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Early View

Task Force Report

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Task Force report
European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis

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ABSTRACT

There is increasing awareness of bronchiectasis in children and adolescents, a chronic pulmonary disorder associated with poor quality-of-life for the child/adolescent and their parents, recurrent exacerbations and costs to the family and health systems. Optimal treatment improves clinical outcomes. Several national guidelines exist, but there are no international guidelines.

The European Respiratory Society (ERS) Task Force for the management of paediatric bronchiectasis sought to identify evidence-based management (investigation and treatment) strategies. It used the ERS standardised process that included a systematic review of the literature and application of the GRADE approach to define the quality of the evidence and level of recommendations.

A multidisciplinary team of specialists in paediatric and adult respiratory medicine, infectious disease, physiotherapy, primary care, nursing, radiology, immunology, methodology, patient advocacy and parents of children/adolescents with bronchiectasis considered the most relevant clinical questions (for both clinicians and patients) related to managing paediatric bronchiectasis. Fourteen key clinical questions (7 'Patient, Intervention, Comparison, Outcome' [PICO] and 7 narrative) were generated. The outcomes for each PICO were decided by voting by the panel and parent advisory group.

This guideline addresses the definition, diagnostic approach and antibiotic treatment of exacerbations, pathogen eradication, long-term antibiotic therapy, asthma-type therapies (inhaled corticosteroids, bronchodilators), mucoactive drugs, airway clearance, investigation of underlying causes of bronchiectasis, disease monitoring, factors to consider before surgical treatment and the reversibility and prevention of bronchiectasis in children/adolescents. Benchmarking quality of care for children/adolescents with bronchiectasis to improve clinical outcomes and evidence gaps for future research could be based on these recommendations.

SCOPE AND OBJECTIVES

This European Respiratory Society (ERS) guideline provides evidence-based recommendations for managing children and adolescents (aged ≤18-years) with bronchiectasis unrelated to cystic fibrosis (CF). We focus on key management questions. Other important issues, such as environmental exposures, and rare cases of non-tuberculous mycobacterial (NTM) pulmonary disease in children/adolescents without CF, are not addressed in this report.

The target audience are those involved in the care of children/adolescents with bronchiectasis, including specialists in respiratory medicine, infectious diseases, paediatricians, thoracic surgeons, primary care physicians, pharmacists, respiratory physiotherapists, nurses, regulatory authorities, pharmaceutical companies and policy makers. The guideline also aims to inform adolescents and parents of children/adolescents with bronchiectasis, which will assist discussions with healthcare teams and help facilitate access to appropriate care. However, as bronchiectasis is a complex disease with many causes, this guideline does not substitute for sound clinical judgement and requires appropriate adaptations to local circumstances (e.g., where tuberculosis prevalence is high). All recommendations should be interpreted according to the child/adolescent's circumstances, patients' perceptions, values and preferences, and the clinical setting.

INTRODUCTION

Bronchiectasis, a chronic pulmonary disorder, is an umbrella term for a clinical syndrome of recurrent or persistent wet/productive cough, airway infection and inflammation, and abnormal bronchial dilatation on chest computed-tomography (CT) scans, which if detected early may be reversible over time with effective treatment [1,2].

Bronchiectasis is no longer considered rare [1,3,4], but is one of the most neglected lung disorders [5], with high individual disease burden [6], economic cost [7] and poor quality-of-life (QoL) in children/adolescents [8] and their parents [9]. Also, there are large disparities in the standards of care and outcomes between bronchiectasis and other chronic lung diseases [10], including those with bronchiectasis from the same country [11].

Multiple risk and/or aetiological factors may lead to bronchiectasis in children/adolescents [1,12]. Its prevalence shows geographical variation, but shares common features of chronic cough and recurrent exacerbations with lower airway infection/inflammation, which persist if left untreated. Interrupting the infection/inflammation cycle as early as possible with effective treatment is necessary to reverse and/or halt disease progression and further lung injury [1,13]. Indeed, bronchiectasis may be preventable in some children and thus their evaluation for possible treatable underlying causes is important [1,12].

The pathophysiology of bronchiectasis is complex and poorly understood with varying aetiologies and modifying factors [12]. These factors are likely dependent on the sampling frame studied (e.g. different aetiologies in different countries/settings). Nevertheless, the infection/inflammation paradigm, which is likely applicable to all aetiologies, involves airway infection causing inflammation, impaired muco-ciliary clearance and airway destruction, which in turns predisposes the damaged airway to further infection [12].

Exacerbations or 'attacks' are particularly important in children/adolescents with bronchiectasis as they are associated with increased respiratory symptoms, impaired QoL [6], accelerated lung function decline (-1.9 forced expiratory volume in 1-second percent (FEV_1%) predicted per hospitalised exacerbation) [14] and high healthcare resource use [15] and costs (~€20,400 per hospitalisation in 2016) [7]. Importantly, patients and parents responding to the European Lung Foundation (ELF) survey, rated exacerbations among the top three factors affecting their child's QoL. Thus, impact on exacerbations is a dominant outcome measure when assessing efficacy of interventions [16,17].

Bronchiectasis in children/adolescents and adults have some similarities (e.g. wet/productive cough being the dominant symptom along with recurrent exacerbations), but there are also substantial differences. Children/adolescents require developmentally appropriate care, support and supervision from their parents. Mild radiographic bronchiectasis (bronchial dilatation) is reversible if treated optimally early, thereby avoiding the later deterioration in lung function [1]. In contrast, adults with untreated bronchiectasis symptoms from childhood have worse disease and poorer prognosis (c.f. adult-onset bronchiectasis) [18]. Australian data indicate that >60% of adults with bronchiectasis have symptoms from childhood [18]. Thus, early diagnosis is important as is disease characterisation (e.g. defining exacerbations) and providing evidence-based management.

Furthermore, children/adolescents with bronchiectasis have different lower airway microbial profiles (bacterial pathogens [19] and microbial communities [20]), age-related immunological responses [21] and likely treatment outcomes [1]. Some diagnostic [1] and treatment methods also differ; e.g. airway clearance techniques (ACT), which are age- and cognition-dependent [22]. Moreover, aetiology and co-morbidities can vary substantially between adults and children/adolescents [12].

Thus, the recent ERS [23] and British Thoracic Society [24] bronchiectasis guidelines were for adults only. The present guideline addresses this gap of an up-to-date international evidence-based guideline for managing children/adolescents with bronchiectasis unrelated to CF. It includes those with primary ciliary dyskinesia [PCD], where older ERS guidelines exist, but required updating [25,26]. The objectives of managing children/adolescents with bronchiectasis are to; (a) optimise lung growth, (b) preserve lung function, (c) optimise QoL, (d) minimise exacerbations, (e) prevent complications and (f) if possible, reverse structural lung injury.

METHODS

This guideline, developed by an ERS Bronchiectasis Task Force (TF), included specialists in paediatric respiratory medicine with expertise in managing children/adolescents with bronchiectasis as well as paediatric experts in infectious disease, allergy-immunology, radiology, physiotherapy and nursing, two global leaders in adult bronchiectasis, the Cochrane Airways Group coordinating editor (also a general practitioner), ELF representative, bronchiectasis parent/patient advisory group (PAG) members and ERS methodologists. The ELF representative and two PAG representatives were full members of the TF and contributed to all recommendations. Conflict of interest were declared at commencement of this project and prior to final submission and managed in accordance

with ERS policies. The specific expertise of the panel is outlined in the Supplement-Methods file.

Between November 2018 and June 2020, the panel met ten times (nine video-conferences and one face-to-face meeting) and a smaller methodology sub-group met a further 11 times on-line. The most relevant clinical questions on managing bronchiectasis in children/adolescents (for both clinicians and patients/parents) were discussed and agreed by the panel and PAG (Figure-1). Following ERS processes [27], we formulated seven questions using the 'Patient, Intervention, Comparison, Outcome' (PICO) format and seven narrative questions (NQ). The panel and the entire PAG voted on the outcomes of interest for each PICO a-priori, based on their relative importance to children/adolescents with bronchiectasis and to clinical decision making. Following the GRADE approach [28], these outcomes were deemed as 'critical', 'important' or 'not important for clinical decision making' (the latter were then excluded from data extraction and further analysis), as listed in the evidence table for each PICO (see also Supplement-methods). Systematic reviews (SR) were conducted to answer these questions. For NQs, systematic searches were conducted and evidence was reviewed in a narrative manner.

Systematic reviews

The Cochrane Airways Group information specialist designed and ran the search (Supplement-search strategy) for all questions. The initial searches undertaken in May 2019 were updated in April 2020. Results of the search were sent to panel member pairs and RF or AC. Searches were independently screened by at least two people using inclusion and exclusion criteria determined by the TF (Supplement-methods). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was generated for each question (Supplement-figures). For selected PICOs, we undertook additional searches to seek supportive evidence from the literature, including the CF literature (described in (Supplement-methods) for a narrative review of supportive evidence when the panel considered it was important to undertake this additional task. Articles were summarised using the ERS framework for guideline development, including both systematic (for PICO questions) and pragmatic/narrative (for NQs) reviews of the evidence [27].

Assessing the level of evidence and degree of recommendations

Evidence summary tables and evidence to decision (EtD) frameworks were generated for each PICO, whilst only EtDs were generated for NQs (Supplement-EtDs). For NQs, in accordance with the updated ERS methodologies [27], the approach is narrative; that for the evidence was a partial narrative approach (i.e. we did not undertake meta-analysis, but did include numbers). These were used by the panel to formulate recommendations and strength by consensus and/or voting. In accordance with ERS requirements [27], we used GRADE [29] to assess the confidence in the evidence (quality) and strength of the recommendations. The recommendations are graded as strong or conditional with key considerations summarised in Table-1. In line with GRADE [29], the terms "we recommend" are used for strong recommendations and "we suggest" for conditional ones. Opinions of patients/parents of children/adolescents were captured from: (a) two parents participating in discussions on every recommendation and, (b) the ELF survey undertaken in 2019-2020 on the priorities and needs of parents whose children/adolescents have bronchiectasis or adults with bronchiectasis as a child/adolescent.

RESULTS

PICO/NQ's PRISMA diagrams (Supplementary-figures) depict the number of studies identified and selected for each question. The EtDs for all questions (complete version in Supplement-EtDs) are summarised below and grouped into clinically relevant topics (diagnosis, evaluating causes, defining exacerbations, management, monitoring and, reversibility and prevention).

DIAGNOSIS

In children/adolescents suspected of bronchiectasis: (a) Should multidetector chest computed tomography (MDCT) scans with high-resolution CT (HRCT) be used instead of conventional HRCT alone for diagnosing bronchiectasis? (b) What CT criteria for broncho-arterial dilatation (BAR) should be used? (PICO1)

Recommendations

- In children/adolescents suspected of bronchiectasis, we suggest that high-resolution MDCT-scans with HRCT is used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents *(Conditional recommendation, very low-quality of evidence).*
- In children/adolescents suspected of bronchiectasis, we suggest that paediatric derived BAR (defined by the ratio of the inner diameter of the airway to the outer diameter of the adjacent artery) >0.8 is used to define abnormality instead of the adult cut-off of >1-1.5 *(Conditional recommendation, very low-quality of evidence stemming from narrative review of the evidence).*

Summary of evidence

No direct evidence in children/adolescents was available. Two non-blinded observational studies in adults [30,31] reported MDCT-scans (contiguous helical scan with 1 mm collimation) were superior at detecting and determining the extent of bronchiectasis, compared to conventional HRCT (1 mm collimation at 10-20 mm intervals [30]). Using high-resolution MDCT as the gold standard, the sensitivity of conventional HRCT for diagnosing the number of patients with bronchiectasis was 96% (95% confidence interval [CI] 90-98%) and specificity was 69% (95%CI 54-81%). That for detecting the number of lobes with bronchiectasis was 89% (95%CI 84-92) and 81% (95%CI 78-84%) respectively (GRADE table in Supplement-EtD).

BAR correlates with age in adults without cardio-respiratory problems [32]. Our narrative summary of evidence includes two studies in children/adolescents [33,34] without lower airway disease. Both [33,34] found the mean BAR is significantly lower in children/adolescents (mean=0.63 [standard deviation; SD=0.07] in children/adolescents versus 0.70 [SD=0.1] in adults) and the mean + 2xSD=0.77 (the upper limit of normal, rounded up to 0.80) [33].

Other supportive evidence

The narrative evidence depicts the impact of diagnosing bronchiectasis, particularly when diagnosed early. Treatment in children/adolescents post-radiographic diagnosis of bronchiectasis can stabilise, or even improve, lung function in heterogenous patient cohorts

[14,35,36], including those with immunodeficiency [37]. One study [38] reported early diagnosis of bronchiectasis was important for improving QoL.

Justification of recommendation

This recommendation places a relatively higher value on more accurate and early detection of bronchiectasis and its importance on subsequent management and a relatively lower value on evidence directness and quality. It is widely accepted that HRCT is the radiographic gold standard for confirming bronchiectasis. Many types of CT-scanners are currently available and will continue to improve with greater precision and less radiation for patients. Adult-derived data (evidence table in Supplement-EtD) showed MDCT detects more cases of bronchiectasis than conventional HRCT. However, no paediatric data exist currently. The narrative summary provided circumstantial evidence that diagnosing bronchiectasis changes management and optimal management stabilises or improves lung function, reduces exacerbations and improves QoL.

The early diagnosis of bronchiectasis was one of the top priorities articulated by parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child. As BAR correlates with age [32] and increases as bronchiectasis becomes more severe (from cylindrical to varicose to cystic [1]), we suggest clinicians use a lower threshold in children/adolescents (BAR >0.80) to define abnormality when suspecting bronchiectasis.

Implementation considerations

CT-scans need to be performed promptly to diagnose bronchiectasis early and there is a need to develop strategies to improve (i) availability and access to high-quality scanners that reduce radiation exposure and (ii) interpretation of paediatric chest CT-scans. Using the suggested paediatric-defined threshold of 0.8 may result in more radiographic-based diagnoses of bronchiectasis in children with chronic wet cough, and reduce problems of drug reimbursement in some countries. However, as there are false positives with diagnosing bronchiectasis based purely on BAR, the panel advocated that BAR alone should not be used to diagnose bronchiectasis i.e. it is best based on the presence of clinical features consistent with this diagnosis and confirmed radiographically.

EVALUATING THE CAUSE

In children/adolescents with suspected or confirmed bronchiectasis, what standard tests that impact on clinical outcomes should be undertaken when managing this group of patients? (NQ1)

Recommendations

- In children/adolescents with suspected or confirmed bronchiectasis, we suggest they have a minimum panel of tests undertaken, as done currently by most experts in the field *(Conditional recommendation, very low-quality of evidence stemming from narrative review of the evidence*).
  The minimum panel of tests are: (i) chest CT-scan (to diagnose bronchiectasis), (ii) sweat test, (iii) lung function tests (in children/adolescents who can perform spirometry), (iv) full blood count, (v) immunological tests (total IgG, IgA, IgM, IgE, specific antibodies to vaccine antigens) and (vi) lower airway bacteriology.

- In selected children/adolescents with bronchiectasis, we suggest additional tests are considered based on their clinical presentation. These include additional in-depth immunological assessments (in consultation with a paediatric immunologist), diagnostic bronchoscopy with bronchoalveolar lavage (BAL) analysis (microbiology), tests for airway aspiration, PCD and gastro-oesophageal reflux disease (GORD). *(Conditional recommendation, low-quality of evidence stemming from narrative review of the evidence).*

Remarks: In settings where tuberculosis or human immunodeficiency virus (HIV) have a high prevalence and/or there is a history of close contact with tuberculosis, assessment for tuberculosis infection/disease or HIV respectively is also undertaken as part of the minimum panel of tests.

Summary of evidence

We identified 21 studies; all were observational studies. Of these studies 18 were retrospective and 3 prospective (Supplement-EtD). Two [39,40] of the three prospective studies [39,40,41] reported diagnostic yields for some tests. Nevertheless, several investigations were undertaken consistently (minimum panel above) by experts in the field. From these tests, the aetiology of bronchiectasis varied (34-86%). In the two studies that reported specifically on diagnostic yields; immunology evaluation provided a diagnosis in 42% [42] and bronchoscopy with BAL gave useful information in 12-41% [40,42].

Justification of recommendation

A conditional recommendation was selected based on the large desirable effect and likely trivial undesirable effects of setting a standard set of investigations as well as the risk and harm of not managing common or critical conditions related to bronchiectasis in children/adolescents. Finding causes of bronchiectasis was one of the research priorities identified by the PAG and the ELF survey. Lung function and respiratory cultures are part of minimum assessment. Although they do not identify the cause, these tests help assess severity and guide antibiotic choices, thus optimising treatment.

Implementation considerations

Identifying the aetiology has management implications (e.g. specific treatment for immunodeficiency, genetic causes for future family planning, etc). Health services should increase accessibility to centres practising standard of care management for children/adolescents with bronchiectasis that includes undertaking the recommended minimum panel of tests.

DEFINING EXACERBATIONS

In children/adolescents with bronchiectasis, what criteria should be used to define an exacerbation? (NQ6)

Recommendations

For clinical purposes:

- In children/adolescents with bronchiectasis, we suggest that a respiratory exacerbation is considered present when a child/adolescent has increased

respiratory symptoms (predominantly increased cough +/- increased sputum quantity and/or purulence) for ≥3-days. (*Conditional recommendation, low-quality of evidence stemming from narrative review of the evidence*).

Remarks: Other important, but less common respiratory symptoms 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 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 C-reactive protein, neutrophilia and interleukin-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.

- In children/adolescents with bronchiectasis, we recommend that the presence of dyspnoea (increased work of breathing) and/or hypoxia should be considered a severe exacerbation, irrespective of duration. (*Strong recommendation, low-quality of evidence stemming from narrative review of the evidence).*

Summary of evidence

We identified 13 paediatric papers and one adult-based consensus document [16]. Of the paediatric-focused papers, two were defined within the published protocols [43,44] (with the corresponding randomised-controlled trials [RCTs] published [45,46]) using antibiotics at the onset of an exacerbation and three were published RCTs [17,47,48] where exacerbations were outcomes. Two cohort (one prospective [49], one retrospective [50]) studies specifically evaluated exacerbation definitions. Four papers were related solely to PCD (retrospective review [51], one protocol [52] that was published after the latest search [53] and two consensus-derived descriptions [54,55] for children/adolescents and adults with PCD, which differed substantially from one another).

While there are some similarities, overall, the definitions used in these studies varied widely (eg. defining exacerbations for initiating antibiotics can be different to when it is used as an outcome measure for RCTs).

Other supportive evidence

The adult-derived consensus definition for research (i.e. not for clinical use) was framed around a deterioration in 3 or more symptoms (cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis) for ≥48-hours. The definition also required 'a change in treatment' [16].

Justification of recommendation

The recommendation was based upon several prospective studies and evidence that parents' value recognising and treating respiratory exacerbations early. We considered that at least 3-days of increased symptoms is required for the definition, except when immunodeficiency or hypoxia/dyspnoea are present. For those with immunodeficiency, a lower threshold is suggested (as commencing treatment earlier may be required). No

timeframe is required for those with hypoxia/dyspnoea as immediate treatment is mandated as there is a risk of acute deterioration and death.

Implementation considerations

Managing exacerbations is a key component of bronchiectasis care and one of the three top issues for parents. Thus, it is important to increase patient, parent/carer and health professional education in recognising exacerbations and commencing additional treatments.

Also, children/adolescents with neurodevelopmental conditions may have subtle and/or individually recognised symptoms of an exacerbation, whereby earlier treatment may be necessary.

MANAGEMENT

Airway clearance

In children/adolescents with bronchiectasis, should regular airway clearance techniques (ACT) (compared to no ACT) be undertaken? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states. (PICO4)

Recommendation

- In children/adolescents with bronchiectasis, we recommend they are taught and receive regular ACT or manoeuvres (*Strong recommendation, very low-quality of evidence).*

Remarks: Individualised ACT that is development- and age-appropriate is best taught by a paediatric-trained chest physiotherapist (see Figure-2). The frequency of ACT is best individualised. As children/adolescents mature, techniques may need to be changed and thus, the ACT type and frequency is best reviewed at least biannually by physiotherapists with expertise in paediatric respiratory care During acute exacerbations of bronchiectasis, children/adolescents should receive ACT more frequently.

Summary of evidence

We identified one small (n=24) RCT in children/adolescents [56] and two RCTs [57,58] in adults (Supplement-EtD). The paediatric study [56] that compared 1-month hospital-supervised, personalised ACT with unsupervised therapy at home (we equated this to controls without effective treatment) described a better median FEV_1%predicted in the intervention group (86.3%) versus controls (68.8%) at 1-month and 1-year (86.0% versus 69.3%). All three RCTs showed consistent improvement in lung function. For other critical outcomes, data were lacking in children/adolescents. Data from the adult-based RCTs [57,58] (GRADE evidence tables, Supplement-EtD) showed consistent results with improved QoL indices and sputum volume with ACT (versus no ACT), but no significant difference in the number of exacerbations (despite favouring ACT).

Additional evidence from adults (included here as mentioned in the methods) The benefits of ACT are supported by recent SRs [23,24,59,60,61] of studies in adults (no available meta-analyses of data), but with very low to low-level evidence. One SR of acute exacerbations found six adult-based studies involving 120 people, but none included a ‘no-treatment’

group [61]. The authors reported ACT during acute exacerbations resulted in no adverse events, improved sputum clearance and a non-statistically significant improvement in lung function and symptoms [61].

Other supportive evidence

Three recent CF-related SRs [62,63,64] provided data supporting ACT, and one study [65] described significant declines in lung function (FEV_1 and forced vital capacity (FVC) %predicted) without 3-weeks of ACT and improved lung function following its recommencement.

Justification of recommendation

Although the evidence for ACT improving clinical outcomes is very low, a strong recommendation was selected based on moderate desirable and trivial, but time-consuming undesirable effects for undertaking ACT and the risk of harm if ACT is not undertaken. Where data exist, results are consistent and favour ACT compared with controls. Also, the panel and PAG described ACT as a key intervention and one that is universally advocated for children/adolescents with bronchiectasis.

As there are many ACT techniques, and the developmental stage and cognitive abilities vary widely between children/adolescents (0-18 years), individualised therapy taught, and reviewed at least biannually, by paediatric-trained chest physiotherapists (Figure-2) is recommended. Exacerbations increase airway secretions and enhancing their clearance would be beneficial.

Implementation considerations

Individualised ACT that are development- and age-appropriate are best taught by paediatric-trained chest physiotherapists (Figure-2). Access to paediatric-trained physiotherapists was raised by the PAG. Adherence to the prescribed regime, especially over prolonged periods is challenging. Also, the frequency and best ACT method(s) remain uncertain. Adjustment to the type of ACT during exacerbations may be necessary (eg. exercises may not be feasible).

Mucoactive agents

In children/adolescents with bronchiectasis, should mucoactive agents (compared to no mucoactive agents) be used routinely? Subgroup analyses for (a) short versus long-term, (b) stable versus exacerbation states, and (c) type of mucoactive agent. (PICO3)

Recommendations

- In children/adolescents with bronchiectasis, we recommend that recombinant-human DNAse is not used routinely *(Strong recommendation, very low-quality of evidence)*.

- In children/adolescents with bronchiectasis, we suggest that bromhexine is not used routinely*(Conditional recommendation, very low-quality of evidence).*

- In children/adolescents with bronchiectasis, we suggest that neither inhaled mannitol nor hypertonic saline are used routinely. *(Conditional recommendation, very low-quality of evidence)*.

Remarks: Inhaled mannitol or 6-7% hypertonic saline (HS) may be considered in selected patients e.g. those with high daily symptoms, frequent exacerbations, difficulty in expectoration and/or poor quality of life (QoL). If well tolerated, the use of HS or mannitol could improve the QoL and facilitate expectoration. For HS and mannitol, children should be old enough to tolerate these interventions and the panel also considered that SABAs should be used prior to inhaling either HS or mannitol. The first dose of HS or mannitol should be administered under medical supervision. The substantially higher cost of mannitol compared with HS should also be taken into consideration.

Summary of evidence

We identified only adult-based RCTs involving rhDNAse (n=2 [66,67]), HS (n=3 [68,69,70]), mannitol (n=2 [71,72]) and bromhexine (n=1 [73]). Quality of evidence was very low to low, depending on the intervention

Regular rhDNAse for 24-weeks (c.f. placebo) significantly increased exacerbation rates (relative risk [RR] =1.35, 95%CI 1.01-1.79), worsened FEV_1 and FVC [66]. Data from the smaller and shorter RCT [67] were consistent, but could not be combined with the larger study (see supplement-EtD). rhDNase was also associated with increased hospitalisation and adverse events. Studies using mannitol failed to meet their primary end point, but mannitol significantly improved some QoL sub-domains, prolonged time-to-next exacerbation and sputum volume. The effect of HS was like mannitol, however data from RCTs could not be combined. Although the small study on bromhexine favoured its use for sputum volume and FEV_1, there were more adverse events (Odds ratio [OR] =2.93, 95%CI 0.12-73.97). (see GRADE evidence tables, Supplement-EtD).

Justification of recommendation

The panel considered that the overall weight of the literature, combined with biological plausibility, would lead most clinicians to be very concerned about using recombinant human DNAse (rhDNAse) due to the potential adverse effects. Although the quality of evidence for rhDNAse is very low, there is risk of substantial harm (increased risk of exacerbations and faster lung function decline). The panel also considered that the overall weight of the literature would lead most clinicians to be very concerned about using bromhexine due to the potential adverse effects. Thus, the balance of the evidence favours not using rhDNAse and bromhexine routinely based on patient/parents' values, the substantial adverse effects described above and the lack of efficacy of these treatments.

The balance probably favours administering HS and mannitol in some patients. For example, in adults, mannitol (c.f. controls) was beneficial (significantly fewer exacerbations, prolonged time-to-next exacerbation and symptomatic improvement) in the subgroup with a high symptom burden [74].

Implementation considerations

Health professionals should be warned of the potential harmful effects of rhDNAse. For HS and mannitol, children should be old enough to tolerate these interventions with pre-inhalation of short-acting beta2-agonists (SABA). Education on using these medications and equipment care are also needed.

Use of antibiotics

In children/adolescents with bronchiectasis, should systemic courses of antibiotics (compared to no antibiotics) be used to treat an acute respiratory exacerbation (type and duration)? (PICO5)

Recommendation

- In children/adolescents with bronchiectais and an acute respiratory exacerbation, we recommend a systemic course of an appropriate antibiotic is used for 14-days. *(Strong recommendation, moderate-quality of evidence).*

Remarks: The empiric antibiotic of choice is amoxicillin-clavulanate, but type of antibiotics chosen should be based on the patient's airway cultures (e.g. those with *Pseudomonas aeruginosa* require different treatment regimens to those without) and history of antibiotic hypersensitivity reactions. When the exacerbation is severe (e.g. child/adolescent is hypoxic) and/or when the child/adolescent does not respond to oral antibiotics, intravenous antibiotics will be needed.

Summary of evidence

The evidence summary shows a single high-quality RCT supporting antibiotics for treating exacerbations. In that trial [45], amoxicillin-clavulanate was superior to placebo at resolving symptoms after 14-days treatment. Azithromycin was associated with improvement, but did not reach statistical significance of superiority over placebo. Amoxicillin-clavulanate also significantly reduced exacerbation duration, while this was similar between azithromycin and placebo amongst those whose symptoms resolved by day-14 [45]. No between-group differences were detected for time-to-next exacerbation, QoL or hospitalisations, although hospitalisation was uncommon in all groups [45]. The optimal duration of treatment with antibiotics is yet to be studied.

Other supportive evidence

Although no comparable placebo-controlled RCTs in adults exist, recommendations in adult guidelines [23,24] are similar. Also, antibiotic treatment for acute exacerbations of bronchiectasis are considered standard of care.

Justification of recommendation

Our strong recommendation is based on a single high-quality RCT in children/adolescents and extensive clinical experience. Exacerbation resolution and duration both showed a benefit from the intervention. Importantly, the trial did not detect an increase in adverse events in the antibiotic treatment groups compared to placebo, although such events were uncommon.

An earlier RCT, which did not meet the inclusion criteria [46] comparing amoxicillin-clavulanate to azithromycin for treating non-severe exacerbations found that by day-21 azithromycin was non-inferior to amoxicillin-clavulanate (within 20% margin). However, symptom resolution in those receiving azithromycin took a median 4-days longer than those receiving amoxicillin-clavulanate, a statistical and clinically significant result [46].

Implementation considerations

Patients should have access to appropriate antibiotics for the recommended duration of treatment.

In children/adolescents with bronchiectasis and recurrent exacerbations, should long-term (≥2-months) antibiotics (compared to no antibiotics) be used to reduce exacerbations? (PICO7)

Recommendation

- In children/adolescents and adolescents with bronchiectasis and recurrent exacerbations, we recommend treatment with long-term macrolide antibiotics to reduce exacerbations *(Strong recommendation, low-quality of evidence).*

Remarks: Based on the panel's experience, we suggest long-term macrolide antibiotics only in those who have had >1 hospitalised or ≥3 non-hospitalised exacerbations in the previous 12-months. Such a course should be for at least 6-months with regular reassessment to determine whether the antibiotic continues to provide a clinical benefit.

Children/adolescents receiving longer treatment courses (>24-months) should continue to be evaluated for risk versus benefit. This suggestion is in the context of lacking data concerning when long-term azithromycin should be initiated and the need for caution because of increasing antibiotic resistance amongst bacterial pathogens within patients and the community. While non-tuberculous mycobacteria (NTM) are very rarely detected in children/adolescents with bronchiectasis, we suggest a lower airway specimen is obtained (when possible) to exclude their presence before commencing long-term macrolide antibiotics. We encourage strategies to ensure adherence to the macrolide regimen as ≥70% adherence improves efficacy and reduces antibiotic resistance.

Summary of evidence

There were three RCTs [17,47,48] and the combined data showed that macrolides reduced the number of children/adolescents experiencing any exacerbations during the trial period (RR=0.86, 95%CI 0.75-0.99). Of these RCTs, one involved only children/adolescents with HIV [48] and it was a small study that found no effect. The largest of the RCTs described that using long-term azithromycin halves the frequency of exacerbations (incidence rate ratio [IRR]=0.5, 95%CI 0.35-0.70 and also likely reduces hospitalisation (p=0.06) [17].

There was no significant difference in serious adverse events when azithromycin was used compared to placebo. Indeed, serious adverse events were numerically lower in the azithromycin group (RR=0.57, 95%CI 0.31-1.05). However, there were significant increases in

macrolide-resistant bacteria in the upper airways (nasopharyngeal swabs) in those receiving long-term azithromycin compared to placebo.

Other supportive evidence

Although the single high-quality study was undertaken in Indigenous children/adolescents, the efficacy of macrolides at reducing exacerbations is consistent. Meta-analysis examining the efficacy of macrolides in adults with bronchiectasis show similar effects (RR of being exacerbation-free when taking azithromycin c.f. placebo was 1.66, 95%CI 1.37–2.02 in adults [75]). Studies in adults were substantially shorter in duration (6-12 months versus up to 24-months in the main paediatric RCT [17]). A recent RCT on azithromycin in adults with primary immunodeficiency and previous respiratory exacerbations (85% had bronchiectasis) also showed similar results (c.f. placebo, hazard ratio [HR] for exacerbation=0.5 [95%CI 0.3-0 9, p=0.03]; for hospitalisation HR=0.5 [95%CI 0.2-1.1, p=0.04]); additional antibiotic required rate/patient-year=2.3 [95%CI 2.1-3.4] in the azithromycin group versus placebo=3.6 [95%CI 2.9-4.3; p=0.004]) [76]. Following our final search date, a study involving children/adolescents and adults with PCD found 6-months of azithromycin (versus placebo) significantly reduced exacerbation rates (rate ratio=0.45, 95%CI 0.26-0.78) [53], a similar effect-size to this PICO's main contributing RCT [17].

Justification of recommendation

Although the overall quality of evidence was low, our strong recommendation is from the large effect on exacerbations, the panel's clinical experience, consistency of effect with adult-based RCTs and preventing exacerbations being one of the key issues for the PAG. The importance and impact of exacerbations on children and families were crucial considerations for the strong recommendation. Also, there was relatively minimal possible harms of the intervention. Indeed, the sole study in the evidence table with low risk of bias for all factors [17], reported (post-hoc analyses) antibiotic use for non-pulmonary infections was significantly lower in the azithromycin group (versus placebo); IRR=0.50; 95% CI 0.31–0.81, p=0.005.

Implementation considerations

While an electrocardiogram is not necessary before commencing macrolides, a family history of prolonged QT syndrome, arrhythmias and acute cardiac events should be obtained and, when appropriate, an electrocardiogram ordered. Also, azithromycin should not be used in children/adolescents with contraindications to macrolides. This includes those with an abnormal electrocardiogram, liver function abnormality and azithromycin hypersensitivity.

Adherence ≥70% is important for efficacy [17] as well as reducing antibiotic resistance [77]. Adherence ≥70 % (versus <70 %) in the Australian azithromycin group was associated with lower carriage of any pathogen [OR -0.19, 95 %CI 0.07-0.53] and fewer macrolide-resistant pathogens (OR 0.34, 95 % CI 0.14-0.81) [77].

In children/adolescents with bronchiectasis, should eradication treatment be used (irrespective of symptoms) when there is a new isolate of a potentially pathogenic microorganism (compared to no eradication treatment)? (PICO6)

Recommendation

- In children/adolescents with bronchiectasis, we suggest eradication therapy following an initial or new detection of *Pseudomonas aeruginosa* (*Conditional recommendation for the intervention, very low-quality evidence*).

Remarks: Evidence in bronchiectasis is indirect and limited to three small observational studies in adults focussed on *P. aeruginosa* eradication. However, we suggest that eradication therapy should commence promptly after confirming *P. aeruginosa* is present (Figure 3). Due to lack of evidence, we are unable to comment on eradication treatment for pathogens other than *P. aeruginosa*, which is informed on a case by case basis according to the clinical status of the child and the pathogen type. Antibiotic treatment should be made available in every setting where children/adolescents with bronchiectasis are managed.

Summary of evidence

There were no published studies in children/adolescents. Evidence was from three before-and-after trials in adults [78,79,80] who underwent eradication for *P. aeruginosa*. These indicate patients may experience improved QoL (compared to pre-eradication) and reduced exacerbation rates and hospitalisation. One study reported the mean number of antibiotic courses was 3.93 in the year before and 2.09 in the year post-eradication (p=0.002) [79]. Another study reported significant reductions in exacerbations, antibiotic use and hospitalisations (mean total exacerbations were 3.4 (SD 4.21) in the year before and 1.98 (SD3.62) in the year during eradication using inhaled colistin (p<0.001). Corresponding values for hospitalisation and cycles of antibiotics were 1.94 (SD 2.8) and 1.18 (SD 1.73) (p=0.018) respectively [80]. The earlier study reported a non-significant reduction in the mean number of hospitalisations (0.39 pre-eradication, 0.29 post-eradication) [79]. However, before-and-after studies are subject to bias, including Hawthorne effects and regression to the mean.

In one study 11/28 patients who received eradication therapy were without *P. aeruginosa* at 15-months [78] and in another, 13/24 patients were also without this pathogen at a median 14.3-months [79]. The most recent study [80] reported that 8/35 (22.9%) patients who received 2-weeks of intravenous antibiotics and another 5/50 (10%) 3-weeks of oral anti-pseudomonal treatment had eradicated *P. aeruginosa*. The 41/67 (61.2%) who were then treated further with inhaled colistin were free of *P. aeruginosa* 3-months later and 40.3% at 12-months.

Other supportive evidence

Limited supportive data from a recent CF-related SR [81] found eradicating *P. aeruginosa* with nebulised antibiotics either alone or combined with oral antibiotics, compared to placebo or no treatment, can eradicate the organism for up to 2-years [81]. However, the impact on

clinical outcomes is uncertain. A second CF review [82] on recent detection of methicillin-resistant *Staphylococcus aureus* in the lower airways reported short-term (28-days) eradication rates are better in those receiving targeted antibiotic treatment, but the effects are not sustained and clinical benefits uncertain.

SRs involving adults with bronchiectasis and chronic *P. aeruginosa* infection reported on eradication using inhaled antibiotics compared to placebo (OR=3.36, 95%CI 1.63-6.91, p=0.001) with significant reduction in exacerbation frequency (rate ratio=0.81, 95%CI 0.67-0.97, p=0.020) and proportion of patients with ≥1 exacerbation (OR=0.85, 95%CI 0.74-0.97, p=0.015) [83]. These data were consistent with another SR by different authors that focused on other treatment aspects [84].

Justification of recommendation

There is an established association between lower airway infection with pathogenic microorganisms and deteriorating clinical status and lung function in both the bronchiectasis [85] and CF [86,87] literature. While there is currently no evidence for early eradication from well-conducted trials in children/adolescents with bronchiectasis, the panel suggests eradication treatment for *P. aeruginosa.* This recommendation places a higher value on the theoretical benefits of eradication and patient/carer values and preferences, and a lower value on possible treatment-related adverse effects.

Implementation considerations

Eradication therapy should employ a targeted antibiotic strategy for the minimum time necessary and measures should be instituted to support full adherence to the prescribed regimen. Like the adult ERS guideline [23], without clear evidence for one regimen over another, Figure-3 illustrates commonly used approaches in children/adolescents by experts in the field.

Asthma-based medications

In children/adolescents with bronchiectasis, should asthma-type treatments (inhaled corticosteroids [ICS], short-acting beta$_2$-agonists [SABA], long-acting beta$_2$-agonists [LABA]), compared to no asthma-type treatment, be used routinely? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states. (PICO2)

Recommendation

- In children/adolescents with bronchiectasis, we suggest not using ICS with or without LABAs routinely in either the short or long-term, irrespective of stability or exacerbation. *(Conditional recommendation, very low-quality of evidence).*

Remarks: ICS maybe beneficial in those with eosinophilic airway inflammation. In the absence of any studies on the use with SABAs in bronchiectasis, we cannot make any recommendation, but suggest an objective evaluation is undertaken if such asthma-type medications are considered. For some, SABAs may be beneficial as pre-airway clearance therapies.

Summary of evidence

The evidence is based on 5 RCTs in adults (but not all contributed to all outcomes) and a single observational study in children/adolescents. The latter related to withdrawing ICS and had a high risk of bias and the reported outcome measures were of doubtful clinical significance (FEV_1 and PC_{20} changes were small) [88]. Overall, there is a lack of direct evidence for the use of ICS alone and in combination with LABA in children/adolescents with bronchiectasis. The studies are all very low-quality with only five RCTs in adults identified from SRs [89,90]. Four of the RCTs involved ICS versus placebo [91,92,93,94], whilst one examined ICS/LABA compared to ICS [95]. Where critical outcomes were obtained from these RCTs, the effect size for benefit is small and non-significant between groups.

For exacerbations, there was no difference between those who received vs those who did not receive ICS [(Studies ≤6 months: average number of participants-mean difference=-0.17 (95%CI 00.56, 0.22; number of participants with at least one exacerbation-OR=0.27, 95%CI 0.02, 3.09, hospitalization-OR=0.2, 95%CI 0.02, 1.90); (Studies >6 months: number participants with improved frequency exacerbation-OR=1.61, 96%CI 0.68, 3.81)]. Please see GRADE evidence table (Supplement-EtD) for other outcomes.

RCT data in adults with bronchiectasis show increased adverse events when ICS are used and the risk increases with higher ICS doses. Also, there is observational study evidence of increased risk of NTM infection and pneumonia in adults with bronchiectasis and other chronic respiratory diseases who received ICS [96,97].

Other supportive evidence

The panel considered that there is good evidence from the non-bronchiectasis literature that ICS can lead to adrenal suppression [98] and growth failure [99,100,101], as well as other adverse effects [97]. As there is no reason to suppose this would be different in bronchiectasis, these medications should not be used routinely unless there is objective evidence of benefit. Further, in adults with bronchiectasis, those commencing ICS had poorer outcomes than those starting macrolides (higher risk of hospitalised respiratory infection [HR=1.39, 95%CI 1.23–1.57] and exacerbations [HR=1.56, 95% 1.49–1.64]) [102].

Justification of recommendation

The evidence (albeit very low-quality) shows a lack of efficacy for these medications. The panel considered the overall weight of the literature, examining the efficacy and safety of ICS in adults and in other conditions. This, combined with biological plausibility and the absence of any reason to suppose the effects are any different in children/adolescents, would lead most clinicians to be very concerned about potential adverse events from ICS, alone and in combination with LABA. Data on important adverse events is supported by systematic reviews in other chronic respiratory diseases. These potential serious adverse events (increased risk of NTM infection, pneumonia and tuberculosis) with strong biological plausibility for causation, suggest against routine use of ICS with or without LABAs in either the short or long-term. Also, there is supportive evidence of other possible harm as outlined above.

The fiscal cost associated with ICS prescription globally is substantial. Hence, prescribing ICS/LABA needs positive justification, which cannot be found in the current literature.

Implementation considerations

As bronchiectasis and eosinophilic asthma symptoms overlap, we recommend that if treatment with ICS or ICS/LABA is contemplated, every effort should be made to document acute bronchodilator sensitivity (acute spirometric response to SABA), atopy (skin prick tests, specific IgE) and airway eosinophilia (peripheral blood eosinophil count, sputum eosinophils, exhaled nitric oxide). It should be noted that the sensitivity and specificity of all these tests vary across the globe, but if there is no evidence of atopy or airway eosinophilia in a given patient, ICS and ICS/LABA are unlikely to have a role. If a blind trial of ICS or ICS/LABA is contemplated, because the above tests are equivocal or unavailable, objective evidence of benefit should be obtained if the medications are continued.

There is a subgroup however with asthma-type responses where using SABA pre-ACT may prove useful.

Surgery

In children/adolescents with bronchiectasis, what factors should be taken into account when considering surgical removal of the diseased lung? (NQ7)

Usual practice statement: It is important to emphasise that surgery is rarely undertaken in the panel's experience, although we are aware that it is not uncommon in some settings. Surgery is only considered after maximal medical therapies (e.g. ACT, long-term antibiotics, etc.) have failed and the child/adolescent's QoL remains significantly impaired. When contemplated, a multidisciplinary approach is essential, and the decision should be based on the individual's clinical state and local surgical expertise.

Recommendation

- In children/adolescents with bronchiectasis, we recommend when considering surgery, factors to be taken into account include age, symptoms and disease burden, localisation of the bronchiectatic areas on chest CT-scans, the underlying aetiology (influencing recurrence of disease), facility where surgery is undertaken (surgical expertise and availability of pre- and post-surgical care), and optimisation of the child's clinical state. (*Strong recommendation, very low-quality of evidence stemming from the narrative review*).

Remarks: The benefits from surgery are higher in those with localised disease where complete resection can be done and when the disease is not recurrent (i.e. absence of underlying aetiology such as immunodeficiency). Careful preoperative evaluation as well as rehabilitation post-surgery improves outcome. Ideally, bronchoscopy and BAL are performed prior to surgery to exclude a foreign body and obtain microbiological samples. A ventilation-perfusion scan to delineate non-ventilated areas confirming the localised disease to plan for the surgery is likely beneficial. Optimisation of the child/adolescent's clinical state, including using appropriately targeted antibiotics, ACT and improving nutritional status pre and post-surgery is also necessary.

Summary of evidence

The narrative summary only identified observational studies. There was a single prospective [103] study and the rest (n=43) were retrospective. One meta-analysis [104] included the results of five paediatric studies. Also, 18/42 (43%) studies were undertaken by surgical groups from one country; thus raising the possibility of selection and reporting bias. The limited evidence suggests better results if surgery is undertaken in specialised centres after a series of tests (VQ-scan, bronchoscopy, chest CT-scans) and optimising the patient's lung function pre-surgery). Factors to be considered include the underlying aetiology (influencing recurrence of disease), location and extent of disease (lobes affected).

Other supportive evidence

Surgery for bronchiectasis is now undertaken rarely in high-income countries, but is not uncommon in low-middle income countries. Members of the panel rarely advocate surgery to control bronchiectasis.

Justification of recommendation

Although evidence for assessing factors favouring lung surgery for children/adolescents with bronchiectasis is very low, the data from the studies are consistent and inform the current standard of care in specialist settings. Also, the panel and PAG expressed the view that standardised clinical care is very important when surgery is being considered, allowing risks versus benefits to be balanced.

Implementation considerations

Increasing accessibility to a multidisciplinary team with expertise in optimal preoperative evaluation and careful patient selection is recommended. Video-assisted thoracoscopic surgery, compared to open thoracotomy, is associated with fewer complications and shorter postoperative hospital stay.

Systematic care

In children/adolescents with bronchiectasis, should attention be paid to other paediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc)? (NQ3)

Recommendations

- In children/adolescents with bronchiectasis, we suggest that nutrition is optimised, including Vitamin D status (*Conditional recommendation, very low-quality of evidence stemming from the narrative review)*.

Remarks: There is no evidence upon which to recommend additional nutritional supplements.

- In children/adolescents with bronchiectasis we suggest that exercise is encouraged on an ongoing basis; short periods of exercise training are unlikely to have a long-term effect (*Conditional recommendation, very low-quality of evidence stemming from the narrative review).*

***Remarks**:* There is insufficient evidence to make a recommendation for establishing formal exercise and rehabilitation programmes.

- In children/adolescents with bronchiectasis, we suggest they are fully immunised according to their national immunisation programmes, including pneumococcal and annual seasonal influenza vaccines if these are not part of this programme. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review).*

- In children/adolescents with bronchiectasis, we suggest they receive psychological support and education on equipment use and care (*Conditional recommendation, very low-quality of evidence stemming from the narrative review).*

Summary of evidence

The evidence is overall of very low-quality. The 14 included studies were: nine reviews, two RCTs [105,106] in adults, one RCT in children/adolescents [107] and two observational studies [108,109].

The desirable effects of routine immunisation, exercise and good nutrition are undeniable, but their magnitude is uncertain. Additional vaccinations for children/adolescents with bronchiectasis is likely beneficial, but the quality of the evidence is very low [107,110]. The positive effects of psychological support and teaching appropriate equipment use and care for children/adolescents with chronic illness are also likely highly desirable, but there are no data on type, duration or intensity of support or how to assist with maintaining equipment. The data relevant for vitamin D were limited to adult-based studies [111].

Exercise training for short periods is unlikely to have prolonged effects, and the implication is that exercise support must be ongoing. There is low-quality evidence supporting fewer pulmonary exacerbations and longer time-to-first exacerbation with exercise training. There are no agreed formal pulmonary rehabilitation programmes in children/adolescents, and there are no data on what exercise interventions are most important. Whether a formal exercise programme is superior to encouragement of an active lifestyle is unclear.

Justification of recommendation

Recommendations are based upon placing a higher value on low-moderate quality of evidence for clinical improvement over a low value for concerns over uncertainty of magnitude and duration of benefit. The need for good nutrition, immunisation and exercise in childhood would be widely supported.

Implementation considerations

Increase the accessibility of children/adolescents to centres practising standard of care in low-middle income countries settings.

How should cross-infection be minimised? (NQ4c)

Recommendation

- In children/adolescents with bronchiectasis, we suggest that they and their family are counselled on cough and hand hygiene. Wherever possible, they should also avoid those with symptoms of viral respiratory infections. Children/adolescents managed within a CF clinic must follow their infection control policies (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).

Addendum: The guideline was written pre-COVID-19, but in view of this, children/adolescents with bronchiectasis should follow measures recommended by local health authorities.

MONITORING

How frequently should patients be seen in outpatient clinics? (NQ4b)

Recommendation

- In children/adolescents with bronchiectasis, we suggest they are reviewed every 3-6 months in outpatient clinics to monitor their general wellbeing, respiratory status, including lung function when age appropriate, and to detect any complications. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review).*

How often should airway microbiology testing be conducted in outpatients? (NQ4a)

Recommendation

- In children/adolescents with bronchiectasis, we suggest in those able to expectorate that routine spontaneous or induced sputum samples is collected every 6-12 months as a means of identifying new pathogens, specifically *P. aeruginosa,* and to help guide initial empiric antibiotic therapy for future exacerbations. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review)*.

Summary of evidence (for NQ4a-c)

The data presented in the supplement-EtD support outpatient clinic reviews every 3-6 months and standard infection control policies without segregating patients. However, for each of the three parts of the NQ, there are no RCTs and evidence is based predominantly on observational studies in both children/adolescents [14,35,51,112,113,114,115]. The desirable frequency of outpatient clinic attendance and airway microbiology surveillance is dependent upon patient factors (e.g. age, underlying aetiology, illness severity, co-morbidities and ability to reliably expectorate spontaneous or induced sputum) and circumstances (e.g. traveling long distances for clinic attendance). Outpatient sputum culture surveillance every 6-12 months is based on expert opinion [24].

Limited evidence prevents robust recommendations on infection control policies for patients with bronchiectasis. If managed within a CF centre, local CF infection control policies should be followed and direct contact with CF patients avoided. Standard infection control

procedures should be discussed with patients/families and hand and cough hygiene measures followed. Influenza and other recommended vaccines by national authorities are also endorsed.

Post-writing the guidelines, the onset of the COVID-19 pandemic led local health authorities to introduce additional non-pharmacologic public health measures to interrupt virus transmission.

Other supportive evidence

The panel's collective clinical experience supports the approach outlined in the research evidence and the pre-COVID-19 pragmatic recommendations of the EMBARC statement on infection control [116].

Justification of recommendation

Although the quality of evidence for the above interventions leading to improving clinical outcomes is very low, the suggestions above were based upon indirect evidence that current standard of care in specialist settings leads to improved lung function post-diagnosis. Also, the panel and PAG advocated for regular clinical care and monitoring by specialists, and for advice on avoiding cross-infection.

Implementation considerations

Increased accessibility of children/adolescents to centres practising standards of care. It is also important to educate clinicians, families and patients on the role of surveillance sputum cultures in those with clinically stable bronchiectasis. As upper airway swabs are unreliable at predicting lower airway pathogens, spontaneous or induced sputum samples in children/adolescents able to expectorate are recommended for surveillance cultures. BAL is reserved for treatment failures, especially if sputum cultures are negative, and/or unusual pathogens are suspected.

Are there any routine tests that should be undertaken to detect complications when attending outpatient clinics? (NQ5d)

Recommendation

- In children/adolescents with bronchiectasis, we suggest the following routine tests are undertaken to detect complications when attending outpatient clinics: (a) lung function (spirometry for FEV_1 and FVC) when age-appropriate, (b) sputum when they can expectorate and (c) pulse oximetry (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).

In gradually deteriorating (i.e. non-acute) patients, what investigations should be undertaken? (NQ5f)

Recommendation

- In children/adolescents with bronchiectasis whose clinical status is gradually deteriorating, we suggest they are assessed for new infections (sputum or lower

airway microbiology) and possible co-morbidities (e.g. asthma, GORD, nutritional deficiencies, dental or sleep disorders) (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).

Remarks: These children/adolescents often require hospitalisation for intravenous antibiotics and airway clearance therapy.

When should repeat chest CT-scans be undertaken? (NQ5e)

Recommendation

- In children/adolescents with bronchiectasis, we suggest the decision to repeat chest CT-scans is individualised based on the clinical status and setting (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).

Remarks: Repeat chest CT-scans should be considered to answer a question which will change management.

Summary of evidence (for NQ5d-f)

The evidence provided in the narrative summary found only indirect evidence for using routine tests to detect complications of bronchiectasis, investigations required for gradually deteriorating patients and whether chest CT-scans should be repeated. Our search did not identify any RCTs that address these questions. The current evidence is based on 11 observational studies (10 retrospective and one prospective cross-sectional study [41]) and it is highly unlikely that any RCT will be undertaken.

The desirable interventions are patient (e.g. age [young children require general anaesthesia for chest CT-scans], illness severity, costs of tests) and circumstance (e.g. underlying disease, patients travelling long distances) specific. Thus, desirable effects vary.

Specialists in respiratory clinics at tertiary paediatric hospitals currently use a model of care that, although not fully described, includes standardised care assessing stability and detecting deterioration based on clinical history and investigations. In these settings, studies report this model leads to improved lung function post-diagnosis of bronchiectasis [2,14,35]. The monitoring component of the standardised care includes 3-6 monthly clinical reviews with

- Spirometry to assess FEV_1 and FVC
- Assessment for new infection (sputum for bacteria culture during exacerbations and 6-monthly as routine) and assessing (and when indicated investigating) for new co-morbidities (e.g. asthma GORD, nutritional deficiencies, dental or sleep disorders).

Tertiary paediatric respiratory clinics monitor clinical symptoms, frequency and severity of respiratory exacerbations, and lung function indices. When deterioration occurs, the narrative evidence [2,14,35,117,118] supports assessing and investigating for the treatable traits listed above.

Evidence from the narrative summary found several studies repeating chest CT-scans in children/adolescents with bronchiectasis [41,118,119,120,121,122]. However, the reasons

given for repeating scans were largely based on clinical grounds. Indications include documenting reversal of bronchiectasis (e.g. for medical insurance or reducing care burden for parents) or when there is an acute or gradual deterioration (e.g. to assess for new treatable disease or justify more intensive treatments).

Other supportive evidence

Other supportive data include reducing exacerbations by following standards of care [123]. The panel's collective clinical experience supports the approach outlined in Supplement-EtD for NQ5.

Justification of recommendation

Although the evidence for the above interventions improving clinical outcomes is very low, the suggestions above were based upon indirect evidence that the current standard of care in specialist settings leads to improved lung function post-diagnosis. Also, the panel and PAG advocated for standardised clinical care, especially in primary care settings.

Implementation considerations

Increase accessibility of children/adolescents to centres practising the recommended standard of care. Obtaining additional CT-scans needs to be balanced against the reported increased lifetime cancer risk, which is age and dose-dependent. Although relatively negligible at the individual level and lower with newer CT protocols, children previously have been estimated to have 10-times increased life-time cancer risk following CT-scans compared to middle-aged adults undergoing this investigation [124]. Currently, specialists in tertiary paediatric respiratory clinics individualise the need to repeat the chest CT-scans.

REVERSIBILITY and PREVENTION

In children/adolescents, is bronchiectasis (a) reversible and/or (b) preventable? (NQ2)

In some children/adolescents, their bronchiectasis is reversible and/or preventable. Factors important for reversibility and/or prevention of bronchiectasis include early identification and treatment of inhaled foreign bodies, preventing early and severe pneumonia, preventing recurrent protracted bacterial bronchitis (PBB), treating primary immunodeficiency disorders causing bronchiectasis, promoting breastfeeding and immunisation, and avoiding tobacco smoke and other pollutants.

Good practice statement

- In children/adolescents with bronchiectasis, we suggest wherever possible, interventions that reverse and/or prevent bronchiectasis are undertaken. However, these measures are context and patient specific.

Summary of evidence

While the evidence is very low, all six studies showed with appropriate management early bronchiectasis in some children/adolescents is reversible and thus preventable [2,37,118,125,126,127]. The resolution or improvement rates after appropriate treatment in children/adolescents with radiographically-confirmed bronchiectasis may be as great as 64% [2]. However, the proportion of resolution or improvement likely varies with bronchiectasis

severity, underlying aetiology, treatment provided and how bronchiectasis was defined (the diagnostic criteria used).

Identifying and removing aspirated foreign bodies from the airways, especially within 14-days prevents bronchiectasis developing [128]. When treatment is delayed >30-days, bronchiectasis occurred in 60% of children with retained foreign bodies [129]. Treating primary immunodeficiency is warranted, irrespective of whether bronchiectasis is present.

A single-blind RCT showed community clinic-based primary care review of young children in New Zealand post-hospitalisation for pneumonia/bronchiolitis did not prevent future bronchiectasis (found in 3.7% of the cohort) [130]; thus, interventions other than clinical review are required. There is only indirect observational evidence on other potential risk factors for developing bronchiectasis in children/adolescents, which includes strategies targeting household crowding, prematurity and frequent, early onset and severe acute lower respiratory tract infections (especially hospitalised pneumonia) [131,132]. Preventing recurrent PBB, non-typeable *H. influenzae* lower airway infection and increasing breastfeeding may also prevent future bronchiectasis [131,133]. However, the evidence is low and effect size is uncertain.

Justification of recommendation

The evidence for preventing and/or reversing bronchiectasis in children/adolescents is very low to low. We called this a best practice statement, as not seeking to prevent or revers a disease (if possible) would be unethical.

Implementation considerations

Access and strategies to improve early diagnosis and interventions to prevent and/or reverse bronchiectasis are required.

CONCLUSIONS

The recommendations from the TF on the management of children and adolescents with bronchiectasis are summarised in Tables 2 and 3. The guidelines aim to assist health professionals with optimising postnatal lung growth, preserving lung function, enhancing QoL, minimising exacerbations, preventing complications and, if possible when diagnosed early, reversing bronchial wall dilatation as a marker of structural lung injury. In so doing, we also seek to balance benefits and risks associated with each of the recommended treatment approaches. As knowledge gaps and identified research priorities are addressed, the guideline will need ongoing development in the years ahead.

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FIGURE LEGENDS

Figure 1

Schematic overview of methodology used to develop the questions and outcomes used for this guideline.

Figure 2

There are many different airway clearance techniques. In children/adolescents, these are age-specific and best taught by physiotherapists experienced in managing children/adolescents with bronchiectasis.

Figure 3

Suggested management approach used by the panel when *Pseudomonas aeruginosa* is first or newly isolated in a child with bronchiectasis. The suggested approach depends upon (a) the specimen type and (b) whether the child is symptomatic. However, panel members acknowledged the approach to initiating eradication treatment is controversial. Some physicians may still feel it is appropriate to initiate eradication therapy based only on a single upper airway specimen, even when symptoms and evidence of benefit in such circumstances are absent.

* If no lower airway specimen available, no treatment if asymptomatic; treat with intravenous anti-pseudomonal antibiotics for 2-weeks if symptomatic.
† Although there is no trial evidence, many paediatricians use a combination of two intravenous antibiotics. The recommendation for administering two antibiotics when employing short (2-week) IV antibiotic courses is made to align with the studies included in the systematic review and the ERS adult guidelines [23].
‡ Antibiotics choices are dependent upon patient factors (e.g. adherence, tolerance and preference), availability of antibiotics and *P. aeruginosa* susceptibility profile.

TABLE 1: GRADE-based recommendations used in this document, based on GRADE [29] and used in accordance with the European Respiratory Society (ERS) methods [27]

Target group	Strong recommendations*	Conditional (weak) recommendations
Patients/carers and their parents	All or almost all informed people would follow the recommended advice for or against an intervention. They would request the recommended intervention if it is not offered	Most informed people would choose the recommended course of action, but many would not
Clinician	Most carers/patients should follow the recommended advice for or against an intervention	Recognise that different choices will be appropriate for different carers/patients in different circumstances. Clinicians and other healthcare providers must be cognisant of the need to devote more time for shared decision making by which the carers/patients ensure that the informed choice reflects individual values and preferences
Policy makers	The recommendation can be adopted as a policy in most situations	Policy making will require substantial debate and involvement of many stakeholders

Recommendations are graded as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation [134]. Strong recommendations are worded as “we recommend”, while conditional recommendations are worded as “we suggest”.

*While strong recommendations are generally based on high or moderate-quality evidence, applicable to most patients for whom these recommendations are made, they may not apply to all patients in all settings. No recommendations can address all of the unique features of individual patients and clinical circumstances.

TABLE 2: Summary of PICO questions and recommendations

PICO	Title	Recommendations
1	In children/adolescents suspected of bronchiectasis: (a) Should multidetector chest computed tomography (MDCT) scans with high-resolution CT (HRCT) be used instead of conventional HRCT alone for diagnosing bronchiectasis? (b) What CT criteria for broncho-arterial dilatation (BAR) should be used?	• In children/adolescents suspected of bronchiectasis, we suggest that high-resolution MDCT scans is used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents suspected of having bronchiectasis (*Conditional recommendation, very low-quality of evidence*). • In children/adolescents suspected of bronchiectasis, we suggest that paediatric derived BAR (defined by the ratio of the inner diameter of airway to the outer diameter of adjacent artery) of >0.8 is used to define abnormality in children/adolescents instead of the adult cut-off of >1-1.5 (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).
2	In children/adolescents with bronchiectasis, should asthma-type treatments (inhaled corticosteroids [ICS], short-acting beta2-agonists [SABA], long-acting beta2-agonists [LABA]), compared to no asthma-type treatment, be used routinely? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states.	• In children/adolescents with bronchiectasis, we suggest not using ICS with or without LABAs routinely in either the short or longterm, irrespective of stability or exacerbation. *(Conditional recommendation, very low-quality of evidence).* **Remarks**: ICS maybe beneficial in those with eosinophilic airway inflammation. In the absence of any studies on the use with SABAs in bronchiectasis, we cannot make any recommendation, but suggest an objective evaluation is undertaken if such asthma-type medications are considered. For some, SABAs may be beneficial as pre-airway clearance therapies.
3	In children/adolescents with bronchiectasis, should mucoactive agents (compared to	• In children and adolescents with bronchiectasis, we recommend that recombinant human DNAse is not used routinely*(Strong recommendation, very low-quality of evidence)*.

	no mucoactive agents) be used routinely? Subgroup analyses for (a) short versus long-term, (b) stable versus exacerbation states, and (c) type of mucoactive agent.	• In children and adolescents with bronchiectasis, we suggest that bromhexine is not used routinely*(Conditional recommendation, very low quality of evidence).* • In children and adolescents with bronchiectasis, we suggest that neither inhaled mannitol nor hypertonic saline are used routinely. *(Conditional recommendation, very low-quality of evidence)*. **Remarks**: Inhaled mannitol or 6-7% hypertonic saline (HS) may be considered in selected patients e.g. those with high daily symptoms, frequent exacerbations, difficulty in expectoration and/or poor quality of life (QoL). If well tolerated, the use of HS or mannitol could improve the QoL and facilitate expectoration. For HS and mannitol, children should be old enough to tolerate these interventions and the panel also considered that SABAs should be used prior to inhaling either HS or mannitol. The first dose of HS or mannitol should be administered under medical supervision. The substantially higher cost of mannitol compared with HS should also be taken into consideration.
4	In children/adolescents with bronchiectasis, should regular airway clearance techniques (ACT) (compared to no ACT) be undertaken? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states.	• In children/adolescents with bronchiectasis, we recommend that they are taught and receive regular ACT or manoeuvres (*Strong recommendation, low-quality of evidence*). **Remarks**: Individualised ACT that is development- and age-appropriate is best taught by a paediatric-trained chest physiotherapist (see Figure-2). The frequency of ACT is best individualised. As children/adolescents mature, techniques may need to be changed and thus, the ACT type and frequency is best reviewed at least biannually by physiotherapists with expertise in paediatric respiratory care. During acute exacerbations of bronchiectasis, children/adolescents should receive ACT more frequently.

5	In children/adolescents with bronchiectasis, should systemic courses of antibiotics (compared to no antibiotics) be used to treat an acute respiratory exacerbation?	• In children/adolescents with bronchiectais and an acute respiratory exacerbation, we recommend a systemic course of an appropriate antibiotic is used for 14-days. (*Strong recommendation, moderate-quality of evidence*) **Remarks**: The empiric antibiotic of choice is amoxicillin-clavulanate, but type of antibiotics chosen should be based on the patient's airway cultures (e.g. those with *Pseudomonas aeruginosa* require different treatment regimens to those without) and history of antibiotic hypersensitivity reactions. When the exacerbation is severe (e.g. child/adolescent is hypoxic) and/or when the child/adolescent does not respond to oral antibiotics, intravenous antibiotics will be needed.
6	In children/adolescents with bronchiectasis, should eradication treatment be used (irrespective of symptoms) when there is a new isolate of a potentially pathogenic microorganism (compared to no eradication treatment)?	• In children/adolescents with bronchiectasis, we suggest eradication therapy following an initial or new detection of *Pseudomonas aeruginosa* (*Conditional recommendation for the intervention, very low-quality evidence*). **Remarks**: Evidence in bronchiectasis is indirect and limited to three small observational studies in adults focussed on *P. aeruginos*a eradication. However, we suggest that eradication therapy should commence promptly after confirming *P. aeruginos*a is present (Figure 3). Due to lack of evidence, we are unable to comment on eradication treatment for pathogens other than *P. aeruginosa*, which is informed on a case by case basis according to the clinical status of the child and the pathogen type. Antibiotic treatment should be made available in every setting where children/adolescents with bronchiectasis are managed.
7	In children/adolescents with bronchiectasis and recurrent exacerbations, should long-term	• In children/adolescents with bronchiectasis and recurrent exacerbations, we recommend treatment with long-term macrolide antibiotictics to reduce exacerbations (*Strong recommendation, low-quality of evidence*).

	(≥2-months) macrolide antibiotics (compared to no antibiotics) be used to reduce exacerbations?	**Remarks**: We suggest long-term macrolide antibiotics only in those who have had >1 hospitalised or ≥3 non-hospitalised exacerbations in the previous 12-months. Such a course should be for at least 6-months with regular reassessment to determine whether the antibiotic continues to provide a clinical benefit. Children/adolescents receiving longer treatment courses (>24-months) should continue to be evaluated for risk versus benefit. This suggestion is in the context of lacking data concerning when long-term azithromycin should be initiated and the need for caution because of increasing antibiotic resistance amongst bacterial pathogens within patients and the community. While non-tuberculous mycobacteria (NTM) are very rarely detected in children/adolescents with bronchiectasis, we suggest a lower airway specimen is obtained (when possible) to exclude their presence before commencing long-term macrolide antibiotics. We encourage strategies to ensure adherence to the macrolide regimen as ≥70% adherence improves efficacy and reduces antibiotic resistance.

TABLE 3: Summary of narrative questions (NQ) and recommendations

NQ	Title	Recommendations
1	In children/adolescents with suspected or confirmed bronchiectasis, what standard tests that impact on clinical outcomes should be undertaken when managing this group of patients?	• In children/adolescents with suspected or confirmed bronchiectasis, we suggest they have a minimum panel of tests undertaken, as done currently by most experts in the field (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*) 1) Chest computed tomography-scan 2) Sweat test 3) Lung function tests (in children/adolescents who can perform spirometry) 4) Full blood count 5) Immunological tests (total IgG, IgA, IgM, IgE, specific antibodies to vaccine antigens) 6) Lower airway bacteriology • In selected children/adolescents with bronchiectasis, we suggest additional tests are considered based on their clinical presentation. These include additional in-depth immunological assessments (in consultation with a paediatric immunologist), diagnostic bronchoscopy with bronchoalveolar lavage analysis (microbiology), tests for airway aspiration, primary ciliary dyskinesia and gastro-oesophageal disease (GORD). (*Conditional recommendation, low-quality of evidence stemming from the narrative review*). **Remarks**: In settings where tuberculosis or human immunodeficiency virus (HIV) have a high prevalence and/or there is a history of close contact with tuberculosis, assessment for tuberculosis infection/disease or HIV respectively is also undertaken as part of the minimum panel of tests.
2	In children/adolescents, is bronchiectasis (a) reversible and/or (b) preventable?	In some children/adolescents, their bronchiectasis is reversible and/or preventable. Factors important for reversibility and/or prevention of bronchiectasis include early identification and treatment of inhaled foreign bodies, preventing early and severe pneumonia, preventing recurrent protracted bacterial bronchitis (PBB), treating primary immunodeficiency disorders causing

		bronchiectasis, promoting breastfeeding and immunisation, and avoiding tobacco smoke and other pollutants. **Good practice statement** • In children/adolescents with bronchiectasis, we suggest wherever possible, interventions that reverse and/or prevent bronchiectasis are undertaken. However, these measures are context and patient specific.
3	In children/adolescents with bronchiectasis, should attention be paid to other paediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc)?	• In children/adolescents with bronchiectasis, we suggest that nutrition is optimised, including Vitamin D status (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). **Remarks**: There is no evidence upon which to recommend additional nutritional supplements. • In children/adolescents with bronchiectasis we suggest that exercise is encouraged on an ongoing basis; short periods of exercise training are unlikely to have a long-term effect (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). **Remarks**: There is insufficient evidence to make a recommendation for establishing formal exercise and rehabilitation programmes. • In children/adolescents with bronchiectasis, we suggest that they are fully immunised according to their national immunisation programmes, including pneumococcal and seasonal influenza vaccines if these are not part of this programme (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). • In children/adolescents with bronchiectasis, we suggest that they receive

		psychological support and education on equipment use and care (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).
4	When monitoring children/adolescents with bronchiectasis: a. How often should airway microbiology testing be conducted in outpatients? b. How frequently should patients be seen in outpatient clinics? c. How should cross-infection be minimised?	• In children/adolescents with bronchiectasis, we suggest in those able to expectorate that routine spontaneous or induced sputum samples is collected every 6-12 months as a means of identifying new pathogens, specifically *P. aeruginosa*, and to help guide initial empiric antibiotic therapy for future exacerbations. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). • In children/adolescents with bronchiectasis, we suggest they are reviewed every 3-6 months in outpatient clinics to monitor their general wellbeing, respiratory status, including lung function when age appropriate, and to detect any complications. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). • In children/adolescents with bronchiectasis, we suggest that they and their family are counselled on cough and hand hygiene. Wherever possible, they should also avoid those with symptoms of viral respiratory infections. Children/adolescents managed within a CF clinic must follow their infection control policies. (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). **Addendum**: The guideline was written pre-COVID-19, but in view of this, children/adolescents with bronchiectasis should follow measures recommended by local health authorities.
5	When monitoring children/adolescents with bronchiectasis: d. Are there any routine tests that should be undertaken to detect	• In children/adolescents with bronchiectasis, we suggest the following routine tests are undertaken to detect complications when attending outpatient clinics: (a) lung function (spirometry for FEV_1 and FVC) when age-appropriate, (b) sputum when they can expectorate and (c) pulse oximetry (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*).

	complications when attending outpatient clinics? e. When should repeat chest CT-scans be undertaken? f. In gradually deteriorating (i.e. non-acute) patients, what investigations should be undertaken?	• In children/adolescents with bronchiectasis, we suggest the decision to repeat chest CT-scans is individualised based on the clinical status and setting (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). **Remarks**: Repeat chest CT-scans should be considered to answer a question which will change management. • In children/adolescents with bronchiectasis whose clinical status is gradually deteriorating, we suggest they are assessed for new infections (sputum or lower airway microbiology) and possible co-morbidities (e.g. asthma, GORD, nutritional deficiencies, dental or sleep disorders, etc) (*Conditional recommendation, very low-quality of evidence stemming from the narrative review*). **Remarks**: These children/adolescents often require hospitalisation for intravenous antibiotics and airway clearance therapy.
6	In children/adolescents with bronchiectasis, what criteria should be used to define an exacerbation?	For clinical purposes: • In children/adolescents with bronchiectasis, we suggest that a respiratory exacerbation is considered present when a child/adolescent has increased respiratory symptoms (predominantly increased cough +/- increased sputum quantity and/or purulence) for ≥3-days. (*Conditional recommendation, low-quality of evidence stemming from the narrative review*). **Remarks**: Other important, but less common, respiratory symptoms 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 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 C-reactive protein,

		neutrophilia and interleukin-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. • In children/adolescents with bronchiectasis, we recommend that the presence of dyspnoea (increased work of breathing) and/or hypoxia is considered a severe exacerbation, irrespective of the duration (*Strong recommendation, low-quality of evidence stemming from the narrative review*).
7	In children/adolescents with bronchiectasis, what factors should be taken into account when considering surgical removal of the diseased lung?	**Usual practice statement:** It is important to emphasise that surgery is rarely undertaken in the panel's experience, although we are aware that it is not uncommon in some settings. Surgery is only considered after maximal medical therapies (e.g. ACT, long-term antibiotics, etc.) have failed and the child/adolescent's QoL remains significantly impaired. When contemplated, a multidisciplinary approach is essential, and the decision should be based on the individual's clinical state and local surgical expertise. • In children/adolescents with bronchiectasis, we recommend when considering surgery, factors to be taken into account include age, symptoms and disease burden, localisation of the bronchiectatic areas on chest CT, the underlying aetiology (influencing recurrence of disease), facility where surgery is undertaken (surgical expertise and availability of pre and post-surgical care), and optimisation of the child's clinical state. (*Strong recommendation, very low-quality of evidence stemming from the narrative review*). **Remarks**: The benefits from surgery are higher in those with localised disease where complete resection can be done and when the disease is not recurrent (i.e. absence of underlying aetiology such as immunodeficiency) Careful preoperative workup as well as rehabilitation post-surgery improves outcome.

		Ideally, bronchoscopy and BAL are performed prior to surgery to exclude a foreign body and obtain microbiological samples. A ventilation-perfusion scan to delineate non-ventilated areas confirming the localised disease to plan for the surgery is likely beneficial. Optimisation of the child/adolescent's clinical state, including using appropriately targeted antibiotics, ACT and improving nutritional status pre and post-surgery is also necessary.

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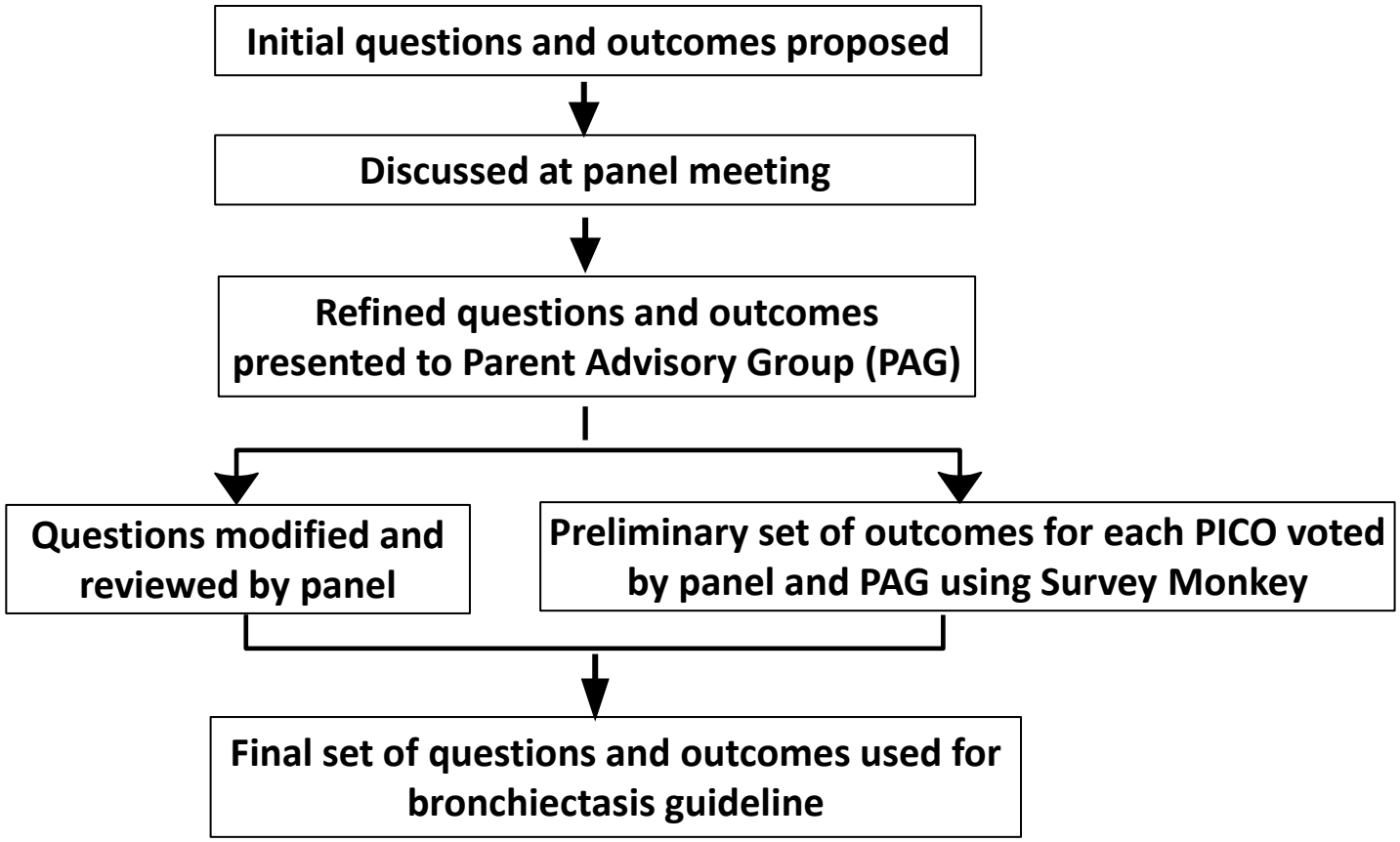


Figure 1

Schematic overview of methodology used to develop the questions and outcomes used for this guideline

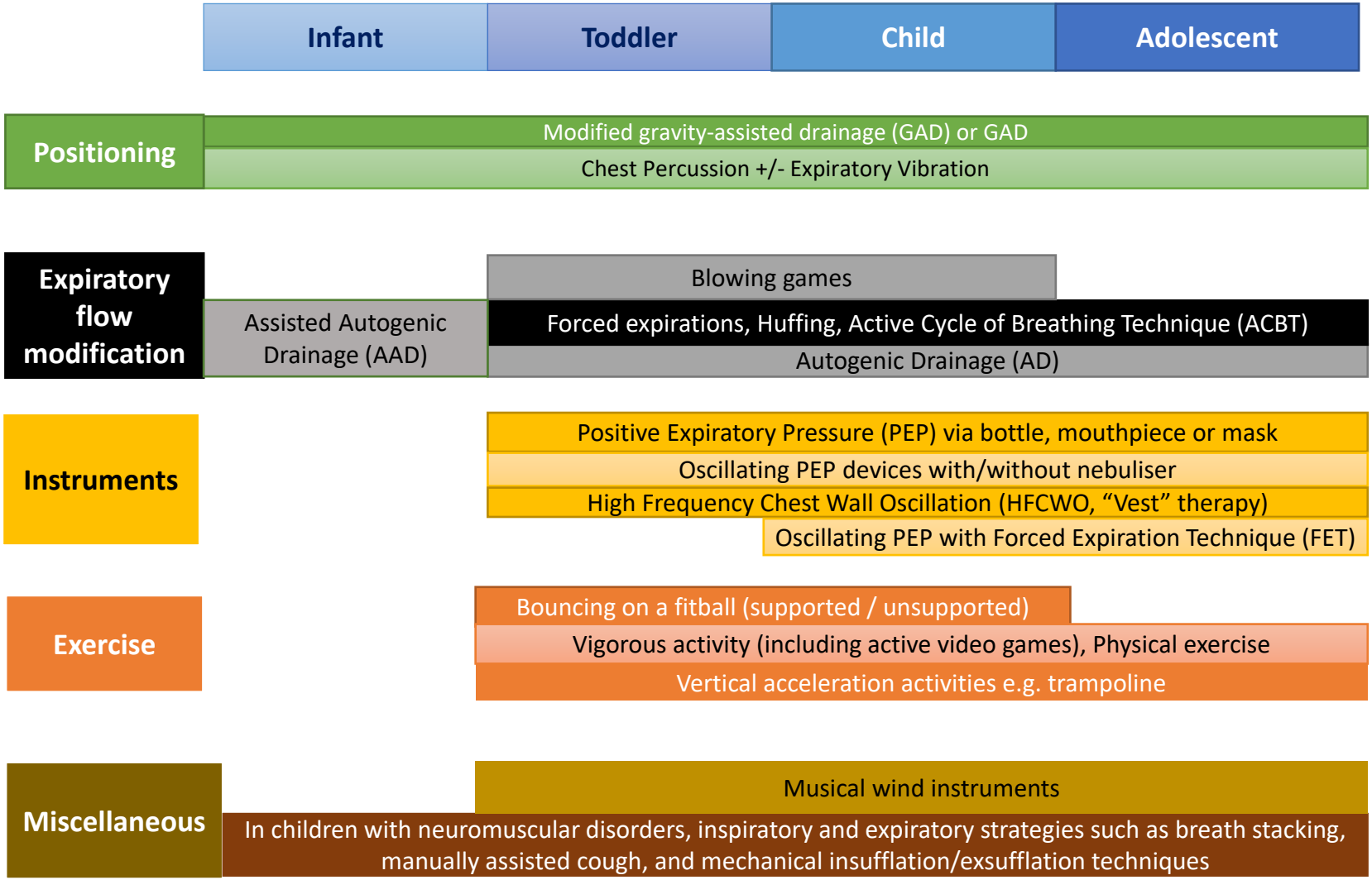
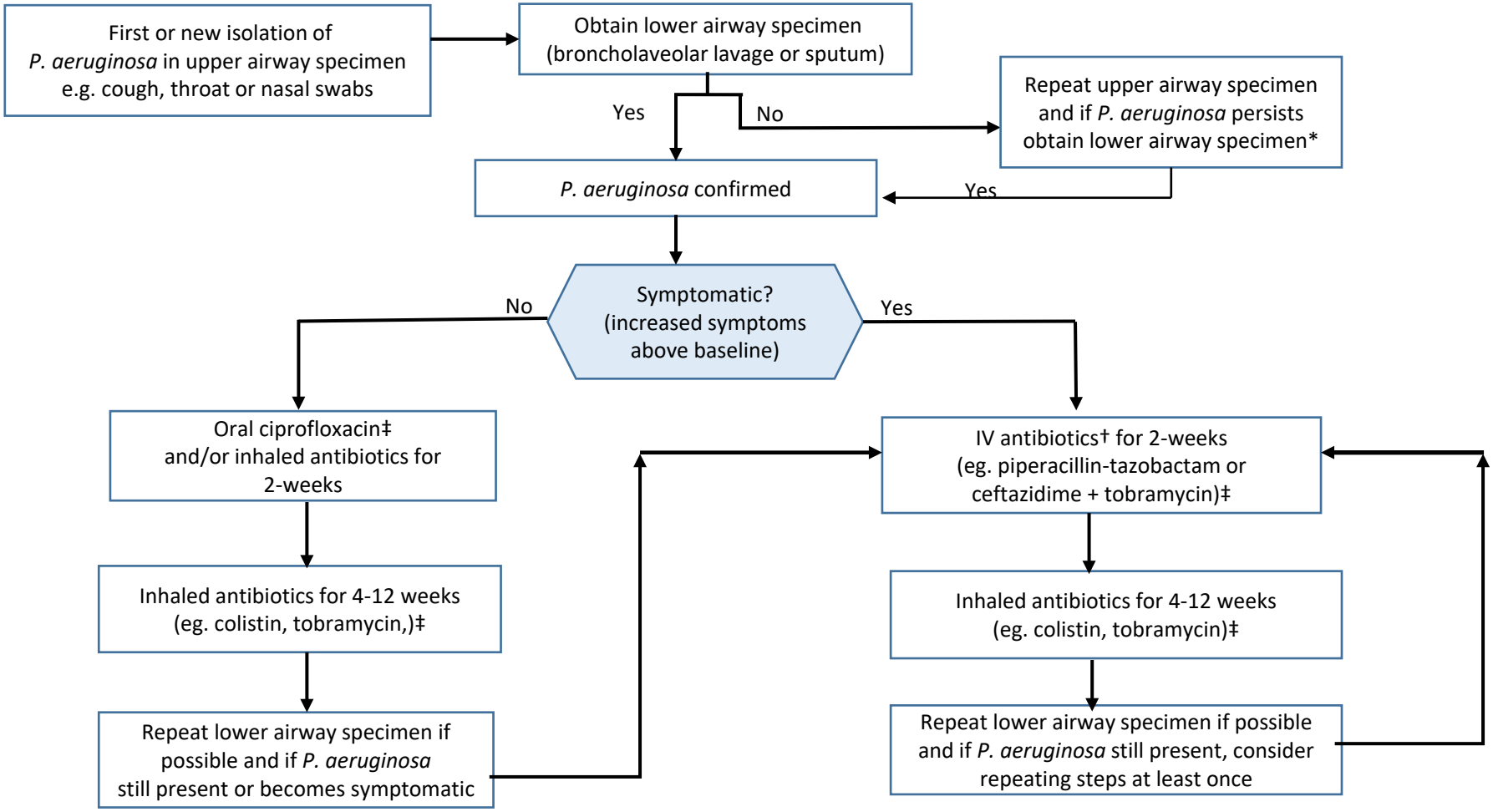


Figure 2

There are many different airway clearance techniques. In children/adolescents, these are age-specific and best taught by physiotherapists experienced in managing children/adolescents with bronchiectasis



* If lower airway specimen unobtainable, no treatment if asymptomatic; treat with intravenous anti-pseudomonal antibiotics for 2-weeks if symptomatic;
†Although there is no trial evidence, many paediatricians would employ a two-drug combination of intravenous antibiotics. The recommendation for administering two antibiotics when employing short (2-week) IV antibiotic courses aligns with the studies included in the systematic review and the ERS adult guidelines;
‡Antibiotics choices are dependent upon patient factors (e.g. adherence, tolerance, preference), availability of antibiotics and *P. aeruginosa* susceptibility profile.

Figure 3

Suggested management approach used by the panel when *Pseudomonas aeruginosa* is first or newly-isolated in a child with bronchiectasis. The approach depends upon (a) the specimen type and (b) whether the child is symptomatic. However, panel members acknowledged the approach to initiating eradication treatment is controversial. Some physicians may still feel it is appropriate to initiate eradication therapy based only on a single upper airway specimen, even when symptoms and evidence of benefit in such circumstances are absent.

SUPPLEMENT-EtD
DATA ON EVIDENCE TABLES AND EtD FOR ALL PICO AND NARRATIVE QUESTIONS

PICO question 1: In children/adolescents suspected of bronchiectasis:

(a) Should multidetector chest computed tomography (MDCT) scans with high-resolution CT (HRCT) be used instead of conventional HRCT alone for diagnosing bronchiectasis?

(b) What CT criteria for broncho-arterial dilatation (BAR) should be used?

Setting: Tertiary setting (Specialist hospitals)

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Quality assessment							№ of patients	Diagnostic accuracy	Quality	Outcome Importance
№ of studie	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Sensitivity and Specificity**		
CRITICAL OUTCOME REPORTED IN THE STUDIES INCLUDED IN THE ANALYSIS: Diagnostic accuracy (sensitivity and specificity) using multidetector CT-scan as the gold standard										
2	Observational studies	Serious[1]	Not serious	Serious[2]	Serious[3]	Undetected	133 133	Sensitivity and specificity by the number of patients 96% (95%CI 90, 98] and 69% (95%CI 54, 81) respectively Sensitivity and specificity by the number of lobes with bronchiectasis was 89% (95%CI 84, 92) and 81% (95%CI 78, 84%) respectively	VERY LOW	CRITICAL
CRITICAL AND IMPORTANT OUTCOMES NOT REPORTED IN THE STUDIES INCLUDED IN THE ANALYSIS: Change in clinical management, exacerbation rate or proportions, any hospitalisation, QoL, cough indices (e.g. score), lung function, adverse events										
	See summary table below for narrative evidence									

1. Non-blinded studies. Downgrade once for risk of bias.
2. Studies in adults. Downgrade once for risk for indirectness.
3. Downgrade once for wide range of estimates.

PICO question 1: Narrative Evidence- Summary of studies table

First author, year, country	Setting; Study design	Inclusion, exclusion criteria	N; Age; Follow-up duration	Main aim(s)	Primary findings relating to narrative question	Other major findings and additional comment	Implications for PICO
Chang [1], 2003, Australia	Hospital; Prospective enrolled and retro chart review	Inc: ≤15 yrs with non-CF chronic suppurative lung disease CSLD (>4mo daily moist cough and/or productive cough) Exc: Not described	n=65 at 2 yr FU; Median age=5.4 yrs (IQR 0.7-15)	To describe the demographics and evaluate routine investigations and relationship between spirometry and radiology scoring systems in children with CSLD from Central Australia	Change in management occurred in 8 (12.3%) children, which included treatment for aspiration lung disease/severe GORD (n=3), regular immunoglobulin transfusion (n=2), tuberculosis treatment (n=1), management for moderate tracheomalacia (n=1), congenital lung abnormality requiring surgery (n=1). No significant correlation between spirometry values with CT severity scores.	Protocol used for HRCT with children <5 yrs requiring general anaesthetic. BE diagnosed if inner bronchial diameter greater than that of adjacent artery (ratio >1)	BE found on HRCT changed management.
Coren [2], 1998, England	Specialist, hospital; Prospective study	Inc: children aged between 7 wks to 15 yrs with any HRCT scan during 1 August 1995 to 31 July 1996 Exc: Not described	n=102; median age 5 yrs (IQR not reported)	To analyse HRCT results of all paediatric HRCT scans over a 12 mo period to determine whether current use of investigation was appropriate	Of a possible 106 HRCT scans, reasons for clinical indication were classified into 7 groups (productive cough, n=48; interstitial lung disease, n=14; empyema, n=12; focal abnormality on x-ray; n=10 known CF, n=8; neonatal chronic lung disease, n=7 and post cardiac surgery, n=3) of which 21 (19.8%) children with chronic productive cough had BE confirmed on HRCT	HRCT scan protocol included either 1.5mm or 3mm thicknesses at 6 or 10mm intervals.	Accurate diagnosis of BE allows clear management plan for physiotherapy, use of prophylactic antibiotics and more detailed investigations.

Eastham [3], 2004, England	Specialist hospital; Retro chart review	Inc and Exc, not defined but data was on consecutive children with BE duing November 1996 and May 2002	n=93; Median age=7.2 yrs (range 1.6, 18.8); FU duration not mentioned	Report local experience of HRCT defined BE in children	Difficult to control asthma was the reason for referral in 49% of cohort	Crude estimate of prevalence of BE was 1 in 5800	HRCT results changed diagnosis in 49%. While authors did not mention about change in management, a change in diagnosis would alter clinical management and consequently improve clinical outcomes
Gokdemir [4], 2014, Turkey	Specialist, outpatient clinic, Prospective study	Inc: Children with stable non-CF BE aged between 9 and 18 yrs Exc: Not described	n=42, age yrs 12.7 (SD 2.3). 12 mo FU between November 2011 to April 2012	In children with BE, to evaluate HR-QoL (St George's Respiratory Questionnaire [SGRQ] and generic short-form-36 [SF-36]) and assess risk factors associated with HR-QoL (e.g. age at diagnosis, lung function, HRCT score and socioeconomic status (SES)	SGRQ symptoms scores inversely correlated with duration of regular follow-up (r=-0.3, p= 0.04) SGRQ scores did not correlate with current age, age at diagnosis, height and weight Z-scores, aetiology of BE, sputum microbiology, HRCT score or SES	SF-36 mental component summary with SGRQ symptoms score: r =-0.396, p= 0.005, activity score: r =-0.533, p= 0.000 and impact score: r=-0.512, p= 0.000)	Early diagnosis and regular FU with BE important for improving QoL. Severity and frequency of symptoms inversely related to lung function
Haidopoulou [5], 2009, England	Hospital; Retro chart review	Inc: Children <16 yrs with primary immunodeficiency and BE and FU chest HRCT scan min 2 yrs apart and availability of	n=18; median age 3.4 yrs (range 1-13 yrs) for diagnosis of primary immunodeficiency,	To a) determine the progression of BE secondary to primary immunodeficiency in children after starting treatment; and b) review extent and severity of BE at	Change in management occurred in 4 children who were diagnosed with immunodeficiency and BE simultaneously requiring immunoglobulin supplementation and treatment for BE Lung function in 13 (72.2%) children. FU FEV_1 and FVC %pred were	HRCT scan protocol used 1mm section at 10mm intervals. Median interval between two HRCT scans=3.5 yrs (range 2.2-4.8 yrs). No significant	With diagnosis of BE, introducing aggressive aetiology-specific and respiratory treatment may halt the progression or lead to improvements of

		lung function results within 4-6 wks of HRCT scan (if aged >6 yrs) Exc: Not described	and 9.3 yrs (range 3.1-13.8) yrs for BE diagnosis. FU 3.5 Yrs (range 2.2-4.8) years between HRCT scans	baseline and changes of BE progression at FU	significantly higher than baseline values 86% [49-124%] vs. 75% [36-93%], p<0.005, and 86% [47-112%] vs. 78% [31-96%], p<0.05 respectively	differences between HRCT at baseline (median score=6, [range 1-13] and FU [7.5, 0-15], p=0.20) but score worse in 10 (55%), improved in 6 (34%) and unchanged in 2 (11%). HRCT score did significantly correlate with FEV_1 and FVC rom baseline and FU	BE in children with primary immunodeficiency.
Herman [6], 1993, Czech Republic	Hospital; Cross-sectional prospective study	Inc: Children aged 3 to 17 yrs with repeated lung infections and/or changes on chest films suggestive of BE. FU during a non-symptomatic period (to avoid mis-diagnosis) Exc: Not described	n=20; Mean age 10.7 yrs (SD not reported)	To assess the possibilities, usefulness and limitations of HRCT in children with suspected BE	BE identified in 10 (50%), 9 were normal and 1 scan was low quality and not used. One child with BE had surgical intervention, with preoperative bronchography confirming HRCT findings of BE	HRCT scan protocol used 2mm slice thickness, 4.3-sec scanning time. 10mm slice spacing in suspected BE areas, the rest were 25-30mm interslice spacing.	HRCT limits the need for bronchography. HRCT finding of severe BE may assist in the decision for considering surgery (change in management).
Kapur [7], 2011, Australia	Tertiary paediatric hospital	Inc: Children undergoing MDCT chest scan for non-pulmonary	n=41; Median age 99 months (range 5-	To determine the range of bronchial arterial diameter ratio in children.	Mean BAR was 0.626 (0.068), range (0.437-0.739). No correlation was found with age in cohort (r=-0.21, p=0.19).		Airway diameter significantly smaller than adjoining vessel. Using radiological criteria

		conditions. Exc: history of chronic cough (>4 wks), CF, asthma, CSLD, previous pneumonia, cardiac disorders etc, pulmonary metastasis, past/current chest surgery or radio-therapy, insufficient inspiration level judged by radiologists	214) between October 2009 and May 2010.				for BAR >1 in adults would underestimate BE. BAR in children needs redefining.
Kapur [8], 2010, Australia	Specialist hospital; Retro chart review	Inc: BE (HRCT diagnosis) and reliable spirometry and growth data for ≥3 yrs. Exc: CF	n=52; Median age=8 yrs (range 2, 14); FU=3 yrs in 52 children, 5 yrs in 25	In children with BE, to evaluate (a) lung function measurements and growth over 3- and 5-yrs and, (b) factors associated with the change	Over 3 yrs, statistical improvement in lung function in $FEF_{25-75\%}$ (slope 3.01, 95%CI 0.14, 5.86, p=0.04) but trend present for FEV_1 %pred (slope 1.17; 95%CI -0.38, 2.7) and FVC (slope 1.57; 95%CI -0.18, 3.34) per annum. 5-yr trends similar. BMI z-scores significantly improved (BMI z -scores (slope 0.09; 95%CI, 0.02, 0.15, p=0.01) per annum		Diagnosis of BE and optimal treatment leads to improvement and/or disease stability.
Maglione [9], 2012, Italy	Specialist hospital; Retro chart review	Inc: available HRCT scan and spirometry during stable state and a second HRCT scan plus spirometry	n=20 PCD patients; Median age at 11.6 yrs (range 6.5, 27.5); FU median time	Evaluate the relationship between spirometry and HRCT data in stable and unstable lung disease in children with PCD	HRCT total scores significantly related to z-scores of FEV_1 (time 1: r=-0.5, p=0.01, time 2: r=-0.7, p=0.001) and FVC (time 1: r=-0.6, p=0.008, time 2: r=-0.7, p=0.001) at both evaluations Change in HRCT scores did not		HRCT scan more sensitive than spirometry in detecting change.

		during unstable lung disease Exc: aged <6 yrs or unable to perform spirometry	between scans: 2.3 yrs (range 1.3, 3.4)		correlate to change in spirometry values (FEV_1: r=-0.02, p=0.9, FVC: r=-0.02, p=0.9)		
Magnin [10], 2012, France	Specialist hospital; Retro chart review	Inc: aged <15 yrs, FU > 8 yrs, ≥2 concomitant HRCT and lung function while stable and PCD Exc: not stated	n=20; Median age at 7.6 yrs (range 0.8, 18.1); FU median 15.4 yrs (8.7, 22)	Describe relationship between changes in lung function and structure to evaluate progression lung disease in children with PCD. 74 HRCTs analysed; median=3 (range 2–7) HRCTs/child; median interval of 2.1 (0.6–11.7) yrs	HRCT scores increased with age; mean increase 0.95 points/yr Significant negative longitudinal correlation between lung function and HRCT-score (PaO2: r=-0.47, p=0.05; FVC: r=-0.64, p=0.005; FEV_1 r=-0.65, p<0.005)	All children eventually developed bronchiectasis based on HRCT scan.	Spirometry values (FEV_1 and FVC) and repeat HRCT scans useful for monitoring disease.
Patria [11], 2016, Italy	Specialist, outpatient clinic, Retro cohort study	Inc: children with recurrent pneumonia (RP) >2 Xray confirmed pneumonia in 1 yr or >3 episodes at any time, absence of CF, HRCT available and done ≥8 wks after last acute episode, with available clinical data	n=42; mean age 12.2 (SD 4.5 yrs); FU January 2009 and December 2013	Analyse clinic records of children with RP to identify factors that may lead to early suspicion of BE, to improve early diagnosis and effective management	BE was identified in 21 (50%) children with RP. FEV_1 and FEF_{25-75} %pred values were significantly lower in children with BE than in those without (77.9 ± 17.8 vs 96.8 ± 12.4, p = 0.004; 69.3 ± 25.6 vs 89.3 ± 21.9, p = 0.048).	HRCT scan protocol used 1mm slice thickness and scan interval of 1mm with additional slices at 5mm intervals for areas of concern. Significant correlation between baseline and FU FEV_1 and FVC %pred scores respectively	Study did not mention change in management as a result of HRCT but lung function at FU was significantly better than baseline with treatment.

Zaid [12], 2010, Ireland	Three Dublin Hospitals; Retro chart review	Inc: children <18 Yrs with HRCT confirmed BE. Exc: CF and radiology review of HRCT	n=92; median age 6.4 Yrs (range 1.5-13 Yrs); FU 1996-2006	To determine the clinical presentation, aetiology, co-morbidity, severity and lobar distribution of HRCT confirmed BE	Lung function was reported in 23 children; mean FEV_1=82% %pred, FVC=84 %pred. IQR not reported With BE diagnosed, airway clearance recommended for all, surgical intervention undertaken in 23 (25%), rigid bronchoscopy for removal of inhaled foreign body in 2, 8 received regular immunoglobulin therapy		Diagnosis leads to further investigations that result in change of management. Early diagnosis may lead to fewer lung resections and permanent loss of lung function
Redding [13], 2014, Australia and USA (Alaska)	Specialist and outpatient, Prospective study	Inc: Indigenous children from Alaska and Australia, aged 0.5 to 8 yrs with CSLD/or HRCT-confirmed BE Exc: cancer, CF, central nervous system or neuro-muscular disorder	n=123, 93 observed for ≥3 yrs, median age at original enrolment was 36 mo (range 9-107 mo). FU=3 yrs	Characterise the pattern of AREs and identify clinical features that increase the risk of recurrent and severe AREs requiring hospitalisation	Among the 93 children, 69 (74%) experienced >2 ARE over the 3 yr FU, with 28 (30%) having >1 ARE in each study yr	The frequency of AREs significantly declined over each yr of FU	Children with CSLD/BE need optimal care and management, although individualised care and treatment will be needed, based on changing risk for AREs during each year of care
Chang [14], 2015, Australia and New Zealand	Evidence based guideline (latest update used)	Inc: CSLD and BE children and adults from Australia and New Zealand	NA	Aims to a) increase awareness of CSLD/BE in children and adults; b) encourage earlier and improved diagnosis and management of CSLD/BE; and c)	Chest HRCT remains the diagnostic gold standard, although multi-detector (MDCT) scan is substantially more sensitive than conventional chest HRCT	Children are at increased risk from radiation-induced cancer later in life, the protocol for chest HRCT must be the lowest possible radiation exposure while	MDCT recommended with paediatric derived BAR ratio data

				present an updated guideline relevant to Australian and New Zealand settings		obtaining adequate assessment Radiographic criteria of BAR in people is age dependent	
Chang [15], 2018, Australia and UK	Systematic review	Inc: Children with BE	NA	To present current knowledge and updated definition of BE and review controversies relating to the management of children with BE	Reviewed and highlighted four reasons for redefining radiographic features in children with BE instead of using adult criteria.		Authors suggested that radiographic confirmed BE in children needs to use paediatric BAR data (abnormal when >0.80).
Polverino [16], 2017, Spain	Evidence based guidelines	Inc: Adult BE Exc: Not described	NA	Adult European management guidelines for BE to be used to benchmark quality of care for people with BE across Europe to improve clinical outcomes	BE diagnosis involves multiple steps, including clinical history, physical examination, tests and HRCT scanning		HRCT considered the gold standard for radiological confirmed BE diagnosis.
Hill [17], 2018, UK	British Thoracic Society Guideline for BE in adults	Inc: Adult BE Exc: Not described	NA	To provide recommendations and good practice points for managing adults with BE	Perform a thin section HRCT scan to confirm BE diagnosis when clinically suspected. Should be performed during clinically stable disease for optimal diagnostic and serial comparison purposes		Imaging protocol will vary according to scanner technology and patient factors.

AREs=acute respiratory exacerbations, BAR=broncho-arterial ratio, BE=bronchiectasis, CSLD=Chronic Suppurative Lung Disease, CF=cystic fibrosis, Exc=exclusion, FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity, FU=follow-up, Hosp=hospital, GORD=gastroesophageal reflux disease, HRCT= chest high-resolution computed tomography, HR-QoL=Health-related Quality of Life, Inc=inclusion, IQR=interquartile range), mo=months NA=not applicable, PCD=primary ciliary dyskinesia, pred=predicted, PsA=*Pseudomonas aeruginosa*, Retro=retrospective, SD=standard deviation, wks=weeks, yr=year

Evidence to Decisions (EtD) framework

PICO question 1: In children/adolescents suspected of bronchiectasis, (a) Should multidetector chest computed tomography (MDCT) scans with high-resolution CT (HRCT) be used instead of conventional HRCT alone for diagnosing bronchiectasis?
(b) What CT criteria for broncho-arterial dilatation (BAR) should be used?

Domain	Judgement	Research evidence	Additional considerations
PRIORITY **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Chest CT-scans are important for accurate diagnosis, determining extent of disease to guide clinical management. A more accurate diagnostic method would be generally advantageous.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	No direct evidence in children/adolescents was available. Two non-blinded observational studies in adults reported that MDCT-scans (contiguous helical scan with 1 mm collimation) were superior in detecting and determining the extent of bronchiectasis, compared to conventional HRCT-scans (1 mm collimation at 10-20 mm intervals [23]. Using high-resolution MDCT as the gold standard, the sensitivity of conventional HRCT-scans for diagnosing the number of patients with bronchiectasis was 96% (95%CI 90-98%) and specificity was 69% (95%CI 54-81%). That for detecting the number of lobes with bronchiectasis was 89% (95%CI 84-92) and 81% (95%CI 78-84%) respectively. The data on other outcomes are circumstantial. We did not find any data that related findings comparing MDCT versus HRCT-scans with clinical outcomes (e.g. change in management, QoL). Thus, we provided narrative evidence (see below) on whether detecting bronchiectasis impacted on the critical and	Early diagnosis of bronchiectasis was one of the top priorities articulated by parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child/adolescent (from the European Lung Foundation survey undertaken in 2019). Abnormally dilated airways are the main radiographic characteristic of bronchiectasis. The definition of abnormally

		important outcomes chosen (by the panel and parent advisory group) for this PICO. We found studies that described diagnosing bronchiectasis objectively resulted in a change in management. The narrative evidence also showed that with treatment, post-CT scan diagnosis of bronchiectasis, lung function in children can stabilise or even improve in a heterogenous cohort [8], including children with immunodeficiency [5]. QoL outcomes with bronchiectasis was reported in one study. Lastly, diagnosing bronchiectasis objectively is recommended in the Australasian guideline that includes children [14]. BAR correlates with age in adults without cardio-respiratory problems (none of the adults aged 20-40 years had BAR >1 whilst 41% of those aged >65-years had BAR ratio >1) [24]. Our narrative summary of evidence includes two studies in children [7,25] without lower airway disease. These studies found that the mean BAR is significantly lower in children (mean 0.63 (standard deviation (SD) 0.07) in children versus 0.70 (SD 0.1 in adults [24]) and the mean + 2 x SD equals 0.77 [7]. Thus, we suggest that clinicians use a BAR >0.80 to define abnormality when bronchiectasis is suspected.	dilated airways in adults (inner diameter of bronchial to adjacent artery ratio (BAR) >1.0 as a single cut-off irrespective of age) was based on just six adults [26] (see review [21]). Increasing BAR is the key marker of severity in bronchiectasis radiolographic scores. To diagnose bronchiectasis earlier thus requires using an appropriate BAR cut-off to define abnormality.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies Don't know	No relevant side effects were specifically reported in any study. However, there are undesirable effects from radiation that are more marked in young children. Current techniques using modern CT-scanners require much lower radiation. Also, young children may need general anaesthesia with its own possible adverse events. Over-diagnosis bronchiectasis could lead to unnecessary treatment.	There are false positives in diagnosing bronchiectasis based purely on BAR. Based on clinical expertise, the panel advocated that BAR alone should not be used to diagnose bronchiectasis.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	There are no studies in children/adolescents. There is very low evidence in adults with bronchiectasis that MDCT-scans are superior to conventional HRCT for diagnosing bronchiectasis.	

VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	Bronchiectasis is a heterogenous condition with wide aetiological variability. Parents/patient and clinicians value the certainty of an early and accurate diagnosis, as well as determining the extent and severity of disease to guide clinical management. Early diagnosis was one of the top research priorities identified by parents of children/adolescents with bronchiectasis and adults who had bronchiectasis as a child/adolescent.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Despite the radiation exposure the balance probably favours use of MDCT to HRCT-scans. Diagnosis based on child-specific BAR thresholds (which is lower than the one used for adults) leading to earlier treatment is favoured on balance, compared to later diagnosis (where an increase in BAR is a marker of bronchiectasis severity).	
	How large are the resource requirements (costs)? ○ Large costs	Accessing hospitals with paediatric expertise (especially when general anaesthesia is required) may be difficult for those living in isolated and remote communities or in countries where healthcare resources are limited. When general anaesthesia is necessary, an anaesthetist as well as a radiologist and	This is based on clinical expertise.

RESOURCES REQUIRED	● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	imaging equipment are required.	
CERTAINTY OF RESOURCE EVIDENCE	● Very Low ○ Low ○ Moderate ○ High ○ No included studies	In the absence of published studies, the certainty of evidence is very low.	In the absence of studies, this is based on clinical expertise.
COST-EFFECTIVENESS	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	There are no studies on cost-effectiveness. However, the panel holds the opinion that accurate diagnosis leading to appropriate management substantially outweighs the cost of treatment and morbidity related to more severe disease from delayed diagnosis. This is based on clinical expertise.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There is no published literature on health equity.	In some settings/countries access to specialist services and tertiary centres is limited, suggesting an imbalance and inequity between population groups (e.g. people in low-income countries or remote regions in high-income countries).
	Is the intervention acceptable to key stakeholders?	No available studies	Probably yes, as it is important for both patients/families and clinicians to have an accurate diagnosis in order to optimise

ACCEPTABILITY	○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		clinical management.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies Don't know	No available studies	Although generally accepted, there are likely limitations to accessibility, cost and availability in some settings/countries where MDCT-scans and/or general anaesthesia for children are unavailable.

PICO 1: In children/adolescents suspected of bronchiectasis, (a) Should multidetector chest computed tomography (MDCT) scans with high-resolution CT (HRCT) be used instead of conventional HRCT alone for diagnosing bronchiectasis? (b) What CT criteria for broncho-arterial dilatation (BAR) should be used?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• In children/adolescents suspected of bronchiectasis, we suggest that high-resolution MDCT-scans with HRCT is used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents (*Conditional recommendation, very low-quality of evidence*). • In children/adolescents suspected of bronchiectasis, we suggest that paediatric derived BAR (defined by the ratio of the inner diameter of the airway to the outer diameter of the adjacent artery) >0.8 is used to define abnormality instead of the adult cut-off of >1-1.5 (*Conditional recommendation, very low-quality of evidence stemming from narrative review of the evidence*).				
JUSTIFICATION	This recommendation places a relatively higher value on more accurate and early detection of bronchiectasis and its importance for subsequent management. It is widely accepted that HRCT-scans are the gold standard for radiographic confirmation of bronchiectasis. Many types of CT-scanners are available currently and will continue to evolve with faster scanning times, greater imaging quality and less radiation exposure. Data in adults (presented in the evidence table) show that MDCT is capable of				

	detecting more cases of bronchiectasis over conventional HRCT-scans. However, no paediatric data exist currently. The narrative summary provided circumstantial evidence that diagnosing bronchiectasis changes management and optimising management stabilises or improves lung function, reduces exacerbations and improves QoL. As BAR is larger in healthy adults and increases with age, we suggest that clinicians use a BAR >0.80 in children to define abnormality when the diagnosis of bronchiectasis is suspected. This allows an earlier diagnosis of bronchiectasis, which would lead to earlier appropriate treatment, one of the expressed priorities from the parent advisory group.
SUBGROUP CONSIDERATIONS	Patients with: ○ Different causes of bronchiectasis e.g. in children with altered pulmonary blood flow (e.g. cardiac disease), the BAR ratio suggested above may not be applicable ○ Cerebral palsy/severe disabilities - in this group with high co-morbidities and where general anaesthesia is likely to be necessary, the potential benefits versus harm from undertaking chest CT-scans need to be taken into consideration.
IMPLEMENTATION CONSIDERATIONS	Strategies to improve availability and accessibility to high-quality scanners in order to reduce radiation exposure risk and ensure correct interpretation of paediatric chest CT-scans. Using the suggested threshold of 0.8 may be important for reimbursement issues in some countries, where the reimbursement of several treatment regimens for patients with bronchiectasis is based on a radiographic-based diagnosis.
MONITORING/EVALUATION	Monitor the quality of CT-scanners and their interpretation in the healthcare system
RESEARCH PRIORITIES	One of the parent advisory group's top research priorities is how bronchiectasis can be diagnosed earlier. Using MDCT routinely (instead of HRCT-scans) and using a lower threshold to define BAR are two such measures. However, there are no high-quality data on how these measures impact clinical outcome. Thus, for children/adolescents suspected of having bronchiectasis, research priorities include studies to delineate: ○ the effect of using MDCT to diagnose bronchiectasis on clinical outcomes (change in clinical management, QoL, lung function, exacerbation rate, hospitalisation and adverse events with concomitant data on cost-effectiveness) ○ the appropriate BAR to define abnormality in young children versus adolescents and how using the diagnostic thresholds influences the aforementioned clinical outcomes.

PICO question 2: In children/adolescents with bronchiectasis, should asthma-type treatments (inhaled corticosteroids [ICS], short-acting beta$_2$-agonists [SABA], long-acting beta$_2$-agonists [LABA]), compared to no asthma-type treatment, be used routinely? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states.

Setting: Outpatient clinics
Subgroup: Inhaled corticosteroids versus placebo/usual care in people with bronchiectasis – sub-grouped by short term (≤6 months) and long term (>6 months)
Bibliography: [a]Hernando R, Drobnic ME, Cruz MJ, Ferrer A, Sune P, Montoro JB, et al. Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. Int J Clin Pharmacy 2012;34:644–50. [b]
[b]Martinez Garcia MA, Perpina-Tordera M, Roman-Sanchez P, Soler-Cataluna JJ. Inhaled steroids improve quality of life in patients with steady state bronchiectasis. Respir Med 2006;100:1623–32.
[c]Tsang KW, Ho P, Lam W, Ip M, Chan K, Ho C, et al. Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. Am J Respir Crit Care Med 1998;158:723–7.
[d]Tsang KW, Tan KC, Ho PL, Ooi GC, Ho JC, Mak J, et al. Inhaled fluticasone in bronchiectasis: a 12-month study. Thorax 2005;60:239–43.
[e]Guran T, Ersu R, Karadag B, Karakoc, F, Demirel GY, Hekim N, Dagli E. Withdrawal of inhaled steroids in children with non-cystic fibrosis bronchiectasis. J Clin Pharmacy & Ther 2008;33:603-11.
NB: Data for studies a-d were extracted from Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB. Inhaled corticosteroids for bronchiectasis. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD000996. DOI: 10.1002/14651858.CD000996.pub3.

Quality assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute (95%CI)**	**Quality**	**Outcome Importance**
Exacerbations – average number per participant (short-term, ≤6 months)												
2[a,b]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	66	61	Mean difference -0.17 (-0.56, 0.22)		⊕◯◯◯ VERY LOW	CRITICAL
Exacerbation – number of participants with one or more (short-term, ≤6 months)												
1[c]	RCT in adults	Not serious	Not serious	Serious[2]	Serious[3]	No additional considerations	1/12	3/12	OR 0.27 (0.02, 3.09)	In the control group 250 people out of 1000 had an exacerbation, compared to 83 (95%CI 7 to 507) out of 1000 in the intervention group	⊕◯◯◯ VERY LOW	CRITICAL
Exacerbations – number of participants with improved exacerbation frequency (long-term, > 6 months)												
1[d]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	21/43	16/43	OR 1.61 (0.68, 3.81)	In the control group 630 people out of 1000 had improved exacerbation frequency compared to 514 (95%CI 309, 715)	⊕◯◯◯ VERY LOW	CRITICAL

										out of 1000 in the intervention group		
Hospitalisations – number of participants with one or more hospitalisation (short-term, ≤6 months)												
1[a]	RCT in adults	Not serious	Not serious	Serious[2]	Serious[3]	No additional considerations	1/37	4/33	OR 0.20 (0.02, 1.90)	In the control group 120 people out of 1000 had a hospitalisation compared to 27 (95%CI 3 to 206) out of 1000 for the intervention group	⊕⊕◯◯ LOW	CRITICAL
Quality of life – SGRQ total score change from baseline (short-term, ≤6 months)												
2[a,b]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[4]	No additional considerations	66	61	MD -3.54 (-8.00, 0.92)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV_1 mL change from baseline (short-term, ≤6 months)												
2[a,b]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	95	61	MD -0.09 mL (-0.26, 0.09)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FVC mL change from baseline (short-term, ≤6 months)												
2[a,b]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	95	61	MD 0.01 mL (-0.16, 0.17)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV1 % predicted change from baseline (long-term, > 6 months)												
1[d]	RCT in adults	Serious[5]	Not serious	Serious[2]	Serious[3]	No additional considerations	43	43	0.30 (-17.43, 18.03)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FVC % predicted change from baseline (long-term, > 6 months)												
1[d]	RCT in adults	Serious[5]	Not serious	Serious[2]	Serious[3]	No additional considerations	43	43	-0.90 (-14.59, 12.79)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV1 % predicted before and after withdrawal of ICS (short-term, ≤6 months)												
1[e]	Observat-ional study in children	Serious[8]	Not serious	Not serious	Serious[3]	No additional considerations	27	27	Medians and IQRs: FEV1 % before and after ICS withdrawal: 82 (72 – 93), 83 (72.5 – 95)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – PC20 mg/mL before and after withdrawal of ICS (short-term, ≤6 months)												
1[e]	Observat-	Serious[8]	Not serious	Not serious	Not	No additional	27	27	Geometric means:		⊕◯◯◯	CRITICAL

	ional study in children				serious	considerations			PC20 mg/mL before ICS withdrawal: 8.2, after withdrawal 3.8, p=0.03	VERY LOW	
Adverse events – any event (short-term, ≤6 months)											
1[b]	RCT in adults	Serious[6]	Not serious	Serious[2]	Serious[3]	No additional considerations	62	31	Only reported for 2 active treatment arms; adverse events to be more frequent in 1000 mcg fluticasone arm vs. 500 mcg arm (19 vs. 7; p=0.04).	⊕◯◯◯ VERY LOW	CRITICAL
Other critical outcomes not reported: lost days of school (child) or work (parent) and duration of symptoms. Other important outcome not reported: time to next exacerbation.											
Not reported in the studies identified											

CI: Confidence interval; **IQR:** inter-quartile range; **MD:** mean difference; **NNT:** number needed to treat; **OR:** odds ratio **RCT:** randomised controlled trial

1. High risk of performance and detection bias, attrition bias and selective reporting in one/both trials. Downgrade once for risk of bias.
2. Study(ies) recruited only adult participants. Downgrade once for indirectness.
3. Confidence interval includes both possible harm and benefit of the intervention. Downgrade once for imprecision.
4. Confidence interval includes no difference. Downgrade once for imprecision.
5. High risk of attrition and other biases in trial. Downgrade once for risk of bias
6. High risk of performance and detection bias, attrition bias and selective reporting in this trial. Downgrade once for risk of bias
7. Trial at high risk of bias in several domains (performance and detection, attrition, selective reporting and other). Downgrade once for risk of bias

Setting: Outpatient clinics

Subgroup: Combination inhaled corticosteroids/long-acting beta2-agonists versus inhaled corticosteroids in people with bronchiectasis – sub-grouped by short term (≤6 months) and long term (>6 months)

Bibliography: 1) Goyal V, Chang AB. Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis. Cochrane Database Syst Rev 2014;Issue 6:CD010327 [Cochrane data used from original paper: Martinez-Garcia MA, Soler-Cataluna JJ, Catalan-Serra P, et al. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest 2012;141:461-8]

Quality assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention (ICS/LABA)**	**Control (ICS)**	**Relative (95%CI)**	**Absolute (95%CI)**	**Quality**	**Outcome Importance**
Exacerbation – number of participants with one or more (short-term, ≤6 months)												
1	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No Placebo	4/20	7/20	RR 0.57 (0.12, 1.65)	In the control (ICS) group 200 people out of 1000 had an exacerbation, compared to 350 out of 1000 (95%CI 81,	⊕◯◯◯ VERY LOW	CRITICAL

										416) in the intervention (combined ICS/LABA) group		
Hospitalisations – number of participants with one or more hospitalisation (short-term, ≤6 months)												
1	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	1/20	3/20	RR 0.89 (0.73, 1.10)	In the control (ICS) group 150 people out of 1000 had a hospitalisation compared to 50 out of 1000 (95%CI 9, 236) for the intervention (combined ICS/LABA) group	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life – SGRQ total score change from baseline (short-term, ≤6 months)												
[1]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	20	20	MD -4.57 (-12.38, 3.24)		⊕◯◯◯ VERY LOW	CRITICAL
Duration of symptoms – % of cough free days (short-term, ≤6 months)												
1	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[4]	No additional considerations	20	20	MD 12.3% (2.38, 22.22)		⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV_1 mL change from baseline (short-term, ≤6 months)												
1	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	20	20	MD 14 mL (-84.14, 56.14)		⊕◯◯◯ VERY LOW	CRITICAL
Adverse events – any event (short-term, ≤6 months)												
1	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[5]	No additional considerations	20	20	Study authors 37 events in the control group (1600 ugm/day of budesonide) and 12 in the intervention group (640 ugm budesonide with 18 ugm formoterol). It unknown whether any of the events occurred in the same individuals		⊕◯◯◯ VERY LOW	CRITICAL
Other critical outcomes not reported: lost days of school (child) or work (parent). Other important outcome not reported: time to next exacerbation.												
Not reported in the study identified												

CI: Confidence interval; **IQR:** inter-quartile range; **NNT:** number needed to treat; **RCT:** randomised controlled trial

1. High risk of performance and detection bias and selective reporting in the trial. Downgrade once for risk of bias.
2. Study recruited only adult participants. Downgrade once for indirectness.
3. Confidence interval includes both possible harm and benefit of the intervention. Downgrade once for imprecision
4. Single RCT with wide confidence interval
5. Confidence interval includes both possible harm and benefit of the intervention. Downgrade once for imprecision (unknown whether any of the events occurred in the same individuals).

Observational studies from adults to highlighting adverse events relating to use of ICS in patients with bronchiectasis
(see supplement-methods why this was done)

Setting: Outpatient clinics
Subgroup: **Inhaled corticosteroids** versus placebo/usual care in people with bronchiectasis – sub-grouped by short term (≤6 months) and long term (>6 months)
Bibliography: [a] Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax 2013;68: 256-62.
[b] Jang EJ, Lee CH, Yoon HI, Kim YJ, Kim JM, Choi SM, Yim JJ, Kim DK. Association between inhaler use and risk of haemoptysis in patients with non-cystic fibrosis bronchiectasis. Respirology 2015;20:1213-21.
[c] Holme J, Tomlinson JW, Stockley RA, Stewart PM, Barlow N, Sullivan AL. Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids. Eur Respir J 2008;32:1047-52.

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95%CI)**	**Absolute (95%CI)**		
Adverse events – non-tuberculous mycobacteria infection												
1[a]	Observational study in adults	Very serious[3]	Not serious	Serious[1]	Serious[2]	No additional considerations	332 cases, 3320 controls		Current ICS use: OR 29.1 (13.3 to 63.8). Higher doses associated with stronger associations		⊕◯◯◯ VERY LOW	CRITICAL
Adverse events – clinically significant haemoptysis												
1[b]	Observational study in adults	Serious[4]	Not serious	Serious[1]	Serious[2]	No additional considerations	90/6180 cases, 418/27486 controls using ICS		ICS use associated with no increased risk of haemoptysis: adjusted OR 1.0 (0.8, 1.2), p=0.75		⊕◯◯◯ VERY LOW	CRITICAL
Adverse events – adrenal suppression measured by short synacthen test (short-term, ≤6 months)												

1[c]	Observational study in adults	Serious[4]	Not serious	Serious[1]	Serious[2]	No additional considerations	16/33	4/17	OR: 3.06 (0.82, 11.36)	In the control group 235 people out of 1000 had adrenal suppression compared to 485 (95%CI 201 to 777) out of 1000 for the ICS group	⊕◯◯◯ VERY LOW	CRITICAL

1. Study(ies) recruited only adult participants. Downgrade once for indirectness.
2. Confidence interval includes no difference. Downgrade once for imprecision.
3. Before and after study; no blinding. Downgrade once for risk of bias.
4. Cross-sectional study with lack of detail about selection bias and no blinding. Downgrade once for risk of bias.

Evidence to Decisions (EtD) framework

PICO2: In children/adolescents with bronchiectasis, should asthma-type treatments (inhaled corticosteroids [ICS], short-acting beta$_2$-agonists [SABA], long-acting beta$_2$-agonists [LABA]), compared to no asthma-type treatment, be used routinely? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states.

Domain	Judgement	Research evidence	Additional considerations
PRIORITY **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children/adolescents and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few randomised controlled trials (RCTs) [15,21]. The European Respiratory Society guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Acute exacerbations or attacks have major negative health impacts on people with bronchiectasis and are particularly important in children/adolescents as they are associated with increased respiratory symptoms, impaired QoL, accelerated lung function decline (-1.9 FEV_1% predicted per hospitalised exacerbation) and substantial healthcare costs.[8,27]
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ●Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The studies are of very low-quality with RCTs only in adults. Where critical outcomes were obtained from these RCTs, the effect size for benefit are small and non-significant between groups. The single observational study in children/adolescents on withdrawing ICS has a high risk of bias and the reported outcome measures of doubtful clinical significance (FEV_1 and PC_{20} change were small).	The panel considered that the benefit of routinely using the medications was trivial, if any. Based on the panel's collective practice, there is little role for ICS +/- LABA and SABA.

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○Trivial ○ Varies ○ Don't know	RCT data in adults with bronchiectasis show increased adverse events when ICS are used and the risk increases with higher ICS doses. Also, there is observational study evidence of increased risk of non-tuberculous mycobacterial (NTM) infection and pneumonia in adults with bronchiectasis who received ICS.	The panel considered that there is good evidence from the non-bronchiectasis literature that ICS can lead to adrenal suppression [28] and growth failure [29], as well as other side-effects. As there is no reason to suppose that this would be any different in bronchiectasis, these medications should not be used routinely unless there is objective evidence of benefit. Also, very large studies in the adult literature involving other chronic respiratory conditions (asthma and COPD), identify ICS usage being associated with increased risk of pneumonia, tuberculosis, and NTM infection, with strong biological plausibility for causation [30,31,32,33]. These adverse events are of concern in bronchiectasis, which is characterised by chronic lower airway infection.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low for all the critical outcomes. RCTs were found only in adults with bronchiectasis. There is only a single observational study on withdrawal of ICS in children/adolescents with bronchiectasis.	The panel considered that the overall weight of the literature for all conditions, combined with biological plausibility and the absence of any reason to suppose the effects are different in children/adolescents, would lead most clinicians to be very concerned about ICS, either alone or in combination with SABA. Data on important adverse events are supported by systematic reviews in other chronic respiratory diseases.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Probably important uncertainty or variability ○ Probably no	No available studies	Parent/patient advisory group give low value to ICS, LABA and SABA as a therapeutic modality and commented on the substantial adverse events as well as the additional burden of therapy. The parent advisory group also expressed their experience that ICS were wrongly prescribed for their children/adolescents for years before the diagnosis of bronchiectasis was made leading to cessation of ICS. However, there is likely important uncertainty in a subgroup that have asthma-type responses.

	important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes		SABA pre-airway clearance therapy, especially when hypertonic saline is administered, may be beneficial in some.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ● Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○Favours the intervention ○ Varies ○ Don't know	The balance favours not using ICS, LABA or SABA routinely based on patient/parents' values, the substantial adverse effects described above and the lack of efficacy of these treatments.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings	No available studies	Based on clinical experience, resource implications differ as the costs of medications vary between countries

	● Varies ○ Don't know		
CERTAINTY OF RESOURCE EVIDENCE	○ Very low ○ Low ○ Moderate ○ High ● No included studies	No available studies.	The fiscal costs associated with ICS prescriptions vary worldwide. Hence, the use of ICS/LABA needs positive justification, which cannot be found in the current literature.
COST-EFFECTIVENESS	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies.	The panel considered that using the medications is not likely to be cost-effective.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies.	Not using additional medications would not impact on equity. However, advocating children use objective tests to document benefit from these medications may be inequitable in areas with little access to clinics for respiratory testing.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies	No available studies.	Probably no. The lack of efficacy, additional costs and adverse events would likely render these interventions unacceptable.

	○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies.	Either using or avoiding these medications is entirely feasible. It is however, not desirable to administer these medications without objective documentation of benefit. However, objective documentation of the individual's response to the medications may not always be feasible because of access and resource limitations.

PICO 2: In children/adolescents with bronchiectasis, should asthma-type treatments (inhaled corticosteroids [ICS], short-acting beta$_2$ agonist [SABA], long-acting beta$_2$ agonist [LABA]), compared to no asthma-type treatment, be used routinely? Subgroup analyses for (a) short versus long-term and (b) stable versus exacerbation states					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ●	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• In children/adolescents with bronchiectasis, we suggest not using ICS with or without LABAs routinely in either the short or long-term, irrespective of stability or exacerbation. (*Conditional recommendation, very low-quality of evidence*). **Remarks**: ICS maybe beneficial in those with eosionophilic airway inflammation. In the absence of any studies on the use with SABAs in bronchiectasis, we cannot make any recommendation, but suggest an objective evaluation is undertaken if such asthma-type medications are considered. For some, SABAs may be beneficial as pre-airway clearance therapies.				

JUSTIFICATION	The evidence (albeit very low-quality) shows a lack of efficacy for these medications. This, combined with concerns over very important adverse events (increased risk of NTM infection, possibly pneumonia and tuberculosis) with strong biological plausibility for causation, suggest ICS +/- LABAs should not be prescribed for either short or long-term treatment courses. Further, there is uncontroversial evidence from the non-bronchiectasis literature that ICS can lead to adrenal suppression and growth failure, as well as other side-effects, and there is no reason to suppose that this would be different in bronchiectasis, which is an additional reason to be cautious when prescribing them unless there is objective evidence of benefit. The fiscal cost associated with ICS prescription globally is also substantial. Hence, using ICS/LABA needs positive justification, which is not found in the current literature.
SUBGROUP CONSIDERATIONS	There is no evidence that bronchiectasis protects against the development of eosinophilic airway disease (asthma) where the prevalence of this asthma phenotype in bronchiectasis will likely reflect that found in the local population. In such patients, it is reasonable to use ICS, ICS/LABA and SABA as treatment of the coincident eosinophilic airway disease.
IMPLEMENTATION CONSIDERATIONS	Given that the symptoms of bronchiectasis and eosinophilic asthma overlap, we recommend that if treatment with ICS or ICS/SABA is contemplated, every effort should be made to try to document acute bronchodilator sensitivity (acute spirometric response to SABA), atopy (skin prick tests, specific IgE) and airway eosinophilia (peripheral blood eosinophil count, sputum eosinophils, exhaled nitric oxide). It should be noted that the sensitivity and specificity of all these tests vary across the globe, but if there is no evidence of atopy or airway eosinophilia in an individual patient, there is unlikely to be a role for ICS and ICS/LABA. If a blind trial of ICS or ICS/LABA is thought desirable because the above tests are equivocal or unavailable, objective evidence of benefit should be obtained if the medications are to be continued.
MONITORING AND EVALUATION	In many parts of the world, patients may begin ICS and ICS/LABA for an incorrect diagnosis of asthma, and whether these medications are needed should be reviewed when the diagnosis of bronchiectasis is made. If prescription of these medications is considered, the ongoing requirement should be reviewed regularly, as mandated by International asthma guidelines.
RESEARCH PRIORITIES	Research priorities include multicentre studies to determine the subgroup of children with bronchiectasis who may benefit from these therapies. Outcomes for RCTs should include QoL, exacerbations, symptoms, hospitalisations, days of school/work lost and lung function indices. Also, identifying biomarkers for any such subgroup, especially if they are easy to measure and able to be utilised in the clinic, including in low-middle income countries.

PICO question 3: In children/adolescents with bronchiectasis, should mucoactive agents (compared to no mucoactive agents) be used routinely? Subgroup analyses for (a) short versus long-term, (b) stable versus exacerbation states, and (c) type of mucoactive agent.

Setting: Outpatient clinic in London
Subgroup: **Recombinant human deoxyribonuclease (rhDNAse)** vs placebo in adults with bronchiectasis
Bibliography: [a]Willis PJ, Wodehouse T, Corkery K, Mallon K, Wilson R, Cole PJ. Short-term recombinant human DNase in bronchiectasis. Am J Respir Crit Care Med 1996; 154: 413-417 [note: twice daily arm data used; study was only for 2 weeks]

Setting: Outpatient clinics in adults (multicentre RCT involving 23 centres in North America, Britain and Ireland)
Subgroup: **Recombinant human deoxyribonuclease (rhDNAse)** vs placebo in adults with bronchiectasis (twice daily for 24 weeks)
Bibliography: [b]O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. Chest 1998;113 (5):1329-1334

NB: Some data for studies were extracted from Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I. Mucolytics for bronchiectasis. Cochrane Database Syst Rev 2014; 5: CD001289.

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rhDNAse**	**Control**	**Relative (95%CI)**	**Absolute (95%CI)**		
Exacerbation – number of participants with one or more (short-term, ≤6 months)												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	3 of 20	0 of 20	OR 8.2 95%CI 0.4, 170)	In the control group 0 people out of 1000 had an exacerbation, compared to 150 (95%CI 40 to 389) out of 1000 in the intervention group	⊕◯◯◯ VERY LOW	CRITICAL
Exacerbation – rate of any exacerbations (short-term, ≤6 months)												
1[b]	RCT in adults	Serious[1]	Not serious	Serious[2]	Not serious	No additional considerations	173	176	Relative risk 1.35 (95%CI 1.01, 1.79) favouring placebo. See also comment[#]		⊕⊕◯◯ LOW	CRITICAL
Hospitalisations – number of participants with one or more hospitalisation (short-term, ≤6 months)												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	2 of 20	0 of 20	OR 5.54 (95%CI 0.25, 123)	In the control group 0 people out of 1000 had an exacerbation, compared to 100 (95%CI 18 to 331) out of 1000 in the	⊕◯◯◯ VERY LOW	CRITICAL

										intervention group		
Exacerbation – rate of hospitalised exacerbations per 168 days (short-term, ≤6 months)												
1[b]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	173	176	Relative risk 1.85 (CIs not reported)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life (short term < 6 months)												
2[a,b]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	193	196	Data could not be combined (different scales were used*). Both studies reported no significant difference between groups	⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV_1 % predicted change from baseline (short-term, < 6 months)												
2[a,b]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	193	196	Data could not be combined but both studies favoured the placebo group for FEV_1 indices. Study[b] reported that the decline in FEV_1 was significantly worse in rhDNAse group (-3.6%) compared to placebo (-1.7%), p<0.05. Study[a] reported change (final visit compared to baseline) of -2.3% (SD 1.4) in rhDNAse group and 2% (1.4) in placebo	⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FVC % predicted change from baseline (short-term, < 6 months)												
2[a,b]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[4]	No additional considerations	193	196	Data could not be combined but in both studies, end of study FVC indices was significantly better in the placebo group than the rhDNAse group. Study[b] reported that FVC change was significantly worse in rhDNAse group (-3.4%) compared to placebo (0.3%), p<0.01. Study[a] reported change (final visit minus baseline) of -0.9% (SD 1.4) in rhDNAse group and 4.6% (1.5) in placebo	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events – any event (short-term, ≤6 months)												
2[a,b]	RCT in	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional	193	196	The smaller trial[a] reported	⊕◯◯◯	CRITICAL

	adults					considerations			significantly more adverse events in the rhDNAse group. The larger trial[b] reported 10.2% in placebo group and 15% in rhDNAse group	VERY LOW	
Sputum characteristics – sputum colour end of treatment measured using BronkoTest (short-term, < 6 months)											
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	20	20	MD 0.28 (-0.04, 0.60) favouring placebo	⊕◯◯◯ VERY LOW	Important
Other critical outcomes not reported: lost days of school (child) or work (parent) and duration of symptoms. Other important outcome not reported: time to next exacerbation											

CI: Confidence interval; **IQR:** inter-quartile range; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial

1. Unclear risk of random sequence generation, allocation concealment bias, attrition bias and selective reporting in the trials. Downgrade once for risk of bias.
2. Study(ies) recruited only adult participants. Downgrade once for indirectness.
3. Confidence interval includes no difference or cannot be calculated. Downgrade once for imprecision.
4. Data from the studies could not be pooled. Thus, we cannot be confident about the precision of the effect. Downgrade once for imprecision.

*****RCT[a] used the Functional Status Questionnaire for which the minimal important difference (MID) is unknown and RCT[b] used a 7 domain QoL first used in a cystic-fibrosis based RCT [34] where the MID is also unknown.

[#]Authors also reported significantly lower use of antibiotics in the placebo (44.1 days) c.f. rhDNAse (56.9 days) group, p<0.05 but 95%CI were not provided

Setting: Outpatient clinics (multi-centre clinics based in Australia, New Zealand, UK, Europe, USA, South America)

Subgroup: Mannitol vs placebo in adults with bronchiectasis (12[a] and 52[b] weeks)

Bibliography: [a]Bilton D, Daviskas E, Anderson SD, Kolbe J, King G, Stirling RG, Thompson BR, Milne D, Charlton B. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest 2013; 144: 215-225.

[b]Bilton D, Tino G, Barker AF et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. *Thorax* 2014; 69: 1073-1079

NB: Some data for studies were extracted from W Hart A, Sugumar K, Milan SJ, Fowler SJ, Crossingham I. Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev* 2014; 5: CD002996.

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mannitol**	**Control**	**Relative (95%CI)**	**Absolute (95%CI)**		
Exacerbation – number of participants with one or more												
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	187 of 464	189 of 340	OR 0.78 95%CI 0.51, 1.04)	In the control group 403 people out of 1000 had an exacerbation, compared to 556	⊕⊕◯◯ LOW	CRITICAL

										(95%CI 525 to 587) out of 1000 in the intervention group		
Exacerbation – rate of any exacerbation (long-term, >6 months)												
1[b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	233	228	Rate ratio 0.92 (95%CI 0.78, 1.08)	⊕⊕◯◯ LOW	CRITICAL
Exacerbation – rate of hospitalised exacerbations (long-term, >6 months)												
1[b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	233	228	Rate of 0.14 in mannitol group vs 0.20 in placebo group (p=0.18)	⊕⊕◯◯ LOW	CRITICAL
Quality of life – St George Respiratory Questionnaire (improvement from baseline*)												
2[a,b]	RCTs in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	464	340	MD 1.83 (95%CI -0.28, 3.94) favouring mannitol group. Both studies reported that some subscales were significantly better in the mannitol group	⊕⊕◯◯ LOW	CRITICAL
Lung function – FEV_1 (change from baseline in mls)												
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	464	340	Data could not be combined but both studies reported no significant difference between groups. Study[a] reported that mean FEV_1 after 12 weeks of mannitol was 1.95L (SD 0.59) and 1.92 (0.58) in the placebo group. Study[a] reported that after 52 weeks, mean FEV_1 change was 0.02L (95%CI -0.24, 0.28) in the mannitol group and -0.05L (95%CI -0.32, 0.22) in the placebo group	⊕⊕◯◯ LOW	CRITICAL
Lung function – FVC (change from baseline in mls)												
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	464	340	Data could not be combined but both studies reported no significant difference between groups. Study[a]	⊕⊕◯◯ LOW	CRITICAL

									reported that mean FVC after 12 weeks of mannitol was 2.93L (SD 0.86) and 2.89 (0.86) in the placebo group. Study[a] reported that after 52 weeks, mean FVC change was 0.02L (95%CI -0.24, 0.28) in the mannitol group and -0.16L (95%CI -0.54, 0.22) in the placebo group		
Adverse events (AE) – any event											
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	464	340	Both RCTs reported no significant difference between groups in any type of AEs. Any AEs in the smaller RCT[a] were 80.4% in placebo and 82% in mannitol group. In the larger trial[b] serious AEs were 28.1% in placebo and 21.5% in mannitol groups	⊕⊕◯◯ LOW	CRITICAL
Sputum characteristics – change in 24 hour sputum weight; end of treatment minus baseline											
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Not serious	No additional considerations	464	340	MD 3.42 (1.37, 5.47) favouring mannitol	⊕⊕⊕◯ MODERATE	Important
Time to next exacerbation											
2[a,b]	RCT in adults	Not serious	Not serious	Serious[1]	Serious[2]	No additional considerations	464	340	The larger trial[b] reported that time to the next exacerbation was significantly longer in the mannitol (164 days) than in placebo group (124 days), p=0.021. The smaller RCT reported no significant difference between groups (p=0.202) but favoured the mannitol group	⊕⊕◯◯ LOW	Important
Other critical outcomes not reported: lost days of school (child) or work (parent) and duration of symptoms											

CI: Confidence interval; **IQR:** inter-quartile range; **MD:** mean difference; **OR:** Odds ratio; **RCT:** randomised controlled trial

1. Study(ies) recruited only adult participants. Downgrade once for indirectness.
2. Data from the studies could not be pooled. Thus, we cannot be confident about the precision of the effect. Downgrade once for imprecision.

* The minimal important difference for the St George Respiratory Questionnaire is 4 units

Setting: Outpatient clinic in Great Britain

Subgroup: **Hypertonic saline** (HS) 7% vs isotonic saline (IS) for adults with bronchiectasis for 3 months (single blind RCT)
Bibliography: [a]Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. *Respir Med* 2011; 105: 1831-1835

Setting: Outpatient clinic in Australia
Subgroup: **Hypertonic saline** (HS 6% vs IS for adults with bronchiectasis, 12 months duration)
Bibliography: [b]Nicolson CH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. *Respir Med* 2012; 106: 661-7.

Setting: Outpatient clinics in Netherlands
Subgroup: **Hypertonic saline** (HS 7% vs IS for adults with primary ciliary dyskinesia (most also had with bronchiectasis, 3 months duration)
Bibliography: [c]Paff T, Daniels JM, Weersink EJ, Vonk Noordegraaf A, Haarman EG. A randomised controlled trial on the effect of inhaled hypertonic salineon quality of life inprimary ciliary dyskinesia. *Eur Resp J* 2017; 49: pii: 1601770

Quality assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hypertonic saline**	**Control**	**Relative (95%CI)**	**Absolute (95%CI)**	**Quality**	**Outcome Importance**
Exacerbation – rate of any exacerbation (short-term, <6 months)												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	28 Cross-over	28 RCT	Risk difference in annualised rate (HS minus IS) 2.71 (95%CI not provided; authors indicated p<0.05)		⊕◯◯◯ VERY LOW	CRITICAL
Exacerbation – number of participants with one or more exacerbations												
2[b,c]	RCT in adults	Not serious	Not serious	Serious[2]	Serious[3]	No additional considerations	31	31	Both studies reported no difference between groups. In the longer duration study[b] median number of exacerbations was 3 (IQR 0-6) in HS group and 1 (0-4) in IS group, p=0.24. In the shorter duration study[c] the median was 0 (IQR 0-1) in both groups		⊕◯◯◯ VERY LOW	CRITICAL
Exacerbation – number of participants hospitalised for and exacerbations												
2[b,c]	RCT in adults	Not serious	Not serious	Serious[2]	Serious[3]	No additional considerations	2 of 31	4 of 31	OR 0.47 95%CI 0.08, 2.75)	In the control group 129 people out of 1000 were hospitalised for an exacerbation, compared to 65 (95%CI	⊕◯◯◯ VERY LOW	CRITICAL

										51 to 82) out of 1000 in the intervention group		
Quality of life – St George Respiratory Questionnaire total score (improvement from baseline)												
3[a,b,c]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	48	48	The studies were inconsistent with one study[a] reporting a significant difference between groups for overall QoL and the other 2 studies[b,c] reported no significant difference. However, all reported some subscales were significantly better in the HS group. The data could not be combined as summary variables given were presented differently. Study[a] reported a significant difference between groups (6 units in HS group and ~1 in IS group, p<0.05). Study[b] reported the mean score at end of study was ~35 in HS group and ~32 in IS group, p not significant). The third study[c] reported no significant difference between groups (p=0.38); median change −2.6 (IQR −9.0, 1.5) in HS group and −0.3 (−8.1, 6.1) in controls	⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV_1 change from baseline in mls												
1[b]	RCT in adults	Not serious	Not serious	Serious[2]	Very serious[4]	No additional considerations	20	20	MD 0.19 (95%CI -0.37, 0.75) favouring controls.	⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FVC change from baseline in mls												
1[b]	RCT in adults	Not serious	Not serious	Serious[2]	Very serious[4]	No additional considerations	20	20	MD 0.11 (95%CI -0.57, 0.79) favouring controls	⊕◯◯◯ VERY LOW	CRITICAL
Lung function – FEV_1 % change at end of study from baseline												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	28 Cross-over	28 RCT	MD 13.30 (95%CI -0.49, 27.09) favouring HS	⊕◯◯◯ VERY LOW	CRITICAL

									Study[c] described no significant difference in mean FEV_1% change between groups (1.2%)		
Lung function – FVC % change at end of study from baseline											
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	28 Cross-over	28 RCT	MD 10.51 (95%CI 0.66, 20.36) favouring HS Study[c] described no significant difference in mean FVC% change between groups (1.5%)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events (AE) – any event											
2[b,c]	RCT in adults	Not serious	Serious[5]	Serious[2]	Serious[6]	No additional considerations	31	31	Study[b] reported 3 AEs in the HS group and none in the IS group. Study[c] reported that "AEs to the study medication were seen in almost all patients, but occurred more frequently during the hypertonic saline treatment phase"	⊕◯◯◯ VERY LOW	CRITICAL
Other critical outcomes not reported: lost days of school (child) or work (parent) and duration of symptom. **Other important outcomes not reported: time to next exacerbation and sputum characteristics**											

CI: Confidence interval; **IQR:** inter-quartile range; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial

1. High risk of bias for blinding of participants. Unclear risk of random sequence generation, allocation concealment bias, attrition bias and selective reporting in one or more trials. Downgrade once for risk of bias.
2. Study(ies) recruited only adult participants. Downgrade once for indirectness.
3. No CI reported and/or data could not be combined. Downgrade once for imprecision.
4. Cl includes no difference. Downgrade twice for small sample size and for imprecision
5. Downgrade once for inconsistency between studies
6. Study[a] did not report on AEs. Data from the studies could not be combined as adverse events were incompletely reported

Setting: Outpatient clinics in Italy

Subgroup: Bromhexine vs placebo in adults with bronchiectasis (30 mg tds for 15 days)

Bibliography: [a]Olivieri D, Ciaccia A, Marangio E, Marsico S, Todisco T, Del VM. Role of bromhexine in exacerbations of bronchiectasis. Double-blind randomized multicenter study versus placebo. Respiration 1991; 58: 117-121

NB: Some data for studies were extracted from Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I. Mucolytics for bronchiectasis. Cochrane Database Syst Rev 2014; 5: CD001289.

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bromhexine	Control	Relative (95%CI)	Absolute (95%CI)		
Lung function – mean FEV_1 at end of treatment (in mls)												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	34	33		MD 184.00 (95%CI 126.32, 241.68) favouring bromhexine	⊕◯◯◯ VERY LOW	CRITICAL
Sputum – score relating to difficulty in expectoration (higher score worse) at end of study												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	34	33		MD -0.53 (95%CI -0.81 to -0.25) favouring bromhexine	⊕◯◯◯ VERY LOW	Important
Sputum – amount at end of study												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	34	33		MD -21.5% (95% CI -38.9 to -4.1) favouring bromhexine	⊕◯◯◯ VERY LOW	Important
Adverse events (AE) – any event												
1[a]	RCT in adults	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	34	33		Reported adverse events (OR 2.93, 95%CI 0.12 to 73.97)	⊕◯◯◯ VERY LOW	CRITICAL
Other critical outcomes not reported: exacerbation, hospitalisation, FVC, lost days of school (child) or work (parent), quality of life and duration of symptom. Other important outcomes not reported: time to next exacerbation												

CI: Confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial

1. Unclear risk of random sequence generation, allocation concealment bias, attrition bias and selective reporting in the trial. Downgrade once for these risks of bias.
2. Study recruited only adult participants. Downgrade once for indirectness.
3. Single RCT with small sample size. Downgrade once.

Evidence to Decisions (EtD) framework

PICO question 3: In children/adolescents with bronchiectasis, should mucoactive agents (compared to no mucoactive agents) be used routinely? Subgroup analyses for (a) short versus long-term, (b) stable versus exacerbation states, and (c) type of mucoactive agent.

Domain	Judgement	Research evidence	Additional considerations
PRIORITY **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Mucoactive agents are medications that impact on mucus to improve mucociliary clearance. As people with bronchiectasis have impaired mucociliary clearance [21], these medications are sometimes used and include expectorants, mucolytics (e.g.N-acetylcysteine and recombinant human deoxyribonuclease [rhDNase]), and inhaled osmotic agents, such as mannitol and hypertonic saline. Mucoactive agents are sometimes used independently or concurrently with airway clearance techniques. Examining the efficacy of mucoactive agents for children/adolescents with bronchiectasis is thus important.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	There were no studies in children/adolescents. The RCTs were only in adults and the evidence table above shows that the evidence was of very low to low-quality. Where critical outcomes were obtained from these RCTs, the effect size for benefit varied among the different mucoactive agents, whilst that for rhDNAse showed harm. Potential benefits were found with mannitol as its use improved spirometry, some QoL domains and sputum volume, as well as prolonging time-to-next exacerbation. However, there was no effect on reducing exacerbations.	Despite the potential benefits of mannitol, hypertonic saline and bromhexine, the panel considered that there is insufficient evidence to recommend these interventions for all children/adolescents with bronchiectasis.

		One small (n=28) cross-over study [35] reported daily nebulised 7% hypertonic saline significantly reduced exacerbations compared to isotonic saline. However, two other studies (combined n=31 per arm) did not find any significant effect with hypertonic saline (c.f. isotonic saline) reducing exacerbations. Nevertheless, hypertonic saline significantly improved some QoL domains. A small study observed bromhexine improves several sputum characteristics and FEV_1, but there is insufficient data to recommend its use, particularly considering its potential adverse events.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○Trivial ○ Varies ○ Don't know	Using bromhexine is associated with increased adverse events (OR 2.93) [36] compared to placebo. rhDNAse has substantial undesirable effects as it significantly increases risk of exacerbations, exacerbation rate, hospitalisations and decreases lung function (FEV_1).	The panel considered that there is good evidence to suspect rhDNAse is harmful in children/adolescents with bronchiectasis. The panel also considered that the increased risk of adverse events when bromhexine is used (although not significant when compared to placebo) outweighs any potential benefits.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence is very low. RCTs were found only in adults with bronchiectasis. All studies were in stable state i.e. there were no studies during an exacerbation. The evidence for mannitol improving QoL was only evident in some domains and for exacerbations was inconsistent. For rhDNAse, the smaller study [37] was only of 2-weeks duration and the larger study was for 24-weeks [38]; there were no studies of >6-months and none during acute exacerbations. The updated search revealed two additional RCTs in adults	

		with bronchiectasis. One involved ultrasonic nebulisation of warm saline compared to ambroxol [39] and the second RCT examined oral N-acetylcysteine [40]. As both RCTs did not fulfil our inclusion criteria for this PICO, these RCTs were not included.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Probably important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	Parent/patient advisory group gave low value to nebulised interventions as a therapeutic modality because of the burden of therapy involved and therefore benefits needed to be substantial.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects is in favor of the intervention or the alternative?** ○ Favors the alternative ○ Probably favors the alternative ○ Does not favor either the intervention or the alternative ○ Probably favors the intervention ○Favors the intervention	The balance favors not using rhDNAse and bromhexine routinely based on patient/parents' values, the substantial adverse effects described above and the lack of efficacy of these treatments. The balance probably favors the use of hypertonic saline and mannitol in selected cases.	Situations where hypertonic saline and mannitol may be beneficial are in children/adolescents with a high level of daily symptoms, frequent exacerbations, poor QoL and/or difficulties with expectoration. The children/adolescents needed to be able to tolerate these interventions and the panel also considered that SABA should be used before administering either inhaled hypertonic saline or mannitol.

	● Varies ○ Don't know		
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	No available studies	Based on clinical experience, resource implications vary as the costs of medications differ between countries.
CERTAINTY OF RESOURCE EVIDENCE	Very low ○ Low ○ Moderate ○ High ● No included studies	No available studies.	The costs associated with mucoactive agent prescriptions vary worldwide. Hence, using these agents needs positive justification, which has been only found in the current literature in cases where expectoration is difficult and QoL is low.
COST-EFFECTIVENESS	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	The panel considered that using the medications likely has low cost-effectiveness.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ●Don't know	No available studies	Not using additional medications would not impact on equity. However, using hypertonic saline (including the equipment required e.g. nebulisers) and inhaled mannitol is likely inequitable as these medications and/or equipment may not be available in some countries.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No available studies	This varies. The lack of efficacy, additional costs and adverse events would render using rhDNAse unacceptable, and that for bromhexine is also likely to be unacceptable. The evidence of a modest effect for mannitol and hypertonic saline on QoL and sputum expectoration in adults could favour using these mucoactive agents in selected children with bronchiectasis. However, any benefit must be balanced with the burden of treatment as tolerance of these therapies is highly variable among children/adolescents.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No available studies	Both using and avoiding these medications are entirely feasible. Nevertheless, it is not desirable to use these medications without objective documentation of efficacy. Objective documentation of the individual's response to the medications may however, not be always feasible.

<table>
<tr><th colspan="6">PICO 3: In children/adolescents with bronchiectasis, should mucoactive agents (compared to no mucoactive agents) be used routinely? Subgroup analyses for (a) short versus long-term, (b) stable versus exacerbation states, and (c) type of mucoactive agent.
*There are three different recommendations that refer to the different interventions</th></tr>
<tr><td>TYPE OF RECOMMENDATION</td><td>Strong recommendation against the intervention for rhDNAse
●</td><td>Conditional recommendation against the intervention for bromhexine
●</td><td>Conditional recommendation for either the intervention or the alternative for hypertonic saline and mannitol
●</td><td>Conditional recommendation for the intervention
o</td><td>Strong recommendation for the intervention
o</td></tr>
<tr><td>RECOMMENDATION</td><td colspan="5">• In children/adolescents with bronchiectasis, we recommend against the routine use of recombinant-human DNAse (Strong recommendation, very low quality of evidence).

• In children/adolescents with bronchiectasis, we suggest against the routine use of t bromhexine (Conditional recommendation, very low quality of evidence).

• In children/adolescents with bronchiectasis, we suggest that neither inhaled mannitol nor hypertonic saline are used routinely. (Conditional recommendation, very low quality of evidence).

Remarks: Inhaled mannitol or 6-7% hypertonic saline may be considered in selected patients e.g. those with high daily symptoms, frequent exacerbations, difficultly with expectoration and/or poor QoL. If well tolerated, hypertonic saline or mannitol could improve QoL and facilitate expectoration. For hypertonic saline and mannitol, children should be old enough to tolerate these interventions and the panel also considered that short-acting beta$_2$ agonists should be used prior to inhaling either hypertonic saline or mannitol. The first dose of each should be undertaken under medical supervision. The substantially higher cost of mannitol compared with hypertonic saline should also be considered.</td></tr>
<tr><td>JUSTIFICATION</td><td colspan="5">Although the quality of evidence for rhDNAse is very low, the risk of harm with rhDNase in adults is consistent and evident in several outcomes i.e. increased exacerbations, hospitalisations and accelerated lung function decline.

For bromhexine, the potential benefits are outweighed by increased adverse events.

Nebulised hypertonic saline or mannitol may be considered in selected patients and settings. In adults, mannitol (c.f. controls) was beneficial (significantly fewer exacerbations, prolonged time-to-next exacerbation and symptom improvement) in the subgroup with high symptom burden (assessed by St George Respiratory Questionnaire, but not the Bronchiectasis Severity Index or FEV$_1$ %predicted) [41]. Thus, there is some, but insufficiently strongly evidence for using hypertonic saline or mannitol. Also,</td></tr>
</table>

	the burden of treatment for these medications is relatively substantial. In the context of cost, hypertonic saline is generally preferred as mannitol costs are substantantially higher than hypertonic saline. It is the usual practice of the panel that the first test dose is undertaken under medical supervision, preferably with spiromtery performed before and after the test dose when age-appropriate.
SUBGROUP CONSIDERATIONS	Patients with: ● Daily productive/wet cough ● Exacerbation frequency or severity
IMPLEMENTATION CONSIDERATIONS	Health professionals should be warned of the potential harmful effects of rhDNAse. Parents should be taught how to use these inhaled medications as well as equipment care (for hypertonic saline). Also, as hypertonic saline and mannitol can cause bronchoconstriction, the first dose should be undertaken under medical supervision, with prior inhaled short acting $beta_2$ agonist. When possible, spirometry before and after the initial test dose should be undertaken.
MONITORING AND EVALUATION	If any of these medications are used, the continuing need for the medications should be reviewed regularly.
RESEARCH PRIORITIES	Research priorities include multicentre studies to determine the subgroup of children with bronchiectasis who may benefit from the inhaled hyperosmolar therapies. Outcomes for RCTs should include QoL, exacerbations, symptoms, hospitalisations, days of school/work lost, lung function indices and adverse events. Also, identifying biomarkers for subgroups of children with bronchiectasis who will respond favourably to mucoactive agents.

<u>PICO question 4</u>: In children/adolescents with bronchiectasis, should regular airway clearance techniques (ACT) (compared to no ACT) be undertaken? Subgroup analyses for (a) short versus long-term and (b) stable vs exacerbation states.

Setting: Tertiary care (Children's pulmonology clinic)
Subgroup: Stable state, short term (one month)
Bibliography: [a]L. Indinnimeo, G. Tancredi, M. Barreto, Castro G. De, A. M. Zicari, F. Monaco, and M. Duse. Effects of a program of hospital-supervised chest physical therapy on lung function tests in children with chronic respiratory disease: 1-year follow-up. Int.J Immunopathol.Pharmacol 2007;20 (4):841-845.

Setting: Tertiary care (Specialist bronchiectasis clinic for adults)
Subgroup: Stable state (3-12 months)
Bibliography: [b]M. P. Murray, J. L. Pentland, and A. T. Hill. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. Eur Respir J 2009;34 (5):1086-1092.
[c]G. Munoz, J. de Gracia, M. Buxo, A. Alvarez, and M. Vendrell. Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. Eur Respir J 2018;51:1701926

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**No Intervention**	**Relative (95%CI)**	**Absolute (95%CI)**		
FEV_1%predcited; measured at end of study; better indicated by higher values												
1[a]	RCT in children	Serious[1]	Not serious	Serious[7]	Serious[3]	Undetected	13	12	Median FEV_1%predcited values: 86.3% in intervention vs 68.8% in controls (at one month) and 86.0% vs 69.3% (at 1 year)#		VERY LOW ⊕◯◯◯	CRITICAL
QoL; measured with Leicester Cough Questionnaire (LCQ) [higher score means better QoL] and St George Respiratory Questionnaire (SGRQ) [higher score means poorer Qol)]: measured at end of intervention												
2[b,c]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[4]	Undetected	42	42	Both studies showed improvement in QoL scores in both LCQ and SGRQ with the intervention **LCQ**[a]: intervention: median 1.3 (IQR -0.17, 3.3) vs control 0.0 (IQR -1.5, 0.5) at 3 months; p=0.002 **LCQ**[b]: intervention median 1.96 (IQR 0.2, 3.8) vs control (IQR 2.0 (IQR -2.8, -1.2) at 12 months; p <0.001 **SGRQ**[a]: intervention: median		VERY LOW ⊕◯◯◯	CRITICAL

									7.8 (IQR -1, 14.5) vs control 0.7 (IQR -2.3, 0.1) at 3 months; p=0.005 **SGRQ**[b]: intervention: median 6.8 (IQR 15, 15.1) vs control -11.4 (IQR -6.9, -15.9) at 12 months; p<0.001			
Exacerbations- Number people with exacerbation during study period												
2[b,c]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[5]	Undetected	18 of 42	23 of 42	RRR 0.22 (-0.22, 0.50)	0.12 (-0.09, 0.32)	VERY LOW ⊕◯◯◯	CRITICAL
Exacerbations- Time to next exacerbation												
1[c]	Parallel placebo-controlled RCT in adults over 12 months	Not serious	Not serious	Serious[2]	Serious[6]	Undetected	22	22	Authors reported time to next exacerbation was 226 days (IQR 40, 299) in intervention group vs 85 (54, 161) in placebo group; p value for difference between groups was 0.131		LOW ⊕⊕◯◯	IMPORTANT
Sputum characteristics												
2[b,c]	RCTs in adults	Serious[1]	Not serious	Serious[2]	Serious[4]	Undetected	20	20	Both studies showed improvement in 24-hour sputum volume between end-study and baseline with the intervention Study[a]: intervention: median volume 2 (IQR 0, 6) vs controls -1 (IQR -5, 0); p=0.02 Study[b]: intervention: median volume 10 mls (IQR -5, 25) vs placebo 0 (IQR -10, 3.8) in placebo group; p=0.015 Study[a] also reported non-significant improvement in bacterial density with the intervention; Intervention: -1 x 10^3 (IQR -2.78, 0.17 x 10^6) cfu/ml vs controls 1 x 10^3 (IQR -0.65, 6.4 x 10^6); p value 0.72		VERY LOW ⊕◯◯◯	IMPORTANT

Adverse events												
2[b,c]	RCTs in adults	Serious[1]	Not serious	Serious[3]	Not Serious	Undetected	0 of 42	0 of 42	Not applicable	0% difference b/w groups (95%CI -0.8, 0.8)	LOW ⊕⊕◯◯	CRITICAL
Other CRITICAL outcomes: Lost days of school/work, duration of symptoms, number of hospitalizations												
Not reported in any studies											-	

CI: Confidence interval; **LCQ:** Leicester Cough Quality; **MD:** mean difference; **SGRQ:** St George Respiratory Questionnaire; **RCT:** randomised controlled trial

1. Studies[a,b] were non-blinded RCTs
2. Studies[b,c] in adults
3. The precision of the overall effect cannot be estimated as the authors do not present comparisons between groups
4. The precision of the overall effect cannot be estimated as data cannot be pooled as median and IQR were presented in papers
5. Wide range of effect estimates
6. The precision of the overall effect could not be estimated as the authors only present a p value for comparisons between groups
7. Study's control group was 'no effective treatment' as opposed to 'no treatment'

Remarks

- Effect size were unavailable as data could not be combined; the systematic reviews in adults (ERS bronchiectasis guideline in adults[16] EtD included pulmonary rehabilitation studies that are not applicable to children).
- A single RCT[42] in adults with bronchiectasis were identified from the adult-based systematic review and an additional RCT[43] identified through the search
- Data on ACT during acute exacerbations are presented narratively in the EtD framework below
- Other supportive data including a single withdrawal study[44] was identified from CF-based systematic reviews and presented narratively in the EtD framework below.

Evidence to Decisions (EtD) framework

PICO question 4: In children/adolescents with bronchiectasis, should regular airway clearance techniques (ACT) (compared to no ACT) be undertaken? Subgroup analyses for (a) short versus long-term and (b) stable vs exacerbation states.

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Having access to physiotherapists with expertise in paediatric lung diseases and being taught the techniques and how to use the equipment at home were management priorities articulated by the Parent Advisory Group and parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child/adolescent (from the European Lung Foundation survey undertaken in 2019).
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Evidence provided by a single RCT [45] in children/adolescents and two RCTs in adults during the stable state. The paediatric study [52] that compared 1-month hospital supervised ACT with unsupervised therapy at home described a better median FEV1%predicted in the intervention group (86.3%) versus controls (68.8%) at 1-month and 1-year (86.0% versus 69.3%). In the second parallel RCT [43], median FEV_1 difference between end-study and baseline values was -0.004 L (IQR -0.01, 0.03) in the intervention group versus -0.1 L (IQR -0.2, 0.004) in the placebo group (at 12-months). Thus, data from all three RCTs showed a consistent effect favouring improved lung function data. For other critical outcomes, there were no data in children/adolescents. Data from two adult-based RCTs[42,43] presented in the evidence table above showed consistent results with significant between-group differences for improved QoL indices and sputum volume (favouring ACT), but no significant difference in the number of exacerbations. Acute state: In adults, a systematic review [46] found six small studies (range 2	There is supportive data from recent CF-related systematic reviews [47,48,49], but none contained a meta-analysis. A Cochrane review comparing ACT versus no ACT from eight studies (total of 96 participants with CF) found ACT had short-term effects by increasing mucus transport. However, no conclusions concerning long-term effects were drawn [47]. A study [44] identified from the systematic reviews, described a significant fall in lung function (including FEV_1 and FVC %predicted) when halting ACT for 3-weeks and improved lung function after recommencing ACT.

		to 30 people) assessing the effect of airway clearance techniques during an acute exacerbation. The authors found that using ACT had no adverse events, improved sputum clearance, but did not significantly improve lung function or respiratory symptoms.[46] The active cycle of breathing technique is likely more effective than postural drainage and percussion. Several studies reported patient preference for oscillating positive pressure devices over the active cycle of breathing technique.	Quantitative data from the study [44] was provided only graphically.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small • Trivial ○ Varies ○ Don't know	No relevant side effects were identified in the single paediatric RCT, [45] adult-based RCTs [42,43] or systematic reviews. Undesirable effects corresponded to the burden of care. Systematic reviews undertaken as part of the adult-based British Thoracic Society, CHEST and European Respiratory Society guidelines found no adverse events. Also, a systematic review [46] found that ACT during an acute exacerbation had no adverse events.	In adolescence and/or when children are well for long periods of time, the burden of treatment may not be considered trivial from the patients' and parents' perspective.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low due to very low certainty for at least one critical outcome. There is a lack of good quality scientific evidence in children/adolescents, but there is low to moderate evidence in adults with bronchiectasis in both the stable and acute exacerbation states of bronchiectasis.	Data are supported by systematic reviews in children with CF.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or	Parent/patient advisory group give high value to airway clearance as a therapeutic modality and commented on the lack of access in some settings. They and the panel value individual and age-targeted airway clearance to reduce lost days school/work, duration of symptoms, exacerbation rate, any hospitalisation, QoL, lung function and adverse events. Less weight was placed on the outcomes of sputum characteristics and 'time-to-next exacerbation'.	When children/adolescents are well for long periods of time, adherence and the burden of treatment may reduce its value.

	variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ● Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Some benefit can be expected for many patients. The balance favours using ACT based on patient/parents' values, the positive effects described above and absence of reported adverse events.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No available studies	Based on clinical experience, the resource requirements are access to physiotherapists with expertise in paediatric respiratory care to teach ACT, monitor adherence and ability to perform ACT. In the modern era, digital technology may facilitate teaching, which will reduce costs. Many of the commonly used techniques, such as the active cycle of breathing technique and postural drainage do not cost any money, apart from access to paediatric respiratory physiotherapists described above.

			There are devices that can aid chest clearance, such as positive expiratory pressure devices and muco-active therapies. RCTs evaluating these treatments are needed in children/adolescent to inform evidence-based and cost-effective therapies.
CERTAINTY OF RESOURCE EVIDENCE	● Very Low ○ Low ○ Moderate ○ High ○ No included studies	No available studies	Based on clinical experience that regular ACT prevents exacerbations and hospitalisation.
COST EFFECTIVENESS	○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know ● No included studies	No available studies.	The panel considered that ACT is likely cost-effective based on clinical experience that regular ACT prevents exacerbations and hospitalisation.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There is no published literature on health equity, but differential access (from living remotely or away from a major centre and specific expertise) suggests presence of imbalance between patients, settings and countries.	There might be inequity with ensuring all children/adolescent have access to a paediatric respiratory physiotherapist.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	Probably yes, as specialist physicians routinely advocate regular use of ACT, especially during exacerbations to improve patient symptoms. The patient advisory group requests access to high-quality therapists, including access to paediatric respiratory physiotherapists and appropriate ACT. Economic constraints may however limit acceptability to health administrators.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	There are likely some limits related to availability of paediatric-trained physiotherapists and healthcare organisational requirements within local settings. The feasibility of this intervention may therefore be variable, although generally acceptable.

PICO 4: In children/adolescents with bronchiectasis, should regular airway clearance techniques (ACT) (compared to no ACT) be undertaken? Subgroup analyses for (a) short versus long-term and (b) stable vs exacerbation states.					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ●

RECOMMENDATION	• In children/adolescents with bronchiectasis, we recommend they are taught and receive regular ACT or manoeuvres (*Strong recommendation, low-quality of evidence).* **Remarks**: Individualised ACT that is development and age-appropriate is best taught by a paediatric-trained chest physiotherapist (see Figure 2). As children/adolescents mature, techniques may need to be changed and thus, the ACT type and frequency is best reviewed at least biannually by physiotherapists with expertise in paediatric respiratory care. During acute exacerbations of bronchiectasis, children/adolescents should receive ACT more frequently.
JUSTIFICATION	Although the evidence for ACT improving clinical outcomes is very low to low, a strong recommendation was selected based on moderate desirable and trivial, but time-consuming undesirable effects for undertaking ACT and the risk of harm if ACT is not undertaken. Also, the panel and parents advisory group expressed that ACT is a key intervention for children/adolescents with bronchiectasis that is universally advocated. There are many different types of ACT methods. As the developmental stage and cognitive ability vary between individuals, as well as over a large age (0 to 18-years) range, therapy targeted for individual children/adolescents, taught by physiotherapists with expertise in paediatric respiratory care is recommended. However, there is a lack of high-quality evidence in children. During exacerbations, there is an increase in airway secretions. Therapy that enhances clearance of the airway secretions would be beneficial. While there are some data in adults [46], there are no data in children/adolescents.
SUBGROUP CONSIDERATIONS	Patients with: ○ Daily productive/wet cough ○ Stable disease ○ Cerebral palsy/severe disabilities/neuromuscular disease ○ Underlying causes of bronchiectasis (e.g. primary ciliary dyskinesia, primary immunodeficiency) ○ Acute versus stable states
IMPLEMENTATION CONSIDERATIONS	Strategies to improve acceptability and adherence. Increase accessibility of children/adolescents to paediatric-trained chest physiotherapists. See Figure-2 for the different types of strategies.
MONITORING AND EVALUATION	Evaluate at the start of training and follow-up to check adherence and capability, and then at least biannually to ensure age appropriate techniques are used, especially those with moderate and severe bronchiectasis or frequent exacerbations.

RESEARCH PRIORITIES	In the current era, placebo RCTs are not feasible as ACT is universal and clinicians advocate ACT. Research priorities include multicentre studies to determine cost-effectiveness, efficacy based on frequency of ACT and different ACT methods for children/adolescents with bronchiectasis. Outcomes for RCTs should include QoL, exacerbations, symptoms, hospitalisations, days of school/work lost and lung function indices.

PICO question 5: In children/adolescents with bronchiectasis, should systemic courses of antibiotics (compared to no antibiotics) be used to treat an acute respiratory exacerbation (type and duration)?

Setting: Four paediatric centres in Australia and New Zealand
Subgroup: Children with acute exacerbations of bronchiectasis
Bibliography: [a]Goyal V, Grimwood K, Ware RS, Byrnes CA, Morris PS, Masters IB, McCallum GB, Binks MJ, Smith-Vaughan H, O'Grady KF, Champion A, Buntain HM, Schultz A, Chatfield M, Torzillo PJ, Chang AB. Efficacy of oral amoxicillin-clavulanate or azithromycin for non-severe respiratory exacerbations in children with bronchiectasis (BEST-1): a multicentre, three-arm, double-blind, randomised placebo-controlled trial. Lancet Respir Med. 2019 Sep;7(9):791-801. doi: 10.1016/S2213-2600(19)30254-1.

Quality assessment							№ of patients		Effect		Quality	Outcome importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Placebo**	**Relative (95%CI)**	**Absolute (95%CI)**		
Resolution of exacerbation – proportion of participants with resolved exacerbation after 14 days treatment												
1[a]	RCT in children	Not serious	Not serious	Not serious	Not serious	Undetected	Amoxicillin-clavulanate=41/63	29/67	Amoxicillin-clavulanate vs placebo RR=1.50 (95%CI 1.08 to 2.09), p=0.015	Amoxicillin-clavulanate vs placebo NNT 5 (95%CI 3 to 20)	⊕⊕⊕⊕ HIGH	CRITICAL
1[a]	RCT in children	Not serious	Not serious	Not serious	Not serious	Undetected	Azithromycin=41/67	29/67	Azithromycin vs placebo RR=1.41 (95%CI 1.01 to 1.97), p=0.042	Azithromycin vs placebo NNT 6 [95%CI 3 to 79)	⊕⊕⊕⊕ HIGH	CRITICAL
Exacerbation duration – median (IQR) days to exacerbation resolution												
1[a]	RCTs in children	Not serious	Not serious	Not serious	Not serious	Undetected	Amoxicillin-clavulanate=63	67	Amoxicillin-clavulanate=7 days (IQR 6 to 10); vs placebo p=0.018 Placebo=10 days (IQR 6 to 12)		⊕⊕⊕⊕ HIGH	CRITICAL
1[a]	RCTs in children	Not serious	Not serious	Not serious	Serious[1]	Undetected	Azithromycin=67	67	Azithromycin=8 days (IQR 5 to 12); vs placebo p=0.24 Placebo=10 days (IQR 6 to 12)		⊕⊕⊕◯ MODERATE	CRITICAL

Time to next exacerbation over 6 month follow up – median (IQR) days											
1[a]	RCTs in children	Not serious	Not serious	Not serious	Serious[2]	Undetected	Amoxicillin-clavulanate=63	67	Amoxicillin-clavulanate=89 days (IQR 31 to 180) vs placebo p=1.00 Placebo=89 days (IQR 40 to 180)	⊕⊕⊕◯ MODERATE	IMPORTANT
1[a]	RCTs in children	Not serious	Not serious	Not serious	Serious[2]	Undetected	Azithromycin=67	67	Azithromycin=83 days (IQR 51 to 180); vs placebo p=0.86 Placebo=89 days (IQR 40 to 180)	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of life – median (IQR) change from baseline to 14 days, measured using PC-QOL; higher scores=better quality of life											
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Amoxicillin-clavulanate=53	54	Amoxicillin-clavulanate=0.8 (IQR 0.2 to 2.1) Placebo= 0.7 (IQR 0.1 to 1.5)	⊕⊕⊕◯ MODERATE	CRITICAL
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Azithromycin=53	54	Azithromycin=1.3 (IQR 0.4 to 2.3) Placebo= 0.7 (IQR 0.1 to	⊕⊕⊕◯ MODERATE	CRITICAL
Hospitalisations while on study drug (14 days)											
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Amoxicillin-clavulanate=1/63	1/67	Amoxicillin-clavulanate vs placebo RR 1.06 (95%CI 0.07 to 16.64)	⊕⊕⊕◯ MODERATE	CRITICAL
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Azithromycin=2/67	1/67	Azithromycin vs placebo RR 2.00 (95%CI 0.19 to 21.53)	⊕⊕⊕◯ MODERATE	CRITICAL
All adverse events while on treatment (14 days)											
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Amoxicillin-clavulanate=19/63	14/67	Amoxicillin-clavulanate vs placebo RR 1.44 (95%CI 0.79 to 2.63)	⊕⊕⊕◯ MODERATE	CRITICAL
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[4]	Undetected	Azithromycin=20/67	14/67	Azithromycin vs placebo RR 1.34 (95%CI 0.79 to 2.59)	⊕⊕⊕◯ MODERATE	CRITICAL

Change in antibacterial resistance – paired day 1 and day 14 samples											
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[5]	Undetected	Amoxicillin-clavulanate=39	47	"In the azithromycin group, the proportion of azithromycin resistant bacterial isolates increased from day 1 (two [9%] of 22 patients with pathogenic bacterial isolates) to day 14 (five [63%] of eight), whereas these proportions of antibiotic-resistant bacteria did not change substantially between days 1 and 14 in the amoxicillin–clavulanate or	⊕⊕⊕◯ MODERATE	IMPORTANT
1[a]	RCT in children	Not serious	Not serious	Not serious	Serious[5]	Undetected	Azithromycin=42	47	"In the azithromycin group, the proportion of azithromycin resistant bacterial isolates increased from day 1 (two [9%] of 22 patients with pathogenic bacterial isolates) to day 14 (five [63%] of eight), whereas these proportions of antibiotic-resistant bacteria did not change substantially between days 1 and 14 in the amoxicillin–clavulanate or placebo groups"	⊕⊕⊕◯ MODERATE	IMPORTANT
Other CRITICAL outcomes: Lost days of school/work											
Not reported in the study identified											

CI: Confidence interval; **IQR:** inter-quartile range; **NNT:** number needed to treat; **RCT:** randomised controlled trial

1. Azithromycin vs placebo comparison is imprecise. Downgrade once for imprecision
2. Estimates include wide inter-quartile ranges. Downgrade once for imprecision
3. Quality of life outcome only reported in those who completed follow up. Reasons for drop out and proportions similar in all groups (16% - 21%). No downgrade.
4. Effect estimates do not confirm or rule out a between group difference. Downgrade once for imprecision
5. Small numbers of events. Downgrade once from imprecision.

Evidence to Decisions (EtD) framework

PICO question 5: In children/adolescents with bronchiectasis, should systemic courses of antibiotics (compared to no antibiotics) be used to treat an acute respiratory exacerbation (type and duration)?

Domain	Judgement	Research evidence	Additional considerations
PRIORITY **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Acute exacerbations or 'attacks' have major negative health impacts on people with bronchiectasis and are particularly important in children/adolescents as they are associated with increased respiratory symptoms, impaired QoL, accelerated lung function decline (-1.9 FEV_1% predicted per hospitalised exacerbation) and substantial healthcare costs [8,27].
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large	The evidence summary shows a single high-quality study supporting antibiotics to treat exacerbations. In that trial [50], amoxicillin-clavulanate (amox-clav) versus placebo shows a significant benefit in the proportion of patients with exacerbation resolved after 14-days of treatment. Azithromycin also showed a similar	

	○ Varies ○ Don't know	benefit versus placebo, but this just failed to reach pre-set statistical significance. Amox-clav also reduces the duration of exacerbations. In contrast, the duration of exacerbation was similar between azithromycin and placebo among the children whose exacerbations resolved by day-14. However, no between-group differences were detected for time-to-next exacerbation, QoL or hospitalisations, although hospitalisations were uncommon in all groups.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No significant increase in adverse events when either antibiotic or pooled results for amox-clav and azithromycin were compared to placebo.	Antibiotic associated side effects are generally minor and do not outweigh the benefits. Induction of macrolide-resistance in upper airway bacterial pathogens was associated with azithromycin use.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	Overall certainty of evidence is moderate, stemming from the lowest certainty for critical outcomes.	Most endpoints were rated as moderate certainty of evidence with imprecision of estimates the main concern. The exception is exacerbation resolution, which was rated as high certainty for amox-clav versus placebo and high certainty for exacerbation duration for amox-clav versus placebo. The data are nevertheless derived from a single RCT and so uncertainty around the magnitude of benefit in other populations must be acknowledged.
VALUES	**Is there important uncertainty about or variability in how much**	Most parents value when their child/adolescent's exacerbations resolve. The European Lung Foundation parents' survey showed that	Resolution of symptoms by a specified timepoint may be important to some patients/investigators and less to others. Some investigators may value time-to-the

	people value the main outcomes? ○ Important uncertainty or variability ○ Probably important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	exacerbations was one of the top three factors that affected the child/adolescent's QoL.	next exacerbation or duration of symptoms over resolution by day-14 (for example). The optimal endpoint to identify response to antibiotics in the context of exacerbations is not known. Some may consider that there is modest uncertainty.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ●Favours the intervention ○ Varies ○ Don't know	From a single well-conducted RCT we have identified clear evidence of benefits, which are clinically relevant without evidence of clinically meaningful adverse events. The balance of risk and benefit clearly favour the intervention.	
RESOURCES REQUIRED	**How large are the resource requirements costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings	We did not identify any studies providing a formal economic analysis	The antibiotics used are inexpensive and any costs may be offset by savings in terms of repeat attendance at primary or secondary care for unresolved exacerbations (this is based on clinical experience).

	○ Large savings ○ Varies ○ Don't know		
CERTAINTY OF RESOURCE EVIDENCE	○ Very low ○ Low ○ Moderate ○ High ● No included studies	No available studies	In the absence of studies, this is based on clinical experience.
COST-EFFECTIVENESS	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	There are no studies on cost-effectiveness. However, the panel holds the opinion that antibiotics for exacerbations are cost-effective
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify any studies addressing equity.	Timely treatment of exacerbations may be a problem in some settings where patients do not have easy access to healthcare facilities or to appropriate antibiotics (This is based on clinical expertise).
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no	We did not identify any studies formally addressing acceptability.	Antibiotic treatment of exacerbations is current standard of care and is acceptable to clinicians and patients.

	○ Probably yes ● Yes ○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	Using antibiotics should be feasible in most settings. Feasibility may be an issue in settings where parents/children/adolescents have reduced access to healthcare and appropriate antibiotics (this is based on clinical experience).

PICO 5: In children/adolescents with bronchiectasis, should systemic courses of antibiotics (compared to no antibiotics) be used to treat an acute respiratory exacerbation (type and duration)?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ●
RECOMMENDATION	• In children/adolescents with bronchiectais and an acute respiratory exacerbation, we recommend a systemic course of an appropriate antibiotic is used for 14-days. (*Strong recommendation, moderate quality of evidence*) **Remarks**: The empiric antibiotic of choice is amoxicillin-clavulanate, but the type of antibiotic chosen should be based on the patient's airway cultures (e.g. those with *Pseudomonas aeruginosa* require different treatment regimens to those without) and history of antibiotic hypersensitivity reactions. When the exacerbation is severe (e.g. child/adolescent is hypoxic) and/or when the child/adolescent does not respond to oral antibiotics, intravenous antibiotics will be needed.				
JUSTIFICATION	Our strong recommendation is based on a single high-quality RCT in children/adolescents and extensive clinical experience. All				

	outcomes were rated at least moderate certainty and exacerbation resolution and duration both showed a benefit of the intervention, were rated high/moderate certainty, and are the most critical outcome for this intervention. Importantly, the trial did not detect an increase in adverse events in the antibiotic treatment groups compared to placebo, although such events were uncommon. Due to the different mechanisms of action of the two antibiotics, we chose not to pool the results. A second RCT [51] published by the trial authors [51] comparing amoxicillin-clavulanate to azithromycin for treating non-severe exacerbations found that by day-21 azithromycin was non-inferior to amoxicillin-clavulanate within a 20% margin. However, in this study those receiving azithromycin took a median 4-days longer for their symptoms to resolve than those taking amoxicillin-clavulanate, a significant result. Nevertheless, azithromycin does have the advantage of being an option in children with penicillin hypersensitivity and the once-daily dosing may also improve adherence. Antibiotic treatment for acute infective exacerbations of bronchiectasis in children is considered standard of care in most settings and is supported by the findings of this trial.
SUBGROUP CONSIDERATIONS	None
IMPLEMENTATION CONSIDERATIONS	Patients should have access to appropriate antibiotics for the recommended duration of treatment.
MONITORING AND EVALUATION	Patients should be monitored for resolution of symptoms since the study demonstrated a high rate of non-resolution even in the treatment groups.
RESEARCH PRIORITIES	RCTs are required to establish the optimal dosing and duration of antibiotic treatment in children/adolescents with bronchiectasis. Studies should recruit children/adolescents with bronchiectasis confirmed by appropriate imaging, carefully document any important effect modifiers (including: age; aetiology and severity of underlying bronchiectasis, co-morbidities, co-infection; exacerbation frequency) and should measure patient-important outcomes including: time-to-next exacerbation, hospitalisations, QoL, days of school/work lost, recovery of lung function and induction of antimicrobial resistance.

PICO question 6: In children/adolescents with bronchiectasis, should eradication treatment be used (irrespective of symptoms) when there is a new isolate of a potentially pathogenic microorganism (compared to no eradication treatment)?

Setting: Secondary and tertiary adult outpatient units
Subgroup: Patients with a new isolate of P. aeruginosa
Bibliography: [a]Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration. 2015;90(4):299-305.
[b]White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis., Respir Med. 2012;106(3):356-60.
[c]Blanco-Aparicio M, Saleta Canosa JL, Valino LP, Martin Egana MT, Vidal G, I, Montero MC. Eradication of Pseudomonas aeruginosa with inhaled colistin in adults with non-cystic fibrosis bronchiectasis. Chron Respir Dis 2019; 16: 1479973119872513

Quality assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**No Intervention**	**Relative (95%CI)**	**Absolute (95%CI)**	**Quality**	**Importance**
Quality of Life (SGRQ change from baseline (total)); range 0-100; better quality of life indicated with lower scores												
1[a]	Observational data	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	28	28	Mean baseline SGRQ 31.67. MD after eradication therapy 8.71 lower [18.68 lower to 1.26 higher]	N/A	⨁◯◯◯ VERY LOW	CRITICAL
Bacteria density or presence/absence (eradication of P. aeruginosa)												
3[a,b,c]	Observational studies	Serious[1]	Not serious	Serious[2]	Serious[4]	No additional considerations	24/52 eradicated at approx. 12-15 months post-treatment	0/65 (all colonised at baseline)	In one study[a] 11/28 patients who received eradication Rx were free from *PsA* at 15 mo. In the second study[b] 13/24 patients who received eradication Rx were free from P*sA* at median 14.3 mo. In the third study[c] 8/35 (22.9%) of patients who received 2 wks IV and 5/50 (10%) 3 wks oral eradication Rx were free		⨁◯◯◯ VERY LOW	CRITICAL

									from PsA. The 41/67 (61.2%) who were then Rx with inhaled colistin were free PsA at 3 mo and 40.3% at 12 mo		
Recurrence											
1[b]	Observational study	Serious[1]	Not serious	Serious[2]	Serious[5]	No additional considerations	24	24	11/24 patients subsequently re-cultured P. aeruginosa with median time to reinfection 6.2 months	⨁◯◯◯ VERY LOW	CRITICAL
Hospitalisations											
2[b,c]	Observational study	Serious[1]	Not serious	Serious[2]	Serious[3]	No additional considerations	30 67	30 67	One study[a] reports mean number of hospital admissions were 0.39 in the year pre-eradication and 0.29 in the year post-eradication (p=non-significant) One study[c] reported mean number of hospital admissions were 1.14 (SD 1.56) in the year pre-eradication and 0.42 (SD 1.33) in the year during eradication using inhaled colistin (p<0.001).	⨁◯◯◯ VERY LOW	CRITICAL
Exacerbations											
2[b,c]	Observational study	Serious[1]	Not serious	Serious[2]	Serious[5]	No additional considerations	30	30	One study reports that exacerbation frequency was significantly reduced post-eradication, with mean number of antibiotic courses 3.93 in the year pre-eradication, and 2.09 in the year post-eradication (p=0.002) One study[c] reported	⨁◯◯◯ VERY LOW	CRITICAL

							67	67	mean number of total exacerbations were 3.4 (SD 4.21) in the year pre-eradication and 1.98 (SD3.62) in the year during eradication using inhaled colistin (p<0.001). Corresponding values for cycles of antibiotics were 1.94 (SD 2.8) and 1.18 (SD 1.73) (p=0.018).		
Adverse events											
1[b]	Observational study	Serious[1]	Not serious	Serious[2]	Serious[5]	No additional considerations	35	35	One study reports that no auditory acuity changes were found in either antibiotic eradication group. Serum creatinine concentration remained within the normal range throughout the study period in all patients.	⨁◯◯◯ VERY LOW	CRITICAL
Resistance											
2[a,b]	Observational studies	Serious[1]	Serious[6]	Serious[2]	Serious[4]	No additional considerations	65	65	One study[a] reports that tobramycin-resistant PsA was not detected in sputum during the study. Second study[b] reports that in four out of 11 patients in whom PsA was re-cultured, new antibiotic resistance occurred: aztreonam (n=1), ciprofloxacin, (n=1), ciprofloxacin and gentamicin (n=1), amikacin and gentamicin (n=1)	⨁◯◯◯ VERY LOW	IMPORTANT

Other CRITICAL outcomes: Cure/resolution of symptoms; duration of symptoms
Not assessed as no studies identified reporting these outcomes

Abbreviations: CI: Confidence interval; **PsA**: *Pseudomonas aeruginosa*; **Rx**: treatment

a. Randomised controlled trial in adults comparing intravenous plus inhaled eradication regimen for *P. aeruginosa* to intravenous alone. Baseline and post-eradication data (both groups combined) are used in the evidence table as both groups received an active intervention, hence treated as a before-and-after study for the purposes of this table. Therefore, this trial is classified as an observational study for the purposes of this analysis. *P. aeruginosa* diagnosed by sputum sample culture.

b. Retrospective before-and-after study in adults comparing outcomes before-and-after eradication therapy for patients identified from medical records with a new isolate of *P. aeruginosa*, which was detected by sputum sample culture.

GRADE

1. Downgraded once for risk of bias. Study design, possible confounding and lack of blinding considered a weakness in both studies contributing to evidence table
2. Downgraded once for indirectness; studies in adults assessing only P. aeruginosa.
3. Downgraded once for imprecision; small studies in which confidence intervals include no difference and possible harm or benefit from the intervention
4. Downgraded once for imprecision; small studies which we were unable to pool
5. Downgraded once for imprecision; single small study with few participants
6. Downgraded once for inconsistency; one study did not identify any resistance, while the other identified resistance in 4/11 patients in whom P. aeruginosa was re-cultured

Evidence to Decisions (EtD) framework

PICO question 6: In children/adolescents with bronchiectasis, should eradication treatment be used (irrespective of symptoms) when there is a new isolate of a potentially pathogenic microorganism (compared to no eradication treatment)?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in adults and children/adolescents, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged [15,21,22]. Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The European Respiratory Society guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation parent advisory group for this guideline.	Eradication of recently isolated *Pseudomonas aeruginosa* is now standard practice in people with CF. While intuitively, the practice in those with bronchiectasis should be similar, antibiotic regimes need to be balanced with appropriate antibiotic stewardship, which is a global priority.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We found no direct evidence in children/adolescents with bronchiectasis to answer this question. Evidence from three before-after trials in adults who underwent *P. aeruginosa* eradication indicate that patients may experience improved QoL compared to pre-eradication (mean change in SGRQ score -8.71, 95%CI -18.68 to 1.26). One study [52] reported a reduced exacerbation rate (mean number of antibiotic courses 3.93 in the year pre-eradication, and 2.09 in the year post-eradication, p=0.002). Another [53] reported the mean number of total exacerbations were 3.4 (SD 4.21) in the year pre-eradication and 1.98 (SD3.62) in the year during eradication with inhaled colistin (p<0.001). Corresponding values for cycles of antibiotics were 1.94 (SD 2.8) and 1.18 (SD 1.73) (p=0.018). The authors [53] also reported the mean number of hospital admissions were 1.14 (SD 1.56) in the year pre-eradication and 0.42 (SD 1.33) in the year during eradication using inhaled colistin (p<0.001) [53]. The	The panel considered it is likely that virtually all physicians with specific expertise in paediatric bronchiectasis would undertake interventions to eradicate initial or new isolates of *P. aeruginosa.* Once *P. aeruginosa* is confirmed present (eg. not a transient coloniser in upper airway samples from a clinically stable patient) eradication treatment should be administered promptly. There are limited supportive data from recent CF-related systematic reviews [55,56]. Both Cochrane Reviews looked for RCTs investigating interventions for the early eradication of specific bacteria in participants with CF. One review [55] found that eradication of

		earlier smaller study [52] however, reported a non-significant reduction in the mean number of hospitalisations in the year after treatment compared to the year before, but this finding was uncertain (0.39 in the year pre-eradication and 0.29 in the year post-eradication (p=non-significant, value not stated). In one study 11/28 patients who received eradication therapy were free from *P. aeruginosa* at 15-months [54] and in the second study 13/24 patients who received eradication therapy were free from *P. aeruginosa* at median 14.3-months [52]. The most recent study [53] reported that 8/35 (22.9%) of patients who received 2-weeks of intravenous antibiotics and 5/50 (10%) 3-weeks oral eradication treatment were free from *P. aeruginosa*. The 41/67 (61.2%) who were then treated with inhaled colistin no longer had *P. aeruginosa* detected at 3-months, declining to 40.3% at 12-months. We did not identify any evidence addressing symptom resolution or duration.	*P. aeruginosa* with nebulised antibiotics either alone or combined with oral anti-pseudomonal antibiotics, compared to placebo or no treatment, can achieve eradication in this population which may be sustained for as long as 2-years. However, the impact on clinical outcomes is uncertain. A second review [56] synthesised evidence from two studies in CF patients with lower airway infection by methicillin-resistant strains of *Staphylococcus aureus*. Authors report that while short-term (28-days) eradication rates are better in those receiving antibiotic treatment, the effects are not sustained, and clinical benefits are uncertain. Two further Cochrane Reviews [57,58], searched for interventions for eradicating *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia* respectively in CF, but did not identify any relevant RCTs.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Findings from the two adult before-after studies are inconsistent regarding antibiotic resistance, with one reporting tobramycin-resistant *P. aeruginosa* was not detected in sputum during the study [54], while the other found 4/11 patients in whom *P. aeruginosa* was re-cultured, had become antibiotic resistant [52]. The new resistance was to aztreonam (n=1), ciprofloxacin (n=1), ciprofloxacin and gentamicin (n=1), amikacin and gentamicin (n=1) [52]. The only study reported adverse events and found no auditory acuity changes in either antibiotic eradication group and serum creatinine concentrations remained within the normal range throughout the study period in all patients [54]. Recurrence was reported in one study [52]; 11/24 patients who successfully eradicated *P. aeruginosa*, re-cultured the organism during follow-up at median time of 6.2 months. Whether or not the same strain of *P. aeruginosa*-was recultured is unknown.	There was insufficient evidence in the Cochrane Reviews of CF patients to comment on undesirable effects. Potential undesirable effects include serious drug reactions, drug toxicity and inducing antibiotic resistance. Long-term intravenous antibiotics also expose an individual to risks associated with intravenous catheterisation, including line-site infections. Emergence of resistance is a serious concern for the wider community. Courses of nebulised or intravenous antibiotics, especially those delivered for extended periods, can place a high burden on children/adolescents and their carers.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low across all the outcomes assessed. Our certainty is reduced by methodological weaknesses of the three included studies, substantial indirectness of evidence, and for two outcomes, imprecision and inconsistency.	There is limited evidence from systematic reviews in CF to support the findings from the adult studies in bronchiectasis.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	We found limited indirect evidence for eradication, recurrence, antibiotic resistance and impact upon QoL, exacerbations and hospitalisations. Parent/patient advisory group and the panel consistently assessed all these outcomes to be of critical importance, other than antibiotic resistance, which was rated as important.	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The benefits and undesirable effects of the intervention in children/adolescents with bronchiectasis are uncertain from the evidence presented. Although benefits for the individual are potentially moderate-to-large, they have not been clearly demonstrated in well-conducted studies. Treatment for individual children/adolescents must be weighed against the well-established risks of antibiotics, both to the individual and the wider society.	The panel considered it is likely that virtually all physicians with specific expertise in paediatric bronchiectasis would undertake interventions to eradicate new isolates of *P. aeruginosa.* Once *P. aeruginosa* is confirmed present (eg. not a transient coloniser in upper airway samples from a clinically stable patient) eradication treatment should be administered promptly.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	We did not find any evidence to assess the resource requirements	Clinical experience suggests that the cost of delivering antibiotics will vary, depending on setting, duration, route and type of antibiotic, as well as between countries. Costs will be larger if the child/adolescent is hospitalised for intravenous antibiotics for 2-weeks, the current standard used by most specialists in resource rich countries when the child/adolescent is symptomatic with recently isolated *P. aeruginosa.* However, potential costs may be balanced by clinical improvements leading to savings, such as reduction in future exacerbations and hospitalisations.
CERTAINTY OF RESOURCE EVIDENCE	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	
COST EFFECTIVENES	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs	We did not find any evidence to assess cost-effectiveness.	

S	○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know ● No included studies		
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There is no published literature on health equity, but differential access (from living remotely or away from a major centre and specific expertise, costs) suggests presence of imbalance among patients, settings and countries.	Equity for the intervention is likely reduced as it requires access to facilities capable of isolating new pathogens (including the need for bronchoalveolar lavage in some cases where children are unable to expectorate or to provide reliable induced sputum specimens), securing and maintaining intravenous line access, availability of antibiotics (e.g. inhaled colistin or tobramycin), funding for hospitalisations and cost of antibiotics.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have limited evidence from included studies to comment on acceptability.	Clinical experience suggests that antibiotics are considered a routine part of care in bronchiectasis and most children/adolescents and their families will be accustomed to their intermittent use.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have limited evidence from included studies to comment on feasibility.	In most clinical settings where children/adolescents with bronchiectasis are cared for, provision of antibiotics will form a standard part of care. Feasibility may be limited in some settings by access to nebulised medications or intravenous access.

PICO 6: In children/adolescents with bronchiectasis, should eradication treatment be used (irrespective of symptoms) when there is a new isolate of a potentially pathogenic microorganism (compared to no eradication treatment)?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• In children/adolescents with bronchiectasis, we suggest eradication therapy following an initial or new detection of *Pseudomonas aeruginosa* (*conditional recommendation for the intervention, very low-quality evidence*) **Remarks**: Evidence in bronchiectasis is indirect and limited to three small observational studies in adults focussed on *P. aeruginosa* eradication. However, we suggest that eradication therapy should commence promptly after confirming *P. aeruginosa* is present (see Figure 3 in the main manuscript). Due to lack of evidence, we are unable to comment on eradication treatment for pathogens other than *P. aeruginosa*, which is informed on a case-by-case basis according to the clinical status and the pathogen type. Antibiotic treatment should be made available in every setting where children/adolescents with bronchiectasis are managed.				
JUSTIFICATION	There is an established association between lower airway infection with pathogenic microorganisms and deteriorating lung function and clinical status. While there is currently no evidence for early eradication from well-conducted trials in children/adolescents with bronchiectasis, the panel suggests eradication treatment for *P. aeruginosa*. This recommendation places a higher value on the theoretical benefits of eradication and patient/carer values and preferences and a lower value on possible treatment-related adverse effects.				
SUBGROUP CONSIDERATIONS	Patients with: ○ Daily productive/wet cough ○ Cerebral palsy/severe disabilities/neuromuscular disease ○ Underlying causes of bronchiectasis (e.g. primary ciliary dyskinesia, primary immunodeficiency) ○ Acute vs stable states ○ Co-infections ○ Exacerbation frequency				

IMPLEMENTATION CONSIDERATIONS	Eradication therapy should employ a targeted antibiotic strategy for the minimum time necessary and measures should be instituted to support full adherence to the prescribed regimen.
MONITORING AND EVALUATION	Clinical and microbiological data should be collected to determine the success of the eradication therapy. Depending on the antibiotic used, appropriate monitoring may be required, guided by local policy. This may include serum drug levels, renal and liver function and auditory function.
RESEARCH PRIORITIES	RCTs comparing immediate to delayed eradication may help to address this area of uncertainty, but are unlikely to be acceptable to healthcare practitioners and patients/care givers, as immediate eradication of pathogens, such as *P. aeruginosa* is considered standard practice in most settings. Well-designed RCTs in children/adolescents comparing different eradication regimes (eg. oral versus nebulised anti-pseudomonal antibiotics, alone or in combination, or parenteral antibiotics as single or dual agents, and for how long) would improve the directness of the available evidence. Studies should recruit children/adolescents with bronchiectasis confirmed by appropriate imaging, carefully document any important effect modifiers (including: age; aetiology and duration of bronchiectasis; symptoms; co-morbidities, co-infection; exacerbation frequency) in order to identify key subgroups who might most likely benefit from, or be harmed by, the intervention, and should measure patient-important outcomes including: eradication; exacerbations; hospitalisations; QoL; symptoms, days of school/work lost, and antibiotic resistance as well as carefully monitoring objective markers of lung function.

PICO question 7: In children/adolescents with bronchiectasis and recurrent exacerbations, should long-term (≥2-months) antibiotics (compared to no antibiotics) be used to reduce exacerbations?

Setting: Indigenous children in Australia and New Zealand
Subgroup: Children with bronchiectasis
Bibliography: [a]Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, Masters IB, Diaz A, McCallum GB, Mobberley C, Tjhung I, Hare KM, Ware RS, Chang AB. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013;1:610-620. doi: 10.1016/S2213-2600(13)70185-1.

Setting: South Korean centre
Subgroup: Children with bronchiectasis and increased airway hyper responsiveness
Bibliography: [b]Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. Eur Respir J. 1997;10:994-9.

Setting: Children in a South African chest clinic
Subgroup: Children with HIV and bronchiectasis
Bibliography: [c]Masekela R, Anderson R, Gongxeka H, Steel HC. Lack of efficacy of an immunomodulatory macrolide in childhood HIV-related bronchiectasis: a randomised, placebo-controlled trial. Journal of Antivirals and Antiretrovirals 2013;5:44–9.

Bibliography: Systematic reviews
[d]Gao YH et al. PLoS One. 2014;9(3):e90047. doi: 10.1371/journal.pone.0090047.
[e]Kelly C, Chalmers JD, Crossingham I, Relph N, Felix LM, Evans DJ ,Milan SJ, Spencer S. Macrolide antibiotics for bronchiectasis. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012406. DOI: 10.1002/14651858.CD012406.pub2.

Quality assessment							№ of patients		Effect		Quality	Outcome Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Long term macrolides**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
EXACERBATIONS - number of patients with exacerbations												
3[d] (data from a-c)	RCTs in children	not serious	not serious	not serious	not serious[1]	none	56/70 (80.0%)	50/75 (66.7%)	**RR 0.86** (0.75 to 0.99)	**93 fewer per 1.000** (from 167 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
EXACERBATIONS - number of respiratory exacerbations per patient on azithromycin (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	not serious	none	median of 2 (range of 0 to 9) exacerbations with azithromycin versus 4 (range 0 to 14) with placebo, corresponding to a incidence rate ratio of 0.50 (95% CI 0.35 to 0.71) (p<0.0001)				⊕⊕⊕⊕ HIGH	CRITICAL

HOSPITALISATION - children hospitalised (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	serious[2]	none	3/45 (6.7%) [i]	9/44 (20.5%)	**RR 0.33** (0.09 to 1.12)	**137 fewer per 1.000** (from 186 fewer to 25 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
DAYS LOST FROM SCHOOL												
1[a]	RCT in children	not serious	not serious	very serious[3]	not serious	none	Non significant difference in the reduced school attendance as a result of children cough (3 of 18 [17%] in the azithromycin group vs six of 22 [27%] in the placebo group, p=0·48).				⊕⊕◯◯ LOW	CRITICAL
LUNG FUNCTION - FEV_1 % predicted (by the end of the study)												
2[e] (Data from a and b)	RCTs in children	not serious	not serious	not serious	serious[4]	none	31	34	-	MD **1.73 higher** (3.32 lower to 6.78 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
ADVERSE EVENTS - serious adverse events (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	serious[6]	none	11/45 (24.4%) [i]	19/44 (43.2%)	**RR 0.57** (0.31 to 1.05)	**186 fewer per 1.000** (from 298 fewer to 22 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ADVERSE EVENTS - any adverse events (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	serious[7]	serious[6]	none	26/45 (57.8%) [i]	28/44 (63.6%)	**RR 0.91** (0.65 to 1.27)	**57 fewer per 1.000** (from 223 fewer to 172 more)	⊕⊕◯◯ LOW	CRITICAL
ANTIBIOTIC RESISTANCE - macrolide-resistant bacteria (any) in nasopharyngeal swab (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	serious[8]	none	19/41 (46.3%)	4/37 (10.8%)	**RR 4.29** (1.61 to 11.45)	**356 more per 1.000** (from 66 more to 1.000 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

ANTIBIOTIC RESISTANCE - macrolide-resistant *Streptococcus pneumoniae* in nasopharyngeal swab (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	serious[8]	none	11/41 (26.8%)	1/37 (2.7%)	**RR 9.93** (1.35 to 73.22)	**241 more per 1.000** (from 9 more to 1.000 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
ANTIBIOTIC RESISTANCE - macrolide-resistant *Staphylococcus aureus* in nasopharyngeal swab (follow up: median 20.7 months)												
1[a]	RCT in children	not serious	not serious	not serious	serious[1]	none	11/41 (26.8%)	3/37 (8.1%)	**RR 3.31** (1.00 to 10.95)	**187 more per 1.000** (from 0 fewer to 807 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Other CRITICAL outcomes: Lost days of work, time to next exacerbation, quality of life												
Not reported in the studies identified												

CI: Confidence interval; **IQR:** inter-quartile range; **RR:** relative risk; **RCT:** randomised controlled trial

1. Although the total sample size is relatively small, we did not downgrade on the balance of other factors
2. Limited sample size in a study designed to show differences in terms of exacerbations; in consequence estimates for secondary outcomes could be unpowered (large confidence intervals)
3. Surrogate measure of the outcome of interest
4. Imprecise estimates due to the limited sample size from the studies
5. Downgrade once from indirectness as all children had HIV and receiving anti-retrovirals.
6. Study with limited sample size designed to show differences in terms of exacerbations; in consequence estimates for secondary outcomes could be unpowered (large confidence intervals
7. Adverse events in study were not restricted to those that are directly attributable to treatment, and reported some related to disease exacerbations
8. Effect estimate and the values in the 95% CI show a large impact from the intervention, but CI shows wide boundaries and the trial showed a non-balanced attrition which may affect the effect estimate

Evidence to Decisions (EtD) framework

PICO 7: In children/adolescents with bronchiectasis and recurrent exacerbations, should long-term (≥2-months) antibiotics (compared to no antibiotics) be used to reduce exacerbations?

Domain	Judgement	Research evidence	Additional considerations
PRIORITY **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Long-term antibiotics are often used to reduce exacerbations or 'attacks'. The panel and parents advisory group consider this important as acute exacerbations have major negative health impacts on people with bronchiectasis and are particularly important in children/adolescents as they are associated with increased parental stress, anxiety and depression [59], increased respiratory symptoms, impaired QoL, accelerated lung function decline (-1.9 FEV_1% predicted per hospitalised exacerbation) and substantial healthcare costs.[8,27]
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The evidence summary shows that using long-term macrolides reduces acute respiratory exacerbations. There is high-level evidence of azithromycin halving the frequency of exacerbations (incidence rate ratio [IRR] of 0.5, 95%CI 0.35- 0.70) [60] and moderate quality evidence that it also reduces the number of children with any exacerbations over the trial period. Long-term azithromycin also likely reduces hospitalisation and improves lung function, but these outcomes are not statistically significant, limited by the small sample sizes.	The panel considered that the desirable effects are large as preventing exacerbations is one of the goals of managing children with bronchiectasis.
UNDESIRABLE	**How substantial are**	There was no significant difference in serious adverse	Antibiotic associated side effects are generally minor

EFFECTS	**the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	events when azithromycin was compared to placebo. In fact, serious adverse events were non-statistically lower in the azithromycin group (RR 0.57, 95%CI 0.31 to 1.05). However, there was a significant increase in macrolide-resistant bacteria (any) in the upper airways (nasopharyngeal swabs) in those on long-term azithromycin compared to placebo. Furthermore, in-depth microbiological analysis showed that post-intervention (median 6-months), macrolide-resistance in *Streptococcus pneumoniae* declined significantly in the azithromycin group, from 79 % (11/14) to 7 % (1/14) of positive swabs, but *S. aureus* strains remained 100 % macrolide-resistant [61].	and do not outweigh the benefits. Selection of macrolide-resistant pathogens in the upper airways, whose clinical significance in regard to treating lower airway infections is uncertain at an individual level, and potential for transmitting these organisms to others at a community level means caution should be used when prescribing these agents long-term. The sole study in the evidence table with low-risk of bias for all factors, [60] reported in their post-hoc analyses that antibiotic use for non-pulmonary infections was significantly lower in the azithromycin group compared to placebo; IRR 0.50; 95% CI 0.31–0.81, p=0.005. This result was driven by episodes of otitis media and impetigo, and is biologically plausible as further data showed that nasopharyngeal carriage by *Haemophilus influenzae* and *Moraxella catarrhalis* was significantly lower in azithromycin compared to placebo groups and azithromycin is also active against *Streptococcus pyogenes* [61]. Other data have demonstrated that adherence of at least 70% is important for efficacy [60] as well as reducing the risk of antibiotic resistance [61]. Further analysis of the RCT showed that adherence ≥70 % (versus <70 %) in the Australian azithromycin group was associated with lower carriage of any pathogen [odds ratio (OR) 0.19, 95 %CI 0.07-0.53] and fewer macrolide-resistant pathogens (OR 0.34, 95 % CI 0.14-0.81).
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low	The overall certainty of evidence is moderate. For the critical outcomes, the certainty of the evidence of effects was high for one (exacerbation), low in one (days lost from school) and moderate in the remainder. Most endpoints were rated as moderate certainty of evidence with imprecision of estimates the main concern. The outcome 'days lost from school' was substantially limited by parent-	

	○ Moderate ○ High ○ No included studies	reporting and small sample size; we therefore decided not to downgrade the overall certainty of the evidence for this question based on this outcome alone.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Probably important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The European Lung Function parents' survey showed that exacerbations were one of the top three factors that affected the child/adolescent's QoL. A reduction in exacerbation frequency and/or severity is considered important.	The panel and parents advisory group consider reducing exacerbations important as acute exacerbations have major negative health impacts on people with bronchiectasis and are particularly important in children/adolescents as they are associated with increased parental stress, anxiety and depression [59], increased respiratory symptoms, impaired QoL, accelerated lung function decline (-1.9 FEV_1% predicted per hospitalised exacerbation) and substantial healthcare costs.[8,27]
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative	From a single well-conducted RCT, we have identified clear evidence of benefits, which are clinically relevant without evidence of clinically meaningful adverse events. The selection of macrolide-resistant respiratory pathogens is acknowledged, but the available evidence does not indicate this compromises clinical care, at least in the short to intermediate-term in patients with frequent exacerbations. Additional data from two other RCTs support the benefit of other critical outcomes, albeit with only moderate certainty (rather than a definite significant difference between groups). The balance of risk and	

	○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	benefit clearly favour the intervention.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No available studies	The antibiotics used are inexpensive and any costs may be offset by savings in terms of repeat attendance at primary or secondary care for recurrent exacerbations (this is based on clinical experience).
CERTAINTY OF RESOURCE EVIDENCE	○ Very low ○ Low ○ Moderate ○ High ● No included studies	No available studies.	In the absence of studies, this is based on clinical experience.
COST-EFFECTIVENESS	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	There are no studies on cost-effectiveness. However, the panel holds the opinion that the use of long-term antibiotics for reducing exacerbations are cost-effective for the group of patients with recurrent exacerbations. A recent Australian study based in a tertiary hospital reported that each hospitalised exacerbation cost the

			health sector in 2016 ~$AUD31,000 and the parents ~$AUD2,700 [62] (€19,000 and €1,650 and £16,900 and £1,475 respectively).
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	Timely treatment of exacerbations may be a problem in some settings where patients do not have easy access to healthcare facilities or to appropriate antibiotics (This is based on clinical expertise).
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	Although experts continue to highlight the risk of antibiotic resistance, long-term antibiotic treatment to prevent or reduce exacerbations is generally acceptable to most clinicians and patients. (This is based on clinical experience).
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	Using long-term antibiotics should be feasible in most settings. Feasibility may be an issue in settings where parents/children/adolescents have reduced access to healthcare and appropriate antibiotics (this is based on clinical experience).

<table>
<tr><th colspan="6">PICO7: In children/adolescents with bronchiectasis and recurrent exacerbations, should long-term (≥2-months) antibiotics (compared to no antibiotics) be used to reduce exacerbations?</th></tr>
<tr><td>TYPE OF RECOMMENDATION</td><td>Strong recommendation against the intervention

○</td><td>Conditional recommendation against the intervention

○</td><td>Conditional recommendation for either the intervention or the alternative

○</td><td>Conditional recommendation for the intervention

○</td><td>Strong recommendation for using macrolides for reducing exacerbation

●</td></tr>
<tr><td>RECOMMENDATION</td><td colspan="5">In children/adolescents and adolescents with bronchiectasis and recurrent exacerbations, we recommend treatment with long-term macrolide antibiotics to reduce exacerbations (Strong recommendation, low-quality of evidence).
Remarks: We suggest long-term macrolide antibiotics only in those who have had >1 hospitalised or ≥3 non-hospitalised exacerbations in the previous 12-months.

Such a course should be for at least 6-months with regular reassessment to determine whether the antibiotic continues to provide a clinical benefit. Children/adolescents receiving longer treatment courses (>24-months) should continue to be evaluated for risk versus benefit.

This suggestion is in the context of lacking data concerning when long-term azithromycin should be initiated and the need for caution because of increasing antibiotic resistance amongst bacterial pathogens within patients and the community.

While non-tuberculous mycobacteria (NTM) are very rarely detected in children/adolscents with bronchiectasis, we suggest a lower airway specimen is obtained (when possible) to exclude their presence before commencing long-term macrolide antibiotics.

We encourage strategies to ensure adherence to the macrolide regimen as ≥70% adherence improves efficacy and reduces antibiotic resistance amongst respiratory bacterial pathogens.</td></tr>
<tr><td>JUSTIFICATION</td><td colspan="5">Our strong recommendation is based on one high-quality 24-month RCT in children/adolescents and two other lower quality RCTs in addition to extensive clinical experience. All, but one, outcome was rated at least moderate certainty and the substantial reduction in exacerbations showed a benefit for the critical outcomes for this intervention.

Importantly, the trial did not detect an increase in adverse clinical events in the antibiotic treatment groups compared to placebo.</td></tr>
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	However, there is an increase in azithromycin-resistant bacteria in the upper airways of children who received long-term azithromycin. Nevertheless, the RCT showed that non-macrolide antibiotic use for non-pulmonary infections was significantly lower in the azithromycin group compared to placebo. Prevention of respiratory exacerbations of bronchiectasis in children is considered important for future clinical outcomes, and accords with views of parents and children.
SUBGROUP CONSIDERATIONS	None
IMPLEMENTATION CONSIDERATIONS	While an electrocardiogram is not necessary before commencing macrolides, a family history of prolonged QT syndrome, arrhythmias and acute cardiac events should be obtained and when appropriate an electrocardiogram obtained. Azithromycin should not be used in children/adolescents with contraindications to macrolides. This includes children/adolescents with an abnormal electrocardiogram, liver function abnormalityand hypersensitivity to azithromycin.
MONITORING AND EVALUATION	Patients should be monitored for liver function abnormalities, if possible lower airway microbiology, and clinical response to the long-term macrolides at least annually while receiving macrolides. Some children also develop abdominal discomfort, diarrhoea, nausea and vomiting. The need to continue the long-term antibiotic should be evaluated with a trial of time-off macrolides that is individualised, but takes place no longer than 24-months post-commencement of azithromycin.
RESEARCH PRIORITIES	RCTs are required to identify children/adolescents with bronchiectasis who are most likely to benefit from long-term azithromycin (e.g. number of exacerbations/year), as well as to define the optimum duration of treatment, describe how long these beneficial effects persist, and establish the clinical significance of acquiring azithromycin-resistant pathogens. Studies should recruit children/adolescents with bronchiectasis confirmed by appropriate imaging, carefully document any important effect modifiers (including: age; aetiology and severity of underlying bronchiectasis, co-morbidities, lower airway pathogens (including microbiota), exacerbation frequency). Outcome measure should include patient-important outcomes including: time-to-next exacerbation, hospitalisations, QoL, days of school/work lost, adverse events and induction of antimircobial resistance.

NQ1 – Narrative summary of evidence table

In children/adolescents with suspected or confirmed bronchiectasis, what standard tests that impact on clinical outcomes should be undertaken when managing this group of patients?

First author, year, country	Study design	Inclusion and exclusion criteria	N; age	Main aim (s)	Primary findings related to narrative question	Other major findings and additional comment	Implications for narrative question
Babaygit [63] 2009, Turkey	Retrospective; single centre	Inclusion: HRCT-confirmed bronchiectasis	n=66; Mean age 9.2 years SD 4.38	Determine the characteristics of children with bronchiectasis and evaluate the aetiology	All: Sweat chloride, serum IgA, IgG and subgroups, IgM, IgE and α1 antitrypsin. All patients aged > 6 years had spirometry. Selected patients: CFTR mutation analysis; FB (n=15) in those where the etiology of bronchiectasis could not be found to exclude foreign body aspiration and to obtain BAL; Barium fluoroscopy or/and gastroesophageal reflux scinti-scans undertaken in those with symptoms of swallowing problems and gastroesophageal reflux, cilia electron microscopy for PCD with history of recurrent sinusitis, otitis, pneumonias, situs inversus	Attributed aetiology identified in 44 (66.7%). Four most common attributed were post-infections (21.2%), asthma (16.7%), aspiration syndromes +/- gastroesophageal reflux disease (9.1%) and immunodeficiency syndromes (7.6%)	Standard panel used with additional tests undertaken in selected children. None had alpha-1 antitrypsin deficiency or foreign body.
Bahçeci [64] 2016, Turkey	Retrospective; single centre	Inclusion: HRCT-confirmed bronchiectasis Exclusion: CF	n=110; Mean age=167 months, SD 39	To determine the changes in etiology of bronchiectasis in the last 10 years	All: FBC, sputum culture, immunologic tests (pneumococcal vaccine response, IgG, IgA, IgM, IgE and IgG subgroups, lymphocyte panel, complement levels), sweat test, tuberculin skin test, -antitrypsin level, saccharin test) Selected: gastroesophageal scintigraphy, FB with BAL, Mantoux	Attributed underlying aetiology identified in 93 (84.6%). Most common attributed aetiology were PCD 26.4% (n=29), persistent bacterial bronchitis 22.8% (n=25), immunodeficiency 11.8% (n=13). Aetiologic factors changed over time with reduction in asthma and tuberculosis	Standard panel used with additional tests undertaken in selected children. Foreign body found in 2 children. None had alpha-1 antitrypsin deficiency
Beckeringh [65], 2019, Netherlan	Retrospective; single	Inclusion: HRCT-confirmed	n=69; Children aged ≤18	Map and evaluate all diagnostic data of a pediatric non-	Planned but all: (1) bacterial culture of sputum or cough swab; (2) spirometry if possible; (3) immunology (serum Ig, IgG subclasses, specific	Attributed underlying aetiology identified in 63 (91%). Most common was	Knowing aetiology from tests led to change in

ds	centre	bronchiectasis diagnosed 2003-2017 Exclusion: CF	years	CF bronchiectasis cohort	antibody responses to vaccines, lymphocyte subsets and proliferation tests Selected: Tests for autoimmune diseases; bronchoscopy and bronchoalveolar lavage (if bronchiectasis is limited to 1 lobe), obtain bacterial culture and biopsy for PCD diagnostics	post-infection 29% (n=20), immunodeficiency 29% (n=20), congenital 10% (n=7), aspiration 7% (n=5)	management in 22% (n=15) including 2 from bronchoscopy (foreign body and carcinoid tumour)
Chang [1] 2003, Australia	Retrospective; single centre; First Nations	Inclusion: HRCT-confirmed bronchiectasis Exclusion: CF	n=65; age <15 years	Describe demographics, evaluate the effectiveness of routine investigations	Routine : FBC, serum IgA, IgG and subgroups, IgM, Ig response to diphtheria and tetanus, Mantoux Selected: CH50, lymphocyte stimulation test, neutrophil function test, pHmetry, oesophagoscopy or barium meal, echocardiography, FB	Tests altered specific management in 12.3% of cohort (immunoglobulins n=2, tuberculosis treatment n=1, aspiration n=3, surgery for congenital abnormality n=2	Standard panel used with additional tests undertaken in selected children. Even in setting of high infection rate, panel of tests leads to altered management
Dogru [66] 2005, Turkey	Retrospective; single centre	CXR, broncho-graphy, or CT or biopsy-based bronchiectasis Exclusion: CF	n=204; mean age =7.2 years SD 3.72	Determine number of children with non-CF bronchiectasis, and evaluate the risk factor	All: CXR, FBC, nasal smear, serum IgA, IgG, IgM, IgE and spirometry if aged > 6 years Selected: Rigid bronchoscopy, bronchography, plain sinus x-ray, nasal biopsy, lung scintigraphy, Mantoux (If history of contact present) and echocardiogram	Attributed underlying aetiology identified in 51%. Most common attributed aetiology were post-infections 16.1%, asthma 11.8%, PCD 11.8%, immunodeficiency 5.4%	Standard panel used with additional tests undertaken in selected children. Foreign body found in 7 children
Eastham [3] 2004, UK	Retrospective; single centre	Inclusion: HRCT-confirmed bronchiectasis Exclusion: CF	n=93; median age symptom onset 1.1 years (range: 0-16 years)	Describe cohort of children with bronchiectasis	All: Cough swab, sputum or BAL. Selected 'at discretion of the attending paediatrician': FB, serum IgA, IgG and subgroups, IgM, Ig response to diphtheria and tetanus, Ig response to tetanus, *H. influenzae* type b, *S. pneumoniae*, nasal brushings for ciliary beat frequency and electron microscopy. Sweat tests performed in all cases unless bronchiectasis was limited to one lobe and there was an obvious associated clinical diagnosis, or if the child had received a cardiac transplant	Attributed underlying aetiology identified in 72%. Most common attributed aetiology were post-infection (30%), immunodeficiency(21%), bronchiolitis obliterans (9%), congenital lung abnormalities (5%)	Fewer tests in standard panel.

Edwards [67] 2003, New Zealand	Retrospective	Inclusion: HRCT-confirmed bronchiectasis between 1998-2000 and lived in Auckland region. Exclusion: CF	n=60; median age 10 years (range 1-17)	Document the number of children in Auckland with bronchiectasis, their severity, clinical characteristics and possible aetiologies	All: FBC, erythrocyte sedimentation rate, sweat test, serum and specific Igs. Selected: respiratory virology, barium meal or video fluoroscopy, tests for allergic bronchopulmonary aspergillosis, humoral immunity (specific antibodies and response to vaccines) and cellular immunity (T and B cell function, lymphocyte markers), complement pathways and NBT, cilia structural analysis, FB, CF mutational analysis, sinus CT scan and oesophageal pHmetry	Attributed underlying aetiology identified in 50%. Most common attributed aetiology were post-infection 25%, immunodeficiency 12%, aspiration 10%	Standard panel used with additional tests undertaken in selected children.
Erdem [68], 2011, Turkey	Case control	Inclusion of cases: HRCT-confirmed bronchiectasis Exclusion: CF Controls: healthy age matched	n=54; mean age 11.5 years, SD 3.1	Assess sleep quality and associated factors in children with bronchiectasis	All: serum IgG and subclasses, IgA, IgM, IgE, lymphocyte subset, neutrophil function (NBT, chemotaxis), skin prick tests, sweat test, Mantoux. Selected: barium fluoroscopy and pHmetry (swallowing problems and gastroesophageal reflux), electron microscopy of nasal cilia ultrastructure (recurrent otitis and sinusitis), FB and α1 antitrypsin levels (not specified).	Attributed underlying aetiology in 54%. Most common attributed aetiology: immune-deficiency 24%, PCD 13%, post-infection 9%. Sleep quality of children with bronchiectasis compared to controls were poor	No foreign body or α1 antitrypsin deficiency mentioned as aetiology
Guran [69], 2007, Turkey	Prospective cross-sectional	Inclusion: HRCT-based bronchiectasis Exclusion: CF	n=27; median age 11.4 years (IQR 9.5–13.6)	Describe clinical, radiological and laboratory features of children	All: serum IgG and subclasses, IgA, IgM, IgE, lymphocyte subset analysis, skin prick tests, spirometry with bronchodilator response, sweat test and Mantoux Selected: FB, ciliary studies, aspiration and gastro esophageal reflux studies, α1 antitrypsin level	Attributed underlying aetiology in 37%. Most common attributed aetiology: PCD 11%, post-infection 11%, gastroesophageal reflux 7.4%. Parents of 48% of cohort were first cousins	Standard panel used with additional tests undertaken in selected children. No foreign body or α1 antitrypsin deficiency mentioned as aetiology
Karadag [70] 2005, Turkey	Retrospective, single centre	Inclusion: HRCT-confirmed bronchiectasis and followed up for at least	n=111; mean age 7.4 8 years SD 3.7	Describe the characteristics, underlying causative factors and long-term follow-up	All: serum IgG and subclasses, IgA, IgM, IgE, NBT sweat test, Mantoux, sputum cultures, spirometry (when possible), skin prick, Selected: FB (recurrent/persistent atelectasis or consolidation), barium fluoroscopy and 24-hour pH monitoring (swallowing problems and	Attributed underlying aetiology in 62.2%. Most common attributed aetiologies: post-infection 29.7%, immunodeficiency 15.3%, PCD 6.3%, asthma	Standard panel used with additional tests undertaken in selected children. Foreign body in 4

		2 years			gastroesophageal reflux symptoms), cilia ultrastructure, α1 antitrypsin level	4.5%	(3.6%)
Kim [71], 2011, Korea	Retrospective; single centre	Inclusion: CT-confirmed bronchiectasis	n=92; median 7.6 years age (range 2 months to 18 years)	Determine the characteristics, clinical features, underlying aetiologic factors	Test "at discretion of physician": serum Igs, α1-antitrypsin, complement levels, lymphocyte subsets, and nitroblue-tetrazolium test, respiratory virus (nasopharyngeal aspirate); sputum; Mantoux test, pHmetry, barium esophagography; bronchoscopic biopsy and BAL electron microscopy of the nasal or bronchial mucosa cilia; sweat test; and genetic studies.	Attributed underlying aetiology identified in 86%. Most common attributed aetiologies: bronchiolitis obliterans 33%, post-infection 21%, interstitial lung disease 17%, immunodeficiency 9%, PCD 4%	53% managed according to specific aetiology identified
Kumar [20], 2015, India	Retrospective, single centre	Inclusion: HRCT-based bronchiectasis	n=80; mean 9.6 years (range 2-15)	Describe clinical profile, etiology and outcomes	Study did not describe whether a standard panel of tests were undertaken in all. Tests described were CXR, sputum, BAL and gastric aspirates, Mantoux test, immunoglobulin profile, FB, nuclear med scan, barium swallow, exhaled nitiric oxide, tests for ABPA	Attributed underlying aetiology identified in 63.8%. Most common attributed aetiologies: post-infection 23.8%, suspected PCD 15%; immunodeficiency 6.2%, ABPA 7.5%	Foreign body in one child
Lee [72], 2019, Korea	Retrospective/ multi-centre (28 hospitals)	CT-confirmed bronchiectasis	n=387; mean age of 9.2 years of age (range 0, 24)	Investigate aetiologies and clinical features	Study did not describe whether a standard panel of tests were undertaken in all. Tests described Mantoux test in 22.7% (positive response of 4/80, 15.7%), immunoglobulin profile in 27.1%, FB in 26.8%, alpha-1 antitrypsin levels 6.1% (all negative), genetic testing in 3.2% of which 6/11 were positive	Attributed underlying aetiology identified in 63.8%. Most common attributed aetiologies: post-infection 55.3%, bronchiolitis obliterans 14.3%, tuberculosis 12.3%, heart diseases 5.6%	
Nathan [19], 2014, Malaysia	Cross-sectional and retrospective, single centre	Chronic suppurative lung disease, bronchiectasis (including CF) and bronchiolitis obliterans	n=60; median age 7.4 years (range 0.7-18.8) at diagnosis	Investigate the impact of chronic suppurative lung disease on growth and lung function in the child and quality of life	All: Serum IgG, IgA, IgM, IgE levels, T and B lymphocytes, complement levels, FBC, sweat test and faecal fat, gastric lavage or induced sputum, Mantoux test for tuberculosis, lung function, HRCT with contrast Selected: electrocardiogram, echocardiogram, barium swallow	Attributed underlying aetiology identified in cohort selected for study was 81.7%. Most common attributed aetiologies: post-infection 40.1%, CF 16.7, syndromes 8.3, congenital malformation 10%	Standard panel used with additional tests undertaken in selected children.

Li [73], 2005, UK	Retrospective, 2 hospitals	Inclusion: HRCT-confirmed bronchiectasis Exclusion: CF	n=136; median age 12.1 yrs (range 3.1, 18.1)	Review aetiology of bronchiectasis; determine how often making a specific diagnosis leads to management change; assess whether bronchiectasis aetiology can be differentiated based on HRCT findings	Planned for all: serum IgG, IgA, IgM, IgE levels, complement levels, FBC, specific antibody response to pneumococcus, haemophilus and tetanus, lymphocyte subsets, antigen/mitogen stimulation tests, staphylococcal and candida killing-ability tests and HIV screening test, α1-antitrypsin, cough swab and sputum culture; Mantoux test; pH metry; FB and BAL (lipid-laden macrophages and culture), nasal ciliary beat frequency using light microscopy, spirometry (age appropriate). Selected: α1-antitrypsin genotype (if levels abnormal); cilia electron microscopy (clinical suspicion or light microscopy abnormal), barium meal (aspiration or gastrointestinal anomalies suspected), videofluoroscopy (dysfunctional swallowing suspected)	Attributed underlying aetiology identified in 101 (74.3%). Most common attributed aetiologies: immunodeficiency 46 (33.8%), aspiration 25 (18.4), PCD 20 (14.7%) post-infection 5 (3.7%), congenital malformation 5 (3.7%) Underlying cause of bronchiectasis had no correlation to distribution of HRCT abnormalities	Not all children had planned assessment e.g. 101 had immunology assessment (yield rate 42%), FB and BAL (yield rate 8/68, 12%) In 77 children (56.6%), identifying cause led to change in management.
Pizzutto [74] 2013, Australia	Prospective, single centre	Inclusion: HRCT-confirmed bronchiectasis Exclusion: CF	n= 56 Median age 2.2 years (range 0.8, 9.8)	Evaluate the contribution of FB and BAL to the initial management of children newly diagnosed with bronchiectasis	All: FBC, serum IgG, IgA, IgM, IgE levels, antibody responses to tetanus protein and pneumococcal polysaccharide vaccine antigens, sweat test, FB and BAL (culture and cell differential count)	25 occasions where FB and BAL altered clinical management in 23 (41%) children	In selected cohorts, FB and BAL are useful as its findings alter management
Santamaria [75], 2009, Italy	Retrospective, two centres	HRCT-confirmed bronchiectasis Exclusion: CF	n=105; median age of 7.9 years (range 0.1–17)	Assess HRCT localisation and extent and determine whether asthma status, atopy and bronchiectasis distribution are associated with bronchiectasis aetiology	Paper did not mention whether standard panel was used in all listed a large gamete of test to determine underlying aetiology. These were all the test listed in box above	List of aetiology not provided. Atopy higher prevalence in children without underlying aetiology c.f. with underlying aetiology. Spirometry and extend of bronchiectasis on CT were similar in both groups	
Satirer [76], 2018, Turkey	Retrospective, single	CT-diagnosed bronchiectasis, Exclusion: CF	n=187; median age 16.2	Describe clinical characteristics, laboratory, and	Paper did not describe if standard panel was undertaken. Tests described were: sputum cultures, FB with BAL, immunoglobulin titers (IgA,	Attributed underlying aetiology identified in 77.5%. Most common	

	centre Exclusion : CF		years (range 4, 28)	radiological findings	IgM, IgG, IgE), spirometry, lymphocyte subsets, NBT, complement, radiological assessment of swallow oesophagus stomach duodenum, pH metry, nasal NO, video microscopy, electron microscopy	attributed aetiologies: PCD 51%, immunodeficiency 15%, tuberculosis 11, post-infection 3.2%. Parents consanguineous marriage in 59%	
Scala [77], 2000, Italy	Retrospective, single centre	Inclusion: Underwent FB and broncho-graphy for recurrent upper airway purulent infections or hemoptysis in last 6 months	n=144; age 2-65 yrs Bronchiectasis n=49, mean age= 28.1 years, SD 15.4	To evaluate the prevalence, age distribution and aetiology of bronchiectasis	All: serum IgG and subclasses, IgA, IgM, IgE, ABPA assessment, alpha1-antitrypsin, lymphocyte subpopulations, HIV, sweat test, CXR and sinus X-rays Selected: echocardiography and abdominal ultrasound (when dextrocardia suspected)	Bronchiectasis found in 49 (34%), underlying cause for symptoms found in 29/144 (20.1%): middle lobe syndrome 4/29 (13.8%), airway malformation 4/29 (13.8%), post-infection 3/29 (10.3%), immunodeficiency 2/29 (6.9%). Aetiology for bronchiectasis found in 22/49 (44.9)	Standard panel used with additional tests undertaken in selected children.
Twiss [78], 2005, New Zealand	Prospective, multi centre	Inclusion: HRCT-confirmed bronchiectasis, daily productive cough >6 wks or 3 months per yr for 2 yrs, persistent CXR changes and no CF	n=64; age <15 years	Estimate incidence of bronchiectasis, aetiology and severity, and evaluate regional and ethnic variation	Standard panel was not undertaken. FBC done in 97%, Ig levels in 88% (30% elevated, 2% low); specific antibody responses in 46%, Ig subclass in 26%, complement in 25%; nitroblue-tetrazolium test in 14%; ciliary beat in 8% (all normal), reflux/aspiration in 28% (48% abnormal), sputum (n not reported), sweat test in 73%	Attributed underlying aetiology identified in 65%. Most common attributed aetiologies: post-infection 34.4%, post oncology 17.2%, immunodeficiency 9.4%, aspiration 9.4%	Standard panel was not undertaken but attributed aetiology for bronchiectasis was still high
Zaid [12], 2010, Ireland	Retrospective, 3 hospitals	Inclusion: HRCT-confirmed bronchiectasis, diagnosed 1996-2006. Exclusion: CF	n=95; median age 6.4 years (range 1.5-13)	Determine clinical presentation, aetiology, co-morbidity, severity and lobar distribution of NCFBC in Irish children	All: FBC, sweat test, sputum microbiology, Igs, complement levels, specific antibody response to pneumococcus, Haemophilus and tetanus. Selected: extended immunologic evaluation, genetics, Mantoux test, lower oesophageal pH probe, pulmonary function tests, barium swallow, video fluoroscopy, FB & BAL, cilia (beat frequency and electron microscopy)	Attributed underlying aetiology identified in 67%. Most common attributed aetiologies: post-infection 17%, immunodeficiency 16%, aspiration 16%, PCD 9%, chronic aspiration with immunodeficiency 5%	Standard panel used with additional tests undertaken in selected children.

ABPA=allergic broncho-pulmonary aspergillosis, BAL=bronchoalveolar lavage fluid; CF=cystic fibrosis; CT=computed tomography, CXR=chest X-ray, FB: flexible bronchoscopy; FBC=full blood count; HRCT=high-resolution computed tomography; Ig=immunoglobulin; NBT=nitroblue-tetrazolium test, PCD=primary ciliary dyskinesia

Evidence to Decisions (EtD) framework

NQ1: In children/adolescents with suspected or confirmed bronchiectasis, what standard tests that impact on clinical outcomes should be undertaken when managing this group of patients?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to CF, than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	The panel considered that early identification and treatment of underlying conditions is highly important, as the intervention may improve long-term clinical outcomes. Thus, the determination of a standard set of investigations will help screen major causes of bronchiectasis that are common or critical, such as immunodeficiency, infection, or cystic fibrosis, at an early stage of management.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The narrative summary only identified (mostly retrospective) observational studies. There were only two studies that reported the yield of the tests used. Nevertheless, the narrative summary found that there are several investigations that are commonly undertaken in addition to a HRCT-scan (to confirm the diagnosis of bronchiectasis in children/adolescents suspected of this chronic disorder). These are: sweat test (to exclude CF), spirometry, full blood count, and immunological tests (total IgG/A/M/E, and immune responses to vaccine antigens) and lower airway bacteriology. Spirometry helps identify disease severity and is used for monitoring. Full	As this question was reviewed only narratively and GRADEing of the evidence was not performed, our confidence in our conclusions is limited

		blood counts screen for signs of immunodeficiency, such as lymphopenia, neutropenia or lymphocytosis. A panel of the immunological tests may also help to identify immunodeficiencies, where in selected cases immunoglobulin replacement therapy can help improve clinical outcomes. However, while most studies undertook a panel of tests, these differed between studies. Given the prevalence of tuberculosis in some settings, tuberculin skin test (also interferon-γ release assays) was a standard screening investigation taken in countries where tuberculosis is prevalent. While some studies undertook α1-antitrypsin levels, none of the studies identified α1-antitrypsin deficiency as a cause of bronchiectasis. Additional tests frequently considered by experts include, diagnostic bronchoscopy with bronchoalveolar lavage (BAL), additional tests for tuberculosis (sputum smear microscopy, mycobacterial culture or molecular-based tests; eg Xpert MTB/RIF according to clinical circumstances), aspiration, and primary ciliary dyskinesia. These are generally undertaken based on clinical presentation although one study undertook flexible bronchoscopy in every child. From the tests undertaken, an underlying aetiology of bronchiectasis was identified in 34-86% of cases investigated. In the two studies, which reported specifically on the diagnostic yields for tests, that for immunology evaluation was 42% [73] and for bronchoscopy with BAL 12-41% [73,74].	
CURRENT PRACTICE			Members of the panel's practice is to undertake a minimum set of tests in all children/adolescents with suspected or confirmed bronchiectasis. In most settings, these are: a sweat test, full blood count, immunological tests (total IgG, IgA, IgM, IgE, and immune responses to vaccine antigens) and lower airway bacteriology and spirometry (when age appropriate).

			In settings with a high prevalence of HIV or tuberculosis, tests for these are also usually undertaken. Other tests performed are dependent upon the child/adolescent's specific symptoms and signs.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● Not important uncertainty or variability ○ No known undesirable outcomes	As the tests result in defining the cause of bronchiectasis, there is likely no important uncertainty or variability. Also, standard investigations have major roles in screening for diseases and the tests usually have trivial undesirable effects.	Finding causes of bronchiectasis was one of the research priorities articulated by the Parent advisory group and parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child/adolescent (from the European Lung Foundation survey undertaken in 2019)

BENEFITS AND HARMS	**How substantial are the benefits of the intervention compared to harms?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know ○	Evidence available from the narrative summary found high rates of identifying underlying aetiology and thus considerable large benefits. There is no substantial concern over undesirable effects from the standard investigations. Thus, the balance is highly likely to favour the use of standard sets of investigation. Tests included in the standard diagnostic protocols are generally well-tolerated, but not invasive. Thus, harmful effects are trivial.	The panel considered that irrespective of the very low evidence for undertaking tests to impact on clinical outcomes, the severe consequences of missing treatable causes warrant these tests be undertaken. Further, based on clinical experience, cost-effectiveness is likely beneficial as early treatment of primary immunodeficiency disorders leads to better outcomes and eventual lower costs as studies have described early diagnosis of primary immunodeficiency disorders leads to reduced illness and decreased healthcare costs [79].
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	There is no published literature on health equity, but differential access (from living remotely or not having access to a major centre, including specific expertise in bronchiectasis) suggests probable imbalance between patients, settings and countries.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	The panel and parents considered that a standard panel of tests is warranted as it will likely influence treatment and monitoring of the illness.

NQ1. In children/adolescents with suspected or confirmed bronchiectasis, what standard tests that impact on clinical outcomes should be undertaken when managing this group of patients?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ●	**Strong** recommendation **for** the intervention ○
RECOMMENDATION	• In children/adolescents with suspected or confirmed bronchiectasis we suggest they have a minimum panel of tests undertaken, as done currently by most experts in the field *(Conditional recommendation, very low-quality of evidence stemming from narrative review of the evidence).* The minimum panel of tests are: 1) Chest computed tomography-scan 2) Sweat test 3) Lung function tests (in children/adolescents who can perform spirometry) 4) Full blood count 5) Immunological tests (total IgG, IgA, IgM, IgE, specific antibodies to vaccine antigens) 6) Lower airway bacteriology • In selected children/adolescents, we suggest additional tests are considered based on their clinical presentation. These include additional in-depth immunological assessments (in consultation with a paediatric immunologist), diagnostic bronchoscopy with bronchoalveolar lavage analysis (microbiology), tests for airway aspiration, PCD and gastro-oesophageal disease (GORD). *(Conditional recommendation, very low-quality of evidence stemming from narrative review of the evidence).* **Remarks**: In settings where tuberculosis or human immunodeficiency virus (HIV) have a high prevalence and/or there is a history of close contact with tuberculosis, assessment for tuberculosis infection/disease or HIV respectively is also undertaken as part of the minimum panel of tests.				
JUSTIFICATION	Although the evidence level is very low, a conditional recommendation was selected based upon the large desirable effect and likely trivial undesirable effects of setting a standard set of investigations as well as the risk and harm of not managing common or critical conditions related to bronchiectasis in children/adolescents.				
SUBGROUP CONSIDERATIONS	Patients with: ○ Different risks profiles of future bronchiectasis (e.g. settings with high prevalence of tuberculosis, Indigenous populations, risk of foreign body inhalation)				

IMPLEMENTATION CONSIDERATIONS	Health services should increase accessibility to centres practising standard of care for children/adolescents with bronchiectasis as identifying the aetiology has management implications (e.g. specific treatment for immunodeficiency, genetics causes for future family planning, etc).
MONITORING AND EVALUATION	Evaluation of the standard of care received by children/adolescents with bronchiectasis should include whether the minimum panel of tests conducted to identify an underlying aetiology is undertaken.
RESEARCH PRIORITIES	It is unlikely that this recommendation will be amendable to placebo RCTs as the suggested panel of tests above are standard paediatric practice. Research priorities include determining the yield of the additional tests under different circumstances e.g. flexible bronchoscopy when bronchiectasis is not localised to one segment/lobe of the lung.

NQ2 – Narrative summary of evidence table

In children/adolescents, is bronchiectasis (a) reversible and/or (b) preventable?

First author, year, country	Study design	Inclusion Criteria	N; Age; Follow-up length	Main aim(s)	Primary findings relating to question	Management or other findings	Implications for narrative question
NQ2a. Is bronchiectasis in children reversible?							
Baris [80], 2011 Turkey	Specialist hospital; Retro review	Children with CVID and BE with >1 yr of follow-up before and after IVIG	N=29 mean age, 11.8 yrs (SD 6.1) bronchiectasis in 12 patients	Evaluate the role of IVIG on the clinical outcome of patients with CVID Follow-up mean 5.6 (3.5) years	Progression of BE in 5 patients, regression observed in 4 patients, and resolution in 3 patients	Management: IVIG, prophylactic antibiotics, physiotherapy, inhaled corticosteroids and bronchodilator	Even in children with CVID, IVIG therapy may reverse BE and prevent development of severe BE
Crowley [81], 2010, Norway	Case report	Not applicable	Female 9-week-old with persistent wet cough and respiratory distress	To describe a child with BE as a sequelae of pulmonary infection and follow-up after 6 months	Reversible bronchiectasis	Management: supplementary oxygen, antibiotics and steroids	Prolonged treatment with antibiotics may be helpful in resolving bronchiectasis in infants
Eastham [3], 2004, England	Specialist hospital; Retro chart review	Not defined but data was on consecutive children with BE	n=93; Median age=7.2 yrs (range 1.6, 18.8); FU duration not mentioned	Report local experience of HRCT defined BE in children Repeat HRCT scans performed in 18 (for clinical reasons-unspecified), at 1.5–5 yrs after initial HRCT	6 completely resolved (4 post-pneumonic, 2 idiopathic), 1 improved (post-pneumonic), 6 unchanged (2 post-pneumonic, 2 immuno-compromised, 1 idiopathic, 1 bronchiolitis	Management following investigations	Resolution of bronchiectasis (based on HRCT scans). Bronchiectasis in children may not be always permanent or progressive with clinical management

				diagnosis and treatment initiated	obliterans), 5 deteriorated (2 post-pneumonic, 2 immuno-compromised, 1 hypersecretory)		
Gaillard [82], 2003, England,	Specialist hospital; Retro review	Inc: BE with repeat CT scan undertaken Exc: CF	n=22, age range 1-16 yrs; Repeat FU HRCT: median=24 mo (range 2-43)	Report findings and FU of children with BE who had at least one repeat CT scan Interval=21 months (range 2-43)	Post treatment, radiological BE completely resolved in 6 children, improved in 8, unchanged in 3, 4 had lobar resection and worsened in 1	Management details not specified	Radiological bronchiectasis may be reversible post treatment and maybe dependent on underlying aetiology. Radiological improvement or resolution in 63.7%
Haidopoulou [5], 2009, England	Single centre, specialist hospital; Retro review	Inc: Age <16 yrs with PID and BE and FU chest HRCT scan min 2 yrs apart and lung function within 4-6 wks of HRCT scan available Exc: Not described	n=18; median age 3.4 yrs (range 1-13 yrs) for diagnosis of PID, and 9.3 yrs (range 3.1-13.8) yrs for BE diagnosis.	Determine the progression of bronchiectasis secondary to PID in children after starting treatment Median interval=3.5 yrs (range 2.2-4.8) years between HRCT scans	No significant difference between baseline and follow-up: median HRCT scores (6 [range 1–13] and 7.5 [0– 15] respectively) . HRCT scores deteriorated in 10 (55%), improved in 6 (34%), and unchanged in 2 (11%)	Management: antibiotics and chest physiotherapy, IVIG	Bronchiectasis secondary to primary immunodeficiency in childhood is not always progressive. Appropriate treatment may slow or prevent the disease progression
Mansour [83], 1998, Israel	Case report	Not applicable	3½ year old girl with recurrent pneumonia with retained	Describe the 2 yr follow-up after the removal of a foreign body removal	Reversible bronchiectasis on CT scan	Management: foreign body removal, antibiotics and intensive physiotherapy	Even severe bronchiectasis following prolonged retention of a foreign body may

			organic foreign body for 18 months				be reversible if the airway obstruction is removed and BE treated
NQ2b. Is bronchiectasis in children/adolescents preventable?							
Byrnes [84], 2020, New Zealand	Single centre, single-blind RCT	Inc: Children aged <2 yrs hospitalised with severe LRTI (pneumonia or bronchiolitis) Exc: ≥2 previous LRTI admissions, <32 wks gestation or prior known chronic lung disease or other chronic condition	Intervention group n= 203, mean age 8.4 mo (SD 6.3). Controls n=197, mean age 7.4 mo (SD 5.9) FU: 321 of randomised 400 children at 24-mo	To reduce intermediate respiratory morbidity with a community intervention program initiated at time of hospital discharge Intervention=FU 1-mo post-discharge, and 3 monthly general practitioner review (community clinic) till final FU at 24-mo Control=usual care	Community clinic review of children in New Zealand post hospitalisation for pneumonia or bronchiolitis did not prevent future bronchiectasis. High incidence of BE post pneumonia or bronchiolitis	At 24-mo, high levels of respiratory morbidity were present (32% cohort had chronic cough, 22.7% crackles and/or digital clubbing) and 17% had focal CXR changes. No difference between groups for any outcome (wet cough, crackles or clubbing, CXR findings, readmission with LRTI, presence of wheeze, asthma diagnosis, presence of skin infections, ear disease or dental caries, immunisations completed and on time)	12/321 (3.7%) of children hospitalised with pneumonia or bronchiolitis found to have had BE at 24- months. Preventing BE needs more than review by general practitioners
Karakoc [85], 2002, Turkey	Single centre, tertiary hosp, Retrospective	Inc: Treated for foreign bodies Exc: Asthma or chronic lung disease before foreign boy	n=174; Mean age=45.4 months (range 5, 216) Follow-up in 110 children at mean duration of	Determine the complications after removal of airway foreign body	Long term complications (BE or persistent respiratory symptoms) associated with time lag from aspiration of organic material. In those with >30 days delay, 60%	Inorganic (80%) c.f. organic (42.8%) material were significantly more likely to be diagnosed within 3 days of aspiration (p=0.002) Organic material in 76%; inorganic in 23% [does not add to 100% in paper]	Early detection and removal of foreign bodies in the airways prevent development of persistent respiratory symptoms and BE

			37.8 months (range 1, 88)		had complications (BE in 25%).		
Karakoc [86], 2007, Turkey	Single centre, tertiary hosp, Retrospecti ve	Inc: Children who had flexible bronchoscopy between 1997 and 2004	Of 654 children, foreign body found in 32 (4.9%); median age=29.5 months (IQR 17.0, 84.7)	Determine the incidence of clinically unsuspected foreign bodies and its complications from flexible bronchoscopy service	9/32 (28.8%) patients had chronic respiratory problems and 6/32 (18.8%) developed bronchiectasis. Median duration of symptoms was 3.0 months (range 1-132)	All with BE present in had >3 months of symptoms	Early detection and removal of foreign bodies in the airways prevent development of BE
Mallick [87], 2005, Saudi Arabia	Single centre, tertiary hosp, Retrospecti ve	Inc: Rigid broncho-scopy for suspected airway foreign body from 2001-10	152 of 158 (96.2%) had foreign body; Mean age=3.3 yrs (range 0.75, 12).	Examine symptoms, signs, complications and foreign body and causes of delayed (2 weeks) diagnosis	Diagnosis delay (>2 wks in 48 (30.3%) which was significantly associated with complications (BE n=8, pneumonia n=2, atelectasis n=9) in 29 (60.4%)	Commonest symptoms and signs: cough (100%), choking (72%), diminished breath sounds (66.4%), rhonchi (43%)	Early detection and removal of foreign bodies (<2 weeks) in the airways prevent development of BE
Sırmalı [88], 2005, Turkey	Specialist hospital; Retro review	Inc: Aged <16 yrs with airway foreign bodies between 1990-2005	n=263 (176 males); Mean age 4.2 yrs, (range 10 months to 16 yrs).	Examine relationship between the time of foreign body aspiration with complications	Chest CT scans in 51 children; BE present in 26 (51%)	Earliest BE found in delay of 25 days. Organic foreign bodies and retention period of ≥30 days were risk factors in finding BE	Early detection and removal of foreign bodies in the airways prevent development of BE
Singleton [89], 2014, Australia, USA , New Zealand	Multi-center, regional and specialist hospitals;	Inc: Alaska, New Zealand or Australian Indigenous children aged 0.5-8 yrs with CSLD or CT-	n=182 children (57% boys); Median age at recruitmen	Evaluate similarities and differences in medical and socio-demographic features of children	Household crowding, prematurity, and frequent and early onset of acute lower respiratory		Interventions that address household crowding, prematurity, early onset of ALRIs may prevent BE

	retrospecti ve study	confirmed BE Exc: cancer, CF, central nervous system or neuro-muscular disorder	t=3.2 yrs (range 0.5, 9.0).	with CSLD/BE and compare these features with their respective regional indigenous population and country of origin	infections (ALRIs) were more common in those with CSLD/BE. Children with BE had similar prevalence of poverty indices and tobacco smoke exposure with their respective local indigenous populations.		
Valery [90], 2004, Australia	Single center, regional hospital; case control study	Cases= Indigenous children with BE; Controls= Indigenous children hospitalised with other conditions matched for gender, age and year of diagnosis	BE n=61, controls n=183; median age=5.3 yrs (range 8 months, 15 yrs)	Examined the relationship between hospitalised pneumonia and the risk of radiologically proven BE	Hospitalised pneumonia significantly associated with BE adjusted odds ratio =15.2; 95%CI 4.4, 52.7, especially when recurrent (p_{trend} <0.01), severe (longer hospital stay (p_{trend} =0.01), or oxygen requirement (p_{trend} <0.01). Being born <31 wks gestation associated with BE (p_{trend}=0.03)	Breast-feeding was a protective factor (adjusted odds ratio=0.2; 95%CI 0.1, 0.7)	Interventions that reduce prematurity, early onset and severe ALRIs and increase breast feeding may prevent BE
Wurzel [91], 2016, Australia	Specialist hospital; Prospective cohort study	Inc: protracted bacterial bronchitis (PBB) cohort= fulfils PBB criteria* and FU for ≥2 yrs. Controls= no cough	PBB n=161; median age= 22 mo (IQR 13-50) Controls n=25; median	In children with PBB, to: (a) determine the medium-term risk of BE and (b) identify risk factors for BE and	13 (8.1%) were diagnosed with BE; Major risk factors for BE were: *H. influenzae* lower airway infection (≥10^4 cfu/ml BAL)	Most *H. influenzae* were non-typeable *H. influenzae* CT done in 25 children at a median duration of 9 months (IQR, 4-19) after recruitment; median	Interventions that reduce recurrent PBB or non-typeable *H. influenzae* lower airway infection may prevent BE

		Exc: known chronic lung disease	age= 44 mo (IQR 7-97) Median FU duration=25 mo (IQR 24-28) in children with PBB, 27 mo (IQR 26-29) in controls	recurrent episodes of PBB	(Hazard Ratio=7.6 (95%CI 1.7, 34.3), p=0.009) and recurrent (>3/yr) PBB (p=0.003) c.f. those without *H. influenzae* infection and non-recurrent PBB respectively	age=38 months (IQR, 27-58)	

BE=bronchiectasis, CF=cystic fibrosis, CT=computed tomography, CVID=common variable immunodeficiency; FB=foreign body, FU=follow-up, HRCT=high-resolution computed tomography, IVIG=intravenous immunoglobulin, mo=months, PID=primary immunodeficiency, IQR=interquartile range, CSLD=chronic suppurative lung disease

*PBB criteria= (a) a history of chronic (>4 weeks) wet cough, (b) prospective evidence (supported by cough diaries) of response to 2 weeks of treatment with amoxicillin clavulanate, and (c) an absence of clinical pointers suggesting an alternative cause for cough.

Evidence to Decisions (EtD) framework

NQ2: In children/adolescents is bronchiectasis (a) reversible and/or (b) preventable?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low due to absence of any RCTs. The evidence is largely based on retrospective observational studies. As in the narrative summary, there were only a few studies relating to whether bronchiectasis in children/adolescents is reversible or preventable. Most studies were retrospective and several were case reports. There was only a single case-control study and one prospective study. However, all studies showed that at least in some children/adolescents, their airway dilatation signifying radiographic bronchiectasis is reversible with appropriate management and it therefore follows that this is also potentially preventable. Evidence available from the narrative summary found that the resolution or improvement rates after appropriate treatment in	As this is a narrative question (as opposed to a PICO question), GRADEing of the evidence was not done and thus, our confidence in our conclusions is limited

		children/adolescents with radiographically-proven bronchiectasis may be as much as 67%. However, the proportion of resolution or improvement likely varies with severity of bronchiectasis, underlying aetiology, treatment provided and how bronchiectasis was defined (the diagnostic criteria used). Identifying the presence and treatment of an aspirated foreign body in the airways, especially before 14-days prevents the development of bronchiectasis. Treatment of primary immunodeficiency is warranted, irrespective of whether bronchiectasis can be prevented in children with primary immunodeficiency. The evidence provided in the narrative summary found only indirect observational evidence on potential risk factors for developing bronchiectasis in children/adolescents. These risk factors include strategies that target household crowding, preterm birth and frequent, early onset and severe acute lower respiratory tract infections (especially hospitalised pneumonia). Prevention of recurrent protracted bacterial bronchitis, non-typeable *H. influenzae* lower airway infection and increasing breastfeeding may also prevent future bronchiectasis. However, the evidence is low and effect sizes are unclear.	
CURRENT PRACTICE			Members of the panel's practice is patient (e.g. symptoms, signs, tests) and setting-dependent (e.g. prevalence of tuberculosis). Examples include early detection and removal of foreign bodies in the airways, early evaluation of children with a recurrent pneumonia or chronic wet cough unresponsive to 4-weeks of antibiotics followed by intense treatment of any chronic airway suppuration (antibiotics and airway clearance) to achieve a cough-free status aim to prevent bronchiectasis developing.

VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	There is likely no important uncertainty or variability, although this is likely dependent upon the child/adolescent, risk factor and clinical setting.	Finding how to prevent bronchiectasis was the top research priority articulated by the parent advisory group and parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child/adolescent (from the European Lung Foundation survey undertaken in 2019)
BENEFITS and HARMS	**How substantial are the benefits of the intervention compared to harms?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The benefits of preventing andor reversing bronchiectasis are large while that of harm are intervention dependent.	The panel considered that irrespective of the very low evidence for the potential interventions in preventing bronchiectasis, the severe consequence of not addressing the risk factors described warrant these interventions. However, each intervention will need to be assessed and this is beyond the remit of this taskforce.

EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	There is no published literature on health equity, but differential access (from living remotely or access to a major centre and specific expertise in managing bronchiectasis) suggests probable imbalance between patients, settings and countries

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	Strategies that reserve and/or prevent bronchiectasis are very likely to be worthwhile and acceptable to key stakeholders. Further, prevention of bronchiectasis was the top research priority articulated by the parent advisory group and parents of children/adolescents with bronchiectasis or adults who had bronchiectasis as a child/adolescent (from the European Lung Foundation survey undertaken in 2019)
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	There may be some limits related to availability of the interventions at local settings. The feasibility of the intervention may be variable.

NQ2. In children/adolescents is bronchiectasis (a) reversible and/or (b) preventable?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention ○	**Conditional** recommendation **against** the intervention ○	Conditional recommendation for either the intervention or the alternative ○	**Conditional** recommendation **for** the intervention ○	**Strong** recommendation **for** the intervention ○

RECOMMENDATION	In some children/adolescents, their bronchiectasis is reversible and/or preventable. Factors important for reversibility and/or prevention of bronchiectasis include early identification and treatment of inhaled foreign bodies, preventing early and severe pneumonia, preventing recurrent protracted bacterial bronchitis (PBB), treating primary immunodeficiency disorders causing bronchiectasis, promoting breastfeeding and immunisation, and avoiding tobacco smoke and other pollutants. **Good practice statement** • In children/adolescents with bronchiectasis, we suggest wherever possible, interventions that reverse and/or prevent bronchiectasis are undertaken. However, these measures are context and patient specific.
JUSTIFICATION	Although the evidence for reversing and/or preventing bronchiectasis in children is very low to low, a strong recommendation was selected based on the large desirable effect and likely trivial undesirable effects, as well as the risk of harm of not treating the identified risk factors that reverse/prevent bronchiectasis. Also, the panel and parents advisory group expressed that finding how to prevent bronchiectasis as their top research priority.
SUBGROUP CONSIDERATIONS	Patients with: • Different risks profiles for future bronchiectasis (e.g. Indigenous populations). Different interventions may be required for those at higher risk of bronchiectasis.
IMPLEMENTATION CONSIDERATIONS	Access to paediatric specialist respiratory services and strategies to improve early diagnosis and interventions addressing the identified risk factors that can reverse and/or prevent bronchiectasis are required.
MONITORING/ EVALUATION	
RESEARCH PRIORITIES	One of the parent advisory group's top research priorities is to identify how bronchiectasis can be prevented. Thus, for children/adolescents, especially those at risk of developing bronchiectasis, research priorities include studies to delineate interventions that reduce and/or prevent the development of bronchiectasis. These require long-term studies that include objective diagnosis of bronchiectasis (CT-scan) and clinical outcomes (QoL, lung function, exacerbation rate, hospitalisation and adverse events) with concomitant data on cost-effectiveness. Examples of such interventions include maternal vaccinations, longer duration antibiotics for pneumonia in 'at risk' children, and long-term azithromycin in children with recurrent PBB.

NQ3 – Narrative summary of evidence table

In children/adolescents with bronchiectasis, should attention be paid to other paediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc)?

First author, year, country	Setting; Study design	Inclusion, exclusion criteria	N; Age; Follow-up duration	Main aim(s)	Primary findings relating to narrative question	Other major findings and additional comment	Implications for narrative question
Alison [92], 2017, Australia	Clinical Practice guideline	Not stated explicitly; known diagnosis of bronchiectasis implied, patient clinically stable	Not stated explicitly, assume all age sought; 8 weeks PR	Assess whether pulmonary rehabilitation should be offered to patients with bronchiectasis	Three RCTs with 135 participants (Lee, 2014; Mandal, 2012; Newall, 2005). HRQoL (-4.6, 95%CI -6.5 to -2.6), and Incremental Shuttle Walk Test (64.5 metres, 49.4 to 97.6) improved	One study reported a longer time to first exacerbation with PR One study showed benefits not sustained at 6- and 12- months (Lee, 2014)	Weak recommendation; moderate evidence that pulmonary rehabilitation should be offered to bronchiectasis patients; no paediatric data
Bradley [93], 2002, UK	Cochrane review	RCTs of any physical training regime in bronchiectasis	Adults and children	Determine the effectiveness of any physical training regime in bronchiectasis	Two studies published in abstract only, minimal details. Inspiratory muscle training improved exercise endurance (means of assessment not stated) 264 metres (95%CI 16.4-512 metres), inspiratory muscle strength (25 cm H2), 11.6 to 38.4) and quality of life (means of assessment not stated)	None	Very weak evidence of benefit. Data captured in more recent systematic reviews
Chang [94], 2009, Australia	Cochrane review	RCTs of pneumococcal immunisation in bronchiectasis	Adults and children	Determine effectiveness of Pneumococcal immunisation in adults and children with bronchiectasis	No RCT data	Non-randomised trial in children with no clinical outcomes showed increased elimination of *Streptococcus Pneumoniae* from sputum	Neither supports nor refutes the question

Dona [95], 2018, Spain	RCT, hospital	Known diagnosed bronchiectasis, not malnourished	N=60 adults 18-80, 30 in each limb	Compare PR with PR and nutritional supplement	CPET, HRQOL spirometry and dyspnoea improved in both groups, no additional benefit from nutritional supplement	None	No placebo group, so impossible to determine if PR was helpful; adult data only. Neither supports nor refutes the question
Irons [96], 2010, Australia	Cochrane review	RCTs of singing in patients with bronchiectasis	Adults and children	Assess effectiveness of singing on quality of life, respiratory muscle strength, morbidity and pulmonary function	No RCTs identified	None	Neither supports nor refutes the question
Joschtel [97], 2018, Australia	Systematic review and meta-analysis	RCTs assessing the effects of exercise training on physical and psychosocial health in children with chronic respiratory disease	Children, definition not overt but likely ≤18 years. Studies excluded if population's median age ≥21 years	Assess the effects of any form of exercise training in children	No RCTs found in bronchiectasis	Benefits shown in asthma and cystic fibrosis, in terms of cardiovascular fitness, HRQoL, and a small effect on spirometry	No direct evidence to confirm or refute the question. Benefit in other diseases can be taken as supportive of exercise training in bronchiectasis
Kelly [98], 2018, UK	Cochrane review	RCTs of benefits and harms of self-management programs	Adults and children	Assess effectiveness and value for money of self-management for bronchiectasis compared with standard care	No self-management studies in children identified	Two UK studies in 84 adults showed no benefit	No direct evidence to confirm or refute the question
Lavery [99], 2007, UK	Focus group study. Non-randomised, hospital study	Inclusion criteria: known diagnosis of bronchiectasis	N=32 adults, age ≥18 years	Obtain patients perspective on self-management plans	Adults supportive of the concept of self-management; big impact of the disease on quality of life	Guidance for developing self-management tools	No direct evidence to confirm or refute the question

Lee [100], 2014, Australia	RCT. Hospital study	Known bronchiectasis, COPD excluded	N=65 adults, mean age 65 years	8 weeks supervised exercise training and review of airway clearance (n=42) vs. standard therapy (n=43)	Exercise training increased shuttle walking test (62 metres, 95%CI 24-101) and 6 minute walk distance (41 metres, 19-63), but the benefits were not sustained over a year.	Dyspnoea (p=0.009) and fatigue (p=0.01) were reduced. Cough related QoL and mood not impacted. Intervention led to fewer exacerbations (median 1, IQR 1-3) and longer time to first exacerbation (8 months, 95%CI 7-9) vs. 6 months, 5-7) p=0.047	No direct evidence to confirm or refute the question, but supportive of proposing ongoing exercise training. However, a short sharp burst unlikely useful
Lee [101], 2017, Australia	Systematic Review; 4 trials, 164 participants	Bronchiectasis excluding only cystic fibrosis	Adults	Examine effect of 8 weeks PR or exercise training on exercise capacity, HRQOL, symptoms, frequency of exacerbations and mortality compared with no treatment	Increased shuttle walk difference (67 metres, 95%CI 52-82) and disease specific HRQOL) immediately after intervention, not sustained at 6 months. Exacerbations reduced over 12 months	PR initiated during an exacerbation had no effect	No direct evidence to confirm or refute the question, but supportive of proposing ongoing exercise training. However, a short sharp burst unlikely useful
Magis-Escurra [102], 2015, Netherlands	Systematic review	Bronchiectasis excluding only cystic fibrosis	Adults and children	Exercise and physical training: Lee[100] (above) only study	Exercise and physical training likely to be beneficial	None	Nothing to add to Lee 2014(above)[100]
Mirra, [103], 2015, Italy	Observational study, hospital based	PCD, bronchiectasis status not stated	22 adults and children 2-34	Relate vitamin D levels to pulmonary function tests, sputum microbiology, self-reported physical activity and QoL by SGRQ	72% vitamin D deficient and had poorer QoL	None	Very low quality evidence, supportive (weak evidence) that optimising Vitamin D levels should be attempted

O'Grady. [104], 2018, Australia	RCT	Inclusion: PBB, CSLD, bronchiectasis. Exclusion criteria: cystic fibrosis, immunosuppression, prior receipt of either study vaccines	74 children 2/12 to <18 years	Compared PHiD-CV or quadrivalent meningococcal ACYW135 conjugate vaccine two doses, 2-months apart	Children receiving PHiD-CV had a trend for fewer fortnights with respiratory symptom sand antibiotic courses	Fewer hospitalised exacerbations in the PHiD-CV group, however the actual number of events and affected children were small. PHiD-CV also induced serum and salivary anti-PD antibodies and was generally well tolerated, although there were more local reactions	Did not achieve sample size. However supportive evidence for PHiD-CV immunisation in children with bronchiectasis
Zanini, [105], 2015, Italy	Retrospective review	Bronchiectasis	108 adults, mean age 71 years	Assess the efficacy of a 3 week PR program	After PR, there were significant improvements in 6 minute walk distance, dyspnoea index and QoL	Male gender, FEV_1/FVC<70% and >2 exacerbations in previous year predictors of benefit. Duration of follow up not stated	No direct evidence to confirm or refute the question, but supportive of proposing ongoing exercise training

CI=confidence intervals; COPD=chronic obstructive pulmonary disease; CPET=cardiopulmonary exercise test; CSLD=chronic suppurative lung disease; FEV_1=first second forced expired volume; FVC=forced vital capacity; HRQoL=health related quality of life; IQR=interquartile range; PD=protein D; PHiD-CV= 10-valent pneumococcal-Haemophilus influenzae protein D conjugate vaccine; PPB=persistent bacterial bronchitis; PR=pulmonary rehabilitation; RCT=randomised controlled trial; SGRQ=St George Respiratory Questionnaire

Evidence to Decisions (EtD) framework

NQ3: In children/adolescents with bronchiectasis, should attention be paid to other paediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc)?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	Good nutrition, exercise and vaccinations are all part of a normal healthy childhood, and there is nothing to suggest that the presence of bronchiectasis should alter this. Psychological support and equipment care are part of good management of anyone with chronic illness
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	The research evidence is overall of poor quality. There were eight reviews of various types, three RCTs, two observational studies and one retrospective study. The desirable effects of routine immunisation, exercise and good nutrition are indisputable, but their magnitude is unclear. Additional vaccinations for children with bronchiectasis is likely beneficial, but the quality of the evidence is very low. The desirable effects of psychological support and education for appropriate equipment use and care for children/adolescents with chronic illness are also likely highly desirable, but no data exist on type, duration, intensity (etc) of support or for equipment use and care. With exercise training, a short period is unlikely to have prolonged effects, and the implication is that exercise support must be ongoing. There is low quality evidence of reducing pulmonary exacerbations and time-to-first exacerbation with exercise training. There are no agreed formal pulmonary rehabilitation programmes in children, and there are no data on what exercise interventions are most important. Whether a formal exercise programme is superior to encouragement of an active lifestyle is unclear.	The data presented in the table of summary of studies support the approach, but the RCTs and observational study evidence are of low quality

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No available studies	Other than local injection site reactions and occasional systemic responses, such as fever, as reactions to vaccines, no adverse effects are anticipated from other interventions. Supported by the experience of clinical experts in the field
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low as collectively the randomised studies did not address all the interventions and thus GRADEing of the evidence. The RCT evidence mentioned above was restricted to vaccinations and/or provided no definitive evidence.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	No available studies	The need for good nutrition, full immunisations and exercise in childhood/adolescence would be widely supported by virtually all parents

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	Benefit can be expected for all patients with minimal harm from all the interventions.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ●Varies ○ Don’t know	No available studies	The costs will depend on whether a formal exercise programme is put in place, or merely whether an active lifestyle is encouraged. Immunisation and good nutrition are part of normal childcare and would not incur additional costs
CERTAINTY OF RESOURCE EVIDENCE	○ Very Low ○ Low ○ Moderate ○ High ● No included studies	No available studies	Based on clinical experience, the costs are variable dependent on programs put in place (above)

COST EFFECTIVENESS	○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know ● No included studies	No available studies	Further work is needed to determine if a formal exercise program is cost-effective. All others would be deemed cost-effective, based on clinical experience
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	In low and middle-income settings, advocating for good nutrition and immunisation would probably reduce health inequalities
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	Yes, as all routine, except a formal exercise program (above)

FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	All are already in place, with the sole exception of a formal exercise/rehabilitation programme

NQ3: In children/adolescents with bronchiectasis, should attention be paid to other paediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc)?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention	**Conditional** recommendation **against** the intervention	Conditional recommendation for either the intervention or the alternative	**Conditional** recommendation **for** the intervention	**Strong** recommendation **for** the intervention
	○	○	○	●	○

RECOMMENDATION	• In children/adolescents with bronchiectasis, we suggest that nutrition is optimised, including Vitamin D status (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence)*. **Remarks**: There is no evidence upon which to recommend additional nutritional supplements. • In children/adolescents with bronchiectasis, we suggest that exercise is encouraged on an ongoing basis; short periods of exercise training are unlikely to have a long-term effect (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence).* **Remarks**: There is insufficient evidence to make a recommendation for establishing formal exercise and rehabilitation programmes. • In children/adolescents with bronchiectasis, we suggest they are fully immunised according to their national immunisation programmes, including pneumococcal and annual seasonal influenza vaccines if these are not part of this programme (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence).* • For children/adolescents with bronchiectasis, we suggest they receive psychological support and education on equipment use and care (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence)*.

JUSTIFICATION	Recommendations are based upon placing a higher value upon on low-moderate quality of evidence for clinical improvement over a low value for concerns over uncertainty of magnitude and duration of benefit.
SUBGROUP CONSIDERATIONS	Patients with: ○ Underlying causes of bronchiectasis (e.g. primary ciliary dyskinesia, primary immunodeficiency, aspiration) ○ Limited accessibility to standard of care e.g. in remote regions
IMPLEMENTATION CONSIDERATIONS	Increase accessibility of children to standard of care in low and middlie-income settings.
MONITORING AND EVALUATION	Not applicable.
RESEARCH PRIORITIES	It is unlikely that these interventions will be amendable to placebo RCTs as the interventions suggested above are standard paediatric practice. Research priorities include whether formal exercise or rehabilitation programmes are cost-effective in all, or particular subgroups of, children/adolescents with bronchiectasis.

NQ4: Narrative summary of evidence table

When monitoring children/adolescents with bronchiectasis:

a) How often should airway microbiology testing be conducted in outpatients?

b) How frequently should patients be seen in outpatient clinics?

c) How should cross-infection be minimised?

First author, year, country.	Setting; Study design.	Inclusion, exclusion criteria.	N; Age; Follow-up duration.	Main aim(s).	Primary findings relating to narrative question.	Other major findings and additional comment.	Implications for narrative question.
Alanin [106], 2015, Denmark	Specialist hospital; Retro chart review.	Inc: PCD and evaluable bacteriological data. Excl: None stated	N=107. Median age =17 yrs (range 0-74). Median FU duration =9 yrs (range 1-11).	Describe the serial respiratory bacteriology in sputum or endo-laryngeal secretions collected every 3 mo in those with PCD.	Hi was the most frequently isolated bacterial pathogen with a PePR of 62% (range 46-80), followed by PsA with a PePR of 32% (range 15-47). Both incidence and prevalence of PsA increased with age (p<0.05). There was no evidence of cross-infection.	92% of PsA are from sputum samples. Genotyping of PsA by PFGE did not detect shared strains. Those with chronic PsA are segregated from those (i) without PsA and (ii) other Gram -ve bacteria.	No evidence of PsA cross-infection when those with PCD are seen every 3 mo in a shared facility with CF patients using common infection control strategies.
Bastardo [107], 2009, England	Specialist hospital; Retro, chart review.	Inc: BE (HRCT diagnosis) and reliable spirometry and growth data for ≥2 yrs. Excl: CF.	N=59 at 2 yr FU. N=31 at 4yr FU. Median age =8.2 yrs (range 4.8, 15.8). FU duration not stated.	In children with BE, to evaluate the clinical course of lung function and growth over 2-and 4-yrs.	At 2 yrs, those with reduced FEV_1 at baseline (<-2 z-score) had poorer weight (slope 20.3, 95%CI 20.5, 20.1; p=0.017) and BMI z-scores (slope 20.3, 95%CI 20.5, 20.0, p=0.049) and greater lung function deterioration (FEV_1 slope: -1.8, 95%CI -2.1, -1.5; p<0.005; FVC slope: -1.8, 95%CI -2.1 to -1.5; p<0.005 than those with normal FEV_1 at presentation.	Overall, there was a mean z-score improvement per yr. In the 1st 2 yrs: FEV_1=0.17 (95%CI 0.01, 0.34; p=0.039), FVC=0.21 (95%CI 0.04, 0.39, p=0.016). After 4 yrs, height-for-age z-scores had improved (slope 0.05, 95%CI 0.01, 0.095; p=0.01), but no change in other spirometry values or weight.	Current standard of care in specialist settings leads to improved lung function post-diagnosis. The monitoring component includes 3-4 mo review with lung function test, assessment (and investigation when appropriate) for new infection (sputum), co-morbidities (e.g. asthma GORD, nutrition, etc) [108].
Cohen-	Specialist	Inc: PCD, FU ≥3	N=217.	Review associations	Change in FEV_1 over 5 yrs was -3%	Those with PsA were	When reviewing

Cymberknoh [108], 2017, 11 European centres	hospitals; Retro chart review and database.	yrs and ≥2 sputum cultures recorded. Excl: None stated.	Mean age =19.9 yrs (SD 13.9). FU duration not stated for whole cohort.	between PsA and lung disease in patients with PCD.	(SD 12.7) in those PsA colonised and -0.9% (SD 12.8) in those non-colonised, but inter-group difference was not statistically significant.	older and had lower FEV_1 than those without. Limitation was that most centres did not routinely culture sputum.	children, consider the presence of PsA infection. Thus, routine sputum assessment is useful.
Hare [109], 2019, Australia	One specialist and one general hospital; Prosp cross-sectional study.	Inc: Consecutive children undergoing bronchoscopy for chronic cough. Excl: None stated.	N=397. Median age =2.3 yrs (IQR 1.5-4.2) 57% males. 61% Indigenous Australians.	Determine if culture-based detection of respiratory bacterial pathogens in NP and/or OP samples predicted lower airway infection as judged by BAL cultures.	LAI ($\geq 10^4$ CFU/mL in BAL fluid) by Hi, Spn and Mc was in 42% of cases (95%CI 37,48). PsA was in 4 upper airway cultures only. Sensitivity and specificity for LAI using combined NP and OP swab cultures was 89% (95%CI 83,94) and 58% (95%CI 50,65) respectively. The PPV and NPV for LAI by combined swab cultures was 61% (95%CI 54,68) and 88% (95%CI 81,93) respectively.	Subgroup analysis of the 220 children with BE and 24 with CSLD gave similar results: Sensitivity 87% (95%CI 79,93), specificity 57% (95%CI 49,65), PPV 57% (95%CI 48,65), and NPV 88% (95%CI 79,93). In children with BE, PsA is seen in advanced BE, FBs and co-morbidities [110,111]. NTM is uncommon [110,111].	Upper airway cultures using NP and OP swabs, either alone or in combination do not reliably predict lower airway infection in young children with BE.
Kapur [8], 2010, Australia	Specialist hospital; Retro chart review.	Inc: BE (HRCT diagnosis) and reliable spirometry and growth data for ≥3 yrs. Excl: CF.	N=52. Median age =8 yrs (range 2, 14). FU=3 yrs in 52 children, 5 yrs in 25.	In children with BE, to evaluate: (i) lung function measurements and growth over 3- and 5-yrs and, (ii) factors associated with the change.	Frequency of hospitalised exacerbations statistically associated with FEV_1 %pred decline. Age of diagnosis, number of lobes with BE, aetiology of BE and sex were not associated (age of diagnosis was a large but statistically non-significant factor).	Over 3 yrs, statistical improvement in lung function only seen in $FEF_{25-75\%}$ (slope 3.01, 95%CI 0.14, 5.86; p=0.04), but trend present for FEV_1 %pred (slope 1.17, 95%CI -0.38, 2.7) and FVC (slope 1.57;	Current standard care in specialist settings leads to improved lung function post-diagnosis. Monitoring involves 3-4 mo review with lung function tests, assessment (and

						95%CI -0.18, 3.34) per annum. 5-yr trends similar. BMI z-scores significantly improved (BMI z -scores (slope 0.09; 95%CI, 0.02, 0.15; p=0.01) per annum.	investigation when appropriate) for new infection (sputum), co-morbidities (e.g. asthma GORD, nutrition, etc) [15,112].
Munro [113], 2011, New Zealand	Specialist hospital; Retro chart review.	Inc: BE (HRCT diagnosis) and FU for ≥5 yrs. Excl: CF.	N=91. Median age =7.3 yrs (range 0.9–16). Median FU =6.7 yrs (range 5–15.3).	Describe outcomes for BE following ≥5 yrs of management in a specialist respiratory clinic.	Sputum/BAL from 88 children detected Hi in 30%, PsA in 5%. FEV_1 declined by a mean of 1.6% predicted/yr over the FU period. Trend of greater reduction in FEV_1 associated with chronic PsA (largest predictor at -2.8%/yr), Maori ethnicity, high poorer socioeconomic status, presence of digital clubbing or chest wall deformity.	Lower mean FEV_1 found in males, comorbid asthma, presence of digital clubbing and chest wall deformity. Chronic Hi associated with worse CXR scores (r^2=0.33, p<0.001) Clinic absentee rate 28%	When reviewing children, consider presence of asthma and PsA infection. Thus, routine lung function test and sputum assessment when available recommended.
Prentice [114], 2019, Australia	Specialist hospital; Case-control study.	Inc: BE (HRCT diagnosis) with spirometry (cases). Excl: no reliable spirometry data. Controls: Child with CF of the same age and sex.	Cases: N=22. Mean age =11.0 yrs (SD 3.0). FU =6 yrs. Controls: N=22 Mean age =10.8 yrs (SD 3.1).	Compare the management model of care and clinical outcomes of children with BE and children with CF in a single tertiary paediatric centre.	Compared with CF controls, in any calendar yr, children with BE had fewer clinic visits (median [range] 1 [0-3] Vs 5.5 [3-12]), physiotherapy interventions (0 [0-6] Vs 3.5 [2-6]), outpatient lung function testing (1 [1-3] Vs 4 [1-7]) and respiratory cultures (1 [0-5] Vs 5.5 [1-11]; all p<0.001).	In the same calendar yr, those with BE had significantly lower best FEV_1 %pred results than matched CF children (mean [SD] 78.7 [20.0] Vs 105 [12.5]; p<0.001). Chronic PsA infection occurred in 3/22 (14%) CF children, but in none of the children with BE.	Although aetiologies are different, those with BE require regular multi-disciplinary clinic reviews in the same manner as those receiving the CF model of care.

Sunther [115], 2016, England	Specialist hospital; Retro review from PCD database.	Inc: Aged 6-16 yrs and able to perform spirometry. Excl: 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.	Responders (FEV_1 recovered to baseline) =77% of cohort. No difference between responders and non-responders in baseline characteristics (age, gender, ethnicity, BMI, baseline FEV_1 <40%, mean baseline FEV_1, mean admission FEV_1, persistent infection, use of oral prophylactic antibiotics, nebulised hypertonic saline or rhDNase)	2/7 (29%) non-responders had persistent infection with PsA in the 12 mo prior to pulmonary exacerbation compared to none of the responders (p=0.05).	Highlights importance of detecting PsA and thus using sputum for monitoring.
Studies in adults supporting narrative							
Angrill [116], 2002, Spain	Specialist hospital; Prosp cross-sectional study.	Inc: Adults with BE (HRCT diagnosis) and clinically stable. Excl: Admission to hospital in previous 2 mo, antibiotics in prior 4 wks, or serious co-morbidity.	N=77. Mean age =58 yrs (SD 14). 66% female.	Analyse bacteria colonising the airways and to compare non-invasive samples (OP and sputum) with bronchoscopic collected samples.	71 OP swabs, 42 sputum samples, 75 PSB and 59 BAL specimens were collected and analysed. More than 60% had LAI. Using 10^2 CFU/mL in the PSB as the gold standard, OP swabs had a sensitivity, specificity, PPV and NPV of 24%, 89%, 77% and 44% respectively for respiratory bacterial pathogens in the lower airways. The comparable values for sputum (spontaneous and induced) were 69%, 86%, 90% and 60% respectively.	The results of sputum and PSB agreed in 75% of patients when both specimens were cultured. Thus, sputum, including induced sputum, may provide useful microbiological data in clinically stable patients. However, the NPV was only 60%, meaning that 40% of patients with -ve sputum cultures might still have LAI.	In contrast with OP swabs, spontaneous or induced sputum samples with +ve cultures provide reasonably reliable specimens for identifying lower airway pathogens in older patients with BE.
Chalmers [117], 2018, Europe	EMBARC cross-infection statement	Scoping review of PubMed (search terms: 'cross-infection'	117 articles, 8 Abstracts and 4 more papers found.	123 papers excluded, leaving 6, including 1 Abstract, for review.	Cross-infection may occur, but this appears to be a rare event. Studies have focused upon PsA, are small in number and limited by lacking	Insufficient evidence to show that cross-infection is associated with	Infection control should be discussed with all patients and their families.

	.	OR 'transmission' AND 'bronchiectasis'.			robust epidemiological and/or longitudinal data. Evidence is also lacking for the effectiveness of face masks. There are no studies on cross-infection by Sa, MRSA, NTM or other organisms in those with BE. Patients wanted to know more about infection control, especially avoiding viral infections, and worried over being stigmatised by wearing face masks.	clinical deterioration. Except for one study, highly abundant shared strains seen in CF clinics have not been detected. Where BE patients are managed in CF clinics, the same infection control policies should be applied as for CF patients. BE patients should not have direct contact with those with CF.	Cohorting BE patients by organism is not justified, standard infection control and hygiene measures should continue, including vaccinations according to local guidelines. Face masks are not recommended.
Cramer [118], 2019, Germany	Specialist hospital; Retro analysis of PsA isolates.	Inc: All PsA isolates from patients attending a BE outpatient clinic. Excl: None stated.	49/143 (34%) harboured PsA. No patient details provided. Study duration 6mo.	Identify whether there was molecular epidemiological evidence of PsA transmission within BE clinics.	22%, 28% and 24% of the local BE PsA infected population shared strains that belong to the 15 most abundant clones found in the environment, causing acute infection and in CF respectively. Of those with shared genotypes, all but one belonged to abundant clones in the environment and clinical isolates.	Matching epidemiological and typing data failed to identify evidence of PsA being acquired within the BE clinic by the 12 patients with shared strains.	Risk of acquiring PsA within the BE clinic from person-to-person transmission is small. This study was published after the EMBARC statement [117].
King [119], 2007, Australia	Specialist hospital; Prosp descriptive cohort study.	Inc: Adults with BE (HRCT diagnosis) attending a specialist clinic and able to produce a sputum sample.	N=89. Mean age =57 yrs (SD 14). 70% female. Mean FU period =5.7 yrs (SD 3.6).	Describe the sputum bacteriological profile in adults with BE.	On initial assessment the predominant bacterial pathogens isolated were: Hi (47%) and PsA (12%). FU sputum samples yielded overall similar results: (Hi [40%] and PsA [18%]). Of those with initial Hi, 64% had Hi on FU, while 73% with initial	Those with the same isolate on FU had a significantly higher number of exacerbations than those who were not sputum colonised by bacterial pathogens (3.5 [SD 1.9] Vs 2.7	Highlights importance of detecting PsA and thus using sputum for monitoring.

		Excl: Not stated			PsA had this organism on FU too.	[SD 1.7] per yr; p=0.04, OR=1.3, 95%CI 1.0,1.7). Those with PsA had the worst lung function.	
McDonnell [120], 2015, England	Specialist hospital; Retro descriptive cohort.	Inc: Adults with BE (HRCT diagnosis) attending a specialist clinic. Excl: Microbiologic data unavailable.	N=155. Mean age =61.3 yrs (SD 13.9). 60% female. Median FU period =46 mo (IQR 35-62).	Assess the longitudinal sputum bacteriological profile in adults with BE and determine association with clinical status.	N=2287 sputum cultures. Hi detected in 89 (57.4%) patients, PsA in 76 (49.0%) and Sp in 51 (32.9%). 34% of those with PsA became culture negative. PsA was isolated in 5/39 (12.8%) with minimal airflow limitation, whereas it was present in 18/38 (47.4%) with severe airflow limitation; p<0.001.	Independent factors associated with PsA sputum isolation on FU included: low FEV_1% pred (OR=2.29, 95%CI 1.28,4.09); polymicrobial colonisation (OR=2.78, 95%CI 1.09, 7.13); and mortality (OR=3.55, 95%CI 1.15, 12.35).	Highlights the importance of PsA as a prognostic factor and of employing ongoing sputum microbiological surveillance irrespective of lung function.
Stockwell [121], 2019, Australia	Specialist hospital; (i) cross-sectional cough aerosol study; (ii) Retro PsA genotyping study.	Inc: Adults with BE (HRCT diagnosis) involving ≥2 lobes and prior PsA +ve sputum cultures attending a specialist clinic. Excl: CF, clinically unstable and/or recent haemoptysis or pneumothorax	Cough study: N=16. Mean age =62.5 yrs (SD 11.0). 70% female. PsA typing study: N=29. Mean age =64.0 yrs (SD 8.8). 67% female. Median FU duration =8.1 mo (IQR 2.8-45.2).	Determine: (i) if BE patients can produce cough aerosols containing viable PsA. (ii) if there is evidence of shared PsA strains in BE patients attending a single centre co-located with a CF clinic and where there were no infection control policies to segregate BE patients from one another or from those with CF.	(i) Viable PsA was detected in cough aerosols in 4/16 (25%) BE patients at 2 and 4 metres, and 2/16 (13%) at 15 minute duration. While the mean PsA sputum concentration was 1.1 $x10^7$ CFU/mL, it was only 1-3 CFU in cough aerosols. No viable PsA were detected in either the 5 or 45 minute duration rig tests. (ii) 95 PsA isolates (range 1-8 per patient) genotyped. Isolates had genotype profiles shared with local environmental, animal and clinical (non-respiratory) strains.	Hi was also cultured from cough aerosols in 2 patients with BE. In contrast with CF, only 25% of those with BE produced cough aerosols with viable PsA. Moreover, the colony counts in aerosols was much lower and the distance travelled and the duration remaining suspended was much less in CF than in BE patients. This study was	This study provides further confirmation that PsA cross-infection is uncommon between BE patients and cough aerosols are unlikely to provide an important transmission pathway. The study was published after the EMBARC statement [117].

			13 participated in both studies.		No commonly shared abundant (epidemic) PsA strains seen in CF patients were observed. There was no evidence of PsA transmission events.	limited by its small numbers of participants and PsA isolates, the typing of only 1 isolate/sample, not knowing what is the infectious inoculum and FU of the genotyping study to <12 mo.	
Visser [122], 2019, Australia	Australian BE Registry. Cross-sectional retro review of the Registry database.	Inc: Adults with BE (HRCT diagnosis) from 14 sites whose data were entered into the database. Excl: CF, if aged <18 yrs, or data incomplete.	N=589. Median age =71 yrs (IQR 64-77). 71% female. Baseline data when first entered into the database were used.	Assess the proportion of patients receiving respiratory treatments according to current Australian [14] and international [16] guidelines.	Only 59% of the cohort had standard bacterial culture results and only 29% had NTM culture results available.	The Australian and New Zealand guidelines recommend surveillance of airway or sputum microbiology to help guide antibiotic therapy, but do not specify their frequency [14]. The adult guidelines recommend sputum cultures at least annually to detect PsA [16].	New BTS guidelines recommend sputum cultures annually if mild disease and 6 mo if moderate-severe BE [17]. Sputum NTM cultures recommended at diagnosis, starting macrolides or if deteriorating [17].
Woo [123], 2018, Canada	Specialist hospital; Retro longitudinal chart and laboratory database review of	Inc: Adults with BE (radiographic confirmed) and ≥2 PsA isolates ≥6 mo apart in the biobank. Excl: CF Control cohort	N=39. Median age at enrolment =58 yrs (IQR 23-81). Median FU duration =3.2 yrs	Characterise the epidemiology, transmission and clinical outcomes of PsA infection in BE patients in a setting adjacent to a CF clinic.	Overall, 203 PsA were genotyped by MLST and PFGE. Patients had unique strains without evidence of cross-infection. 67% of patients were chronically infected with the same PsA strain, while 33% experienced strain	PsA isolates from BE and CF patients with similar PFGE pulsotypes shared these profiles and MLST genotypes with other clinical and environmental strains.	Reinforces the evidence that PsA acquisition is primarily from independent environmental sources. Cross-infection of

	prosp collected samples.	of 812 PsA isolates from CF patients over the last 30 yrs (including 65 globally distributed epidemic strains), 22 local environmental isolates (natural and hospital) and 35 strains from community-acquired blood stream infections.	(range 0.5-21).		displacement. No epidemic PsA strains were identified in BE patients, despite the prevalence of these strains in almost 40% of CF adults attending the adjacent clinic. Isolates from 4 patient pairs had indistinguishable MLST profiles. However, the patient pairs were epidemiologically unconnected and whole genome sequencing, showed the isolates differed much more between patients than within patients. This suggested independent acquisition rather than person-to-person transmission.	Clinical course was independent of PsA infection history, including strain displacement. Within the centre, strict hand and cough hygiene were enforced, patient contact with one another was discouraged and they did not share clinic, waiting or inpatient rooms. However, strict contact segregation was not undertaken and face masks were not requested to be worn by BE patients. Limitations include small sample size.	PsA between BE patients in settings using standard infection control procedures remains an uncommon event. The study was published after the EMBARC statement [117].

BAL=bronchoalveolar lavage, BE=bronchiectasis, BMI=body-mass index, CF=cystic fibrosis, CFU-colony-forming units, CI=confidence interval, CSLD=chronic suppurative lung disease, CXR=chest x-ray, EMBARC=European Multicentre Bronchiectasis Audit and Research Collaboration, Excl=exclusion, FBs=foreign bodies, FEV_1=forced expiratory volume in 1 second, FU=follow-up, GORD=gastroesophageal reflux disease, Hi=*Haemophilus* influenzae, HRCT=high-resolution computed tomography, Inc: inclusion, IQR=interquartile range, IV=intravenous, LAI=lower airway infection, MLST=multi-locus sequence typing, mo=months, MRSA=methicillin-resistant *Staphylococcus* aureus, Np=nasopharyngeal, NPV=negative predictive value, NTM=non-tuberculous mycobacteria, Op=oropharyngeal, OR=odds ratio, PCD=primary ciliary dyskinesia, PePR=period prevalence of rate (% of patients who harboured the pathogen of interest at least once during a calendar yr), PFGE= pulsed-field gel electrophoresis, PPV=positive predictive value, pred=predicted, Prosp=prospective, PsA=*Pseudomonas aeruginosa*, PSB=protected specimen brush, Retro=retrospective, rhDNase=recombinant human deoxyribonuclease, Sa=*Staphylococcus aureus*, SD=standard deviation, Sp=*Streptococcus pneumoniae*, Vs=versus, Wks=weeks, Yr=year.

Evidence to Decisions (EtD) framework

NQ4: When monitoring children/adolescents with bronchiectasis:

a) **How often should airway microbiology testing be conducted in outpatients?**
b) **How frequently should patients be seen in outpatient clinics?**
c) **How should cross-infection be minimised?**

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	In any chronic illness, disease monitoring is an important component of routine clinical care. Similarly, in any healthcare setting, attention to standard infection control is paramount.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	The narrative summary found only indirect evidence for how often to undertake airway microbiology testing in outpatients and how frequently patients should be seen in outpatient clinics. There was limited evidence to suggest cross-infection with *Pseudomonas aeruginosa* between patients with bronchiectasis or between CF and bronchiectasis patient populations at the same clinic and none for person-to-person transmission by other respiratory pathogens in patients with bronchiectasis. No RCTs addressing these questions were identified. The current evidence is based on observational studies (mainly retrospective and often conducted in adults) and it is highly unlikely that any such RCTs will be undertaken. The desirable frequency of outpatient clinic attendance and airway microbiology surveillance is dependent upon patient factors (e.g. age, underlying aetiology, illness severity, co-morbidities and ability to reliably expectorate spontaneous or induced sputum) and circumstances (e.g travelling long distances for clinic attendance). Thus effects vary. Respiratory clinics in paediatric hospitals use a model that is not fully validated,	The data presented in the Study Summary Table support the approach of 3-6 monthly outpatient clinic reviews and standard infection control policies without segregating patients. Outpatient sputum culture surveillance every 6-12 months is based on expert opinion [17]. However, for each of the 3 parts of NQ4, there are no RCTs and evidence is based predominantly on observational studies in

		involving assessment of stability and detecting deterioration based on clinical history and investigations. In these settings, studies show such a model leads to improved lung function post-diagnosis of bronchiectasis. The monitoring component includes 3-4 monthly clinical review with: • lung function tests when able to be performed (spirometry to assess FEV_1 and FVC) • assessment for new infection (sputum for culture during exacerbations and 6-12 monthly routine when available) and assessing (and if needed investigating) for new co-morbidities (e.g. asthma, GORD, nutritional deficiencies, dental or sleep disorders, etc.). Upper airway swabs are unreliable at predicting lower airway pathogens. Spontaneous or induced sputum samples in children able to expectorate are recommended for surveillance cultures. Bronchoalveolar lavage specimens are reserved for when treatment is failing, especially if sputum cultures are negative, and/or unusual pathogens are expected. A lack of evidence prevents robust recommendations on infection control policies for patients with bronchiectasis. If managed within a CF centre, local CF infection control policies should be followed and direct contact with CF patients avoided. Standard infection control procedures should be discussed with patients/families and hand and cough hygiene measures followed. If possible, contact with viral infections should be avoided, and influenza and other vaccinations promoted. **Addendum:** The guideline was written pre-COVID-19, but in view of this, children/adolescents with bronchiectasis should follow measures recommended by local health authorities.	both children/adolescents and adults. The panel's collective clinical experience supports the approach outlined in the research evidence. The panel also supports the overall conclusions and pragmatic recommendations of the EMBARC statement on infection control [117].
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ●Varies ○ Don't know	The undesirable effects vary according to patient factors (eg. in non-expectorating children/adolescents, not only are upper airway cultures unreliable for monitoring airway microbiology in stable patients [109,124] but induced sputum/cough swabs are time consuming, cause discomfort and are not the sampling method preferred by children [125]). Context is also important and may include the time needed for patients to travel long distances to attend specialist clinics. For young children with bronchiectasis, local infection control policies may mandate wearing a face mask, which they may find difficult to tolerate [126].	

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low due to absence of any RCTs and GRADEing of the evidence. The evidence is based on observational and predominantly retrospective studies.	The data are supported by the experience of clinical experts in the field.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	Parent/patient advisory groups valued regular review and monitoring by expert clinicians. However, the values likely vary depending upon the child, clinical setting and context. Adult patients chronically infected with respiratory bacterial pathogens, such as *P. aeruginosa*, are more concerned over transmitting these agents to other patients than acquiring new pathogens themselves [117]. They would appreciate further advice on how to reduce the risk to others and how to avoid viral respiratory infections.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative	Some benefit can be expected for many patients. The balance favours regular clinic attendance, sputum monitoring for new pathogens and standard infection control procedures as well as counselling.	

	○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ●Varies ○ Don't know	The costs are variable dependent on disease severity and patient context.	.
CERTAINTY OF RESOURCE EVIDENCE	● Very Low ○ Low ○ Moderate ○ High ○ No included studies	No available studies	Based on clinical experience, the costs are variable depending upon disease and patient context.
COST-EFFECTIVENESS	○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know ○ No included studies	No available studies	The panel considered that regular 3-6 monthly clinic attendance and 6-12 monthly sputum monitoring (if available) are likely cost-effective, based on clinical experience of good clinical care improves lung function, QoL and prognosis. Standard infection control procedures should be

			practised in all clinics.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published literature on health equity.	Differential access (from living in rural regions or away from a major centre with all the necessary specialist expertise) suggests presence of imbalance between patients, settings and countries.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	Probably yes, as specialist physicians routinely recommend regular clinic attendance and monitoring as well as standard infection control measures. Administrators and economic limitations may however reduce acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Regular attendance at outpatient clinics may depend upon availability of transport or the parent/guardian's capacity to be absent from work or to make alternative arrangement for the care of other dependent family members. In regional and smaller rural centres, attendance may also depend upon the availability of visiting specialist physicians and other health professionals. Sputum collection may also require the aid of a physiotherapist, while appropriate specimen handling and transport to the nearest laboratory must also be planned. Standard infection control procedures should operate in all clinical settings.	The feasibility of these interventions may be highly variable, although generally acceptable.

NQ4: **When monitoring children/adolescents with bronchiectasis:**
(a) How often should airway microbiology testing be conducted in outpatients?
(b) How frequently should patients be seen in outpatient clinics?
(c) How should cross-infection be minimised?

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention	**Conditional** recommendation **against** the intervention	Conditional recommendation for either the intervention or the alternative	**Conditional** recommendation **for** the intervention	**Strong** recommendation **for** the intervention
	○	○	○	●	○

RECOMMENDATION

- In children/adolescents with bronchiectasis, we suggest in those able to expectorate that routine spontaneous or induced sputum samples is collected every 6-12 months as a means of identifying new pathogens, specifically *P.* a*eruginosa,* and to help guide initial empiric antibiotic therapy for future exacerbations. (*Conditional recommendation, very low quality of evidence stemming from narrative review of evidence*).

- In children/adolescents with bronchiectasis, we suggest they are reviewed every 3-6 months in outpatient clinics to monitor their general wellbeing, respiratory status, including lung function when age appropriate, and to detect any complications. (*Conditional recommendation, very low quality of evidence stemming from narrative review of evidence).*

- For children/adolescents with bronchiectasis, we suggest that they and their family are counselled on cough and hand hygiene. Wherever possible, they should also avoid those with symptoms of viral respiratory infections. Children managed within a CF clinic must follow their infection control policies (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence*).

  Addendum: The guideline was written pre-COVID-19, but in view of this, children with bronchiectasis should follow measures recommended by local health authorities.

JUSTIFICATION	Although the evidence for the interventions leading to improving clinical outcomes is very low, the suggestions above were based upon indirect evidence that current standard of care in specialist settings leads to improved lung function post-diagnosis. Also, the panel and parent advisory group advocated regular clinical care and monitoring by specialists and for advice on avoiding cross-infection.
SUBGROUP CONSIDERATIONS	Patients with: ○ Underlying causes of bronchiectasis (e.g. primary ciliary dyskinesia, primary immunodeficiency, aspiration) ○ Limited access to standardised care e.g. in rural regions or not near centres with expertise in managing bronchiectasis.

IMPLEMENTATION CONSIDERATIONS	Increase accessibility of children to centres practising the standard of care.
MONITORING AND EVALUATION	Important to conduct surveillance for evidence of cross-infection within the clinic and that current infection control measures are being followed.
RESEARCH PRIORITIES	It is unlikely that these interventions will be amendable to RCTs as the monitoring suggested above is standard practice in most specialist respiratory clinics. Research priorities include multicentre studies to determine cost-effectiveness, optimal frequency of clinic visits and sputum culture monitoring. Additional studies evaluating non-invasive techniques for predicting lower airway pathogens in young children are needed, as are larger, longitudinal studies to determine the incidence and clinical impact of cross-infection.

NQ5 – Narrative summary of evidence table

When monitoring children/adolescents with bronchiectasis:

d) Are there any routine tests that should be undertaken to detect complications when attending outpatient clinics?

e) When should repeat chest CT-scans be undertaken?

f) In gradually deteriorating (i.e. non-acute) patients, what investigations should be undertaken?

First author, year, country	Setting; Study design	Inclusion, exclusion criteria	N; Age; Follow-up duration	Main aim(s)	Primary findings relating to narrative question	Other major findings and additional comment	Implications for narrative question
Bastardo [107], 2009, England	Specialist hospital; Retro, chart review	Inc: BE (HRCT diagnosis) and reliable spirometry and growth data for ≥2 yrs. Exc: CF	n=59 at 2 yr FU, n=31 at 4yr FU; Median age=8.2 yrs (range 4.8, 15.8); FU duration not stated	In children with BE, to evaluate the clinical course of lung function and growth over 2- and 4-years	At 2 years, reduced FEV_1 at baseline (<-2 z-score) associated with poorer weight (slope 20.3, 95%CI 20.5, 20.1, p=0.017) and BMI z-scores (slope 20.3, 95%CI 20.5, 20.0, p=0.049) and greater lung function deterioration (FEV_1 slope: -1.8, 95%CI -2.1, -1.5, p<0.005; FVC slope: -1.8, 95%CI -2.1 to -1.5, p<0.005 Improved lung function (see next column)	Mean z-score improvement per yr. Over 2 yrs: FEV_1=0.17 (95%CI 0.01, 0.34, p=0.039), FVC=0.21 (95%CI 0.04, 0.39, p=0.016). Over 4 yrs height-for-age z-scores improved (slope 0.05, 95%CI 0.01, 0.095, p=0.01), no change in spirometry or weight.	Current standard care in specialist settings leads to improved lung function post diagnosis. The monitoring component includes 3-4 monthly review with lung function test, assessment (and investigation when appropriate) for new infection (sputum), co-morbidities (e.g. asthma GORD, nutrition, etc) [15]
Banjar [127], 2007, Saudi	Specialist hospital; Retro chart review	Not described	n=151; Mean age=7.3 yrs (SD 4.1); FU=5.5 (SD 3.9) yrs	Describe aetiology and associated diseases in Saudi children with BE	48% had disease progression and associated with symptoms before aged 5 years, persistent atelectasis	Of 900 referred for recurrent chest infections, 151 had BE Comment: 65% of cohort had consanguineous parents	Consider repeating radiology assessment in children whose disease is gradually deteriorating
Bilan [128], 2014, Iran	Specialist hospital; Retro chart	Inc: BE (HRCT diagnosis with clinical symptoms),	n=374; Mean age=8.6 yrs (SD 3.4);	Evaluate factors effecting outcome of BE	3 groups compared: (a) Recovered group (improved clinical findings, CT scan improved and medication	Statistical analysis difficult to comprehend	Suggests treatment of asthma and/or GORD in children with BE is important. Thus,

	review. Children "treated for 2-3 yrs using steroid inhalers, broncho-dilator, and continuous low-dose oral antibiotic"	repeated CT every 6-12 months and FU for 2-3 yrs (CF not excluded) Exc: "concurrent medical disorders, congenital anomalies, or previous medication"	FU=5.5 (3.9) yrs	in children.	ceased), (b) "partially recovered" (continued but decreased medication dose as cough partially improved), (c) "non-recovered" (no improvement clinically and CT scan findings). Authors reported complete recovery was more in patients with GORD (undefined) or asthma (undefined).		considering, and investigating for, the presence of co-morbidities in children with BE is important
Cohen [108], 2017, 11 European centers	Specialist hospitals; Retro chart review and database	Inc: PCD, FU ≥3 yrs and ≥2 sputum cultures recorded. Exc: None stated	n=217; Mean age=19.9 yrs (SD 13.9); FU duration not stated for whole cohort	Review associations between PsA and lung disease in patients with PCD	Change in FEV_1 over 5 yrs was -3% (SD 12.7) in those PsA colonised and -0.9% (SD 12.8) in those non-colonised but inter-group difference b/w was not statistically significant	Those with PsA were older and had lower FEV_1 than those without	In reviewing children, consider the presence of PsA infection. Thus, routine sputum assessment is useful

Eastham [3], 2004, England	Specialist hospital; Retro chart review	Not defined but data was on consecutive children with BE	n=93; Median age=7.2 yrs (range 1.6, 18.8); FU duration not mentioned	Report local experience of HRCT defined BE in children	Repeat HRCT scans performed in 18 (for clinical reasons-unspecified), at 1.5–5 yrs after initial HRCT diagnosis and treatment initiated: 6 completely resolved (4 post-pneumonic, 2 idiopathic), 1 improved (post-pneumonic), 6 unchanged (2 post-pneumonic, 2 immunocompromised, 1 idiopathic, 1 bronchiolitis obliterans), 5 deteriorated (2 post-pneumonic, 2 immunocompromised, 1 hypersecretory)	Crude estimate of prevalence of BE was 1 in 5800. Difficult to control asthma was reason for referral in 49%	Consider repeating chest CT in children whose disease is gradually deteriorating or substantially changed
Gaillard [82], 2003, England	Specialist hospital; Retro review	Inc: BE with repeat CT scan undertaken Exc: CF	n=22, age range 1-16 yrs; Repeat FU HRCT: median=24 mo (range 2-43)	Report findings and FU of children with BE who had at least one repeat HRCT scan	Post treatment, radiological BE completely resolved in 6 children, improved in 8, unchanged in 3, 4 had lobar resection and worsened in 1.		Consider repeating chest CT in children whose disease is gradually deteriorating or substantially changed
Guran [69], 2007, Turkey	Specialist hospital; Cross-sectional prosp	Inc: BE (HRCT), able to do spirometry, FEV_1 >50% pred, stable clinically and can FU for ≥1 yr. Exc: CF or previous lobectomy	n=27; Median age=11.4 yrs (IQR 9.5, 13.6); FU=3.5 (IQR 2, 6.5) yrs	Evaluate relationship between clinical, radiographic, spirometry and inflammatory parameters of children with BE	HRCT severity scores correlated with symptom scores ($r=0.64$, $p<0.0001$; pulmonary function tests (FEV_1 %pred $r=-0.68$, $p<0.0001$, FVC %pred $r=-0.57$, $p=0.002$), sputum inflammation markers (IL-8 $r=0.58$, $p=0.003$, TNF-α $r=0.41$, $p=0.04$).	No relationship of parameters to physical findings Comment: 50% of children had parents who were first degree relatives. All children were receiving inhaled corticosteroids, none received prophylactic antibiotics	Consider repeating chest CT in children whose disease is gradually deteriorating.

Kapur [8], 2010, Australia	Specialist hospital; Retro chart review	Inc: BE (HRCT diagnosis) and reliable spirometry and growth data for ≥3 yrs. Exc: CF	n=52; Median age=8 yrs (range 2, 14); FU=3 yrs in 52 children, 5 yrs in 25	In children with BE, to evaluate (a) lung function measurements and growth over 3- and 5-yrs and, (b) factors associated with the change	Frequency of hospitalised exacerbations statistically associated with FEV_1 %pred decline. Age of diagnosis, number of lobes with BE, aetiology of BE and sex were not associated (age of diagnosis was a large but statistically insignificant factor)	Over 3 yrs, statistical improvement in lung function only seen in $FEF_{25-75\%}$ (slope 3.01, 95%CI 0.14, 5.86, p=0.04) but trend present for FEV_1 %pred (slope 1.17; 95%CI -0.38, 2.7) and FVC (slope 1.57; 95%CI -0.18, 3.34) per annum. 5-yr trends similar. BMI z-scores significantly improved (BMI z -scores (slope 0.09; 95%CI, 0.02, 0.15, p=0.01) per annum	Current standard care in specialist settings leads to improved lung function post diagnosis. The monitoring component includes 3-4 monthly review with lung function test, assessment (and investigation when appropriate) for new infection (sputum), co-morbidities (e.g. asthma GORD, nutrition, etc) [15]
Manglione [9], 2012, Italy	Specialist hospital; Retro chart review	Inc: available CT scan and spirometry during stable state and a second CT scan plus spirometry during unstable lung disease Exc: aged < 6 yrs	n=20; Median age at 11.6 yrs (range 6.5, 27.5); FU median time between scans: 2.3 yrs (range 1.3, 3.4)	Evaluate the relationship between spirometry and HRCT data in stable and unstable lung disease in children with PCD	CT scores significantly related to z-scores of FEV_1 (time 1: r=-0.5, p=0.01, time 2: r=-0.7, p=0.001) and FVC (time 1: r=-0.6, p=0.008, time 2: r=-0.7, p=0.001) at both evaluations. Change in CT scores did not correlate to change in spirometry values (FEV_1: r=-0.02, p=0.9, FVC: r=-0.02, p=0.9)	FEV_1/FVC ratio was not evaluated	CT scan more sensitive than spirometry in determining disease progression. Thus, useful to repeat CT under certain clinical circumstances
Magnin [10], 2012, France	Specialist hospital; Retro chart review	Inc: aged <15 yrs, FU > 8 yrs, ≥2 concomitant CT and lung function while stable and PCD Exc: not stated	n=20; Median age at 7.6 yrs (range 0.8, 18.1); FU median 15.4 yrs (8.7,	Describe relationship between changes in lung function and structure to evaluate	CT scores increased with age; mean increase 0.95 points/yr. Significant negative longitudinal correlation between lung function and CT-score (PaO2: r=-0.47, p=0.05;	All children eventually developed bronchiectasis based on HRCT scan	Spirometry values (FEV_1 and FVC) and repeat CT scans useful for monitoring disease. FEV_1/FVC ratio is not

			22	progression lung disease in children with PCD 74 CTs analysed; median=3 (range 2–7) CTs/child; median interval of 2.1 (0.6–11.7) yrs.	FVC: r=-0.64, p=0.005; FEV_1 r=-0.65, p<0.005). FEV_1/FVC ratio stable throughout FU and no correlation with any parameter		useful for monitoring disease
Manson [129], 1997, Canada	Specialist hospital; Retro chart review	Not specified but all children had antibody deficiency disorder	n=37; Age at CT=5-20 yrs; 70 scans in total, repeated for clinical concern of disease progression	Define incidence and role of HRCT in identifying higher risk group and following success or failure of therapy	7 of the 9 with BE had repeat CT over 5 yrs. In 4 of the 7, CT severity of BE improved and 3 worsened. Factors statistically significantly correlated with BE severity at first CT scan: duration of respiratory symptoms before treatment, success in attaining adequate IgG level, spirometry abnormality (defined as FEV_1 and FVC %pred <80%)	Factors not statistically significantly correlated with CT severity were: age at diagnosis of antibody deficiency, type of deficiency, age at each CT scan, number of treated pneumonias before diagnosis, diagnosis of asthma, length and type of previous immunoglobulin re-placement therapy, and patient compliance Comment: Small numbers. For example, only one child was non-adherent.	Useful to repeat CT under certain clinical circumstances e.g. re-evaluation of clinical status

Marino [130], 2018, England	Specialist hospital; Prosp cohort study	Not specified but all children with PCD seen in the clinic aged 0-16 yrs enrolled	n=43; Mean age=7 yrs (SD 3.6); FU=not specified	Define associations between nutritional status, biomarkers of inflammation and lung function in children with PCD	FEV_1 z-score related to height z-score (r=0.4, p=0.049). Those whose free fat mass index (FFMI) were <-2 z scores) had a significantly lower FVC z score (-1.5 ± 1.0 vs. 0.3 ± 1.3 (p=0.01)) and a lower BMI z score (-1.3 ± 1.2 vs. 0.8 ± 0.7 (p=0.0002). Vitamin D levels associated with FFMI (r=0.4, p=0.02)	Vitamin D levels deficiency (<50 nmol/L) common in cohort (54%)	Consider vitamin D deficiency in children whose disease is gradually deteriorating. Also, Vitamin D deficiency is associated with poorer clinical outcomes in adults with BE
Munro [113], 2011, New Zealand	Specialist hospital; Retro chart review	Inc: BE (HRCT diagnosis) and FU for ≥5 yrs. Exc: CF	n=91; Median age=7.3 (0.9–16) yrs; Median FU=6.7 yrs (5–15.3)	Describe outcomes for BE following ≥5 yrs of management in specialist respiratory clinic	FEV_1 declined by a mean of 1.6% predicted/yr over the FU period Trend of greater reduction in FEV_1 associated with chronic PsA (largest predictor at -2.8%/yr), Maori ethnicity, high poorer socioeconomic stats, presence of digital clubbing, or chest wall deformity	Lower mean FEV_1 found in males, comorbid asthma, presence of digital clubbing and chest wall deformity. Comment: High absentee rate at clinics (28%)	In reviewing children, consider presence of asthma and PsA infection. Thus, routine lung function test and sputum assessment
Santamaria [131], 2014, Italy	Specialist hospital; cross-sectional, prosp study	Inc: PCD, stable state, can perform lung function and had recent (<3 mo) HRCT. Exc: recent (<4 wks) infection or asthma, heart, cranio-facial, neuro-muscular disease or syndromes; require oxygen, anti-convulsant	n=16; Median age=10.4 yrs (range, 4.9–17.2); FU: not stated Matched controls n=42	Evaluate relationship between sleep poly-somnography (PSG) with mother-reported sleep quality using Sleep Disturbance scale for children (SDSC) with lower airways	Oxygen desaturation index (ODI) [defined abnormal if >1/hour] related with HRCT score (r=0.6, p=0.03) and to FRC (r=0.8, p=0.02), but not to other lung function data. HRCT BE score did not significantly relate with other PSG parameters, SDSC, lung function or nasal endoscopy data. No significant correlations between PSG parameters and	Although reported by parents to be normal sleeper, all had OSAS, (mild=19%, moderate=50%, severe=31%)	Consider sleep disorders in children whose disease is gradually deteriorating

		or psychoactive drugs; broncho-dilator in last 24h or cortico-steroids in last 2 wks		involvement in children with PCD	body mass index; neck and waist circumferences; SDSC data and nasal endoscopy.		
Sunther [115], 2016, England	Specialist hospital; Retro review from PCD database	Inc: aged 6-16 yrs and able to perform spirometry. Exc: incomplete spirometric assessments	n=30; Median age=11.4 yrs (range 6, 16.2); FU: not stated	In children with PCD treated with intra-venous antibiotics for an exacerbation, to determine: (a) proportion who recover to baseline FEV_1 within 3 mo and (b) identify factors associated with failure to regain pre-exacerbation FEV_1	Responders (FEV_1 recovered to baseline)=77% of cohort No difference between responders and non-responders in baseline characteristics (age, gender, ethnicity, BMI, baseline FEV_1 < 40%, mean baseline FEV_1, mean admission FEV_1, persistent infection, use of oral prophylactic antibiotic, nebulized hypertonic saline or DNase) 2 out of 7 (29%) non-responders had persistent infection with PsA in the 12 mo prior to pulmonary exacerbation compared to none of the responders (p=0.05)		Highlights importance of detecting PsA and thus using sputum for monitoring

BE=bronchiectasis, CF=cystic fibrosis, Exc: exclusion, FU=follow-up, Hosp=hospital, GORD=gastroesophageal reflux disease, HRCT= chest high-resolution computed tomography, Inc: inclusion, mo= months PCD=primary ciliary dyskinesia, pred=predicted, PsA=*Pseudomonas aeruginosa*, Prosp=prospective, Retro=retrospective, Wks=weeks, Yr=year

Evidence to Decisions (EtD) framework

NQ5: When monitoring children/adolescents with bronchiectasis:

d. Are there any routine tests that should be undertaken to detect complications when attending outpatient clinics?

e. When should repeat chest CT-scans be undertaken?

f. In gradually deteriorating (i.e. non-acute) patients, what investigations should be undertaken?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in adults and children/adolescents, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged [15,21,22]. Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The European Respiratory Society guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation parent advisory group for this guideline.	In any chronic illnesses, disease monitoring is part and parcel of clinical care
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	The evidence provided in the narrative summary found only indirect evidence for using routine tests to detect complications of bronchiectasis, investigations required for gradually deteriorating patients and whether chest CT-scans should be repeated. Our search did not identify any RCTs that address these questions. The current evidence is based on observational studies (predominantly retrospective) and it is highly unlikely that any such RCT will be undertaken. The desirable interventions are patient (e.g. age [young children require general anaesthesia for a chest CT-scan], severity of illness, costs of tests) and circumstance (e.g. underlying disease, patients travelling long distances for tests) specific. Thus, the desirable effects vary. Specialists in tertiary paediatric respiratory clinics currently use a model of care that, although not fully described, includes standardised care involving an assessment of stability and deterioration based on clinical history and tests. In these settings, studies	The data presented in the table of summary of studies support the approach, but there are no RCTs and evidence is based upon observational studies (predominantly retrospective). Other supportive data include the reduction in exacerbations with specialist-supervised management [13]. The panel's collective clinical experience supports the approach outlined in the research evidence.

		have shown that such a model leads to improved lung function post-diagnosis of bronchiectasis. The monitoring component of the standardised care includes 3-6 monthly clinical review with • lung function test (spirometry to assess FEV_1 and FVC) • assessment for new infection (sputum for bacteria culture during exacerbations and 6-12, monthly routine) and assessing (and when indicated investigating) for the presence of new co-morbidities (e.g. asthma GORD, nutritional deficiencies, dental or sleep disorders). The monitoring process in tertiary paediatric respiratory clinics consists of clinical symptoms, frequency and severity of respiratory exacerbations and lung function indices. When deterioration occurs, the narrative evidence supports assessing and investigating for treatable traits: new infection, asthma, GORD, nutritional deficiencies, dental or sleep disorders. Evidence from the narrative summary found several studies where repeated chest CT-scans in children/adolescents with bronchiectasis were undertaken. However, the reasons given for doing so were largely based upon clinical indications. These included documenting reversal of airway dilatation that previously had led to a diagnosis of bronchiectasis (e.g. for medical insurance or to reduce the care burden for parents and patients) or when there is an acute or gradual deterioration (e.g. to assess for new treatable disease or to justify more intensive treatments).	There is insufficient evidence at present for using magnetic resonance imaging as a monitoring tool.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ●Varies ○ Don't know	The undesirable effects vary according to patient (e.g. age [young children require general anaesthesia for chest CT-scans] disease severity) and context (e.g. underlying disease, need for patients to travel long distances for tests, associated test costs) specific factors. Obtaining a CT-scan needs to be balanced against the reported increased lifetime cancer risk, which is age and dose-dependent. Although relatively negligible and lower with newer CT-protocols, young children have been estimated previously to have 10 times the risk compared to middle-aged adults [132].	
CERTAINTY OF	**What is the overall certainty of the evidence of effects?** ● Very Low	The certainty of the evidence is very low due to absence of any RCTs and GRADEing of the evidence. The evidence based on observational studies (predominantly retrospective).	Data are supported by the experience of clinical experts in the field.

EVIDENCE	○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○Probably no important uncertainty or variability ○No important uncertainty or variability ○ No known undesirable outcomes	Patient/parent advisory group valued regular review and monitoring by expert clinicians. However, the values likely vary dependent of the child/adolescent, clinical setting and context.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the alternative?** ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Some benefit can be expected for many patients. The balance favours the interventions for monitoring and most, but by no means all, tests.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings	No available studies	The costs are variable dependent upon disease and patient context.

	●Varies ○ Don't know		
CERTAINTY OF RESOURCE EVIDENCE	● Very Low ○ Low ○ Moderate ○ High ○ No included studies	No available studies	Based on clinical experience, the costs are variable dependent upon disease and patient context.
COST EFFECTIVENESS	○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know ○ No included studies	No available studies	The panel considered that monitoring with the simple tests (but not routine repeat chest CT-scans) is likely to be cost-effective. Based upon clinical experience, good clinical care improves lung function, QoL and future outcomes.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	There is no published literature on health equity, but differential access (from living remotely or away from a major centre with specific expertise) suggests presence of imbalance between patients, settings and countries.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	Probably yes, as specialist physicians routinely advocate regular monitoring. Administrators and economic limitations may however limit acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No available studies	The simple tests are likely feasible, but there may be some limits related to availability of these interventions at some local settings. The feasibility of these intervention may therefore be variable, although generally acceptable.

NQ5. When monitoring children/adolescents with bronchiectasis:

(d) Are there any routine tests that should be undertaken to detect complications when attending outpatient clinics?

(e) When should repeat chest CT-scans be undertaken?

(f) In gradually deteriorating (i.e. non-acute) patients, what investigations should be undertaken?

TYPE OF RECOMMENDATION	**Strong** recommendation **against** the intervention	**Conditional** recommendation **against** the intervention	Conditional recommendation for either the intervention or the alternative	**Conditional** recommendation **for** the intervention	**Strong** recommendation **for** the intervention
	○	○	○	●	○

RECOMMENDATION	• In children/adolescents with bronchiectasis, we suggest the following routine tests are undertaken to detect complications when attending outpatient clinics: (a) lung function (spirometry for FEV1 and FVC) when age-appropriate, (b) sputum when they can expectorate and (c) pulse oximetry (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence)*. • In children/adolescents with bronchiectasis, we suggest the decision to repeat chest CT-scans is individualised based on the clinical status and setting (*Conditional recommendation, very low quality of evidence stemming from narrative review of evidence).* **Remarks**: Repeat chest CT-scans should be considered to answer a question which will change management. • For children/adolescents with bronchiectasis whose clinical status is gradually deteriorating, we suggest they are assessed for new infections (sputum or lower airway microbiology) and possible co-morbidities (e.g. asthma, GORD, nutritional deficiencies, dental or sleep disorders) (*Conditional recommendation, very low-quality of evidence stemming from narrative review of evidence).* **Remarks**: These children/adolescents often require hospitalisation for intravenous antibiotics and airway clearance therapy.

JUSTIFICATION	Although the evidence for the above interventions improving clinical outcomes is very low, the suggestions were based upon indirect evidence that current standard of care in specialist settings leads to improved lung function post-diagnosis. Also, the panel and parent advisory group advocated standardised clinical care, especially in primary care settings.
SUBGROUP CONSIDERATIONS	Patients with: ○ Underlying causes of bronchiectasis (e.g. primary ciliary dyskinesia, primary immunodeficiency, aspiration) ○ Limited accessibility to standardised care e.g. in remote and/or rural communities or not near a centre with specialist care of bronchiectasis
IMPLEMENTATION CONSIDERATIONS	Increase accessibility of children to centres practising the recommended standard of care. Obtaining a CT-scan needs to be balanced against the reported increased lifetime cancer risk, which is age and dose-dependent. Although relatively negligible and lower with newer CT-protocols, children previously have had 10-times increased cancer risk compared to middle-aged adults [132]. Currently, specialists in tertiary paediatric respiratory clinics individualise the need to repeat chest CT-scans. Indications to do so include documenting reversal of bronchiectasis (e.g. for medical insurance or to reduce the care burden for parents and patients) or when there is an unexpected acute or gradual deterioration (e.g. to assess for new treatable disease or to guide the need for more intensive treatment).

MONITORING AND EVALUATION	Not applicable.
RESEARCH PRIORITIES	It is unlikely that these interventions will be amendable to placebo RCTs as the monitoring suggested above is standard practice in most paediatric specialist respiratory clinics. Research priorities include multicentre studies to determine cost-effectiveness, optimal frequency of monitoring and prospective studies to determine factors identifying treatable traits (e.g. asthma, GORD, etc) in children bronchiectasis. Outcomes should include QoL, exacerbations, symptoms, hospitalisations, lost school/work days and lung function indices.

NQ6 – Narrative summary of evidence table

In children/adolescents with bronchiectasis, what criteria should be used to define an exacerbation?

First author, year, country	Study design	Inclusion and exclusion criteria	N; Age; Follow-up length	Main aim(s)	Definition of exacerbation	Other findings	Implications for narrative question
Chang [133] 2012, Australia and New Zealand	Protocol for 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 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 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 before study enrolment) of Pseudomonas; receipt of beta-lactam or macrolide antibiotics within 3 wks preceding study entry for the exacerbation; or current treatment for cancer	From RCT [51] 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 azithromycin, are superior to placebo in achieving resolution of non-severe exacerbations by day 14 of treatment	An increase in sputum volume or purulence, or change in cough [>20% increase in cough score or type (dry to wet)] for ≥3 days Resolved exacerbations: when symptoms and signs are the same as the baseline state	RCT published.[50] Oral amox–clav for 14 days for non-severe exacerbations of bronchiectasis 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 exacerbations and parent reported criteria
Chang [134] 2013, Australia and New Zealand	Protocol for RCT, multi-centre, double-	Inclusion: <19 yrs, CT-proven BE in the last 5 yrs (or if diagnosed earlier, regularly follow-up by a respiratory physician for	From RCT[51] Median age in yrs (IQR):	Primary question: 'Is daily oral azithromycin non-inferior (within a 20% margin) to oral	An increase in sputum volume or purulence, or change in cough [>20% increase in cough score or type (dry to wet)] for ≥3	RCT published.[51] By 21 days of treatment, azithromycin is non-	Limited to mild exacerbations and parent reported criteria

	dummy, double blind (BEST-2)	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 before study enrolment) of Pseudomonas; receipt of beta-lactam or macrolide antibiotics within the preceding 3 wks for the exacerbation; or current treatment for cancer	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 exacerbat ion	amox-clav, at achieving resolution of exacerbations by day 21 of treatment?'	days Resolved exacerbations: when symptoms and signs are the same as the baseline state	inferior to amox-clav, for resolving non-severe exacerbations. Exacerbations were significantly shorter in the amox-clav, than in the azithromycin group (median 10 days [IQR 6–15] vs 14 days [8–16]; p=0.014)	
Kapur [135] 2009, Australia	Retrospecti ve cohort, single centre in specialist hospital	Inclusion: Children with CT-proven bronchiectasis 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 exacerbat ions in 3 0 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-	Intravenous antibiotics required in 39 (35%) exacerbations within 4 weeks 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 symptoms and signs. Spirometry data insensitive.

					103) (p=0.36). FVC% predicted during exacerbation (median 81%, range 50.9- 102) and stable state (median 85.5%, range 52.4-114) (p=0.34). CXR performed during 35 exacerbations, 8 (22.9%) had new changes		
Kapur [136] 2012, Australia	Prospective cohort, single centre in specialist hospital	Inclusion: Children with CT-proven bronchiectasis Exclusion: CF Paediatric pulmonologist defined exacerbation was taken 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.'	69 children with 81 exacerbations. Median age=7 yrs (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 hours of: (1) Significant frequency of cough (median cough score ≥2) (2) Wet cough B. Minor Criteria (1) Sputum colour ≥3 BronkoTest (2) Parent/child perceived breathlessness, (3) Chest pain, (4) Crepitations, (5) Wheeze, (6) Hypoxia. C. Laboratory Criteria (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	Inter-observer kappa value for each of the factors in the assessment form was >0.75 Spirometry and impulse oscillatory indices during exacerbation was not different from baseline Haemoptysis was significantly more likely to occur during an exacerbation but very rare in cohort	The sole prospective study that used clinical 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.

					major with 2 minor criteria		
Karadag [70] 2005, Turkey	Retrospective, single centre	Inclusion: HRCT-confirmed bronchiectasis and followed up for at least 2 years	n=111; mean age 7.4 8 years SD 3.7	Describe the characteristics, underlying causative factors and long-term follow-up	Persistent (>24 h) increase in respiratory symptoms, new opacification on chest X-rays or worsening in physical examination findings of the chest		Retrospective review
Koh [137] 1997, South Korea	Double blind RCT, single centre	Inclusion: HRCT-confirmed bronchiectasis and presence of airway hyperresponsiveness (PC_{20} <25 mg/ml to methacholine) Exclusion: antibiotics or corticosteroids within 1 month before enrolment	N=25 13 in roxithromycin, 12 placebo Mean age= 13.1 yrs (SD 2.6)	Determine effect of 12 weeks of roxithromycin on degree of airway hyperresponsiveness (AHR) in bronchiectasis	Fever, increased cough and sputum production	In roxithromycin group c.f. placebo, sputum features and AHR significantly improved. PD_{20} increased from 87.1 (47.3–160.4) to 169.2 (83.2–344.2) breath units ($p<0.01$)	Exacerbation was not an outcome of study and not properly defined
Kobbernagel [138] 2016, Europe	Protocol for RCT, multi-centre	Inclusion: PCD, FEV_1% predicted >40%, ≥30 days of antibiotics for exacerbations in last 2 yrs, not on azithromycin in last 30 days, not on inhaled or maintenance antibiotics	Age 7-70 years	Determine efficacy of 6-mo of azithromycin on respiratory exacerbations in PCD	Respiratory symptoms 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	Study not published yet	One way to define exacerbation although RCT includes adults and restricted to PCD. Also, definition does not include duration of symptoms
Hill [139] 2017, Europe	Consensus, multicentre	Systematic review of definitions of exacerbations used in adult bronchiectasis clinical trials (Jan 2000 to Dec 2015) followed by a Delphi process and a round-table meeting	Adults	Develop a consensus definition of an exacerbation for use in clinical research for adults with bronchiectasis	"Deterioration in ≥3 of the following key symptoms for ≥48 hours: (1) cough, (2) sputum volume and/or consistency, (3) sputum purulence, (4) breathlessness and/or exercise tolerance, (5)	50 papers with 20 different definitions. >80% included a requirement for antibiotic use, and the symptoms of increased dyspnoea, increased cough,	Definition for research use in adults with bronchiectasis i.e. not in children or for clinical use

		involving bronchiectasis experts			fatigue and/or malaise, (6) haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required"	increased sputum volume and a change in sputum colour. All other criteria were used in <80% of definitions	
Lucas [140] 2019, Multiple countries	Consensus, multicentre	Systematic review that used pulmonary exacerbations in PCD patients as a variable (Jan 2000 to April 2017) followed face-face meeting and e-Delphi 16 members of the panel	Adults and children	Develop a consensus for defining pulmonary exacerbations in children and adults with PCD for clinical trials and other research	Children and adults with PCD. ≥3 of the following: Increased cough, Change in sputum volume and/or colour, Increased shortness of breath perceived by the patient or parent, Decision to start or change antibiotic treatment because of perceived pulmonary symptoms, Malaise, tiredness, fatigue or lethargy, New or increased haemoptysis, Temperature >38°C		Lacks time element e.g. single episode vs days would result in different interpretation
Masekela [141] 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 function tests (ALT/AST > 2.5x normal), abnormal urea, creatinine or using carbamazepine, warfarin, cyclosporin or long-term midazolam	N=31 erythromycin n=17, Mean age=8.4 yrs (SD 2.4) Placebo n=14 Mean age=9.1 (SD 2.1)	Evaluate the efficacy of 52 wks of erythromycin (c.f. placebo) in 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 chest X-ray	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%) erythromycin than placebo (0%) had no exacerbations during the study duration. High attrition rate (28%)	Limited to HIV-related BE

Redding [13] 2014, USA and Australia	Prospective multicentre	Inclusion: Australian Aboriginal and Alaska Native children, aged 0.5-8 yrs, with either CT-confirmed bronchiectasis CSLD (>3 months of daily wet cough) and has ≥3 consecutive years of observation Exclusion: (1) underlying cause of bronchiectasis (immunodeficiency, PCD, CF), (2) diabetes or cancer or (3) central nervous system or neuro-muscular disorder affecting respiratory system	N=93 children Median age=36 mo, (range 9-107)	(1) Characterize the pattern of acute BE exacerbations and (2) identify clinical features that increased the risk of recurrent and severe exacerbations requiring hospitalisation	Acute respiratory-related episodes requiring new antibiotic treatment for any of the following reasons: increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in predicted FEV_1% predicted by >10%, or haemoptysis. Clinical encounters within 2 wks considered a single exacerbation	Risks of recurrent and severe exacerbations: age ≤3 yrs who have experienced multiple and/or hospitalised in the first year of life and in the year prior to enrolment	Limited to indigenous children
Shapiro [142] 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 centred research consortium	Acute changes in cough, sputum production, respiratory rate or work of breathing	See document for other recommendations	Document specific to PCD
Sunther [115] 2016 England	Specialist hospital; Retro review from PCD database	Inclusion: Aged 6-16 yrs and able to perform spirometry. Excl: 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 anti-biotics for an exacerbation to: (i) determine proportion who recover baseline FEV_1 within 3 mo and (ii) identify factors associated with failure to	"A change in respiratory status for which intravenous antibiotics were prescribed"	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	Hospitalised only data

				regain pre-exacerbation FEV_1.		antibiotics, nebulised hypertonic saline or rhDNase)	
Valery[60] 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 years, lived within the study area, and had at least one pulmonary exacerbation in the past 12 months. Exclusion: receiving chemotherapy, immune-suppressants or long-term antibiotics, has CF or primary immune-deficiency, other chronic disorders (eg, cardiac, neurological, renal, hepatic abnormality), or macrolide hypersensitivity		Establish whether 24 mo of once weekly azithromycin 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 FEV_1 %predicted by >10%, or haemoptysis. Visits for a respiratory infection within 2 weeks as part of the same 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)	

Amoxicillin-clavulanate=amox-clav, BE=bronchiectasis, CF=cystic fibrosis, CSLD=chronic suppurative lung disease, CT=computed tomography of chest, FU:follow-up, PCD=primary ciliary dyskinesia, RCT=randomised controlled trial

Evidence to Decisions (EtD) framework

NQ6: In children/adolescents with bronchiectasis, what criteria should be used to define an exacerbation?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	The panel considered that recognising respiratory exacerbations early is important. In children with bronchiectasis, exacerbations are particularly important clinically as they are associated with increased rspiratory symptoms and psychological stress, impaired QoL, accelerated lung function decline (-1.9 FEV1% predicted per hospitalised exacerbation) and substantial healthcare costs [8,62]. Pulmonary exacerbations are key outcome measures in clinical trials and epidemiological research of chronic lung diseases. Despite the importance of pulmonary exacerbations, there has been no consensus definition and individual researchers have used different definitions.
SUMARY AND CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence in the literature?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The narrative summary identified 13 papers in children/adolescents and one consensus document [139] in adults. Of the paediatric-focused papers, two were protocols [133,134] (with the corresponding RCTs published [50,51]) relating to using antibiotics at the onset of an exacerbation and three were published RCTs [60,137,141] where exacerbations were outcomes. Two cohort (one prospective [136] and one retrospective [135]) studies were specifically dedicated to defining exacerbations and one a prospective study [13] that included children/adolescents with chronic suppurative lung disease (in addition to those with bronchiectasis). Four papers related solely to primary ciliary dyskinesia; one was a retrospective review [115], one a protocol [138] (RCT not published) and two were consensus-derived descriptions [140,142] related to children/adolescents and adults with primary ciliary dyskinesia, but they differed substantially from one another.	As this question was reviewed only narratively and GRADEing of the evidence was not performed, our confidence in our conclusions is limited.

		While there are some similarities, the definitions used in these studies varied widely (depending upon the reason i.e. defining an exacerbation to initiate antibiotic treatment differs from that used as an outcome measure for clinical research).	
CURRENT PRACTICE			Panel members considered that managing exacerbations is a key component of bronchiectasis care. Thus, recognising exacerbations (both parents' and doctors' perspectives) is important. Exacerbations invariably result in an increase of respiratory symptoms (mostly cough +/- sputum) and less commonly (but important) other symptoms like haemoptysis, chest pain, breathlessness and wheeze. Changes in chest auscultation findings and chest x-ray are important, but not always present. Systemic symptoms (fever, fatigue, malaise, change in child's behaviour, appetite) are also sometimes present. In severe exacerbations, tachypnoea +/- hypoxia may also develop. Blood indices are considered less important for the clinical definition (as opposed for research). The panel considered that at least 3-days of increased symptoms is required for the definition, except for those with underlying immunodeficiency and when hypoxia or age-adjusted tachypnoea are present. The panel considered that a shorter timeframe may be more appropriate for those with immunodeficiency (i.e. >1-day rather than 3-days) whilst no timeframe is required for those with hypoxia/tachypnoea.
	Is there important uncertainty or variability in how much patients value certain	There is probably some uncertainty as individuals differ with respect to the first symptom of exacerbations. Also, some of the symptoms overlap with upper respiratory tract infections that are common in all children. Further, there are many causes of bronchiectasis, of which some may	

VALUES	criteria over others? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ Not important uncertainty or variability ○ No known undesirable outcomes	warrant earlier treatment (e.g. in those with immunodeficiency).	

BENEFITS	**How substantial are the benefits of using specific criteria for defining an exacerbation?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The benefits of using these criteria include having a standardised definition of exacerbations that allows parents and health professionals who look after children/adolescents with bronchiectasis to have the confidence to recognise exacerbations early and thus lead to more rapid treatment and earlier resolution. Exacerbations of bronchiectasis are associated with poorer QoL, parental stress and anxiety [59,143]. Thus, earlier resolution of symptoms would improve QoL and parental concerns.	Based on the narrative review and clinical experience, the panel considered that the criteria which includes a timeframe of 3-days (cf. adults' definition of 2-days [139]) and recognises common (as well as less common) symptoms and signs is the most appropriate approach. Stipulating that chest auscultation findings are often absent is important as parents often inform us that their local doctors refuse to treat their child/adolescents's exacerbation when the chest sounds clear to auscultation.
HARMS	**How substantial are the harms of using specific criteria for defining an exacerbation?** ○ Trivial ● Small ○ Moderate ○ Large	There were no data on harms, but these were considered small	The panel considered it is possible early treatment may not always be necessary (as seen in the placebo arm of a RCT [50]). In such circumstances, the child/adolescent would be exposed to the adverse events related to treatment (e.g. diarrhoea and nausea from antibiotics) without benefit.

	○ Varies ○ Don't know		
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No available studies	There is no published literature on health equity, but differential access to quality care for children/adolescents with bronchiectasis suggests that there will be inequitable care across regions and countries. The experience and ability of health professionals to manage children/adolescents with bronchiectasis (and recognise exacerbations) vary substantially within and between countries. Also, health literacy among parents vary widely and thus, equity is likely reduced.
ACCEPTABILITY	**Is the definition acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	The panel and parents considered that irrespective of the low level of evidence, recognising exacerbations (leading to effective management) is important.

NQ6. In children/adolescents with bronchiectasis, what criteria should be used to define an exacerbation?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** using the criteria ○	**Conditional** recommendation **against** using the criteria ○	Conditional recommendation for either using the criteria or the alternative ○	**Conditional** recommendation for using the criteria ●	**Strong** recommendation **for** using the criteria ○
RECOMMENDATION	For clinical purposes: • In children/adolescents with bronchiectasis, we suggest that a respiratory exacerbation is considered present when a child/adolescent has increased respiratory symptoms (predominantly increased cough +/- increased sputum quantity and/or purulence) for >3-days. (*Conditional recommendation, low-quality of evidence stemming from narrative review of the evidence*). **Remarks**: Other important, but less common respiratory symptoms 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 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 C-reactive protein, neutrophilia and interleukin (IL)-6) provide supportive evidence for 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. • In children/adolescents with bronchiectasis, we recommend that the presence of dyspnoea (increased work of breathing) and/or hypoxia should be considered a severe exacerbation, irrespective of duration. (*Strong recommendation, low-quality of evidence stemming from narrative review of the evidence*).				

JUSTIFICATION	Although the evidence for the above criteria is very low, the suggestions were based upon several prospective studies and evidence that parents' value recognising and treating respiratory exacerbations early.
SUBGROUP CONSIDERATIONS	Patients with: ○ Immunodeficiency (primary or secondary): a lower threshold for exacerbation and commencing treatment earlier may be required ○ Primary ciliary dyskinesia: considerations for ear and nasal symptoms may be required ○ Children with neurodevelopmental conditions may have more subtle and/or individually recognised symptoms of an exacerbation, whereby earlier treatment is necessary
IMPLEMENTATION CONSIDERATIONS	Increase education of patients, parents/carers and health professionals to recognise exacerbations and to commence additional treatment.
MONITORING AND EVALUATION	Local practices and evaluation of outcomes
RESEARCH PRIORITIES	For future research, we suggest prospective collected data from multi-centre studies using the validity of the definition above based on different duration of symptoms (such as 5-days instead of 3) and defining the benefit and harm arising from the different definitions. Studies addressing gaps in the inflammatory and immune responses and biomarkers of exacerbations are also needed.

NQ7 – Narrative summary of evidence table

In children/adolescents with bronchiectasis, what factors should be taken into account when considering surgical removal of the diseased lung?

First author, year, country	Study design	Inclusion criteria	N; Age; Follow-up (FU) length	Main aim(s)	Primary findings relating to narrative question	Management or other findings	Implications for narrative question
Adebonojo. [144], 1980, Nigeria	Retrospective study. Jan 1975-Dec 1978 single centre	Inclusion: consecutive inpatients with cardio-respiratory surgery for suppurative lung diseases	n=483 (most empyema). BE n=70 of which n=37 medically treated (2 deaths), n=33 Sx (5 deaths) Mean age: 32 yrs (17% in paediatric age - unspecified). FU: 6-60 mo	Determine incidence of major diseases of lung presenting to large university hospital thoracic surgery unit Note: Bronchograms used for diagnosis of BE	20% who survived Sx had BE reoccurrence in segments with no BE on initial bronchogram.	1/3 malnourished, 1/2 anaemic. *S. aureus*: 60 % Pneumococcus: 8%	Preoperative preparation important: reduce secretions, treat with antibiotics, optimise nutrition and consider bronchoscopy Lack of facilities, drug availability and poor hygiene were major concerns
Agastian. [145], 1996, USA,	Retrospective study of all hospital charts of patients with BE; Jan 1976 - Jan 1993 single centre	Inclusion: consecutive patients undergoing surgery for BE	n=134 (3.9% of 3421 with BE) had Sx Age: mean 48.4 yrs (range 4-89); Age < 20 yrs n =18 (13.4%) FU: 6 yrs (range 1-16)	Evaluate outcomes of Sx	Complete resection of BE segments resulted in better outcomes. Complete resection: 65.2% asymptomatic. Incomplete: 21.4% asymptomatic. Authors advocated pre-Sx bronchoscopy in all	Operative mortality 2.2%, Sx complications 24.6%. Overall post Sx outcomes: asymptomatic =59.2%, improved=29%.	Select patient group: localised disease allowing complete resection leads to better outcomes
Aghajanzadeh [146] 2006, Iran	Retrospective study, single centre	Inclusion: Staged Sx for bilateral BE	n=29 of overall 210 has staged Sx. Age: mean 30	Report experience of staged removal of bilateral BE.	Sx complications in 38 %, (atelectasis 14%, air leak 6%), one death (3.4%)	Complications more common in those with RUL BE, longer	Staged bilateral resection for bronchiectasis may be safer option than simultaneous bilateral surgery

			yrs (range 5-60) FU: mean 1 yr (range 1, 6) [as reported in paper]	Second Sx performed 2-3 months after first Sx	Outcomes: asymptomatic=19 (66%), improved=5 (17%), unchanged =4 (14%)	duration of disease, post TB and presence of Pseudomonas	
Al-Kattan. [147], 2005, Saudi Arabia	Prospective, single centre	Inclusion: Consecutively operated for BE between Jan 1998 - Jan 2004 Exclusion: active TB and systemic disease (CF, PCD)	Total n=66; Unilateral group n=53: Age: mean 37.5 yrs SD 3.8 (range 6, 40) (20%) bilateral disease) age unilateral group: Bilateral group: n=13; mean age= 29.9 yrs SD 10.8 (range 9-55) FU: mean 52 mo (range 24-82)	Determine surgical indications and outcomes according to hemodynamic classification (CT scan cystic vs cylindrical; VQ scan Target for Sx was cystic non-perfused BE (<10% expected perfusion)	All had bronchoscopy before or at point of Sx to exclude obstructive lesions Outcomes: asymptomatic=73 %, Improved=26%. All had received medical, antibiotic therapy, with persistent chronic symptoms (recurrent infections in 47%, haemoptysis in 35%, exertional dyspnea 29%, unresolved pneumonia 10%	Operative mortality 1.5 %; morbidity 18 %. (bleeding, air leak, empyema)	Functional and morphological (hemodynamic) classification superior to morphological alone as indication for Sx. Target for Sx was cystic non-perfused BE (<10% expected perfusion). no indication for surgery in those with cylindric changes that are still perfused. Bronchoscopy should be undertaken pre-Sx to exclude obstructive lesions (e.g. tumour, foreign body) Poor prognostic factors: Pseudomonas and chronic obstructive airway disease.
Andrade. [148], 2014, Brazil	Retrospective study of medical charts Jan 1998 - Dec 2009, single centre	Inclusion: Children with Sx for BE Exclusion: CF	n=109 Age: mean 7.6 yrs (range 1-15.5 range). FU: mean 667 days (range not provided)	Determine clinical characteristics, indications and results of children who had Sx for BE	Main cause for clinical treatment failure (indication for Sx) was “low socioeconomic status leading to poor adherence and progression of disease”. Bronchoscopy undertaken 1-2 weeks preSx and	Most common: segmentectomy (43%), left lower lobectomy (38%). Post-Sx: mortality 0.9% at day 30, minor complications in 36 % (atelectasis 26%, air leak 6%, pain 4 %).	Authors reported “important care protocols to avoid complications in the post-op period showed to reduce post-op complications”. Consider bronchoscopy with BAL pre-Sx to optimize lung hygiene.

					treated if bacteria found. Outcomes: Improved in 61%, unchanged in 14%, unknown in 24%.	Mean hospital stay=11.7 days (range not provided)	
Ashour [149], 1999, Saudi Arabia	Retrospective July 1987 - Jan 1997, single centre	Patients with BE	n=85, Age: mean 29.4 yrs (SD-9.7) (range 6–55); FU:45.2 mo, SD 21 (range 2–120 mo)	Rationale for and outcome of surgery in patients with unilateral or bilateral BE	No mortality reported. Outcomes post surgery: 74% 'excellent'; 22.4% 'good', 3.5% no benefit	Non perfused area was resected. Left sided more involved (73%)	Consider VQ scan pre surgical resection
Ayed [150], 2004 Kuwait	Retrospective cohort study of children with MLS January 1995 - December 1999, single centre	Children undergoing Sx for pulmonary resection of MLS (includes lingual)	n=13 age 7.5 yrs (range 5 -10) FU mean 3.5 yrs (3-5)	Report characteristics, indications, and results of pulmonary resection in children with MLS	All had bronchoscopy pre-Sx. Post-Sx standard care with "early mobilization and aggressive mobilization". Outcomes: n=9 asymptomatic, n=4 improved.	No mortality; post op complications in 2 (15.4%) (atelectasis and pneumothorax.	Consider bronchoscopy pre Sx. Need for post-Sx expert care
Balci [151] 2014, Turkey	Retrospective study 2000-2013, single centre	Consecutive presenting patients as inpatients	n=86 age 37.8 years SD 14.5 n=11 aged ≤16 yrs. FU in 78 (90.7%) at mean of 5.4 yrs SD 3.2 (range 0.5-8.7).	Analyze outcome and indication of surgery	Sx done if (a) medical treatment fails (b) proven perfusion defect in VQ scan (c) chronic symptoms (d) good cardiopulmonary reserve and (e) localised disease. Bronchoscopy done pre-Sx Overall	Operative mortality 1.1 % Outcomes: asymptomatic in 82.5%, improved in 17.5%. Complete resection of localized perfusion defects led to better results (all asymptomatic post Sx) and	Preoperative preparation is vital including bronchoscopy and VQ scan pre Sx. Sx improves outcomes in properly selected patients

					complications in 14.6%	significantly less complications 9.4% (c.f. incomplete resection 27.3%)	
Balkani [152], 2003 Turkey	Retrospective study Jan 1992 -Dec 2001, single centre	Inclusion: Sx for BE	n=238 Age: mean 23.7 yrs (range 15-48) FU: mean 9 mo (3 mo-4 yrs)	Describe surgical experiences and early and long-term outcomes	PreSx bronchoscopy to rule out obstruction. Complete resection in 154 (64.7%) patients. Outcomes: asymptomatic in 79%; improved 12.2%; no change in 4.6%	Post-Sx: no mortality; complications in 8.8% (2.9% atelectasis from secretions requiring bronchoscopy, 3.4% bronchopleural fistula/air leak, 0.8% empyema, 1.7% repeat Sx for haemorrhage	Bronchoscopy pre Sx
Blyth [153], 2000, South Africa	Retrospective analysis over two periods: 1. 1991-92 2. 1996-97, single centre	Patients undergoing PNE for inflammatory lung disease	n=155 (116 males) Age: mean 30.2 yrs (range 1-68) PNE in 129 (83.2%)	Describe clinical indication for investigation, Sx and radiographic findings	"Systematic approach minimises complications". Sterilised lung has better outcomes. Outcomes: asymptomatic 90%	Post-Sx: Mortality 1.2%, major complications in 23% (empyema 23 [14.8%], fistula in 4 [2.6%], etc) Histology: BE in n=53 (34%), end-stage disease n=49 (31.6%), active TB in 48 (30.9%)	Systematic approach to pre and post-Sx
Caylak [154], 2010, Turkey	Retrospective study, Jan 1992 - Dec 2009, single centre	Patients undergoing Sx for BE	n=339 (n=301 (88.8% male) Age: mean 22.4 yrs (range 15–50)	Report surgical treatment and outcomes after Sx for BE	Pre-Sx, at induction and immediate post-Sx to aspirate secretions to prevent atelectasis. Aim for complete	Post Sx: mortality n=2 (0.6%), complication n=43 (12.7%)	Bronchoscopy pre and post-Sx, and complete resection advocated.

			Median FU: 13.6 mo		resection of all BE sites. Outcomes: asymptomatic 71%, improved 23.3%, no change 5.7%		
Choudhury [155] 2007, India	Retrospective study between 1998 - 2006, single centre	Children with lung resection	n=35 Age: mean 3 yrs (range 8 d-12 yrs) BE n=9	Evaluate the clinical manifestations, management and outcome of childhood lung abscess	Bronchoscopy in 3/9	Post Sx: no mortality in BE group. Complications n=3/9 (33.3%) (fluid collection n=2, pneumo-thorax n=1)	
Cohen [156], 1994, Canada	Retrospective case study, single centre	Bronchiectasis and pulmonary infections in patients with hypogamma-globulinaemia	n=4 aged 9, 15, 28, 39 yrs) from cohort of n=65 patients with hypogammaglobulinaemia follow up: 3.5 - 5 years	Describe patients with hypogamma-globulinaemia who had pulmonary resection for BE	One (25%) had postoperative empyema. All had localised BE only with lobectomy undertaken	Sx associated with diminution of symptoms, requirement for antibiotic therapy, need for medical care, and improvement in the quality of life	Sx for localised BE only. Very small study and data in contrast with data from Freeman et al[157]
Einarsson [158], 2001, Iceland	Retrospective study of clinical records 1984 to 2006 identified through registry	Inclusion: patients with Sx for MLS, radiological abnormalities seen pre-Sx and other lobes normal. Exclusion: neoplasms other than carcinoid	n=18 (15 female). Age: mean 55 yrs (range 2-86) FU: median 6.9 yrs (range 0.4-14.8)	Study clinical, radiological, histological features and outcomes of patients who had Sx for MLS	Histopathology BE iin 50%, foreign body in 11% Postoperative complications in 4 (22.2%): prolonged air leak in n=2 (11%), chronic atelectasis in one, and one required repeat Sx.	By FU, 3 died (unrelated to Sx) Authors concluded "MLS can be treated effectively with lobectomy with low mortality and rate of complications"	BE should be considered in children with MLS. Surgical complications relatively high and given 11% had foreign body, pre-Sx bronchoscopy is advocated

Emiralioglu [159], 2019, Turkey	Retrospective analysis, single centre	Children with BE. Surgical group=had lobectomy, segment-ectomy or PNE and FU for >2 yrs. Medical group= Age- and gender-matched only medically treated for > 3 yrs	Surgery group n=29, mean age 8.5 yrs SD 3.6. Medical group n=33, mean age 8.5 yrs SD 2.7 FU: 2 yrs.	Compare growth and clinical parameters (exacerbation rate, lung function, clinical course) of medically and surgically treated children with BE	Most patients in the surgery group had multi-lobe involvement whilst some in medical group had only localized disease.	Surgical group: height z-score improved, IV antibiotics use decreased. No difference in exacerbation rate, oral antibiotic use or lung function. Medical group: exacerbation rate, and oral and IV antibiotics decreased. No change in spirometry	Indications of surgery are not established fully in children with BE i.e. individual decision Those with more than one lobe of BE should be carefully taken, and the underlying etiology should be taken into consideration
Eren [160], 2003, Turkey	Retrospective study, , single centre	Inclusion: all files of those who had PNE between 1987 and 2002	n=17 (for BE n=11) Whole cohort median age: 9.1 yrs (3-16) Median FU: 5.2 yrs of 13 children (range 1-12)	Describe Sx experience and outcomes	Patients should be well prepared (nutritional status, infective process) Median duration of hospital stay: 15.5 days. Post-Sx complications: Mortality in 2 (11.7%), morbidity in 4 (23.5%) with haemorrhage, fistula, empyema and atelectasis (all required further Sx intervention)	Children grew and developed normally after PNE. 6/13 developed scoliosis (Cobb angle >10°) of which 5/6 had PNE before aged <7 yrs. FU spirometry: all restrictive pattern (FVC <80%) of which 6 had FVC <65% predicted	Avoid PNE in young children
Fan [161], 2015, Multi-country	Meta-analysis	Inclusion: (a) Any Sx type intervention in management of patients	38 studies in the meta-analysis n=5541	Assess the effects of Sx in patients with BE	Post-Sx outcomes: Asymptomatic 66.5% (95%CI, 61.3, 71.7), improved 27.5% (95%CI, 22.5,	Pooled mortality (34 studies, n=4788 patients: 1.5% (95%CI 0.9, 2.5); morbidity	Studies rare in developed countries especially after the year of 2001. The mortality was relatively

		with BE diagnosed with HRCT. (b) effect size of mortality, morbidity, symptomatic changes or complications. Exclusion: (a) CF, COPD, asthma or transplant (b) case reports; editorials, or (c) Data could not extracted	n=5 studies in children Database search on 8th July 2015		32.5%) no improvement: 9.1% (95%CI 7.3, 11.5)	(33 studies n=4583 patients): 16.7% (95%CI 14.8, 18.6) Mortality higher in children than in adults	higher in children and those with symptom duration >5 years
Findik [162], 2008, Turkey	Retrospective study Jan 2000- Dec 2004	Inclusion: children aged <16 yrs.	n=196 Mean age: 9.1 yrs (3 mo-15) FU: range 1 mo - 3 yrs	Review childhood thoracotomy indications, methods and complications BE n=39 (25%); Hydatid n=68 (35%), Chronic pleuritis n=25 (13%), Chest wall deformity n=20 (10%)	Outcomes specific for BE not reported. Overall complications in (18%): atelectasis and secretion retention (54%), wound infection (17%), hemorrhage (3%), chylothorax (3%), intrathoracic space (3%), and postoperative extended air leakage (20%).	Duration hospital stay mean=15 days (range 7, 83) Lateral thoraco-tomy was more appropriate choice for thoracotomy with fewer post-Sx complications. Post-Sx expertise important including pain management	Surgical and post-operative expertise and care important

Freeman [157], 2013, multicenter	Retrospective study of medical records from 1960 to 2011, two centres	Inclusion: Autosomal dominant hyper-IgE syndrome (AD-HIES) who had lung Sx for management of lung infections	n=32 patients had 36 lung Sx. Age: mean 16.8 yrs (range 1.5 - 47)	Assess incidence and clinical sequalae of lung surgery in patients with AD-HIES. Sx for pneumatocoele, bronchiectasis, abscess and/or recurrent infections	High complication rates: broncho-pleural fistula in 17/36 (47%) lasting 2 wks to 4 yrs and resulted in empyema in 10/17 (58.8%). Clinical features similar in those with or without complications.	HIES patients have marked infection susceptibility. No genotype-phenotype correlation	Patient selection important – surgical option as last resort
Garrett-Cox [163], 2008, UK	Retrospective study between Feb 2000 -Nov 2005, single centre	Inclusion: thoracoscopic lobectomy in children in 2 UK centers	n=12 (BE:4) Median age: 3.5 yrs (range 8 mo -15)	Report on use of thoracoscopic lobectomy in children in 2 UK centers	58% completed thoracoscopic lobectomy, 42% converted to open thoracotomy. History of pulmonary infection had higher conversion rate to open thoracotomy	Median operating time 4 hours (range 2.8, 6 4). Duration hospital stay range 3, 18 days	Selection of patients important for type of surgery
Giubergia [164], 2017, Argentina	Case series, single centre	Inclusion: Case series on children who had PNE.	n=51 Median age: 7.4 yrs Indications for PNE: BE 61%, tumours 17%, lung malformation 17%, aspiration 14%, CF 6%, immune-deficiency 4%, trauma 2%.	Analyse the risk factors associated with adverse outcome post PNE in children.	Mortality: 4% at 1 mo; major and minor morbidities: 23% and 27% Risk factors for development of morbidities after PNE were age ≤3 yrs (OR 16.7, 95%CI 2.4–117) and mechanical ventilation ≥4 days (OR 8, 95%CI 1.5–43.6).	Major=death pneumonia, empyema, sepsis, adult respiratory distress syndrome, bronchopleural fistula, bleeding, pneumothorax and post-PNE syndrome. Minor=scoliosis, wound infection, atelectasis.	Children are at high risk of death, major and minor morbidities following PNE. Caution is recommended

Gursoy [165], 2010, Turkey	Retrospective study of medical records, Jan 2002- Jun 2007, single centre	Inclusion: patients with surgical resection for BE	n=92 Age: mean 38.7 yrs (range 10–67) Mean FU: 15.3 mo in 75	Evaluate post-operative characteristics and outcomes in patients who had Sx for bronchiectasis	Bronchoscopy undertaken in all to clear secretions and exclude obstruction. Outcomes: asymptomatic: n=63 (84%), improved n=8 (10.7%), no change n=4 (5.3%)	Post-Sx: mortality 1%, other complications 16% Lobectomy in 38, lobectomy and segmentectomy in 32, PNE in 10	
Haciibrahimoglu [166], 2004, Turkey	Retrospective study, single center, from 1985-2001	Inclusion: consecutive patient undergoing surgery aged below 14 yrs	n=35 Age: mean (range 1-12) FU 5.4 yrs	Estimate operative risk and identify risk factors of adverse prognosis	Surgery for childhood bronchiectasis can be performed with low mortality and morbidity mortality 2.8%, morbidity 17.6%	after surgery,: asymptomatic: 64.7% improvement: 23.5%, no improvement: 11.7%	Complete resection should be performed when possible
Halezeroglu [167], 1997, Turkey	Retrospective Study over 10-years, Jan 1986-March 1996, single centre	Inclusion: consecutive patients who had PNE for "destroyed lung"	n=118 Age: mean 29 yrs SD 9.5 (range 7-55) Sx for BE in n=52 (44.1%), for TB in n=43 (36.4%)	Evaluate effect of specific risk factors on postoperative complications	Bronchopleural fistula higher in those with preoperative empyema and tuberculosis	Post-Sx: mortality 5.9%, morbidity 11.9%. morbidity and mortality rate significantly higher in patients with preoperative empyema, tuberculosis and right PNE	Selection of patients and pre-operative preparation important to reduce post-Sx complications
Hamad [168], 2012, Egypt	Retrospective study, single centre, Jan 2000 - Dec 2011	Inclusion: Consecutive patients who had lobectomy for atelectasis and/or BE of	n=17 atelectasis or BE with lobectomy 16 children: Age: mean 6.2	Describe experience with patients who had lobectomy for atelectasis and/or BE of left	Bronchoscopy done for all to exclude foreign body, evaluate trachea-bronchial tree and obtain samples for	Indication for Sx: BE or failure of bronchoscopy and intensive medical therapy to resolve lobar	

		left lower lobe Exclusion: BE due to congenital predisposition, sequestration or foreign body	yrs SD 2.6 (1 adult aged 52 yrs). FU: not regular,	lower lobe BE in 11/17 (64.7%)	microbiology. Outcomes "most patients doing well"	atelectasis after 2 months	
Jin [169], 2014, China	Retrospective study, single centre, Jan 2000 -Dec 2010	Inclusion: consecutive patients who had Sx for BE	n=260 Age: mean 30.2 yrs recurrent FU in255 (98.1%), mean of 6.7 yrs (range 3-10)	Analyze the risk factors related to surgical outcomes	Age (<45 yrs), low sputum volume (<30 mls/day), absence of Gram-negative bacillus infection and bronchial stump coverage (using intercostals muscles or pedicle pleura) were independent factors for better surgical outcomes	Post Sx mortality n=2 (0.8%), complications occurred in 30 (11.5%). Outcomes: Asymptomatic n=199 (76.5%), still symptomatic n= 52 (20.0%)	Selection of patients and pre-operative preparation important to reduce post-Sx complications
Karadag [70], 2005, Turkey	Retrospective study, single centre, 1987 -2001	Inclusion: BE diagnosed with CT between 1987-2001 and followed up for at least 2 years. All received medical treatment modalities including	n=111 (medical group n=85, Sx group n=26) Age at diagnosis: mean 7.4 yrs, SD 3.7 (range 1-17.5) FU mean for 4.7 yrs (SD 2.7, range 2-14) at mean	Describe characteristics, underlying causative factors and FU results of medical and surgical interventions	Both medical and Sx groups improved: exacerbations/yr reduced [mean 6.6 (SD 4.0) to 2.9 (2.9), p<0.0001], lung function improved [mean FEV_1 63.3% (21.0) to 73.9 (27.9) p=0.01; FVC 68.1 (22.2) to 74.0 (24.8), p=0.04]. No	Sx rate lower in later cohort (15.3% of those in 1996–2001, 38.5% for the 1987-95 group). High consanguinity rate 42.6% (21% in general population)	Authors stated "Surgery increasingly less applied in the management of children with bronchiectasis due to early detection and improved medical treatment modalities"

		prompt antibiotic use in exacerbations, bronchodilators and physiotherapy	age of 12.8 yrs, SD 4.4 (range 4-24)		significant difference between groups for exacerbations, lung function or clinical improvement (medical=70.1%, Sx=73%).		
Kosar [170], 2010, Turkey	Retrospective study, single centre, between 1991 and 2007	Inclusion: Children who had PNE for "destroyed lung".	n= 18 Age: mean 12.3 yrs (range 5-16) BE n=13 Mean FU 64.9 mo (range 19-164 mo)	Study experience of Sx for destroyed lung	Post-Sx: No mortality, complications n=3 Outcomes: "children grew and developed normally after PNE". Scoliosis in 1 (5.6%)	Authors considered that antibiotics and anti-TB with good timing for PNE essential	Selection of patients and pre-operative preparation important to reduce post-Sx complications
Kutlay [171], 2002, Turkey	Retrospective study, single centre	Inclusion: consecutive patients with Sx for BE	n=166 Age: mean 34.1 yrs (range 7–70) FU n=148 at mean of 4.2 yrs	Study morbidity, mortality and outcomes of surgical treatment for BE	VQ scan done in those with poor lung function (undefined). Bronchoscopy performed. Post-Sx: mortality n=3 (1.7%), morbidity n=18 (10.5%)	Outcomes: asymptomatic n=111 (66.9%), improved n=31 (18.7%), unchanged or worse n=6 (3.6%)	Surgical treatment of BE more effective in patients with localised disease.
Lieber [172], 2015, Germany	Retrospective study, single centre	Inclusion: patients with pulmonary pathologies undergoing thoracoscopic Sx between 2004 and 2013	n=76, n=3 with BE Cohort mean age 6.5 yrs (range 7 days - 17 yrs) FU:	Report minimally invasive thoracoscopic lung Sx in children	Conversion of thoracoscopic to open Sx was13% Little data specifically related to children with BE	Limitations exist in cases with infectious adhesions	
Mazieres [173], 2003, France	Retrospective study between 1990 - 1999	Inclusion: severe multi-segmental	n=16 Age: 44 yrs (range 16-71)	Report data regarding feasibility and	Limited Sx may improve clinical status in non-	Outcomes: recurring infections	Selection of patients and pre-operative preparation important

		bilateral BE with Sx removal of non-localised disease	FU: 5.2 yrs (range 2 to 10)	utility surgical removal of non-localised BE report mortality and morbidity rates	localised bilateral BE. Pre-Sx, all had bronchoscopy and received targeted sequential IV antibiotics, Post-Sx: no mortality, complications in 3 (18%) (1 air leak, 2 infections)	decreased in frequency in n= 8 and disappeared completely in 5. Lung function unchanged.	
Ötgun [174], 2014, Turkey	Retrospective study between 1991 and 2002, single centre	Inclusion: children who had Sx for BE	n=54 with 58 Sx. Age: mean 9.3 yrs, SD 3.9 (range 1.5 - 17) FU: mean 48.4 mo, SD 41 mo (range 1 - 192)	Analyse type of resection, operative morbidity, mortality and outcomes	Bronchoscopy one pre-Sx. Authors' conclusion "Decision for BE Sx should be made in cooperation with the chest diseases unit. Anatomic localization of the disease should be mapped clearly by radiologic and scintigraphic investigations".	Mortality in 9.3% (2 intra-operative), complications in 11.1% (2intra-operative). Outcomes: well n=23 (42.5%), improved n=23 (42.5%), worse or unchanged in n=5 (9.4%)	Multi-disciplinary approach. Bronchoscopy and VQ scan pre-Sx
Polverino [16], 2017, multiple European countries	ERS guideline for the management of adult patients with BE	Inclusion: Adults with BE Exclusion: CF, children or and non-tuberculous mycobacteria (NTM)	Meta-analysis on 38 studies, 5541 patients (all observational studies)	Question: Are surgical interventions more beneficial compared to standard (non-surgical) treatment for adult bronchiectasis patients?	Lobectomy is the most frequent Sx performed but numerous options exists. Sx in unstable patients associated with higher morbidity and mortality reaching 37% Overall mortality from 29 studies rate of 1.4% (95%CI	No RCTs of surgical treatment versus standard care identified Post-operative pooled morbidity for adults in 26 studies was 16.2% (95%CI 12.5, 19.8)	ERS adult guideline suggest not offering surgical treatments except for patients with localised disease, high exacerbation frequency (weak recommendation, very low quality of evidence) Recommendations only applies to patients with clinically significant BE

					0.8, 2.5).		
Prieto [175], 2001, Portugal	Retrospective study, single centre, between 1988 and 1999	Inclusion: Patients with pulmonary resection for BE	n=119 Age: mean 42.2 yrs (range 11 - 77) FU: 4.5 yrs (minimum 2a)	Assess benefits of Sx analyse complication	Post-Sx :no mortality, complications in n=15 (12.6%) Outcomes: asymptomatic: 68%, improved 29%, unchanged or worse 3.7%	No change in respiratory function Complete resection of the disease (91%) had better	Best clinical improvement occurred in patients with complete resection of the disease
Rothenberg [176], 2008, USA	Retrospective study, Jan 1995 - March 2007, single centre	Inclusion: Patients with lung pathology requiring resection using VATs. Exclusion: solid mass lesions occupying >50% of chest or extreme respiratory compromise	n=97 Age: mean 2 days -18 yrs BE in n=21	Evaluate the safety and efficacy of thoracoscopic lobectomy in infants and children	3 intraoperative complications (3.1%) requiring conversion to open thoracotomy. 93 were completed thoracoscopic-ally	Hospital stay ranged from 1- 12 d (mean 2.4 days) Compared to published data, VATs associated with decrease in postoperative pain, recovery, and hospital stay	Thoracoscopic lung resection is safe and efficacious

Rothenberg [177], 2009, USA	Retrospective study, Jul 1994 -Aug 2008, single centre	Inclusion: thoracoscopic lobectomy for treatment of severe BE confined to a single lobe	n=19 (non-CF n=10, CF n=8) note numbers as reported in paper i.e. do not add up to 19) Age range 14 mo – 22 yrs	Describe experience and results with thoracoscopic lobectomy for treatment of severe BE confined to a single lobe	Post-Sx: no mortality, complications in 3 (2 required further intervention). Outcomes: "All patients showed an improvement in both FEV_1 and with an improvement in FVC ranging from a low of 10 to 80% and FEV_1 from 13 to 70%"	FU period not reported and uncertain how lung function undertaken in the very young children	
Sahin [178], 2014, Turkey	Retrospective study, Jan 2000 and Jan 2013, single centre	Inclusion: surgical resection of BE	n=60 Age: mean 9.5 yrs (range 2–15) FU: mean 3.5 yrs (range not stated)	Describe surgical practice and outcomes	Bronchoscopy with lavage pre-Sx undertaken in all. Risk factors for post complications: FEV_1, haemoptysis and duration of symptoms (OR all >2 but direction not stated)	Post-Sx: mortality 3.3 %, complications 20%. Outcomes: "Complete recovery 71.7%, satisfactory 20%", "unsatisfactory" in 8.3%	Complete and early resection of bronchiectasis provided better outcome
Sayir [179], 2019, Turkey	Retrospective study, 2005-2017, single centre	Inclusion: Patients with PNE for destroyed lung	n=32 Age: mean 31.7 yrs SD 10.8 range 12-52; 8 children) BE n=20 FU: 35.5 mo SD 28.3 (range 9-180)	Evaluate surgical technique, post-Sx morbidity and mortality, and long-term outcomes in patients with a diagnosis of lung destruction undergoing PNE	Pre-Sx, bronchoscopy, airway micro-biology, IV antibiotics, physio-therapy and tests for TB done. Sx not done if TB positive. Post-Sx: mortality 3.1%, complications 14.2%. Outcomes: improved in 81.2%	Mean pre -Sx FEV1 54 (42-70), post-Sx FEV1 reduced by 19% (range 15-20%).	Careful patient selection, appropriate pre-operative work-up and surgical technique considered important

Sehitogullari [180], 2011, Turkey	Retrospective study, April 2002 –April 2010, single centre	Inclusion: Patients with surgery for BE	n= 129 Age: mean 21.8 yrs (range 4-67) FU n=123 at mean 5.3 yrs (range 1-8)	Present surgical experience	Pre-Sx medical treatment and bronchoscopy undertaken in all. Outcomes better when complete resection possible. Complications in n=29 (22%) mortality <1%	Preoperatively 79% had normal function tests	Complete resection preferred. Multi-disciplinary approach. Bronchoscopy and medical treatment pre-Sx.
Sehitogullari [181], 2012, Turkey	Retrospective study. Jan 2002-Jan 2011, single centre	Inclusion: Children with middle lobe syndrome treated with Sx resection	n=20 Age: mean 10.5 yrs (range 5 -15) FU: mean 4.5 yrs (range 2 mo -12 yrs)	Clinical and laboratory characteristics, indications for Sx management, postoperative courses and FU	BE in 11 (55%), BE and atelectasis n=5 (25%) patients, and destroyed lung in n=4 (20%) patients	Post Sx: mortality n =1 (5%), complications in 3 (15%) [1 brain abscess, 1 haemorrhage requiring re-operation, 1 atelectasis	
Sirmali [182], 2007, Turkey	Retrospective study between January 1991 and April 2006, single centre	Inclusion: Children with BE aged 16 yrs and below operated for BE	n=176 Age: mean 12.3 yrs (range 3.4—16) FU: mean 4.3 yrs (range 14 mo to 7.2 yrs	Assess morbidity and mortality rates and outcomes of surgical treatment for childhood BE	All had VQ scan and pre-Sx had intensive chest physiotherapy, antibiotics in accordance to airway micro-biology and bronchoscopy. Outcomes 'perfect' in n=129 (73.3%), 'improved' 41 (23.3%), 'no changes' 6 (3.4%). BE bilateral in n=19 PNE n=6. Complete resection n=165, (93.8%),	Mortality 0%, morbidity 13% (n=23). Mean hospitalisation duration 8.9 days (range 5-39). BE cylindrical in n=72 (40.9%), saccular 95 (54%), varicose 9 (5.1%). Indication for Sx: localized disease that did not respond well to antibiotic, mucolytic, bronchodilator and steroids;	Patient selection and appropriate pre-operative work-up and treatment

					incomplete resection n=11 (6.25%).	growth retarded, frequent exacerbations or haemoptysis	
Stephen [183], 2007, India	Retrospective study, single center, 1992-2003	Inclusion: Sx for BE CT done after 1995 in 108 patients	n=149 Age: mean mean 33.7 yrs (range 5-66) FU in n=94 at mean of 4.8 yrs (range 3 mo-12 yrs)	Review experience of surgical resection for BE	Pre-operative bronchoscopy, intensive chest physiotherapy, antibiotics and bronchodilators to ensure that sputum volume was< 50 mL undertaken in all. Outcomes: Those with complete resection - excellent in 34%, good in 12%, no change/worse in 29% vs incomplete 35%, 12%, 53% respectively.	PNE in n=55 (37%), lobectomy 55 (37%), bi-lobectomy 37 (25%), lobectomy +/-segment-ectomy 2 (1%) Mortality: 0.67%, morbidity 14.8% (n=22)	Importance of patient selection and pre-Sx treatment
Tkebuchava [184], 1996, Switzerland	Retrospective study, single centre	Inclusion: Any surgical intervention in people with Kartagener syndrome	N=4 of the 9 children had a surgical procedure.	Assess the role of additional cardiac malformations and their Sx repair in patients with Kartagener syndrome	Bilateral lung transplant in one child (age unstated), other 3 procedures were cardiac anomalies repair.		Bilateral lung transplantation possible
Yalcin [185], 2013, Turkey	Study retrospective 1988 -2011	Inclusion: Pediatric PNE	n=20 age: mean 8 years (range 0.5-17) BE n=14 FU: mean 2 yrs	Report experience and outcomes of pediatric PNE	Pre-Sx, VQ scan, bronchoscopy and medical treatment undertaken in most. Outcomes: n=14	Post Sx: mortality=nil, complications n=3 (30%) including one fistula. FEV_1 median=	Careful selection and preoperative preparation, and postoperative follow up and rehabilitation essential for good outcome

			(1-10 range)		asymptomatic, n=5 improved. Scoliosis n=1	69.5% predicted (range 40, 89) FVC=79% predicted (range 43, 109).	
Zaid [12], 2010, Northern Ireland	Retrospective study from hospital charts period 1996-2006, single centre	Inclusion: Children with BE. Exclusion: CF	n=92 Mean age at diagnosis was 6.4 years, age of surgery not reported. Follow up not reported	Determine aetiology, clinical presentation, co-morbidity, severity and lobar distribution of BE	Lobectomy performed in n=11 (12%), PNE in n=2 (2%). Outcomes and indications for Sx not stated	Underlying aetiology determined in 68% (63), 'no cause' in 32% (n=29). "BE under-recognised in Irish children"	
Zhang [186], 2010, China	Retrospective study, Jan 1989- Dec 2008 single centre	Inclusion: Patients who had Sx treatment for BE, identified from database. Exclusion: CF	n=790 had 810 Sx. Age: mean 41.6 yrs (range 6-79); ~70 were aged <20 yrs FU in 706 at mean 4.2 yrs (range, 1 mo-10 yrs)	Determine operative mortality, morbidity, and outcomes of surgery for BE.	Pre-Sx, all hospitalised for medical treatment. Outcomes : asymptomatic: n=478 (60.5%) improved n=111 (14.1%), worse or no improvement n= 117 (14.8%).	Post Sx: Major complications in 20 (2.5%). No intraoperative deaths, n=9 (1.1%) patients died later. Pre-x renal failure associated with increased mortality. Lobectomy (497; 62.9%), segment resection (37 4.7%), PNE (90; 11.3%), bilob-ectomy (56; 7.1%), lobectomy with segment-ectomy (110; 14.0%)	

BE=bronchiectasis, CF=cystic fibrosis, ERS=European Respiratory Society, FVC=forced vital capacity, IV=intravenous, mo=months, MLS=middle lobe syndrome, PCD=primary ciliary dyskinesia, PNE=pneumectomy, Sx=surgery, TB=tuberculosis, VATs=Video assisted thoracoscopic surgery, VQ=ventilation-perfusion, yrs=years

Evidence to Decisions (EtD) framework

NQ7: In children/adolescents with bronchiectasis, what factors should be taken into account when considering surgical removal of the diseased lung?

Domain	Judgement	Research evidence	Additional considerations
Priority **Is the problem a priority**	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an 'orphan disease', bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent [13,18] and less affluent countries [19,20]. With the increasing appreciation of bronchiectasis in children and adults, there is now renewed interest in bronchiectasis, but it remains a neglected disease. Also, the global resurgence of bronchiectasis in children/adolescents and adults is increasingly acknowledged. [15,21,22] Yet, the unmet needs of people with bronchiectasis are huge and there are few RCTs [15,21]. The ERS guideline for adults with bronchiectasis was published in 2017 [16]. The need for a paediatric companion guideline is obvious. This is supported by the European Lung Foundation's parent advisory group for this guideline.	The panel considered that surgical intervention is an 'intervention of last resort'
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very Low ○ Low ○ Moderate ○ High ○ No included studies	The narrative summary only identified observational studies. There was a single prospective [147] study and the remaining studies (n=43) were retrospective. One meta-analysis [161] included the results of five paediatric studies. Also, 18/42 (43%) studies were undertaken in one country by surgical groups; thus raising the possibility of local practice leading to selection and reporting bias	As this question was reviewed only narratively and GRADEing of the evidence was not performed, our confidence in our conclusions is limited.

CURRENT PRACTICE			Surgery for bronchiectasis is rarely undertaken in high-income countries, but is not uncommon at several centres in low and middle-income countries. Members of the panel rarely advocate surgery to control bronchiectasis. In our practice, any consideration for surgery is discussed with a multidisciplinary team and the surgery is undertaken in specialised centres after a series of tests (VQ-scan, bronchoscopy, chest CT-scans) and optimising the patient's lung pre-surgery. Also factors to consider include the underlying aetiology (influencing recurrence of disease), location and extent of disease (lobes affected).
VALUES	**Is there important uncertainty or variability in how much patients value** the different factors that are usually taken into account?**?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● Not important uncertainty or variability ○No known undesirable outcomes	Important uncertainty about the variability is unlikely as most patients will value that all aspects of the child/adolescent is considered before surgery and that adverse events related to surgery are minimised.	

BENEFITS AND HARMS	**How substantial are the benefits and harms of (not) considering specific factors?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies	The benefits of assessing factors which need to be evaluated when considering surgical removal are high. The narrative above suggests that a well-defined subgroup most likely to benefit from surgery are those with localised bronchiectasis where complete excision is possible. In-depth assessment of children/adolescents most likely to be asymptomatic after surgery with minimal adverse events would also be highly beneficial. The harms of	The panel considered that the adverse events from surgery include mortality and postoperative morbidity, while the benefits included being asymptomatic or experiencing much fewer symptoms. To reduce operative mortality and morbidity and to avoid unnecessary lung surgery, the panel considered that it is important to select the right patient for the right operation undertaken in a hospital with specific expertise in managing these patients surgically, as well as pre- and post-operatively.

	○ Don't know	not considering these factors are likely large, but could not be quantified.	Furthermore, based on narrative review and clinical experience, the panel considered that in-depth assessment (VQ-scan, bronchoscopy and CT-scans) pre-surgery assists in patient selection and surgical planning. Pre-surgical optimisation of the child (nutrition, airway clearance, antibiotics) would also likely reduce operative and post-operative adverse events.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Surgery for removal of lung segments with bronchiectasis needs considerable expertise, especially in young children. Not every hospital will have a thoracic surgery department with the knowledge, skill and expertise to perform the procedure. Thus, there will be reduced access for some patients compared to others. Not assessing the risk factors would also produce reduced health equity.	There is no published literature on health equity, but differential access (from living remotely or away from a major centre with the required specific expertise) suggests probable imbalance between patients, settings and countries.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No available studies	The panel and parents considered that irrespective of the low level of evidence, attention to the factors above pre-surgery is acceptable and should be part of the clinical assessment.

NQ7. In children/adolescents with bronchiectasis, what factors should be taken into account when considering surgical removal of the diseased lung?					
TYPE OF RECOMMENDATION	**Strong** recommendation **against** taking the factors into account ○	**Conditional** recommendation **against** taking the factors into account ○	Conditional recommendation for either taking factors into account or the alternative ○	**Conditional** recommendation for taking the factors into account ○	**Strong** recommendation **for** taking factors into account ●
RECOMMENDATION	Usual practice statement: It is important to emphasise that surgery is rarely undertaken in the panel's experience, although we are aware that it is not uncommon in some settings. Surgery is only considered after maximal medical therapies (e.g. ACT, long-term antibiotics, etc.) have failed and the child/adolescent's QoL remains significantly impaired. When contemplated, a multidisciplinary approach is essential, and the decision should be based on the individual's clinical state and local surgical expertise. ● In children/adolescents with bronchiectasis, we recommend when considering surgery, factors to be taken into account include age, symptoms and disease burden, localisation of the bronchiectatic areas on chest CT-scans, the underlying aetiology (influencing recurrence of disease), facility where surgery is undertaken (surgical expertise and availability of pre- and post-surgical care), and optimisation of the child's clinical state. (*Strong recommendation, very low-quality of evidence stemming from narrative review of evidence*). **Remarks**: The benefits from surgery is higher in those with localised disease where complete resection can be done and when the disease is not recurrent (i.e. absence of underlying aetiology, such as immunodeficiency). Careful preoperative workup as well as rehabilitation after surgery improves outcome. Ideally, bronchoscopy and BAL are performed prior to surgery to exclude a foreign body and obtain microbiological samples. A ventilation-perfusion scan to delineate non-ventilated areas confirming the localised disease to plan for the surgery is likely beneficial. Optimisation of the child/adolescent's clinical state, including using appropriately targeted antibiotics, ACT and improving nutritional status pre- and post-surgery is also necessary.				

JUSTIFICATION	Although the evidence is very low for taking into account the above factors when considering lung surgery as part of management for children/adolescents with bronchiectasis, the data from the studies are consistent. Also, this multi-disciplinary approach is the current standard of care in specialist settings. The panel and parents advisory group expressed that such standardised clinical care is very important when considering surgery, including making an informed judgement from balancing the risk versus benefits of surgery for the individual child/adolescent.
SUBGROUP CONSIDERATIONS	Patients with: ○ Potential to further improve with conservative treatment. Here surgery should not be performed, but delayed while conducting a comprehensive clinical assessment and optimising treatment to address not just lung disease, but any associated co-morbidities. ○ Groups with localised disease and the possibility of complete resection are reported to show a favourable outcome and more likely to be asymptomatic after surgery. ○ Patients with hyper-IgE Syndrome, symptom duration >-5years, *Pseudomonas aeruginosa* infection or of a young age have higher complications rates
IMPLEMENTATION CONSIDERATIONS	Increase accessibility to providing a multidisciplinary approach with expertise for optimal pre-operative workup and careful patient selection. In general, video-associated thorascopic surgery is associated with fewer complications and a shorter post-operative hospital stay.
MONITORING AND EVALUATION	Local practices and evaluation of outcomes
RESEARCH PRIORITIES	It is unlikely that this recommendation will be amendable to placebo RCTs. However, for future research, prospectively collected data from a control group (where surgery was not performed) to define pre and post-data relating to nutritional status, antibiotic usage and adherence with medical therapy, other treatments and chest airway clearance therapy as well as long-term outcomes.

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