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Cystic Fibrosis Pulmonary Exacerbation – Natural History, Causative Factors and Management

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1. Introduction

Cystic Fibrosis (CF) is the most common life-threatening inherited disease in the United Kingdom, affecting over 9,000 people, 56% of which are 16 years or older (UK CF Registry Annual Data Report 2009). Life expectancy currently remains well below the general population, but with improvement of care most CF patients born after 1980 are expected to reach adulthood. Much of the morbidity and mortality associated with CF are related to the respiratory system (Goss & Burns, 2007).

Recurrent acute infective pulmonary exacerbations are one of the most important features of CF. Pulmonary exacerbations are common events throughout the lifetime of a patient with CF. Frequent exacerbations are associated with impaired quality of life and accelerated decline in lung function (Marshall, 2004; Britto et al., 2002; Liou et al., 2001; Ramsey, 1996). Statistical models have demonstrated that frequent pulmonary exacerbations are also associated with premature mortality (Liou et al., 2001).

Preventing and treating pulmonary exacerbations promptly and appropriately are therefore key therapeutic goals of the CF community that clinicians endeavour to employ in the effort to positively impact on long term outcomes, survival and quality of life of CF patients.

2. The pathophysiology of CF lung disease

Despite CF being one of the most studied and understood genetic diseases, the exact pathophysiology of recurrent CF pulmonary exacerbations is still not completely understood. The most accepted hypothesis to explain how the primary defect in CF, the mutations in the

cystic fibrosis transmembrane conductance regulator gene (CFTR), leads to the colonisation of the airways by bacteria, chronic infection and inflammation and ultimately airway injury is the "low volume hypothesis" (Boucher, 2004).

The airways are covered by airway surface liquid, composed by two separate fluid layers, a superficial mucus layer and an underlying lubricating pericellular environment near the cell surface. A thin layer of surfactant separates the mucus and the periciliary fluid layer (figure 1).

The mucus layer is produced by goblet cells and submucosal glands and is composed of water, carbohydrates, proteins and lipids, extending from the intermediate airways to the upper airways. It normally is composed of a network of mucous glycoproteins or mucin. Its adhesive characteristic means that the mucus layer binds and traps deposited particles and its viscoelastic properties facilitate cilia movement into transporting mucus and also its clearance by cough. Mucus containing cellular debris and possible trapped microorganisms is transported from the lower respiratory tract to the pharynx by mucociliary clearance and air flow (Rubin, 2002). Mucus clearance is considered a most important innate airway defence mechanism (Randell & Boucher, 2006; Knowles & Boucher, 2002), and disruption of the normal mucus secretion and mucociliary clearance impairs lung defence and increases the risk of infection.

The periciliary fluid provides a watery environment that enables the cilia to beat and propel the mucus away towards the upper airways. Appropriate clearance and hygiene maintenance of the respiratory tract requires coordinated interaction of the mucus and periciliary layers and for this to be effective, adequate hydration of the near-cell airway surface is critical.
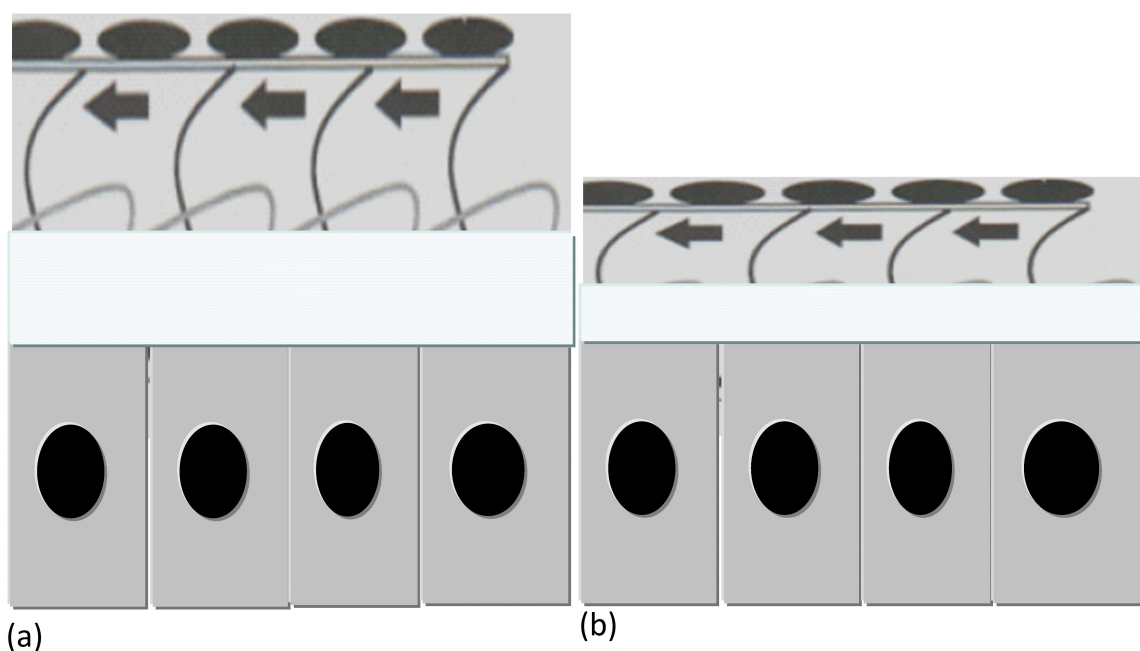

(a)   (b)

Figure 1. The fluid surface area in normal patients (a) and in patients with CF (b). The epithelial cells are covered by two layers of fluid – a serous layer (white band) and a mucous layer (grey area). In CF patients and due to the disease process, both layers shrink and the shape of the cilia and its movement are adversely affected.

The volume of the periciliary airway surface fluid is normally precisely regulated and is critical for efficient mucus flow and elimination. In the normal airway epithelium, the amount of fluid is determined by a combination of ion channels that promote the secretion of salt and water, such as the CFTR and alternative anion channels, and others that promote absorption of sodium and fluid, such as epithelial sodium channels (ENaC) in the apical cell membrane. The CFTR also acts as a conductance regulator, influencing and down regulating the latter.

In the CF epithelium, in consequence of the CFTR mutations, the CFTR gene product is faulty, whilst in normal conditions it is a transmembrane protein that functions as a chloride channel. The CFTR down regulatory function of ENaC activity is absent or compromised, resulting in abnormal ion transport properties due to the combined defects of accelerated sodium transport and failure to secrete chloride, resulting in overall increased absorption of sodium and fluid from the airway surface and consequently reduced, low volume of the airway surface liquid (Guggino & Guggino, 2000).

The loss of functional height of the periciliary layer in which the cilia beat, defined by the length of extended cilia, interferes with cilia motion and causes impaired ciliary function, resulting in slower mucociliary clearance with accumulation of mucus with trapped debris, microorganisms and airway secretory products, such as cytokines (e.g., interleukin-8), neutrophil proteases and growth factors that promote airway inflammation and mucus cell hyperplasia. In consequence of increased number of mucus secreting goblet cells, there is persistent mucin secretion, which generates high volume of thick, inspissated mucus, which adheres to and obstructs the airways and is resistant to cough clearance and is an ideal site and reservoir for bacterial growth. The poor liquid content and hypoxic environment in these thick mucus plaques promote biofilm bacterial formation and bacterial overgrowth.

Mucus stasis and the presence of accumulated secretory products and bacteria triggers the recruitment of neutrophils to the airways and the release of pro-inflammatory cytokines, which lead to a vicious cycle of inflammation, airway obstruction, chronic infection, repeated pulmonary exacerbations and resultant airway tissue damage and loss of lung function (Frizzell & Pilewski, 2004).

3. Microbiology in the CF lung disease and relationship with pulmonary exacerbations

Pulmonary exacerbations in CF are caused by recognised typical pathogens that are acquired following a characteristic age-dependent pattern (figure 2). Whilst still very young, CF patients suffer their first infections most frequently caused by *Staphylococcus aureus* and *Haemophilus influenzae*. *S. aureus* is often the first organism isolated from children with CF, but the role of this bacteria in the pathogenesis of CF remains under debate as studies reveal conflicting results in regards to clinical benefits from anti-staphylococcal therapy (Smyth & Walters, 2003; Lyczak et al., 2002). Non-typeable *H. influenzae* is also commonly cultured from CF children as early as in their first year of life, but although it can cause exacerbations in patients with non-CF bronchiectasis (Barker, 2002), its role in CF is still unclear (Goss & Burns, 2007).

Other relevant pathogens in CF usually cultured later in the course of the disease include *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*. The *B. cepacia* complex has at least 10 distinct genomovars and is related with rapid clinical deterioration. The most virulent and transmissible form is the genomovar III, B. cenocepacia, due to its well recognised association with severe necrotising pneumonia and death first described over 20 years ago (Isles et al., 1984). *S. maltophilia* and *A. xylosoxidans* are more prevalent than the *B. cepacia* complex, but seem to be less virulent, although their role in the pathogenesis of the CF lung is not yet completely understood (Goss et al., 2002).
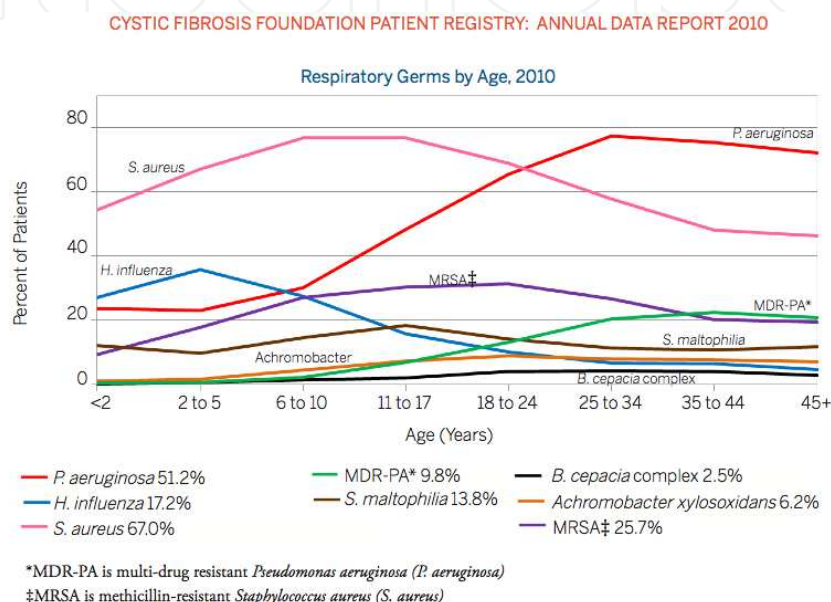

Figure 2. Prevalence of respiratory pathogens according to patient's age. Data from Cystic Fibrosis Foundation Patient Registry, 2010 Annual Data Report.

Pseudomonas aeruginosa is considered to be the most important pathogen in CF. By the time patients reach adulthood, up to 80% of them become infected with *P. aeruginosa*. The transformation of *P. aeruginosa* from the non-mucoid to the mucoid strains, which often occurs during adolescence years (figure 3a), is pivotal and is known to be associated with clinical (figure 3b) and radiological deterioration (figure 3c) (Li et al., 2005). At initial colonisation, *P. aeruginosa* presents a phenotype similar to environmental strains, but this changes dramatically with time and prolonged infection as *P. aeruginosa* has the potent ability of quorum sensing which leads to biofilm formation (Drenkard & Ausubel, 2002). Biofilm is a matrix of proteins, carbohydrate and collagen and muco-polysaccharide within which the bacteria reside. This layer is often called alginate formation. The formation of alginate biofilm has 3 important consequences:

1. The bacteria are protected from antibiotics, which increases the minimal-inhibitory concentration.

2. The film reduces the activity of aminoglycosides and beta-lactam antibiotics by changing the pH of the respiratory mucosa and by production of beta-lactamase – ironically,

mucoid *P. aeruginosa* tend to exhibit greater in vivo sensitivity to antibiotics than non-mucoid strains in the same patient.

3. The biofilm formation is highly immunogenic and tends to accelerate structural lung damage leading to significant histological and radiological changes.

The incidence and clinical impact of mucoid *P. aeruginosa* (figure 3a) in the sputum of a co-hort of patients with CF according to age. The emergence of these bacteria is associated with decline in FEV1 (figure 3b) and worsening of radiograph appearance (figure 3c). (Adapted from Li et al., 2005).
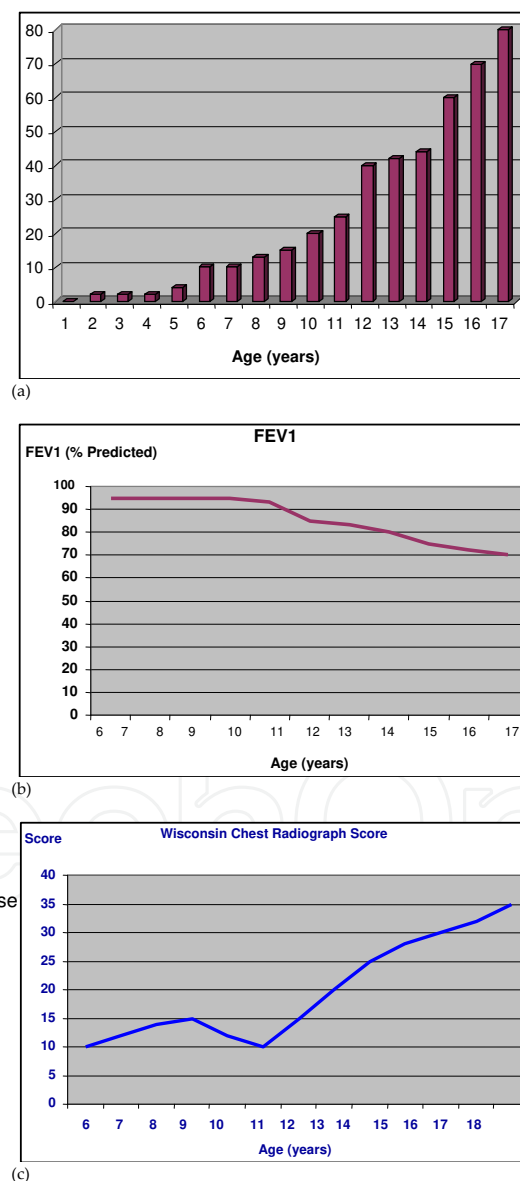

(a)

(b)

(c)

Figure 3. (a): Proportion (%) of *P. aeruginosa* with mucoid strains per age group. (b): Change in FEV1 for the same CF group as in 3a. (c): Change in the chest radiograph appearance in the same CF group as in 3a

4. Acute pulmonary exacerbations in CF

Pulmonary exacerbations in CF are an important feature of the disease. Frequency of pulmonary exacerbations is associated with accelerated decline in lung function tests, impaired quality of life and premature mortality. Nevertheless, defining what constitutes a pulmonary exacerbation remains controversial.

To date there is not yet a consensus or a standardised diagnostic criteria as to what clinically characterises pulmonary exacerbations in CF (Abbot et al., 2009; Dakin et al., 2001), but all descriptions point to that patients present with a combination of symptoms. Although, not stated clearly, the implication is that symptoms during exacerbations are greater than symptoms during 'disease stability'.

Pulmonary exacerbations are usually described by patients in subjective terms as an increase in one or more respiratory symptoms, such as cough, sputum volume, viscosity and colour change, breathlessness; altered systemic symptoms, such as increased fatigue, decreased appetite and energy levels. This is usually, but not always associated with an increase in objective clinical signs and changes in biomarkers. These included: weight loss, tachypnoea, tachycardia, decreased lung function parameters, chest radiographic changes and raised serum inflammatory markers (Ramsey et al., 1999; Fuchs et al., 1994).

The lack of a standardised definition is also present when it comes to classifying pulmonary exacerbations according to their severity. Pulmonary exacerbations are broadly divided into: a) mild exacerbations requiring treatment with oral antibiotics and b) severe exacerbations needing treatment with intravenous (IV) antibiotics. It also remains unclear if mild exacerbations are the originators of severe infections, if they are earlier milder versions of severe pulmonary exacerbations or in fact differentiated clinical episodes with no correlation between mild and severe infections (Goss & Burns, 2007).

Despite the lack of agreement, several diagnostic systems are described in the literature and used in CF clinical trials, such as the Fuchs et al. (1994) Pulmozyme® study and the Ramsey et al. (1999) inhaled Tobramycin study diagnostic criteria, and the consensus document by the US CF Foundation, 1994 (tables 1, 2 and 3).

These definitions, often called "symptom-related definitions", although widely used, have 3 shortcomings:

1. They do not account for differences of CF pulmonary exacerbations in children and adults. For example, the presence of fever and acute changes in chest radiographs are often seen in children, but not in adults.

2. They do not quantify symptom severity and do not give allowance for increased severity of a single symptom, which may make patients seek medical consultation and receive treatment. For example, marked increase in breathlessness, significant increase in cough production of viscous sputum or increased lethargy alone could be a single symptom that may constitute an exacerbation requiring treatment with antibiotics.

3. The above definitions do not stipulate that increase in symptoms should be sustained and should be beyond the natural fluctuation of symptoms encountered in most CF patients.

- Increased cough

- Dyspnoea or increased respiratory rate

- Change in appearance of sputum (i.e. consistency, increased purulence or volume)

- Lassitude and decreased exercise tolerance

- Decreased appetite

- Absenteeism from work or place of education

- Fever (>38°C)

- Progressive physical findings (crackles or wheeze) on chest auscultation

- New infiltrate on the chest X-ray

- Deterioration of 10% or more of the highest FEV1 measured in the last 6 months

Table 1. Signs and symptoms of pulmonary exacerbations as agreed by the consensus document of the US Cystic Fibrosis Foundation, 1994. Typically a combination of 3 or more signs and symptoms represent a pulmonary exacerbation.

- Change in sputum

- New or increased haemoptysis

- Increased cough

- Increased dyspnoea

- Malaise, fatigue, or lethargy

- Temperature above 38°C

- Anorexia or weight loss

- Sinus pain or tenderness

- Change in sinus discharge

- Change in physical examination of the chest

- Decrease in pulmonary function by 10% or more from a previously recorded value

- Radiographic changes indicative of pulmonary infection

Table 2. Fuchs et al. (1994) Pulmozyme Study: "Exacerbation of respiratory symptoms": a patient treated with parenteral antibiotics for any 4 of the following 12 signs or symptoms:

- Fever (oral temperature >38°C)

- More frequent coughing (increase of 50%)

- Increased sputum volume (increase of 50%)

- Loss of appetite

- Weight loss of at least 1 kg

- Absence from school or work (at least 3 or preceding 7 days) due to illness

- Symptoms of upper respiratory tract infection

- These symptoms had to have been associated with at least 1 of the following 3 additional criteria:

- Decrease in FVC of at least 10%

- An increase in respiratory rate of at least 10 breaths/min

- A peripheral blood neutrophil count of 15,000/mm3

Table 3. Ramsey et al. (1999) Inhaled Tobramycin Study: Pulmonary exacerbation indicated by at least 2 of the following 7 symptoms during the study.

In a retrospective analysis of 77 pulmonary exacerbations in 88 adult patients, the authors found that IV antibiotics were given to 18 patients (24.4%) whose symptoms did not meet the US CF criteria (table 1) (Jeffcote et al., 2004). This would suggest that nearly one quarter of patients presented with sufficiently severe symptoms to warrant treatment with IV antibiotics, although the combination of factors did not meet the pre-designed criteria.

For this reason, we explored another definition of pulmonary exacerbations, which resembled the internationally accepted definition of exacerbation in chronic obstructive pulmonary disease (COPD). In such patients, pulmonary exacerbations are defined as "an event in the course of the disease in which there is a sustained worsening of the patient's respiratory symptoms from the stable state that is beyond normal day-to-day variations, that is acute in onset and necessitates escalation of treatment". This is often termed as "an action-definition" in which an exacerbation is regarded to be present when the following 3 criteria are met:

1. The increase in respiratory symptoms is sustained (lasting 2-3 days).

2. The symptoms are subjectively more than the patient's own baseline symptoms – enough so that the patient seeks medical treatment.

3. The symptoms are objectively compelling to the physicians as to be deemed to require escalation of treatment with antibiotics.

This definition has its problems too. Patients have different thresholds for seeking medical care and therefore some may present more frequently than others, despite similar severity of symptoms. Another problem is that in countries where patients have to pay for their treatment, financial restraint may prevent patients from seeking medical treatment for exacerbation of symptoms.

To try to resolve this issue, Sarfaraz et al. (2010) conducted a study using electronic remote daily telemonitoring of symptoms in a cohort of adult CF patients. The study highlighted several issues in the management of CF exacerbations. Out of the 51 patients enrolled in the study, 32 (63%) patients were subsequently excluded as their recordings were not frequent enough to form a baseline data or insufficient to look into the natural history of the disease (Figure 4). Furthermore, for the remaining 19 patients who completed the study, an average of only 60% of the total number of study days was recorded.

Despite these significant deficiencies, there were enough CF pulmonary exacerbations for analyses. The authors noticed that 75% of all CF exacerbations had a "prodromal" phase in which one or more than one symptom increased in the 2 weeks prior to exacerbations (Figure 5).

In order to examine whether the problem with daily recording was related to the introduction of a modern system, a parallel study in COPD patients was carried out (Sund et al., 2009). A systematic comparison between the 2 groups was later published (Jarad & Sund, 2011). The comparison revealed that the dropout rate was much smaller for COPD patients, who recorded daily data in 77% of the total number of study days (figure 6). In accordance with the higher recording rate by COPD patients, the number of early exacerbations diag-

nosed was higher than that in CF patients and the number of hospitalisation was much reduced in COPD patients (but not in CF patients) compared to a similar period without daily monitoring the year prior to the study.

Figure 4. An example of the daily recording of a 23 male CF patient. The Y axis is the score of each symptom (cough, sputum, breathlessness and fatigue). For FEV1, the Y axis is the value in litres. The time line on the X axis is divided in weeks. Note that only 9 days were recorded by the patients out of possible 49 days (7 weeks). This patient was withdrawn from the study.
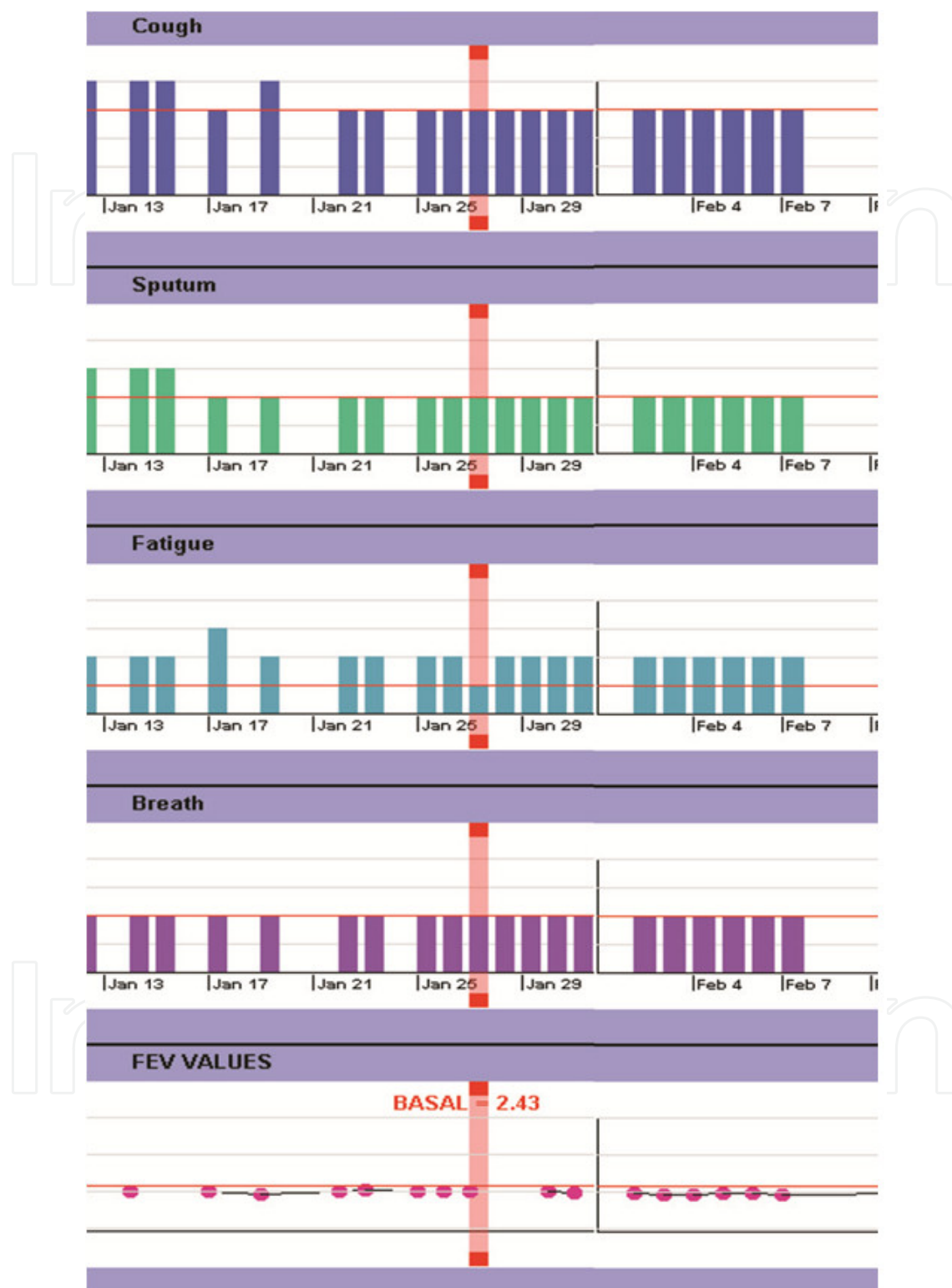
Figure 5. A 24 year old female CF patient who had a pulmonary exacerbation (marked with the red vertical line) defined by the decline in FEV_1. Note that there was a "prodromal phase" manifested by increase in cough and fatigue within the 2 weeks prior to the exacerbation.
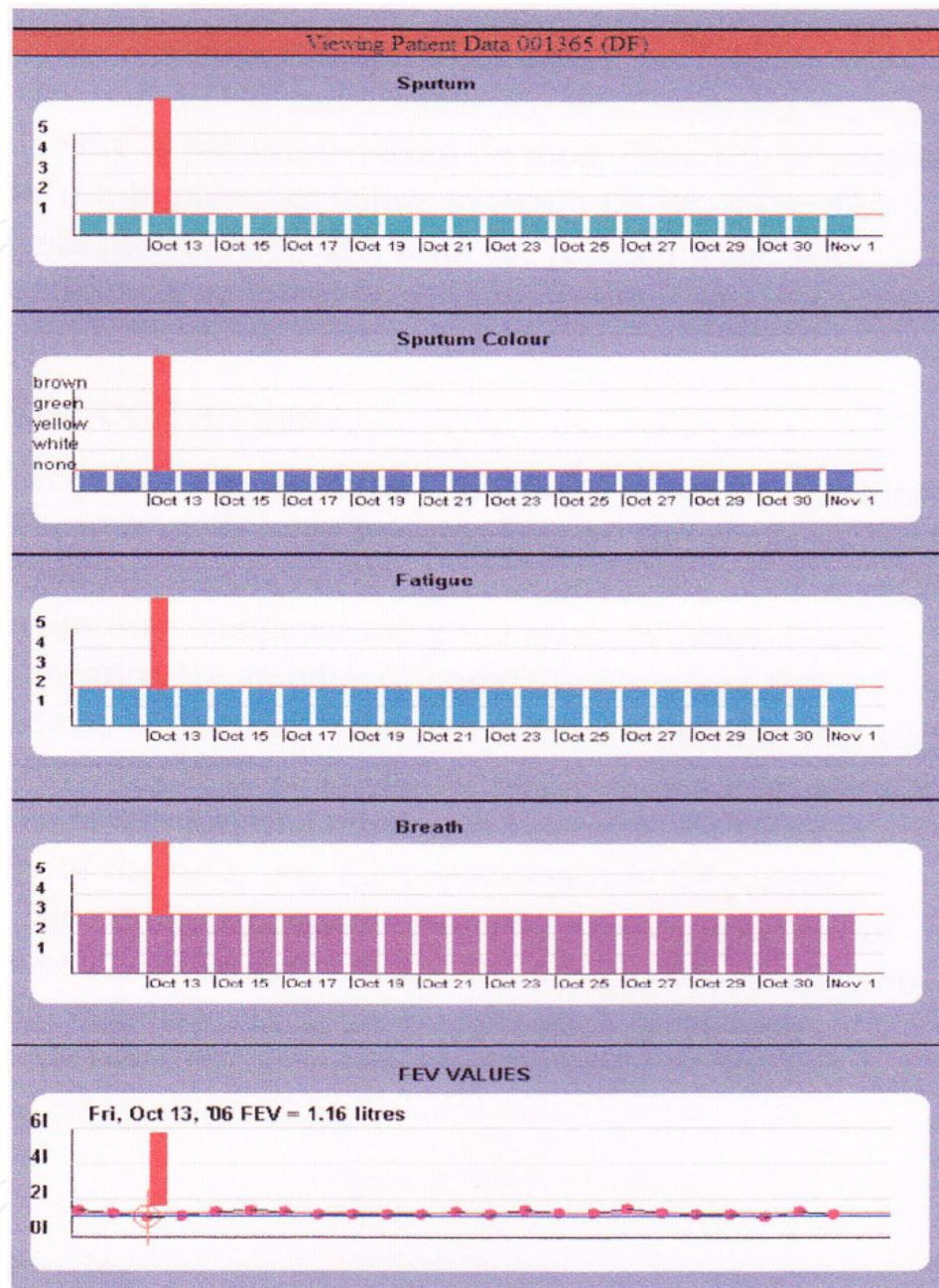
Figure 6. A recording from a patient with COPD. The red line represents an exacerbation defined as 15% decline in FEV1 below the baseline. Note the patient performed a daily recording without interruption allowing a proper identification of acute exacerbation.

Differences between the two groups may not only reflect differences in disease processes and age groups. They may also disclose the differences in the system of care for CF patients who tend to have a privileged access to hospital care through direct contact with a CF multidisciplinary team. This is not available to COPD patients, whose contact with healthcare takes place through a general practitioner.

5. Causes of pulmonary exacerbations

Whilst still not completely understood, causes of pulmonary exacerbations are most likely multi-factorial, and may differ amongst patients.

Nevertheless, CF pulmonary exacerbations are probably a consequence of a loss of equilibrium between host defence mechanisms and the airway microorganisms. It is believed that viruses, including respiratory syncytial virus, have a role in pulmonary exacerbations (Hiatt et al., 1999), and whilst these have also been associated with the acquisition of new organisms, for the majority of adult CF patients a new pulmonary exacerbations seems to be caused much more commonly by a clonal expansion of already present colonising bacteria (Aaron et al., 2004).

Only rarely are pulmonary exacerbations a consequence of newly acquired bacteria. The increase in bacterial load in conjunction with an inflammatory response of the airways result in a local influx of polymorphonucleocytes and the release of inflammatory mediators such as interleukins – (IL) 8, 6, 1β, tumour necrosis factor alpha (TNF-α), leukotriene B4 and free neutrophil elastase.

Treatment with antimicrobial agents is associated with decreased levels of inflammatory mediators and bacterial density and improvement of symptoms and lung function parameters (Colombo et al., 2005; Ordonez et al., 2003; Sagel et al., 2001; Bonfield et al., 1995; Konstan et al., 1994; Konstan et al., 1993). This suggests that the increased density of microbes plays an important role in pulmonary exacerbations. What remains unclear is the lack of ability of powerful antibiotics given at great doses in eradicating pulmonary microbes in CF patients. Rather it would seem that the role of antibiotics is akin to cutting the grass in a front garden lawn, only for the grass to grow again.

6. Epidemiology and risk factors

CF pulmonary exacerbations are common and the impact they have on patient care, especially in terms of labour intensiveness, is the main reason for the establishment of CF centres and teams. In addition, treatment of pulmonary exacerbations accounts for a significant part of the cost of CF care.

In a cross sectional study on adult CF patients in the South West of England, Jarad & Giles (2008) found that a significant number of patients did not suffer from any pulmonary exacerbation. Many patients, however, suffered from at least one exacerbation every year (figure 7). When examining risk factors of exacerbations, reduced FEV1 (figure 8), infection with *P. aeruginosa* (figure 9) and cystic fibrosis related diabetes (CFRD) were correlated with increased rate of exacerbations (figure 10) (adapted from Jarad & Giles, 2008). Remarkably, genetic profile, diagnostic sweat chloride, body mass index, age and gender did not correlate with frequency of pulmonary exacerbations.

In addition, this study concords with previous studies that have demonstrated factors associated with pulmonary exacerbations, such as young age, female gender, lower FEV1, CFRD and previous history of multiple exacerbations (Block et al., 2006; Marshall et al., 2005).

Conversely inhaled antibiotics such as aminoglycosides, oral macrolides, mucolytics and inhaled hypertonic saline have been shown to reduce the rate of pulmonary exacerbations (Gibson et al., 2003; Saiman et al., 2003; Ramsey et al. 1999; Fuchs et al., 1994), presumably by reducing the bacterial load and inflammation and clearing the airways, reducing the volume of retained secretions.
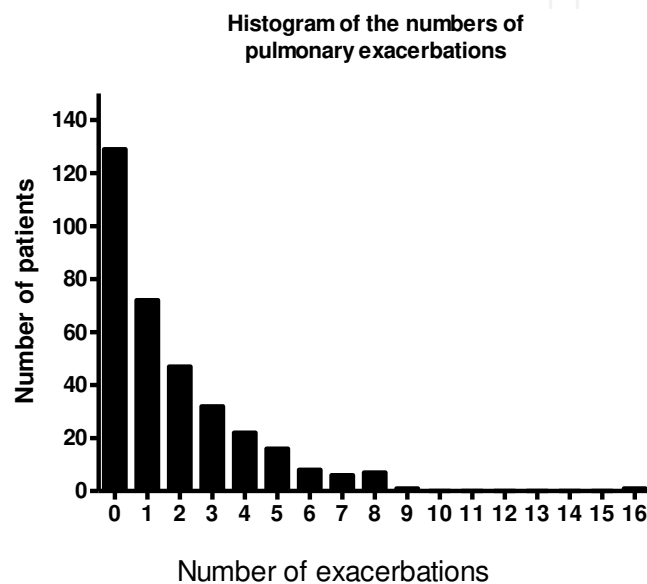

Figure 7. A histogram of the number of exacerbations experienced in one year by 680 patients in the South West of England.
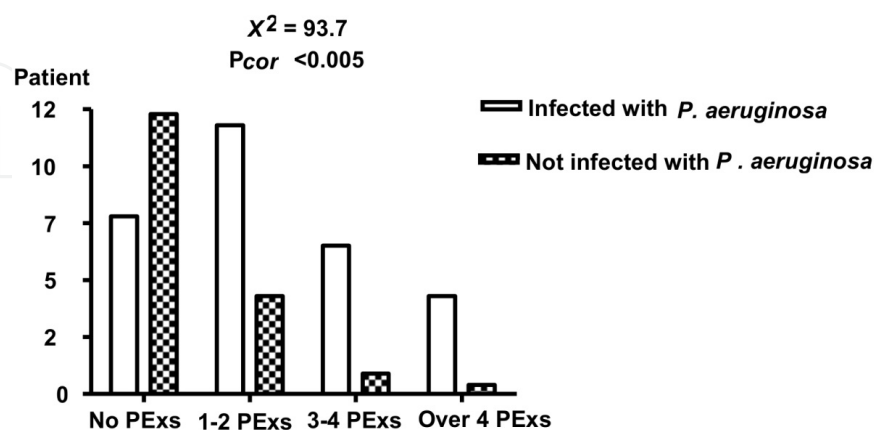

Figure 8. Patients with and without chronic infection with *P. aeruginosa* in 4 annual exacerbations category. Note that the proportion of those who are infected is greater with increased frequency of annual exacerbations. PExs = number of pulmonary exacerbations per year.
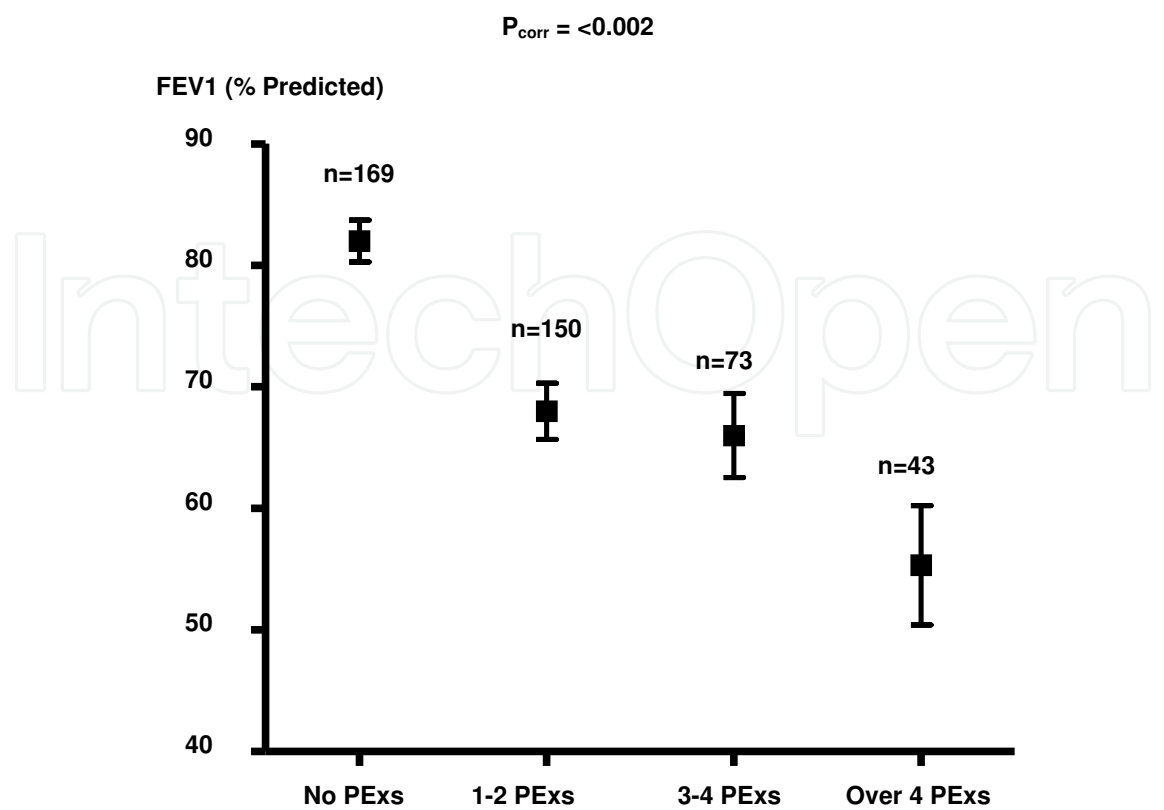
$$P_{corr} = <0.002$$

FEV1 (% Predicted)

Figure 9. Annual exacerbation frequency increases in patients with lower FEV1. N = number of patients per group. PExs = number of pulmonary exacerbations per year.
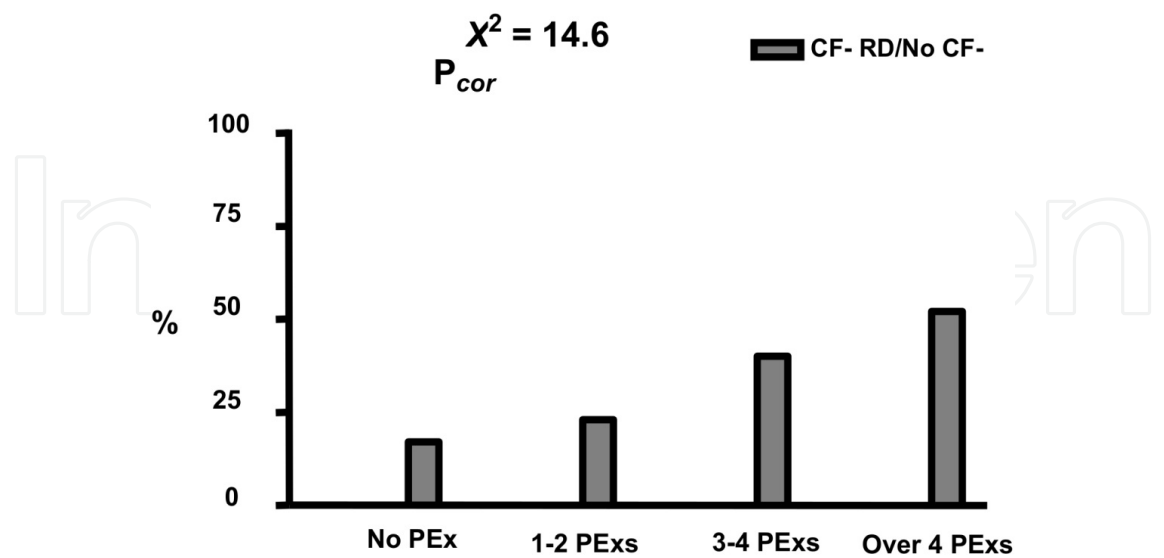
$$X^2 = 14.6$$
$$P_{cor}$$

CF- RD/No CF-

Figure 10. Proportion of patients with CFRD and without CFRD according to annual exacerbation frequency. PExs = number of pulmonary exacerbations per year.

7. What affects the time until the subsequent CF pulmonary exacerbations?

Time from the end of one pulmonary exacerbation until the subsequent exacerbation (time until the next exacerbation) is a significant health outcome and one of the significant end points in many CF clinical trials. Shorter periods until the following exacerbation is a marker of increased impact of disease on patients. In a prospective study on 170 exacerbations in 58 adult CF patients, (Sequeiros & Jarad, 2012), the median time until subsequent exacerbations was 112 days, although this varied considerably (figure 11).
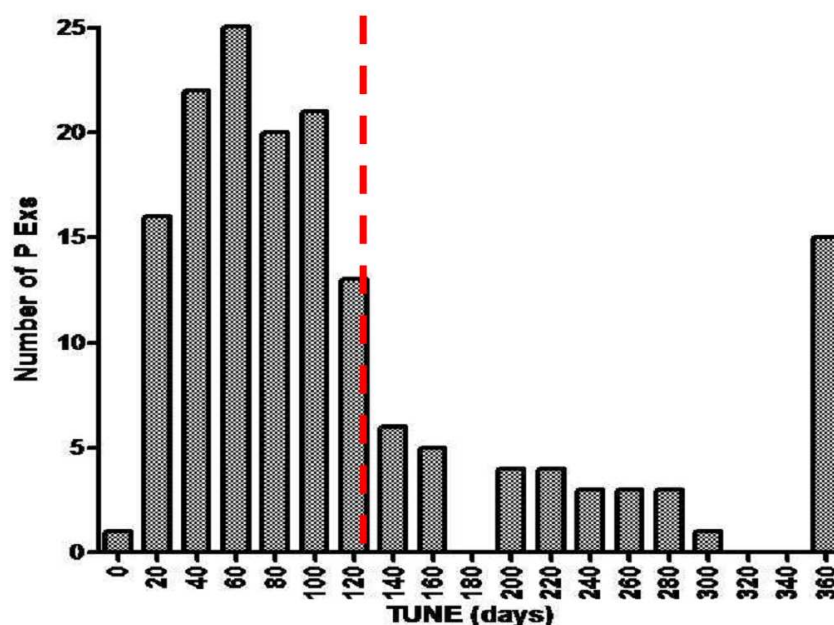

Figure 11. A histogram of time until the next exacerbation on the X axis. Median time (red vertical line) was 121 days, although this varied considerably. Those patients who did not have an exacerbation during the subsequent year after the first pulmonary exacerbation were regarded to have a time until the next exacerbation of 360 days (adapted from Sequeiros & Jarad, 2012).

Factors affecting shorter periods until the following pulmonary exacerbation were examined, including age, lung disease severity, CF related complications (CFRD, allergic broncho-pulmonary aspergillosis (ABPA)), chronic infection with *P. aeruginosa* and site of administration of antibiotics – either home or in hospital. In addition, symptom scores, lung function tests and inflammatory biomarkers at the end of the IV treatment were examined.

When analysing individual variables, patients with lower FEV1, greater symptom scores and higher C-reactive protein (CRP) at the end of the exacerbation treatment were associated with shorter time until the next exacerbation. Also patients with ABPA and CFRD had a shorter time until the next exacerbations than those without. After adjustments to confounding factors, however, older CF patients and those with lower FEV1 at the end of course of treatment were found to be the two independent risk factors.

8. Management of pulmonary exacerbations

The mainstay of treatment of pulmonary exacerbations is administration of antibiotics. For mild exacerbations oral antibiotics are usually administered – mainly quinolones. This approach is based on little evidence, since a large proportion of patient have quinolone resistant *P. aeruginosa*.

More severe exacerbations are prescribed IV antibiotics. As most patients with frequent exacerbations commonly grow *P. aeruginosa* in their sputum, CF physicians prescribe two antibiotics aiming to effectively decrease the bacterial load and reduce the probability of developing antibiotic resistance. The choice of antibiotic class range would often include an aminoglycoside (tobramycin, gentamycin and amikacin) and a beta-lactam (ceftazidime, aztreonam, pipracillin or ticarcillin) or a quinolone (ciprofloxacin). In more recent years, carbopenims (imipenim or meropenim) are being more frequently used. Occasionally IV colistine is prescribed in cases of bacterial resistance. The duration of treatment is often 2 weeks.

The doses of antibiotics given for CF patients are often larger than those given to other respiratory and non-respiratory infections. This is, theoretically, thought to be necessary due the high bacterial load in the damaged and inflamed lungs and the difficulty of antibiotics penetrating the thick layer of inspissated sputum to reach the bacteria – in particular when mucoid *P. aeruginosa* is present.

Lack of evidence of how to optimally manage CF pulmonary exacerbations is, in part, due to the fact that the determinants of the successful outcome of treatment of an exacerbation have not yet been clearly identified. In most CF centres improvement in general clinical status and in lung function tests are accepted to determine the 'end' of the exacerbation. For those patients who do not show sufficient improvement in the opinion of the treating physicians, the course of antibiotics is either extended or the combination of antibiotics is changed. Despite its shortcomings, this approach has been endorsed in a consensus document published by the UK CF Trust (UK CF Trust Antibiotic Guidelines 2008).

For pulmonary exacerbations treated with IV antibiotics, the combination of choice is often determined on arbitrary grounds. Previous *in vitro* sensitivity and previous clinical response normally determine the choice of antibiotics. However, several retrospective and prospective studies found that the concordance of *in vitro* sensitivity did not affect any of the outcomes of the CF exacerbations, including lung function tests and the time until the subsequent pulmonary exacerbation (Jarad et al., 2007; Foweraker et al., 2005).

Frequent and longer courses of IV treatment, particularly with aminoglycosides, have been shown to be associated with renal impairment (Smyth et al., 2008; Al Aloul et al., 2005) and ototoxicity (Mulheran et al., 2001; Scott et al., 2001), as well as increased rate of antibiotic allergy (Moss et al., 1984). In addition, extension of duration of IV antibiotic treatment is associated with added volume of work to patients and CF staff and in incremental cost pressure of CF care.

Two retrospective studies (Sanders et al., 2010; Rosenberg & Scharamm, 1993) found that administration of antibiotics for 14 days in adolescent and young adult CF patients resulted in

clinical recovery in 72% and 75% of patients respectively. A recent guideline committee for treatment of CF pulmonary exacerbations that studied the literature of management of exacerbations found no evidence for the optimal duration of treatment of CF pulmonary exacerbations (Flume et al., 2009). The committee recommended that future studies should examine short and long term subjective and objective outcomes of management of exacerbations according to duration of treatment.

Risk factors and efficacy of extending the course of antibiotics have been prospectively examined (Sequeiros & Jarad, 2012). As in previous studies, nearly 23% of 168 pulmonary exacerbations in 58 adult CF patients did not recover after 2 weeks of IV antibiotic treatment, needing extension of duration of treatment. For those prescribed extended courses, most patients required additional 7 days of treatment, but some needed doubling of the duration of treatment (figure 12). Unlike previous studies, a validated symptom score was used and biomarkers measured at the end of treatment were examined.
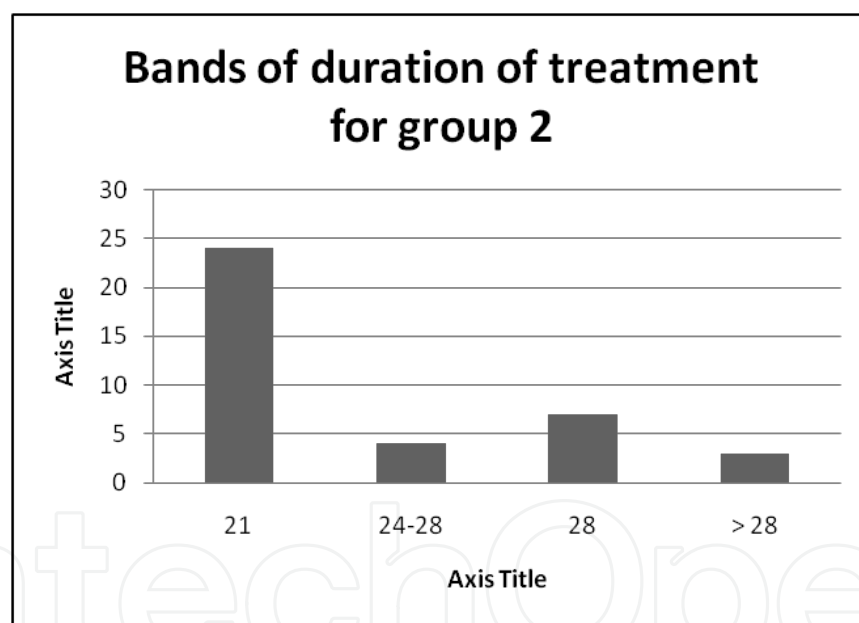

Figure 12. A histogram of the number of patients (Y axis) and duration of treatment for exacerbations for patients needing extension of IV treatment (X axis). Most patients needed additional 7 days, but some needed at least doubling the duration of treatment (Adapted from Sequeiros & Jarad, 2012).

Risk factors for extending the IV course were found to be more severe lung disease and persistent respiratory symptoms and systemic inflammation as assessed by CRP at the end of treatment. The extension of treatment beyond 14 days resulted in improvement of symptoms, but not of FEV1. Extension of treatment did not result in increased time to the next exacerbation.

9. What measurements determine the outcome of CF pulmonary exacerbations?

The aim of management of CF pulmonary exacerbations is to restore patients to pre-exacerbation clinical status. In most CF centres, determining the end of an exacerbation is done arbitrarily during clinical consultation.

Sequeiros et al. (2009) examined several clinical parameters throughout the duration of treatment of exacerbations with IV antibiotics to assess which one best correlated with the patient's clinical picture. These included spirometry, airway calibre and airway resistance assessed by high frequency test. A novel symptom scoring system was also used, which has been more recently validated (Jarad & Sequeiros, 2012).

The symptom score was the parameter that changed most frequently at the end of treatment of exacerbations, more so than FEV1 and FVC (figure 13). As for airway calibre and resistance, these did not significantly change at the end of exacerbations. Changes in symptom score correlated with changes in FEV1 and FVC. The authors concluded that the novel symptom scoring system is sensitive to change with treatment and can be a useful tool for the assessment of treatment of pulmonary exacerbations.
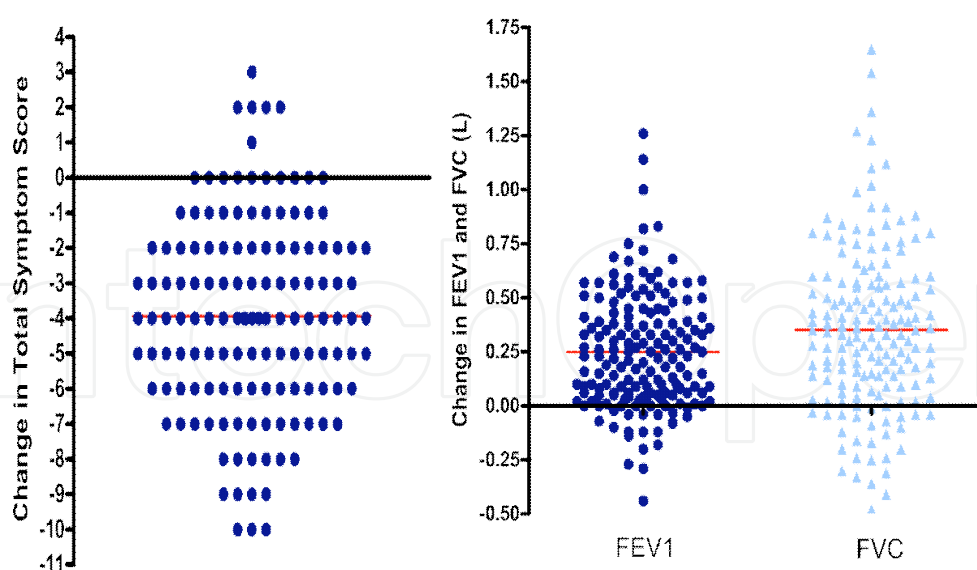

Figure 13. Change after 14 days of IV antibiotics in symptom score (lower score is better health status), FEV1 and FVC in a cohort of adult CF patients treated for acute pulmonary exacerbations. The symptom score improved in a higher proportion of patients in comparison with FEV1 and FVC.

10. Oral corticosteroids as an adjuvant to antibiotics

As discussed above, in addition to excessive bacterial growth, exuberant local lung inflammation is considered to play an important role in CF pulmonary exacerbations. In this context, using corticosteroids in addition to antibiotics during the treatment of exacerbations would be thought to be a logical approach.

Managing exacerbations with corticosteroids and antibiotics is the norm in patients with COPD. In a prospective study on inpatients with severe COPD who were hospitalised due to acute exacerbations, Davies et al. (1999) found that adding 30mg prednisolone for 14 days to usual treatment resulted in improvement of FEV1 and shortening of length of hospital stay compared with placebo-treated patients.

For CF patients, an open label study found that adding oral corticosteroids resulted in an improvement of FEV1 in a small cohort of adult CF patients (Dovey et al., 2007). Furthermore, a national UK survey performed in the authors' unit, found that all UK CF physicians had used adjuvant corticosteroids to different extents in managing CF pulmonary exacerbations (Hester et al., 2007).

This is important because of the increased propensity of CF patients to develop diabetes and osteoporosis by virtue of the CF disease process. Corticosteroids are bound to adversely affect the likelihood of these two complications, (increase the incidence and severity), as a significant negative side effect of the drug. To date there are no large trials to answer the question of whether adding corticosteroids to antibiotics improves outcome of treatment of CF exacerbations, and the issue remains contentious.

11. Elective courses of antibiotics versus symptomatic treatments

Elective regular administration of IV antibiotics several times per year has been a practice adopted by many CF teams to improve symptoms and reduce decline in lung function tests. In a national UK survey of CF centres (Higgs & Jarad, 2005), the authors found that greater proportion of paediatric patients received regular (elective) courses of IV antibiotics compared to adult CF patients (figure 14).

This is despite the fact that a previous study showed no differences in spirometry improvement in patients who received elective 3 monthly anti-pseudomonal antibiotic treatment compared to those who received conventional symptomatic treatment, triggered by increased symptoms. The elective group received an average of 4 courses of antibiotics per year, compared with an average of 3 courses per year in the symptomatic group (Elborn et al., 2000).
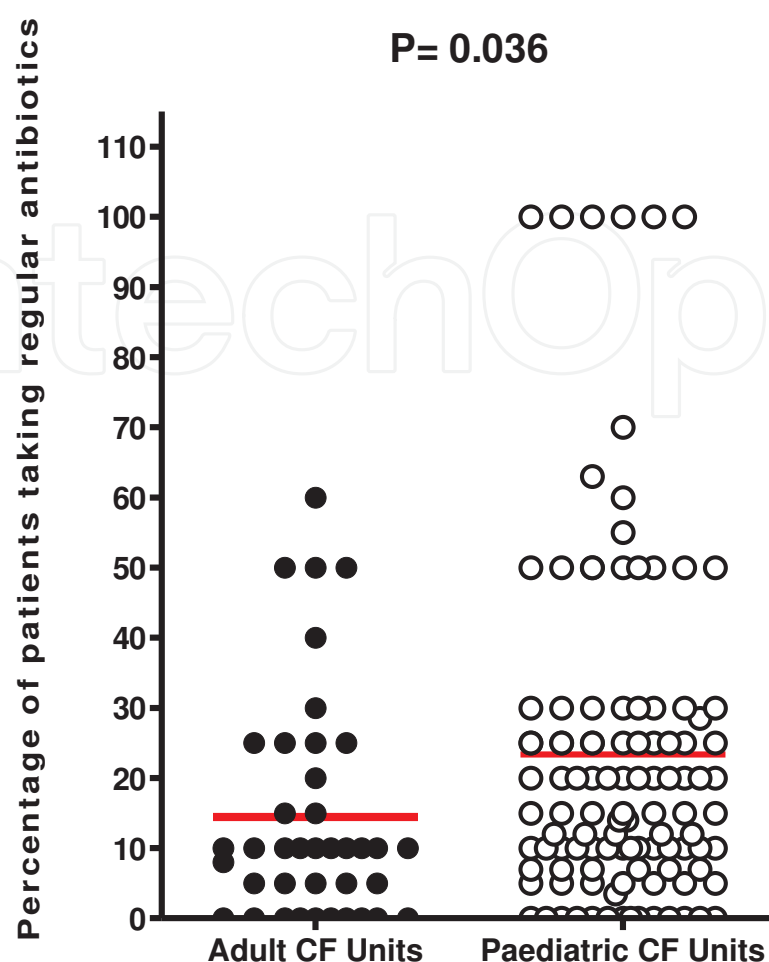
Figure 14. Larger proportion of paediatric CF patients received elective IV antibiotics in comparison to adult CF patients (Higgs & Jarad, 2005).

12. Self-administration of IV antibiotics

Delivery of healthcare for CF patients has changed significantly over the past 20 years. Previously all patients were managed in hospital, but there has been a drive for the management of chronic conditions at home. Although not specifically suggested, management of acute exacerbations of clinical conditions such as COPD, bronchiectasis and CF is also frequently being done at home.

CF patients with pulmonary exacerbations requiring IV antibiotics place a great strain on the capacity of hospitals in terms of the available number of beds, on their manpower and other financial resources with repeated admissions. Accommodation and boarding for patients and, sometimes, members of their families account for the largest fraction of hospital costs for inpatients. Equipment and drugs make up the largest proportion of home therapy costs (Wolter et al., 1997).

Self-administration of antibiotics was first introduced 30 years ago. This practice has been facilitated by improvement in technology and increased familiarity of patients and CF teams with antibiotics.

For patients with available peripheral venous access and infrequent exacerbations, antibiotics are administered via a peripherally inserted central catheter (PIC line) (figure 15). If such lines are inserted in the non-dominant arm, patients can self-administer their antibiotics.
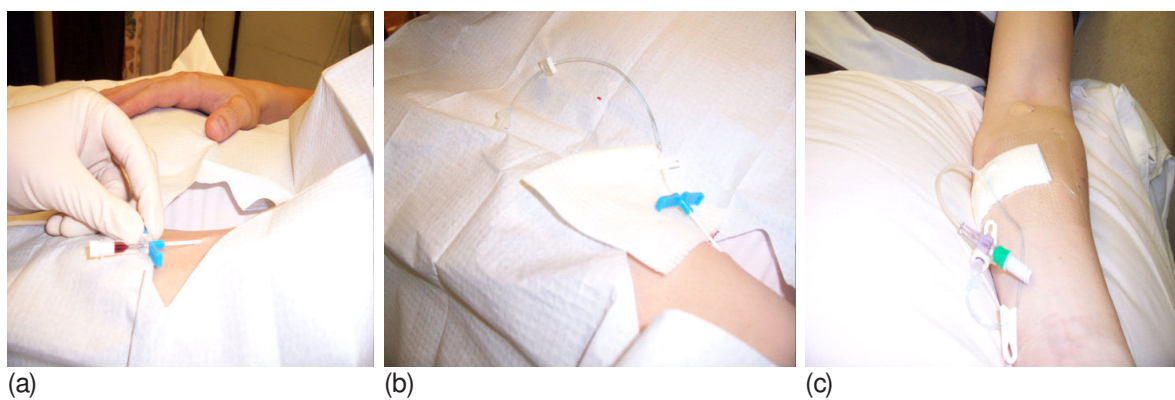

(a) (b) (c)

Figure 15. Insertion of a PIC line in the left arm of a right handed CF patient. The patient is able to self-administer antibiotics using his right hand.

Over the years, venous access frequently becomes more difficult to attain due to repeated use and occlusion of peripheral veins. In such patients, placement of a long-term totally implantable venous access system is an option. One of these methods, a port-a-cath, consists of a reservoir surgically inserted under the skin in the upper chest or arm, with the use of sedation or general anaesthesia. The reservoir is covered by a silicone mesh and appears as a bump under the skin. It leads to a long venous catheter, which is inserted into a central vein, usually a subclavian vein, and terminates in the superior vena cava. It is completely internal, so bathing and swimming are not a problem, although contact sports are contra-indicated due to risk of trauma and dislodgement of the device (figure 16).

Ports and peripherally inserted lines have their own complications and require specific care, such anti-septic manipulation and monthly local anticoagulation to prevent blockage from blot clots. Despite careful maintenance, infection and blockage are not uncommon. Irreversible occlusion of ports almost inevitably necessitates complete replacement.
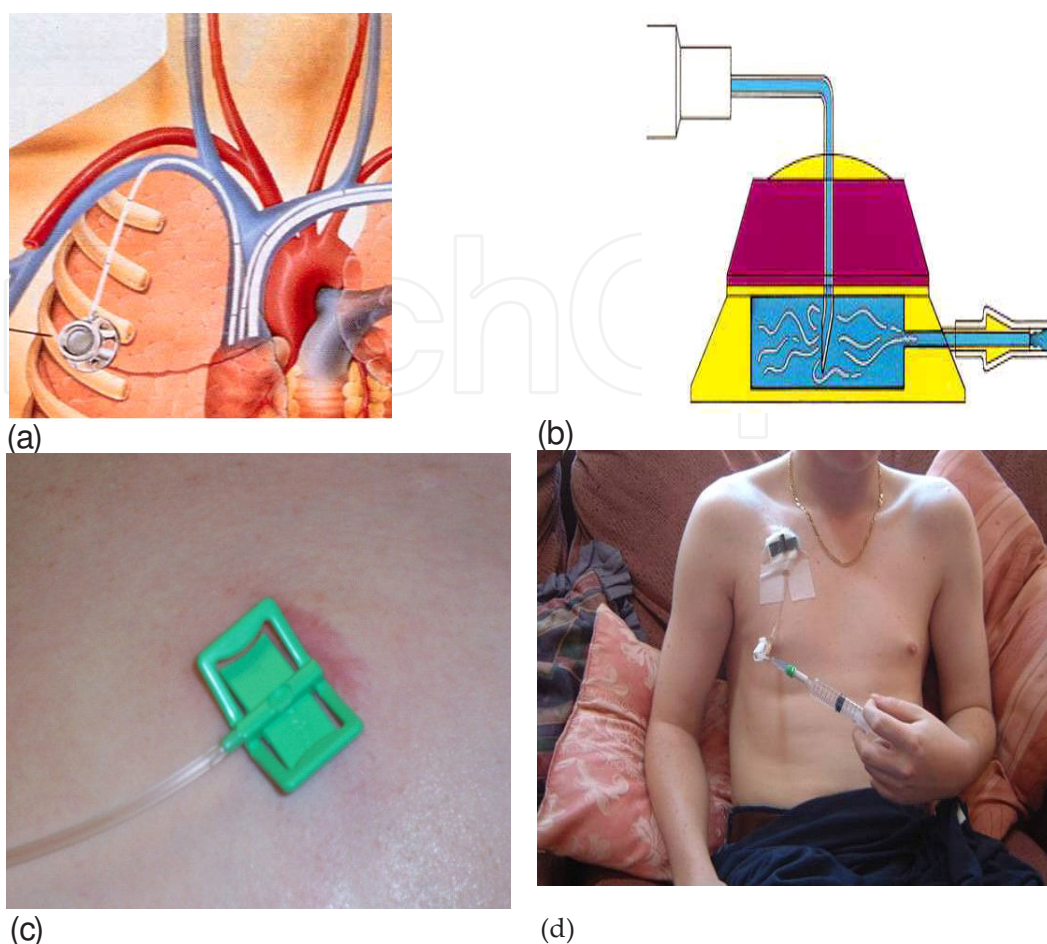
Figure 16. The port-a-cath. (a): schematic representation of the position of a port-a-cath. (b): accessing the device chamber by a specifically designed needle. (c) and (d): a needle is inserted into the port-a-cath chamber and a patient self-administering IV antibiotic via his port-a-cath.

13. Managing cystic fibrosis pulmonary exacerbations at home versus in hospital

Home therapy is becoming a preferred treatment option for patients with CF suffering from pulmonary exacerbations in the UK and other parts of the world. With the widespread practice of home based IV antibiotic therapy, concern has been expressed by CF healthcare workers about whether the outcome of care for those treated at home by self-administering IV antibiotics might be inferior to that of patients treated in hospital.

Hospital management is not favoured by most CF patients, who prefer home therapy (Thornton et al., 2005; Pond et al., 1994; Strandvik et al., 1992; Donati et al., 1987). Hospital treatment is probably disruptive to patients and their families, taking patients away from school or work commitments and social activities for considerable amounts of time. There are also financial strains on patients due to earning losses as a result of time off from work and travelling to hos-

pital expenses, especially if the treatment centre/hospital is at a considerable distance from the patient's home. After numerous admissions throughout their lives, patients and their families become acquainted with many aspects of IV drug administration and often want to start self-administration of these medications, avoiding hospital admissions (Gilbert et al., 1988). Reasons for patients' preference for home treatment are outlined in table 4.

- Less interruption to education and career

- Reduced earning losses and travelling expenses

- Tastier food

- More facilities to exercise

- Less disruption to sleep

- More convenient timing of drug administration

- Improved quality of life

- Reduced risk of cross infection

- Lack of hospital beds

Table 4. Reasons why patients prefer home IV antibiotic treatment.

The superior outcome of hospital management over home treatment has been attributed to closer supervision and direct input by the multidisciplinary team, including physiotherapists, dieticians and nursing staff, throughout the period of hospital stay (Thornton et al., 2004; Pond et al., 1994), ensuring increased adherence to treatment. Albeit unproven, bed rest during exacerbations has also been widely regarded as another reason for the favourable outcome of hospital treatment.

Conversely, there are numerous reasons why home treatment could be clinically less effective in treating exacerbations in CF patients (table 5). Considerable commitment is required from patients who are on home based treatment, as, in addition to their treatment schedules, they may wish to maintain their domestic routines and social lives, as well as fulfil educational and work commitments. Continuing with normal life and not taking time off work or school would mean maintaining higher general activity levels. These patients are probably not getting the amount of rest they need as part of their treatment (Thornton et al., 2005). Self-performed physiotherapy may not be as effective during exacerbations compared to the treatment provided by a professional physiotherapist and calorie intake may suffer without daily encouragement (Pond et al., 1994).

- Reduced medical input

- Reduced input from physiotherapists and dieticians

- Reliance on patients to diagnose own complications

- Possible lack of compliance with the IV treatment

- Lack of rest

Table 5. Reasons why healthcare professionals are concerned about the practice of home IV treatment.

Some antibiotic regimens for home treatment are adapted to make administration more convenient and more compatible with work and school hours (Pond et al., 1994). This includes twice daily beta-lactam antibiotics versus the recommended thrice-daily regime.

Another important issue is adherence, which is recognised as being potentially poor in CF (Dodd & Webb, 2000) and may be worse in some patients on home IV treatment. Although assessed by the multidisciplinary team for competency in terms of self-administration of drugs, the level of adherence of patients to treatment is not truly known. This is a widely anecdotally known phenomenon, often revealed when considerable amounts of unused antibiotics and other drugs are returned by patients and their families to the caring CF centre.

The conflict between patients' preference for home treatment and health providers' concern to achieve a favourable outcome of care during stages of clinical instability in CF is ongoing. This is currently handled in variable ways by different CF centres. Most centres feel that they have to offer some kind of home treatment, although a small number do not. Others prefer a happy medium of starting treatment in hospital and then discharging patients a few days later to complete the antibiotic course at home. Some CF centres prefer not to treat patients at home for two successive exacerbations.

More recently, Collaco et al. (2010) published a large retrospective study with a total of 834 treated exacerbations in both paediatric and adult patients in the United States. They conclude that similar decline in long term FEV1 was observed regardless whether antibiotics were administered in hospital or at home, with equivalence also found in regards to interval duration in between successive exacerbation episodes. Interestingly though, subjects treated in hospital had a statistically significant greater improvement of lung function immediately after treatment (immediate recovery) in comparison to the home treated group, despite similar pre-treatment spirometry. Also, patients treated in hospital had shorter total number of days of IV antibiotic treatment, implying that patients overcame their exacerbations quicker when treated in hospital (12.7 days versus 18.9 days), which of course impacts on quality of life, drug toxicity, antibiotic resistance and healthcare costs.

Given the controversy around this subject, Sequeiros & Jarad (2010) prospectively examined the effect of home treatment with intensive assistance from CF nurses, physiotherapists and dieticians on patient outcomes. The authors compared outcomes of this intensive intervention with outcomes of exacerbations treated at home without intensive assistance and in hospital.

The study showed that, unlike previous studies, those who were treated in hospital had initially poorer quality of life and were underweight compared to those who were treated at, but these recuperated to match post treatment levels similar to home based patients. The research also showed that, despite intensive home intervention, outcomes did not differ from standard home treatment and were inferior to those treated in hospital. The study has been published in abstract form (Sequeiros & Jarad, 2010) and is presently being prepared as a full manuscript for publication (figure 17).

Ideally, outcome of care for home treatment should be at least equal to outcome for hospital treatment and clinical improvement not sacrificed on the basis of economic considerations

and convenience (Pond et al., 1994). Selection of patients that are considered competent and safe for self-administered home treatment should be made carefully. A hygienic environment and adequate knowledge of preparation and administration of antibiotics should be ensured, as well as regular physiotherapy, rest and suitable nutrition, which are crucial for the successful treatment of CF exacerbations. Better still is the availability of support from family and friends, who are familiar with home treatment methods, as well as from the CF multidisciplinary team.

Patients need to be aware of the perceived reasons for an inferior outcome of home treatment and the CF community should definitively address these.
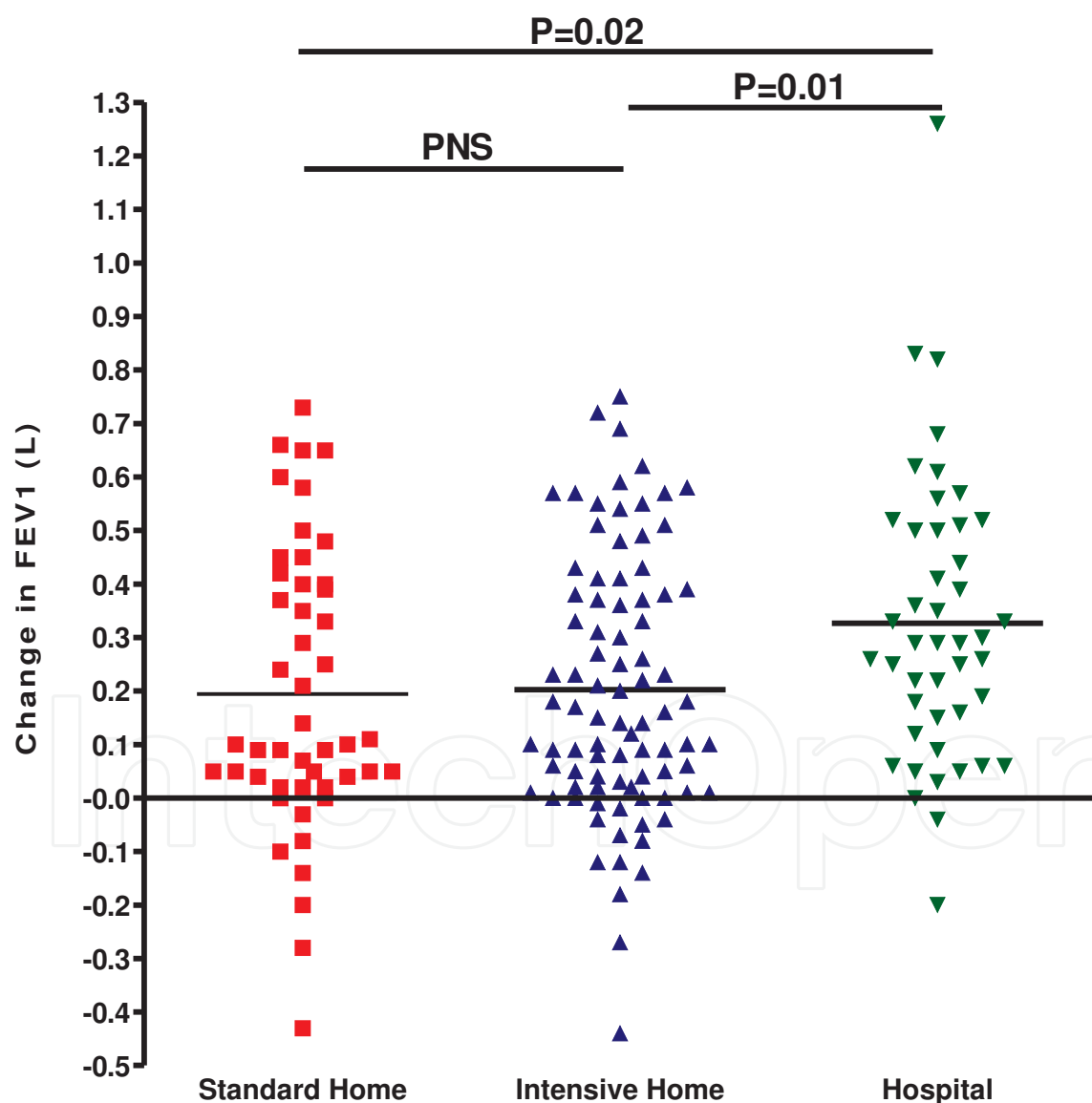

Figure 17. Changes in FEV1 with treatment of exacerbations treated at home with and without intensive assistance and in hospital. Best outcome is seen in the hospital treatment group (Sequeiros & Jarad, 2010).

14. Conclusion

CF exacerbations are complex and still not completely understood. However, they remain an important part of the CF lung disease due to their great negative impact on quality of life, resultant decline in lung function and mortality.

This chapter addresses the natural history, causes and aspects of management, and prognosis of CF exacerbations pertinent mainly to adult CF patients. Until introduction of more effective and disease modifying treatments for CF, better understanding and management of CF exacerbations remain an important goal for the CF community.

Prevention, accurate identification and treatment of pulmonary exacerbations are key to the improved survival and quality of life of CF patients. Efforts should be made to standardize treatments and ensure high standards of care throughout different CF centres worldwide.

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