




Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research

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An expert conference has developed a consensus definition of a bronchiectasis exacerbation for clinical research <http://ow.ly/oKPY309yTaX>

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ABSTRACT There is a need for a clear definition of exacerbations used in clinical trials in patients with bronchiectasis. An expert conference was convened to develop a consensus definition of an exacerbation for use in clinical research.

A systematic review of exacerbation definitions used in clinical trials from January 2000 until December 2015 and involving adults with bronchiectasis was conducted. A Delphi process followed by a round-table meeting involving bronchiectasis experts was organised to reach a consensus definition. These experts came from Europe (representing the European Multicentre Bronchiectasis Research Collaboration), North America (representing the US Bronchiectasis Research Registry/COPD Foundation), Australasia and South Africa.

The definition was unanimously approved by the working group as: a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required.

The working group proposes the use of this consensus-based definition for bronchiectasis exacerbation in future clinical research involving adults with bronchiectasis.

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Introduction

Patients with bronchiectasis have frequent exacerbations that are a cause of significant morbidity and sometimes mortality, and are desirable to prevent [1]. The British Thoracic Society has defined exacerbations requiring antibiotics based on expert consensus as a deterioration in local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, dyspnoea, haemoptysis) and/or systemic upset [1].

Exacerbation frequency or time to next exacerbation are key end-points in clinical trials evaluating new treatments in adults with bronchiectasis. This is a view supported by investigators, clinicians involved in the care of bronchiectasis patients and individuals with bronchiectasis, and aligns with the current European Medicines Agency and US Food and Drug Administration mandates to use time to first exacerbation or the mean or median number of exacerbations in recent clinical trials of inhaled antibiotics [2, 3]. However, heterogeneity in the definition of exacerbation used can hinder comparisons of treatment effect.

An international group of investigators with interest in bronchiectasis gathered at the first World Bronchiectasis Conference in Hannover, Germany (July 7, 2016) to address the definition of bronchiectasis exacerbation. The aim of this working group was to develop a consensus definition of exacerbation for clinical trials involving patients with bronchiectasis. This consensus definition is for clinically significant bronchiectasis in adults, *i.e.* persistent symptoms consistent with bronchiectasis plus confirmation of bronchiectasis with computed tomography scan of the chest, and excludes patients with cystic fibrosis (CF).

Methods

A systematic review of exacerbation definitions used in clinical research from January 2000 until December 2015, involving adults with bronchiectasis not related to CF, was conducted [2, 4–23]. Search terms used from a PubMed search were “definition” and “exacerbation” and “exacerbation definition”. Studies related to review articles, descriptive cohorts and editorials were excluded.

Definitions of exacerbations were identified and individual criteria extracted. All identified criteria were then included in a Delphi process [24] involving bronchiectasis experts from Europe (representing the European Multicentre Bronchiectasis Research Collaboration (EMBARC)), North America (representing the US Bronchiectasis Research Registry/COPD Foundation (BRR)), Australasia and South Africa. Between May and June 2016, an online survey was conducted to determine which criteria, signs and symptoms identified by the systematic search should be included in a consensus definition. During the first round of the Delphi process, experts were able to add criteria that they deemed important. These new criteria were then graded in the further rounds.

There were three Delphi rounds to reach consensus. Criteria were graded as: 1, should not be a part of the exacerbation definition; 2, possibly suggestive of an exacerbation; 3, highly suggestive of an exacerbation; 4, must be present to define an exacerbation. Criteria were excluded if $\geq 80\%$ of participants rated them 1 or 2 and factors were considered for inclusion if $\geq 80\%$ of participants rated them 3 or 4, or the average score was ≥ 2 on all three Delphi rounds.

Shortlisted criteria were then discussed by the committee with majority voting used to determine the final criteria and structure of the definition.

Results

The systematic review identified 50 articles with 20 different definitions of exacerbation identified. More than 80% of published criteria included a requirement for antibiotic use, and the symptoms of increased dyspnoea, increased cough, increased sputum volume and a change in sputum colour. All other criteria were used in <80% of definitions.

All possible criteria were considered in the Delphi survey. After three rounds, the Delphi process resulted in the following signs and symptoms scoring mean ≥ 2 in the grading process (graded lowest to highest): haemoptysis, chest pain, decreased exercise tolerance, wheeze, hypoxia, fever, auscultation findings, patient self-reporting an exacerbation, systemic disturbance [13], fatigue, sputum viscosity, worsening shortness of breath, symptoms ≥ 24 h, worsening sputum colour, increased cough, worsening sputum volume, symptoms ≥ 48 h, exclusion of other causes and antibiotics used for the exacerbation (figure 1).

Although some previous criteria had used a combination of “major and minor” symptoms, the working group agreed (90% consensus) criterion based on a combination of symptoms with equal weighting was more operational.

Not all definitions identified in the systematic review required treatment with antibiotics or a change in treatment. Notably, in chronic obstructive pulmonary disease studies the concept of mild exacerbations that do not receive treatment is well established. In the case of bronchiectasis, 90% of our committee agreed that antibiotic treatment was not required to define an exacerbation, but 81% agreed that a change in management was required (which may include a new treatment with antibiotics and/or systemic steroids, or an increase in airways clearance, inhaled therapy or another intervention).

The outputs from the systematic review and subsequent Delphi process were discussed by the working group and a consensus (>80% participant approval) definition for a bronchiectasis exacerbation was agreed as: a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise

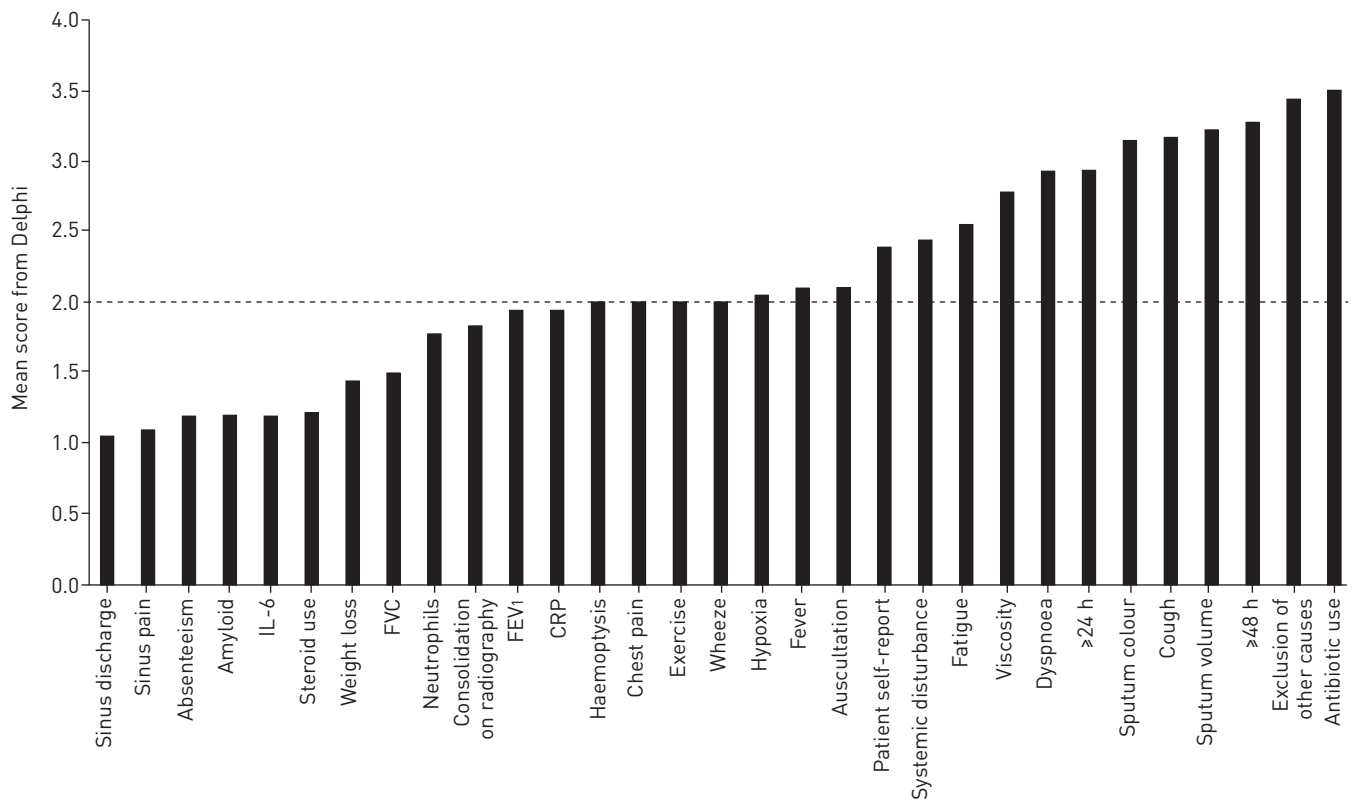


FIGURE 1 Results from the Delphi process. IL: interleukin; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; CRP: C-reactive protein. The scores were graded as: 1, should not be a part of the exacerbation definition; 2, possibly suggestive of an exacerbation; 3, highly suggestive of an exacerbation; 4, must be present to define an exacerbation. Scores ≥ 2 were targeted for discussion at the working group.

tolerance; fatigue and/or malaise; haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required (figure 2). This definition was unanimously approved by the working group.

The following factors, signs and symptoms did not reach a sufficient threshold for consideration to be included by the working group as part of the consensus definition: sinus discharge, sinus pain, absenteeism, systemic inflammatory markers such as neutrophil count, C-reactive protein (CRP), interleukin (IL)-6 and amyloid, steroid use, weight loss, reduction in forced expiratory volume in 1 s (FEV1) and/or forced vital capacity (FVC), and chest radiographic findings of pneumonia.

Discussion

This consensus definition of exacerbation may serve to standardise a key outcome measure of clinical trials involving adults with bronchiectasis and allow more meaningful comparisons of treatment effect between interventions. Although the remit of the working group was to define pulmonary exacerbation in adults with bronchiectasis in the context of prospective clinical trials, it is anticipated that this definition will inform patients and clinicians to more accurately identify exacerbations. We acknowledge that this definition is not a validated instrument, which might be more useful in determining if treatment of an exacerbation is efficacious. However, it does provide an agreed-upon definition by a group of bronchiectasis experts using a systematic approach intended to define a clinical end-point in the treatment of bronchiectasis and represents a proposed definition to be used for validation in future investigations.

The systematic review performed prior to the working group meeting provided an evidence-based platform for the factors included in the Delphi process. The subsequent outputs then enabled investigators to discuss and establish arguments so as to agree on the key components of the definition.

The consensus definition has three core components: collection of symptoms, time and decision to change treatment. Owing to the lack of evidence and validation data, any recommended criteria are preliminary and may be modified as more data become available.

Previous definitions used in trials had included a wide variety of symptoms but only six made the final list for this proposed definition. For some criteria it was deemed they were not related to exacerbation of lower airways disease (e.g. sinus disease and heart failure), while for others the criteria were felt to be infrequently measured in clinical practice to be relevant (e.g. CRP, serum IL-6 and serum amyloid) [1, 25, 26]. Spirometric measures were discounted because, unlike in CF, changes in FEV1 and FVC are not reliable indicators of exacerbation or response to treatment in patients with bronchiectasis [25]. Auscultatory findings were also felt to not be sufficiently bronchiectasis specific and are largely dependent on the severity of the predominant underlying lung condition. Chest radiograph changes were excluded as it can be difficult to distinguish pneumonia from mucus plugging, a finding that is common in bronchiectasis, and because most exacerbations occur in outpatient settings without access to radiology. A further important consideration during definition development was the lack of availability of some factors in domiciliary and certain healthcare settings. A symptom-based definition was therefore deemed preferable.

There was considerable debate regarding the requirement of a minimum number of criteria within the definition. It is assumed that a greater number of criteria met would increase the specificity of the diagnosis, and a consensus view that three out of six criteria be met was based upon a desire to achieve sufficient balance between sensitivity and specificity for use in clinical trials. This does not suggest that a patient cannot have an exacerbation when meeting only two out of six criteria. Nor is it known that such

Definition of a bronchiectasis pulmonary exacerbation for clinical trials

A person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h:

- 1) Cough
- 2) Sputum volume and/or consistency
- 3) Sputum purulence
- 4) Breathlessness and/or exercise tolerance
- 5) Fatigue and/or malaise
- 6) Haemoptysis

AND a clinician determines that a change in bronchiectasis treatment is required[#]

FIGURE 2 Results of the exacerbation definition. [#]: other potential causes of clinical deterioration have been discounted.

exacerbations are the types we wish to prevent and future trials validating the number of symptoms that best define a diagnosis of exacerbation are needed.

Time was included in the definition to address the recognised day-to-day variability of symptoms in people with bronchiectasis. The international group recognised some patients feel worse over a 24-h period and then spontaneously improve without the need for augmentation or change of their treatment. Symptom duration of ≥ 48 h to be certain there was a real change in the condition was considered more appropriate than a threshold of only 24 h. This element of the definition was thought to reduce inappropriate antibiotic prescribing and support adherence to the principal of antibiotic stewardship. If, however, there is a severe attack within 48 h necessitating treatment, such patients would still qualify with the proposed definition as they will have symptoms lasting ≥ 48 h, as the treatment takes time to improve symptoms.

Finally, there is the inclusion of a need for intervention. Although most exacerbations are treated with antibiotics, the committee felt that not all exacerbations require antibiotic therapy as they could be self-limiting (e.g. viral illness) or respond to alternate therapy (e.g. steroids for allergic bronchopulmonary aspergillosis). Studies of specific medications may elect to define the specific intervention. Symptoms of sufficient severity warranting a change in bronchiectasis treatment were also thought to represent a minimum threshold for definition of exacerbation for potential intervention and purposes of development of a definition for clinical intervention trials. Formal grading of the severity of exacerbation into mild, moderate and severe was not felt to be critical for the objective of this work.

It is important to capture all exacerbations in which a physician makes a decision to treat as part of the outcomes in clinical trials. The purpose of a definition is not to override the clinical judgement of physicians but to achieve some objective verification of that decision in multicentre, often international trials, where the threshold for that decision to treat is variable.

In conclusion, the working group comprising bronchiectasis experts from Europe (representing EMBARC), North America (representing BRR), Australasia and South Africa proposes the use of this consensus-based definition for bronchiectasis exacerbation (figure 2) in clinical trials involving adults with bronchiectasis. Although there was no representation from Asia, we believe this definition will be applicable internationally but will need to be validated in different settings. Although the evidence base was limited, international experts propose this workable definition and the plan is that there will be validation of this definition in future trials.

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