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Outcome Measures for Respiratory Physiotherapy in Cystic Fibrosis — Challenges and Advances

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Abstract

Respiratory physiotherapy is part of the routine management of patients with cystic fibrosis. It normally consists of airway clearance techniques and exercise training. The evidence of such interventions has been questioned. Nevertheless, the lack of evidence should not be interpreted as lack of benefit. Instead, attention to methodological issues, such as the selection of the outcome measures, is needed, as they may hamper the establishment of the effectiveness of respiratory physiotherapy techniques. Hence, this chapter presents and discusses the strengths and weaknesses of conventional and emerging outcome measures possibly to be used (i) in clinical practice before, during and after each session of respiratory physiotherapy to monitor its effectiveness; (ii) before and after the respiratory physiotherapy treatment (i.e., normally characterised by weeks of intervention) and (iii) in applied research in respiratory physiotherapy used in the management for cystic fibrosis. A comprehensive overview of the available outcome measures is provided, with particular emphasis on their strengths and limitations that should be recognised when interpreting the results.

Keywords: Respiratory physiotherapy, outcome measures, cystic fibrosis

1. Introduction

Respiratory physiotherapy is a non-pharmacological treatment commonly provided to patients with cystic fibrosis (CF) [1]. According to international guidelines, respiratory

physiotherapy is a key element of care for patients with CF, as it aims at both rehabilitation and prevention [2]. Specifically, respiratory physiotherapy is used to deal with the progressive loss of pulmonary function accompanied by symptoms of cough, excessive sputum production, dyspnoea, exercise intolerance, reduced functionality and impaired quality of life. To respond to these multiple problems and needs, respiratory physiotherapy involves a range of strategies and techniques, such as airway clearance, exercise training and breathlessness management, which have an overall aim of reducing the progression of the disease [3, 4].

However, there is a lack of evidence to suggest the superiority of one technique over the other [5] and to determine which strategies promote the adherence of this population to regular physical activity [6]. Nevertheless, the lack of evidence does not mean lack of benefit. Instead, methodological issues, such as the selection of the outcome measures, may hamper the establishment of the effectiveness of the respiratory physiotherapy techniques.

Respiratory physiotherapists use several outcome measures to monitor and evaluate their interventions. Most of the clinically available outcome measures are not specific for the physiotherapy intervention employed and may be affected by other factors. This means that there are no gold standard outcome measures specifically related to respiratory physiotherapy interventions. Thus, in all areas of respiratory physiotherapy, one of the barriers to generate evidence has been the lack of accurate, reliable, sensitive and valid outcome measures. To overcome this problematic issue, new measures have been emerging.

This chapter starts by providing an overview of the problem. It then presents and discusses the strengths and weaknesses of the commonly used clinical outcome measures and other measures that have been gaining interest in the assessment and monitoring of respiratory physiotherapy interventions in CF. The chapter ends with a brief conclusion. A comprehensive overview of the available outcome measures is sought to be provided, with particular emphasis on their strengths and limitations that should be recognised when interpreting the results.

2. Outcome measures for respiratory physiotherapy

Respiratory physiotherapy in CF involves a wide range of interventions and among them airway clearance techniques and exercise training are recognised as the most important. The primary aim of airway clearance techniques is to relieve the airway obstruction by promoting the normal mucociliary clearance mechanism of the lungs and facilitating expectoration, thus reducing the risk of infection and inflammation. A variety of airway clearance techniques have been developed. Some involve airway oscillation, some are independently performed and others require electricity or physical assistance [5]. Exercise training is advocated as an important package of care delivered to patients with CF [5], since exercise intolerance has been associated with reduced survival [45]. Observed benefits of exercise training include slow pulmonary function decline [46], reduced dyspnoea and improved exercise capacity, muscle strength and health-related quality of life (HRQoL) [47].

Although adhering to airway clearance techniques [7] and exercise training is generally regarded as beneficial for patients with CF, there is no consensus about the superiority of one

technique over the other [5]. Methodological issues, such as the underpowered samples or the selection of the outcome measures, may explain this lack of evidence and thus hamper the establishment of the effectiveness of these interventions. A clear example of this issue has been the use of forced expiratory volume in the first second (FEV_1) as a gold standard to assess the impact of the mentioned interventions for many years, which is currently considered as not a sensitive measure to be used in respiratory physiotherapy [5].

Most of the clinically available outcome measures are not specifically related to the physio‐ therapy intervention employed and may be affected by other factors. This means that there is no gold standard outcome measure that is specifically related to respiratory physiotherapy interventions. Moreover, there are many doubts about the accuracy, reliability, sensitivity and validity of the current measures. Given this problematic situation, several researchers have been investigating the potential of other objective, simple and non-invasive measures to be used as outcome measures in respiratory physiotherapy.

The outcome measures most commonly used by respiratory physiotherapists to monitor their interventions and evaluate their practice are: FEV_1, respiratory sounds, sputum weight, measures of oxygenation, chest radiography, dyspnoea, exercise capacity and HRQoL. Computerised respiratory sounds, lung ultrasound, fat-free mass, inspiratory muscle strength and endurance, physical activity and burden of treatment are some examples of these emerging outcome measures to assess and monitor respiratory physiotherapy interventions in CF. Each one of these outcome measures, their strengths and weaknesses are presented in detail below according to their novelty in the field (i.e., conventional and emerging).

2.1. Conventional outcome measures

2.1.1. Forced expiratory volume in the first second

The most common pulmonary function test performed to assess respiratory physiotherapy interventions is the forced spirometry, i.e., the volume and/or flow of air that can be inhaled and exhaled as a function of time. The procedure consists in three distinct phases: (1) maximal inspiration followed by an expiration at functional residual capacity; (2) a ''blast'' of exhalation; and (3) continued complete exhalation until the end of test [8]. First, the patient should exhale until he or she reaches the functional residual capacity and then be instructed to inhale rapidly and completely. In this phase, the mouthpiece should be placed in the patient's mouth and indications should be given for the patient to blow as much and as fast as possible and to keep blowing until totally emptying the lungs. Spirometry has been described as a cost-effective, simple, reliable, valid and easy-to-interpret bedside measure [8]. The most used pulmonary function parameter is the forced expiratory volume in the first second (FEV_1), followed by the forced vital capacity (FVC) and the ratio between FEV_1/FVC. Measurements are taken considering patient's gender, age, height, weight and race and are then compared with predicted values.

Spirometry, namely FEV_1, has been used to assess the effectiveness of respiratory physiother‐ apy interventions. However, contradictory findings have emerged. Pfleger et al. (1992) found significant improvements in FEV_1 after autogenic drainage and high-pressure PEP-mask (n=14,

Cohen's d_z 0.09 and 0.22) [9]. Jarad, Powell and Smith (2010) reported a statistically significant reduction in FEV1 following hydro-acoustic therapy (n=19, Cohen's dz=0.12) or flutter (n=19, Cohen's dz=0.06) [10]. Nevertheless, these changes returned to baseline on the second study day [10].

In two recent reviews where conventional physiotherapy [11] and the active cycle of breathing techniques (ACBT) [12] were compared with other airway clearance techniques, no significant differences were observed between the techniques in terms of pulmonary function measured with spirometry [11]. Nevertheless, when oscillating devices for airway clearance were used, significant results were observed in pulmonary function, the FEV_1 being the primary outcome measure more frequently reported [13].

Findings in the literature about the effectiveness of respiratory physiotherapy interventions in CF remain controversial when FEV_1 is considered as the outcome measure. This is in part due to the fact that accuracy and sensitivity of spirometry depends on many factors that are difficult to control and not related to the intervention itself. Some examples of these factors are the transducer characteristics, presence or absence of an in-line filter, presence or absence of a display, patient's mood and motivation to cooperate, relationship between the patient and the technician, among others. Therefore, spirometry might be unsuitable or its reliability may be affected in a number of situations, for example if the equipment or settings change, if patients are unwilling or unable to collaborate (e.g. children, people with dementia), or if pain or discomfort is present. Hence, this measure should be routinely used to characterise the pulmonary function of patients with CF, but not to assess the effectiveness of respiratory physiotherapy interventions.

2.1.2. Respiratory sounds

Lung auscultation, performed with conventional stethoscopes, is one of the oldest and most used techniques to diagnose and monitor respiratory diseases [14, 15]. It consists in acquiring acoustic signals from the lung structures during spontaneous or controlled volume or flow breathing, and classifying the respiratory sounds as normal or abnormal (e.g., adventitious respiratory sounds, such as crackles and wheezes) [15]. Auscultation is recognised as an efficient and safe method for the early detection of respiratory diseases as it is non-invasive, practical, low cost and easy to apply in all clinical settings and patients, irrespective of patients' age and severity of the disease [14-16].

The efficiency of this method depends on the hearing ability of the health professionals [17], their capacity to memorise different sound patterns [18] and on the quality of the acoustic properties of the stethoscope being used [17]. Considering these limitations and subjectivity, reliability studies have been performed. In CF there are no reliability studies using conventional stethoscopes. However, in other respiratory diseases, poor to fair correlations between different raters have been reported, either in taped recorded sounds (kappa=0.26 and coefficient of reliability of less than 60%) [19, 20] and real-time auscultation (–0.02<kappa<0.77) [21]. Using digital stethoscopes, one study conducted in adult patients with CF assessed the inter-rater agreement between real-time manual annotation of respiratory sounds and automatic detection of respiratory sounds through a computerised system [22]. Poor to moderate

correlations were found (–0.20<kappa<0.60) [22]. Similar results were found in children with respiratory diseases (–0.08<kappa<0.86) [23–25]. Direct comparisons between conventional and digital stethoscopes showed that, although digital stethoscopes have a better sound quality [26], the performance of health professionals to detect respiratory sounds is not enhanced by its use [27].

It is also important to note that, in all the studies, the recognition of crackles was always less accurate than the recognition of wheezes. As respiratory sounds in CF are mainly characterised by the presence of crackles [28] and conventional auscultation has provided poor reliability results, particularly for detection of crackles, it can be concluded that respiratory sounds are not a reliable outcome measure for CF diagnosis and monitoring. Also due to its poor reliability, conventional auscultation has not been used as an outcome measure for respiratory physiotherapy interventions in recent research [7]. Nevertheless, due to its simplicity and wide availability in all clinical settings, it is still recurrently used in clinical practice by physiotherapists to monitor patients with CF and to define therapeutic approaches [3]. Despite these limitations, the advantages of using lung auscultation should not be overlooked, and currently significant research efforts are being conducted to create equipment capable of overcoming the subjectivity associated with conventional auscultation while preserving its main advantages (i.e., portability, patients' minimal cooperation and cost-effectiveness) [16].

2.1.3. Sputum weight

Mucus is transported from the bronchial airways towards the exterior by mucociliary clearance, spontaneous cough and through a range of airway clearance techniques, such as directed huffs and coughs. Subsequently, secretions are either expectorated or swallowed. During respiratory physiotherapy sessions, patients are encouraged to expectorate to a cup. Sputum volume or weight can then be used as an outcome measure for respiratory physiotherapy.

While sputum volume has shown to be difficult to determine with precision, sputum weight (either dry or wet) has shown to be more accurate [29]. In a recent Cochrane review on the effectiveness of respiratory physiotherapy interventions in respiratory diseases, five of the eight studies used sputum weight as an outcome measure, out of which four were conducted in patients with CF [7]. Mortensen et al. (1991) found that patients expectorated 8–8.6g of sputum weight after airway clearance techniques and 0 g during a control day (range 0–2.1 g) [30]. In Pfeger et al. (1992), the mean weight of expectorated mucus with spontaneous cough was approximately 17g whereas with airway clearance techniques ranged from 34 to 45g (n=14) [9]. Although no mean and standard deviation was provided, Rossman et al. (1982) also found a higher volume of expectorated secretions during the different forms of chest physiotherapy compared to a control session (n=6) [31]. However, Jarad et al. (2010) found no significant differences in wet or dry sputum weight between a positive expiratory pressure (PEP) device (flutter) or a placebo [10].

Another study conducted by Osman et al. (2010) compared high-frequency chest wall oscillation with conventional airway clearance techniques in 29 patients with CF using wet sputum weight. Expectorated sputum in a single session was significantly different between the techniques ($p<0.001$; Cohen's $d_z=0.72$) [32].

The problem with sputum weight remains that the lack of expectoration during respiratory physiotherapy techniques does not mean that airway clearance techniques are not effective. It is very common to expectorate after respiratory physiotherapy sessions or to swallow secretions even during the session, which means that sputum weight expectorated during a session may underestimate the effect of airway clearance techniques. On the other hand, expectoration may be contaminated with saliva [30]. Sputum weight can, therefore, be both over- and under-estimated and it is not surprising that contradictory findings have been found in the literature.

Although simple to collect and measure, sputum collected during and following the treatments is not considered a reliable measure of alveolar recruitment, airway clearance or even sensitive to small changes. In fact, this outcome measure has been frequently questioned [29, 30, 33–35] and is no longer considered as a valid outcome measure for studies in airway clearance techniques [36].

2.1.4. Measures of oxygenation

Blood gas measurements are used to evaluate a person's lung function and acid–base balance, i.e., it measures the amount of oxygen and carbon dioxide that is in the blood and determines its levels of acidity (pH). The test results provide information about the partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and hydrogen ion activity (pH) in arterial blood, as well as indices of bicarbonate concentration, base excess and oxygen saturation. The analysis is performed on the blood collected from a person's artery and is therefore, an invasive and relatively complex procedure. Although it is possible to measure oxygenation more accurately, given the nature of the procedure, it is not practical to be performed on a routine basis to monitor respiratory physiotherapy treatments. Hence, transcutaneous pulse oximetry (reported as the percentage of saturation of arterial haemoglobin by oxygen [SaO_2]) has become the most common method in clinical practice and research for measuring oxygenation [37].

Peripheral oxygen saturation is commonly used as it is simple to perform via pulse oximeters and finger probes. Pulse oximeters monitor the saturation of haemoglobin with oxygen (i.e., oxyhaemoglobin). This is possible because blood changes its colour as haemoglobin absorbs various amounts of light depending on its saturation with oxygen. Oxyhaemoglobin absorbs greater amounts of infrared light and does not absorb much red light, but as the haemoglobin oxygen saturation drops, more and more red light is absorbed and the blood becomes darker. Hence, pulse oximeters emit two wavelengths of light, red at 660 nm and near-infrared at 940 nm from the finger probe [38]. The pulse oximeter directly senses the absorption of light and translates it through complex signal processing to a function of the arterial oxygen saturation. A microprocessor integrates the data and, through an elaborate calibration algorithm based on human volunteer data, the oxygen saturation can be estimated. This measure allows constant monitoring of heart rate as well, being ideal to monitor patient's safety during interventions.

Nonetheless, this measure can provide unreliable readings due to several factors such as haemoglobin level, arterial blood flow to the vascular bed, oximetry sensor location and

temperature, fluorescent or direct sunlight, jaundice, discoloration of the nail bed, nail polish, bruising under the nail, motion artefacts, intravascular dyes and skin pigmentation. All these are discussed in detail elsewhere [38].

In two Cochrane reviews about respiratory physiotherapy techniques, insufficient evidence was found regarding peripheral oxygen saturation as an outcome measure [7,12]. Osman et al. (2010) compared high-frequency chest wall oscillation with conventional airway clearance techniques in 29 patients with CF. It was found that, compared to the baseline, non-significant changes in peripheral oxygen saturation were observed during or after any of the treatments applied (Cohen's d_z from 0 to 0.28) [32]. However, in a recent study, the addition of non-invasive ventilation to chest physiotherapy resulted in a significant reduction in the proportion of treatment time with peripheral oxygen saturation below 90% (p<0.001) [39].

Controversial evidence exists on the potential of peripheral oxygen saturation as an adequate measure to assess the effectiveness of respiratory physiotherapy. Hence, this measure seems ideal to monitor patients' safety but it may not present the required specificity and/or sensitivity to assess changes caused by respiratory physiotherapy interventions.

2.1.5. Dyspnoea

Dyspnoea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [40]. In a study conducted with 123 patients with CF, dyspnoea was reported to be present in 74% of the patients [41] and therefore, it is an important problem to consider in this population. As a subjective experience, adequate assessment depends on patient self-report. Depending on the circumstances in which breathing discomfort occurs and the history of similar sensations, dyspnoea may be perceived as a threat associated with anxiety, fear or depression, and it may be viewed as a sign of disease. This symptom has multidimensional aspects involving physiological, psychological, social and environmental factors that result in a behavioural response. The assessment of multidimensional aspects of dyspnoea has assumed significance in recent years [40].

Dyspnoea has been assessed using scales and questionnaires, however, important differences exists between these instruments, particularly in what they measure (e.g., one instrument may ask what breathing feels like, whereas another may ask how distressing it is or how it impacts on patient's performance or quality of life), in the rating task (i.e., what patients are instructed to rate), and in whether measurements are performed on real time or involve the recall of a specific episode. These differences make comparisons across studies difficult.

In one study exploring the effectiveness of non-invasive ventilation during chest physiotherapy [39], it was found that dyspnoea scores, assessed with the Borg scale, increased in slightly lesser extent following chest physiotherapy assisted with non-invasive ventilation than chest physiotherapy alone (2.26±1.96 vs. 2.69±1.82, p=0.02, Cohen's d_z=0.23). Marques (2008), however, found that dyspnoea assessed with the modified Borg scale was not significantly different after one session of airway clearance techniques (Cohen's d_z=0.06) [42]. Enright et al. (2004) investigated the effect of an 8-week inspiratory muscle training (n=19) and also did not

find significant differences is dyspnoea, using the dyspnoea domain of the Chronic Respiratory Disease Questionnaire (Cohen's d_z 0.07 to 0.37) [43].

A combination of unidimensional and multidimensional tools will probably be the best approach for clinical assessment. Measurement of dyspnoea has to be seen in context, taking into consideration the patient's history, physical examination and diagnostic tests [44]. As dyspnoea is a symptom perceived by patients, it has the potential to contribute for early management of the disease, for adjusting the respiratory physiotherapy interventions and, thus, for improving outcomes in patients.

2.1.6. Chest radiography

Several imaging techniques are available to diagnose and monitor a respiratory condition. Within the respiratory field, chest radiography is the most commonly used. Although relatively simple to perform, and in itself being relevant and reliable, the measure presents several important limitations to be used as an outcome measure for respiratory physiotherapy. The interpretation of chest radiography imaging is somewhat complex and presents high levels of inter-observer subjectivity [45], the reports detailing either the presence or the absence of any abnormalities are not commonly available immediately after the exam, its portability is limited to places where health and safety radiation protection standards can be ensured, as considerable doses of radiation are involved and is difficult to perform in non-collaborative populations such as children or people with dementia. These factors prevent the use of this measure to monitor respiratory physiotherapy patients with the required frequency.

In two long-term studies (n=36 and n=32), conducted for approximately one year comparing different respiratory physiotherapy airways clearance techniques in patients with CF, chest radiography was used as an outcome measure. However, no significant differences were shown between interventions [46, 47]. In the most recent Cochrane reviews [11, 12] about physiotherapy in CF, chest radiography is no longer reported as an outcome measure in the included studies.

It therefore, seems that chest radiography is ideal for contributing to diagnosis and providing a measure of improvement or deterioration over time but might not be the most appropriate to be used as an outcome measure for respiratory physiotherapy.

2.1.7. Exercise capacity

The assessment of exercise capacity, expressed as the maximal workload achievable or the peak oxygen consumption on a progressive maximal test, has been used to measure patients' functional capacity and limitation, facilitates a safe exercise prescription and identifies changes in patients' performance as a result of an intervention [48, 49]. There are two types of clinically applicable tests to assess exercise capacity in patients with CF: laboratory-based tests and field tests [50, 51].

Laboratory-based tests, such as the cardiopulmonary exercise testing (CPET) [48, 49], are the gold standard for evaluating the causes of exercise intolerance in patients with respiratory

diseases, as they provide a comprehensive assessment of the physiological responses to exercise involving the respiratory, cardiovascular and musculoskeletal systems [52]. CPET consists of a progressive exercise performed at increasing levels of intensity either on a treadmill or cycle ergometer, with simultaneous monitoring of breath-by-breath measures of airflow (e.g., VO_2, VCO_2) along with heart rate, peripheral oxygen saturation and exercise-related symptom responses (e.g. dyspnoea, leg discomfort) [49]. There are a number of protocols that can be used to perform a CPET in patients with CF, but the most commonly reported is the Godfrey protocol [53]. The CPET has been shown to be reproducible in young and adult patients with CF [54, 55]. In patients with CF (n=23) enrolled in a strength and endurance training for 6 months, significant differences were observed in VO_2 peak between 3 and 6 months (Cohen's d_z=2.01) and between 18 and 24 months (Cohen's d_z=2.22) [56]. Despite its sensitivity to change, the application of CPET is still limited in clinical settings [57]. This may be attributable to the need for expensive equipment and technical expertise. For this reason, field tests are more commonly used by physiotherapists to assess changes in exercise capacity [58].

Field tests are simple clinical exercise tests that do not require expensive equipment [59] and, thus, are suitable to be used at different settings of respiratory physiotherapy practice, such as hospitals, private practices, at home or in community environments. In patients with CF, the field tests most frequently used are the 6-minute walk test (6MWT), the 3-min step test (3MST) and the modified shuttle test (MST) [51, 58]. The 6MWT measures the maximal distance that a patient can walk in 6 minutes over a marked course (usually a corridor) following a standardised protocol [60]. The 6MWT has been recommended for patients with CF [60] and is valid and reliable for assessing exercise capacity in children [61, 62] and adults [63] with CF. The product of the distance walked during a 6MWT and body mass have been reported to correlate with aerobic capacity (VO_2max) in children with CF [64], thus supporting the use of this test in clinical settings. Furthermore, the 6MWT was found to be valuable for identifying patients who might experience oxygen desaturation and physical impairment in daily activities [65]. For this reason, the 6MWT has been considered more reflective of activities of daily living than other walk tests [59]. Numerous reference equations of the 6MWT are available for children [66–69] and adults [70].

The 3MST is a simple test that requires the patient to step at a rate of 30 steps per min on and off a step with 15 cm (6 inch) of height, during 3 minutes. This test was developed for children with CF by Balfour-Lynn et al. (1998) [71] based on the original Master two-step exercise test (1929) [72]. One major advantage of the 3MST is that it does not depend on patient's motivation, since the cadence of steps is fixed and determined by a metronome. One limitation concerns to the fact that, as step height and rate are kept constant, the workload varies between patients depending on their height and lower limb length [51, 58]. The 3MST has been found to be repeatable [71] and sensitive to changes in pulmonary function and peripheral oxygen saturation in children with CF following a course of intravenous antibiotics for acute respiratory exacerbations [73]. This is an important finding since even physiotherapists without access to a formal exercise laboratory may evaluate the response to an intervention using a simple field test. When compared to the 6MWT, the 3MST elicited a significantly greater change in

heart rate and breathlessness in children with CF, along with a comparable [71] or higher [74] fall in oxygen saturation, suggesting that this test is a more vigorous exercise challenge. Nevertheless, Narang et al. (2003) showed that, in children with mild disease, important information such as the exercise-related desaturation that occurs at higher exercise levels may be missed with this test [75].

While the 6MWT and 3MST may be submaximal tests for patients with mild-to-moderate CF, the MST allows maximal exercise capacity to be reached [58]. The MST [76] consists of a validated adaptation of the Incremental Shuttle Walk Test [77], specifically developed for adults with CF. This adaptation allowed individuals to walk and run at increasing speeds over 15 levels with a maximum speed of 10.2 km/h [76]. Bradley et al. (1999, 2000) studied the validity, reliability and sensitivity of the MST in adults with CF [76, 78]. When compared to a laboratory-based treadmill test, they showed that 90% of the variation of directly measured VO_2 peak was explained by the variation in MST performance [76]. Moreover, the MST was effective in evoking a symptom-limited exercise response (i.e., peak heart rate and peak rating of perceived dyspnoea) similar to what is found in treadmill tests [76]. Thus, it may be a valid alternative when laboratory-based exercise testing cannot be performed. The validity of the MST has also been assessed in children with CF (correlation of the MST distance with VO_2peak, r=0.663 p<0.01) [79]. In adults with CF, the MST was found to be reliable (correlation between trials for distance completed and symptoms reported, r=0.99, p<0.01) and repeatable (coefficients of repeatability: distance completed, four shuttles; peak heart rate, 6 beats/min; peak oxygen saturation, 4%) [78]. The sensitivity of the test was assessed by measuring the change in MST performance after 2 weeks of antibiotic therapy in patients admitted to hospital with acute respiratory exacerbations. An effect size of 1.18 was achieved, suggesting that this is a highly sensitive measure [78]. This test has also been used to assess changes in exercise capacity after 2 months of exercise training and significant differences were found (median number of shuttles: from 100 (range 21–150) to 105 (44–150)) [80]. Despite the good measurement properties, it was recently argued that the 15-level MST developed by Bradley et al. (1999) [76] still remained sub-maximal for some patients with CF and, thus, levels were extended to 25 in order to create a truly maximal test [81].

There is no "best" exercise test. The selection of the test will depend upon the aspect of exercise capacity of interest, availability of resources (i.e., time to perform the test, staff and equipment) and patient's characteristics (e.g., age, disease stage) [50, 51]. For example, if the aetiology of a patient's reduced exercise capacity is of interest, a laboratory-based test would be more appropriate, while a field test could be used in large population studies. In addition, a young child (< 7 years old) may not be able to cooperate sufficiently for a formal laboratory exercise testing. Physiotherapists have the important role of selecting the best exercise test for a specific individual according to the specific question being asked and the specificities of each test.

2.1.8. Health-related quality of life

Health-related quality of life (HRQoL) has been extensively studied in patients with CF, especially in the last decades due to the improvement in patients' life expectancy [82]. Several instruments have been used to assess HRQoL in CF, either generic [83-85] or disease-specific

[85-87]. One disadvantage of generic questionnaires is that they lack the sensitivity needed to assess areas of functioning that are critically important for patients with CF [88]. Disease-specific questionnaires were developed in an attempt to better understand CF specific issues in clinical practice and research.

The most commonly used disease-specific questionnaires include the Cystic Fibrosis Questionnaire (CFQ) and the Cystic Fibrosis Quality of Life questionnaire. The CFQ was developed for assessing HRQoL of patients with CF and encompasses general domains of HRQoL (physical functioning, role functioning, vitality, health perceptions, emotional functioning and social functioning), as well as domains specific to CF (body image, eating disturbances, treatment burden, and respiratory and digestive symptoms) [89]. Three versions of the instrument have been developed: one for adolescents aged 14 years or older and adults (CFQ-Teen/Adult), and two for assessing children 6–13 years old, one to be completed by the child (CFQ-Child) and the other by parents (CFQ-Parent) [89, 90]. Each version takes around 15 minutes to fill in. The different versions of the CFQ questionnaire have shown good psychometric properties (validity [88-90], reliability [89, 90], internal consistency [88-90] and responsiveness [90]). Hebestreit et al. (2010) found that patients with CF (n=23) enrolling in strength and endurance training for 6 months improved their subjective health perception (CFQ domain) significantly between months 3 and 6 (Cohen's d_z=0.92) [56]. Schmidt et al. (2011) evaluated a 12-week individually tailored unsupervised aerobic exercise programme in 14 patients with CF and also found significant differences in emotional functioning and treatment burden domains of the CFQ (Cohen's d_z of 0.29 and 1.03) [91]. Thus, this questionnaire may be used in clinical practice to assess HRQoL of patients with CF, document the progression of disease and explore the effects of respiratory physiotherapy interventions.

The Cystic Fibrosis Quality of Life questionnaire was specifically developed for adolescents (14 years old or older) and adults, presenting good validity (concurrent and discriminate), internal consistency, test–retest reliability results and responsiveness [92]. One advantage of this instrument is the inclusion of domains concerning wider impacts of the disease on patient's lives (e.g., interpersonal relationships, career issues and future concerns), which are not found in other CF questionnaires. Though, it is not adaptable to children.

In sum, disease-specific instruments present good psychometric properties and seem appropriate for several different applications in patients with CF, such as to identify problems and intervene on an individual basis, compare different CF groups, or detect changes in patients' HRQoL as a result of disease progression or interventions.

2.2. Emerging outcome measures

2.2.1. Computerised respiratory sounds

Computerised auscultation consists of recording patient's respiratory sounds with a digital stethoscope and automatically analysing and classifying them based on specific signal characteristics [93]. Computerised auscultation allows to objectively detect, characterise and identify both normal and adventitious (i.e., crackles and wheezes) respiratory sounds within the breathing cycle [93].

To assess computerised respiratory sounds, the patient is positioned in the sitting or supine position (for long-term assessments) and instructed to breath from his/her mouth. Successive or simultaneous recordings are taken from the trachea plus six chest locations (i.e., right and left: anterior, lateral and posterior positions), using a single or a multichannel equipment (Figures 1 and 2) [94].
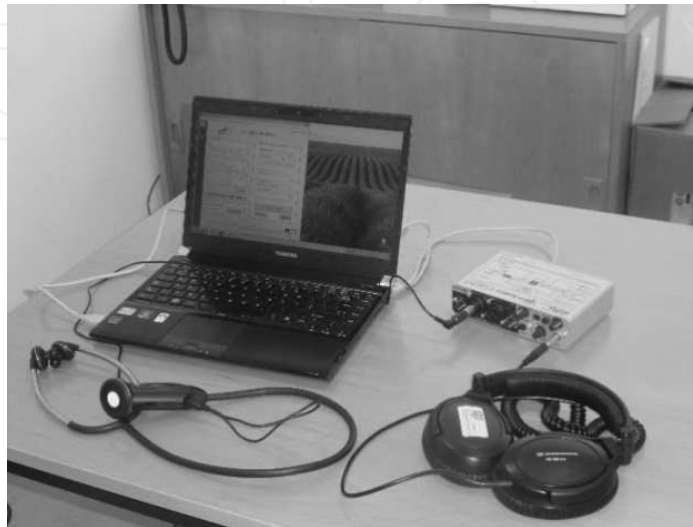
Figure 1. Single-channel equipment for computerised respiratory sound analysis.

Figure 2. Multi-channel equipment for computerised respiratory sound analysis.

Seven to ten respiratory cycles at tidal breathing or at a flow of 1 to 1.5 L should be recorded to ensure the stability of sound and quality of the analysis [94]. Then, the sound is filtered using a combination of low-pass and high-pass filters in cascade to reduce sound artefacts (e.g., muscle, heart sounds and movement frequencies) and specialised algorithms for respiratory sound detection and analysis are implemented [94].

A wide range of analysis methods exists and new ones are continuously being proposed. However, the ones with more evidence are time-frequency analysis, fast Fourier and wavelet transformations, neural networks, periodogram and auto- regressive models [93, 95-97]. Specifically for patients with CF, a time-frequency wheeze detector has already been validated, demonstrating high levels of sensitivity (77.2%) and specificity (98.4%) [98]. Nevertheless, algorithms for the detection of crackles in patients with CF were not found and, thus, further studies are needed.

The reliability of computerised respiratory sounds has been mainly studied in adults with CF [99] and children with asthma, pneumonia [100] and bronchiolitis [23]. In adults with CF, one study assessed the test–retest reliability of two main parameters of crackles (i.e., the initial defection width and the two cycle duration). The intra-subject reliability of crackle parameters was found to be 'good' to 'excellent' (0.76<intraclass correlation coefficients<0.94) with no systematic bias. The smallest real difference found for the initial defection width was between 0.30 and 0.66 ms, and for the two-cycle duration between 1.57 and 2.42 ms. The reliability of wheezes has only been assessed in children with bronchiolitis, presenting moderate to good agreement (0.77<kappa<0.79) [99]. The reliability of computerised respiratory sounds to assess wheezing in adults and its overall reliability in children with CF is still unexplored.

Due to its simplicity and increasing reliability, computerised respiratory sounds have been used as outcome measures for pharmacological and respiratory physiotherapy interventions in children and adult patients with several respiratory diseases, including CF [93]. Marques et al. (2008) investigated the effect of one single session of respiratory physiotherapy using the ACBT in 17 adult patients with CF [42]. The initial defection width and two cycle duration of crackles were analysed. Considering the mean of all participants, no significant differences were found in the analysed parameters. However, when the individual data of each participant was considered, significant changes were observed in the initial defection width of 9 patients (53%) and in the two-cycle duration of 10 participants (59%).

Considering the detection of wheezes and their analysis, one study assessing the sensitivity of computerised respiratory sounds to defect bronchial hyperactivity in 23 children with CF, following an induced methacholine challenge, found a sensitivity of 50% and a specificity of 100% [101]. Studies in patients with lower respiratory tract infection, a common form of exacerbation in CF [102], have shown that computerised respiratory sounds are effective in detecting changes following pharmacological and respiratory physiotherapy interventions [93]. Small to large effects were found in the number of crackles (Cohen's d_z: 0.14 to 1.65), peak frequency (Cohen's d_z: 0.11 to 0.47), two-cycle duration (Cohen's d_z: 0.83 to 0.85) and initial/ largest deflection width (Cohen's d_z: 0.38 to 1.25). Better results have been found in the detection and characterisation of wheezes, with medium to large effect sizes for the number and occupation rate of wheezes (Cohen's d_z: 0.34 to 4.30) [93].

One of the disadvantages of computerised respiratory sounds concerns the complexity and costs associated with the equipment and subsequent sound analysis. Nevertheless, an emerging body of health and engineer researchers have been gathering efforts to produce more simple and efficient hardware/software that can be used in clinical practice [101, 103].

Despite the scarce evidence of computerised respiratory sounds in CF, it seems that this measure might offer potential to assess the short- and long-term effects of respiratory physiotherapy interventions in these patients. However, more research is still required to determine the parameters of computerised respiratory sounds (i.e., number, frequency, duration) that are more sensitive to change after an intervention and to establish the reference values that will allow physiotherapists to interpret with confidence the results obtained from the computerised auscultation.

2.2.2. Lung ultrasound

Lung ultrasound (LU) is a simple, non-invasive and radiation-free methodology [104] mainly used in critical care, emergency medicine, trauma surgery and pulmonary medicine for diagnostic purposes [105]. However, due to its practical and secure character, which enables its use as often as required, LU has become an attractive alternative imaging technique for monitoring patients on whom thoracic computed tomography (CT) cannot be performed on a routine basis or where chest X-ray presents serious limitations in terms of sensitivity and specificity [106]. In fact, the international evidence-based guidelines for LU recommend this technique to monitor aeration changes and the effects of therapy in a number of acute respiratory diseases, including acute pulmonary edema, acute respiratory distress syndrome, acute lung injury, community-acquired pneumonia, ventilator-associated pneumonia and recovery from lavage of alveolar proteinosis (level A) [105].

Usually, LU is performed using a 3–5 MHz convex transducer to visualise deeper lung structures [107, 108]. A high-frequency 5–12 MHz linear probe is most effective in visualising the chest wall, pleura and the lung peripheral parenchyma [108]. A complete examination of the chest requires longitudinal, transversal and oblique-array probes to be placed along the rib spaces, proceeding from top to bottom in the ventral-dorsal direction, along of 12 regions of interest (parasternal, medial clavicular, anterior axillary, medial, and posterior right and left chest walls) [106, 108]. Anterior examination should be performed with the patient in the supine or semi-lateral position [106] while posterior examination should take place with the patient seated [107].

LU has shown to be reliable in the diagnosis of several acute respiratory conditions, such as pneumothorax (sensitivity of 65–100%; specificity of 78–100%) [108-110], including the diagnosis of this condition in patients with CF (specificity of 100%) [109], interstitial syndrome (sensitivity and specificity of 94%), lung consolidation (sensitivity of 90 to 95%; specificity of 95%), pleural effusion (sensitivity of 90 to 100%; specificity of 100%) [110] and atelectasis (sensitivity of 88%; specificity of 89%) [104]. One study assessed the inter-subject reliability of LU in the detection of atelectasis and reported a very good agreement (kappa=0.90; 95%CI 0.75 to 1) [104]. When compared with other imaging equipment (e.g. chest X-ray and MRI), this measure showed similar or even better reliability results [104, 107, 110].

No data has been found regarding the use of LU to monitor respiratory physiotherapy interventions in stable or exacerbated patients with CF. Nevertheless, considering its high accuracy in detecting signals commonly presented in CF exacerbations, such as atelectasis and consolidation [111], and its increasing impact in the management of acute respiratory condi-

tions [105], it is reasonable to conclude that LU may be a promising measure to monitor the effectiveness of respiratory physiotherapy in patients with acute exacerbations of CF. Considering stable CF, one study used LU to characterise diaphragm thickness as a way to infer about its muscle mass. The authors reported an excellent inter- and intra-subject agreement (90% and 91%, respectively) and showed that LU was capable of detecting differences between patients with low and high rates of fat-free mass [112]. From these findings, it can be hypothesised that LU may also play a role in the assessment of the effectiveness of inspiratory muscle training and general exercise training programmes in increasing the diaphragm thickness of patients with stable CF, and thus, its muscle mass. Nevertheless, studies assessing the LU validity, reliability and responsiveness to change are needed before it can be recommended as an outcome measure for respiratory physiotherapy interventions.

At this point, there is no evidence to recommend LU as an outcome measure for respiratory physiotherapy in patients with CF. However, the advantages presented by LU over other imaging measures and its good performance as a diagnostic tool, should motivate further investigation on the validity and reliability of this measure to assess respiratory physiotherapy interventions in this population.

2.2.3. Fat-free mass

Fat free mass (FFM) is the component of body mass that represents muscle mass and protein stores [113] and it is a critical determinant of maximal exercise capacity [114]. It is known that, in patients with CF, lower FFM is also associated with lower FEV_1 percentage predicted and more frequent respiratory exacerbations [115, 116]. Maintaining appropriate levels of FFM is therefore crucial for maintaining the overall functional capacity in patients with CF [114].

The gold standard to assess FFM are the 4-C models, which divide body weight into fat, water and remaining fat-free dry tissue, with the last item further divided into proteins and minerals. The 4-C models require measurements of body weight, body water, body volume and bone mineral [117] and thus several specialised equipment, such as dual-energy X-ray, measures of air displacement plethysmography (BOD POD) and D_2O analysis, are needed. The partial measures are then pulled together in a predictive equation [118]. Although all devices involved are valid and reliable (intraclass correlation coefficient>0.99), the improved accuracy of the 4-C models may be offset by the potential propagation of errors due to the inherent measurement error of each device used to assess each variable [118]. Also, it appears not to be suitable for widespread clinical use due to the need for specialised equipment, experienced personnel and large amount of time. Thus, its main value lies in the quality of its evidence in supporting treatment approaches, rather than in routine practical application [117, 119].

For application of respiratory physiotherapy clinical practice, 2-C models, which require only the use of one device, are the most recommended and have shown large correlations with the 4-C models. These are bioelectrical impedance (r>0.79, R^2=0.70), CT scans (r>0.83, R^2=0.96), MRI (r>0.91), and specially dual-energy X-ray (r>0.91) [120, 121]. Indirect strategies involving calculations based on anthropometric measurements, such as skinfold thickness analysis, are controversial. Measuring FFM by measurement of skinfolds implies that no index of this component of weight is directly measured, and thus it is based on the assumption that

measuring fatness reflects lean body mass as well. Therefore, its use has not been recommended [117]. Nevertheless, studies that show medium correlations between measurements of skinfold thickness and 4-C models (R^2=0.62) exist [120] and support the usability of this measure to monitor FFM irrespective of the clinical severity of CF [122].

FFM has been used as an outcome measure in respiratory physiotherapy interventions for children and adults with CF, mainly for the assessment of different types of exercise training. In the study of Selvadurai et al. (2002), 66 children with exacerbated CF significantly increased their FFM after five sessions of exercise training (aerobic or resistance training) or chest physiotherapy, independently of the protocol applied (Cohen's d_z: 1.65 to 5.22) [123]. Sosa et al. (2012) did not find improvements in the percentage of FFM of children with stable CF following an 8-week exercise training protocol (78.1 to 79.4%; Cohen's d_z 0.47) [119], however, significant differences were reached when a component of inspiratory muscle training was added (81.6 to 82.6%; Cohen's d_z 0.85) [124]. Gruber et al. (2014) compared the effect of a 6-week interval exercise training vs. standard exercise training in 43 adults with CF [125]. Significant improvements in FFM were only observed in the standard exercise training group (41.7 to 43.3 kg; Cohen's d_z 0.29). These four studies, with its medium and large effect sizes, demonstrated that FFM is an adequate outcome measure to assess the effectiveness of respiratory physiotherapy or just exercise training protocols in patients with CF.

Despite the limited evidence available, FFM assessed with 2-C or 4-C models appears to be a valid, reliable and usable measure to assess respiratory physiotherapy interventions in CF.

2.2.4. Inspiratory muscle strength

One of the functions of the muscles is to develop strength. In the specific case of the inspiratory muscles, strength is usually estimated as pressure [126]. Several techniques have been described to measure inspiratory muscle strength, however, the maximum static inspiratory pressure at the mouth (Pimax) is one of the most widely used [126].

The assessment of Pimax requires patients to make a maximum inspiratory (Mueller manoeuvre) effort at or near the residual volume, maintained for at least 1–1.5 seconds. These tests are volitional and require patient's full cooperation. For these reasons, this technique is usually performed by an experienced health professional to assure adequate instruction and encouragement. The manoeuver is repeated until the variation between measures is less than 20%. Pimax is usually expressed in absolute values (cmH_2O) or as a percentage of the predicted values.

Pimax is a simple, low-cost and well tolerated technique. In addition, through the hand-held and portable electronic pressure transducers, the technique is easily used by physiotherapists in a wide range of clinical settings (e.g., primary care, hospital wards, intensive care units). Another advantage of using this technique is the availability of reference values for healthy children, adults and the elderly, enabling the interpretation of results [127, 128].

The reliability of this measure is well established in people with non-CF bronchiectasis [129] and healthy people [130]. In patients with CF, only one study was found assessing the test–retest reliability of Pimax [131]. Pimax had an excellent coefficient of reliability (89%) and

intraclass correlation coefficient (0.88) in patients with CF (n=20), in line with the results obtained in healthy individuals (coefficient of reliability 91%; intraclass correlation coefficient 0.87) [131]. One of the disadvantages of this study is the fact that it was conducted only with adult patients with CF (22.7±3.4 years old). The reliability of Pimax in children with CF is still unexplored.

Due to its simplicity and adequate reliability, Pimax has been used as an outcome measure of inspiratory muscle training programmes. In the study by de Jong et al. (2001), seven patients with CF improved their Pimax from 105 to 123cmH$_2$O after 6 weeks of inspiratory muscle training (Cohen's d$_z$ 0.82) [132]. Enright et al. (2004) investigated the effect of an 8-week inspiratory muscle training with a high (n=9) and low (n=10) training intensity. Large effects were found using the Pimax, with improvements from 114–134cmH$_2$O to 155–159cmH$_2$O (Cohen's d$_z$ 1.01 and 1.34) [43]. Amelina et al. (2006), after a 6-week inspiratory muscle training, found that patients with CF (n=10) had a mean improvement from 77% to 91% of the predicted Pimax (p=0.023; Cohen's d$_z$ 0.73) [133]. These three studies, with its medium and large effect sizes, demonstrated that Pimax is an adequate outcome measure to assess the effectiveness of inspiratory muscle training.

Pimax has also been used as an outcome measure to determine the effectiveness of non-invasive ventilation during chest physiotherapy [39]. It was found that Pimax was maintained following ACBT assisted with non-invasive ventilation, resulting in a significant difference compared with ACBT alone (mean difference from standard treatment 9.04cmH$_2$O, 95%CI 4.25 to 13.83, p=0.006) [39].

Despite the limited evidence available, it seems that physiotherapists can confidently rely on Pimax to assess the effectiveness of respiratory physiotherapy interventions in patients with CF.

2.2.5. Inspiratory muscle endurance

Inspiratory muscles, in addition to developing strength, have to be able to sustain muscular tasks over time – also known as endurance [126]. Inspiratory muscle endurance is a highly complex ability, which provides insight about the resistance to fatigue of inspiratory muscles and about the function of the inspiratory pump.

Dyspnoea, one of the primary complaints of patients with CF, has been related to inspiratory muscle fatigue. In adults with CF (n=18), inspiratory muscle endurance was found to be strongly correlated with exercise dyspnoea (r=−0.72) and explained 48% of the variability of this symptom [134]. In patients with advanced CF, the assessment and monitoring of inspiratory muscle endurance may have a greater importance since, in these patients, activities of daily living may be limited by their ability to sustain ventilation. Therefore, the measure of inspiratory muscle endurance seems to be useful to evaluate the determinants of dyspnoea and fatigue in patients with CF.

A number of distinct techniques have been employed to measure endurance of the inspiratory muscles [126]. In CF, two main techniques have been employed: (i) ventilatory endurance tasks [43, 112, 131] and (ii) endurance to external loads [132, 134].

In ventilatory endurance tasks, inspiratory muscle endurance has been measured through the sustained maximum inspiratory pressure (SMIP). This sustained pressure is determined using an electronic manometer, with a fixed leak via a 2 mm diameter during the inspiratory manoeuver, and a specific computer software. The leak sets a maximum flow during the inspiratory effort and allows continuous measurement of pressure over a full range of lung volumes, until no further pressure can be generated. During this technique, patients are asked to take a maximal and sustained inspiratory effort from residual volume to total lung capacity. SMIP is measured as the area under the pressure–time curve and is generally expressed in absolute values (pressure–time units) [43, 112, 131].

The coefficient of reliability for measurements of SMIP in CF was previously established as 90% [131]. Albinni et al. (2004) reported that inspiratory muscle endurance, measured by the SMIP, improved significantly in patients with CF (n=16) after 12 weeks of inspiratory muscle training (p=0.0002) [135]. Enright et al. (2004) investigated the effect of an 8-week inspiratory muscle training with a training intensity of either 80% of maximal inspiratory effort (n=9) or 20% of maximal inspiratory effort (n=10) [43]. The SMIP improved significantly in the two groups (from 654–782 to 808–923 pressure–time units; Cohen's d_z 0.46 and 0.51) [43].

In endurance to external loads, inspiratory muscle endurance has been determined with incremental loading tests using threshold devices. During these tests, patients have to generate sufficient inspiratory pressure to open the valve and allow inspiratory flow. The test starts with an inspiratory load of 20–30% of Pimax for 2 min. The load is then increased every 2 min in increments of 10% of Pimax. The maximal load is defined by the maximal inspiratory pressure sustained for 1 or 2 min (Plim), which can be expressed in absolute values and as a percentage of the Pimax [132, 134].

The reliability of the Plim in CF has not yet been explored. In patients with COPD and in healthy people, however, it has been demonstrated that the reproducibility of the inspiratory pressure of the threshold was excellent, with small coefficients of variation in both groups (<1%) [136]. Future studies should assess the reliability and test–retest reliability of the Plim in the CF population.

Only one small study was found using Plim as an outcome measure in CF population. In this study, patients with CF (n=7) were submitted to a 6-week inspiratory muscle training. Plim, expressed as a percentage of the Pimax, increased significantly from 49% to 66% (Cohen's d_z 1.29) [132]. Using Plim, inspiratory muscle training was also found to have large effect sizes in patients with COPD (n=16; Cohen's d_z 0.83) [137] and with chronic heart failure (n=16; Cohen's d_z 1.09) [138]. Further research is needed to assess the sensitivity and responsiveness of Plim to inspiratory muscle training in patients with CF.

Both SMIP and Plim appear to be adequate outcome measures to assess the effectiveness of inspiratory muscle training in the inspiratory endurance of patients with CF. Nevertheless, this evidence emerges from few studies with small sample sizes. More research is needed to determine the responsiveness of these two outcome measures to inspiratory muscle training, as well as to other respiratory interventions, such as respiratory retraining.

2.2.6. Physical activity

Given the clinical implications of regular physical activity in patients' pulmonary function [139], exercise tolerance [140] and airway clearance [141], its assessment and monitoring in patients with CF has also become a topic of great interest in research and clinical practice. An assessment of physical activity (and inactivity) in the free living environment can be performed using subjective and objective methods [142, 143], although no gold standard is still available.

Subjective methods rely on the individuals' self-report through physical activity question-naires. These instruments are simple, inexpensive and easy to employ for routine assessment of patients' physical activity levels [142]. Examples of questionnaires used in CF include the Habitual Activity Estimation Scale [144] and the Seven Day Physical Activity Recall [145]. Although the Habitual Activity Estimation Scale has presented good test–retest reliability results (intraclass correlation coefficients of 0.72) in patients with CF [146], a previous system-atic review concluded that these two instruments were not able to generate valid activity data or provide a valid assessment of aerobic fitness at the individual level [147]. Thus, the use of these questionnaires for individual assessment and counselling may provide imprecise data. For these purposes, objective measures are recommended.

Objective measures to assess daily physical activity include heart rate monitoring devices and motion sensors, such as pedometers, accelerometers and multisensor devices [143, 148]. These measures have been used in studies involving patients with CF [149-151] and show promising results in evaluating the impact of respiratory physiotherapy interventions [56, 123]. Given the small size of the devices, low participant burden and relatively low cost, objective measures are appropriate for use in research and clinical practice [148]. Heart rate monitoring devices enable the assessment of patients' level of exertion since heart rate increases in a linear fashion with oxygen consumption, especially in moderate to strenuous intensity activities [152]. As such, these devices have been mostly used as a feedback tool to ensure patients' compliance with the intensity recommendations when exercising at home [56, 153]. Regarding motion sensors, there are a large number of options available that makes the choice of the best device challenging. Pedometers are designed to measure the number of steps taken by an individual by detecting vertical movement at the hip or waist. They may be desirable in simpler studies due to their lower cost and limited data [143]. Furthermore, since pedometers provide immediate feedback to the user [143], they may be valuable in self-monitoring interventions delivered to patients with CF. Despite their potential applications, no data is still available regarding the validity and reliability of pedometers in CF [154]. Still, pedometers have provided good reliability results in healthy and chronic respiratory diseases except when walking at slower speeds [155].

Although more expensive than pedometers, accelerometers provide a more detailed analysis of daily physical activity by capturing the frequency, duration and intensity of physical activity through the collection of body accelerations during movements [143]. They have also the advantage of storing the data for several weeks [143]. Multisensor devices combine acceler-ometry data with physiologic information collected from other sensors, such as heart rate and skin temperature, and also have a memory function. The use of accelerometers and multisensor devices in CF has increased dramatically in recent years [140, 146, 156–158] and this will likely

continue with the technology advances. The clinimetric properties of these devices in CF are described in a recent systematic review [154]. The authors found that only one accelerometer (ActiGraph model 7164) and one multisensor device (BodyMedia SenseWear armband) were tested. The ActiGraph presented good convergent validity [157, 159], test–retest reliability (intraclass correlation coefficient of 0.63) and feasibility [146, 157] in adolescent and adult patients with CF. Discriminate validity [160] and responsiveness [123] were only evaluated in children with CF. Selvadurai et al (2002), exploring the effects of exercise training in children with CF admitted to hospital (n=66), found a significant improvement in activity levels after five sessions of endurance training (8.64%, p<0.001, Cohen's d_z 0.82) or resistance training (3.81%, p<0.001, Cohen's d_z 0.85) measured by accelerometry [123]. Therefore, accelerometers may be a useful tool to assess changes in physical activity levels of patients with CF in response of respiratory physiotherapy interventions. Regarding the SenseWear armband device, its validity (discriminate, convergent and concurrent) [140, 161] was only determined for adult patients with CF and no data on reliability and responsiveness exist. Further research is needed to determine which motion sensors provide the best clinimetric properties in CF in order to improve physiotherapy assessment. Moreover, as children have typically higher physical activity levels than adults [162], validation studies should be conducted in children and adults with CF. Finally, it would be useful to develop specific guidelines for the use (e.g., number of monitoring days, duration) of these motion sensors in CF, in order to standardise the collection of activity data and optimise their interpretation.

2.2.7. Burden of treatment

The concept of burden of treatment has been receiving increasing attention in patients with CF. Burden of treatment is described as the increased demand experienced from performing self-care activities required to undertake treatment regimens and monitor health outcomes [163]. Recent evidence demonstrated, however, that from a patient's perspective, treatment burden is beyond the workload arising from treatment regimens, being experienced in three disruption domains: biological (physical side effects), biographical (sense of self) and relational (impact on valued relationships) [164].

A large observational cohort study explored treatment complexity in patients with CF (n=7252) over a 3-year period [165]. It may be hypothesised that treatment regimens would be more complex only among patients with more severe disease. Indeed, in this cohort, the highest treatment complexity was presented by patients with more severe disease. Nevertheless, over the 3-year period, the complexity of treatment regimens increased in all age and disease severity groups. This study showed that the recommended management of CF resulted in high burden of treatment for patients.

In the specific case of respiratory physiotherapy, vigorous airway clearance and exercise regimens are recommended for patients with CF [166], which may result in increased burden of treatment. Burden of treatment, in turn, is associated with non-adherence and poor health outcomes [158, 163, 167–169]. This is particularly important for physiotherapists since the level of adherence to exercise and physiotherapy is generally reported to be poor (40–55%) [170, 171], in contrast with moderate to high adherence to nebulised medications, pancreatic enzymes and antibiotics (65–95%) [170, 172].

These levels of adherence suggest that patients with CF make decisions based on the com‐ plexity of recommended therapies they can complete, while fulfilling their responsibilities and commitments to family and work. As the number of adjunct therapies increase in CF, there may be a point at which perceived treatment burden outweighs the benefits of new or adjunct therapies, adversely affecting patient's adherence. Physiotherapists therefore, need to be sensitive recognising, understanding and supporting the reduction of burden of treatment, in order to balance the potential benefits and burdens of physiotherapy interventions and maximise adherence [158, 173].

The recognition of this concept led to the development of specific instruments for assessing burden of treatment. Burden of treatment has been incorporated into the CFQ [89]. Specifically, the burden of treatment domain is comprised of three questions: 'to what extent do your treatments make your daily life more difficult?', 'how much time do you currently spend each day on your treatments?' and 'how difficult is it for you to do your treatments each day?'. The score ranges from 0 to 100, with lower scores representing higher burden of treatment.

The burden of treatment domain of the CFQ has been used in recent studies evaluating the effectiveness of novel interventions [91, 174]. In a trial with patients with CF (n=12), assessing the effect of a nebulised hypertonic saline therapy, a significant improvement was found in respiratory symptoms together with an increased in perceived burden of treatment (Cohen's d_z 3.05) [174]. Schmidt et al. (2011) evaluated a 12-week individually tailored unsupervised aerobic exercise programme in patients with CF (n=14) [91]. Patients were instructed to exercise at least 30 minutes, three times a week with a heart rate target above 70% of their maximum. This study showed that an exercise programme could significantly increase VO_2max and, at same time, significantly decrease the perceived burden of treatment (Cohen's d_z 1.03) [91]. These two studies, despite being distinct, show that the burden of treatment domain of the CFQ is sensitive to change over time and demonstrate large effect sizes. Physiotherapists can, therefore, confidently rely on the burden of treatment domain of the CFQ to assess their interventions.

One of the disadvantages of the burden of treatment domain is the fact that it mainly addresses the complexity and time consuming routine of self-care. However, recent research has demonstrated that burden of treatment goes beyond these aspects and is experienced as biological, biographical and relational disruptions [164]. Therefore, when designing future instruments and methods for assessing burden of treatment, these three disruption domains should also be taken into account. This highlights the relevance of assessing burden of treatment as an outcome measure of respiratory physiotherapy in CF. The evaluation of burden of treatment will also inform the development of new and minimally disruptive interventions.

3. Conclusions

This chapter presented and discussed the strength and weaknesses of the outcome measures currently applied or emerging in CF respiratory physiotherapy interventions. It provided a comprehensive overview of the most commonly used, and also addressed the less used and

some even emerging, outcome measures, which show potential to overcome some of the barriers to build an evidence base for respiratory physiotherapy practice in patients with CF.

The chapter presented outcome measures possibly to be applied (i) in clinical practice before, during and after each session of respiratory physiotherapy to monitor its effectiveness; (ii) before and after the respiratory physiotherapy treatment (i.e., normally characterised by weeks of intervention) and (iii) clinically, but which main interest is fundamental and/or applied research in CF respiratory physiotherapy.

In a time where the relationship between "best care" versus "burden of treatment" is discussed, two factors seem crucial for respiratory physiotherapy: (1) to take into consideration family and patient's preferences when providing treatments and (2) build a sound evidence base. For the latter, a shift of the commonly used outcome measures, namely FEV_1, is essential, and a strong consideration to start applying new outcome measures is recommended.

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