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# The Importance of Adherence and Compliance with Treatment in Cystic Fibrosis

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## 1. Introduction

Over the last few years, the survival of cystic fibrosis (CF) patients has increased markedly. This is attributed to earlier diagnoses of the disease, the improvement of patient care involving multidisciplinary teams and more effective therapeutic options.

The therapeutic requirements of patients with CF are highly complex. Many patients require continuous care at home with many prophylactic medications, such as nebulised or oral antibiotics, pancreatic enzymes, mucolytic agents, vitamin and nutritional supplements as well as daily physiotherapy and a healthy lifestyle with adequate nutrition and exercise. These treatments are intensified and become more complicated during the exacerbation of the disease. Throughout its evolution, other pathologies associated with CF may also occur which require extra treatment regimens.

The complexity of the therapeutic requirements of these patients has added to their longevity. The life-long duration of the treatment and their complexity, have been pointed to as the main determinants of therapeutic adherence. Preventative management and symptomatic treatment are introduced in early childhood for most people with CF, and so management and treatment routines have been a daily concern for most adults for many years. (Kettler et al., 2002; Modi et al., 2006).

All of these difficulties have been identified as determinants of adherence and they are shared with the patients of other chronic diseases. Accordingly, the compliance rate in CF cases is very similar as that of the other chronically ill. In 1979, Sackett and Snow reviewed 537 studies on adherence in chronic disease cases, indicating that the range of adherence for long term preventative regimens was 33-94% with a mean adherence rate of 57% and for long term treatment the range was 41-61% with a mean adherence rate of 54%. Later, poor compliance with medical advice and prescribed treatments in the chronically ill in general is well-documented in the literature, and adherence rarely exceeds 80% and more often it is between 30% and 70%. (Abbott et al., 1996; Conway et al., 1996; Daniels et al., 2011; Kettler et al., 2002; Michaud et al., 1991; Modi et al., 2006).

## 2. The definition of adherence and compliance

The term compliance is applied when patients follow closely and correctly all the therapeutic indications prescribed by physicians. So, the definition of compliance is "the

extent to which patients are obedient and follow the instructions, proscriptions and prescriptions of health professionals". We talk about adherence meaning the extent to which the patient responds to these indications, taking them and 'endorsing' them as his own. This refers not only to medication, but it also includes non-pharmacological measures, such as hygiene, diet controls, etc. (Kettler et al., 2002, as cited in Meichenbaum & Turk, 1987). So, adherence is defined as an "active, voluntary, collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a desired preventative or therapeutic result". However, both terms receive general use and so are treated indifferently in the literature. No doubt the results of adherence are influenced by the definition adopted. Lots of different classifications of adherence – and extent of this has been described – have been assessed from different points of view. Some authors have suggested that patients should be described as fully-adherent, partially-adherent or non-compliant (Lask, 1994). Koocher differentiates the term non-compliant into three groups: those who have an inadequate understanding of the disease, those who present a psychological resistance to disease, and those who – when properly educated – choose not to be compliant (Koocher et al., 1990).

On the other hand, it has been found to be very difficult to classify an individual as compliant. Studies have found that despite compliance, significantly less than 100% could achieve the desired health outcomes (Kettler et al., 2002). However, the cut off point at which they would stop objectifying favourable results and should promote greater compliance is very difficult to define.

Poor adherence can lead to more rapid disease progression. (Abbott et al., 2001; Patterson et al., 1993). Nonetheless, there are studies that reject the existence of a conclusive association between poor compliance and disease progression (Abbott et al., 1994). However, a lack of compliance may increase the number of consultations and hospital admissions with a consequent increase in health spending. In addition, it may hinder the knowledge of the effectiveness of treatments. On the other hand, it is believed that total adherence may not be necessary, as the complete fulfilment of all of the components of a treatment does not guarantee good health. (Abbott et al., 2001). It is known that a patient with poor compliance may stay well, perhaps because of individual responses to different treatments. It is reasonable, therefore, be able to find a balance between the two sides, but is not an easy task for the specialist in relation to these patients.

### **3. The measurement of adherence**

The measure of treatment adherence is not an easy task. We must find a balance between the errors obtained using certain procedures – such as personal interview – and the difficulty in performing other more objective technical procedures.

The methods most commonly used to study adherence in patients with CF include:

#### **3.1 Personal interview**

The most frequently used method is to ask directly or take a survey of the patient as to whether the treatment takes place and to what extent it does so. However, patients often tend to overestimate their compliance (Abbott et al., 1996; Conway et al., 1996, Kettler et al., 2002) and frequently this does not reflect the opinion of the specialist. This data can be

compared by asking the opinion of the medical team responsible for the patient or else their family. Although this is the easiest and most accessible system for assessing adherence to all kinds of treatments, it cannot be denied that the results are not entirely objective.

### **3.2 Therapeutic response**

Using this method of measuring adherence in such a complex disease as CF and the many variants of treatment can lead to errors. In particular, knowledge of the desired effect achieved by taking a certain drug is almost impossible given the significant interaction between the different treatments.

### **3.3 Serum or urinary excretion of drugs or their metabolites**

The first thing to note is that this is an invasive method and as such it is highly uncomfortable for the patient, who would have to undergo a large number of extractions in order to verify their genuine compliance. This problem is compounded by the pharmacokinetic variations of the substances studied, and it allows the analysis of only certain medications and reports only those drugs that have been recently consumed by the patient.

### **3.4 Monitoring with electronics, such as aerosol dispensers or nebulisers, that record the date and time of each dispensation**

This data would be periodically downloaded for analysis so as to give an idea of adherence. Amongst its advantages it is worth noting that it allows us to guess the behaviour of patients, it is non-invasive, and it allows the collection of data over a long period of time without the patient having to attend hospital. On the other hand, this type of monitoring has its limitations. With its high cost we must also add the fact that data provide information about the use of a medication removed from dispenser. However, it is reasonable to assume that most patients who make the effort to remove medication from the dispenser in the prescribed way will also consume the medication. This technology is limited when used for evaluating physical therapy, and it gives no information on adherence to such treatment regimens as exercise or diet (Kettler et al., 2002; McNamara et al., 2009; Modi et al., 2006).

## **4. Predictors of compliance**

Once the degree of compliance of a patient is measured, it is interesting to know the reasons for why compliance might not be adequate and identify the motivations for good adherence. Understanding the factors that may be related to adherence will enable us to act on them to some degree and so improve compliance and impact upon the course of the disease.

Described below are the factors that have often been studied as predictors of compliance in the literature.

### **4.1 The relationship between the patient and health professionals**

In a chronic disease with a complex treatment such as CF, the relationship of patients with their health professionals is very important. This can have a positive or negative impact on

compliance, and so it should foster an environment of trust that allows for good communications between them. Numerous studies have shown that those who believe that it is important to follow your doctor's instructions and those who have confidence in the benefits of their treatment are more compliant. (Abbott et al., 2001; Patterson et al., 1993) The level of adherence has been linked with the knowledge of the specifics associated with prescribed medical treatments. Therefore, the physician must strive to convey adequate information which is detailed yet easy to understand. After all, in many cases the patient has not properly understood the reason for each prescription, as made clear by the fact that 12%-32% of mothers do not fully understand the medical advice concerning their child (Ievers et al., 1999).

Such appropriate information must convince patients that their actions when performing the treatment will impact on the course of their disease. The fact of involving the patient will give us with the ability to schedule a treatment plan together with them and which allows us to improve adherence. To do this, we must recognise that there is no single treatment for all patients and it should be individualised and simplified wherever possible.

Moreover, the maintenance of adequate adherence to prescribed treatments is very important for care monitoring and the provision of adequate supervision, and we should always try not to judge and accept that a lack of enforcement is, to a certain extent, normal with this type of disease (Conway et al., 1996; Lask et al., 1994).

#### **4.2 The severity of the disease**

The perception of the severity of the disease differs between doctors and patients. From the doctor's point of view, the patients underestimate the severity of their disease and overestimate their care.

Some authors suggest that adherence is worse amongst those patients with more severe cases due to a lack of positive reinforcement in that they do not notice any beneficial effect resulting from adherence to their treatment (Kettler et al., 2002). However, the severity of the disease has often been evaluated as a possible predictor of adherence in CF cases with conflicting results (Abbott et al., 1994, 1996, 2001; Conway et al., 1996; Gudas et al., 1991; Kettler et al., 2002).

#### **4.3 Social and family relationships**

It is very important that patients with CF receive good socio-familial support. Strong family cohesion and adequate social support have been associated with better adherence to treatment. A special importance is attached to the family in the care of patients during childhood, where the burden of treatment compliance during this time of life is maintained by the parents (Battistini et al., 1998; Eddy et al., 1998; Foster et al., 2001; Moise et al., 1987).

However, there are other difficult times, such as adolescence, where receiving strong family support and positive reinforcement is central to maintaining good adhesion to the different treatments that have to meet the needs of these patients. The stresses between parents and children, and poor relationships between parents, are associated with low compliance and could have an adverse impact on the disease and health status of children with CF (Dziuban et al., 2010; Eddy et al., 1998; Foster et al., 2001; Smith et al., 2010).

#### 4.4 Types of treatment

There is wide agreement in the literature over the differences in adherence to the different components of the treatment of patients with CF. While the adherence to antibiotic therapy (80-95%) and intake of enzymes (65-90%) is high, we cannot say the same for habitual physiotherapy, exercise and the taking of vitamins and nutritional supplements, for which compliance is found to be about 40-55%. The high compliance found in relation to certain aspects of the treatment of patients with CF probably reflects the short-term benefit associated with a given treatment or else any immediate unpleasant symptoms which may result from non-compliance. An example of this would be the appearance of steatorrhea as a consequence of ending the intake of pancreatic enzymes in patients with exocrine pancreatic insufficiency. (Abbott et al., 1994; Conway et al., 1996; Daniels et al., 2011; McNamara et al., 2009).

#### 4.5 Age

Treatment adherence tends to decrease with age. Younger children show greater compliance, perhaps because during this time the responsibility for treatment lies with their parents. However, later on during adolescence, adherence decreases when the patient takes responsibility for their own treatment (Bucks et al., 2009; Dziuban et al., 2010; Gudas et al., 1991; Zindani et al., 2006).

The overall compliance of adolescents with CF is around 50%. Several factors, such as the family environment, staff perceptions about their illness, shame of displaying their problem in front of friends, and their relationship with their doctor are all classically associated with compliance, which is difficult to predict at this age due to the multiple factors involved (Michaud et al., 1991). All these factors occur at the time when the adolescent is transferred to the adult specialist (Kettler et al., 2002), and many patients experience suspicion and insecurity which also often tends to affect adherence.

In chronic diseases, the normal behaviour of denial and a reduction of anxiety tend to increase with age in facilitating emotional adjustment in adulthood. So, while these attitudes improve the mental health of these patients they also often negatively affect their adherence (Lask, 1994).

#### 4.6 Epidemiological factors

Demographic factors such as sex, level of educational, knowledge of the disease, socioeconomic status and occupation, and clinical factors such as the age of diagnosis and the frequency of clinical visits, have all been evaluated as possible predictors of adherence in CF cases, and have met with conflicting results (Abbott et al., 1994, 1996, 2001; Dziuban et al., 2010; Gudas et al., 1991; Oerman et al., 2000).

#### 4.7 Ways of coping with the disease

Psychological factors are beginning to emerge as strong predictors of adherence. Classically, it was said that the incidence of mental health disorders in people with CF is recognisably similar to that of the general population. However, high levels of stress are common and require recognition and attention (Abbott et al., 2001; Dziuban et al., 2010; Kettler et al., 2002).

A large percentage of patients with CF and their parents reported elevated symptoms of depression. In a recent study, rates of depressive symptoms were elevated in children with CF and their parents (29% for children, 35% for mothers and 23% for fathers). In addition, child depressive symptoms were significantly associated with lower rates of adherence to airway clearance (Smith et al., 2010).

Moise claims that there are lower levels of psychological distress and better adjustment in patients who use avoidance as a way of coping with illness, and those who use more direct methods and are positive (Moise et al., 1987).

It is well-documented that poor psychological well-being can influence a detrimental physiological function and a disease's progression, morbidity and mortality (Abbott et al., 2001). Perhaps it should be admitted that a degree of non-compliance is normal in these patients.

Concern about their illness and the perception that they have little personal control over its course has been shown to be a facilitator of adherence. The way of coping with CF has a potential influence on the direction and course of their disease. In particular, denial has been associated with rebellion and persistent non-compliance, while the adopting of an attitude of optimism and hope is associated with greater compliance (Abbott et al., 1996, 2001; Dziuban et al., 2010).

Currently, there is a major dilemma amongst health professionals with regard to promoting good mental health, whether they should allow denial and avoidance strategies for the patient to cope with the disease, or else whether they should promote compliance, which is dependent upon the recognition of the disease and the need for treatment.

## **5. Treatment compliance in children and adults with CF**

The irregular adherence to treatment of patients with CF can alter the course of their illness. There are a number of important consequences of a failure to comply in treating CF, namely: deaths from cardiovascular diseases and infections, hospital admissions, increased visits, additional diagnostic testing requirements, additional alternative or unnecessary treatments, the home storage of medications and increased health spending. Knowledge of these aspects which motivate a patient in meeting certain treatments, and the discovery of the reasons given to justify the failure of others, can help the physician to promote adherence among their patients and influence the course of their disease.

In 2008, we published a study designed to determine treatment compliance and how it was perceived by patients, parents and by a team of specialists in CF. We also analysed the relative importance given to each of the prescribed treatments and the reasons that were given for non-adherence, and we investigated the possible predictors of therapeutic compliance. We also looked at the reasons for non-adherence, so as to determine possible predictors of therapeutic compliance (Arias-Llorente et al., 2008).

### **5.1 Patients and methods**

#### **5.1.1 Patients**

Thirty-four CF patients controlled by the outpatient CF clinic of the University Central Hospital of Asturias and which attended periodic revisions (one each trimester) participated

in the study. Up until the age of 14 they are controlled by paediatric gastroenterologists and pneumologists and by an adult specialist from that age on.

### 5.1.2 Study protocol

Data was collected by reviewing the clinical histories of the patients and it included epidemiologic data (age, gender, age at the diagnosis of CF, the timing of the evolution of the disease and CFTR mutation), a respiratory evaluation (the treatment received at the time of the interview, spirometric values, Bhalla score, lung transplantation) and a digestive evaluation (body mass index (BMI), nutritional index (NI), blood levels of alkaline phosphatase, transaminases, gamma-glutamyl transpeptidase, fat soluble vitamins, folic acid, albumin,  $\beta$ -carotene, faecal elastase, and immunoreactive trypsin, 72-hour faecal fat) and global evaluation (associated co-morbidities, Shwachman-Kulczycki score).

### 5.1.3 Questionnaire

A self-administered questionnaire was given to each patient when attending a routine visit to be answered in the clinic. Patients older than 12 years completed the questionnaire themselves, while it was filled out by the parents of younger patients. The questionnaire included four different subsets of questions, one for each of the different treatments usually given to CF patients, namely: physiotherapy, respiratory medication (including DNase, antibiotics and inhaled corticosteroids), digestive medication (including pancreatic enzymes, vitamins, deoxycholic acid and antacids) and nutritional supplements.

For each subset of therapeutic options, the CF patients were asked multiple questions on treatment compliance, the frequency of treatment, the importance attached to the treatment, their personal opinion about their own treatment compliance and the reasons given for non-compliance. At the end of the questionnaire, the CF patients score (from 0 to 100%) their global therapeutic compliance, considering all the treatments received.

According to the score obtained by the questionnaire, patients were then grouped according to their compliance or non-compliance for each of the therapeutic options and globally.

In addition, the paediatric and adult gastroenterologists, pneumologists and nurses of the CF clinic were also asked to subjectively classify the treatment compliance of the CF patients in terms of compliance and non-compliance.

## 5.2 Results

Thirty-four CF patients (21 of which were female) with an age range of 1.6 to 40.6 years (mean 14.5) were included in the study. Fourteen patients were under 10 years of age, 11 between 10 and 20, and 9 were older than 20. The average time of the evolution of the disease was 12.2 years (range from 1.3 to 40.6).

### 5.2.1 Adherence for each type of treatment

At the time of the study the average number of digestive and respiratory medications to be taken by the patients were 3.5 (range 0 to 7) and 4.5 (range 1 to 9) respectively.



Treatment compliance was greater for digestive (88.2%) and respiratory medication (61.8%), compared to physiotherapy (41.2%) and nutritional supplements (59%). This data is shown in Table 1, as well as that extracted from the views of the health professionals with regard to adherence of the patients to each type of treatment. The questionnaire results show a global compliance of 59%, whereby only 56% were compliant according to the opinion of the clinicians. Moreover, when the patient was directly asked, at the end of the questionnaire, to indicate their adherence to the therapy in their opinion, the treatment compliance was higher both for each type of treatment and globally.

	QUESTIONNAIRE	SPECIALISTS	PATIENTS
Physiotherapy	41.2%	35.3%	62.%
Respiratory	61.8%	59%	75.8%
Nutritional	59%	56%	77.7%
Digestive	88.2%	70.4%	91.2%
Global	59%	56%	84.8%

Table 1. The percentage of therapeutic adherence for each type of treatment based upon a questionnaire and specialist opinions and the perception of patients.

In conclusion, CF patients had a greater treatment adherence when prescribed digestive and respiratory medications as opposed to physiotherapy and nutritional supplements.

### 5.2.2 Degree and frequency of compliance

All of the CF patients take their digestive medications daily, although 64.7% admitted that they only consume pancreatic enzymes during principal meals and not during snacks. 50% of the CF patients indicated daily treatment compliance with respiratory medication and nutritional supplements. On the other hand, 14.7% only took their respiratory medications when they felt worse and 5.8% never took them, and nearly 30% of the patients said that they never consume their nutritional supplements.

The data from our questionnaire about physiotherapy is quite remarkable. Only 38.2% admitted to practising physiotherapy daily, while nearly 45% of patients reported as having physiotherapy only when they felt worse, occasionally or else never.

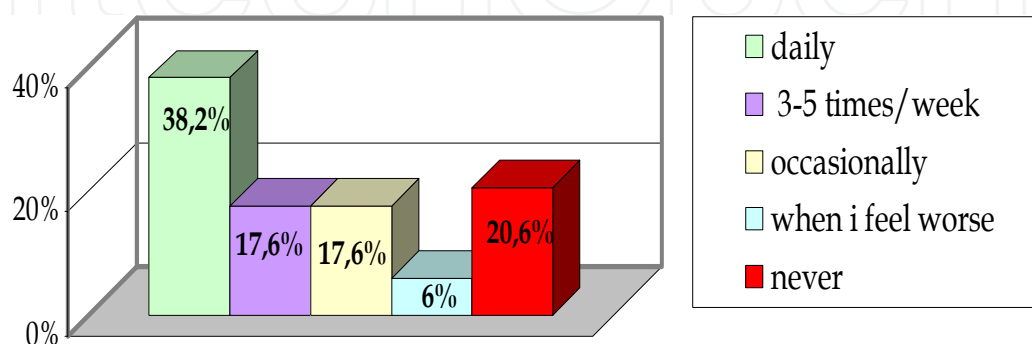


Fig. 1. Frequency of practice of physiotherapy (percentage of patients).

### 5.2.3 The importance given to different types of treatment and their impact on quality of life

The importance attached by patients to each type of treatment (average scores between 1 and 10): physiotherapy, 7.17; respiratory medication, 8; digestive, 9.4; nutritional support, 6.2) influenced compliance, and the treatments with the highest score saw the best level of adherence.

CF patients considered their digestive medication to be indispensable (94.1%) compared to respiratory medications, physiotherapy and nutritional supplements (70.6%, 59% and 44.1% respectively).

Type of treatment effect on quality of life was evaluated by the CF patients, and Table 2 shows the results of this evaluation. While 85.3% of the patients thought that digestive medications significantly improve their quality of life, half of the CF patients considered that physiotherapy plays little or no role on their perceived quality of life.

	Much	Enough	Little	Nothing
Physiotherapy	35.2% (25-45)	17.6% (5-31)	17.6% (5-31)	29.4% (14-44)
Respiratory	26.5% (11-41)	29.4% (14-44)	11.7% (3-28)	14.7% (3-27)
Digestive	38.2% (20-52)	44.1% (27-61)	2.9% (0.08-17)	8.8% (2-27)
Nutritional	11.7% (3-28)	38.2% (20-52)	11.7% (3-28%)	14.7% (3-27)

Table 2. The impact of treatments on quality of life of the patients (95% confidence interval limits in brackets).

### 5.2.4 Satisfaction

Patient satisfaction about their own treatment adherence was significantly higher for digestive medication, with 70.6% of the CF patients considering that they were taking the correct dose of digestive medication, while only 8.8% considered that they should have been more compliant. By way of contrast, only 29.4% of the CF patients considered that they were practising as much physiotherapy as they needed, in comparison to 41.2% who thought that they should practise more frequently.

### 5.2.5 Reasons for poor compliance

The main reason given for not taking digestive medications was forgetfulness. However, the most repeated excuses for not complying with respiratory medication and nutritional supplements were the belief that they didn't need the medications (11.7% and 14.7% respectively), together with a lack of time for respiratory medication (8.8%) and the unpleasant taste or texture for nutritional supplements (14.7%).

The reasons given for not doing physiotherapy exercises included not having enough time (23.5%), not needing the treatment (20.6%) and substitution by other exercises (20.6%). Actually, the median time that our patients employ in practising physiotherapy is noticeably less than the ageing of sickness evolution (7.6 years vs. 12.2 years). A considerable number of patients believe that physiotherapy is not necessary after receiving lung transplantation.

	% patients
<b>Physiotherapy</b>	
Not enough time	29.4%
I don't think need it, I feel well without treatment.	20.6%
Exercise instead	20.6%
I don't believe that it does my any good	14.7%
It interferes with my social life	11.8%
Simply forget	8.8%
Transplantation	5.9%
<b>Respiratory medication</b>	
I don't think need it	11.7%
Not enough time	8.8%
Only when I feel worse	8.8%
It interferes with my social life	5.9%
Simply forget	5.9%
Exercise instead	2.9%
<b>Nutritional supplements</b>	
I don't think need it	14.7%
I don't like the taste or texture	14.7%
Simply forget	8.8%
I don't believe in it	5.9%

Table 3. The predominant reasons for poor compliance with different treatments (percentage of patients).

### 5.2.6 Differences between compliant and non-compliant CF patients

It was objectified that treatment adherence decreases with age. We have observed that 23.8% of patients younger than 15 years were non-compliant, while this percentage rose to 69.2% for those older than 15 years, up to 89% for those older than 20 years. Non-compliant patients were significantly older (the average age of compliant patients was 10.4 years; that of non-compliant patients was 20.5 years,  $p=0.008$ ) and had a longer time of evolution for their disease (compliant 9.4 years; non-compliant 16.8 years,  $p = 0.025$ ). In our study, we have observed that adherence to treatment decreases with the severity of the CF disease (Shwachman score compliant 83.2 vs. non-compliant 73.9 points,  $p = 0.048$ ).

No gender differences were observed. Moreover, compliant CF patients attached more importance to all of the different therapeutic options than non-compliant CF patients (Table 4). Nutritional parameters were also analysed, and compliant CF patients displayed significantly higher albumin values than non-compliant patients. No differences were observed for any of the other biochemical factors studied. No age-adjusted differences were observed in BMI. No differences were observed for faecal fat, NI, and spirometric values.

	COMPLIANT Mean (SD)	NON-COMPLIANT Mean (SD)	P
Physiotherapy	9.5 (2)	5 (0.7)	0.000
Respiratory	8.8 (1.5)	6.4 (3)	0.010
Digestive	9.7 (0.7)	7 (1.7)	0.001
Nutritional	8.6 (1.4)	4.3 (3.1)	0.000

Table 4. The importance attached to different therapeutic options by CF patients on a scale from 1 to 10 points.

### 5.3 Discussion

identified as determinants of adherence to different treatments. At the time of our study, the average number of digestive and respiratory medications to be taken by patients was 3.5 (range 0 to 7) and 4.5 (range 1 to 9) respectively. These medications numbered too many even when compared with other studies, where there are even lists with more than twenty different treatments (Marciel et al., 2010). The explanation for this difference may be that the average age of patients is greater where there is a more prolonged progression of the disease and a possibly more serious illness. Whilst – in our study – the average age of the patients was 14.5 years, the mean time of the evolution of the disease was 12.2 years, and 58.8% of the controlled patients in our unit presented a good global prognostic score according to the Shwachman-Kulczycki scale, and even 26.4% were qualified as excellent.

If these treatments are added to the need for other medications for associated pathologies and daily physiotherapy practice, they can give us an idea of how complicated the treatment was and the time spent on it. Given the long duration and arduous nature of these regimens, the maintenance of good compliance over prolonged periods will be a difficult task for the specialist responsible. Moreover, there are many other factors which may influence a decline in adherence: the perception of the disease which the patient has at any time, their different ways of coping with the disease (which can change throughout life), family, economic or social problems, a lack of trust in the responsible physician, erroneous beliefs about the benefits of different treatments, etc.

As such, the patients who were considered to be particularly compliant could also go through phases of declining adherence. For this reason, it is very important not to relax during the monitoring of these chronic patients and to be alert to any problems that may affect their adherence to their treatment (Duff & Latchford, 2010). During this time, the team of specialists should try to understand and motivate the patient.

Accordingly, there are works that strive to determine not only the degree of compliance of these patients, but also its variation over time and the reasons for this. Using this type of information, it is possible to identify which aspects of the treatment can be improved and to work together with families so as to individualise treatments. For example, a study designed to determine adherence to nebulised antibiotics by monitoring the routine data downloads of an adaptive aerosol delivery nebuliser in children with CF found considerable variation in adherence, both between and within patients, and even over the course of the day (evening adherence was better than morning adherence). Treatment regimens were changed for 8/28 patients, based upon the data on adherence obtained by this study (McNamara et al., 2009).

Treatment adherence in CF cases, as with many other chronic diseases, has been around 50% and has rarely exceeded 80% (Abbott et al., 1996; Conway et al., 1996; Daniels et al., 2011; Kettler et al., 2002; McNamara et al., 2009). According to the data obtained by the questionnaire score, overall treatment compliance with the CF group controlled in our unit was 59%. Also, patients were asked directly as to what their level of compliance was, it was much higher both overall and for each type of treatment. Indeed, half of the patients believe that they comply with the therapeutic indications made by the specialist by at least 90%, a better level of adherence than the indicated by the results obtained by the questionnaire score.

The fact that patients tend to overestimate their adherence to treatment is usually reflected in the literature. By way of contrast, the opinion of health professionals suggests a generally lower level of adherence (Abbott et al., 2001; Conway et al., 1996; Daniels et al., 2011; Modi et al., 2006). Moreover, it is usually the case that the perception of the severity of the disease also differs between physician and patient. A recent study assessed the agreement between rates of adherence to prescribed nebulisers when measured by self-reports, clinician reports and electronic monitoring suitable for long-term use, and differences in adherence were found. Here, median self-reported adherence was 80% whilst median clinician reported adherence was down to 50%-60% (Daniels et al., 2011). This was also observed in our study, as adherence to treatment as assessed by the team of specialists was lower than both the overall and for each type of treatment. So, according to our data, only 70% of those patients who believed themselves to be compliant (according to the questionnaire results) are also considered to be so by their specialised doctors.

However, self-reporting and clinician reporting of adherence does not provide accurate measurement of adherence when compared with more objective measurement methods. In this case, adherence is usually less than as shown in the study mentioned above, where the level of adherence measured by nebuliser downloads was 36% (Daniels et al., 2011).

We are aware that the results of our study are based on subjective data obtained after a personal interview with parents and/or patients, which are then contrasted with the opinions of the clinicians belonging to the CF unit. There are also studies that clearly show that clinical impressions are not accurate enough to determine the real therapeutic adherence of patients, and so it would be also convenient to use a more objective method (Marciel et al., 2010; Modi et al., 2006; Shemesh et al., 2004). It has been mentioned that the level of adherence could vary according to the subjectivity of the method employed, such as with a personal questionnaire, even if the results are corrected with the opinions of the medical professionals or other objective measures, such as blood-serum levels, the urinary excretion of medications or their metabolites, or the monitoring of adherence with electronic recording devices or the dispensers of medications (Conway et al., 1996; Modi et al., 2006; Rand et al., 1992; Teichman et al., 2000). Nevertheless these methods have their own inconveniences. With regard to the drug levels in serum or urine, we must emphasise that they are invasive methods and they may only represent yet another test for patients, due to the multiple samples needed to check their compliance, in addition to the pharmacokinetic variations of the substance are to be studied. Regarding electronic monitoring, the data obtained only provides information about the use of a medication dispenser, but not about whether the patient is actually taking the medication removed from the dispenser; moreover, this type of monitoring remains too expensive. This could also limit other evaluations concerning such aspects as diet, exercise and physiotherapy (Kettler et al., 2002; Rand et al., 1992).

In addition to finding differences in treatment compliance according to the methods discussed above, there are many works that refer to differences in adherence to the different components of the treatment carried out by patients with CF. Traditionally, it is said that adherence is low – between 40% and 55% – to nutritional supplements and physiotherapy. Meanwhile, treatment compliance to pancreatic enzymes and respiratory antibiotics increases to between 75% and 90% (Abbott et al., 2001; Daniels et al., 2011; Kettler et al., 2002; Modi et al., 2006).

In our study, and with regard to the types of treatment, most patients performed digestive medication (88.2% of patients), followed by respiratory medication (61.8%). Meanwhile 59% of patients were considered compliant with respect to nutritional support whilst only 41.2% were compliant with physiotherapy. In our case, the number of patients who were compliant towards digestive medication is similar to the results shown elsewhere (Abbott et al., 1994, 1996, 2001; Daniels et al., 2011; Modi et al., 2006) as well as the fact that only a third of patients took pancreatic enzymes at every meal, including snacks (Michaud et al., 1991). However, the level of adherence to respiratory medication was less than in others studies, which is perhaps explained by the fact that we did not analyse specific compliance with every aspect of respiratory treatment. If we had taken into consideration the individual's adherence to bronchodilators, antibiotics or inhaled corticosteroids, the adherence to treatment would probably have been greater.

When we asked patients about the importance that they attach to the different types of treatment (on a scale from 1 to 10 points), the highest score was assigned to digestive medication (9.4 points), corresponding with the most valued treatment in terms of compliance and its impact on quality of life. As such, 85.3% of the patients thought that digestive medication significantly improved their quality of life. As described in previous publications, our patients displayed better compliance with those treatments that they believed to be more important (Abbott et al., 2001; Patterson et al., 1993) and to have more repercussions for their quality of life (Conway et al., 1996; Czjkowski et al., 1987).

In accordance with the details above, the two types of treatments that most patients seemed to consider essential were digestive and respiratory medications (94.1% and 70.6% respectively). This idea, coupled with the higher compliance observed in these treatments, is collected in earlier studies and it may reflect the short-term benefits of these and the precocity of the appearance of unpleasant symptoms as a result of non-compliance (Abbott et al., 1994, 1996, 2001; Conway et al., 1996; Kettler et al., 2002). Thus, adherence to pancreatic enzyme typically is high in order to avoid steatorrhea and the main reason for not taking this medication is “forgotten” and only one person says no need to take it despite having malabsorption.

At the opposite end are nutritional supplements and physiotherapy. It is of concern that uniquely 44.1% consider nutritional supplements to be an essential treatment in clear concordance to the main reason given for not taking nutritional supplements: “I don't think I need it”. And finally, only 59% of the patients believe physiotherapy is an essential treatment, in clear opposition to what physicians think. In fact, the type of treatment which we found to reflect a greater discrepancy between the opinions of doctors and patients was physiotherapy. This way of thinking agrees with patients' perception of their slight repercussions for their quality of life (half of the CF patients felt that physiotherapy played

little or no role in their treatment) and the different degrees of importance attached to physiotherapy by compliant and non-compliant patients (9.5 points vs. 5 points,  $p < 0.001$ ). In this connection, the data of our questionnaire concerning physiotherapy is remarkable since the practise of physiotherapy was particularly deficient with regard to the number of subjects doing it and its frequency; however, this is also found in the literature (Abbott et al., 1996; Bernard & Cohen, 2004; Passero et al., 1981). The number of patients who practised daily physiotherapy only reached 38.2%, similar to other results in CF clinics (Abbott et al., 2001; Oerman et al., 2000), and 20% even say that they never practice physiotherapy.

On the other hand, the beginning of physiotherapy should be instituted at the time of the diagnosis of CF, a finding which is not supported by the average time that our patients have been practising (mean  $\pm$  SD:  $7.6 \pm 6.1$  years), which is strikingly lower than the average time of the disease ( $12.2 \pm 8.9$  years).

Therefore, the main reasons claimed for non-compliance are a lack of time, the erroneous belief that they don't need it or that they can substitute them with other exercise. As such, the perception that there are no beneficial effects with the treatment is wholesale problem for physiotherapy (Bernard & Cohen, 2004; Conway et al., 1996; Czjkowski et al., 1987; Shemesh et al., 2004; Teichman et al., 2001), and it has been published as being substituted with exercise in 20% of cases, just as we found (20.6%).

A particular time when there is a risk of a decrease in adherence occurs, typically, after lung transplantation. Accordingly, we must emphasise that half of our transplanted patients have given up physiotherapy techniques afterwards, giving this hopeful event as the very reason for their lack of adherence. Even if it is known that medical opinions obviously contrast with this attitude, there is a recognised decrease in their therapeutic fulfilment after a lung transplantation which continues over time. It may be that they experience a better sense of wellbeing and so could hypothesise that they didn't need it anymore. At this time, it is essential to provide them with clear information and to take care in following up with adequate supervision so as to reorient and help them eradicate these erroneous beliefs (Foster et al., 2001; Lask, 1994; Kettler et al., 2002; Oerman et al., 2000; Teichman et al., 2000).

Such beliefs about the benefits of and need for each type of treatment significantly influence in the treatment adherence.

In terms of patient satisfaction about their own adherence, it should be noted that is noticeably higher with the digestive intake of medication, such that 70.6% think that they should take this type of medication and only 8.8% think they should take more. At the other extreme is physiotherapy, where only 29.4% of patients believe that they should practise physiotherapy at all and 41% think that they should do it more often. If we compare this data with those described in previous works, it confirms a trend (Abbott et al., 1994). This is to say that patients are more satisfied with their compliance with digestive or respiratory medication than with their practise of physiotherapy. It is a paradoxical result because, although very few are happy with the practise of physiotherapy, there are few who think that they should do it more often.

There are several factors which should be taken into account as possible predictors of adherence in CF cases, with contradictory results: demographic data such as sex, age, level of education, knowledge of sickness, socio-economic status, socio-familial relations and

profession, as well as clinical factors such as age at diagnosis, the severity of the CF or the frequency of checkups at CF clinics (Bernard & Cohen 2004; Jaffe & Bush, 2001; Kettler et al., 2002; Oerman et al., 2000; Passero et al., 1981; Zindani et al., 2006). Our study found a statistically significant difference both in terms of the average age of each patient group, (compliant at 10.4 years and non-compliant at 20.5 years) and the time of the evolution of the disease (compliant at 9.5 years and non-compliant at 16.8 years). The fact that adherence to treatment tends to diminish with age has also been mentioned in the earlier studies (Conway et al., 1996; Gudas et al., 1991). In childhood, a high level of compliance is frequently observed, which is probably explained due to the fact that during this period of life the responsibility lies with the parents (Battistini et al., 1998; Foster et al., 2001). Family cohesion and adequate social support have both been associated with better adherence to treatment (Eddy et al., 1998; Foster et al., 2001; Hamutcy et al., 2002; Teichman 20009). In addition, the ways of coping with the disease by the mechanisms of denial and avoidance – which have been described as negative predictors of adherence to treatment – tend to increase with age amongst these chronically ill patients as they facilitate their emotional adjustment into adulthood (Kettler et al., 2002; Lask, 1994).

A special time when compliance with treatment tends to decrease significantly is during adolescence, as was also found in our study, whereby parents release their progeny. This notion is reflected repeatedly in the literature for years (Bernard & Cohen, 2004; Bucks et al., 2009; Conway et al., 1996; Mc Laughlin et al., 2008; Passero et al., 1998). So, in a study done in Montreal University 20 years ago on compliance with treatment amongst adolescents affected by chronic illness, such as CF, it was concluded that there was a global adherence of 50%; nevertheless only 11% of the subjects demonstrated the successful accomplishment of all of the therapeutic components (Michaud et al., 1991). In another study at Michigan University several years later, it has been shown that there is a significant difference between those patients who are less than 12 years old and those who are over twelve year old with regard to the intake of liposoluble vitamins amongst CF patients (Jaffe & Bush, 2001).

Adolescence means that the patients are presented with several other challenges apart from their illness, such that all of a sudden they are supposed to take control of themselves; perhaps they are prone to diminish its importance, or perhaps they display a reluctance to chat with their peers about their 'big' problem, or perhaps, even, they adopt a "hide and run" policy. They apologise, arguing with such reasons as "it interferes with my social life," "I don't want my friends to know that I suffer from CF," as we have confirmed. Another reason in the decrease in self-accomplishment could be the transfer from paediatricians to adult medical staff (McLaughlin et al., 2008; Michaud et al., 1991), since initially it could mean a degree of instability and lack of reliance that is traduced into less adherence.

For all of these reasons, there is often a growing recognition of need for support for their transition into adult-oriented healthcare. There is significant variability in the transitional support provided to young adults with CF (Mc Laughlin et al., 2008; Scal & Ireland; 2005). The first problem is the age of transition, because while in many centres the transfer of care for CF occurs at a median age of 19 years, in other programs it has been reported that the introduction of the concept of transition takes place before the age of 15 years (Anderson 2002). In our CF unit, up until the age of 14 (younger than 15 years) they are controlled by paediatric gastroenterologists and pneumologists, and by an adult specialist from that age



onwards. The second problem relates to the different methods of transition that have been used. Few programmes provide educational materials about transition to patients and families, and fewer than half provide a transition time-line or designate a specific team member to be responsible for the key elements of transition (Mc Laughlin et al., 2008; Marciel et al., 2010).

With regard to the severity of the disease, as determined by the score on the Shwachman-Kulczycki scale, significant differences were found between the compliant and non-compliant groups. We have observed that adherence to treatment decreases with the severity of CF. Some authors explain this phenomenon by reasoning to a lack of positive reinforcement whereby patients do not note a beneficial effect with their adherence to treatment (Hamutcy et al., 2002). However, there are also other authors who describe the opposite, with results relating disease severity with adherence to treatment (Oerman et al., 2000; Zindani et al., 2006).

In summary, we can say that there are differences in the degree of compliance by these patients with the various components of the treatment carried out. There is greater adherence to digestive and respiratory medications than to physiotherapy and nutritional supplements. We found a decrease in adherence according to age, the longer the history of the disease and the greater its severity. In addition, the treatments which were evaluated by patients as most important and as having the greatest impact on their quality of life witnessed the most adherence.

## 6. Conclusion

We can conclude that the global compliance with treatment is similar to that of other works, with a tendency of patients to overestimate their accomplishments as compared with the opinions of clinical staff. There are differences in the level of adherence to the various treatments, and this is realised by these patients.

Of all the treatments that patients carry out, it was felt that the treatment which had the greatest impact on their quality of life, that which most considered to be essential and with which they were personally the most satisfied, involved gastrointestinal medicaments. Nevertheless, the practise of physiotherapy was highly deficient with regard to the number of subjects performing it and the frequency with which they did it, influenced by the general belief that it does not make much difference and that it has little repercussion for their quality of life.

We have confirmed a decrease in therapeutic adherence with age, the longer the duration of evolution and the severity of the illness. There was no influence from the gender of the patients, their nutritional parameters, or from the data on pulmonary function. The treatments mostly appreciated by the patients as most essential were coincident with a higher level of adherence, emphasising the need for careful and continuous information, and the modification of erroneous beliefs.

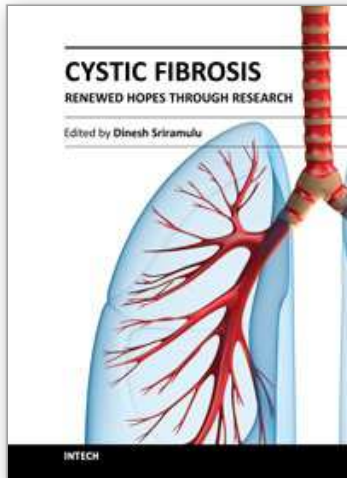
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## **Cystic Fibrosis - Renewed Hopes Through Research**

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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.

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