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UNIVERSITE DE LAUSANNE – FACULTE DE BIOLOGIE ET DE MEDECINE

Département médico-chirurgical de pédiatrie
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Pulmonary Exacerbation Score in Cystic Fibrosis Patients: Reliability and Validity Testing

THESE

préparée sous la direction du Professeur Sergio Fanconi
(avec la co-direction du Docteur Yann Kernen)

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Pulmonary Exacerbation Score in Cystic Fibrosis Patients: Reliability and Validity Testing

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Background: Lung disease in cystic fibrosis (CF) is characterized by recurrent pulmonary exacerbations (PEs), but consensus on diagnostic criteria for PE is lacking. The use of a consistent definition of PE as an outcome measure in CF clinical trials would allow meaningful comparison across centers. The aim of this study was to assess the reliability and validity of a simplified version of the Seattle Pulmonary Exacerbation Score (SPEX).
Materials and Methods: A cross-sectional observational study with review of case notes was conducted on pediatric patients with CF in an outpatient setting. Inter-investigator reliability was assessed using the kappa coefficient of agreement, and intra-investigator reliability was examined following re-evaluation 21 months after the initial assessment. The validity of the SPEX was analyzed using independent clinical assessment as the ''gold standard.'' The performance of the original and simplified scores was compared.
Results: Inter- and intra-investigator reliability of SPEX scores were excellent ($\kappa = 0.91$ and 0.98, respectively). Validity testing yielded a kappa coefficient of 0.63. The sensitivity and specificity of the SPEX in detecting PE were 89.4% and 84%, respectively. The SPEX performed as well as the original measure.
Conclusions: The SPEX is objective and repeatable. This quick and simple-to-use measure performed as well as the original version and is applicable to a real-life pediatric population outside of the context of narrowly defined clinical parameters. The use of the SPEX to diagnose PE consistently in children with CF is thus recommended.

Introduction

Apart from chronic decline in respiratory function, lung disease in cystic fibrosis (CF) is characterized by episodes of recurrent and acute worsening of respiratory symptoms and signs,[1] often referred to as ''pulmonary exacerbations'' (PEs).[2] A variety of insults, including bacterial and viral illnesses, sinusitis, allergens, and other irritants, can alter the fragile homeostasis between airway pathogens and local host defenses, leading to PE.[3] PEs are often associated with a need for treatment with antibiotics, including hospitalization in some cases. Each PE has a negative impact on 5-year survival equivalent to a 12% reduction in predicted percent forced expiratory volume in 1 sec (FEV_1%) and on health-related quality of life.[4] PEs are associated with fragmented sleep[5] and increased mortality,[6] and are considered to be strong risk factors for morbidity.[7] A number of preventive treatment strategies have been developed to reduce the frequency and severity of PEs in patients with CF, and emerging research suggests that PEs play a large role in the overall decline in lung function, which may not subsequently return to baseline.[8,9] Treatments include mucolytic agents, physiotherapy and exercise, antibiotics, nutritional strategies, anti-inflammatory agents, and vaccination against common respiratory pathogens.[10]

Definitions for PEs have been used in numerous clinical trials evaluating new treatments in CF.[11–14] Despite its importance in the clinical course of CF, consensus on the diagnostic criteria for PE is lacking. Since a uniform clinical outcome measure would allow meaningful comparison across studies or centers in CF clinical trials, and as modalities of CF treatment are changing and new treatments are under investigation, the use of a consistent definition of PE is important.[15]

This study aimed to test the inter- and intra-investigator reliability and validity of the Seattle Pulmonary Exacerbation Score (PEX).[16] To the authors' knowledge, the PEX has been evaluated only in the sample of patients used to construct it. It was created to provide a standardized definition of PE for use in clinical trials, based only on patients' clinical status. The PEX was elaborated using patients with CF aged ≥6 years with FEV_1 between 75% and 25% of

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Table 1. Simplified Seattle Pulmonary Exacerbation Score (SPEX)

	Modification of symptoms during the last 15 days	*Yes*	*No*
1	Increased cough (frequency and/or severity) over the past 2 weeks	3	0
2	Increased sputum production or chest congestion over the past 2 weeks	3	0
3	Decreased exercise tolerance, increased dyspnea with exertion, or playing less over the past 2 weeks	3	0
4	Missed day care, school, or work in the past 2 weeks due to illness	3	0
5	Decreased appetite over the past 2 weeks	2	0
6	**Chest exam**: New crackles, rales or rhonchi on auscultation of the chest	2	0
	Total score		

In the score, six items are assessed by presence or absence of the symptom or physical sign over a 2-week period. Three points are given for the four first items, and two for the last two items. A PE is defined as a score of ≥4. The modifications from original score are in the adjunction of day care for absenteeism.

predicted value, positivity for *Pseudomonas aeruginosa* in sputum within 6 months before inclusion, and room-air oximetry values ≥88%. It was developed for a multicentric randomized phase III trial that controlled for tobramycin inhalation. After reflection on the scoring system,[16] the author proposed a simplified draft score sheet: the Simplified Seattle Pulmonary Exacerbation Score (SPEX; pers. comm.; Table 1). Apart from testing the reliability and validity of the SPEX in the real-world setting of a pediatric CF outpatient clinic, as this instrument has not been evaluated previously, this study also compared its performance with that of the original PEX. It was hypothesized that the SPEX would perform as well as the original version, and would be applicable to a real-life pediatric population outside the context of narrowly defined clinical parameters.

Materials and Methods

Study subjects

This cross-sectional observational study involved patients from a single outpatient CF center in the pediatric department of the University Hospital, Lausanne, Switzerland. Patients had CF diagnoses confirmed by two positive sweat tests (chloride >60 mmol/L) or a genotype with two identifiable CF-causing mutations. All consecutive patients attending the clinic for a planned or emergency visit during a 12-month period (1 January–31 December 2008) were included, with repeat inclusion of some patients who had several consultations. As the PEX score does not include a measure of lung function, all patients aged <16 years were included.

Assessments

The SPEX (Table 1) was completed as part of this study. Data were collected retrospectively. The SPEX measures the evolution during the previous 15 days of six items: cough, sputum, exercise tolerance, absenteeism, appetite, and chest examination findings (i.e., appearance of new crackles, rales, or rhonchi). Three points are given for the first four items, and two points are given for the last two items. PE is defined as a score of ≥4.

To act as a ''gold standard'' for validity testing, one CF physician (G.M.H.) examined all study subjects during consultations, taking ordinary medical notes as during routine standard care without filling in the SPEX. As SPEX items measure classical parameters in patients with CF, these data should also appear in regular medical records. Medical records were created using a database (FileMaker©, Inc.) with a template and space to enter free text describing case histories and global evaluations. For the assessment of inter-investigator reliability, two investigators (a medical student, F.K., and a consultant at the clinic, Y.K.) independently completed the SPEX using notes from the clinical consultation, without final evaluations or treatment decisions. The aim was to determine, based on the medical notes, whether subjects were experiencing PE. To test intra-investigator reliability, one investigator (Y.K.) completed the SPEX 21 months later (February 2011) using the original medical notes. Finally, SPEX results were compared with the clinical conclusions of the examining physician.

The institution's review board and the Ethics Committee of the Canton of Vaud, Lausanne, Switzerland, approved the study protocol. Data were treated anonymously.

Statistical analysis

Inter- and intra-investigator reliability were evaluated using the kappa coefficient of agreement.[17] The coefficient interpretation structure of Streiner and Norman[18] was used: poor, $\kappa < 0.40$; fair, $\kappa = 0.40$–0.59; good, $\kappa = 0.60$–0.74; and excellent, $\kappa > 0.74$. Logistic regression was applied to identify the SPEX cutoff score (first measure by Y.K.) that best discriminated between patients with and without PE (as identified by the ''gold standard''). For the calculation of the SPEX cutoff score, only data from patients who were not taking antibiotics were included. The area under the receiver operating characteristic (ROC) curve was calculated, with a value of 1.0 representing 100% sensitivity and specificity. A subgroup analysis was conducted comparing patients taking antibiotics at the time of PE assessment with those newly prescribed antibiotics during consultations. Data were analyzed using Microsoft Excel 2002 (Microsoft plc, Seattle, WA) and Stata v13 (StataCorp LP, College Station, TX) software.

Results

Data from 234 consecutive consultations were included. The population consisted of 32 patients (13 males) ranging in age from 2 months to 16 years (median 8.5 years). Patients with PE were significantly older than those without PE ($M_{age} = 9.98$ years vs. 8.14 years; $p = 0.009$). Nevertheless, age had no effect on the probability of having PE, according to SPEX score. Mean predicted FEV_1% was 85.76% (Table 2). For 37 consultations, patients were already on antibiotic

Table 2. Demographic Table

Number of subjects	32
Males (%)	40.6
Age (years)	
Mean	8.33
Median	8.5
Range	0.16–16
FEV_1% (>6 years, in % predicted)	
Mean	85.76
Median	88
Range	50–124
Number of consultations	234
By males (%)	49.6

FEV_1, forced expiratory volume in 1 sec.

treatment. One consultation was excluded because insufficient data were available to complete the SPEX, and two consultations were excluded because the patients' sex could not be identified.

For the SPEX, the ROC curve was 0.91. The ROC curve data indicated that the probability of experiencing a PE providing optimal sensitivity and specificity was 0.28, corresponding to a score of 4.03. This score had 89.4% sensitivity and 84% specificity, correctly classifying 85.3% of subjects.

A total of 61 PEs were diagnosed by the physician, and 51 PEs were identified using the SPEX, 40 of which were also diagnosed by the physician. No PE was identified by either method for 162 consultations (Table 3). The predictive positive value of the SPEX compared with the physician's determination was 78.4%, and the predictive negative value was 88.5%.

Inter-investigator reliability testing showed discordance in 7/51 PE diagnoses ($\kappa = 0.91$ [95% CI 0.84–0.98]; Table 4). Intra-investigator reliability showed 97.5% concordance (232/234 consultations; $\kappa = 0.98$ [95% CI 0.94–1.00]; Table 5).

To test the validity of the SPEX, concordance was examined between the determinations of the physician and investigator 1 (Table 2). The kappa coefficient was 0.63 [95% CI 0.46–0.702]. The validity was higher in the analysis including only patients not taking antibiotics at the time of consultation ($\kappa = 0.72$), with 86.1% sensitivity and 98.1% specificity.

Discussion

The aim of the current study was to validate a simplified adaptation of a clinical score used to define the presence or absence of PE in pediatric patients with CF, and to compare its performance with that of the original score. The most discriminative SPEX score was 4, which had 89.4% sensitivity and 84% specificity, correctly classifying 85.3% of subjects. These values are similar to those for the original PEX,[16] but the intercept parameter of the PEX renders interpretation difficult. The SPEX showed excellent inter- and intra-investigator reliability ($\kappa = 0.91$ and 0.98, respectively), good validity ($\kappa = 0.63$), 89.4% sensitivity, and 84% specificity. The lower kappa coefficient for validity can be explained by clinicians' ability to account for longitudinal aspects of patients' courses. For example, a clinician can consider a brief deterioration 2–3 days prior to a consultation due to a viral infection in making a decision about the need for a change of therapy. In contrast, the SPEX is a cross-sectional measure of changes in symptoms over the previous 2 weeks that does not account for patients' global evolution. This factor probably constitutes a main limitation of the scoring system.

The predictive positive and negative values of the SPEX compared with the physician's determination were better than reported in other studies.[19] The validity was higher for patients who were not taking antibiotics at the time of consultation, with excellent specificity. Numerous other scoring systems are available. The Fuchs score was used in the DNase study,[11,12] the Ramsey score was used in the tobramycin trial,[13] the Acute Respiratory Illness Checklist was used in a phase 2 trial for a respiratory syncytial virus vaccine,[14] and the Respiratory and Systemic Symptoms Questionnaire was created by Konstan *et al.*[14] to detect PE regardless of requirement for antibiotic treatment. Although they are established scores, they lack validation studies in cohorts of patients other than those in which they were developed. These scores are based on the appearance or worsening of signs and symptoms in the lungs and upper respiratory tract, and some also assess nutrition and general well-being. Although these instruments are established, validation studies conducted with cohorts of patients other than those with which they were developed are lacking. A simple score based on four symptoms was recently developed and validated in adult patients.[20] These definitions of PE have been based on empirical data but have not been formally validated.[12,13] The signs and symptoms most predictive of PE in all studies are increased cough, change in sputum volume or consistency, decreased appetite or weight, and change in respiratory examination findings and rate.[21–23] The Fuchs score was simplified in the Fuchs symptoms,[4] with criteria similar to those measured by the PEX,[16] but its value in everyday clinical

Table 3. Validity Between Physician and Investigator 1 (Y.K.)

Physician/ investigator 1	*No exacerbation*	*Exacerbation*	*Total*
No exacerbation	162	11	173
Exacerbation	21	40	61
Total	183	51	234
Kappa		0.63	

Table 4. Inter-Investigator Reliability

Investigators 1/2	*Score +*	*Score −*
Score +	45	1
Score −	6	182
Total	51	183
Kappa	0.91	

Table 5. Intra-Investigator Reliability After 2 Years

Observation 1/2	*Score +*	*Score −*
Score +	51	0
Score −	2	181
Total	53	181
Kappa	0.98	

practice is limited because it involves the assessment of pulmonary function and radiological changes. Pulmonary function testing limits the age range of patients assessed, and the utility of chest radiography before every course of antibiotic treatment remains a matter of debate.[4] The CF Foundation's clinical practice guidelines also provide commonly used diagnostic criteria.[24] The diagnosis of PE must be independent of the physician's decision on whether to treat it.

Despite the important role of PE in CF, consensus on its definition in children or adults is lacking.[25] A case scenario study showed that definitions vary within and among centers, and even at the level of individual clinicians.[26] The present analysis of the SPEX showed good inter- and intra-investigator correlation, as well as good sensitivity and specificity. These results confirm that the SPEX defines PE accurately according to the clinical standards of the authors' center, in addition to the center in which it was developed.[16] The SPEX was chosen for validation, as it is a very simple-to-use measure that requires no additional examination, such as lung function testing or radiology. This characteristic is of particular relevance for the measure's utilization with young children or in home settings.

This study has several limitations. First, it was not possible to complete all SPEX items using the physician's notes in some cases. For example, it was not always possible to determine clearly whether a patient's appetite had decreased or varied during the 2 weeks prior to assessment. For preschool-aged children, absenteeism is best defined (as in the SPEX) as a parent's absence from work or the child's absence from a daycare facility due to the child's health. For that reason, it was added in the SPEX (Table 1). Second, the use of the CF physician's clinical judgment as the ''gold standard'' for validity testing may be considered a study limitation. However, the physician was very familiar with all patients in the authors' small CF center, optimizing the odds of PE recognition. In addition, the CF physician, although very familiar with clinical scoring systems, did not refer to the SPEX before or during the study period. This does not eliminate the potential bias created by the recording of items believed to be particularly relevant to the SPEX during consultations. However, the lack of some relevant information in the notes suggests that this bias was negligible. Third, a study period was defined rather than running a formal power calculation. The measure also has limitations, as discussed in a report from the EuroCare CF Working Group: ''the defining score does not always correlate with a change in treatment.''[4] Finally, the study was conducted at a single center with a small patient cohort.

In conclusion, the present findings suggest that the SPEX is objective and repeatable. This quick, simple-to-use, clinically based measure performs as well as the original PEX and is applicable to a real-life pediatric population outside the context of narrowly defined clinical parameters. It requires no additional examination. For these reasons, the use of the SPEX is recommended in future clinical trials to identify PE consistently in children with CF.

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Author Disclosure Statement

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