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Early View

Task force report

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Task Force report

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

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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 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, parents' survey and a Delphi 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% to 6.4%). The panel unanimously endorsed the four consensus definitions for: non-severe and severe exacerbations as an outcome measure; non-severe exacerbation for studies initiating treatment and; 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 [4]. Several aspects of acute respiratory exacerbations featured prominently in the 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-second percent (FEV_1%) predicted per hospitalised exacerbation) [12] and high healthcare resource use [13] and costs (Aus$30,182 (~€20,800, £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 European Lung Foundation (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 recent 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 its definition 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 computed-tomography (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 (Supplement).

Systematic review and PAGs survey

The Cochrane Airways Group information specialist designed and ran the search on the 22nd of February 2021 using the search strategy outlined in the Supplement. Search results were uploaded onto Rayyan (https://rayyan.qcri.org/). Two panel members (VG and AZ) independently screened the abstracts. The papers were retrieved and reviewed by same two panel members and a third reviewer (AC) who also summarised the studies. Additional papers and protocol registries were identified from authors' databases. Disagreements were resolved by consensus. A PRISMA diagram revealing the total number of articles found in the search, including those that were subsequently included/excluded, is shown in Figure 2.

The ELF lead (JB) sent a survey (using SurveyMonkey, from the 11th of March 2021, to the 16th of April 2021) to two PAGs (CPG [2] and Brisbane parent advisory groups [<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 3b). The first question had 15 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 (JB) 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 email 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 will be considered achieved if ≥80% agreed with the statements.

The panel reviewed the data from the systematic review and the PAGs' 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:

(i) Exacerbations for trial outcomes (allowing categorisation into (a) non-severe and (b) severe exacerbations),
(ii) A non-severe exacerbation that warrants treatment in clinical trial settings, and
(iii) 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 (the 1st of September, 2021 to the 31st of October, 2021). The survey results were reviewed by the task force and the consensus statements adapted and finalised by the panel. Lastly, these statements were presented to the ELF-PAG for final review and endorsement.

RESULTS

The search identified 1166 potential publications; 38 full-text articles were retrieved (from the search data) with an additional 5 papers identified from references in these articles and from other sources. Twenty-one articles fulfilled the inclusion criteria (Table 1 and Figure 2). The key aspects of the 21 articles of various types (grouped by studies (a) treating an exacerbation, (b) with exacerbation as an outcome and (c) consensus documents) are tabulated in Table-1. Two studies involved treatment of exacerbations, whilst three were consensus documents, 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 or more 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 4 most common indicators were: change in sputum colour or volume, breathlessness/dyspnoea, change in auscultatory findings and new chest x-ray findings (Table 2).

In the PAG survey, for Question-1, ‘Commencement of antibiotics’ and ‘Chest X-ray changes’ were the two highest (of 15 items) ranked items. All but one item was ranked as very-important/essential (i.e. a mean score of >4) (Figure 3a). In Question-2, the PAGs considered 23 of the 25 listed items needed to be present for ≤3-days (Figure 3b). When considering overall symptom duration that need 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 university-based setting, and most (67%) cared for ≥10 children and adolescents with bronchiectasis.

The physicians' Delphi achieved our pre-defined consensus rate at the first iteration with a high agreement rate (strongly agree [score 1] or agree [score 2]) ranging from 82.3 to 92.9% for the four statements. The disagreement rate (strongly disagree or disagree) ranged from 3.6% to 6.4% and the 'neither agree or disagree' rate was between 3.3 and 11.5%. The full data are presented in the Supplement (Figure S1 a-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 PAGs opinion 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 a wide variation in the definition 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 determine when another exacerbation commences if two exacerbations occur closely together. Thus, the panel included statement (iii) as part of this Task force statement.

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 (AH). 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-hours: 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-i.a (**see 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 emails. Based upon the systematic review we undertook (Tables 1-2), 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 share 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 to 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 whilst 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 taskforce document, our paediatric definition of pulmonary exacerbation includes "Onset of new or worsening radiographic changes (e.g chest x-ray)". 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 x-ray 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 awarding of an ERS Clinical Research Collaboration (Child-BEAR-NET [27]) and an Australian National Health and Medical Research Council Centre for Research Excellence (CRE) 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.

CONCLUSION

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.

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Conflict of Interest statement

Drs Alexopoulou, Bush, Constant, Fortescue, Grimwood, Karadag, Hill, Kantar, Goyal, Zacharasiewicz have nothing to disclose. Ms Boyd, Claydon, Powell and Wilson also have nothing to disclose. Dr Chang reports grants from National Health and Medical Research Council, Australia, during the conduct of the study; other from IDMC Member of an unlicensed vaccine (GSK), other from Advisory member of study design for unlicensed molecule for chronic cough (Merck), other from IDMC Member of an unlicensed monoclonal antibody (AstraZeneca), personal fees from being an author of two UpToDate chapters, outside the submitted work. Dr. Grimwood reports grants from Australian National Health and Medical Research Council, and Medical Research Futures Fund, during the conduct of the study. Dr Aliberti reports grants and personal fees from AstraZeneca, grants and personal fees from Insmed, Fisher & Paykel, and Chiesi, and personal fees from GlaxoSmithKline, Gilead Sciences, Novartis, MENARINI, Fondazione Charta, Grifols, Boehringer Ingelheim, Zambon, outside the submitted work.

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FIGURE LEGENDS

Figure 1
Schematic overview of methodology used for this task force document to develop the consensus for the definitions of exacerbations.

Figure 2
PRISMA diagram of articles screened and included for taskforce document.

Figure 3
The parent advisory groups responses to questions posed in the survey undertaken by the European Lung Foundation (ELF):
3a: Which items do you think should be part of defining an acute respiratory exacerbation in a child or a young person with bronchiectasis?
3b: How long do you think these items need to be present before you would consider this is an acute exacerbation episode?
The * refers to additional comments made by some respondents. We have not included these comments in the document

Table 1: Studies on pulmonary exacerbation in children and adolescents with bronchiectasis

Question: In children and adolescents with bronchiectasis, what criteria should be used to define an exacerbation in clinical research studies?
Subgroups: For studies on (A) treatment of exacerbations, (B) where exacerbations were an outcome, and (C) consensus statements

(A) STUDIES ON TREATMENT OF EXACERBATION

First author year, country	Study design	Inclusion and exclusion criteria	N; Age; Follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation/ duration of symptoms	Main study outcomes	Implication for question
Goyal [21], 2018, Australia and New Zealand	RCT, multi-centre, double-dummy, double blind (BEST-2)	Inclusion: <19 yrs, CT-proven BE in the last 5 yrs (or if diagnosed earlier, regular follow-up by a respiratory physician for BE) and ≥2 exacerbations in last 18 mo. Exclusion: current or recent severe exacerbation (dyspnoea, SpO_2 <90% in air or hospitalization) in 8 wks immediately prior to study entry; CF or liver dysfunction; hyper-sensitivity to beta-lactam or macrolide antibiotics; current or recent (4 mo) *P. aeruginosa* infection; receipt of beta-lactam or macrolide antibiotics within the preceding 3 wks for the exacerbation; or current treatment for cancer	Amox-clav =97 Azithro = 82 Median age in yrs (IQR): amox-clav=6·8 (4.3, 10.1. azithro=6.4 (4.0, 9.0) FU: every 3 mo for 18 mo or until next exacerbation	Primary question: 'Is daily oral azithro non-inferior (within a 20% margin) to oral amox-clav, 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 Sx and signs are the same as the baseline state	Non-hospitalised At least 3 days	By 21 days of treatment, azithro was non-inferior to amox-clav, for resolving non-severe exacerbations. Exacerbations were significantly shorter in the amox-clav, than in the azithro group (median 10 days [IQR 6–15] vs 14 days [8–16]; p=0.014)	Limited to mild exacerbation and parent reported criteria

Goyal [20], 2019, Australia and New Zealand	RCT, multi-centre, 3-arm double-dummy, double blind RCT (BEST-1)	Inclusion: <18 yrs, CT-proven BE in the last 5 yrs (or if diagnosed earlier, regularly followed by a respiratory physician for BE) and ≥2 exacerbations in last 18 mo. Exclusion: current or recent severe exacerbation (dyspnoea, SpO_2 <90% in air or hospitalised) in 8 wks immediately prior to study entry; CF or liver dysfunction; hyper-sensitivity to beta-lactam or macrolide antibiotics; current or recent (4 mo) *P. aeruginosa* infection; receipt of beta-lactam or macrolide antibiotics within 3 wks preceding study entry for the exacerbation; or current treatment for cancer	Amox-clav = 63 Azithro = 67 Placebo = 67 Median age in yrs (IQR): amox-clav=6 (3.6, 9.5) azithro=5.9 (3.4, 8.4) Placebo=6 (3.7, 8.6) FU: every 3 mo for 18 mo or until next exacerbation	Determine whether amox-clav, and azithro, 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 Sx and signs are the same as the baseline state	Non-hospitalised. At least 3 days	Oral amox–clav for 14 days for non-severe exacerbations of BE in children was superior to placebo in achieving exacerbation resolution by the end of treatment and in decreasing the duration of exacerbations	Limited to mild exacerbation and parent reported criteria

(B) STUDIES WHERE EXACERBATION WAS AN OUTCOME

	Study design	Inclusion and exclusion criteria	N; Age; Follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation/ duration of symptoms	Main study outcomes	Implications for question
Anuradha [29], 2020, Sri Lanka	Cross-over open-label RCT, single centre	Inclusion: Radiographically confirmed BE Exclusion: CF, FEV_1 < 40% predicted, 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 extra- pulmonary features of CF	n=63 (n=52 finished study). Mean age: 9.3 ± SD 2.6 yrs Follow-up length: 150 days	Determine efficacy of 3% saline premedication before airway clearance technique, 60 days trial; 30 days wash out period, then cross over design	Previous definition [30]: Acute deterioration (usually over several days) with worsening local Sx (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 is not per group, but by phase
Basaran [31] 2018, Turkey	Retro, single centre	Inclusion: HRCT-confirmed BE	n=34; Mean age 13.69±4.67 years SD 4.67	Describe the 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 Sx, increased CRP levels, increased neutrophil proportion, and impairment in respiratory	Hospitalised and non-hospitalised Duration not defined	Annual exacerbation frequency was dependent on severity of disease	Retro review

					function test			
Kapur [15] 2009, Australia	Retro 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	115 exacerbations in 30 children. Median age =5.5 yrs (range 0.8-13)	Determine: (1) the associated clinical and investigational features; (2) the 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 FEV_1% predicted during exacerbation was 78.5% (range 36-95.4) compared to the stable state of 82.5% (range 43.7-103) (p=0.36). FVC% predicted during exacerbation (median 81%, range 50.9-102) and stable state (85.5%, 52.4-114, p=0.34). CXR changes in 8/35 (22.9%) exacerbations	Hospitalised and non-hospitalised No duration specified	Intravenous antibiotics required in 39 (35%) exacerbations within 4 wks of starting oral therapy (median 21 days, range 3-28) with 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 Sx and signs. Spirometry data insensitive
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	69 children with 81 exacerbations. Median age=7 yrs (IQR 3.8, 10.9) FU: 900 child-months	To formulate a clinically useful definition of respiratory exacerbation for children with bronchiectasis	A. Major Criteria At least 72 hrs of: (1) Significant frequency of cough (median cough score ≥2) (2) Wet cough B. Minor Criteria	Hospitalised and non-hospitalised At least 3 days	Inter-observer kappa value for each of the factors in the assessment form was >0.75 Spirometry and impulse oscillatory	The sole prospective study that used clinically relevant exacerbation as the gold

		standard" based on Aspen workshop's 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.'			(1) Sputum colour ≥3 BronkoTest (2) Parent/child perceived breathlessness, (3) Chest pain, (4) Crepitations, (5) Wheeze, (6) Hypoxia. <u>C. Laboratory Criteria</u> (1) high sensitive CRP >3 mg/L; (2) Serum interleukin-6 >2 ng/L. (3) Serum amyloid A >5 mg/L; (4) Raised neutrophil % (age appropriate). Definition options: 2 major criteria or one major plus one lab criteria or one major with 2 minor criteria		indices during exacerbation were not different from baseline Haemoptysis significantly more likely to occur during an exacerbation but very rare in cohort	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: Radiographic-confirmed BE. Exclusion: CF	n=69 Mean age=7 yrs. FU time: 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	Parents reported deterioration was indicator for exacerbation

Karadag [33] 2005, Turkey	Retro single centre	Inclusion: HRCT-confirmed BE and followed up for at least 2 yrs	n=111; Mean age 7.4 yrs, SD 3.7	Describe the characteristics, underlying causative factors and long-term follow-up	Persistent (>24 hrs) increase in respiratory Sx, new CXR opacification or worsening in physical examination findings of the chest	Hospitalised and non-hospitalised At least 1 day		Retro review
Kobbernagel [34] 2020, Europe	Multi-centre	Inclusion: PCD, FEV_1% predicted >40%, ≥30 days of antibiotics for exacerbations in last 2 years, not taking azithro in the last 30 days, not receiving inhaled or maintenance antibiotics	n=90; Mean age in yrs (SD): Azithro=18.6 (8.9) Placebo=19.7 (10.8)	Determine efficacy of 6 mo of azithro on respiratory exacerbations in PCD	Respiratory Sx leading to use of systemic antibiotics irrespective of bacterial culture, or ≥10% FEV_1% predicted drop relative to screening and randomisation whether or not antibiotics are prescribed	Hospitalised and non-hospitalised Duration of Sx not specified	Exacerbations rate significantly lower in azithro group (rate ratio 0.45 (95%CI 0.26-0.78), p=0.004. FEV_1 significantly better in azithro group; no intergroup difference for QoL, lung clearance index, hearing, static lung volumes	RCT includes adults and restricted to PCD. Also, definition does not include duration of Sx
Lovie-Toon [13], 2019, Australia and New Zealand	Prospective cohort study. 3 clinics	Inclusion: HRCT confirmed BE Exclusion: CF, enrolled in another study or receiving treatment for cancer	n=85 Median age 8.7 yrs (IQR 5.4–11.3) 951 child-mo of observation	Assess health resource use and health related QoL over a 12 mo period in children with BE	Unwell for >3 days with at least one of the following Sx: increased cough, change in cough quality, increased sputum volume or purulence	Non-hospitalised >3 days Hospitalised definition not provided	High health resource use. Mean exacerbations 3.3 (SD 2.2) per child-year. 11.4% episodes required hospitalisation	
Masekela [35] 2013, South Africa	Double blind RCT, single centre	Inclusion: children 6-18 yrs with HIV-related CT-confirmed BE and able to perform reliable pulmonary function tests. Exclusion: CF, abnormal liver	Erythromycin n=17 Mean age=8.4 yrs (SD 2.4) Placebo n=14 Mean age=9.1 yrs (SD 2.1)	Evaluate the efficacy of 52 wks of erythromycin (c.f. placebo) at reducing respiratory exacerbations in children with HIV-related BE	Presence of at least two of the following: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on the CXR	Hospitalised and non-hospitalised Duration of Sx not specified	No difference in the mean number of exacerbations between groups (erythromycin: 2.14 ± 2.28 vs. placebo 2.18 ± 1.59 per year (p=0.17). More children (18%)	Limited to HIV-related BE; small sample size with likely Type-1 error

		function tests abnormal urea, creatinine or using carbamazepine, warfarin, cyclosporin or long-term midazolam					allocated erythromycin than placebo (0%) had no exacerbations during the study duration. High attrition rate (28%)	
O'Grady [36] 2018, Australia	Multi-centre double blind placebo controlled RCT	Inclusion: Aged 1.5-18 yrs with recurrent protracted bacterial bronchitis, CSLD or BE, ≥2 exacerbations in last 18 mo, contactable in next 14 mo. Exclusion: other chronic lung disease; prior vaccination with PHiD-CV vaccine; had 23-valent pneumococcal polysaccharide vaccine in last 2 mo, 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 age=6.8 years, SD 3.7. FU: 12 mo	Evaluate the efficacy of the 10-valent 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. At least 3 days	Absolute risk difference between groups was -0.5 (95%CI -2.0, 0.9) exacerbations per 100-weeks at risk favouring PHiD-CV	
Redding [37] 2014, USA and	Prospective multicentre	Inclusion: Australian Aboriginal and Alaska Native children, aged	n=93 children Median age=36 mo,	(1) Characterize the pattern of acute BE exacerbations and	Acute respiratory-related episodes requiring new antibiotic treatment for	Hospitalised and non-hospitalised	Risks of recurrent and severe exacerbations: age	Limited to indigenous children

Australia		0.5-8 yrs, with either CT- confirmed BE or CSLD (>3 mo 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 neuro-muscular disorder affecting respiratory system	(range 9-107)	(2) identify clinical features that increased the risk of recurrent and severe exacerbations requiring hospitalisation	any of the following reasons: increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in FEV_1% predicted by >10%, or haemoptysis. Clinical encounters within 2 wks considered a single exacerbation	Duration of Sx not specified Clinical encounters within 2 wks considered a single exacerbation	≤3 yrs who have experienced multiple episodes and/or hospitalised in the first year of life and in the year prior to enrolment	
Sunther [38] 2016, England	Specialist hospital; Retro review from PCD database	Inclusion: Aged 6-16 yrs and able to perform spirometry. Exclusion: Incomplete spirometric assessments.	n=30. Median age =11.4 yrs (range 6-16.2). FU: 3 mo post-hospital discharge	In children with PCD treated with IV antibiotics for an exacerbation to: (i) determine proportion who recover baseline FEV_1 within 3 mo and (ii) identify factors associated with failure to regain pre-exacerbation FEV_1.	"A change in respiratory status for which IV antibiotics were prescribed"	Hospitalised only Duration of Sx 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	Double blind RCT, multicentre centre	Inclusion: First Nations Australian or New Zealand children with BE or CSLD, aged 1–8 yrs, lived within the study area, and had ≥1 exacerbation in the past 12 mo. Exclusion: receiving chemotherapy, immunosuppressants or long-term antibiotics, had CF or primary immune-deficiency, other chronic disorders (eg, cardiac, neurological, hepatic disease), or macrolide hypersensitivity	Azithro group: n=45, mean age=3.99 yrs (SD 2.14) Placebo group: n=44, mean age=4.22 yrs (SD 2.3) FU length: 24 mo	Establish whether 24 mo of once weekly azithro reduced pulmonary exacerbations in Indigenous children with BE or CSLD	Treatment by clinic or hospital staff with antibiotics for any of the following: increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in FEV_1 %predicted by >10%, or haemoptysis. Visits for a respiratory infection within 2 wks regarded as part of the same exacerbation	Hospitalised and non-hospitalised Duration of Sx not specified Clinical encounters within 2 wks considered a single exacerbation	Compared with the placebo group, children receiving azithromycin had significantly lower exacerbation rates (incidence rate ratio 0.50; 95%CI 0.35-0.71; p<0.0001)	Limited to indigenous children
ACTRN12619001008112 2019, Australia **Study name BREATH**	Study protocol. Multi-centre, observer-blinded RCT	Inclusion: Children aged 6-13 yrs with HRCT confirmed BE, under the regular care of a respiratory paediatrician, ≥1 exacerbation in past 12-mo, and medically able to complete an exercise program. Exclusion: Medical or emotional instability, recent musculo-skeletal injury, other chronic illness, unable	Planned n=174 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377843	To determine the effectiveness of a therapeutic, play-based exercise program in reducing acute exacerbations over a 12-mo in children aged 6-13 yrs with BE, compared to standard care	Treatment by clinic or hospital staff with antibiotics for any of the following (as recorded in the 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 of >10%, or haemoptysis		Not applicable	

		to attend any exercise sessions or FU visits over 12-mo, involved in a interventional clinical trial, or other reasons the investigators or treating physicians consider should be excluded to prevent potential harm or adversely affect study outcomes						
ACTRN12619000564156 2019, Australia **Study name REPEAT**	Study protocol. Multi-centre, double-dummy placebo-controlled RCT	Inclusion: Aged 2-65 yrs with known or suspected PCD with ≥2 exacerbations in the last 18 mo; AND plan to remain at one of the study sites for at least 15 mo. Exclusion: CF, on intervention meds (azithro or placebo), past (last 6 mo) or current infection with non-tuberculous mycobacteria, contraindication for macrolide or erdosteine use, pregnant, pregnancy planned (in next 12 mo) or nursing mothers, abnormal	Planned n=104 Website reference http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377259	To determine the efficacy of azithro and/or erdosteine in reducing exacerbations in people with PCD	An acute respiratory event that: (a) is treated with antibiotics and (b) an increase in sputum volume or purulence, for ≥3 days of altered cough (at least 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 At least 3 days	Not applicable	

		ECG (QTc >460 msec), history of cardiac arrhythmia, previously randomised or hospitalised in the last 4 wks for respiratory instability						
ACTRN12621000315819 2021, Australia **Study name BETTER**	Study protocol. Dual-centre, placebo-controlled RCT	Inclusion: Children aged 2-19 yrs with BE, ≥2 exacerbations in last 18 mo and contactable for 15 mo. Exclusion: CF, contra-indication to using erdosteine, pregnant, pregnancy planned (in next 12 mo), nursing mothers, previously randomised, hospitalised in the last 4 wks for respiratory instability or participating in another intervention RCT	Planned n=128 Website reference https://www.anzctr.org.au/ACTRN12621000315819.aspx	To evaluate the effect of erdosteine on respiratory exacerbation rate of children with BE	An acute respiratory event that: (a) is treated with antibiotics and (b) an increase in sputum volume or purulence, for ≥3 days of altered cough (at least 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 At least 3 days	Not applicable	

(C) CONSENSUS DOCUMENTS

First author, year, country	Study design	Inclusion and exclusion criteria	N; Age; Follow-up length	Main aim(s)	Definition of exacerbation	Type of exacerbation /duration of Sx	Main study outcomes	Implications for question

Chang [2] 2021, Multi-country	Systematic reviews and GRADE-based Clinical practice guideline	For the narrative question relating to exacerbations. Inclusion: Aged 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 Sx (predominantly increased cough +/- increased sputum quantity and/or purulence) for ≥3-days. **Remarks**: Other important, but less common, Sx like haemoptysis, chest pain, breathlessness and wheeze, may not be present. Clinicians should not rely on changes in chest auscultation findings and chest x-rays to diagnose an exacerbation as, although important, these findings are not always present. Systemic Sx (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 interleukin (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 criteria; at least 3 days Hospitalised criteria; any duration	See document for other recommendations	Definition for clinical purposes
Lucas [39] 2019, Multiple countries	Consensus, multicentre	Systematic review that used pulmonary exacerbations in PCD patients as a variable (Jan 2000 to April	Adults and children	Develop a consensus for defining pulmonary exacerbations in children and adults	Children and adults with PCD. ≥3 of the following: Increased cough, Change in sputum volume and/or colour, Increased shortness	Severity not specified. Duration not specified		Lacks time element e.g. single episode vs days would

		2017) followed face-face meeting and e-Delphi 16 members of the panel		with PCD for clinical trials and other research	of breath perceived by the patient or parent, Decision to start or change antibiotic treatment because of perceived pulmonary Sx, malaise, tiredness, fatigue or lethargy, new or increased haemoptysis, temperature >38°C			result in different interpretation
Shapiro [40] 2016, North America	Consensus, multi-centre 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 of Sx not specified	See document for other recommendations	Document specific to PCD

Amox-clav=amoxicillin-clavulanate, azithro=azithromycin, BE=bronchiectasis, BMI=body mass index, CF=cystic fibrosis, CI=confidence interval, CSLD=chronic suppurative lung disease, CRP=C-reactive protein, CT=computed tomography of chest, CXR=chest X-Ray, FEV_1=Forced expiratory volume in one second, FU=follow-up, FVC=forced vital capacity, mo=months, HIV=human immunodeficiency vaccine, HRCT=high resolution CT scan, hrs=hours, HS=hypertonic saline, IQR=interquartile range, IV=intravenous, mo=months, PCD=primary ciliary dyskinesia, PHiD-CV= 10-valent pneumococcal *H. influenzae* Protein D conjugate vaccine, QoL=quality of life, Retro=retrospective, rhDNase-recombinant human deoxyribonuclease, SD=standard deviation, Sx=symptoms, RCT=randomised controlled trial, wks=weeks, yr=year

Table 2: Summary of indicators of bronchiectasis exacerbations in the 21 included studies

INDICATOR	NUMBER OF STUDIES (N=21)	%
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 x-ray 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 SpO_2	3	14
Blood inflammatory indices	3	14
Chest auscultatory crackles	2	9
Malaise/ tiredness	2	9
Duration mentioned	11 (in all but one study, duration was 3-days)	52

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

Statement (i): Definition of exacerbation as an outcome for clinical trials

(a) 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 x-ray)
- Drop in FEV_1 (>10%)

NOTE:

1. Blood markers reflective of pulmonary exacerbation (e.g. elevated C-reactive protein, neutrophils, serum amyloid-A, interleukin-6) may also be present.
2. Systemic symptoms (fever, fatigue, malaise, change in behaviour or appetite) may also herald onset of an exacerbation, but are non-specific.

(b) 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 above) 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 (RR) ≥50 if aged ≤12-months; RR ≥40 if aged 1-2 years; RR >30 if 3-9 years; RR >25 if 10-18 years)
- Onset of new or worsening dyspnoea (increased work of breathing)
- Onset of new or worsening hypoxia (SpO2 persistently <92% in room air or 4% below stable state)
- Any haemoptysis
- Worsening chest pain

Statement (ii): 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 below 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 x-ray) OR
- Drop in FEV_1 (>10%)

NOTE:

1. Blood markers reflective of a pulmonary exacerbation (eg. Blood markers reflective of infection (eg. elevated C-reactive protein, neutrophils, serum amyloid-A, interleukin-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 (iii): 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 and adolescent's clinical state has returned to baseline state (respiratory symptoms and signs) for at least two consecutive days.

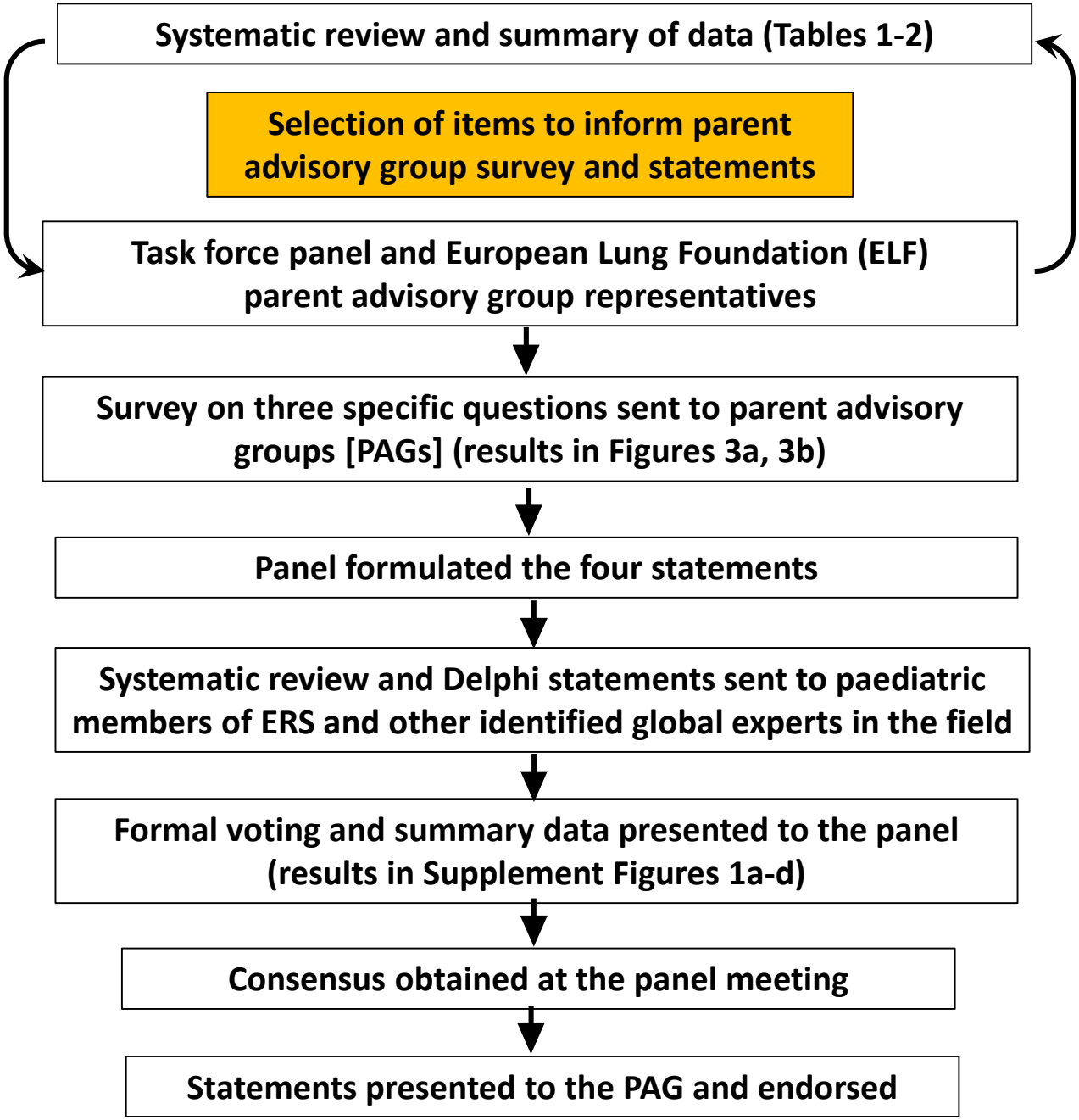

Systematic review and summary of data (Tables 1-2)
Selection of items to inform parent advisory group survey and statements
Task force panel and European Lung Foundation (ELF) parent advisory group representatives
Survey on three specific questions sent to parent advisory groups [PAGs] (results in Figures 3a, 3b)
Panel formulated the four statements
Systematic review and Delphi statements sent to paediatric members of ERS and other identified global experts in the field
Formal voting and summary data presented to the panel (results in Supplement Figures 1a-d)
Consensus obtained at the panel meeting
Statements presented to the PAG and endorsed

Figure 2: PRISMA diagram outlining selection of studies

In children and adolescents with bronchiectasis, what criteria should be used to define an exacerbation for research? PCD=primary ciliary dyskinesia, RCT=randomised controlled trial.

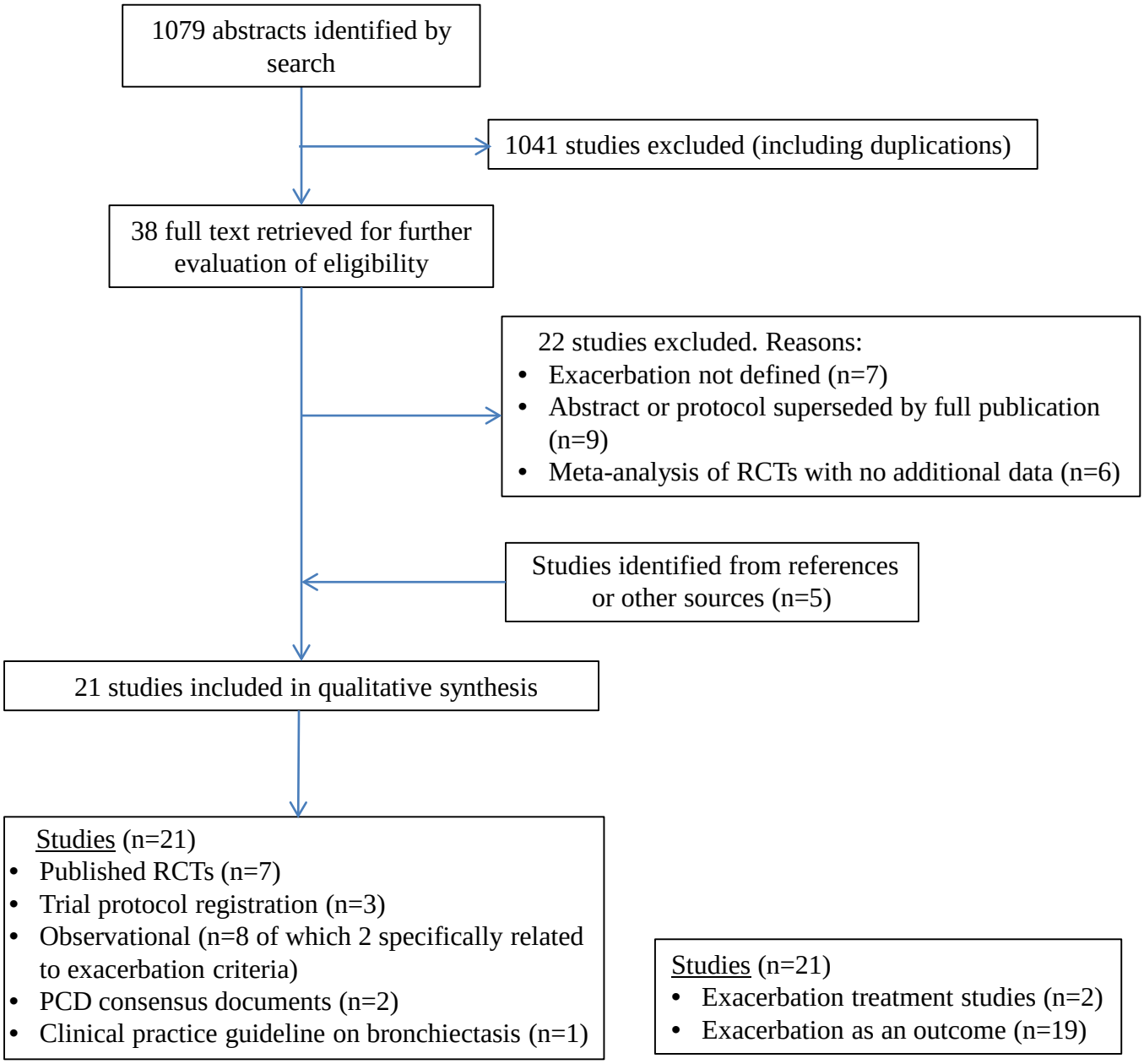
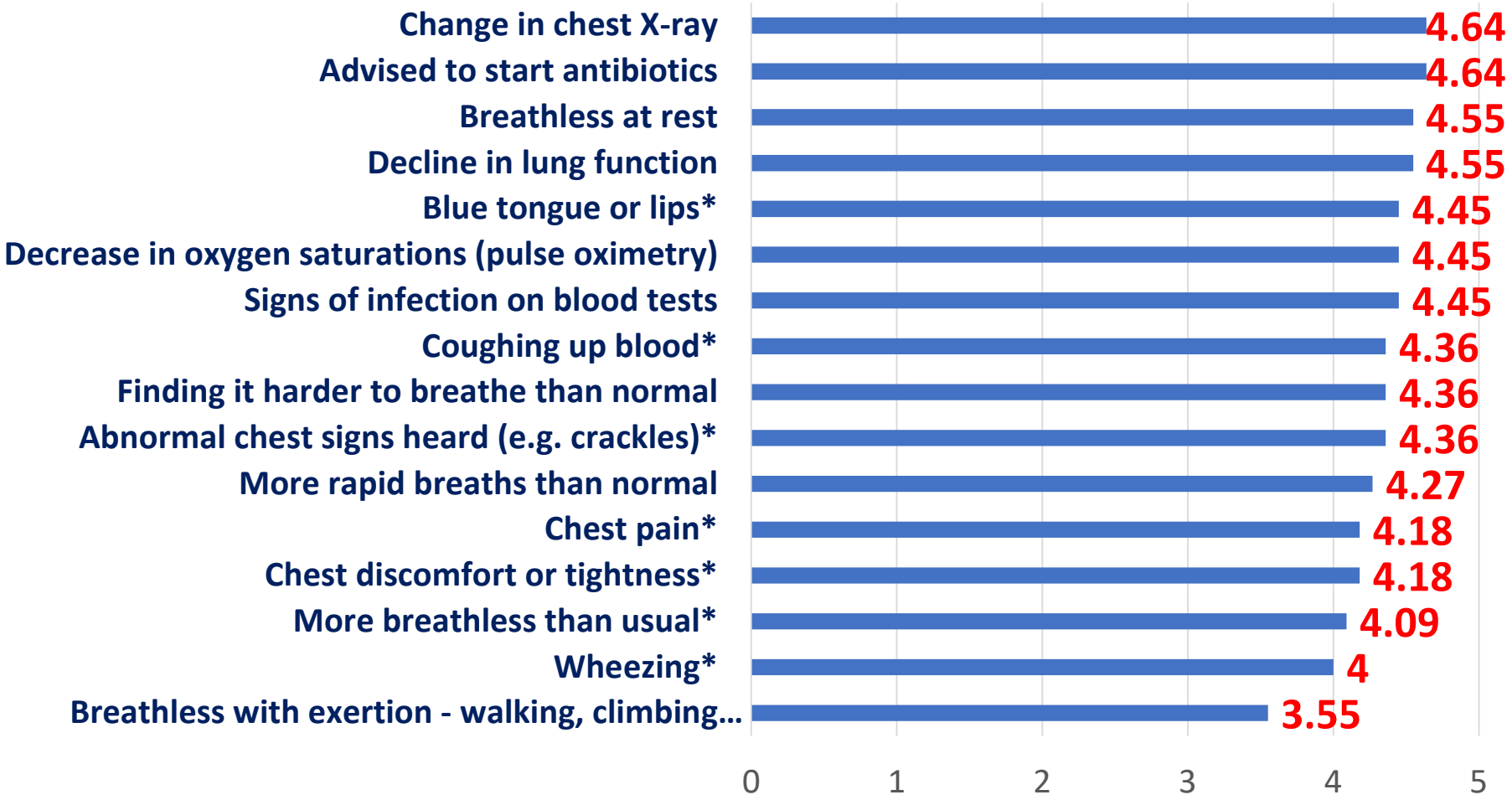


Figure 3a

Which items do you think should be part of defining an acute respiratory exacerbation in a child or a young person with bronchiectasis?

1= not important; 2 = slightly important; 3 = moderately important; 4 = very important and 5 = essential



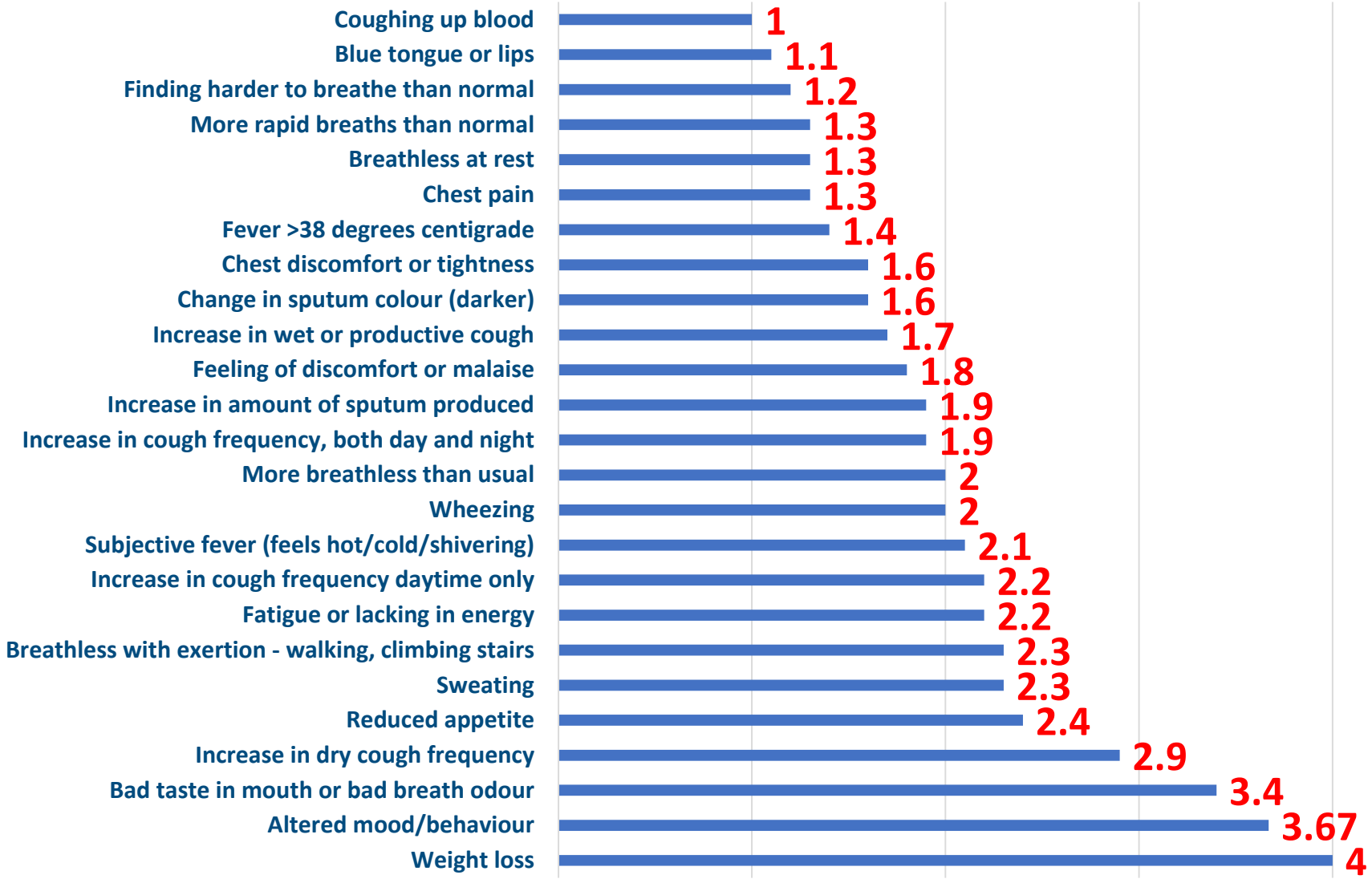
All but one item rated between 4 (Very important) and 5 (Essential).

Most important:

- ✓ Change in chest X-ray
- ✓ Advises to start antibiotics
- ✓ Breathless at rest
- ✓ Decline in lung function

Figure 3b

How long do you think these items need to be present before you would consider this is an acute exacerbation episode? *Options: 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, <7 days*



1 day:

- ✓ Coughing up blood

1 - 1.5 days:

- ✓ Blue tongue or lips
- ✓ Finding harder to breathe
- ✓ More rapid breaths
- ✓ Breathless at rest
- ✓ Chest pain
- ✓ Fever >38 degrees

All items:

Between 1 - 4 days.

Supplement file

Summary of inclusion and exclusion criteria used for the search

Exclude studies published before 2000 (as threshold for using antibiotics for treatment has changed [clinicians and parents' perspectives] and chest CT-scans became available for diagnosing bronchiectasis since 1982).

Inclusion	Exclude	Study design	Setting	Timing
Children/adolescents with BE aged 0-18 years with bronchiectasis	Non-English, adults, CF or papers before 2000	RCTs and observational	Any (hospital, out-patients, home)	Not applicable

- Subgroup summary
    - For studies on (a) treatment of exacerbation and (b) as outcome
    - Severity of exacerbation

Database search strategies (designed and undertaken by Mrs E Stovold, Cochrane Airway Group Information Specialist)

Ovid MEDLINE(R) ALL
Search date: 22 February 2021

1	exp Bronchiectasis/
2	Bronchiect$.tw.
3	bronchoect$.tw.
4	1 or 2 or 3
5	exp disease progression/
6	exacerbation$.tw.
7	5 or 6
8	4 and 7
9	Bronchiectasis/co [Complications]
10	8 or 9
11	defin$.tw.
12	criteria.tw.
13	consensus$.tw.
14	terminolog$.tw.
15	(severe or severity).tw.
16	(mild or moderate).tw.
17	or/11-16
18	10 and 17
19	limit 18 to yr="2000 -Current"

CENTRAL (*the Cochrane Library*, Issue 2 of 12, 2021)
Search date: 22 February 2021

ID	Search
#1	MeSH descriptor: [Bronchiectasis] explode all trees
#2	Bronchiect* or bronchoect*
#3	#1 or #2

#4 MeSH descriptor: [Disease Progression] explode all trees
#5 exacerbation*
#6 #4 or #5
#7 #3 and #6
#8 MeSH descriptor: [Bronchiectasis] explode all trees and with qualifier(s): [complications - CO]
#9 #7 or #8
[Limited to publication year 2000 onwards]

ClinicalTrials.gov
Search date: 22 February 2021

Search field	**Search terms**
Study type	All studies
Condition	Bronchiectasis exacerbation

Supplement Figures
Data from Delphi survey from the 299 respondents on the definition of exacerbation as an outcome for clinical trials

Statement (i): Definition of exacerbation as an outcome for clinical trials

Statement (i)-a

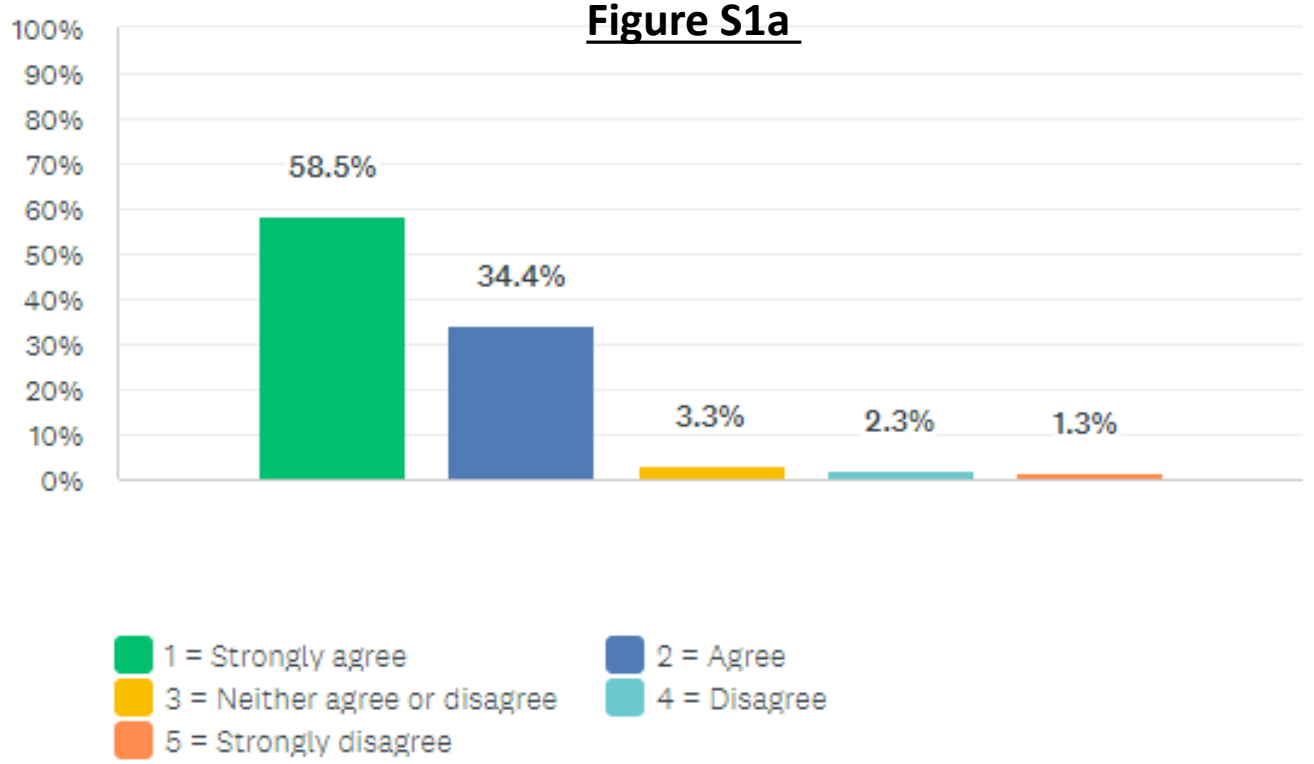
In children/adolescents with bronchiectasis, we suggest that a non-severe respiratory exacerbation is considered present when there is:

A required change in respiratory management (prescribed antibiotics for respiratory symptoms or intensification of airway clearance) AND 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 x-ray).
- Drop in FEV_1 (>10%).

NOTES:
- 1. Blood markers reflective of pulmonary exacerbation (eg .elevated C-reactive protein, neutrophils, serum amyloid-A, interleukin-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.

Figure S1a



Summary: 89% Strongly Agree/Agree

Statement (i): Definition of exacerbation as an outcome for clinical trials

Statement (i)-b

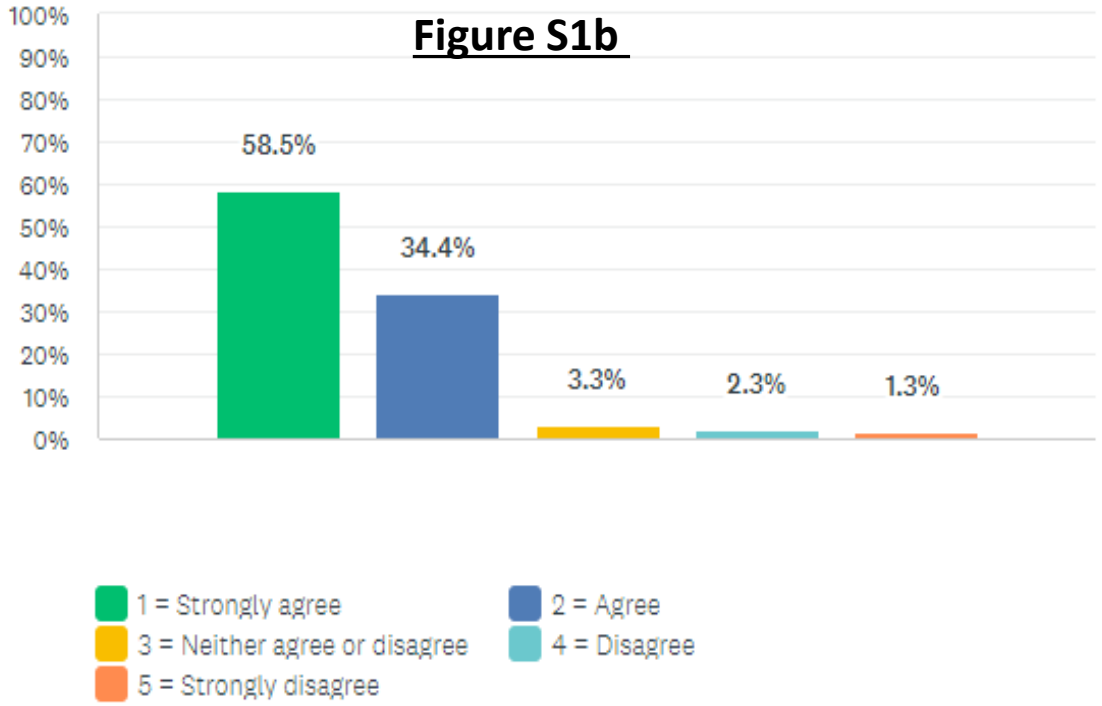
In children/adolescents with bronchiectasis, we suggest that a severe respiratory exacerbation is considered present when the criteria for a non-severe exacerbation (see question above) are met AND:

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 (RR) >50 if aged <12-months; RR >40 if aged 1-2 years; RR >30 if 3-9 years; RR >25 if 10-18 years). Onset of new or worsening dyspnoea (increased work of breathing).
- Onset of new or worsening hypoxia (SpO2 persistently <92% in room air or 4% below stable state).
- Any haemoptysis.
- Worsening chest pain.
- Failed oral antibiotic treatment.

Summary: 93% Strongly agree/Agree

Figure S1b



Statement (ii): Definition of a non-severe exacerbation that warrants treatment for clinical trials

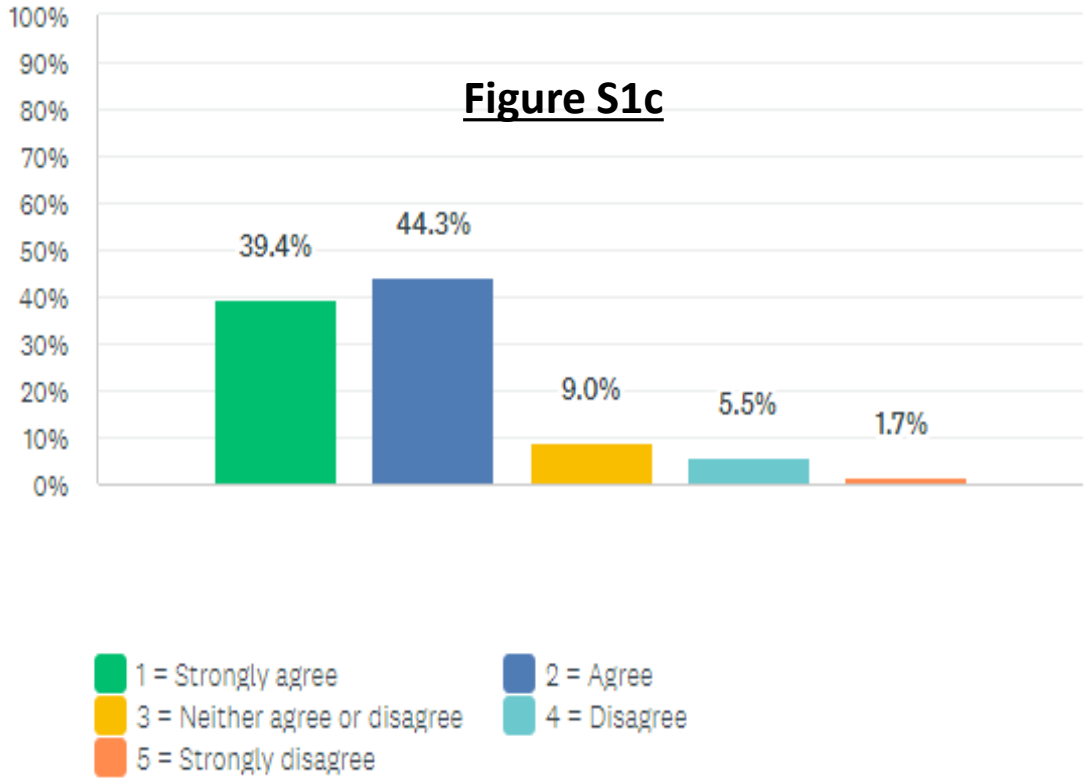
In children/adolescents with bronchiectasis, we suggest that a non-severe respiratory exacerbation is considered present when at least ONE of the following:

- 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 x-ray).Drop in FEV_1 (>10%).

NOTES:

- 1. Blood markers reflective of pulmonary exacerbation (eg .elevated C-reactive protein, neutrophils, serum amyloid-A, interleukin-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.

84% Strongly agree/Agree



Statement (iii): Definition of resolution of a non-severe exacerbation

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

82% Strongly agree/Agree

Figure S1d