








Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials

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ABSTRACT Pulmonary exacerbations are a cause of significant morbidity in patients with primary ciliary dyskinesia (PCD) and are frequently used as an outcome measure in clinical research into chronic lung diseases. So far, there has been no consensus on the definition of pulmonary exacerbations in PCD.

30 multidisciplinary experts and patients developed a consensus definition for children and adults with PCD. Following a systematic review, the panel used a modified Delphi process with a combination of face-to-face meetings and e-surveys to develop a definition that can be used in research settings for children and adults with PCD.

A pulmonary exacerbation was defined by the presence of three or more of the following seven items: 1) increased cough, 2) change in sputum volume and/or colour, 3) increased shortness of breath perceived by the patient or parent, 4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, 5) malaise, tiredness, fatigue or lethargy, 6) new or increased haemoptysis, and 7) temperature >38°C.

The consensus panel proposed that the definition should be used for future clinical trials. The definition should be validated and the usability assessed during these studies.



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Introduction

Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disorder, usually inherited as an autosomal recessive condition [1]. It is estimated to affect 1 per 10000–20000 Europeans and is considerably more common in some populations [2–4]. However, many patients remain undiagnosed because physicians do not recognise the pattern of symptoms, because symptoms can be atypical, access to diagnostic reference centres is geographically limited, and diagnostic testing is complex and may miss some subtle cases [2, 5–8]. Impaired mucociliary clearance typically causes neonatal otherwise unexplained respiratory distress within several hours of birth, persistent wet cough throughout life and progressive bronchiectasis [9]. Patients often have symptoms of chronic rhinosinusitis, fertility issues and conductive hearing impairment. Approximately 50% of patients have situs inversus [9].

Patients with PCD are susceptible to lower airway infections [10–12]; pulmonary exacerbations are a cause of significant morbidity in patients with this condition [13, 14]. Epidemiological, clinical and laboratory evidence from other chronic lung diseases suggests that bacterial and viral infections are major causes of exacerbations; environmental pollution might also contribute. Some patients do not recover the accompanying reduction in lung function despite aggressive treatment of the episode with antibiotics and physiotherapy [15]. Pulmonary exacerbations are key outcome measures in clinical trials and epidemiological research into chronic lung diseases. Despite the importance of pulmonary exacerbations in PCD, there has been no consensus definition and individual researchers have used different versions of definitions [15–17]. Although PCD shares some features with cystic fibrosis (CF) and non-CF bronchiectasis, it is important that a separate definition is available for PCD clinical trials because the pathophysiology, symptoms and prognosis differ between the different diseases [11, 18].

A multidisciplinary, international panel with an interest in PCD aimed to develop a consensus statement for the definition of pulmonary exacerbations in children and adults with PCD for use in clinical trials and other research. The process included face-to-face meetings at two BEAT-PCD meetings (www.beatpcd.org; April 2017 and February 2018 [19, 20]), e-surveys and reviews of the literature.

Methods

Participants

22 clinicians from 17 countries met during a BEAT-PCD conference in Valencia, Spain in April 2017. The panel reflected the disciplines and countries of delegates attending the conference, and included 19 paediatric chest physicians, one adult chest physician and one nurse specialist; clinicians were from Europe (Northern, Southern, Western and Eastern areas represented), Western Asia, the Middle East and Australia.

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Following the conference and before starting the modified Delphi surveys we purposely recruited an additional five adult physicians, three patient representatives and a physiotherapist. The additional members received minutes of the meeting in Valencia. The activities of the panel were coordinated by two facilitators (J.S.L. and S.C.) who also contributed to the consensus and a PCD Research Fellow (F.G.) who did not participate in the e-survey voting. Since the consensus concentrates on lower respiratory tract exacerbations, the panel did not include any otorhinolaryngologists. The composition of the panel is outlined in supplementary table S1.

Literature search

We conducted a systematic literature search to find clinical research studies which had used pulmonary exacerbations in PCD patients as a variable. We searched PubMed from January 1, 2000 to April 1, 2017 using the search terms (ciliary dyskinesia, primary/OR ciliary motility disorders/OR Kartagener's syndrome/) AND exacerbation. We excluded reviews, editorials and case reports. We additionally reviewed literature for definitions of pulmonary exacerbations in patients with CF and non-CF bronchiectasis. The definitions used in the PCD, CF and bronchiectasis literature were discussed at the first face-to-face meeting and sent out to the group afterwards, providing a framework for the e-Delphi surveys.

Reaching a consensus

During the first meeting, it was unanimously agreed that the panel's aim was to provide a consensus for the definition of pulmonary exacerbations in PCD for children and adults participating in clinical research. As a starting point the panel decided that we should concentrate on lower respiratory tract exacerbations; although upper respiratory tract exacerbations cause significant morbidity in PCD, we considered that exacerbations of the upper and lower respiratory tract often occur separately, and have different prognostic implications. We decided to use an e-Delphi approach with 80% agreement signifying consensus. In brief, there were four rounds of e-surveys (www.isurvey.soton.ac.uk). For each survey, participants were sent instructions and a link *via* e-mail, then a second reminder to respond within 2 weeks. Each survey was comprised of questions in a variety of appropriate formats, including single and multiple responses, rankings of importance, and open text boxes (surveys 1–4: supplementary material). Participants had opportunities to provide free-text comments or explanations. Following each round, the quantitative and qualitative data were analysed using appropriate descriptive statistics or content analyses; results were presented to the panel in an anonymised format before completing the next round, with qualitative data presented in thematic areas. Where we failed to reach consensus, questions were modified in subsequent rounds, informed by the free-text comments. For ranked scores, a weighting was given equating to the number of items ranked. If, for example, there were three options for the format of the definition (simple list with equal weighting, list with weighted scoring, and major and minor criteria) and a respondent ranked these first, second and third, then the first format received 3 points, the second format received 2 points and the third format received 1 point. The total score for each format from all respondents provided a combined ranking score.

The primary focus of the first survey was to decide the relative importance to the definition of 1) changes in symptoms, 2) changes in clinical investigations and 3) a physician's decision to treat. We additionally enquired about the impact of exacerbations on patients, their families and society. In the second survey, we further examined which criteria should be used to define an exacerbation and whether any criteria should be an absolute requirement for the definition. Participants were able to modify decisions from previous rounds having seen the voting and comments from other panel members. In the third survey, we considered the number of criteria that should be listed, how many should be present to define an exacerbation and which of the following formats the definition should take: 1) a list of criteria with equal weighting, 2) a list of criteria with varied weighting or 3) major and minor criteria. Participants were asked to rank a list of nine criteria (symptoms, investigations and physician's decision to treat) to provide a weighting for each criterion (on a scale of 1–3) and to indicate for each criterion whether it could be considered as a major or minor criterion for defining pulmonary exacerbations.

16 members of the panel met during a BEAT-PCD conference in Lisbon, Portugal in February 2018 to discuss the final wording of each element of the survey. Finally, the definition was circulated to the whole panel *via* the fourth e-survey to seek agreement for the definition.

Results

The systematic literature search identified eight articles of which five were excluded (two reviews, one case report and two did not include PCD patients). The panel reviewed the included articles [15–17] and proposed one additional PCD clinical trial, but eventually this study was not included because it had not used exacerbations as an outcome variable [21]. Details of the studies are summarised in table 1. In addition, we reviewed 14 articles to understand how exacerbations have been defined in clinical trials

TABLE 1 Clinical trials in primary ciliary dyskinesia (PCD) patients that used a definition for pulmonary exacerbations

First author [ref.]#	Study aims	Study population	Method used to develop the definition	Definition of exacerbation
KOBBERNAGEL [16]	Protocol for randomised controlled trial to determine the efficacy and safety of azithromycin maintenance therapy	PCD children aged >7 years and adults	Face-to-face discussion at BESTCILIA study meeting	<i>Either</i> Respiratory symptoms (not listed) leading to start of systemic antibiotic treatment, irrespective of results of bacterial culture <i>or</i> Decline in FEV ₁ % pred \geq 10% relative to the FEV ₁ % pred at randomisation, irrespective of whether antibiotics are prescribed
RATJEN [17]	Changes in airway inflammation during pulmonary exacerbations	Cystic fibrosis and PCD children aged >6 years	Researcher defined	Increase in respiratory symptoms (not listed) treated with oral antibiotics
SUNTHER [15]	Recovery of baseline lung function after pulmonary exacerbation	PCD children	Researcher defined	A change in respiratory status for which intravenous antibiotics were prescribed

FEV₁: forced expiratory volume in 1 s. #: all three trials were published in 2016.

involving CF and bronchiectasis patients in general (supplementary table S2) [22–35]. All criteria identified in the literature reviews were considered in our Delphi surveys.

The response rates for the four e-surveys were 97%, 93%, 84% and 84% (supplementary table S1). In the first survey there was agreement that pulmonary exacerbations are a key outcome measure for use in clinical trials in PCD (97%), and that exacerbations have a significant effect on quality of life (97%), on missed days from work/school (93%) and on long-term health outcomes (86%). There was poor consensus on whether patients make a full recovery after exacerbations.

Through the iterative process of surveys and face-to-face meetings (table 2 and supplementary table S3) the panel decided that no single item was an absolute requirement. Changes in clinical symptoms were rated most highly to contribute to the definition, without a requirement for defining the duration of symptoms (table 2). In terms of investigations, only a change in pulmonary function (forced expiratory volume in 1 s) and new radiographic changes received initial 75% agreement for being included in a list of criteria that might contribute to the definition, and the panel discounted the role of raised C-reactive protein, erythrocyte sedimentation rate, and white cell and neutrophil counts. Some respondents commented that including any investigations in the definition might complicate research protocols and it was finally agreed that the definition should not require access to spirometry or radiography.

The need for a simple approach was expressed throughout all stages. Using experience from CF and non-CF bronchiectasis, we asked participants to rank three formats which could be used for the definition: a list of criteria with equal weighting, a scoring system with differential weighting of items or a definition using minor and major criteria. Participants without experience of using definitions did not participate in this part of the voting. A simple list of criteria with equal weighting was considered the best approach (supplementary table S4). Several respondents commented on their reason for this approach, explaining that a simple approach is easiest for use in clinical trials and that the statistical rationale does not yet exist for a weighted approach.

A consensus (>80% participant approval) definition of a pulmonary exacerbation in children and adults with PCD for use in clinical research was agreed as the presence of three or more of the following seven items: 1) increased cough, 2) change in sputum volume and/or colour, 3) increased shortness of breath

TABLE 2 Results of voting for which criteria should contribute to the definition

Potential criteria for inclusion	Survey 2 [#]		Survey 3 [†] calculated ranking (1=most important)	Survey 4 [*] % agreement
	Mean score	% agree		
<i>Change in sputum volume and/or colour</i>	1.54	93	2	96
<i>Increased cough</i>	1.64	89	1	100
<i>New/increased haemoptysis</i>	1.86	79	8	92
<i>Increased shortness of breath (parent/patient perceived)</i>	1.54	100	3	92
<i>Increased respiratory rate</i>	2.14	64		
<i>Increased chest discomfort/chest pain</i>	2.07	75		
<i>Malaise, tiredness, fatigue or lethargy</i>	2.14	68	7	92
<i>Decreased activity</i>	2.54	NA		
<i>Decreased exercise tolerance</i>	2.14	71		
<i>Temperature >38°C</i>	1.96	82	9	84
<i>Anorexia or weight loss</i>	2.50	NA		
<i>Change in physical examination of the chest</i>	2.29	NA		
<i>Increased crepitations/crackles</i>	2.21	68		
<i>Increased wheeze</i>	2.43	NA		
<i>New radiographic changes indicative of a pulmonary infection</i>	2.18	75	5	
<i>Decrease in pulmonary function of ≥10% from a previously recorded value (FEV₁ % pred or FVC % pred)</i>	2.11	75	4	
<i>Raised C-reactive protein</i>	2.79	NA		
<i>Prolonged erythrocyte sedimentation rate</i>	3.39	NA		
<i>Raised white cell count</i>	3.00	NA		
<i>Raised neutrophil count</i>	2.96	NA		
<i>Physician decision to change treatment because of perceived change in condition</i>			6	92

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; NA: neither agree nor disagree. [#]: in Survey 2, participants (n=28) indicated whether each item should be included in the definition of pulmonary exacerbations (1=strongly agree; 5=strongly disagree). The mean score and the percentage of respondents who agreed are shown. [†]: items which were considered positively in Survey 2 were ranked in Survey 3 (n=25 participants); "physician decision to treat" was added to the list for ranking. We present the calculated rank score from all participants. ^{*}: in Survey 4 (n=25 participants), the final wording for included items was agreed. The items included in the final definition are in italics.

perceived by the patient or parent, 4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, 5) malaise, tiredness, fatigue or lethargy, 6) new or increased haemoptysis, and 7) temperature >38°C (table 3).

Discussion

A multidisciplinary panel agreed on a consensus definition of pulmonary exacerbations in children and adults with PCD that we anticipate will be used as an outcome in clinical trials. Timing is right for this definition, with the rapidly evolving research into PCD, and the emergence of clinical trials [16, 21] and clinical studies [36–39] involving children and adults with PCD. We expect that physicians will continue making informed decisions concerning pulmonary exacerbations in clinical practice. Much discussion occurred in face-to-face meetings to define the scope and methodology. Although upper respiratory tract infections are problematic in PCD, and often coexist with pulmonary infections, we decided that our definition should concentrate on exacerbations of the lower airway. Recognising that PCD is a multiorgan disease including the entire respiratory system, it is noteworthy that upper respiratory tract symptoms are not captured by this definition. The consensus panel deliberately chose not to include specific ear, nose and throat symptoms because exacerbations of the upper and lower respiratory tract often occur separately, and have different prognostic implications. Upper respiratory tract symptoms impact on quality of life of patients with PCD [40–42] and a separate consensus statement will be needed prior to clinical trials that have upper airway exacerbations as a clinical outcome measure. However, we appreciate that an increase in

TABLE 3 Definition of a pulmonary exacerbation for children and adults with primary ciliary dyskinesia (PCD) participating in clinical research

The following definition can be used in clinical research to define a pulmonary exacerbation in children and adults with PCD:

Three or more of the following must be present:

- Increased cough
- Change in sputum volume and/or colour
- Increased shortness of breath perceived by the patient or parent
- Decision to start or change antibiotic treatment because of perceived pulmonary symptoms
- Malaise, tiredness, fatigue or lethargy
- New or increased haemoptysis
- Temperature $>38^{\circ}\text{C}$

upper and lower airway symptoms may occur together and that in some, especially the young, it may be difficult to differentiate.

While definitions for pulmonary exacerbations in CF and non-CF bronchiectasis informed the initial framework of our discussions, we rapidly focused on our experiences of managing children and adults with PCD. Although PCD shares many features with CF and non-CF bronchiectasis, the panel strongly believed that this distinct syndrome required a bespoke definition since pathophysiology, symptoms and prognosis differ. Unlike a recent symptom-based definition for non-CF bronchiectasis [35], we decided that proposing a timeframe (*e.g.* increased cough for 48 h) was not possible because of lack of evidence; we propose that information concerning duration of symptoms which might indicate a significant exacerbation should be captured during future validation studies. These would also be able to test the robustness of using nonspecific symptoms such as temperature $>38^{\circ}\text{C}$ and malaise. We decided that it was feasible to develop a definition applicable to both children and adults, and we therefore recruited additional adult physicians to the panel. There was little discernible difference between opinions of paediatric and adult physicians during voting. The panel benefited from three patient representatives.

The systematic review of PCD literature and the general review of CF and bronchiectasis definitions for exacerbations were conducted prior to the meetings, providing an evidence base to inform potential formats of the definition and the items that might be included. We agreed to an e-Delphi method, accepting agreement by $\geq 80\%$ to signify consensus. Having started with a potential list of 21 criteria, only seven were included in the final definition.

While investigations such as spirometry and chest radiography are undoubtedly useful in clinical practice, participants highlighted the need for a research definition not dependent on access to tests. Minimising research study visits was considered a priority, particularly as PCD is a rare disease and many patients are located geographically distant from the study sites. Moreover, the panel felt that a pulmonary exacerbation could be adequately defined for research purposes without the need for investigations. The definition is therefore based on symptom changes and the decision to change antibiotic medication because of perceived symptoms. The panel acknowledged that many patients are empowered to start antibiotic treatment when they have signs of an exacerbation and therefore it is not a prerequisite for the therapy to be initiated by a physician. These features will enable the definition to be utilised as a patient-reported outcome (PRO) measure.

The definition will need validation and this might lead to newer updated versions. The BEAT-PCD network plans to perform a validation study of the PRO measure in a longitudinal observational study. However, we recognise that pulmonary exacerbations in PCD are difficult to diagnose even in a clinical setting, and that the physician with access to sputum culture remains at risk of false-positive and false-negative cases. In the experience of the expert panel, diagnosing exacerbations in PCD is confounded by various peculiarities of the condition; in particular, patients have a wet cough even when well, and the cough continues after antibiotic treatment, “technically acceptable” lung function parameters can vary $>10\%$ within the same clinic session and reversible atelectasis occurs on chest radiography even “when well”. Similar to definitions in other lung diseases (*e.g.* non-CF bronchiectasis [35]), the BEAT-PCD panel decided to use a combination of symptoms in our definition of an exacerbation, particularly as we wanted this to be a PRO without need to access clinical tests. We acknowledge that the definition will not be able to distinguish bacterial from viral or fungal exacerbations, but that was not the prime purpose of the definition, particularly as viral and fungal exacerbations might be equally important determinants of prognosis and quality of life. There simply is not a perfect standard. More detailed definitions might be considered in the future in clinical settings, where the patient has investigations, such as chest radiography

or spirometry, providing additional supporting evidence of an exacerbation. A separate definition is now needed for exacerbation of upper airway disease.

In summary, our international, multidisciplinary panel proposes a definition of pulmonary exacerbations for children and adults with PCD for use in clinical trials and other research settings. The definition will be validated in a project led by the BEAT-PCD network [20, 43]. Importantly, the definition was equally acceptable to health professionals working with children and adults and to patient representatives. We have aimed to deliver a definition that will be internationally applicable and can be applied in different research settings.

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