# The BED-Pro Tool: facilitating the detection of bronchiectasis exacerbations

Yong-hua Gao [1,2] and Wei-jie Guan [3,4]

[1]Department of Respiratory and Critical Care Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China. [2]Institute of Respiratory Medicine, School of Medicine, Tongji University, Shanghai, China. [3]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute for Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. [4]Department of Thoracic Surgery, Guangzhou Institute for Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China.

Corresponding author: Yong-hua Gao (gaoyonghuahust@163.com)

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**The Bronchiectasis Exacerbation Diary is an eight-item patient-reported outcome instrument for detecting exacerbations in bronchiectasis** https://bit.ly/3k2IH4p

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Bronchiectasis is characterised by chronic cough, mucus hypersecretion and recurrent exacerbations with varying degrees of abnormal and irreversible dilatation of the bronchi [1]. The clinical course of bronchiectasis is punctuated with exacerbations in the majority of patients [2], defined as a deterioration of at least three symptoms (cough, sputum volume and/or consistency, sputum purulence, dyspnoea and/or exercise tolerance, fatigue and/or malaise, haemoptysis for ⩾48 h requiring alterations in therapy), according to the latest international expert consensus [3]. Consistent with other chronic lung diseases (particularly COPD and asthma), exacerbation in patients with bronchiectasis may confer a notable negative impact on the natural course of disease progression [2]. Recurrent exacerbations have been associated with heightened systemic and airway inflammation, accelerated lung function decline, increased mortality, and rising healthcare cost [2]. Therefore, reducing the frequency of exacerbations is a key goal of treatment and has been used as the primary endpoint in many clinical trials in bronchiectasis [4, 5].

Despite their clinical relevance, exacerbations of bronchiectasis have been defined simply as an increase in symptoms requiring immediate changes in treatment, which is an imprecise definition. To date, there has not been any standardised, reliable or valid method for quantifying these events in the context of clinical practice and clinical trials. Some of the existing quality of life assessment tools, such as the St George's Respiratory Questionnaire [6], QoL-B (Quality of Life – Bronchiectasis) [7] and COPD Assessment Test [8], have been used to detect the onset of exacerbations or quantify their severity. However, these tools might be somewhat complex and allow for a recall period that would limit their widespread application in bronchiectasis. In fact, a very low exacerbation rate during the course of studies was recorded in the RESPIRE clinical trials (a phase III randomised trial of ciprofloxacin dry powder for inhalation in bronchiectasis) [9], despite the attempt to enrich the study population for exacerbators by enrolling those with chronic bacterial infection and two or more exacerbations in the preceding year. Unreported and undetected exacerbations might have, at least in part, contributed to these findings. Interestingly, the unreported exacerbation events in bronchiectasis could have accounted for 44% of the total exacerbation events identified by a newly developed symptom diary (termed BEST (Bronchiectasis Exacerbation and Symptom Tool)) [10], although these events were significantly shorter in duration and milder in severity compared with the reported exacerbation. Because effective strategies have been available to prevent and treat exacerbations, improved reporting and detection of exacerbations through the use of patient-completed diaries, as has been adopted in COPD, may help to refine the treatment strategies, which would ultimately translate into an improved clinical outcome of bronchiectasis.

In this issue of *ERJ Open Research*, Shih *et al.* [11] sought to improve the precision of detecting bronchiectasis exacerbations by developing a patient-centred, content-valid, Food and Drug

Administration-compliant patient-reported outcome (PRO) instrument to monitor the key symptoms on a daily basis and during exacerbations. This study was conducted as the first phase of the multiphase BED-Pro study to develop a novel instrument for standardising the PRO assessment of exacerbations in bronchiectasis. Focused groups and interviews were conducted with patients who had experienced exacerbations of bronchiectasis by using the enrolment criteria, which were similar to those used in pharmaceutical clinical trials for exacerbation prevention to ascertain the patient-reported descriptions of events. International experts in bronchiectasis have participated in the process to assure the content validity from a medical professional perspective. Cognitive debriefing interviews ascertained that participants interpreted the items as intended. Finally, an eight-item, patient-reported questionnaire (BED-Pro) assessing patients' cough, sputum/phlegm production, sputum/phlegm purulence, breathlessness, fatigue and haemoptysis on a daily basis that attempts to accurately capture the exacerbations was constructed. This was consistent with the recommendations of the international expert consensus of bronchiectasis exacerbation. The BED-Pro instrument is currently being adopted to capture an acute worsening of symptoms and enable physicians to identify a potential bronchiectasis exacerbation that may require a change in therapy in the MAHALE study (www.clinicaltrials.gov identifier number NCT05006573) (a phase III clinical trial designed to assess the efficacy and safety of benralizumab in adults with bronchiectasis comorbid with eosinophilic inflammation). Further testing of the validity, reliability and responsiveness of the BED-Pro will be performed based on the data from the MAHALE study.

The BED-Pro, representing one of the novel objective instruments designed to detect bronchiectasis exacerbations, has been developed through the joint efforts of international academia and industry. A tool such as the BED-Pro is urgently needed by the clinical researchers working in the field of bronchiectasis, if it is proven to work well in the future. However, there remain many steps ahead before it can be extensively used among patients with bronchiectasis for the detection of exacerbation with an acceptable reliability. The BED-Pro instrument was developed to qualitatively record the change of symptoms from the stable state (baseline) to detect exacerbation; therefore, it could not provide further information pertaining to the severity and duration of exacerbation by using the dichotomous symptom scale, constraining our exploration of the natural course of bronchiectasis exacerbation. Developing more solid approaches to inform clinicians of the severity and duration of exacerbations is needed, and when the tool does not perform perfectly under these circumstances, the validity of the assessment tool would be doubted. Apart from these, the symptoms in bronchiectasis have notable day-to-day variations in many patients even in the absence of an exacerbation, and therefore it is necessary to make clear the minimal changes in the questionnaire's scores that the clinical event should be deemed as clinically significant. Unfortunately, the threshold that indicates an exacerbation event for the BED-Pro could not be established through the MAHALE study. The lack of the threshold for a symptom diary will decrease the specificity for identifying exacerbations in bronchiectasis. It would also be difficult to determine whether the BED-Pro can outperform the current definition of exacerbations for detecting these events.

As has been demonstrated in COPD [12], a symptom-based instrument (*e.g.* the BED-Pro) might not be sufficiently specific to detect exacerbations, and can be mimicked and/or aggravated by other clinical conditions such as pneumonia and cardiac events. In addition, it does not relate the symptoms to measurable pathophysiological variables that could characterise the event *per se*. Before the results of MAHALE study are available, whether the use of the BED-Pro could increase assay sensitivity and allow investigators to detect unreported events remains an open question.

Exacerbations are and will remain the crucial clinical events in the course of patients with bronchiectasis in the foreseeable future. Accurate and early identification of exacerbations will help to better appreciate the natural course of disease, thereby shedding light on the future strategies to improve the clinical management and research of exacerbations in bronchiectasis. Currently, it is challenging to draw firm conclusions on whether the BED-Pro is a useful tool at measuring bronchiectasis exacerbations, especially when considering the heterogeneity of bronchiectasis and the exacerbation events. However, any efforts to resolve the unanswered question would be welcome due to the lack of the valid objective measurement tool for detecting exacerbation. From this point of view, the BED-Pro instrument represents a further step in the right direction.

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