. Causes of death in CF

Over 95% of known causes of death in CF (including data following lung transplantations of CF patients) are linked to involvement of the respiratory system (CFF Registry, 2000). Amongst the specific and much rarer causes of death, feature complications of liver disease, dehydration and intestinal obstruction in countries where physicians have little knowledge of CF (Verma *et al*., 2000).

4. Prognostic factors

A pragmatic way of looking at prognostic factors of CF is to distinguish those that are linked to the quality of care management and those on which care management has little (e.g. environmental factors) or no grip (genetic factors) (Wolfenden *et al*., 2009). Figure 1 gives an overview of prognostic factors in CF.

Three aspects of the discussion are worth mentioning i) interactions between factors are numerous and their complex statistical evaluation study has probably been too shallow in many publications; ii) the evaluation of the role of certain less easily quantifiable factors, such as treatment adherence, escapes usual means of analysis; iii) our choice is to focus on factors that appear essential to a clinician. The complexity of interactions between the different factors is clearly illustrated by the example of the impact of passive smoking on respiratory function. Although the deleterious effects of passive smoking are well established, they vary according to CFTR genotype and certain alleles of modifying genes (Collaco *et al*., 2008). Moreover, several studies demonstrated a link between passive smoking and socio-economic status (Smyth *et al*., 1994).

One example of 'the clinician's choice' in the discussion is not to dwell on the often reported issue of a 'female disadvantage' (Rosenfeld *et al.*, 1997; Mehta *et al.*, 2010; Olesen *et al.*, 2010), which may not concern adult diagnosed CF patients (Nick *et al.*, 2010). Numerous hypotheses have been brought forward to account for it, without any practical impact to date. Furthermore, though this might have been achieved at the price of a higher burden of treatment in females (Olesen *et al.*, 2010), there is evidence that modern intensive treatment may result in similar key clinical parameters for the two genders (Verma *et al.*, 2008; Olesen *et al.*, 2010).

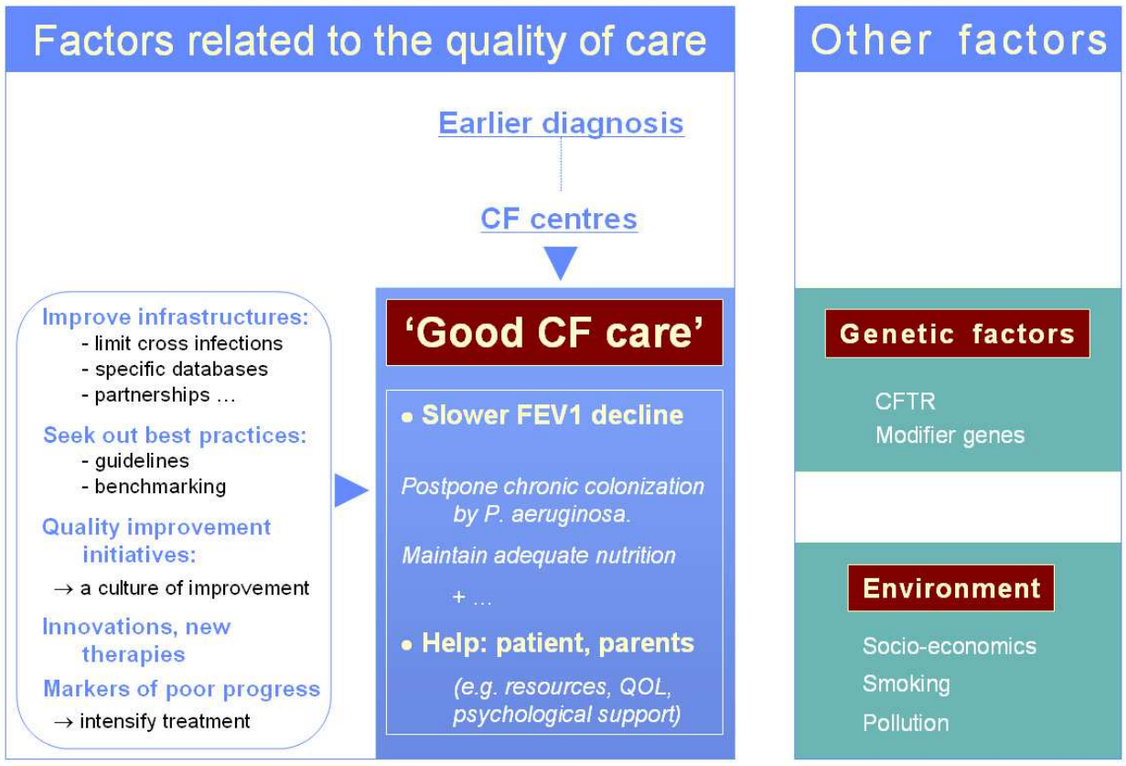


Fig. 1. Prognostic factors in CF

5. Good care management of CF

Early and mostly optimal management of CF is thus the principal reason for the improved prognosis observed over the past decades. Comprehensive follow-up and progress in symptomatic treatment proved essential. Antibiotics are the mainstay of CF therapy. In view of the complexity of this multisystemic and in many ways unique pathology, optimal management is only possible in truly specialized structures. Limiting the impact of economic status on treatment is an important issue. Most impressively, a pioneer clinician had already specifically stressed the importance of every single one of the above-named factors as early as 1974 (Crozier, 1974).

Taken in isolation and often combined to other factors (see discussion below), several complications can be linked to an accelerated rate of FEV_1 decline. Their awareness, prevention or early detection followed by optimal management carries the potential to

reduce the rate of FEV_1 decline. This is well illustrated by the case for CF-related diabetes (CFRD) over the past 20 years. At one large CF centre, early detection and optimal management of CFRD resulted in a decrease on its impact on mortality and the disappearance of a sex difference in mortality (Moran *et al.*, 2009).

Two factors in particular, chronic airway colonisation by *Pseudomonas aeruginosa* (PA) and malnutrition, have such spontaneous prevalence and such prognostic impact, that their prevention constitutes one of the major objectives of CF care management.

Several medications have been associated to slowing down the rate of FEV_1 decline: dornase alpha (Konstan *et al.*, 2011), ibuprofen (Konstan *et al.*, 1995; Konstan *et al.*, 2007), azithromycin (Hansen *et al.*, 2005) and inhaled corticosteroids (De Boeck *et al.*, 2011). This does not mean that *all* patients will benefit from them. In addition, possible side-effects in the long-term have to be kept in mind (cf. e.g. ibuprofen). Also, it cannot be inferred that other drugs are necessarily ineffective: they may simply not have been subjected to appropriate studies, which occasionally may be due to commercial reasons or ethical concerns (e.g. physiotherapy).

5.1 Early diagnosis: CF newborn screening (NBS)

A number of studies using bronchoalveolar lavage (BAL) markers of infection and inflammation, lung function tests or computed tomography of the chest have documented that significant lung damage occurs very early in many, even asymptomatic, infants (Khan *et al.*, 1995; Ranganathan *et al.*, 2001; Davis *et al.*, 2007; Mott *et al.*, 2009). The results of two recent studies concerning very young infants who were investigated routinely after CF diagnosis by NBS are particularly striking (Sly *et al.*, 2009; Stafler *et al.*, 2011). Unsuspected positive cultures were found in 21-27% of them, there was evidence of airways inflammation with BAL neutrophilia in most patients and CT evidence of bronchial dilatation in 18.6%.

CF is a progressive disease for which symptomatic treatment has proven to have a real impact albeit of partial efficiency. So, starting treatment as early as possible is meaningful. CF NBS is now available throughout the USA and in many European countries. For those newborns carrying a genotype clearly associated with the disease, benefits of neonatal screening has long been proven in nutritional terms. Respiratory benefits have only recently been acknowledged (Accurso *et al.*, 2005; Rosenfeld *et al.*, 2010), as these were temporarily obscured by a publication indicating an increased risk of early chronic colonisation by PA in screened newborns (Farrell *et al.*, 2003). This increased risk was eventually linked to the lack of measures aiming to limit cross infections in that particular centre and subsequent studies failed to confirm it (Siret *et al.*, 2003; Sims *et al.*, 2005; Baussano *et al.*, 2006; Collins *et al.*, 2008). In countries with a high level of medical care, neonatal screening enables clinicians to diagnose CF in infants before the age of 2 months, with demonstrable benefits (Sims *et al.*, 2007).

5.2 The case for CF care centres

5.2.1 CF centres are necessary

CF NBS is universally coupled with immediate referral to a specialist centre. Guidelines and international consensus all emphasize this to be the key to efficiency for all CF programs

(Castellani *et al.*, 2009; Comeau *et al.*, 2007). Even outside the context of CF NBS, early referral to a specialist healthcare centre is considered as a major prognostic factor as highlighted in consensus reports on optimal management of CF (Littlewood, 2000; Kerem *et al.*, 2005; Colombo *et al.*, 2011). Though this has long been supported by a number of common sense reasons and has been mentioned as a model for the management of complex diseases (Schechter *et al.*, 2005), most published studies concerning the impact of this centralization on lung disease are either biased due to comparison with historical controls, and/or probably underpowered (Hill *et al.*, 1985; Nielsen *et al.*, 1988; Walters *et al.*, 1994; Collins *et al.*, 1999; Merelle *et al.*, 2001; Van Koolwijk *et al.*, 2002).

Two studies avoid these pitfalls. Mahadeva *et al.* compared two groups of adults who had either received continuous care from paediatric and adult CF centres (n=50) or had received neither paediatric nor adult centre care for their CF (n=36). Excluding body mass index as a covariate, FEV_1 was significantly better in the first group (Mahadeva *et al.*, 2000). More recently, a Belgian retrospective multicentre study clearly showed that earlier referral of children suffering from CF to specialist care was associated with significant pulmonary benefits (Lebecque *et al.* , 2009). Children referred 'early' (less than 2 years after diagnosis) had a better FEV_1 (86.7% pred. ± 19.4 *vs.* 77.2% ± 22.4, p=0.01) and a lower prevalence of PA (17.5% *vs.* 38.6 %, $p<0.05$) than carefully matched patients referred later.

5.2.2 CF centres might not be sufficient

Large differences between outcome variables obtained from the different centres have been recognized for a long time (Bauernfeind *et al.*, 1996) and are now drawing considerable attention as they may provide an opportunity to develop quality improvement initiatives. Striking illustrations of this outcome heterogeneity are provided by recent data from the 2007 US Registry (CFF Registry, 2007 – public data), allowing for comparisons between centres: i) mean FEV_1 (% predicted) for CF children aged 6-17 years ranged from 75 to 103% (national average: 92.6%, reference values: Wang & Hankinson) ii) the percentage of patients under 20 years of age with a BMI < 5th percentile ranged from 32 to 83% (national average: 52.7%) iii) MRSA infection rate ranged from 6 to 42% (national average: 21.2%). These differences persisted after taking into account socio-economic factors. Similar features can be derived from the CF German Registry where a quality management program with an overall coverage of 82% for the year of 2005 confirmed considerable differences between centres in terms of key parameters (Stern *et al.*, 2008). For instance, the percentage of children (6-18 years) with an FEV_1 above 80% of the predicted value ranged from 20 to 100% in centres treating less than 50 patients and from 35% to 100% in larger centres. Globally, the mean FEV_1 in this age group was 88% of the predicted value. A recent Belgian multicentre study confirmed the broad outcome differences between reference centres within this small country, where corresponding values for FEV_1 in children reportedly ranged from 74% to 95% predicted (Lebecque *et al.*, 2009) while the prevalence of *PA* (last visit of the year) ranged from 5 to 46% and the mean weight expressed as percentage of ideal body weight ranged from 88% to 100%.

5.2.3 Marked differences in clinical results between CF centres: Why?

One report of 18,411 patients followed in 194 North American centres in 1995 showed that close monitoring and heavier treatment (more frequent antibiotics in particular) clearly

characterized those north-American centres with better clinical results (Johnson *et al.*, 2003). It is interesting to note that this more intensive management included two modalities which do not correspond to standard management: frequent prescription of nedocromil and more common prophylactic prescription of inhaled antibiotics, particularly in patients with still little pulmonary involvement. The use of nedocromil in CF is not well documented in the literature, neither is the potential of giving prophylactic inhaled antibiotics, which is discussed a little further in this chapter. Another North American study concerned 837 children aged 6 to 12 years (Padman *et al.*, 2007), whose CF centres were classified according to the children's FEV_1 values in 2003. The analysis also suggested that closer follow-up starting before the age of 3 years was characteristic of those centres with the best functional results. This 'more attentive and more active 'attitude' is in line with current standards of care, which are derived as much as possible from evidence-based medicine (Littlewood, 2000; Kerem *et al.*, 2005; Littlewood, 2005; Tiddens, 2009).

In 2002, the CFF launched an innovative Quality Improvement (QI) initiative, which included the vision statement that within 5 years, life expectancy of CF patients could be extended by 5-10 years through the consistent implementation of existing evidence-based clinical care (Quinton, 2007). However, evidence-based medicine has its limitations and possible stumbling blocks (Driever, 2002; Saarni *et al.*, 2004; Miles *et al.*, 2008; Shahar, 2008; Miles *et al.*, 2011), in particular when it concerns diseases as complex as CF for which numerous therapeutic modalities have simply not yet been adequately studied (Cheng *et al.*, 2000; David, 2001; Briggs *et al.*, 2006; Kraynack *et al.*, 2009). Best practice remains individualized in part, although a coherent foundation of evidence-based medicine is absolutely necessary.

One comparative study of 3 CF centres illustrates how even beside care standards, clinician intuition can lead to potentially judicious choices that deserve prospective studies. A better nutritional status was indeed linked to the prescription of dornase alpha (Pulmozyme ®) under the age of 2 years (Padman *et al.*, 2008), whereas the effects of Pulmozyme in this age group have only been reported in one limited study (Berge *et al.*, 2003) where 9 infants were given the drug for 2 weeks. The necessity to conceive and study new strategies stems from the fact that current ones are relatively powerless in preventing pulmonary lesions in early diagnosed infants (Stick *et al.*, 2009).

Information concerning the standards of CF care is widely available as are new drugs in rich countries. Differences in clinical results between various CF centres must therefore have a different origin. One can suspect subtle combinations of several factors resulting in small differences in interventionist attitudes. Beside adequate means i.e. infrastructures and human resources, optimal care requires a careful organisation (structure of the centre, coherence of attitudes, multiple fail safe systems etc.) necessitating considerable long-term thoughtful investment of all those involved.

5.2.4 Variability of outcomes in CF centres: Benchmarking as a right to patients

It is not possible for a CF clinic to function without landmarks. Specific databases prove to be very precious by giving immediate access to progress over time and by age group of essential parameters, thereby constituting a sort of 'compass' for measures that could be

taken to improve care management. Although limiting the objective to FEV_1 improvement would be reductive, it clearly remains an essential parameter. The FEV_1 of patients aged 6-18 years old (Figure 2) is a particularly relevant landmark for the 3 following reasons: i) very few patients die or require transplantation prior to that age ii) a significant proportion of adults has not benefited from immediate specialized care iii) adolescence is a particularly high risk time period with regard to deterioration of respiratory function. Appropriate indicators to define nutritional outcomes are also necessary (Lai *et al.*, 2008). If they are to be used to compare CF centres, these indicators have to be adjusted for risk factors - which does not change the overall outcome variability of CF centres (Schechter *et al.*, 2002) - and several years should be taken into consideration, in order to appreciate their coherence and tendencies.

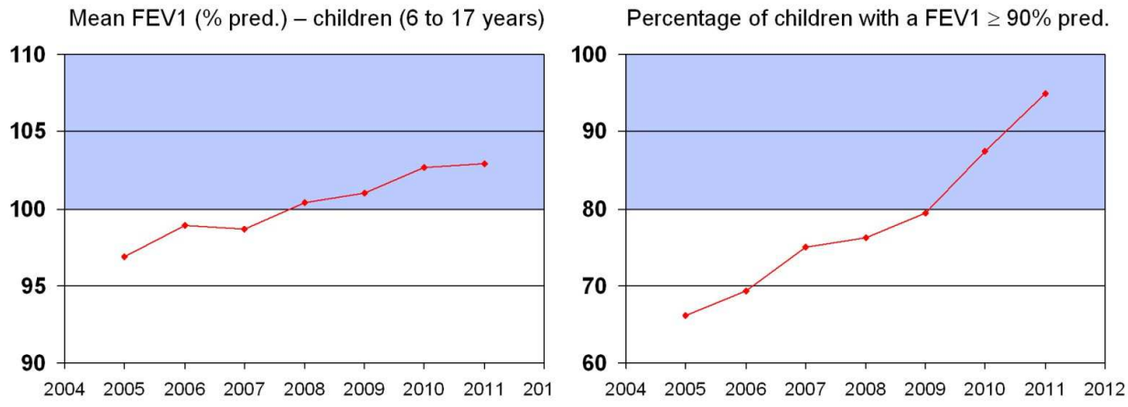


Fig. 2. Lung function in children followed-up at St Luc (last visit of the year, reference equations from Wang et al. for females through age 15 and males through age 17, and Hankinson et al. at older ages) (Wang et al., 1993; Hankinson et al., 1999).

The differences in mean FEV_1 observed in children from various CF centres can exceed 20% of predicted values. Recent data can help to perceive the implications of such differences: i) some centres now report a mean annual FEV_1 decline around 1% (Que, 2006) ii) in terms of FEV_1 (expressed in % pred.), improvements from baseline observed in two major randomized controlled trials of inhaled dornase alfa and tobramycin were less than 4% and 5% respectively (Fuchs *et al.*, 1994; Ramsey *et al.*, 1999) iii) in the USA, from 1990 to 2008, median FEV_1 at 12 years of age increased by 14 % predicted. Thus the prognostic significance of the differences between centres is major, also in terms of life expectancy. For this reason, public access to these data can be considered as a right to the patient and/or parents. In 2006, the outcomes data from the CF Foundation registry became public on the foundation's website, with an accompanying warning against simplistic interpretations. This choice bore witness to the priority given to the patients. Their health is at stake, and keeping them informed has to take precedence over the risk of embarrassing some physicians. In the USA, the fear that some patients may leave CF centres with average performance has not materialised: patients and their family maintain their trust once they realize that everything is done to improve results (Quinton, 2007).

5.2.5 'Good enough' care for CF does not exist: Towards a culture of improvement

Benchmarking, which is the process of identifying practices associated with the best results, may help to understand why certain centres obtain better clinical results. Not only can it be considered a right to the patients, it can also serve as an incentive to CF centres to increase their efforts to improve quality of care delivery. In the USA, most CF healthcare providers actually accepted it as a call to action (Schechter *et al.*, 2005). Public release of meaningful adjusted clinical outcomes data has been used in other fields of medicine, such as cardiac surgery, as a means to stimulate improvement efforts within the medical profession (Ferris *et al.*, 2010). Others have advocated 'softer' uses of benchmarking which do not require to be channelled via public data (Stern *et al.*, 2011). In the field of CF, benchmarking is not an easy task. It is possible when based on well-established CF registries but issues related to quality control and missing data obviously remain crucial (van der Ent, 2008). A number of methodological issues make it even harder to compare data from different countries. These include (but are not limited to) the population coverage level, the choice of reference equations, the type of subjects included in the registry (an increasing number of patients with milder forms of the disease are now being identified in some countries through wide access to CFTR gene sequencing and nasal potential difference measurements, or via CF NBS), a lack of uniform definitions of specific items (FEV_1 has been recorded as the last, the best, the mean or the average of the best value for each quarter of the year; normal FEV_1 has been defined as ≥ 80% or ≥ 90% of the predicted value in different registries) or of clinical conditions (hepatopathy, CF-related diabetes, pulmonary exacerbation), differences in age stratification (in the UK, adults are defined as patients ≥ 16 years old), inclusion or exclusion of lung transplanted patients ('another disease'), wide heterogeneity of CFTR mutations throughout the world, etc. There is indeed an obvious need for standardization in data collection if we are to compare different registries meaningfully. The ever present need to 'always try to do better' that animates so many clinicians and paramedics involved in caring for CF patients has led to the development of several QI initiatives. The latter have tended to improve key indices concerning either nutrition or respiratory function, but can also have other objectives such as a greater involvement of patients as partners in care, by sending them for example a copy of their own medical records (Treacy *et al.*, 2008). Guidelines and evidence-based medicine provide the directions in which changes for QI should be made. Various strategies can be put into place as part of these QI initiatives (Quinton, 2004; VandenBranden, 2004; Schechter, 2004; Quinton *et al.*, 2007; Britton *et al.*, 2008; Schechter *et al.*, 2010; Kraynack *et al.*, 2009; Quon *et al.*, 2011). They all rely on adequate infrastructures, the acknowledgement that changes are needed, relevant and quantifiable objectives identified on the basis of the centre's known clinical outcomes, the deployment of the necessary means and an objective evaluation of the various steps undertaken. Taking into consideration identified obstacles to optimal treatment (Zemanick *et al.*, 2010), trends of medication use over time (Konstan *et al.*, 2010), and the considerable differences in treatment practices (Borsje *et al.*, 2000) or in clinical approach between specialized CF centres (Kraynack *et al.*, 2011) could nurture reflection and help to identify and better discern the objectives and means to be put into place.

5.3 Tools and challenges

The range of responsibilities of a team dedicated to CF patients is vast, in keeping with the complexity of this chronic disease. Close and comprehensive follow-up enables an early start of an efficient symptomatic treatment. Guidelines and specific databases belong to

those tools that are essential to the clinicians. The importance of the latter can not be overemphasized (Kerem *et al.*, 2005; Quinton *et al.*, 2007; Leal *et al.*, 2007; Tiddens, 2009).

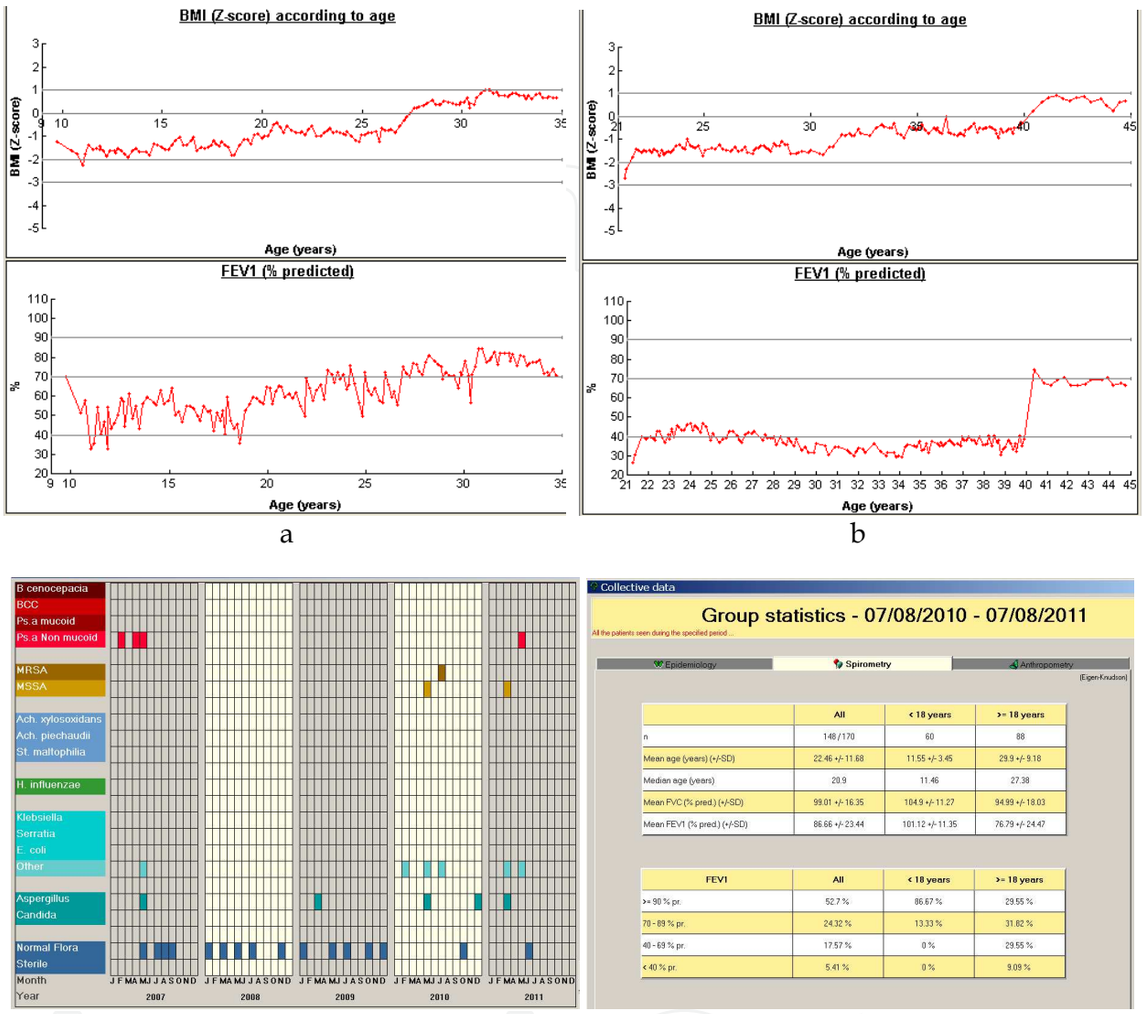


Fig. 3. Specific database provide instant access to critical information at the individual level and at the level of the clinic as a whole. *a*. Current treatment modalities occasionally lead to sustained very long-term improvement of both FEV_1 and BMI. *b*. They can also allow prolonged survival in stable conditions despite severe pulmonary lesions (this patient eventually benefited from a lung transplant following recurrent life-threatening haemoptysis). *c*: This screen summarize bacteriological findings of a given patient over 5 years, also allowing to determine at a glance the state of *Pseudomonas aeruginosa* infection according to a meaningful classification (Lee *et al.*, 2003). *d*: Instant access to key parameters at the scale of the whole clinic.

In the setting of the clinic, visualizing with a simple click trends of essential parameters such as FEV_1 or BMI can help the patient to fully understand the need for treatment modifications.

Regularly updated guidelines and in-depth reviews are essential resources. They cover most areas including standards of care (Kerem *et al.*, 2005), diagnosis (Farrell *et al.*, 2008), adult management (Yankaskas *et al.*, 2004), care of infants diagnosed by CF NBS (Accurso *et al.*, 2009; Sermet-Gaudelus *et al.*, 2010), nutrition (Sinaasappel *et al.*, 2002; CF Trust, 2002; Stallings *et al.*, 2008), antibiotic therapy (CF Trust, 2009), respiratory infections (Ramsey *et al.*, 2003), by *Pseudomonas aeruginosa* in particular (Döring *et al.*, 2000; Saiman *et al.*, 2003; Döring *et al.*, 2004; CF Trust , 2004; Hoiby *et al.*, 2005), microbiology laboratory standards (CF Trust 2010), pregnancy management (Edenborough *et al.*, 2008; Lau *et al.*, 2010) or complications such as Allergic BronchoPulmonary Aspergillosis (ABPA) (Stevens *et al.*, 2003), diabetes (Moran *et al.*, 2010), pneumothorax or haemoptysis (Flume *et al.*, 2010).

5.3.1 Challenge 1: Postpone chronic colonisation by *Pseudomonas aeruginosa*

The reasons for which PA has a predilection for the lungs of CF patients are still unclear (Gibson *et al.*, 2003). Its presence can often be detected early, at times within the first few months of life, even in the absence of any symptom. It will usually be isolated within the first 3 years (Burns *et al.*, 2001; Dakin *et al.*, 2002; West *et al.*, 2002; Hilliard *et al.*, 2007; Sly *et al.*, 2009; Stafler *et al.*, 2011). A prospective study has indicated that 90% of CF children aged 4 years and above presented at least 1 positive culture for PA (Li *et al.*, 2005). The early isolates of PA are generally non-mucoid and antibiotic susceptible. However, PA tends to colonise the airways of CF patients in a chronic, irreversible, fashion often associated to a change to a mucoid phenotype. At this stage, pulmonary function usually worsens and clinical symptoms become evident. Early detection of PA is crucial as there is a window of opportunity for effective eradication at this stage (Koch, 2002; Li *et al.*, 2005).

Chronic PA colonisation is associated with a lower FEV_1 in childhood (Kerem *et al.*, 1990), an accelerated rate of FEV_1 decline (Pamukcu *et al.*, 1995; Kosorok *et al.*, 2001; Emerson *et al.*, 2002), a shorter median life expectancy (CFF Registry, 1996; Emerson *et al.*, 2002) and much higher treatment costs (Baumann *et al.*, 2003). Preventing this colonisation is considered the most important challenge for the CF clinician, as it frequently determines the patient's future quality of life and long-term survival (CF Trust 2002; Koch, 2002). The current approach relies on two strategies (Frederiksen *et al.*, 1999): i) paying attention to segregate patients on bacteriological grounds in order to limit the risk of cross-infections (West *et al.*, 2002; Conway *et al.*, 2008), ii) early antibiotic treatment at the time of the first PA colonisation (Littlewood *et al.*, 1985; Valerius *et al.*, 1991; Frederiksen *et al.*, 1997; Lee *et al.*, 2004). A number of regimens have been evaluated (Stuart *et al.*, 2010) but there is no consensus about the best combination, dosage, or length of treatment course. An initial treatment protocol combining nebulised colistin with oral ciprofloxacin for 3 months is widely used. Combining this approach with intravenous antibiotics has also been reported, with a 5-year failure rate of only 12% (Douglas *et al.*, 2009). A prerequisite for this approach is a close bacteriological follow-up, with a time lapse between visits that cannot exceed 3 months. This interval is shorter (up to monthly) in many centres. An aggressive approach based on repeated BAL has not proven useful (Wainwright *et al.*, 2011). The 20% failure rate of the more commonly used approach (Frederiksen *et al.*, 1997; Lee *et al.*, 2004; Tacetti *et al.*, 2004) underlines the necessity to develop other intervention modalities.

It is paradoxical that prophylactic antibiotic therapy directed against PA has only been the subject of 1 retrospective study (Heinzl *et al.*, 2002) while prophylaxis against *Staphylococcus aureus*, whose threat is yet much easier to manage, has been investigated and hotly debated. The Austrian study was in fact very encouraging but the same group reported that long-term gentamicin inhalation in CF children was associated with reversible raised urinary N-acetyl-beta-D-glucosaminidase (NAG) activity, consistent with subtle subclinical renal tubular damage (Ring *et al.*, 1998). Tobramycin and amikacin however have lower renal toxicity than gentamicin and long-term use of high doses of inhaled tobramycin (TOBI) are now considered safe (Prober *et al.*, 2000). There are several theoretical arguments that make long-term inhaled prophylactic antibiotic therapy attractive (Lebecque *et al.*, 2008). Based on the use of low doses of Tobramycin or Amikacin, this approach has progressively been put into place at our centre over the past 20 years, and has probably contributed, along with other factors, to a distinctly low rate of chronic colonisation rate by PA in patients under 18 years of age (<5% for more than 10 years, according to Lee's definition) (Lee *et al.*, 2003).

5.3.2 Challenge 2: Maintain adequate nutrition

The poorer prognosis associated with being relatively underweight has long been recognized in CF children (Kraemer *et al.*, 1978). An overall parallelism exists between respiratory function and nutritional status progress over time (Zemel *et al.*, 2000; Steinkamp *et al.*, 2002; Konstan *et al.*, 2003; Milla, 2004; Pedreira *et al.*, 2005). While severe pulmonary disease seriously compromises the maintenance of a satisfactory nutritional status, proof of the opposite has also been demonstrated: maintaining a good nutritional status promotes respiratory function preservation. Evidence of the possible influence of maintaining a good nutritional status was first suggested by a comparison of the CF centres of Boston and Toronto (Corey *et al.*, 1988). In Toronto, CF patients had better respiratory function and were better fed, and the main difference in management appeared to be the lack of fat restriction in the Canadian hospital. Maintaining an adequate nutritional status has become a priority of CF care.

5.3.3 Many other challenges…

Early detection and adequate management of poor clinical course find their place here, along with appropriate management of complications, particularly those linked to an accelerated rate of FEV_1 decline as in ABPA (Kraemer *et al.*, 2006), diabetes (Milla *et al.*, 2000), gastro-esophageal reflux (Levy *et al.*, 1986), colonisation by *Burkolderia cenocepacia* (Ledson *et al.*, 2002; Courtney *et al.*, 2004) non-mucoid strains in particular (Zlosnik *et al.*, 2011), or by MRSA (Dasenbrook *et al.*, 2008). In the same vein it is worth insisting on the vulnerable period spanning from pre-adolescence to adolescence (Konstan *et al.*, 2007). The rate of FEV_1 decline is faster at that time, and the various reasons for which this is considered a risk period should especially mobilise the attention and energy of the care management teams (Segal, 2008). In the context of CF, ABPA diagnosis is often delicate, (de Almeida *et al.*, 2006; Thia *et al.*, 2009) as many features overlap with those of infective exacerbations in CF, but it is important: failing to recognize ABPA can lead to irreversible lesions, whereas overtreatment exposes the patient to deleterious side-effects of systemic corticosteroids.

The prevention of cross-infections is a daily preoccupation that predetermines the detailed organisation of the CF centres. One of the major challenges is to limit *Burkholderia cepacia complex* (BCC) infections. The prognostic significance of colonisation by *B. cenocepacia* is particularly dreaded, as its presence is associated to an accelerated rate of FEV_1 decline and a clinical picture that is often fatal (*cepacia* syndrome) (Isles *et al.*, 1984) and can affect patients up to then in very good health. In addition, *B. cenocepacia* is a cause for increased mortality following lung transplantation (Aris *et al.*, 2001; Boussaud *et al.*, 2008). Other germs of the BCC group such as B. *multivorans* or B. *dolosa* have a less gloomy effect on prognosis but have exceptionally also been associated to the occurrence of a *cepacia* syndrome (Zahariadis *et al.*, 2003; Blackburn *et al.*, 2004; Kalish *et al.*, 2006).

Several other essential factors are involved in global care management. There is no equivalent long-term illness to CF today in terms of the heavy burden of its symptomatic treatment. In a recent US study, adult patients - of whom only half had performed airway clearance - reported a mean time spent on treatment activities of 108 minutes per day (Sawicki *et al.*, 2009). Though very difficult to assess (Modi *et al.*, 2006), treatment adherence is undoubtedly a key issue in CF (Eakin et al, 2011) and requires permanent assessment and support (Pendleton, 2000). There is no magic recipe, but this subject has to be bridged at every consultation, in an open manner, with empathy and as part of a 'therapeutic alliance' (Lask, 1994; Cohen-Cymberknoh *et al.*, 2011). Another objective is to be able to propose psychological and/or social support in response to specific situations, either linked to the disease or impacting on treatment in real life.

5.3.4 Flags or indications for treatment intensification

Several clinical or biological markers have been associated with poorer outcome. Their main interest is that they can point to the need for reconsidering and optimizing symptomatic treatment. Some of these associations may appear simple common sense but the reality is often more complex: in-depth statistical analysis can reveal multiple independent factors and it is important to bear in mind that a statistically significant association is not equivalent to the demonstration of a causality link. For instance, a recent Canadian study showed that adult patients with CF who experienced at least 3 pulmonary exacerbations per year over a 3-year follow-up period were clearly high-risk patients, who warranted timely consideration for lung transplantation (de Boer *et al.*, 2011). However, such patients were more likely to be female and diabetic, two risk factors linked to poorer outcome. In addition, while frequent pulmonary exacerbations may predispose a patient to lung transplantation, patients on the list for lung transplants may be more aggressively treated, thereby appearing to have more exacerbations. Raised serum IgG levels (Wallwork *et al.*, 1974; Matthews *et al.*, 1980; Wheeler *et al.*, 1984; Proesmans *et al.*, 2011) and the presence of localized auscultation anomalies (Konstan *et al.*, 2007) also belong to the list of 'flags' for treatment intensification.

6. Environmental factors

6.1 Socioeconomic status

As for all chronic diseases, CF prognosis is more sombre in patients of poor socio-economic status (SES). In 1986, there were 113 deaths registered of CF patients in the UK. Median age of death was 17 years overall, but it was above 20 for patients whose parents had a non-

manual job whereas it was below 10 for the others (Britton *et al.*, 1989). In a study of CF patients in the United States, the adjusted risk of death for indigent patients who qualified for Medicaid was 3.65 times higher than for those not receiving Medicaid. The average FEV_1 of Medicaid patients was less by 9.2% predicted than that of non-Medicaid patients, a difference which slightly increased by 0.54% per year of age (Schechter *et al.*, 1998). In a CFF study of 23,817 white patients diagnosed before the age of 18 years, a strong association was found between the median household income and the mortality rate. At 6 years of age, the absolute differences in mean FEV_1 and weight percentiles from the lowest to the highest income category were already very significant and they persisted into adulthood (O'Connor *et al.*, 2003). Furthermore, this study also clearly showed that the relationship between outcome and SES was incremental, rather than dichotomous and only affecting the most indigent. Though access to health insurance is much better in many European countries than in the US, the overall costs of CF treatment and follow-up are so high that patients with low SES are particularly at risk of inadequate resources and poor adherence. A better understanding of SES-related disparities and its causes is necessary to clarify the respective roles of a link between poverty and other environmental factors, health behaviours and limited access to optimal care. Low SES has recently been associated with lower health-related quality of life in CF patients and parents. After accounting for the effects of disease severity and SES, a negative effect of membership to a racial or ethnic minority on social and emotional functioning was also evident (Quittner *et al.*, 2010).

6.2 Exposure to smoking

Exposure to passive or active smoking has deleterious effects in healthy subjects and in patients with respiratory diseases. An accelerated rate of FEV_1 decline with age is documented in healthy adult smokers. Functional repercussions of passive smoking were assessed in a large study concerning 812 CF patients (Collaco *et al.*, 2008). Over a fifth of them (188, i.e. 23%) were exposed to passive smoking. At the age of 20, the mean FEV_1 of exposed patients was, independently of SES, 8% lower than that of non-exposed patients. This effect was even more pronounced in patients who were not homozygous for the *F508del* mutation, and was twice higher in patients who were also carriers of an unfavourable genotype with respect to the $TGF\beta_1$ modifier gene. Deleterious effects of active smoking should a priori be more severe but have not been investigated specifically in the context of CF. Exposure to smoking is a major environmental factor and screening for it should become routine practice in CF care as several pharmacological and non-pharmacological smoking cessation aids have proven their efficacy, the best results being obtained by combining modalities and tailoring therapy (Laniado-Laborin, 2010).

6.3 Other environmental factors

In a CF registry study, exposure to ozone and annual average exposure to particulate air pollution were both associated with an increased likelihood of pulmonary exacerbations. Exposure to particulate matter with an aerodynamic diameter of 2.5 μm or less was also associated with a decline in lung function (Goss *et al.*, 2004). Though environmental factors are not considered the main pathogenic factors in ABPA, experts have suggested that it may be worth examining the patient's environment in refractory cases (Stevens *et al.*, 2003). Altough the mechanisms are unclear, recent published evidence supports a link between

climatic conditions (ambient temperature) and lung function in CF (Collaco et al., 2011). According to the authors, a hypothetical 18 year old white male with CF (Height: 175cm) with an FEV1 of 73.5% percent living in a cold climate would be expected to have an FEV1 of 66.1% had he resided in a 17 degree (Celsius) warmer climate.

Recreational use of marijuana is common in many countries. In a study of 173 adults, this drug was used by 20% of patients (Stern *et al.*, 1987). In the general population, such use has been associated with pulmonary manifestations (bronchitis, pneumothorax, apical bullae) (Tetrault *et al.*, 2007; Han *et al.*, 2010; Gao *et al.*, 2010) that could overlap clinical and radiological signs of CF, making it challenging to suspect them. Further studies seem warranted in this field.

7. Genetic factors

7.1 CFTR genotype

Depending on their repercussions on the synthesis of the CF Transmembrane conductance Regulator (CFTR) protein, mutations of the CF gene are usually classified into 5 groups (Welsh *et al.*, 1993). Mutations of classes I, II and III lead to the total or near-total absence of functional CFTR protein, whereas those of classes IV or V are associated to residual function of the CFTR protein, corresponding to a small % of normal activity. Pancreatic insufficiency is present in over 95% of patients carrying 2 class I, II or III mutations, whereas it is only rarely observed in patients carrying at least 1 class IV or V mutation (CF genotype-phenotype consortium, 1993; Koch *et al.*, 2001). Diabetes and severe hepatic involvement are 2 important CF complications that usually only occur in patients with exocrine pancreatic insufficiency. A recent study of 505 patients registered in Israel's databases did not observe a single case amongst 139 pancreatic sufficient patients (Augarten *et al.*, 2008). The relationship between CFTR genotype and the severity of the pulmonary involvement is much looser. On the whole, the genotype of patients carrying 2 mutations of class I, II or III is still considered high risk and is associated to earlier mortality than genotypes including at least 1 mutation of class IV or V ('low risk' genotypes) (Mc Kone *et al.*, 2006). Similarly, although their phenotype can be extremely variable, an overall more favourable prognosis has been associated to some mutations of class IV or V. Amongst the latter, there are mutations A455E (Gan *et al.*, 1995), 3849 +10kbC->T (Highsmith *et al.*, 1994; Duguépéroux *et al.*, 2005), 2789+5G->A (Duguépéroux *et al.*, 2005), D1152H (Musaffi *et al.*, 2006; Burgel *et al.*, 2010), R334W (Antinolo *et al.*, 1997), 3272-26A->G (Amaral *et al.*, 2001). The penetrance of the R117H mutation has convincingly been shown to be very low (Thauvin-Robinet *et al.*, 2009) and is modulated by the polypyrimidine variant in the intron 8 acceptor splice site (T7 or T5) in cis with R117H. However, FEV_1 at a given age can be extremely variable in patients sharing a same CFTR genotype and this is observed in patients homozygous for the *F508del* mutation as well as in patients carrying a "milder" genotype (Gan *et al.*, 1995). In practice, the link between CFTR genotype and severity of lung disease is not tight, making CFTR genotype most often of little value in predicting the prognosis at the individual level.

7.2 Modifier genes

Every clinician has in mind extreme examples of the heterogeneity of functional respiratory progress in CF patients, including amongst those that are homozygous for the *F508del* mutation. Though poorly compliant, chronically colonized by PA since adolescence and

diabetic for 10 years, one 40 year-old patient keeps his FEV_1 above 80% of the predicted value whereas a young lady, with an optimal follow-up since birth and only occasionally *Aspergillus fumigatus* in sputum experiences a rapid functional decline from age 12 and requires a lung transplantation at 20. Environmental factors may play a role but admittedly such patients have to be either 'protected' for one or 'condemned' for the other, by particular allele combinations of modifier genes probably modulating the immune and inflammatory response in the lungs.

Family-based studies and especially comparisons of monozygous and dizygous twin pairs have proven fruitful in identifying and assessing the contribution of modifier genes in CF disease. Many studies in this field have yielded conflicting results and it is now realized that the repeatability of SNP–phenotype association studies with positive findings was low when less than 500 participants were included (Boyle, 2007). More recent studies are more powerful and use more sophisticated tools including whole-genome methods. Quite convincing evidence is now available that variants of at least 3 genes can be associated with lung disease severity in CF (Cutting, 2010): i) *MBL2*-deficient (10q) genotype: in normal subjects, mannose binding lectin (MBL) aids the phagocytosis of bacteria and deficiency in MBL seems to predispose to early infection with PA in CF ii) Increased *TGFß1* (19q) expression (Drumm *et al.*, 2005): this gene, which also modulates the risk for asthma and chronic obstructive pulmonary disease, encodes a cytokine playing a role in the regulation of inflammation and tissue remodelling iii) Increased *EDNRA* (4q) expression: Endothelin is a proinflammatory peptide and smooth muscle agonist which is increased in CF airways. Deleterious effects could be related to an impact on smooth muscle tone in the airways and/or vasculature (Darrah *et al.*, 2010). More recently, two loci causing variations in CF lung disease severity have been identified on chromosomes 11p and 20q respectively (Wright *et al.*, 2011). Variation in *TCF7L2* (10q) was reported to increase the risk of diabetes about threefold and even more in patients without previous treatment with systemic steroids (Blackman *et al.*, 2009). Variants of other genes are suspected to increase the risk of liver cirrhosis (Bartlett *et al.*, 2009) or meconium ileus. Further progress in the identification of modifier genes should result in an increased ability to predict severity of CF disease, and hopefully be accompanied by new perspectives for therapeutic intervention.

8. Conclusions

For patients, their relatives and also their carers, facing CF is often compared to running a long-distance race. It is also a team race, where no-one can let go. In terms of life expectancy, prognosis of the disease has been improving continuously since 40 years. However, it is almost always impossible to predict CF prognosis at the individual level. The quality of an early global care management is an essential prognostic determinant. Further progress in symptomatic CF treatment remains necessary, especially towards better prevention of respiratory involvement in early-diagnosed newborns and in the field of immunosuppression in lung transplantation. The discovery of a cure for the respiratory disease in CF would be a real breakthrough. A pharmacological approach tailored to the class mutations of the CFTR gene appears currently the most encouraging route in this direction.

Meanwhile, the essence of the carer's role today remains founded on these two maxims: 'Do not abandon the marathon' and 'Always try to do better'.

9. References

Abbott, J., Hart, A., Havermans T. *et al.* (2011). Measuring health-related quality of life in clinical trials in cystic fibrosis. *J Cyst Fibros*. Vol. 10, Suppl 2, pp 82-85.

Accurso, F., Sontag M. & Wagener J. (2005). Complications associated with symptomatic diagnosis in infants with cystic fibrosis. *J Pediatr.* Vol. 147, Suppl. 3, pp 37-41.

Accurso F., Rowe S., Clancy J. *et al.* (2010). Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med*. Vol. 363, No 21, pp 1191-2003.

Amaral, M., Pacheco P, Beck S. *et al.* (2001). Cystic fibrosis patients with the 3272-26A>G splicing mutation have milder disease than F508del homozygotes: a large European study. *J Med Genet*. Vol. 38, No 11, pp 777-783.

Amaral, M. (2011). Targeting CFTR: how to treat cystic fibrosis by CFTR-repairing therapies. *Curr Drug Targets* Vol. 12, No 5, pp 683-693.

Antinolo G., Borrego S, Gili M. *et al.* (1997). Genotype-phenotype relationship in 12 patients carrying cystic fibrosis mutation R334W. *J Med Genet.* Vol. 34, No 2, pp 89-91.

Aris R., Routh J, LiPuma J. *et al.* (2001). Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type. *Am J Respir Crit Care Med.* Vol. 164, No 11, pp 2102-2106.

Augarten A., Ben Tov A., Madgar I. *et al.* (2008). The changing face of the exocrine pancreas in cystic fibrosis: the correlation between pancreatic status, pancreatitis and cystic fibrosis genotype. *Eur J Gastroenterol Hepatol*. Vol. 20, No 3, pp 164-168.

Balaguer A. & González de Dios J. (2008). Home intravenous antibiotics for cystic fibrosis. *Cochrane Database Syst Rev.* CD001917.

Bartlett J., Friedman K, Ling S. *et al.* (2009). Genetic modifiers of liver disease in cystic fibrosis. *JAMA*. Vol. 302, No 10, pp 1076-1083.

Bauernfeind A., Marks M. & Strandvik B. (1996). Cystic fibrosis pulmonary infections: lessons from around the world. Birkhauser Verlag AG, Basel. ISBN-13: 978-3764350277

Baumann U., Stocklossa C., Greiner W. *et al.* (2003). Cost of care and clinical condition in paediatric cystic fibrosis patients. *J Cyst Fibros.* Vol. 2, No 2, pp 84-90.

Baussano I., Tardivo I., Belleza-Fontana R. *et al.* (2006). Neonatal screening for cystic fibrosis does not affect time to first infection with Pseudomonas aeruginosa. *Pediatrics*. Vol. 118, No 3, pp 888-895.

Berge M, Wiel E, Tiddens H. *et al.* (2003). DNase in stable cystic fibrosis infants: a pilot study. *J Cyst Fibros*. Vol. 2, No 4, pp 183-188.

Blackburn L., Brownlee K., Conway S. *et al.* (2004). 'Cepacia syndrome' with Burkholderia multivorans, 9 years after initial colonization. *J Cyst Fibros.* Vol. 3, No 2, pp 133-134.

Blackman S., Hsu S, Ritter S *et al.* (2009). A susceptibility gene for type 2 diabetes confers substantial risk for diabetes complicating cystic fibrosis. *Diabetologia* Vol. 52, No 9, pp 1858-1865.

Borowitz D., Robinson K., Rosenfeld M. *et al.* (2009). Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr.* Vol. 155, Suppl. 6, pp 73-93.

Boussaud V., Guillemain R, Grenet D *et al.* (2008). Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with Burkholderia cepacia complex: results from two French centres. *Thorax*. Vol. 63, No 8, pp 732-737.

Borsje P, deJongste J, Mouton J *et al.* (2000). Aerosol therapy in cystic fibrosis: a survey of 54 CF centers. *Pediatr Pulmonol*. Vol. 30, No 5, pp 368-376.

Boyle M. (2007). Strategies for identifying modifier genes in cystic fibrosis. *Proc Am Thorac Soc*. Vol 4, No 1, pp 52-57.

Briggs T., Bryant M. & Smyth R. (2006). Controlled clinical trials in cystic fibrosis--are we doing better? *J Cyst Fibros*. Vol. 5, No 1, pp 3-8.

Britton J. (1989). Effects of social class, sex, and region of residence on age at death from cystic fibrosis. *BMJ*. Vol. 298, pp 483-7.

Britton L., Thrasher S. & Guttierez H. (2008). Creating a culture of improvement: experience of a pediatric cystic fibrosis center. *J Nurs Care Qual*. Vol. 23, No 2, pp 115-120.

Burgel P, Fajac I, Hubert D. *et al.* (2010). Non-classic cystic fibrosis associated with D1152H CFTR mutation. *Clin Genet*. Vol. 77, No 4, pp 355-64.

Burns J., Gibson R, McNamara S. *et al.* (2001). Longitudinal assessment of Pseudomonas aeruginosa in young children with cystic fibrosis. *J Infect Dis*. Vol. 183, No 3, pp 444-452.

Bush A. & Götz M. (2006). Cystic fibrosis. *Eur Respir Mon*. Vol. 37, pp 234–290.

Buzzetti R., Salvatore D., Baldo E. *et al.* (2009). An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. *J Cyst Fibros*. Vol. 8, No 4, pp 229-237.

Canadian CF Registry (2008), Available from http://www.fibrosekystique.ca/en/index.php

Castellani C., Southern K, Browlee K. *et al.* (2009). European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros*. Vol. 8, No 3, pp 153-173.

CF Genotype-Phenotype Consortium (1993). Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med.* Vol. 329, No 18, pp 1308-1313.

CFF Registry (1996), Cystic Fibrosis Foundation Patient Registry 1996 Annual Data Report. Bethesda, Maryland

CFF Registry (2000), Cystic Fibrosis Foundation Patient Registry 2000 Annual Data Report. Bethesda, Maryland

CFF Registry (2007), Cystic Fibrosis Foundation Patient Registry 2007 Annual Data Report. Bethesda, Maryland

CFF Registry (2008), Cystic Fibrosis Foundation Patient Registry 2008 Annual Data Report. Bethesda, Maryland Available from http://www.cff.org/research/ClinicalResearch/PatientRegistryRport/

CF Trust (2002). Nutritional management in cystic fibrosis.

CF Trust (2004). Pseudomonas aeruginosa infection in people with Cystic Fibrosis. Suggestions for Prevention and Infection Control.

CF Trust (2009). Antibiotic Treatment for Cystic Fibrosis.

CF Trust (2010). Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis.

Cheng K., Smyth R, Motley J. *et al.* (2000). Randomized controlled trials in cystic fibrosis (1966-1997) categorized by time, design, and intervention. *Pediatr Pulmonol*. Vol. 29, No 1, pp 1-7.

Cohen-Cymberknoh M., Shoseyov D. & Kerem E. (2011). Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med*. Vol. 183, no 11, pp 1463-1471.

Collaco J., Vanscoy L., Bremer L. *et al.* (2008). Interactions between secondhand smoke and genes that affect cystic fibrosis lung disease. *JAMA.* Vol. 299, No 4, pp 417-424.

Collaco J., McGready J., Green D. *et al*. (2011). Effect of temperature on cystic fibrosis lung disease and infections: a replicated cohort study. *PLoS One*. Vol. 6, No 11, e27784.

Collins C., MacDonald-Wicks L., Rowe S. *et al.* (1999). Normal growth in cystic fibrosis associated with a specialised centre. *Arch Dis Child*. Vol. 81, No 3, pp 241-246.

Colombo C. & Littlewood J. (2011). The implementation of standards of care in Europe: state of the art. *J Cyst Fibros*. Vol. 10, Suppl. 2, pp 7-15.

Comeau A., Accurso F., White T. *et al.* (2007). Guidelines for implementation of cystic fibrosis newborn screening programs: Cystic Fibrosis Foundation workshop report. *Pediatrics*. Vol. 119, No 2, pp e495-518.

Conway S. (2008). Segregation is good for patients with cystic fibrosis. *J R Soc Med*. Vol. 101, Suppl. 1, pp 31-35.

Corey M., Mc Laughlin F, Williams M. *et al.* A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol*. Vol. 41, No 6, pp 583-591.

Courtney J., Dunbar K, Mc Dowell A. *et al.* (2004). Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *J Cyst Fibros*. Vol. 3, No 2, pp 93-98.

Crozier D. (1974). Cystic fibrosis: a not-so-fatal disease. *Pediatr Clin North Am*. Vol. 21, No 4, pp 935-950.

Cutting G. (2010). Modifier genes in Mendelian disorders: the example of cystic fibrosis. *Ann N Y Acad Sci*. No. 1214, pp 57-69.

Dakin C., Numa A, Wang H. *et al.* (2002). Inflammation, infection, and pulmonary function in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med.* Vol. 165, no 7, pp 904-910.

Darrah R., Mc Kone E., O'Connor C. *et al.* (2010). EDNRA variants associate with smooth muscle mRNA levels, cell proliferation rates, and cystic fibrosis pulmonary disease severity. *Physiol Genomics*. Vol. 41, No 1, pp 71-77.

Dasenbrook E., Merlo C., Diener-West *et al.* (2008). Persistent methicillin-resistant Staphylococcus aureus and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 178, No 8, pp 814-821.

David T. (2001). Elusiveness of cystic-fibrosis treatment. *Lancet.* Vol. 357, p 633.

Davis P. (2006). Cystic fibrosis since 1938. *Am J Respir Crit Care Med*. Vol. 173, No 5, pp 475-482.

Davis S., Brody A., Emond M. *et al.* (2007). Endpoints for clinical trials in young children with cystic fibrosis. *Proc Am Thorac Soc*. Vol 4, No 4, pp 418-430.

de Almeida M., Bussamra M. & Rodrigues J. (2006). Allergic bronchopulmonary aspergillosis in paediatric cystic fibrosis patients. *Paediatr Respir Rev*. Vol. 7, No 1, pp 67-72.

De Boeck K., Vermeulen F., Wanyama S. *et al.* (2011). Inhaled corticosteroids and lower lung function decline in young children with cystic fibrosis. *Eur Respir J.* Vol. 37, No 5, pp 1091-1095.

de Boer K., Vandemheen K., Tullis E. *et al.* (2011). Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax* Vol. 66, No 8, pp 680-685.

Dodge J., Lewis P., Stanton M *et al.* (2007). Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J*. Vol. 29, No 3, pp 522-526.

Döring G., Conway S., Heijerman H. *et al.* (2000). Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. *Eur Respir J*. Vol. 16, No 4, pp 749-767.

Döring G., Hoiby N & Consensus study group. (2004). Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. *J Cyst Fibros*. Vol. 3, no 2, pp 67-91.

Douglas T., Brennan S., Gard S. *et al.* (2009). Acquisition and eradication of P. aeruginosa in young children with cystic fibrosis. *Eur Respir J.* Vol. 33, no 2, pp 305-311.

Driever, M. (2002). Are evidenced-based practice and best practice the same? *West J Nurs Res*. Vol. 24, No 5, pp 591-597.

Drumm M., Konstan M., Schluchter M. *et al.* (2005). Genetic modifiers of lung disease in cystic fibrosis. N Engl J Med. Vol. 353, No 14, pp 1443-1453.

Duguépéroux I. & De Braekeleer M. (2005). The CFTR 3849+10kbC->T and 2789+5G->A alleles are associated with a mild CF phenotype. *Eur Respir J*. Vol. 25, No 3, pp 468-473.

Eakin M., Bilderback A., Boyle M. *et al.* (2011). Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *J Cyst Fibros*. Vol. 10, No 4, pp 258-64. ISSN 1569-1993

Edenborough F., Borgo G., Knoop C. eta l. (2008). Guidelines for the management of pregnancy in women with cystic fibrosis. *J Cyst Fibros*. Vol. 7, Suppl. 1, pp 2-32.

Elborn J., Shale D. & Britton J. (1991). Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* Vol. 46, No 12, pp 881-885.

Emerson J., Rosenfeld M., McNamara S. *et al.* (2002). Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol*. Vol. 34, No 2, pp 91-100.

Farrell P., Li Z., Kosorok M *et al.* (2003). Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med*. Vol. 168, No 9, pp 1100-1108.

Farrell P., Rosenstein B., White T. *et al.* (2008). Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. Vol. 153, No 2, pp 4-14.

Ferris T. & Torchiana D. Public release of clinical outcomes data – Online CABG report cards. *N Engl J Med* 363: 1593-5.

Flume P., Mogayzel P., Robinson K. *et al.* (2010). Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. *Am J Respir Crit Care Med*. Vol. 182, No 3, pp 298-306.

Frederiksen B., Koch C. & Hoiby N. (1997). Antibiotic treatment at time of initial colonisation with Pseudomonas aeruginosa postpones chronic infection and prevents deterioration in pulmonary function in patients with cystic fibrosis. *Pediatr Pulmonol*. Vol. 23, No 5, pp 330–335.

Frederiksen B., Koch C. & Hoiby N. (1999) Changing epidemiology of Pseudomonas aeruginosa infection in Danish cystic fibrosis patients (1974-1995). *Pediatr Pulmonol*. Vol. 28, No 3, pp 159-166.

Gan K., Veeze H., van den Ouweland *et al.* (1995). A cystic fibrosis mutation associated with mild lung disease. *N Engl J Med*. Vol. 333, No 2, pp 95-99.

Gao Z., Wood-Baker R., Harle R. *et al.* (2010). "Bong lung" in cystic fibrosis: a case report. *J Med Case Reports*. Vol. 4, p 371.

Gibson R., Burns J. & Ramsey B. (2003). Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 168, No 8, pp 918-951.

Goss C., Newsom S., Schildcrout J. *et al.* (2004). Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am J Respir Crit Care Med.* Vol. 169, No 7, pp 816-821.

Han B., Gfroerer J. & Colliver J. (2010). Associations between duration of illicit drug use and health conditions: results from the 2005-2007 national surveys on drug use and health. *Ann Epidemiol*. Vol. 20, No 4, pp 289-297.

Hankinson J., Odencrantz J., Fedan K. (1999). Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* Vol. 159, No 1, pp 79–87.

Hansen C., Pressler T., Koch C. *et al.* (2005). Long-term azitromycin treatment of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection; an observational cohort study. *J Cyst Fibros*. Vol. 4, No 1, pp 35-40.

Heinzl B., Eber E, Oberwaldner B. *et al.* (2002). Effects of inhaled gentamicin prophylaxis on acquisition of Pseudomonas aeruginosa in children with cystic fibrosis: a pilot study. *Pediatr Pulmonol*. Vol. 33, No 1, pp 32-37.

Highsmith W., Burch L, Zhou Z. *et al.* (1994). A novel mutation in the cystic fibrosis gene in patients with pulmonary disease but normal sweat chloride concentrations. *N Engl J Med*. Vol. 331, No 15, pp 974-980.

Hill D., Martin A., Davidson G. *et al.* (1985). Survival of cystic fibrosis patients in South Australia. Evidence that cystic fibrosis centre care leads to better survival. *Med J Aust*. Vol. 143, No 6, pp 230-232.

Hilliard T., Sukhani S. Francis J. *et al.* (2007). Bronchoscopy following diagnosis with cystic fibrosis. *Arch Dis Child*. Vol. 92, No 10, pp 898-899.

Høiby N., Frederiksen B. & Pressler T. (2005). Eradication of early Pseudomonas aeruginosa infection. *J Cyst Fibros*. Vol. 4, Suppl. 2, pp 49-54.

Isles, A., McLusky I., Corey M. *et al.* (1984). Pseudomonas cepacia infection in cystic fibrosis: an emerging problem. *J Pediatr*. Vol. 104, No 2, pp 206-210.

Jackson A., Daly L., Kelleher C. *et al.* (2011). Validation and use of a parametric model for projecting cystic fibrosis survivorship beyond observed data: a birth cohort analysis. *Thorax*. Vol. 66, No 8, pp 674-679.

Johansen H., Nir M., Hoiby N. *et al.* (1991). Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet*. Vol. 337, pp 631-634.

Johnson C., Butler S., Konstan M. *et al.* (2003). Factors influencing outcomes in cystic fibrosis: a center-based analysis. *Chest*. Vol. 123, No 1, pp 20-27.

Kalish L., Waltz D., Dovey M. *et al.* (2006). Impact of Burkholderia dolosa on lung function and survival in cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 173, No 4, pp 421-425.

Kerem E., Corey M., Gold R. *et al.* (1990). Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonization with Pseudomonas aeruginosa. *J Pediatr*. Vol. 116, No 5, pp 714-719.

Kerem E., Corey M., Kerem B. *et al.* (1990). The relation between genotype and phenotype in cystic fibrosis--analysis of the most common mutation (delta F508). *N Engl J Med*. Vol. 323, No 22, pp 1517-1522.

Kerem E., resiman J., Corey M. *et al.* (1992). Prediction of mortality in patients with cystic fibrosis. *N Engl J Med*. Vol. 326, No 18, pp 1187-1191.

Kerem E., Conway S., Elborn S. *et al.* (2005). Consensus Committee. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros*. Vol. 4, No 1, pp 7-26.

Khan T., Wagener J., Bost T. *et al.* (1995). Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 151, No 4, pp 1075-1082.

Koch C., Cuppens H., Rainisio M. *et al.* (2001). European Epidemiologic Registry of Cystic Fibrosis (ERCF): comparison of major disease manifestations between patients with different classes of mutations. *Pediatr Pulmonol*. Vol. 31, No 1, pp 1-12.

Koch C. (2002). Early infection and progression of cystic fibrosis lung disease. *Pediatr Pulmonol*. Vol. 34, No 3, pp 232-236.

Konstan M., Byard P. Hoppel C. *et al.* (1995). Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med*. Vol. 332, No 13, pp 848-854.

Konstan M., Butler S., Whol M. *et al.* (2003). Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr.* Vol. 142, No 6, pp 624 –630.

Konstan M., Scluchter M., Xue W. *et al.* (2007). Clinical use of Ibuprofen is associated with slower FEV1 decline in children with cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 176, No 11, pp 1084-1089.

Konstan M., Morgan W., Butler S. *et al.* (2007). Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr*. Vol. 151, No 2, pp 134-139.

Konstan M., VanDevanter D., Rasouliyan L. *Et al.* (2010). Trends in the use of routine therapies in cystic fibrosis: 1995-2005. *Pediatr Pulmonol*. Vol. 45, No 12, pp 1167-1172.

Konstan M., Wagener J., Pasta D. *et al.* (2011). Clinical use of dornase alpha is associated with a slower rate of FEV1 decline in cystic fibrosis. *Pediatr Pulmonol*. Vol. 46, No 6, pp 545-553.

Kosorok M., Zeng L, West S. *et al.* (2001). Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition. *Pediatr Pulmonol*. Vol. 32, No 4, pp 277-287.

Kraemer R., Rüdeberg A., Hadorn B. *et al.* (1978). Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand*. Vol. 67, No 1, pp 33-37.

Kraemer R., Deloséa N., Ballinari P. *et al.* (2006). Effect of allergic bronchopulmonary aspergillosis on lung function in children with cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 174, No 11, pp 1211-1220.

Kraynack N. & McBride J. (2009). Improving care at cystic fibrosis centers through quality improvement. *Semin Respir Crit Care Med.* Vol. 30, No 5, pp 547-558.

Kraynack N., Gothard M., Falletta L. *et al.* (2011). Approach to treating cystic fibrosis pulmonary exacerbations varies widely across us CF care centers. *Pediatr Pulmonol*. Apr 4. doi: 10.1002/ppul.21442. [Epub ahead of print]

Lai H. & Shoff S. (2008). Classification of malnutrition in cystic fibrosis: implications for evaluating and benchmarking clinical practice performance. *Am J Clin Nutr*. Vol. 88, No 1, pp 161-166.

Laniado-Laborin R (2010). Smoking cessation intervention: an evidence-based approach. *Postgrad Med*. Vol. 122, No 2, pp 74-82.

Lask B. (1994). Non-adherence to treatment in cystic fibrosis. *J R Soc Med*. Vol. 87, Suppl. 21, pp 25-27.

Lau E., Morarty C., Ogle R. *Et al.* (2010). Pregnancy and cystic fibrosis. *Paediatr Respir Rev*. Vol. 11, No 2, pp 90-94.

Leal T., Reychler G., Mailleux P. *et al.* (2007). A specific database for providing local and national level of integration of clinical data in cystic fibrosis. *J Cyst Fibros*. Vol. 6, No 3, pp 187-193.

Lebecque P., Leal T., Zylberberg K. *et al.* (2006). Towards zero prevalence of chronic Pseudomonas aeruginosa infection in children with cystic fibrosis. *J Cyst Fibros*. Vol. 5, No 4, pp 237-244.

Lebecque P., Leonard A., De Boeck K. *et al.* (2009). Early referral to cystic fibrosis specialist centre impacts on respiratory outcome. *J Cyst Fibros*. Vol. 8, No 1, pp 26-30.

Lebecque P, De Boeck K., Wanyama S. *et al.* (2010). CF Registries – plea for annual reports focusing on patients homozygous for the F508del mutation. *J Cyst Fibros*. Vol. 9, Suppl. 1, p 114 (A).

Ledson M., Gallagher M., Jackson M. *et al.* (2002). Outcome of Burkholderia cepacia colonisation in an adult cystic fibrosis centre. *Thorax*. Vol. 57, No 2, pp 142-145.

Lee T., Brownlee K., Conway S. *et al.* (2003). Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. *J Cyst Fibros*. Vol. 2, No 1, pp 29-34.

Lee T., Brownlee K., Denton M. *et al.* (2004). Reduction in prevalence of chronic Pseudomonas aeruginosa infection at a regional pediatric cystic fibrosis center. *Pediatr Pulmonol*. Vol. 37, No 2, pp 104-110.

Levy L., Durie P., Pencharz P. *et al.* (1986). Prognostic factors associated with patient survival during nutritional rehabilitation in malnourished children and adolescents with cystic fibrosis. *J Pediatr Gastroenterol Nutr* Vol. 5, No 1, pp 97–102.

Li Z., Kosorok M., Farrell P. *et al.* (2005). Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. *JAMA*. Vol. 293, No 5, pp 581-588.

Liou T., Adler F., Fitzsimmons S. *et al.* (2001). Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol*. Vol. 153, No 4, pp 345-352.

Littlewood J., Miller M., Ghoneim A. *et al.* (1985). Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. *Lancet*. Vol. 1, p 865.

Littlewood J. (2000). Good care for people with cystic fibrosis. *Paediatr Respir Rev*. Vol. 1, No 2, pp 179-189.

Littlewood J. (2005). European cystic fibrosis society consensus on standards – a roadmap to "best care". *J Cyst Fibros*. Vol. 4, No 1, pp 1-5.

Mahadeva R., Webb K., Westerbeek R. *et al.* (1998). Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study. *BM*J Vol. 316, pp 1771-1775.

Matthews W., Williams M, Oliphint B. *et al.* (1980). Hypogammaglobulinemia in Patients with Cystic Fibrosis. *N Engl J Med.* Vol. 302, No 5, pp 245-249

McKone E., Goss C. & Aitken M. (2006). CFTR genotype as a predictor of prognosis in cystic fibrosis. *Chest*. Vol. 130, No 5, pp 1441-1447.

Mehta G., Macek M., Mehta A. *et al.* (2010). Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries. *J Cyst Fibros.* Vol. 9, Suppl. 2, pp 5-21.

Mérelle M., Schouten J, Gerritsen J. *et al.* (2001). Influence of neonatal screening and centralized treatment on long-term clinical outcome and survival of CF patients. *Eur Respir J*. Vol. 18, No 2, pp 306-315.

Miles A., Louglin M. & Polychronis A. (2008). Evidence-based healthcare, clinical knowledge and the rise of personalised medicine. *J Eval Clin Pract.* Vol. 14, No 5, pp 621-649.

Miles A. & Loughlin M. (2011). Models in the balance: evidence-based medicine versus evidence-informed individualized care. *J Eval Clin Pract*. Vol. 17, No 4, pp 531-536.

Milla C., Warwick W. & Moran A. (2000). Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *Am J Respir Crit Care Med*. Vol. 162, No 3 Pt 1, pp 891-895.

Milla C. (2004). Association of nutritional status and pulmonary function in children with cystic fibrosis. *Curr Opin Pulm Med* Vol. 10, No 6, pp 505–509.

Modi A., Lim C., Yu N. *et al.* (2006). A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros*. Vol 5, No 3, pp 177-185.

Moran A., Dunitz J. & Nathan B. *et al.* 2009. Cystic fibrosis–related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care*. Vol. 32, No 9, pp 1626–1631

Moran A., Becker D., Casella S. *et al.* (2010). Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: a technical review. *Diabetes Care*. Vol. 33, No 12, pp 2677-2683.

Mott L., Gangell C., Murray C. *et al.* (2009). Bronchiectasis in an asymptomatic infant with cystic fibrosis diagnosed following newborn screening. *J Cyst Fibros*. Vol. 8, No 4, pp 285-287.

Mussaffi H., Prais D., Mei-Zahav M. *et al.* (2006). Cystic fibrosis mutations with widely variable phenotype: the D1152H example. *Pediatr Pulmonol*. Vol. 41, No 3, pp 250-254.

Nick J., Chacon C., Brayshaw S. *et al.* (2010). Effects of gender and age at diagnosis on disease progression in long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med*. Vol. 182, No 5, pp 614-626.

Nielsen O., Thomsen B., Green A. *et al.* (1988). Cystic fibrosis in Denmark 1945 to 1985. An analysis of incidence, mortality and influence of centralized treatment on survival. *Acta Paediatr Scand*. Vol. 77, No 6, pp 836-841.

O'Connor G., Quinton H., Kneeland T. *et al.* (2003). Median household income and mortality rate in cystic fibrosis. *Pediatrics.* Vol. 111, No 4 Pt 1, pp e333-339.

Olesen H., Pressler T., Hjelte L. *et al.* (2010). Gender differences in the Scandinavian cystic fibrosis population. *Pediatr Pulmonol*. Vol. 45, No 10, pp 959-965.

Padman R., McColley S., Miller D. *et al.* (2007). Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics*. Vol. 119, no 3, pp e531-537.

Padman R., Werk L., Ramirez-Garnica G. *et al.* (2008). Association between practice patterns and body mass index percentile in infants and young children with cystic fibrosis. *J Cyst Fibros*. Vol. 7, No 5, pp 385-390.

Pamukcu A., Bush A. & Buchdahl R. (1995). Effects of pseudomonas aeruginosa colonization on lung function and anthropometric variables in children with cystic fibrosis. *Pediatr Pulmonol*. Vol. 19, No 1, pp 10-15.

Pedreira C., Robert R., Dalton V. *et al.* (2005). Association of body composition and lung function in children with cystic fibrosis. *Pediatr Pulmonol.* Vol. 39, no 3, pp 276-280.

Pendleton D. The compliance conundrum in cystic fibrosis. *J R Soc Med*. Vol. 93, Suppl. 38, pp 9-13.

Prober C., Walson P. & Jones J. (2000). Technical report: precautions regarding the use of aerosolized antibiotics. Committee on Infectious Diseases and Committee on Drugs. *Pediatrics*. Vol. 106, No 6, p E89.

Proesmans M., Els C., Vermeulen F. *et al.* (2011). Change in IgG and evolution of lung function in children with cystic fibrosis. *J Cyst Fibros.* Vol. 10, No 2, pp 128-131.

Que C., Cullinan P. & Geddes D. (2006). Improving rate of decline of FEV1 in young adults with cystic fibrosis. *Thorax*. Vol. 61, No 2, pp 155-157.

Quinton, H. (2004). Using data to identify opportunities for change and to monitor progress. *Pediatr Pulmonol*. Vol. 38, Suppl. 27, pp 124-125.

Quinton H. & O'Connor G. (2007). Current issues in quality improvement in cystic fibrosis. *Clin Chest Med*. Vol. 28, No 2,pp 459-472.

Quittner A., Schechter M, Rasouliyan L. *et al.* (2010). Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. *Chest*. Vol. 137, No 3, pp 642-650.

Quon B. & Goss C. (2011). A story of success: continuous quality improvement in cystic fibrosis care in the USA. *Thorax*. Aug 3. [Epub ahead of print]

Ranganathan S., Dezateux C., Bush A. *et al.* (2001). Airway function in infants newly diagnosed with cystic fibrosis. *Lancet.* Vol. 358, pp 1964-1965.

Ring E., Eber E., Erwa W. *et al.* (1998). Uinary N-acetyl-beta-D-glucosaminidase activity in patients with cystic fibrosis on long-term gentamicin inhalation. *Arch Dis Child*. Vol. 78, No 6, pp 540-543.

Rogan M. & Stoltz D. (2011). Cystic fibrosis transmembrane conductance regulator intracellular processing, trafficking, and opportunities for mutation-specific treatment. *Chest* Vol. 139, No 6, pp 1480-1490.

Rosenbluth D., Wilson K., Ferkol T. *et al.* (2004). Lung function decline in cystic fibrosis patients and timing for lung transplantation referral. *Chest* Vol. 126, No 2, pp 412-419.

Rosenfeld M., Davis R., Fitzsimmons S. *et al.* (1997). Gender gap in cystic fibrosis mortality. *Am J Epidemiol*. Vol. 145, no 9, pp 794-803.

Rosenfeld M., Emerson J., Mc Namara S. *et al.* (2010). Baseline characteristics and factors associated with nutritional and pulmonary status at enrollment in the cystic fibrosis EPIC observational cohort. *Pediatr Pulmonol*. Vol. 45, No 9, pp 934-944.

Saarni S. & Gylling H. (2004). Evidence based medicine guidelines: a solution to rationing or politics disguised as science*? J Med Ethics*. Vol. 30, No 2, pp 171-175.

Saiman L. & Siegel J. (2003). Infection control recommendations for patients with cystic fibrosis: Microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Am J Infect Control*. Vol. 31, Suppl. 3, pp 1-62.

Sawicki G., Sellers D. & Robinson W. (2009). High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros.* Vol. 8, No 2, pp 91-96.

Schechter M., Shelton B., Margolis P. *et al.* (2001). The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med*. Vol. 163, No 6, pp 1331-1337

Schechter M. (2002). Demographic and center-related characteristics associated with low weight in pediatric CF patients. *Pediatr Pulmonol*. Vol. 34, Suppl. 24, p 331 (A)

Schechter, M. (2004). Key strategies for improving care. *Pediatr Pulmonol*. Vol. 38, Suppl. 27, pp 120-121.

Schechter M. & Margolis P. (2005). Improving subspecialty healthcare: lessons from cystic fibrosis. *J Pediatr*. Vol. 147, No 3, pp 295-301.

Schechter M. & Guttierez H. (2010). Improving the quality of care for patients with cystic fibrosis. *Curr Opin Pediatr*. Vol. 22, No 3, pp 296-301.

Schluchter M., Konstan M., Davis P. (2002). Jointly modelling the relationship between survival and pulmonary function in cystic fibrosis patients. *Stat Med*. Vol. 21, No 9, pp 1271-1287.

Segal, T. (2008). Adolescence: what the cystic fibrosis team needs to know. *J R Soc Med*. Vol. 101, Suppl 1, pp 15-27.

Sermet-Gaudelus I., Mayell S., Southern K. *et al.* (2010). Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. *J Cyst Fibros*. Vol. 9, No 5, pp 323-329.

Shahar E. (2008). Does anyone know the road from a randomized trial to personalized medicine? A review of 'Treating Individuals. From Randomized Trials to Personalised Medicine' *J Eval Clin Pract*. Vol. 14, No 5, pp 726-731.

Sims E., McCormick J., Mehta G. *et al.* (2005). Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. *J Pediatr.* Vol. 147, Suppl. 3, pp 42-46.

Sims E., Clark A., McCormick J. *et al.* (2007). Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics*. Vol. 119, No 1, pp 19-28.

Sinaasappel M., Stern M., Littlewood J. *et al.* (2002). Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros*. Vol. 1, No 2, pp 51-75.

Siret D., Bretaudeau G., Branger B. *et al.* (2003). Comparing the clinical evolution of cystic fibrosis screened neonatally to that of cystic fibrosis diagnosed from clinical symptoms: a 10-year retrospective study in a French region (Brittany). *Pediatr Pulmonol.* Vol. 35, No 5, pp 342-349.

Sly P., Brennan S., Gangell C. *et al.* (2009). Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med.* Vol. 180, No 2, pp 146-152.

Smyth A., O'Hea U., Williams G. *et al.* Passive smoking and impaired lung function in cystic fibrosis. *Arch Dis Child.* Vol. 71, No 4, pp 353-354.

Stafler P., Davies J., Balfour-Lynn I. *et al.* (2011). Bronchoscopy in cystic fibrosis infants diagnosed by newborn screening. *Pediatr Pulmonol.* Vol. 46, No 7, pp 696-700.

Stallings V., Stark L, Robinson K. *et al.* (2008). Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and

pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. Vol. 108, No 5, pp 832-839.

Steinkamp G. & Wiedemann B. (2002). Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax*. Vol. 57, No 7, pp 596-601.

Stern R., Byard P., Tomashefski J. *et al.* (1987). Recreational use of psychoactive drugs by patients with cystic fibrosis. J Pediatr. Vol. 111, no 2, pp 293-299.

Stern M., Wiedemann B., Wenzlaff P. *et al.* (2008). From registry to quality management: the German Cystic Fibrosis Quality Assessment project 1995 2006. *Eur Respir* J. Vol. 31, No 1, pp 29-35.

Stern M., Niemann M., Wiedemann B. *et al.* (2011). Benchmarking improves quality in cystic fibrosis care: a pilot project involving 12 centres. *Int J Qual Health Care*. Vol. 23, No 3, pp 349-356.

Stevens D., Moss R., Kurup V. *et al.* (2003). Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis*. Vol. 37, Suppl. 3, pp 225-264.

Stick S., Brennan S., Murray C. *et al.* (2009). Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. *J Pediatr*. Vol. 155, No 5, pp 623-628.e1

Stuart B., Lin J. & Mogayzel P. (2010). Early eradication of Pseudomonas aeruginosa in patients with cystic fibrosis. *Paediatr Respir Rev*. Vol. 11, No 3, pp 177-184.

Taccetti G., Festini F., Campana S. *et al.* (2004). Neonatal screening for cystic fibrosis and Pseudomonas aeruginosa acquisition. *J Pediatr*. Vol. 145, No 3, p 421.

Tetrault J., Krothers K., Moore B. *et al.* (2007). Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med*. Vol. 167, No 3, pp 221-228.

Thauvin-Robinet C., Munck A., Huet F. *et al.* (2009). The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening. *J Med Genet*. Vol. 46, No 11, pp 752-758.

Thia L. & Balfour-Lynn I. (2009). Diagnosing allergic bronchopulmonary aspergillosis in children with cystic fibrosis. *Paediatr Respir Rev*. Vol. 10, No 1, pp 37-42.

Tiddens H. (2009). Quality improvement in your CF centre: taking care of care. *J Cyst Fibros*. Vol. 8, Suppl. 1, pp 2-5.

UK CF Registry (2008), Available from http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/

Treacy K., Elborn S., Rendall J. *et al.* (2008). Copying letters to patients with cystic fibrosis (CF): letter content and patient perceptions of benefit. *J Cyst Fibros*. Vol. 7, No 6, pp 511-514.

van Koolwijk L., Uiterwaal C., van der Laag J. *et al.* (2002). Treatment of children with cystic fibrosis: central, local or both? *Acta Paediatr*. Vol. 91, No 9, pp 972-977.

Valerius N., Koch C. & Høiby N. (1991). Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. *Lancet*. Vol. 338, pp 725-726.

van der Ent C. (2008). Quality assessment: is the truth in the outcome? *Eur Respir J*. Vol. 31, No 1, pp 6-7.

Verma A., Dodd M., Haworth C. *et al.* (2000). Holidays and cystic fibrosis. *J R Soc. Med.* Vol. 93, Suppl. 38, pp 20-26.

Verma N., Bush A. & Buchdahl R. (2005). Is there still a gender gap in cystic fibrosis? *Chest.* Vol. 128, no 4, pp 2824-2834.

Wainwright C., Vidmar S., Armstrong D. *et al.* (2011). Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. *JAMA*. Vol. 306, No 2, pp 163-171.

Walters S., Britton J. & Hodson M. (1994). Hospital care for adults with cystic fibrosis: an overview and comparison between special cystic fibrosis clinics and general clinics using a patient questionnaire. *Thorax* Vol. 49, No 4, pp 300-306.

Wallwork J., Brenchley P, Mc Carthy J. *et al.* (1974). Some aspects of immunity in patients with cystic fibrosis. *Clin Exp Immunol*. Vol. 18, No 3, pp 303-320.

Wang X., Dockery D., Wypij D. *et al.* (1993). Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* Vol. 15, No 2, pp 75-88.

Welsh M. & Smyth A. (1993). Molecular mechanisms of CFTR chloride channel dysfunction in CF. *Cell.* Vol. 73, No 7, pp 1251-1254.

West S., Zeng L., Lee B. *et al.* (2002). Respiratory infections with Pseudomonas aeruginosa in children with cystic fibrosis: early detection by serology and assessment of risk factors. *JAMA*. Vol. 287, No 22, pp 2958-2967.

Wheeler W., Williams M., Matthews W. *et al.* (1984). Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels: a 5-year longitudinal study. *J Pediatr*. Vol. 104, no 5, pp 695-699.

Wolfenden L., Schechter M. (2009). Genetic and non-genetic determinants of outcomes in cystic fibrosis. *Paediatr Respir Rev*. Vol. 10, No 1, pp 32-36.

Wright F., Strug L, Doshi V. *et al.* (2011). Genome-wide association and linkage identify modifier loci of lung disease severity in cystic fibrosis at 11p13 and 20q13.2. *Nat Genet*. Vol. 43, No 6, pp 539-546.

Yankaskas J., Marshall B, Ebeling M. *et al.* (2004). Cystic fibrosis adult care: consensus conference report. *Chest*. Vol. 125, Suppl. 1, pp 1-39.

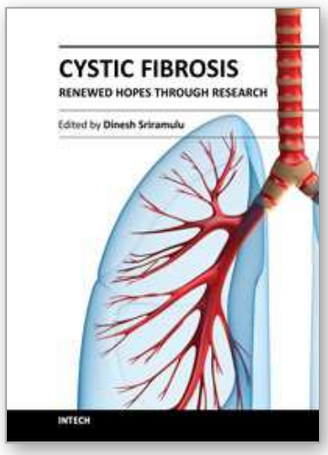
Zahariadis G., Lewy M. & Burns J. (2003). Cepacia-like syndrome caused by Burkholderia multivorans. *Can J Infect Dis*. Vol. 14, No 2, pp 123-125.

Zemanick E., Harris J., Conway S. *et al.* (2010). Measuring and improving respiratory outcomes in cystic fibrosis lung disease: opportunities and challenges to therapy. *J Cyst Fibros*. Vol. 9, No 1, pp 1-16.

Zemel B., Jawad A., Fitzsimmons S. *et al.* (2000). Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J Pediatr*. Vol. 137, no 3, pp 374-380.

Zlosnik J., Costa P., Brant R. *et al.* (2011). Mucoid and Nonmucoid Burkholderia cepacia Complex Bacteria in Cystic Fibrosis Infections. *Am J Respir Crit Care Med*. Vol. 183, No 1, pp 67-72.

Zolin A. (2010). Differences in disease severity of F508del homozygotes across European countries. *J Cyst Fibros*. Vol. 9, Suppl. 1, p 110 (A)



Cystic Fibrosis - Renewed Hopes Through Research
Edited by Dr. Dinesh Sriramulu

ISBN 978-953-51-0287-8
Hard cover, 550 pages
Publisher InTech
Published online 28, March, 2012
Published in print edition March, 2012

Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

How to reference
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Patrick Lebecque (2012). The Prognosis of Cystic Fibrosis - A Clinician's Perspective, Cystic Fibrosis - Renewed Hopes Through Research, Dr. Dinesh Sriramulu (Ed.), ISBN: 978-953-51-0287-8, InTech, Available from: http://www.intechopen.com/books/cystic-fibrosis-renewed-hopes-through-research/the-prognosis-of-cystic-fibrosis-a-clinician-s-perspective

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