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## Macrolide maintenance treatment for bronchiectasis

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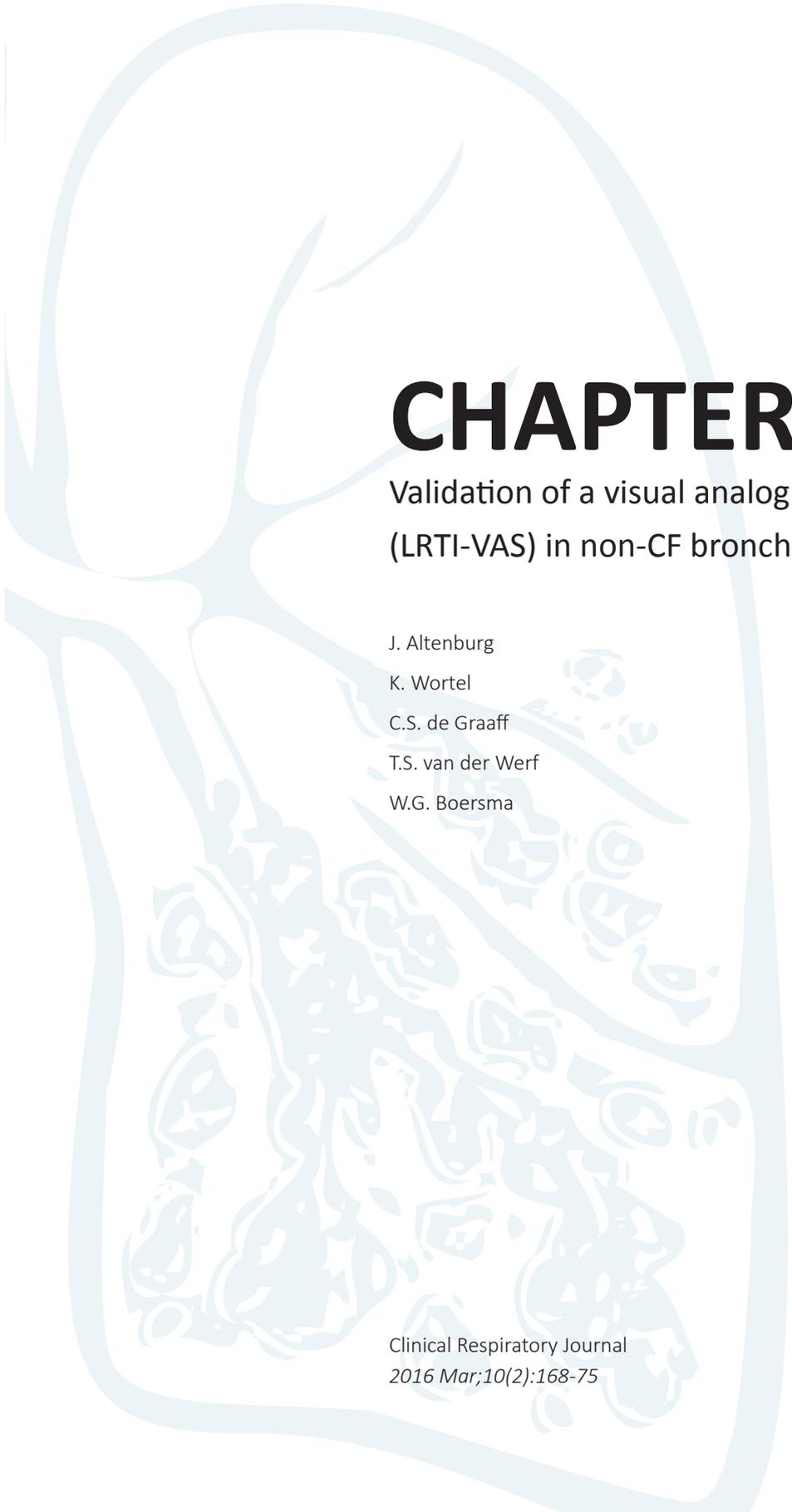
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# CHAPTER 8

Validation of a visual analogue score  
(LRTI-VAS) in non-CF bronchiectasis.

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## Abstract

**Introduction:** Quality of life in patients with non-cystic fibrosis (non-CF) bronchiectasis is largely defined by respiratory symptoms. To date no disease specific tool for symptom measurement in this patient group was available. We developed the Lower Respiratory Tract Infections – Visual Analogue Scale (LRTI-VAS) in order to quickly and conveniently quantify symptoms in non-CF bronchiectasis.

**Objectives:** This study aimed to validate LRTI-VAS for use in non-CF bronchiectasis.

**Methods:** This study included out-patients with radiologically proven bronchiectasis and no evidence of CF. Results of LRTI-VAS were compared to other markers of disease activity (lung function parameters, oxygen saturation and three health-related quality of life questionnaires (SF-36, SGRQ and LCQ) and validity, reliability and responsiveness were assessed.

**Results:** 30 stable and 30 exacerbating participants completed the LRTI-VAS questionnaire. When testing for repeatability on two separate occasions, no statistically significant difference between total scores was found (1.4 (SD 5.3) ,  $p = 0.16$ ). Internal consistency was high across items (Cronbach's alpha 0.86). Correlation with SGRQ-, SF36- and LCQ total scores was high. Following antibiotic treatment, mean (SD) LRTI-VAS total score improved from 18.1 (SD 9.9) to 26.1 (SD 6.6) ( $p < 0.001$ ).

**Conclusions:** LRTI-VAS showed excellent validity, reliability and responsiveness to change and therefore appears a reliable tool for symptom measurement in non-CF bronchiectasis.

## Introduction

Bronchiectasis (BE), first described by Laennec (1) in 1819, is characterized by irreversible, pathologic dilatation of the small and medium-sized bronchi, resulting from a vicious cycle of inflammation and bacterial colonization. Impaired clearance of the lower airways leads to chronic bacterial infection and inflammation, a process that has been referred to as a 'vicious circle', leading to the occurrence and progression of BE. (2) Although the aetiology remains unclear in a large proportion of patients (25-53%), common causes include immune defects, previous severe infections and aspiration.(3;4)

The course of the disease is highly variable, including nearly symptom free periods interspersed with infectious exacerbations. Many patients with BE however, suffer from chronic complaints, such as a productive cough, dyspnoea and fatigue.(5;6) Infectious exacerbations are characterized by worsening of symptoms and signs of airways infection, sometimes complicated by pneumonia.(7) The disease was considered to be offensive and untreatable in the pre-antibiotic era, but infections and symptoms are nowadays relatively well controlled with antibiotics and supportive therapy.(8) However, many patients with bronchiectasis today still experience feelings of embarrassment about their coughing or bronchorrhoea, sometimes leading towards social isolation. As the impact of symptoms on quality of life (QOL) may be considerable, improving QOL through symptom reduction is one of the main goals of non-CF BE management.(9)

We developed the LRTI-VAS (Lower Respiratory Tract Infections – Visual Analogue Scale), a symptom scale that can be used to quantify the degree of dyspnoea, fatigue, cough, pain and sputum colour in patients with non-CF BE. These five domains of the LRTI-VAS reflect the most frequently encountered symptoms reported by individuals with BE in clinical practice.(5-8) The LRTI-VAS is significantly less time consuming than other disease specific questionnaires, has a low administrative burden and a simple design.

**Objective:** The aim of this study was to validate the LRTI-VAS for assessment of symptoms in non-CF BE.

## Materials and methods

### Study population

From 2010 to 2011 non-CF BE patients visiting the out-patient clinic of the Department of Pulmonary Medicine of the Medical Centre Alkmaar, a large teaching hospital, were asked to participate by the primary investigator. Patients were eligible for inclusion if they had HRCT-

confirmed non-CF BE and spirometry performed less than six months prior to inclusion. Exclusion criteria were CF or inability to read or otherwise complete the questionnaires.

Reliability was measured during a clinically stable situation; measurement of responsiveness required the presence of an exacerbation. Validity was tested on both occasions.

To guarantee clinical stability, each participant was instructed to report to the researchers without delay any changes in their clinical condition, pointing towards an infectious exacerbation. In addition, each participant completed daily diary cards, asking about symptoms indicative of an infective exacerbation. Patients were excluded if clinical stability, as defined by any of the two above-mentioned criteria, was compromised/lacking.

In order to test for responsiveness, an additional inclusion criterion was added; the presence of an infectious exacerbation (meeting the criteria of an exacerbation given below) treated in- or out hospital with a course of oral or iv-antimicrobial treatment.

#### Study visits

All participants visited our out-patient clinic on two separate occasions, three weeks apart. On both occasions they were asked to complete the LRTI-VAS, the Medical Outcomes Study Short-Form 36 Health Survey (SF-36), the St George's Respiratory Questionnaire (SGRQ) and the Leicester Cough Questionnaire (LCQ) in a randomized order. In addition, on both study visits all patients performed flow-volume spirometry and arterial oxygen saturation was measured, using a fingertip pulse oximeter (Beurer GmbH Y23/003700). In case of an exacerbation, the first study visit was scheduled just before starting antibiotics.

#### Definition of an exacerbation

In this study an exacerbation was defined as abnormalities in at least four of the following eight symptoms, signs, or laboratory findings: 1) change in sputum production (consistency, colour, volume, or haemoptysis); 2) increased dyspnoea (chest congestion or shortness of breath); 3) increased cough; 4) fever (>38°C); 5) increased wheezing; 6) decreased exercise tolerance, malaise, fatigue, or lethargy; 7) FEV1 or FVC decreased by at least 10% from a previously recorded value; 8) changes in chest sounds.(10)

In order to validate the LRTI-VAS for measuring symptoms in patients with non-CF BE, the validity, reliability and responsiveness of this measure were established as follows:

#### Testing for reliability

30 patients with clinically stable BE were invited to repeat the LRTI-VAS 3 weeks after completion of the initial questionnaire. Reliability is defined as the extent to which a test provides consistent results across repeated measurements.(11) This is estimated by

measuring the test-retest reliability and internal consistency. The test-retest reliability is the ability of the questionnaire to produce consistent scores over a short period of time, higher consistency meaning higher reliability. Internal consistency concerns the degree of association between the questionnaire items.

#### Testing for validity

30 patients with clinically stable bronchiectasis and 30 patients with deterioration of symptoms because of an infectious exacerbation completed the LRTI-VAS, LCQ, SF-36 and SGRQ on two separate occasions, three weeks apart. In addition they performed spirometry and pulse oxygen saturation measurement on both occasions. Correlation of LRTI-VAS results with LCQ, SF-36, SGRQ, FEV1, FVC and oxygen saturation was calculated in order to test for validity, which is the extent to which an indicator represents the intended concept. (11) Validity can be tested by comparing the actual outcomes of a test with a theoretical expectation of these outcomes.

#### Testing for responsiveness

30 patients with an infectious exacerbation completed the LRTI-VAS just before starting antibiotic treatment and two weeks after completion of treatment. The responsiveness of the questionnaire was assessed by comparing changes in scores to changes in markers of disease activity and scores on the other, validated, questionnaires, at two separate points in time.

#### Questionnaires

Apart from the LRTI-VAS, patients were asked to complete the SGRQ, the SF-36 and the LCQ in a randomized order, generated with Graphpad Prism®. All questionnaires were adapted to ask about symptoms in the preceding week.

- LRTI-VAS: consists of a set of horizontal lines with two anchor points, one at each extreme, each line representing a different symptom (fig 1). It is scored from 1 to 10, the subjects being unaware of the numbers. Higher scores indicate more severe symptoms. Five symptom domains are scored: dyspnoea, fatigue, cough, pain and sputum colour (white – dark green). Separate scores are calculated for each symptom and a total score is provided, consisting of all symptom scores added up. Similar weight is assigned to all symptom domains. In our study, a Dutch translation of the LRTI-VAS was used; Its simple and visual design allows for use in other languages, without additional validation studies.
- SGRQ: a condition specific HRQL-measure, that consists of 76 items. These items are partitioned into three sections (Symptoms, Activity, Impact), which are scored separately and can be added up to provide a total score, ranging from 0 to 100, zero indicating no impairment of quality of life. The SGRQ requires about 10 minutes to complete.(12)

- SF-36: a self-administered, generic 36-item HRQL measure. Eight different health concepts are scored, scores ranging from 0-100. A lower score on one of these domains indicates more limitations in this specific domain.(13) Although the SF-36 is primarily designed to measure between-group differences of QoL, this survey is frequently used to measure the effectiveness of medical treatment in clinical trials.(14)
- LCQ: a HRQL questionnaire, validated for assessing chronic cough in non-CF BE.(9;15) It is a 19-item, self-completed questionnaire, exploring the impact of cough severity across three domains; physical, psychological and social.

Figure 1. Lower respiratory tract infections – visual analogue scale (LRTI-VAS).

**SYMPTOM SCALE**

Please place a cross at each one of the following lines:

- 1. SHORTNESS OF BREATH**  
 No shortness of breath |-----| The worst possible shortness of breath
- 2. TIREDNESS**  
 No tiredness |-----| The worst possible tiredness
- 3. COUGH**  
 I don't cough |-----| The worst possible cough
- 4. COLOUR OF PHLEGM**  
 White |-----| Dark green
- 5. PAIN**  
 No pain |-----| The worst possible pain

## Statistical analysis

### Sample size

When comparing parameters at two different time points, at least 30 participants are required at each point to be able to analyze the difference with a paired T-test assuming normality or the Wilcoxon test when there is no normality. In our study, the separate items of the LRTI-VAS were scored on 10-point scales. Standard deviation on t=1 and t=2 is 1,95. To be able to detect a mean difference of 1 point between scores on t=1 and t=2, with alpha being 0,05 and beta 0,20, a sample size of 30 patients on each measuring moment is required assuming a moderate correlation (0.5) between the scores on t=1 en t=2.

### Reliability, validity and responsiveness

Paired T-tests were used to compare LRTI-VAS domain and total scores on two occasions during clinical stability and at the start and end of an exacerbation. In case of a skewed distribution, Wilcoxon's signed ranks test was used. Pearson's correlation was used to assess validity.

Internal consistency of the LRTI-VAS was measured by applying Cronbach's alpha to each of the component scores at entry; accepting >0.7 as sufficient.(16)

During statistical analysis we checked for floor and ceiling effects-. Nominal and ordinal variables were expressed using frequency tables, modus and median. Interval/ratio variables were expressed in terms of mean, standard deviation and confidence intervals. When comparing two variables, p-values of < 0.05 were considered statistically significant. The software package SPSS 16 for Windows (SPSS Inc. Chicago, Illinois, USA) was available for statistical analysis.

## Results

60 patients were included in the study and were followed up according to the study protocol, thirty of whom were clinically stable. Patient characteristics are shown in table 1.

They all completed all questionnaires and had spirometry and oxygen saturation measurements on two occasions. Of these, 30 were clinically stable and 30 had an exacerbation fulfilling our criteria (figure 2) (please find results for LRTI-VAS, SGRQ, LCQ and SF-36 domain scores in e-table 1, online data supplement).

**Table 1. Baseline patient characteristics**

Patient characteristics (n=60)	
Age in years (mean (SD))	66.6 (10.3)
Gender (female)	35 (58.3)
FEV1, percentage predicted mean (SD)	82.3 (28.2)
FVC percentage predicted, mean (SD)	93.2 (25.7)
Aetiology of bronchiectasis	
- idiopathic	30 (50)
- allergic bronchopulmonary aspergillosis (ABPA)	3 (5)
- post-transplant	1 (2)
- primary ciliary dyskinesia	3 (5)
- chronic obstructive pulmonary disease (COPD)	6 (10)
- rheumatoid arthritis	4 (7)
- post- infectious (incl TBC)	9 (15)
- common variable immune deficiency (CVID)	2 (3)
- gastro-intestinal reflux disease (GERD)	2 (3)
Smoking status	
Never	36 (60)
Former	23 (38)
Current	1 (2)
Long term medication:	
- oral antibiotics	19 (31)
- inhaled antibiotics	8 (13)
- oral steroids	8 (13)
- inhaled steroids	40 (67)
<i>Pseudomonas aeruginosa</i> (PA) status	
repeated cultures positive for PA	11 (18)
no PA	49 (80)
No of exacerbations in the year of study participation:	
0	
1	14 (22)
2	11 (18)
3	14 (23)
4	9 (15)
> 4	9 (15)
	3 (5)

Values are no. (%) unless otherwise specified  
FEV1 and FCV within 6 months prior to study inclusion.

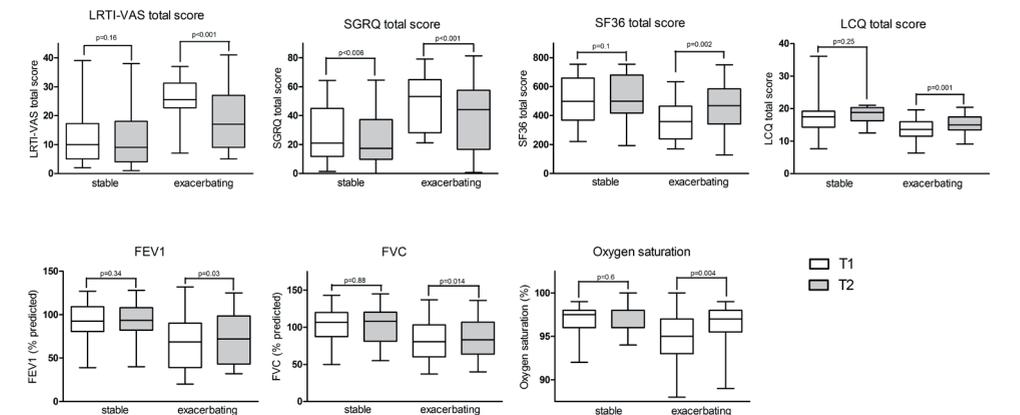
**Reliability:** the repeatability of the LRTI-VAS in stable bronchiectasis over a 3-wk period  
30 stable patients repeated the LRTI-VAS 3 weeks after completion of the initial questionnaire. Mean difference between total scores was 1.4 (SD 5.3),  $p = 0.16$  (fig 2).

Cronbach’s alpha for internal consistency for the five LRTI-VAS domains was 0.86, indicating good consistency between items. Internal consistency decreased when one of the items was deleted.

**Responsiveness:**

30 exacerbations met the study criteria and were eligible for inclusion in the final analysis. LRTI-VAS total score at start of treatment was 26.1 (SD 6.6) as compared to 18.1 (SD 9.9) at end of treatment (mean difference 8.0 (SD 9.1)  $p < 0.001$ ) (fig 2)

**Figure 2. Results for clinical parameters and questionnaires at baseline (T1) and three weeks later (T2) in a clinically stable situation and during an antibioticly treated exacerbation.**

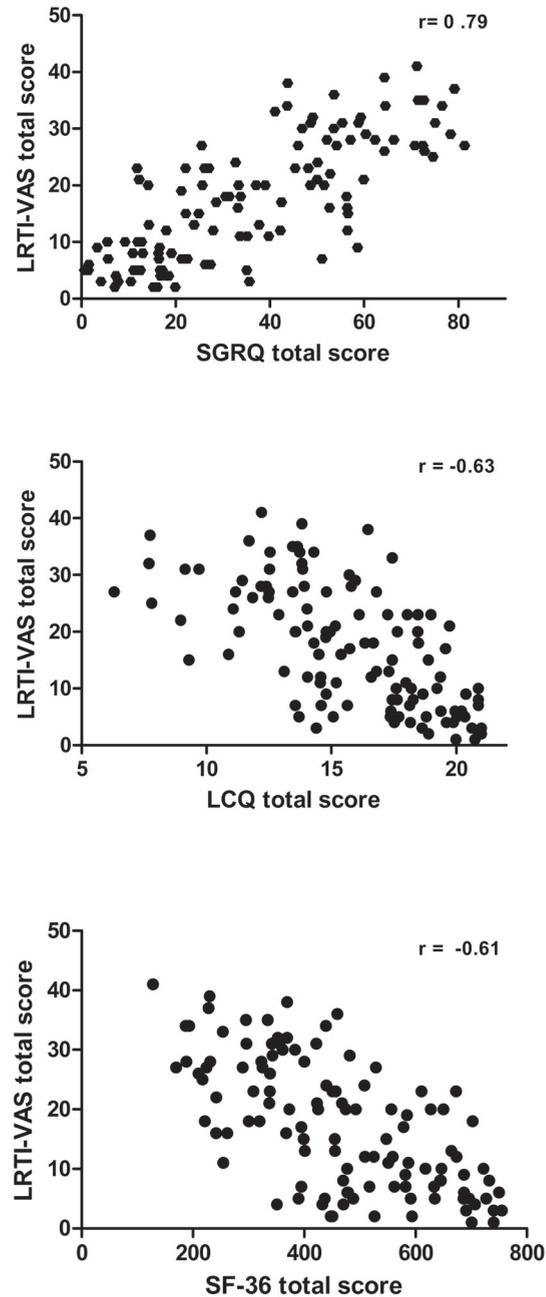


LRTI-VAS: lower respiratory tract infections – visual analogue score. SGRQ: Saint Georges Respiratory Questionnaire . SF-36: Medical Outcomes Study Short-Form 36 Health Survey. LCQ: Leicester Cough Questionnaire. FEV1: Forced expiratory volume in one second. FVC: Forced vital capacity.

**Validity:** comparing the LRTI-VAS with other indicators of disease severity

The correlation coefficients between total scores on validated questionnaires (SF-36, SGRQ and LCQ), and LRTI-VAS total score are shown in figure 3. Correlation between FEV1, FVC, oxygen saturation and LRTI-VAS total score was low ( $r = 0.26-0.39$ ).

Figure 3. Correlation between scores on validated questionnaires and LRTI-VAS total score.  $r$  represents Pearson's correlation coefficient.



LRTI-VAS: lower respiratory tract infections – visual analogue score. SGRQ: Saint Georges Respiratory Questionnaire SF-36: Medical Outcomes Study Short-Form 36 Health Survey. LCQ: Leicester Cough Questionnaire

## Discussion

To our knowledge, the LRTI-VAS is the first clinical tool solely designed for quantification of symptoms in chronic respiratory diseases. Other questionnaires have also been validated for non-CF bronchiectasis patients, the best known being the SGRQ and LCQ.(9;12;15-17) Recently the Quality of Life Questionnaire for Bronchiectasis (QOL-B) was added to our armamentarium.(18) All of these are fairly comprehensive Quality of Life questionnaires which contain a 'symptoms' domain but are not exclusively designed for measurement of symptoms. The LRTI-VAS meets a need of a faster, more simplified tool for patient-reported outcome in trials and clinical settings. In addition, our questionnaire has a simple design and therefore makes it equally acceptable for poorly educated or illiterate patients.

Visual analogue scores have been used in a variety of clinical settings since their first description in 1957, primarily applied for the assessment of variations in intensity of pain. Nowadays evidence to support their use to measure other symptoms, such as dyspnoea and fatigue, is mounting.(19;20) In clinical trials of patients with COPD, asthma, CF or BE, breathlessness or dyspnoea is frequently measured by means of a VAS.(21-26) VAS-scores have also been applied to measure sputum volume, cough frequency and fatigue in patients with a variety of chronic respiratory diseases.(22;25;27;28) Smith et al (29) disclosed VAS as the only measure to correlate well with objective cough rates in CF-patients who were hospitalized for an exacerbation. We used the LRTI-VAS before, to quantify symptoms in 223 patients with acute exacerbations of COPD and to measure clinical outcome in 213 patients with community acquired pneumonia.(30;31) On all occasions the LRTI-VAS was generally well accepted by patients, showed a high response rate and both patients and researchers appeared to quickly familiarize with this questionnaire.

Our patients scored between 2 to 3,5 points per item on the LRTI-VAS 10-point scale for dyspnea, fatigue, sputum colour and cough in a clinically stable situation. Prior to antibiotic treatment of an exacerbation LRTI-VAS scores for these symptoms increased to 5-6 points per item with a statistically significant decrement after antibiotic treatment. Scores for pain were considerably lower during clinical stability and did not change during treatment for an exacerbation, suggesting that this might be a less prominent and less responsive feature in non-CF BE. A large study in 103 patients with non-CF BE revealed that productive cough (96%), sputum expectoration (87%), dyspnea (60%), and fatigue were the most frequently encountered disease symptoms. Only 19% of their patients complained of chest pain.(32) However, leaving out 'pain' as an item reduced reliability.

In BE, clinical measures such as lung function often correlate only moderately with functional capacity and well-being.(33) This might explain why we only found low correlation between LRTI-VAS and FEV1, FVC and oxygen saturation. Health-related quality

of life (HRQL) in these patients is mainly defined by the presence, extent and severity of symptoms, such as dyspnoea and sputum expectoration. LRTI-VAS identifies and quantifies disease symptoms and could therefore be used to guide management in a clinical setting. In addition, symptoms as measured by LRTI-VAS are potentially valuable outcome measures when evaluating treatment effects in clinical trials.

## Conclusion

In this study of 30 stable and 30 exacerbating non-CF bronchiectasis patients LRTI-VAS showed moderate to high correlation with other validated questionnaires. In addition LRTI-VAS responded to clinical changes and showed excellent repeatability and internal consistency. It therefore meets the three key requirements of a questionnaire to be used in monitoring disease severity over time: validity, responsiveness and reliability.

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