European Respiratory Society statement for defining respiratory exacerbations in children and adolescents with bronchiectasis for clinical trials

Anne B. Chang[1,2,3], Angela Zacharasiewicz[4], Vikas Goyal[1,2], Jeanette Boyd[5], Efthymia Alexopoulou[6], Stefano Aliberti[7], Leanne Bell[8], Andrew Bush[9], Alison Claydon[10], Carolina Constant[11], Rebecca Fortescue[12], Adam T. Hill[13], Bulent Karadag[14], Zena Powell[8], Christine Wilson[15], Keith Grimwood[3,16,17,20], Ahmad Kantar[18,20] and other members of Child-BEAR-Net[19]

[1]Australian Centre for Health Services Innovation, Queensland University of Technology, Brisbane, Australia. [2]Dept of Respiratory and Sleep Medicine, Queensland Children's Hospital, Brisbane, Australia. [3]NHMRC Centre for Research Excellence in Paediatric Bronchiectasis (AusBREATHE), Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Australia. [4]Dept of Paediatrics and Adolescent Medicine, Teaching Hospital of the University of Vienna, Wilhelminen Hospital, Klinikum Ottakring Vienna, Vienna, Austria. [5]European Lung Foundation, Sheffield, UK. [6]2nd Radiology Dept, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece. [7]Dept of Biomedical Sciences, Humanitas University and Respiratory Unit, IRCCS Humanitas Research Hospital, Milan, Italy. [8]European Lung Foundation Bronchiectasis Paediatric Patient Advisory Group, Sheffield, UK. [9]Dept of Paediatric Respiratory Medicine, Royal Brompton Hospital, and National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London, UK. [10]Centre for PCD Diagnosis and Research, Dept of Respiratory Sciences, University of Leicester, Leicester, UK. [11]Dept of Paediatrics, Hospital de Santa Maria and Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [12]Population Health Research Institute, St George's University of London, London, UK. [13]Dept of Respiratory Medicine, Royal Infirmary and University of Edinburgh, Edinburgh, UK. [14]Division of Paediatric Pulmonology, Faculty of Medicine, Marmara University, Istanbul, Turkey. [15]Dept of Physiotherapy, Queensland Children's Hospital, Brisbane, Australia. [16]Depts of Infectious Disease and Paediatrics, Gold Coast Health, Southport, Australia. [17]School of Medicine and Dentistry, Menzies Health Institute Queensland, Griffith University, Southport, Australia. [18]Pediatric Asthma and Cough Centre, Istituti Ospedalieri Bergamaschi, University and Research Hospitals, Bergamo, Italy. [19]Other Child-BEAR-Net committee members are listed in the Acknowledgements section. [20]Equal senior co-authors.

Corresponding author: Anne B. Chang (Anne.Chang@menzies.edu.au)

Shareable abstract (@ERSpublications)
This ERS Task Force statement developed internationally derived, consensus-based definitions of respiratory exacerbations for future clinical paediatric bronchiectasis research https://bit.ly/3sqT2YP

Cite this article as: Chang AB, Zacharasiewicz A, Goyal V, *et al*. European Respiratory Society statement for defining respiratory exacerbations in children and adolescents with bronchiectasis for clinical trials. *Eur Respir J* 2022; 60: 2200300 [DOI: 10.1183/13993003.00300-2022].

Received: 9 Feb 2022
Accepted: 4 April 2022

Abstract

Bronchiectasis is being diagnosed increasingly in children and adolescents. Recurrent respiratory exacerbations are common in children and adolescents with this chronic pulmonary disorder. Respiratory exacerbations are associated with an impaired quality of life, poorer long-term clinical outcomes, and substantial costs to the family and health systems. The 2021 European Respiratory Society (ERS) clinical practice guideline for the management of children and adolescents with bronchiectasis provided a definition of acute respiratory exacerbations for clinical use but to date there is no comparable universal definition for clinical research. Given the importance of exacerbations in the field, this ERS Task Force sought to obtain robust definitions of respiratory exacerbations for clinical research. The panel was a multidisciplinary team of specialists in paediatric and adult respiratory medicine, infectious disease, physiotherapy, primary care, nursing, radiology, methodology, patient advocacy, and parents of children and adolescents with bronchiectasis. We used a standardised process that included a systematic literature review, parent survey, and a Delphi approach involving 299 physicians (54 countries) caring for children and adolescents with bronchiectasis. Consensus was obtained for all four statements drafted by the panel as the disagreement rate was very low (range 3.6–7.2%). The panel unanimously endorsed the four consensus definitions for 1a) non-severe exacerbation and 1b) severe exacerbation as an outcome measure, 2) non-severe exacerbation for studies initiating treatment, and 3) resolution of a non-severe exacerbation for clinical trials involving children and adolescents with bronchiectasis. This ERS Task Force proposes using

these internationally derived, consensus-based definitions of respiratory exacerbations for future clinical paediatric bronchiectasis research.

Introduction

Bronchiectasis is a chronic pulmonary disorder, which is used as an umbrella term to describe a clinical syndrome of recurrent or persistent wet/productive cough and lower airway infection and/or inflammation, accompanied by abnormal bronchial dilatation detected by chest computed tomography (CT) scans [1]. Previously considered inevitably progressive, it is now accepted that bronchiectasis in children and adolescents may be reversible over time if detected early in the course of the disease and treated effectively [1, 2].

Bronchiectasis is associated with a high symptom burden [3], and increased patient needs [4] and treatment costs [5, 6]. It remains one of the most neglected pulmonary disorders [7], especially in children [8], and has marked inequity compared with other chronic pulmonary diseases [9, 10]. The need for better health services and clinical research for improving the lives and outcomes of children and adolescents with bronchiectasis, as well as the wellbeing of families, was highlighted by an international parent/patient survey on clinical needs led by the European Lung Foundation (ELF) [4]. Several aspects of acute respiratory exacerbations featured prominently in the ELF survey [4].

Similar to other chronic pulmonary disorders, recurrent acute respiratory (pulmonary) exacerbations ("attacks" or "flare-ups") are common in people with bronchiectasis. Exacerbations are particularly important in children and adolescents with bronchiectasis as they are associated with increased respiratory symptoms, impaired quality of life (QoL) [11], accelerated lung function decline (−1.9% forced expiratory volume in 1 s (FEV_1) predicted per hospitalised exacerbation) [12], and high healthcare resource use [13] and costs (AUD 30 182 (EUR 20 800/GBP 17 040) per hospitalisation in 2016 in Australia [6]). Also, children and adolescents with bronchiectasis have high healthcare attendance and high rates of antibiotic consumption and school/childcare absences due to bronchiectasis exacerbations (30, 50 and 24.9 episodes per 100 person-months of observation, respectively) [13]. Importantly, patients and parents responding to the ELF survey rated exacerbations among the top three factors affecting their child's QoL [4].

Thus, it is unsurprising that parents and the panel designated exacerbations as a critical outcome measure for all the key questions in the 2021 European Respiratory Society (ERS) clinical practice guidelines (CPG) for the management of children and adolescents with bronchiectasis [2]. While the CPG recommendations include a definition of exacerbations for clinical use [2], there is currently no consensus on a definition of exacerbations for paediatric bronchiectasis research, although a definition for adult bronchiectasis is available [14]. Therefore, there is a need to obtain robust and patient/parent-informed definitions of respiratory exacerbations for clinical research relevant for paediatric bronchiectasis. For this document, the definition of bronchiectasis is the same as the one used in the ERS CPG for the management of children and adolescents with bronchiectasis [2], *i.e.* a clinical syndrome of recurrent or persistent wet/productive cough, airway infection and inflammation, and abnormal bronchial dilatation on chest CT scans.

This ERS Task Force statement reviewed the current literature on defining respiratory exacerbations in children and adolescents with bronchiectasis. This Task Force statement on the definition of exacerbations for clinical trials in children and adolescents with bronchiectasis presents an international consensus view, using a Delphi approach on statements formulated after the panel evaluated the systematic review and parents' survey.

Methods

The current statement, developed by an ERS Bronchiectasis Task Force, included specialists in paediatric respiratory medicine with expertise in managing children and adolescents with bronchiectasis as well as paediatric experts in infectious disease, radiology, physiotherapy and nursing, two global leaders in adult bronchiectasis, the Cochrane Airways Group coordinating editor (also a primary care physician), ELF representatives, and representatives of the bronchiectasis/protracted bacterial bronchitis-specific parent/patient advisory group (PAG) members. Conflicts of interest were declared at commencement of this project and prior to the final submission, and managed in accordance with ERS policies. At the first meeting, the panel agreed on the overall approach (figure 1), and both inclusion and exclusion criteria (supplementary material).

Systematic review and PAGs survey

The Cochrane Airways Group information specialist designed and ran the search on 22 February 2021 using the search strategy outlined in the supplementary material. Search results were uploaded onto Rayyan (https://rayyan.qcri.org). Two panel members (V.G. and A.Z.) independently screened the abstracts. The

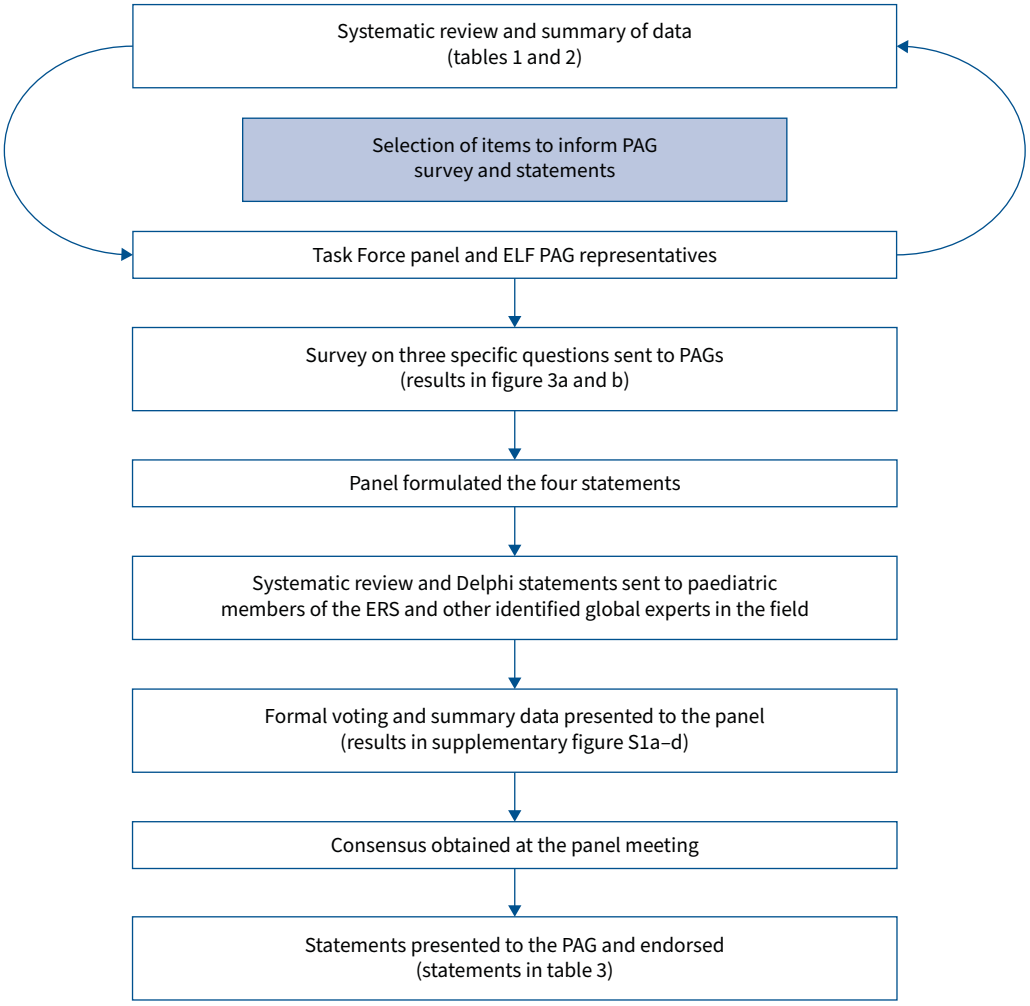

FIGURE 1 Schematic overview of the methodology used to develop the consensus for the definitions of exacerbations. PAG: patient advisory group; ELF: European Lung Foundation; ERS: European Respiratory Society.

papers were retrieved and reviewed by same two panel members and a third reviewer (A.C.) who also summarised the studies. Additional papers and protocol registries were identified from authors' databases. Disagreements were resolved by consensus. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the total number of articles found in the search, including those that were subsequently included/excluded, is shown in figure 2.

The ELF lead (J.B.) sent a survey (using SurveyMonkey (www.surveymonkey.co.uk); from 11 March 2021 to 16 April 2021) to two PAGs (CPG [2] and Brisbane parent advisory groups (www.crelungs.org.au/cre-parent-and-community-advisory-group)) on three specific questions (two on symptoms/signs and one on duration) relating to defining an acute respiratory exacerbation of bronchiectasis in their child (figures 3a and b). The first question had 16 items and the second 25 items. The third question was "Overall, how long do you think the items listed need to be present before you would consider there is a non-severe (non-hospitalised) exacerbation episode present?". Data were then summarised by the ELF panel member (J.B.) and presented to the Task Force panel.

Development of consensus

Between January and December 2021, the panel held three virtual meetings in addition to corresponding by e-mail between meetings. The overall methods were re-presented at these further meetings and the panel agreed on the final overall approach (figure 1), including predetermining that consensus would be considered achieved if ⩾80% agreed with the statements.

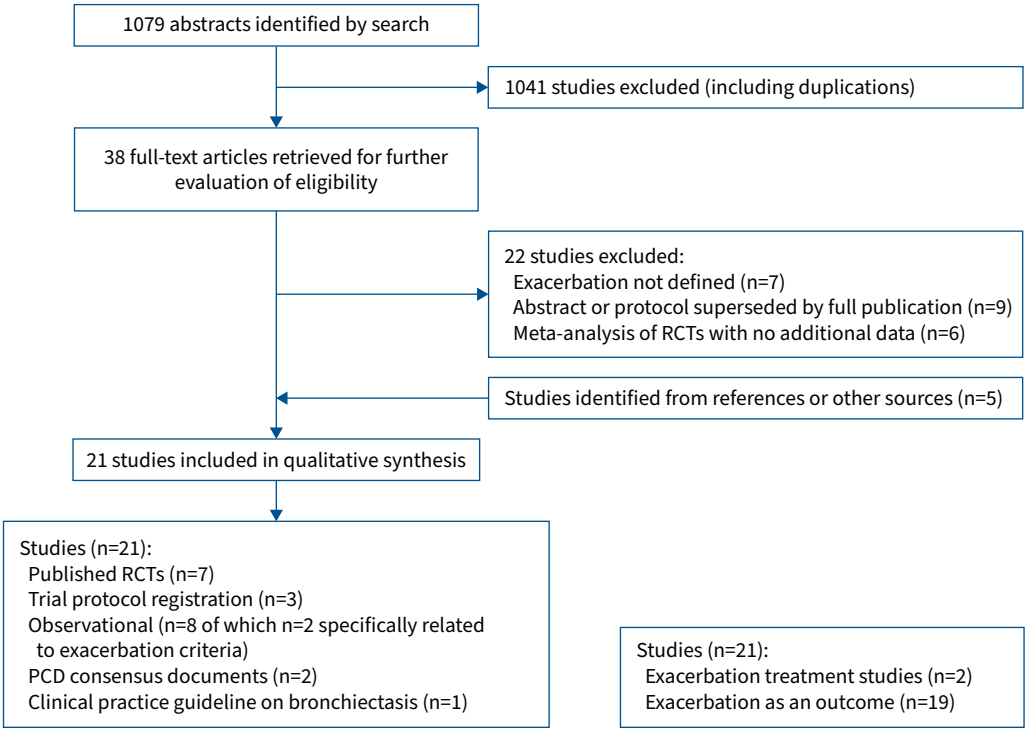

FIGURE 2 PRISMA diagram outlining the selection of studies. RCT: randomised controlled trial; PCD: primary ciliary dyskinesia.

The panel reviewed the data from the systematic review and the PAG survey. Discussions were held based on these data and draft consensus statements modified until all the panel members agreed on all four statements. These four statements defined: 1) exacerbation as an outcome for clinical trials (allowing categorisation into 1a) non-severe and 1b) severe exacerbations), 2) a non-severe exacerbation that warrants treatment in clinical trial settings, and 3) the resolution of a non-severe exacerbation. These statements (using SurveyMonkey) were then circulated to the ERS paediatric assembly members and other global bronchiectasis experts known to the authors and their networks (*e.g.* the Australian National Health and Medical Research Council Centre for Research Excellence for Paediatric Bronchiectasis). Only data from physicians who cared for children with bronchiectasis were included in the survey that was open for 2 months (1 September 2021 to 31 October 2021). The survey results were reviewed by the Task Force, and the consensus statements were adapted and finalised by the panel. Lastly, these statements were presented to the ELF PAG for final review and endorsement.

Results

The search identified 1079 potential publications; 38 full-text articles were retrieved (from the search data) with an additional five papers identified from references in these articles and from other sources. 21 studies fulfilled the inclusion criteria (table 1 and figure 2). The key aspects of the 21 studies of various types (grouped by studies treating an exacerbation, studies with exacerbation as an outcome and consensus documents) are tabulated in table 1. Two studies involved treatment of exacerbations, while two were consensus documents, one was a guideline and in the rest (n=16), exacerbations were an outcome. The combined data from these studies and the indicators used to define an exacerbation are summarised in table 2.

Two studies aimed to define exacerbations: one [15] was retrospective and the second [16] was a prospective study where blood markers were also included. Using symptom duration to define a non-severe exacerbation was mentioned in 11 (52.5%) studies. In all but one study, the duration was ⩾3 days.

From the 21 included studies, there was no universal definition. The most common indicator used to define an exacerbation was “change in cough frequency or character (dry to wet)”, used in 17 (81%) studies. The other four most common indicators were: “change in sputum colour or volume”, “breathlessness/dyspnoea”, “change in auscultatory findings” and “new chest radiography findings” (table 2).

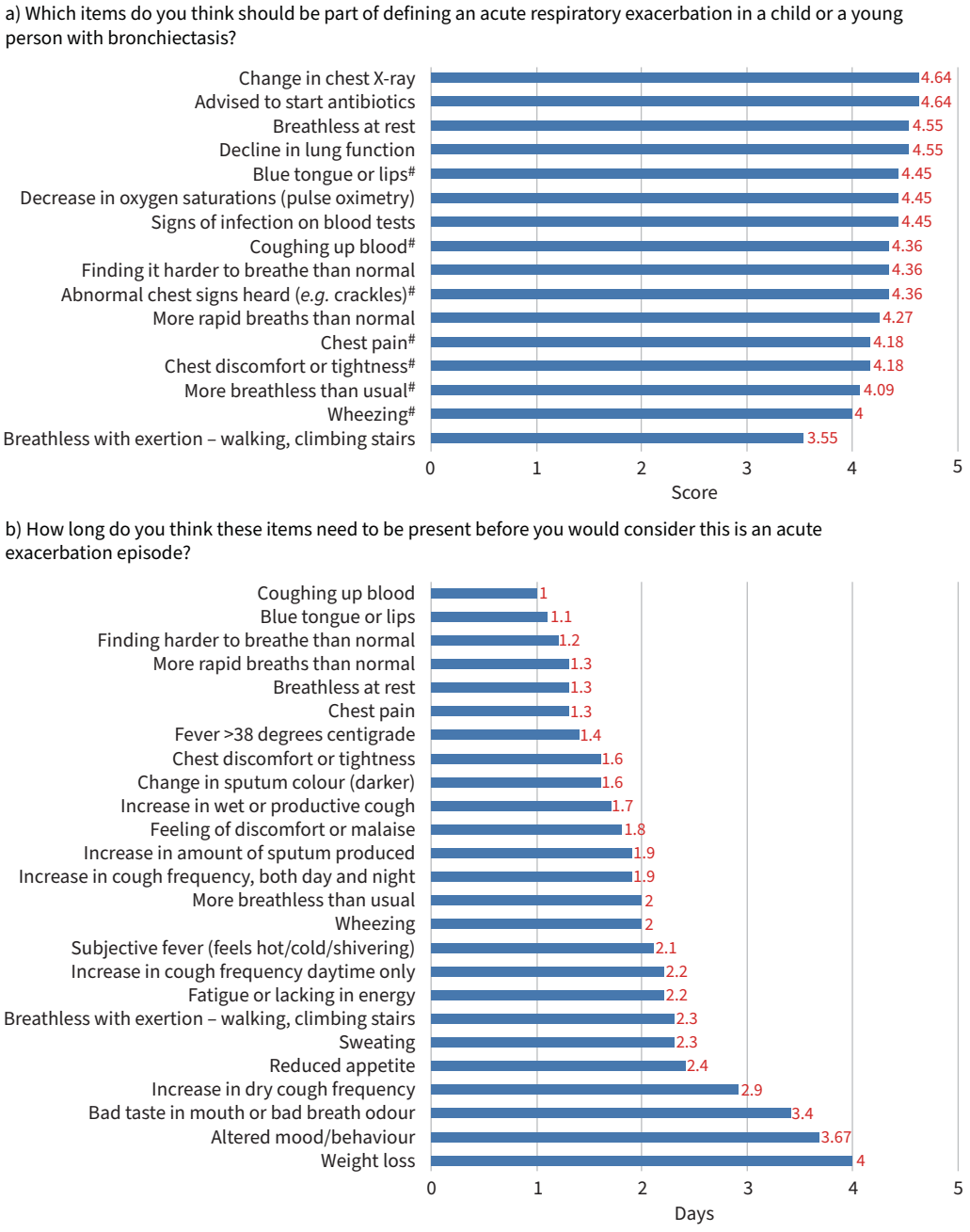

FIGURE 3 The parent advisory groups' responses to the questions posed in the survey undertaken by the European Lung Foundation (ELF). a) Question 1: Which items do you think should be part of defining an acute respiratory exacerbation in a child or a young person with bronchiectasis? Options: 1=not important; 2=slightly important; 3=moderately important; 4=very important and 5=essential. All but one item rated between 4 (very important) and 5 (essential). Most important: "Change in chest X-ray", "Advised to start antibiotics", "Breathless at rest" and "Decline in lung function". b) Question 2: How long do you think these items need to be present before you would consider this is an acute exacerbation episode? Options: 1, 2, 3, 4, 5, 6 and <7 days. 1 day: "Coughing up blood"; 1–1.5 days: "Blue tongue or lips", "Finding harder to breathe than normal", "More rapid breaths than normal", "Breathless at rest", "Chest pain" and "Fever >38 degrees centigrade"; all items: between 1 and 4 days. #: additional comments made by some respondents; we have not included these comments in the document. Mean values are indicated in red.

In the PAG survey, for Question 1, "Change in chest X-ray" and "Advised to start antibiotics" were the two highest (of 16 items) ranked items. All but one item was ranked as very important or essential (*i.e.* a mean score of ⩾4) (figure 3a). In Question 2, the PAGs considered 22 of the 25 listed items needed to be

https://doi.org/10.1183/13993003.00300-2022

TABLE 1 Studies on pulmonary exacerbation in children and adolescents with bronchiectasis (BE), grouped by studies on treatment of exacerbations, studies where exacerbations were an outcome and consensus statements

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
Studies on treatment of exacerbation								
Goyal [21], 2018, Australia and New Zealand	Multicentre, double-dummy, double-blind RCT (BEST-2)	Inclusion: age <19 years, CT-proven BE in last 5 years (or if diagnosed earlier, regular follow-up by respiratory physician for BE) and ⩾2 exacerbations in last 18 months; exclusion: current or recent severe exacerbation (dyspnoea, S_{pO_2} <90% in air or hospitalisation) in 8 weeks prior to study entry, CF or liver dysfunction; hypersensitivity to β-lactam or macrolide antibiotics; current or recent (4 months) *P. aeruginosa* infection, receipt of β-lactam or macrolide antibiotics within preceding 3 weeks for the exacerbation, or current treatment for cancer	AMC n=97, AZM n=82; median (IQR) age: AMC 6.8 (4.3–10.1) years, AZM 6.4 (4.0–9.0) years; follow-up: every 3 months for 18 months or until next exacerbation	Primary question: is daily oral AZM non-inferior (within a 20% margin) to oral AMC at achieving resolution of exacerbations by day 21 of treatment?	An increase in sputum volume or purulence, or change in cough (>20% increase in cough score or type (dry to wet)) for ⩾3 days; resolved exacerbations: when symptoms and signs are same as baseline state	Non-hospitalised; ⩾3 days	By 21 days of treatment, AZM was non-inferior to AMC for resolving non-severe exacerbations; exacerbations were significantly shorter in AMC *versus* AZM group (median (IQR) 10 (6–15) *versus* 14 (8–16) days; p=0.014)	Limited to mild exacerbation and parent-reported criteria
Goyal [20], 2019, Australia and New Zealand	Multicentre, three-arm, double-dummy, double-blind RCT (BEST-1)	Inclusion: age <18 years, CT-proven BE in last 5 years (or if diagnosed earlier, regularly followed by a respiratory physician for BE) and ⩾2 exacerbations in last 18 months; exclusion: current or recent severe exacerbation (dyspnoea, S_{pO_2} <90% in air or hospitalised) in 8 weeks prior to study entry, CF or liver dysfunction; hypersensitivity to β-lactam or macrolide antibiotics; current or recent (4 months) *P. aeruginosa* infection, receipt of β-lactam or macrolide antibiotics within preceding 3 weeks for the exacerbation, or current treatment for cancer	AMC n=63, AZM n=67, placebo n=67; median (IQR) age: AMC 6 (3.6–9.5) years, AZM 5.9 (3.4–8.4) years, placebo 6 (3.7–8.6) years; follow-up: every 3 months for 18 months or until next exacerbation	Determine whether AMC and AZM are superior to placebo in achieving resolution of non-severe exacerbations by day 14 of treatment	An increase in sputum volume or purulence, or change in cough (>20% increase in cough score or type (dry to wet)) for ⩾3 days; resolved exacerbations: when symptoms and signs are same as baseline state	Non-hospitalised; ⩾3 days	Oral AMC for 14 days for non-severe exacerbations of BE in children was superior to placebo in achieving exacerbation resolution by end of treatment and in decreasing duration of exacerbations	Limited to mild exacerbation and parent-reported criteria

Continued

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
Studies where exacerbation was an outcome								
Anuradha [29], 2020, Sri Lanka	Single-centre, crossover, open-label RCT	Inclusion: radiographically confirmed BE; exclusion: CF, FEV_1 <40% pred, chronic *P. aeruginosa* colonisation, unable to have regular follow-up, already taking regular HS nebulisation, history of hypersensitivity for the medications (salbutamol, HS) or with typical extrapulmonary features of CF	n=63 (n=52 finished study); mean±SD age: 9.3±2.6 years; follow-up: 150 days	Determine efficacy of 3% saline pre-medication before airway clearance technique, 60 days trial; 30 days washout period, then crossover design	Previous definition [30]: acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset; for hospitalisation: "In general history, clinical examination and oxygen saturation on air would be used to guide care at the onset of an inpatient stay"	Outpatient treatment; duration suggested "usually over several days"	Mean exacerbations: HS group: phase 1=0.42, phase 2=0.65; control group: phase 1=1.3, phase 2=1.03; HS had significantly lower rate than controls in phase 1 only; significant difference in FEV_1 and FVC in both phases, favouring HS	No other details on exacerbation; analysis not per group, but by phase
Basaran [31], 2018, Turkey	Retrospective, single-centre	Inclusion: HRCT-confirmed BE	n=34; mean±SD age: 13.69±4.67 years	Describe characteristics, underlying causative factors and long-term follow-up	Increase in cough and sputum amount or purulence, chest pain, shortness of breath (reported by family or child), rale, rhonchi, wheezing, hypoxia symptoms, increased CRP levels, increased neutrophil proportion, and impairment in respiratory function test	Hospitalised and non-hospitalised; duration not defined	Annual exacerbation frequency dependent on severity of disease	Retrospective review
Kapur [15], 2009, Australia	Retrospective cohort, single-centre in specialist hospital	Inclusion: children with CT-proven BE seen in respiratory clinics between 1997 and 2007; data extracted for respiratory clinic visits where there was a "respiratory physician-diagnosed exacerbation"; exclusion: CF	n=115 exacerbations in n=30 children; median (range) age: 5.5 (0.8–13) years	Determine: 1) associated clinical and investigational features, 2) proportion of exacerbations requiring hospitalisation after failing to respond to oral antibiotics, and 3) factors predicting and associated with treatment failure	Features of exacerbation: increase in frequency of cough (88%), change in cough character (67%), fever in 32 (28%) exacerbations, chest pain and/or haemoptysis in 4.3% and 2.6%, respectively; new chest auscultatory findings in 65 (56%) exacerbations; median (range) FEV_1 % pred during exacerbation 78.5% (36–95.4%) *versus* stable state 82.5% (43.7–103%) (p=0.36); median (range) FVC % pred during exacerbation 81% (50.9–102%) *versus* stable state 85.5% (52.4–114%) (p=0.34); chest radiography changes in 8/35 (22.9%) exacerbations	Hospitalised and non-hospitalised; duration not specified	*i.v.* antibiotics required in 39 (35%) exacerbations within 4 weeks of starting oral therapy (median (range) 21 (3–28) days); failure of cough to become dry (82%), continued production of purulent sputum (43%) and failure to reduce cough frequency (54%) were the most common reasons	Wide range of symptoms and signs; spirometry data insensitive

Continued

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
Kapur [16], 2012, Australia	Prospective cohort, single-centre in specialist hospital	Inclusion: children with CT-proven BE; exclusion: CF; paediatric pulmonologist-defined exacerbation was taken as the "gold standard" based on the Aspen workshop definition of "a sustained worsening of the patient's condition from stable state and beyond normal day-to-day variations that is acute in onset and necessitates a change in regular medication"	n=69 children with n=81 exacerbations; median (IQR) age 7 (3.8–10.9) years; follow-up: 900 child-months	Formulate a clinically useful definition of respiratory exacerbation for children with BE	Major criteria: ⩾72 h of significant frequency of cough (median cough score ⩾2) and wet cough; minor criteria: sputum colour ⩾3 BronkoTest, parent/child perceived breathlessness, chest pain, crepitations, wheeze and hypoxia; laboratory criteria: high-sensitivity CRP >3 $mg{\cdot}L^{-1}$, serum IL-6 >2 $ng{\cdot}L^{-1}$, serum amyloid A >5 $mg{\cdot}L^{-1}$ and raised neutrophil % (age appropriate); definition options: two major criteria, or one major plus one laboratory criteria, or one major with two minor criteria	Hospitalised and non-hospitalised; ⩾3 days	Interobserver κ for each factor in assessment form >0.75; spirometry and impulse oscillatory indices during exacerbation not different from baseline; haemoptysis significantly more likely to occur during an exacerbation but very rare in cohort	The sole prospective study that used clinically relevant exacerbation as the gold standard, a limiting factor but in the absence of any other standard was arguably appropriate; needs validation in other cohorts
Kapur [32], 2014, Australia	Prospective cohort, single-centre in specialist hospital	Inclusion: radiographically confirmed BE; exclusion: CF	n=69; mean age: 7 years; follow-up: 900 child-months	Determine prevalence of virus detection associated with exacerbation and evaluate clinical/investigational differences between virus-positive and virus-negative exacerbations	A sustained worsening of condition from stable state and beyond day-to-day variations, which is acute in onset and necessitates using antibiotics as determined by the child's treating respiratory specialist	Hospitalised and non-hospitalised	Viruses detected in 48% of exacerbations and when present, significantly more likely to require hospitalisation	Parent-reported deterioration was indicator for exacerbation
Karadag [33], 2005, Turkey	Retrospective, single-centre	Inclusion: HRCT-confirmed BE and followed up for ⩾2 years	n=111; mean±SD age: 7.4±3.7 years	Describe characteristics, underlying causative factors and long-term follow-up	Persistent (>24 h) increase in respiratory symptoms, new chest radiography opacification or worsening in physical examination findings of the chest	Hospitalised and non-hospitalised; ⩾1 days		Retrospective review
Kobbernagel [34], 2020, Europe	Multicentre	Inclusion: PCD, FEV_1 >40% pred, ⩾30 days of antibiotics for exacerbations in last 2 years, not taking AZM in last 30 days, not receiving inhaled or maintenance antibiotics	n=90; mean±SD age: AZM 18.6±8.9 years, placebo 19.7±10.8 years	Determine efficacy of 6 months of AZM on respiratory exacerbations in PCD	Respiratory symptoms leading to use of systemic antibiotics irrespective of bacterial culture or ⩾10% FEV_1 drop relative to screening and randomisation whether or not antibiotics prescribed	Hospitalised and non-hospitalised; duration not specified	Exacerbation rate significantly lower in AZM group (rate ratio 0.45 (95% CI 0.26–0.78); p=0.004); FEV_1 significantly better in AZM group; no intergroup difference for QoL, LCI, hearing or static lung volumes	RCT includes adults and restricted to PCD; definition does not include duration of symptoms

Continued

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
Lovie-Toon [13], 2019, Australia and New Zealand	Prospective cohort, three clinics	Inclusion: HRCT-confirmed BE; exclusion: CF, enrolled in another study or receiving treatment for cancer	n=85; median (IQR) age: 8.7 (5.4–11.3) years; follow-up: 951 child-months of observation	Assess health resource use and health-related QoL over a 12-month period in children with BE	Unwell for >3 days with at least one of: increased cough, change in cough quality, increased sputum volume or purulence	Non-hospitalised >3 days; hospitalised definition not provided	High health resource use; mean±SD exacerbations 3.3±2.2 per child-year; 11.4% episodes required hospitalisation	
Masekela [35], 2013, South Africa	Single-centre, double-blind RCT	Inclusion: age 6–18 years with HIV-related CT-confirmed BE and able to perform reliable pulmonary function tests; exclusion: CF, abnormal liver function tests, abnormal urea/creatinine, or using carbamazepine, warfarin, cyclosporin or long-term midazolam	ERY n=17, placebo n=14; mean±SD age: ERY 8.4±2.4 years, placebo 9.1±2.1 years	Evaluate efficacy of 52 weeks of ERY (*versus* placebo) at reducing respiratory exacerbations in children with HIV-related BE	Presence of at least two of: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on chest radiography	Hospitalised and non-hospitalised; duration not specified	No difference in mean number of exacerbations between groups (ERY 2.14±2.28 *versus* placebo 2.18±1.59 per year; p=0.17); more children (18%) allocated ERY than placebo (0%) had no exacerbations during study duration; high attrition rate (28%)	Limited to HIV-related BE; small sample size with likely type 1 error
O'Grady [36], 2018, Australia	Multicentre, double-blind, placebo-controlled RCT	Inclusion: age 1.5–18 years with recurrent protracted bacterial bronchitis, CSLD or BE, ⩾2 exacerbations in last 18 months, contactable in next 14 months; exclusion: other chronic lung disease, prior vaccination with PHiD-CV vaccine, had 23-valent pneumococcal polysaccharide vaccine in last 2 months, immune suppression or deficiency, acute illness at the time of enrolment, or conditions that could increase the risk of serious adverse events	n=63 randomised; mean±SD age: 6.8±3.7 years; follow-up: 12 months	Evaluate efficacy of PHiD-CV	Increase in sputum volume or purulence, or ⩾3 days of change in cough (>20% increase in cough score or type (dry to wet))	Non-hospitalised; ⩾3 days	Absolute risk difference between groups −0.5 (95% CI −2.0–0.9) exacerbations per 100 weeks at risk favouring PHiD-CV	

Continued

https://doi.org/10.1183/13993003.00300-2022

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question#
Redding [37], 2014, USA and Australia	Prospective, multicentre	Inclusion: Australian Aboriginal and Alaska Native children age 0.5–8 years, with either CT-confirmed BE or CSLD (>3 months of daily wet cough) and ⩾3 consecutive years of observation; exclusion: presence of underlying cause of BE (*e.g.* immune deficiency, PCD, CF), diabetes, cancer, central nervous system or neuromuscular disorder affecting respiratory system	n=93 children; median (range) age: 36 (9–107) months	1) Characterise pattern of acute BE exacerbations, and 2) identify clinical features that increased the risk of recurrent and severe exacerbations requiring hospitalisation	Acute respiratory-related episodes requiring new antibiotic treatment for any of: increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in FEV_1 >10%, or haemoptysis; clinical encounters within 2 weeks considered a single exacerbation	Hospitalised and non-hospitalised; duration not specified; clinical encounters within 2 weeks considered a single exacerbation	Risks of recurrent and severe exacerbations: age ⩽3 years who have experienced multiple episodes and/or hospitalised in the first year of life and in the year prior to enrolment	Limited to indigenous children
Sunther [38], 2016, England	Specialist hospital; retrospective review from PCD database	Inclusion: age 6–16 years and able to perform spirometry; exclusion: incomplete spirometric assessments	n=30; median (range) age: 11.4 (6–16.2) years; follow-up: 3 months post-hospital discharge	In children with PCD treated with *i.v.* antibiotics for an exacerbation to: 1) determine proportion who recover baseline FEV_1 within 3 months and 2) identify factors associated with failure to regain pre-exacerbation FEV_1	"A change in respiratory status for which *i.v.* antibiotics were prescribed"	Hospitalised only; duration not specified	No difference between responders and non-responders in baseline characteristics (age, gender, ethnicity, BMI, baseline FEV_1 <40%, mean baseline or admission FEV_1, persistent infection, use of prophylactic antibiotics, nebulised HS or rhDNase)	Hospitalised only data
Valery [19], 2013, Australia and New Zealand	Multicentre, double-blind RCT	Inclusion: First Nations Australian or New Zealand children with BE or CSLD age 1–8 years, lived within the study area and had ⩾1 exacerbations in past 12 months; exclusion: receiving chemotherapy, immunosuppressants or long-term antibiotics, had CF or primary immune deficiency, other chronic disorders (*e.g.* cardiac, neurological, hepatic disease), or macrolide hypersensitivity	AZM n=45, placebo n=44; mean±SD age: AZM 3.99±2.14 years, placebo 4.22±2.3 years; follow-up: 24 months	Establish whether 24 months of once-weekly AZM reduced pulmonary exacerbations in indigenous children with BE or CSLD	Treatment by clinic or hospital staff with antibiotics for any of: increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in FEV_1 >10%, or haemoptysis; visits for a respiratory infection within 2 weeks regarded as part of the same exacerbation	Hospitalised and non-hospitalised; duration not specified; clinical encounters within 2 weeks considered a single exacerbation	Compared with placebo group, children receiving AZM had significantly lower exacerbation rates (incidence rate ratio 0.50, 95% CI 0.35–0.71; p<0.0001)	Limited to indigenous children

Continued

https://doi.org/10.1183/13993003.00300-2022

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
BREATHE, 2019, Australia	Study protocol: multicentre, observer-blinded RCT	Inclusion: children age 6–13 years with HRCT-confirmed BE, under the regular care of a respiratory paediatrician, ⩾1 exacerbations in past 12 months and medically able to complete an exercise programme; exclusion: medical or emotional instability, recent musculoskeletal injury, other chronic illness, unable to attend any exercise sessions or follow-up visits over 12 months, involved in an interventional clinical trial, or other reasons the investigators or treating physicians consider should be excluded to prevent potential harm or adversely affect study outcomes	Planned n=174	Determine effectiveness of a therapeutic, play-based exercise program in reducing acute exacerbations over a 12-month period in children age 6–13 years with BE compared with standard care	Treatment by clinic or hospital staff with antibiotics for any of (as recorded in medical chart or parent report): increased cough (wet and ⩾3 days duration), dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in FEV_1 >10%, or haemoptysis		Not applicable	
REPEAT, 2019, Australia	Study protocol: multicentre, double-dummy, placebo-controlled RCT	Inclusion: age 2–65 years with known or suspected PCD with ⩾2 exacerbations in the last 18 months and plan to remain at one of the study sites for ⩾15 months; exclusion: CF, on intervention medication (AZM or placebo), past (last 6 months) or current infection with NTM, contraindication for macrolide or erdosteine use, pregnant, pregnancy planned (in next 12 months) or nursing mothers, abnormal ECG (QTc >460 ms), history of cardiac arrhythmia, previously randomised, or hospitalised in last 4 weeks for respiratory instability	Planned n=104	Determine efficacy of AZM and/or erdosteine in reducing exacerbations in people with PCD	An acute respiratory event that is treated with antibiotics and an increase in sputum volume or purulence, for ⩾3 days of altered cough (⩾20% increase in cough score or type (dry to wet/productive)) or physician-confirmed acute change in respiratory rate, work of breathing or chest signs	Hospitalised and non-hospitalised; ⩾3 days	Not applicable	

Continued

https://doi.org/10.1183/13993003.00300-2022

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
BETTER, 2021, Australia	Study protocol: dual-centre, placebo-controlled RCT (BETTER)	Inclusion: age 2–19 years with BE, ⩾2 exacerbations in last 18 months and contactable for 15 months; exclusion: CF, contraindication to using erdosteine, pregnant, pregnancy planned (in next 12 months), nursing mothers, previously randomised, hospitalised in last 4 weeks for respiratory instability or participating in another intervention RCT	Planned n=128	Evaluate effect of erdosteine on respiratory exacerbation rate of children with BE	An acute respiratory event that is treated with antibiotics and an increase in sputum volume or purulence, for ⩾3 days of altered cough (⩾20% increase in cough score or type (dry to wet/productive)) or physician-confirmed acute change in respiratory rate, work of breathing or chest signs	Hospitalised and non-hospitalised; ⩾3 days	Not applicable	
Consensus documents								
Chang [2], 2021, multiple countries	Systematic reviews and GRADE-based clinical practice guideline	For the narrative question relating to exacerbations: inclusion: age 0–18 years with BE from any cause (other than CF); exclusion: papers published before 1982, non-English language articles	Not applicable	For clinical purposes: respiratory exacerbation is considered present when a child/adolescent has increased respiratory symptoms (predominantly increased cough with/without increased sputum quantity and/or purulence) for ⩾3 days Remarks: other important, but less common, symptoms like haemoptysis, chest pain, breathlessness and wheeze may not be present; clinicians should not rely on changes in chest auscultation findings and chest radiography to diagnose an exacerbation as, although important, these findings are not always present; systemic symptoms (fever, fatigue, malaise, change in child's behaviour, appetite) may also herald onset of an exacerbation, but are non-specific; blood markers (*e.g.* elevated CRP, neutrophilia and IL-6) provide supportive evidence of the presence of an exacerbation (however, these indices are less important in defining exacerbations, but are likely useful for research purposes; also, markers like IL-6 are not standard clinical tests) The presence of dyspnoea (increased work of breathing) and/or hypoxia is considered a severe exacerbation, irrespective of the duration	Non-hospitalised: ⩾3 days; hospitalised criteria: any duration	See document for other recommendations	Definition for clinical purposes

Continued

TABLE 1 Continued

First author [ref.]/ trial name, year, country	Study design	Inclusion and exclusion criteria	Subjects; age; follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation; duration of symptoms	Main study outcomes	Implication for question[#]
Lucas [39], 2019, multiple countries	Consensus, multicentre	Systematic review that used pulmonary exacerbations in PCD patients as a variable (January 2000 to April 2017) followed face-to-face meeting and e-Delphi; 16 members of the panel	Adults and children	Develop a consensus for defining pulmonary exacerbations in children and adults with PCD for clinical trials and other research	Children and adults with PCD; three or more of: 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°C	Severity not specified; duration not specified		Lacks time element, *e.g.* single episode *versus* days would result in different interpretation
Shapiro [40], 2016, North America	Consensus, multicentre North American sites and PCD Foundation	Literature review (PubMed and Embase), then drafts created and circulated iteratively to participating physicians and then to PCD Foundation	Not applicable	Present consensus recommendations from North American physicians from PCD research consortium	Acute changes in cough, sputum production, respiratory rate or work of breathing	Hospitalised and non-hospitalised; duration not specified	See document for other recommendations	Document specific to PCD

RCT: randomised controlled trial; CT: computed tomography; S_{pO_2}: peripheral oxygen saturation; CF: cystic fibrosis; *P. aeruginosa*: *Pseudomonas aeruginosa*; AMC: amoxicillin–clavulanate; AZM: azithromycin; IQR: interquartile range; FEV_1: forced expiratory volume in 1 s; HS: hypertonic saline; FVC: forced vital capacity; HRCT: high-resolution computed tomography; CRP: C-reactive protein; *i.v.*: intravenous; IL: interleukin; PCD: primary ciliary dyskinesia; QoL: quality of life; LCI: Lung Clearance Index; ERY: erythromycin; CSLD: chronic suppurative lung disease; PHiD-CV: 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine; BMI: body mass index; rhDNase: recombinant human DNase; NTM: non-tuberculous mycobacteria; GRADE: Grading of Recommendations; Assessment; Development and Evaluation. [#]: in children and adolescents with bronchiectasis, what criteria should be used to define an exacerbation in clinical research studies?

https://doi.org/10.1183/13993003.00300-2022

TABLE 2 Summary of indicators of bronchiectasis exacerbations in the included studies (n=21)

Indicator	Studies, n (%)
Change in cough frequency or character (dry to wet)	17 (81)
Change in sputum colour or volume	14 (67)
Breathlessness/dyspnoea	11 (52)
Change in auscultatory findings	7 (33)
New chest radiography findings	7 (33)
Haemoptysis	7 (33)
Wheeze	5 (24)
Decline in spirometry/lung function	5 (24)
Change in respiratory rate	4 (19)
Fever	4 (19)
Decrease in S_{pO_2}	3 (14)
Blood inflammatory indices	3 (14)
Chest auscultatory crackles	2 (9)
Malaise/tiredness	2 (9)
Duration mentioned	10 (48)[#]

S_{pO_2}: peripheral oxygen saturation. [#]: in all but one study, duration was ⩾3 days.

present for ⩽3 days (figure 3b). When considering overall symptom duration that needs to be present when defining the occurrence of a non-severe (non-hospitalised) exacerbation, none indicated that symptoms should be any longer than "At least 3 days".

The physicians' survey had 348 respondents, of whom 49 were disqualified as they either did not care for children and adolescents or did not complete the survey questions. The remaining 299 physicians were from 54 countries; 89% (n=266) were paediatric respiratory specialists, of whom 77% practiced in a university-based setting, and most (67%) cared for ⩾10 children and adolescents with bronchiectasis.

The physicians' Delphi achieved our predefined consensus rate at the first iteration with a high agreement rate ("strongly agree" or "agree") ranging from 82.3% to 92.9% for the four statements. The disagreement rate ("strongly disagree" or "disagree") ranged from 3.6% to 7.2% and the "neither agree or disagree" rate was between 3.3% and 11.5%. The full data are presented in supplementary figure S1a–d. The panel unanimously endorsed these statements at the final virtual meeting (table 3). Likewise, the ELF PAG also endorsed the four statements.

Discussion

This ERS Task Force document on defining respiratory exacerbations for paediatric bronchiectasis clinical research is the first such consensus document. The multidisciplinary international Task Force panel formulated four statements based upon the 21 included studies identified in the systematic review, our collective clinical research experience and the opinion of the PAGs on defining respiratory exacerbations of paediatric bronchiectasis. We had a high agreement rate (>82%) on the Delphi survey, undertaken by 299 physicians (from 54 countries) who care for children and adolescents with bronchiectasis, on all four statements.

Exacerbations are used widely as either an outcome variable or an analysed end-point measure for intervention studies in chronic airway diseases. These include clinical trials involving children and adolescents with asthma [17], cystic fibrosis [18] or bronchiectasis [19]. Having standardised definitions for exacerbations will help with reducing heterogeneity in patient and physician behaviour, therefore allowing a better comparison between trials aiming to reduce exacerbation frequency. However, our systematic review undertaken for this Task Force document showed that despite some common features, such as increased cough and/or sputum production, there was wide variation in the definitions of exacerbations used in previous studies (table 1). As different aspects of exacerbations are examined in clinical studies, this Task Force statement includes different definitions for the various scenarios that will be encountered. This means the definition of an exacerbation employed as an outcome measure for intervention trials (*e.g.* a multicentre randomised controlled trial seeking to reduce exacerbations [19]) differs from that when the intervention is used to assess treatment of exacerbations themselves (*e.g.* as in two recent multicentre randomised controlled trials of antibiotics [20, 21]). Defining resolution of exacerbation is also required, not only for studies assessing treatment of exacerbations, but also to

TABLE 3 Defining respiratory exacerbations in children and adolescents with bronchiectasis for clinical research

Statement 1: Definition of exacerbation as an outcome for clinical trials

1a: Non-severe exacerbation

In children and adolescents with bronchiectasis, we suggest that a non-severe respiratory exacerbation is considered present when there is a change in respiratory management (prescribed antibiotics for respiratory symptoms and/or intensification of airway clearance) DUE TO at least ONE of the following:

- *An increase in sputum volume/purulence OR change in cough character (dry to wet) OR increased wet/productive cough frequency for ⩾3 days*
- *Onset of chest pain or discomfort*
- *Onset of new or worsening chest auscultation or palpable (vibration) secretion findings*
- *Onset of new or worsening radiographic changes* (e.g. *chest radiography)*
- *Drop in FEV_1 (>10%)*

NOTE: 1) blood markers reflective of a pulmonary exacerbation (*e.g.* elevated CRP, neutrophils, serum amyloid A, IL-6) may also be present; 2) systemic symptoms (fever, fatigue, malaise, change in child's behaviour or appetite) may also herald onset of an exacerbation, but are non-specific

1b: Severe exacerbation

In children and adolescents with bronchiectasis, we suggest that a severe respiratory exacerbation is considered present when the criteria for an exacerbation (see Statement 1a) are met AND a clinician deems hospitalisation for intravenous antibiotics and/or supportive management is indicated BECAUSE of at least ONE of the following:

- *Onset of new or worsening tachypnoea (age-adjusted respiratory rate (breaths·min^{-1}) >50 if aged <12 months; >40 if aged 1–2 years; >30 if aged 3–9 years; >25 if aged 10–18 years)*
- *Onset of new or worsening dyspnoea (increased work of breathing)*
- *Onset of new or worsening hypoxia (S_{pO_2} persistently <92% in room air or 4% below stable state)*
- *Any haemoptysis*
- *Worsening chest pain*

Statement 2: Definition of a non-severe exacerbation that warrants treatment for clinical trials

In children and adolescents with bronchiectasis, we suggest that a non-severe respiratory exacerbation is considered present when at least ONE of the following develops:

- *An increase in sputum volume/purulence OR change in cough character (dry to wet) OR increased wet/productive cough frequency for ⩾3 days OR*
- *Onset of chest pain or discomfort OR*
- *Onset of new or worsening chest auscultation or palpable (vibration) secretion findings OR*
- *Onset of new or worsening radiographic changes* (e.g. *chest radiography) OR*
- *Drop in FEV_1 (>10%)*

NOTE: 1) blood markers reflective of a pulmonary exacerbation (*e.g.* elevated CRP, neutrophils, serum amyloid A, IL-6) may also be present; 2) systemic symptoms (fever, fatigue, malaise, change in child's behaviour or appetite) may also herald onset of an exacerbation, but are non-specific

Statement 3: Definition of resolution of a non-severe exacerbation

In children and adolescents with bronchiectasis, we suggest that a non-severe respiratory exacerbation is considered resolved when the child's or adolescent's clinical state has returned to baseline state (respiratory symptoms and signs) for at least 2 consecutive days

FEV_1: forced expiratory volume in 1 s; CRP: C-reactive protein; IL: interleukin; S_{pO_2}: peripheral oxygen saturation.

determine when another exacerbation commences if two exacerbations occur closely together. Thus, the panel included Statement 3 as part of this Task Force document.

Although the statements in this Task Force document share common features with the recommendation in the paediatric bronchiectasis CPG [2], there are also important differences between the two ERS documents. The CPG focused on a definition for clinical care rather than research, and was a single statement advocating for prompt and optimal treatment of exacerbations. In contrast, the present Task Force statements include four different definitions to align with the particular study objectives (exacerbations as an outcome, to initiate treatment or its resolution). The differences between the definitions for clinical and research purposes are expected as the clinical definition focuses upon prompt recognition, while the research definition promotes robustness of outcome variables for research. While both Task Forces utilised a rigorously conducted systematic review, the present Task Force methods included a Delphi approach that encompassed worldwide expert physicians in the field.

Our statement differs from the adult statement for clinical research [14], which was led by one of our panel members (A.T.H.). The adult group defined an exacerbation 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" [14]. Despite the similarities between the clinical research definition for adults [14] and Statement 1a (table 3) of our Task Force, there are also differences in the duration of symptoms, types of symptoms required and

our categorisation of severe *versus* non-severe exacerbations. Our Task Force paid particular attention to the duration of symptoms, with robust discussions during our meetings and by e-mail. Based upon the systematic review we undertook (tables 1 and 2), and PAG advice, we chose at least 3 days (rather than the 2 days used for adults [14]). The surveyed international physician community with specific expertise in paediatric bronchiectasis supported this decision with an agreement rate of 88.7% (disagreement rate of 6.4% with 5% indicating "neither agree or disagree") on the Delphi statement. Overall, we considered 2 days was too short in children, as the cough may spontaneously improve without the need for any intervention. This element is included to avoid over-prescribing of antibiotics when they may not be necessary.

The above is also not surprising as while bronchiectasis in children and adolescents shares some similarities with adults (*e.g.* wet/productive cough being the dominant symptom with exacerbation periods), there are also substantial differences. Acute respiratory infections are more common in younger children than in adults [22], and haemoptysis in children and adolescents with bronchiectasis is rare [1] compared with its incidence in adults. Also, children require parental care, support and input, and are clearly cognitively different from adults, whereby paediatricians mostly rely upon parent report while adults self-report. In children and dependent adolescents, the burden of illness from bronchiectasis is not just on the patient (*i.e.* the child) but also the entire family. Biologically, differences between paediatric- and adult-based studies include significantly dissimilar pathogen profiles (bacterial [23] and complex microbial community compositions [24]), age-related immunological responses [25] and likely outcomes of treatment [1].

In this Task Force document, our paediatric definition of pulmonary exacerbation includes "Onset of new or worsening radiographic changes (*e.g.* chest radiography)". While this document refers to recommended definitions for clinical research, we acknowledge that in clinical practice it can on occasions be difficult differentiating community-acquired pneumonia from atelectasis and other chest radiography changes related to pulmonary exacerbations of bronchiectasis. In our ERS CPG for the management of children and adolescents with bronchiectasis [2], we did not differentiate between pneumonia and a pulmonary exacerbation.

Bronchiectasis unrelated to cystic fibrosis has gained prominence in the last decade with the increasing recognition that is not as rare as once believed [1, 26]. There is now increasing traction in the field of paediatric bronchiectasis with the establishment of an ERS Clinical Research Collaboration (Child-BEAR-Net [27]) and an Australian National Health and Medical Research Council Centre for Research Excellence in Paediatric Bronchiectasis (AusBREATHE [28]). However, we have a considerable journey ahead to achieve equity for children and adolescents with bronchiectasis and to improve their outcomes.

Conclusions

This ERS Task Force document proposes the internationally derived, systematically evaluated, consensus-based definitions of respiratory exacerbations outlined in table 3. We hope it will contribute to the planning and help improve the quality of future clinical paediatric bronchiectasis research. We believe that our expert panel, combined with the opinion from parents of children and adolescents with bronchiectasis, have derived internationally applicable definitions of respiratory exacerbations for children and adolescents with bronchiectasis.

Acknowledgements: We thank Elizabeth Stovold, the information specialist from the Cochrane Airways Group (London, UK), for having undertaken all the searches. We are also grateful to the extended ELF PAG and the Australian National Health and Medical Research Council Centre for Research Excellence PAG who helped shape the document through sharing their experiences and views on exacerbations. Finally, we are grateful to the physicians who responded to the survey as without their input, we would not have been able to develop a Delphi approach.

This document was endorsed by the ERS Executive Committee on 2 May 2022.

Other Child-BEAR-Net committee members: James Chalmers, Andrew Collaro, Kostas Douros, Matthias Griese, Jonathan Grigg, Andreas Hector, Oleksandr Mazulov, Fabio Midulla, Alexander Möller, Marijke Proesmans and Stephanie Yerkovich.

Conflict of Interest: E. Alexopoulou, L. Bell, A. Bush, C. Constant, R. Fortescue, B. Karadag, A.T. Hill, A. Kantar, V. Goyal, A. Zacharasiewicz, J. Boyd, A. Claydon, Z. Powell and C. Wilson have nothing to disclose. A.B. Chang

reports grants from National Health and Medical Research Council, Australia, during the conduct of the study; is IDMC member for an unlicensed vaccine (GSK), is advisory member of study design for an unlicensed molecule for chronic cough (Merck), and is IDMC member for an unlicensed monoclonal antibody (AstraZeneca); and has received personal fees from being an author of two UpToDate chapters, outside the submitted work. K. Grimwood reports grants from Australian National Health and Medical Research Council, and Medical Research Futures Fund, during the conduct of the study. S. Aliberti reports grants and personal fees from AstraZeneca, Insmed, Fisher & Paykel and Chiesi, and personal fees from GlaxoSmithKline, Gilead Sciences, Novartis, MENARINI, Fondazione Charta, Grifols, Boehringer Ingelheim and Zambon, outside the submitted work.

Support statement: This work was supported by the European Respiratory Society (grant: TF-2020-17) and the National Health and Medical Research Council (grant: 1170958). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. *Lancet* 2018; 392: 866–879.
2 Chang AB, Fortescue R, Grimwood K, *et al.* European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis. *Eur Respir J* 2021; 58: 2002990.
3 Nathan AM, de Bruyne JA, Eg KP, *et al.* Review: quality of life in children with noncystic fibrosis bronchiectasis. *Front Pediatr* 2017; 5: 84.
4 Chang AB, Boyd J, Bell L, *et al.* Clinical and research priorities for children and young people with bronchiectasis: an international roadmap. *ERJ Open Res* 2021; 7: 00122-2021.
5 Chalmers JD, Chang AB, Chotirmall SH, *et al.* Bronchiectasis. *Nat Rev Dis Primers* 2018; 4: 45.
6 Goyal V, McPhail SM, Hurley F, *et al.* Cost of hospitalisation for bronchiectasis exacerbations in children. *Respirology* 2020; 25: 1250–1256.
7 Gibson GJ, Loddenkemper R, Sibille Y, *et al.*, eds. Bronchiectasis. *In:* European Lung White Book. Sheffield, European Respiratory Society, 2013; pp. 176–183.
8 Gao YH, Chalmers JD. Counting the cost of bronchiectasis. *Respirology* 2020; 25: 1223–1224.
9 Prentice BJ, Wales S, Doumit M, *et al.* Children with bronchiectasis have poorer lung function than those with cystic fibrosis and do not receive the same standard of care. *Pediatr Pulmonol* 2019; 54: 1921–1926.
10 McCallum GB, Chang AB. 'Good enough' is 'not enough' when managing indigenous adults with bronchiectasis in Australia and New Zealand. *Respirology* 2018; 23: 725–726.
11 Kapur N, Masters IB, Newcombe P, *et al.* The burden of disease in pediatric non-cystic fibrosis bronchiectasis. *Chest* 2012; 141: 1018–1024.
12 Kapur N, Masters IB, Chang AB. Longitudinal growth and lung function in pediatric noncystic fibrosis bronchiectasis: what influences lung function stability? *Chest* 2010; 138: 158–164.
13 Lovie-Toon Y, Grimwood K, Byrnes CA, *et al.* Health-resource use and quality of life in children with bronchiectasis: a multi-center pilot cohort study. *BMC Health Serv Res* 2019; 19: 561.
14 Hill AT, Haworth CS, Aliberti S, *et al.* Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017; 49: 1700051.
15 Kapur N, Masters IB, Chang AB. Exacerbations in noncystic fibrosis bronchiectasis: clinical features and investigations. *Respir Med* 2009; 103: 1681–1687.
16 Kapur N, Masters IB, Morris PS, *et al.* Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2012; 47: 68–75.
17 Petsky HL, Kew KM, Turner C, *et al.* Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016; 11: CD011439.
18 Rosenfeld M, Ratjen F, Brumback L, *et al.* Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA* 2012; 307: 2269–2277.
19 Valery PC, Morris PS, Byrnes CA, *et al.* Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med* 2013; 1: 610–620.
20 Goyal V, Grimwood K, Ware RS, *et al.* Efficacy of oral amoxicillin–clavulanate or azithromycin for non-severe respiratory exacerbations in children with bronchiectasis (BEST-1): a multicentre, three-arm, double-blind, randomised placebo-controlled trial. *Lancet Respir Med* 2019; 7: 791–801.
21 Goyal V, Grimwood K, Byrnes CA, *et al.* Amoxicillin–clavulanate versus azithromycin for respiratory exacerbations in children with bronchiectasis (BEST-2): a multi-centre, double-blind, non-inferiority randomised controlled trial. *Lancet* 2018; 392: 1197–1206.
22 Leder K, Sinclair MI, Mitakakis TZ, *et al.* A community-based study of respiratory episodes in Melbourne. *Aust NZ J Public Health* 2003; 27: 399–404.
23 Kapur N, Grimwood K, Masters IB, *et al.* Lower airway microbiology and cellularity in children with newly diagnosed non-CF bronchiectasis. *Pediatr Pulmonol* 2012; 47: 300–307.

24 van der Gast CJ, Cuthbertson L, Rogers GB, *et al.* Three clinically distinct chronic pediatric airway infections share a common core microbiota. *Ann Am Thorac Soc* 2014; 11: 1039–1048.

25 Pizzutto SJ, Yerkovich ST, Upham JW, *et al.* Children with chronic suppurative lung disease have a reduced capacity to synthesize interferon-gamma *in vitro* in response to non-typeable *Haemophilus influenzae*. *PLoS One* 2014; 9: e104236.

26 Goyal V, Grimwood K, Masters IB, *et al.* Pediatric bronchiectasis: no longer an orphan disease. *Pediatr Pulmonol* 2016; 51: 450–469.

27 Chang AB, Boyd J, Bush A, *et al.* Children's Bronchiectasis Education Advocacy and Research Network (Child-BEAR-Net): an ERS Clinical Research Collaboration on improving outcomes of children and adolescents with bronchiectasis. *Eur Respir J* 2021; 58: 2101657.

28 Australian National Health and Medical Research Council Centre for Research Excellence in Paediatric Bronchiectasis. AusBREATHE: Australian Bronchiectasis Centre of Research Excellence esp. for Aboriginal and Torres Strait Islander Children. 2021. www.crelungs.org.au Date last accessed: 16 March 2021.

29 Anuradha KWDA, Gunathilaka PKG, Wickramasinghe VP. Effectiveness of hypertonic saline nebulization in airway clearance in children with non-cystic fibrosis bronchiectasis: a randomized control trial. *Pediatr Pulmonol* 2021; 56: 509–515.

30 Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65: i1–i58.

31 Basaran AE, Basaran A, Maslak IC, *et al.* Evaluation of noncystic fibrosis bronchiectasis using clinical and radiological scorings in children. *Turk Thorac J* 2018; 19: 159–164.

32 Kapur N, Mackay IM, Sloots TP, *et al.* Respiratory viruses in exacerbations of non-cystic fibrosis bronchiectasis in children. *Arch Dis Child* 2014; 99: 749–753.

33 Karadag B, Karakoc F, Ersu R, *et al.* Non-cystic-fibrosis bronchiectasis in children: a persisting problem in developing countries. *Respiration* 2005; 72: 233–238.

34 Kobbernagel HE, Buchvald FF, Haarman EG, *et al.* Efficacy and safety of azithromycin maintenance therapy in primary ciliary dyskinesia (BESTCILIA): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2020; 8: 493–505.

35 Masekela R, Anderson R, Gongxeka H, *et al.* Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: a randomised, placebo-controlled trial. *J Antivir Antiretrovir* 2013; 5: 44–49.

36 O'Grady KF, Chang AB, Cripps A, *et al.* The clinical, immunological and microbiological impact of the 10-valent pneumococcal-Protein D conjugate vaccine in children with recurrent protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis: a multi-centre, double-blind, randomised controlled trial. *Hum Vaccin Immunother* 2018; 14: 2768–2779.

37 Redding GJ, Singleton RJ, Valery PC, *et al.* Respiratory exacerbations in indigenous children from two countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. *Chest* 2014; 146: 762–774.

38 Sunther M, Bush A, Hogg C, *et al.* Recovery of baseline lung function after pulmonary exacerbation in children with primary ciliary dyskinesia. *Pediatr Pulmonol* 2016; 51: 1362–1366.

39 Lucas JS, Gahleitner F, Amorim A, *et al.* Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials. *ERJ Open Res* 2019; 5: 00147-2018.

40 Shapiro AJ, Zariwala MA, Ferkol T, *et al.* Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2016; 51: 115–132.