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

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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


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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 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 pediatric 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 (FEV₁) 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 pediatric respiratory medicine with expertise in managing children and adolescents with bronchiectasis as well as pediatric 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
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 \(\geq 80\%\) agreed with the statements.
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 \( \geq 3 \) 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).
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 $\geq 4$) (figure 3a). In Question 2, the PAGs considered 22 of the 25 listed items needed to be present before they would consider this is an acute exacerbation episode. 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 $\geq 4$) (figure 3a). In Question 2, the PAGs considered 22 of the 25 listed items needed to be present before they would consider this is an acute exacerbation episode. Mean values are indicated in red.

### 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. 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 it harder to breathe than normal”, “More rapid breaths than normal”, “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.
<table>
<thead>
<tr>
<th>First author [ref.]/ trial name, year, country</th>
<th>Study design</th>
<th>Inclusion and exclusion criteria</th>
<th>Subjects; age; follow-up length</th>
<th>Main aim(s)</th>
<th>Definition of exacerbation</th>
<th>Type of exacerbation; duration of symptoms</th>
<th>Main study outcomes</th>
<th>Implication for question</th>
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<td><strong>Studies on treatment of exacerbation</strong></td>
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<td>GOYAL [21], 2018, Australia and New Zealand</td>
<td>Multicentre, double-dummy, double-blind RCT (BEST-2)</td>
<td>Inclusion: age &lt;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, (SPO_2&lt;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</td>
<td>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</td>
<td>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?</td>
<td>An increase in sputum volume or purulence, or change in cough (&gt;20% increase in cough score or type (dry to wet)) for ≥3 days; resolved exacerbations: when symptoms and signs are same as baseline state</td>
<td>Non-hospitalised; ≥3 days</td>
<td>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))</td>
<td>Limited to mild exacerbation and parent-reported criteria</td>
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<td>GOYAL [20], 2019, Australia and New Zealand</td>
<td>Multicentre, three-arm, double-dummy, double-blind RCT (BEST-1)</td>
<td>Inclusion: age &lt;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, ( SPO_2&lt;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</td>
<td>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</td>
<td>Determine whether AMC and AZM are superior to placebo in achieving resolution of non-severe exacerbations by day 14 of treatment</td>
<td>An increase in sputum volume or purulence, or change in cough (&gt;20% increase in cough score or type (dry to wet)) for ≥3 days; resolved exacerbations: when symptoms and signs are same as baseline state</td>
<td>Non-hospitalised; ≥3 days</td>
<td>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</td>
<td>Limited to mild exacerbation and parent-reported criteria</td>
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<td><strong>Studies where exacerbation was an outcome</strong></td>
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<td><strong>ANURADHA [29]</strong>, 2020, Sri Lanka</td>
<td>Single-centre, crossover, open-label RCT</td>
<td>Inclusion: radiographically confirmed BE; exclusion: CF, FEV1 &lt;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</td>
<td>n=63 (n=52 finished study); mean±SD age: 9.3±2.6 years; follow-up: 150 days</td>
<td>Determine efficacy of 3% saline pre-medication before airway clearance technique, 60 days trial; 30 days washout period, then crossover design</td>
<td>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”</td>
<td>Outpatient treatment; duration suggested “usually over several days”</td>
<td>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 FEV1 and FVC in both phases, favouring HS</td>
<td>No other details on exacerbation; analysis not per group, but by phase</td>
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<td><strong>BAŞARAN [31]</strong>, 2018, Turkey</td>
<td>Retrospective, single-centre</td>
<td>Inclusion: HRCT-confirmed BE</td>
<td>n=34; mean±SD age: 13.69±4.67 years</td>
<td>Describe characteristics, underlying causative factors and long-term follow-up</td>
<td>Increase in cough and sputum amount or purulence, chest pain, shortness of breath (reported by family or child), rale, wheezing, hypoxia symptoms, increased CRP levels, increased neutrophil proportion, and impairment in respiratory function test</td>
<td>Hospitalised and non-hospitalised; duration not defined</td>
<td>Annual exacerbation frequency dependent on severity of disease</td>
<td>Retrospective review</td>
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<td><strong>KAPUR [15]</strong>, 2009, Australia</td>
<td>Retrospective cohort, single-centre in specialist hospital</td>
<td>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</td>
<td>n=115 exacerbations in n=30 children; median (range) age: 5.5 (0.8–13) years</td>
<td>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</td>
<td>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) FEV1; % 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</td>
<td>Hospitalised and non-hospitalised; duration not specified</td>
<td>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</td>
<td>Wide range of symptoms and signs; spirometry data insensitive</td>
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<tr>
<td>First author [ref.]/ trial name, year, country</td>
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<td>KAPUR [16], 2012, Australia</td>
<td>Prospective cohort, single-centre in specialist hospital</td>
<td>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”</td>
<td>n=69 children with n=81 exacerbations; median (IQR) age 7 (3.8–10.9) years; follow-up: 900 child-months</td>
<td>Formulate a clinically useful definition of respiratory exacerbation for children with BE</td>
<td>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·L⁻¹, serum IL-6 ≥2 ng·L⁻¹, serum amyloid A &gt;5 mg·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</td>
<td>Hospitalised and non-hospitalised; ≥3 days</td>
<td>Interobserver κ for each factor in assessment form &gt;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</td>
<td>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</td>
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<tr>
<td>KAPUR [32], 2014, Australia</td>
<td>Prospective cohort, single-centre in specialist hospital</td>
<td>Inclusion: radiographically confirmed BE; exclusion: CF</td>
<td>n=69; mean age: 7 years; follow-up: 900 child-months</td>
<td>Determine prevalence of virus detection associated with exacerbation and evaluate clinical/investigational differences between virus-positive and virus-negative exacerbations</td>
<td>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</td>
<td>Hospitalised and non-hospitalised</td>
<td>Viruses detected in 48% of exacerbations and when present, significantly more likely to require hospitalisation</td>
<td>Parent-reported deterioration was indicator for exacerbation</td>
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<td>KIRICAOGLU [33], 2005, Turkey</td>
<td>Retrospective, single-centre</td>
<td>Inclusion: HRCT-confirmed BE and followed up for ≥2 years</td>
<td>n=111; mean±SD age: 7.4±3.7 years</td>
<td>Describe characteristics, underlying causative factors and long-term follow-up</td>
<td>Persistent (≥24 h) increase in respiratory symptoms, new chest radiography opacification or worsening in physical examination findings of the chest</td>
<td>Hospitalised and non-hospitalised; ≥1 days</td>
<td>Retrospective review</td>
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<td>KOBBERNAGEL [34], 2020, Europe</td>
<td>Multicentre</td>
<td>Inclusion: PCD, FEV₁ &gt;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</td>
<td>n=90; mean±SD age: AZM 18.6±8.9 years, placebo 19.7±10.8 years</td>
<td>Determine efficacy of 6 months of AZM on respiratory exacerbations in PCD</td>
<td>Respiratory symptoms leading to use of systemic antibiotics irrespective of bacterial culture or &gt;10% FEV₁ drop relative to screening and randomisation whether or not antibiotics prescribed</td>
<td>Hospitalised and non-hospitalised; duration not specified</td>
<td>Exacerbation rate significantly lower in AZM group (rate ratio 0.45 [95% CI 0.26–0.78]; p=0.004); FEV₁ significantly better in AZM group; no intergroup difference for QoL, LCI, hearing or static lung volumes</td>
<td>RCT includes adults and restricted to PCD; definition does not include duration of symptoms</td>
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<td>First author [ref.], trial name, year, country</td>
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<td>LOVE-TOON [13], 2019, Australia and New Zealand</td>
<td>Prospective cohort, three clinics</td>
<td>Inclusion: HRCT-confirmed BE; exclusion: CF, enrolled in another study or receiving treatment for cancer</td>
<td>n=85; median (IQR) age: 8.7 (5.4–11.3) years; follow-up: 951 child-months of observation</td>
<td>Assess health resource use and health-related QoL over a 12-month period in children with BE</td>
<td>Unwell for &gt;3 days with at least one of: increased cough, change in cough quality, increased sputum volume or purulence</td>
<td>Non-hospitalised &gt;3 days; hospitalised definition not provided</td>
<td>High health resource use; mean±SD exacerbations 3.3±2.2 per child-year; 11.4% episodes required hospitalisation</td>
<td>Limited to HIV-related BE; small sample size with likely type 1 error</td>
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<td>MASSELA [35], 2013, South Africa</td>
<td>Single-centre, double-blind RCT</td>
<td>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</td>
<td>ERY n=17, placebo n=14; mean±SD age: ERY 8.4±2.4 years, placebo 9.1±2.1 years</td>
<td>Evaluate efficacy of 52 weeks of ERY (versus placebo) at reducing respiratory exacerbations in children with HIV-related BE</td>
<td>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</td>
<td>Hospitalised and non-hospitalised; duration not specified</td>
<td>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%)</td>
<td></td>
</tr>
<tr>
<td>O’Gara [36], 2018, Australia</td>
<td>Multicentre, double-blind, placebo-controlled RCT</td>
<td>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</td>
<td>n=63 randomised; mean±SD age: 6.8±3.7 years; follow-up: 12 months</td>
<td>Evaluate efficacy of PHID-CV</td>
<td>Increase in sputum volume or purulence, or ≥3 days of change in cough (≥20% increase in cough score or type (dry to wet))</td>
<td>Non-hospitalised; ≥3 days</td>
<td>Absolute risk difference between groups =−0.5 (95% CI −2.0–0.9) exacerbations per 100 weeks at risk favouring PHID-CV</td>
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<tr>
<td>First author [ref.]/ trial name, year, country</td>
<td>Study design</td>
<td>Inclusion and exclusion criteria</td>
<td>Subjects; age; follow-up length</td>
<td>Main aim(s)</td>
<td>Definition of exacerbation</td>
<td>Type of exacerbation; duration of symptoms</td>
<td>Main study outcomes</td>
<td>Implication for question*</td>
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<tr>
<td>REDDING [37], 2014, USA and Australia</td>
<td>Prospective, multicentre</td>
<td>Inclusion: Australian Aboriginal and Alaska Native children age 0.5–8 years, with either CT-confirmed BE or CSLD (&gt;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</td>
<td>n=93 children; median (range) age: 36 (9–107) months</td>
<td>1) Characterise pattern of acute BE exacerbations, and 2) identify clinical features that increased the risk of recurrent and severe exacerbations requiring hospitalisation</td>
<td>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 FEV1 &gt;10%, or haemoptysis; clinical encounters within 2 weeks considered a single exacerbation</td>
<td>Hospitalised and non-hospitalised; duration not specified; clinical encounters within 2 weeks considered a single exacerbation</td>
<td>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</td>
<td>Limited to indigenous children</td>
</tr>
<tr>
<td>SUNTHERA [38], 2016, England</td>
<td>Specialist hospital; retrospective review from PCD database</td>
<td>Inclusion: age 6–16 years and able to perform spirometry; exclusion: incomplete spirometric assessments</td>
<td>n=30; median (range) age: 11.4 (6–16.2) years; follow-up: 3 months post-hospital discharge</td>
<td>In children with PCD treated with i.v. antibiotics for an exacerbation to: 1) determine proportion who recover baseline FEV1 within 3 months and 2) identify factors associated with failure to regain pre-exacerbation FEV1</td>
<td>“A change in respiratory status for which i.v. antibiotics were prescribed”</td>
<td>Hospitalised only; duration not specified</td>
<td>No difference between responders and non-responders in baseline characteristics (age, gender, ethnicity, BMI, baseline FEV1 &lt;40%, mean baseline or admission FEV1, persistent infection, use of prophylactic antibiotics, nebulised HS or rhDNase)</td>
<td>Hospitalised only data</td>
</tr>
<tr>
<td>VALERY [19], 2013, Australia and New Zealand</td>
<td>Multicentre, double-blind RCT</td>
<td>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</td>
<td>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</td>
<td>Establish whether 24 months of once-weekly AZM reduced pulmonary exacerbations in indigenous children with BE or CSLD</td>
<td>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 FEV1 &gt;10%, or haemoptysis; visits for a respiratory infection within 2 weeks regarded as part of the same exacerbation</td>
<td>Hospitalised and non-hospitalised; duration not specified; clinical encounters within 2 weeks considered a single exacerbation</td>
<td>Compared with placebo group, children receiving AZM had significantly lower exacerbation rates (incidence rate ratio 0.50, 95% CI 0.35–0.71; p&lt;0.0001)</td>
<td>Limited to indigenous children</td>
</tr>
<tr>
<td>First author [ref.]/ trial name, year, country</td>
<td>Study design</td>
<td>Inclusion and exclusion criteria</td>
<td>Subjects; age; follow-up length</td>
<td>Main aim(s)</td>
<td>Definition of exacerbation</td>
<td>Type of exacerbation; duration of symptoms</td>
<td>Main study outcomes</td>
<td>Implication for question?</td>
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<tr>
<td>BREATHE, 2019, Australia</td>
<td>Study protocol: multicentre, observer-blinded RCT</td>
<td>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</td>
<td>Planned n=174</td>
<td>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</td>
<td>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 FEV₁ &gt;10%, or haemoptysis</td>
<td>Not applicable</td>
<td></td>
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<tr>
<td>REPEAT, 2019, Australia</td>
<td>Study protocol: multicentre, double-dummy, placebo-controlled RCT</td>
<td>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 &gt;460 ms), history of cardiac arrhythmia, previously randomised, or hospitalised in last 4 weeks for respiratory instability</td>
<td>Planned n=104</td>
<td>Determine efficacy of AZM and/or erdosteine in reducing exacerbations in people with PCD</td>
<td>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</td>
<td>Hospitalised and non-hospitalised; ≥3 days</td>
<td>Not applicable</td>
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### TABLE 1 Continued

<table>
<thead>
<tr>
<th>First author (ref.)/ trial name, year, country</th>
<th>Study design</th>
<th>Inclusion and exclusion criteria</th>
<th>Subjects; age; follow-up length</th>
<th>Main aim(s)</th>
<th>Definition of exacerbation</th>
<th>Type of exacerbation; duration of symptoms</th>
<th>Main study outcomes</th>
<th>Implication for question*</th>
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<tr>
<td>BETTER, 2021, Australia</td>
<td>Study protocol: dual-centre, placebo-controlled RCT (BETTER)</td>
<td>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</td>
<td>Planned n=128</td>
<td>Evaluate effect of erdosteine on respiratory exacerbation rate of children with BE</td>
<td>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</td>
<td>Hospitalised and non-hospitalised; ≥3 days</td>
<td>Not applicable</td>
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**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*
| First author (ref/.) | 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
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<tbody>
<tr>
<td>LUCAS [39], 2019, multiple countries</td>
<td>Consensus, multicentre</td>
<td>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</td>
<td>Adults and children</td>
<td>Develop a consensus for defining pulmonary exacerbations in children and adults with PCD for clinical trials and other research</td>
<td>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 &gt;38°C</td>
<td>Severity not specified; duration not specified</td>
<td>Lacks time element, e.g. single episode versus days would result in different interpretation</td>
<td></td>
</tr>
<tr>
<td>SHAPIRO [40], 2016, North America</td>
<td>Consensus, multicentre North American sites and PCD Foundation</td>
<td>Literature review (PubMed and Embase), then drafts created and circulated iteratively to participating physicians and then to PCD Foundation</td>
<td>Not applicable</td>
<td>Present consensus recommendations from North American physicians from PCD research consortium</td>
<td>Acute changes in cough, sputum production, respiratory rate or work of breathing</td>
<td>Hospitalised and non-hospitalised; duration not specified</td>
<td>See document for other recommendations</td>
<td>Document specific to PCD</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; CT: computed tomography; $S_{pO2}$: peripheral oxygen saturation; CF: cystic fibrosis; *P. aeruginosa*: *Pseudomonas aeruginosa*; AMC: amoxicillin–clavulanate; AZM: azithromycin; IQR: interquartile range; FEV1: 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 *Homoilus 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?
present for \(\leq 3\) 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 \(\geq 10\) 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 2** Summary of indicators of bronchiectasis exacerbations in the included studies (n=21)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Studies, n (%)</th>
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<tbody>
<tr>
<td>Change in cough frequency or character (dry to wet)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Change in sputum colour or volume</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Breathlessness/dyspnoea</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Change in auscultatory findings</td>
<td>7 (33)</td>
</tr>
<tr>
<td>New chest radiography findings</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Decline in spirometry/lung function</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Change in respiratory rate</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Decrease in (S_{\text{PO}_2})</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Blood inflammatory indices</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Chest auscultatory crackles</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Malaise/tiredness</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Duration mentioned</td>
<td>10 (48)</td>
</tr>
</tbody>
</table>

\(S_{\text{PO}_2}\): peripheral oxygen saturation. \(^{*}\): in all but one study, duration was \(\geq 3\) days.

https://doi.org/10.1183/13993003.00300-2022
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 FEV₁ (>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

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 (SaO₂ persistently <92% in room air or 4% below stable state)
- Any haemoptysis
- Worsening chest pain

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 FEV₁ (>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

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.
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.
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.

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10 McCallum GB, Chang AB. ‘Good enough’ is ‘not enough’ when managing indigenous adults with bronchiectasis in Australia and New Zealand. Respir Med 2018; 23: 725–726.


