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Mini-Symposium: Non-CF Bronchiectasis

Diagnosing and preventing chronic suppurative lung disease (CSLD) and bronchiectasis

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EDUCATIONAL AIMS
The reader will be able:
- To discuss the limitation of diagnosis of childhood bronchiectasis on current radiological criteria.
- To define the diagnoses of protracted bacterial bronchitis and chronic suppurative lung disease and describe their relationship to bronchiectasis.
- To examine likely precursors of chronic suppurative lung disease
- To illustrate the merits of early and intense treatment of children with symptoms of bronchiectasis.
- To discuss the limited evidence for early and intense treatment to prevent advancement of disease in children with chronic suppurative lung disease and bronchiectasis.

ARTICLE INFO
Keywords:
Bronchiectasis
suppurative lung disease
children
prevention
diagnosis
chronic lung disease

SUMMARY
Current diagnostic labelling of childhood bronchiectasis by radiology has substantial limitations. These include the requirement for two high resolution computerised tomography [HRCT] scans (with associated adversity of radiation) if criteria is adhered to, adoption of radiological criteria for children from adult data, relatively high occurrence of false negative, and to a smaller extent false positive, in conventional HRCT scans when compared to multi-detector CT scans, determination of irreversible airway dilatation, and absence of normative data on broncho-arterial ratio in children.

A paradigm presenting a spectrum related to airway bacteria, with associated degradation and inflammation products causing airway damage if untreated, entails protracted bacterial bronchitis (at the mild end) to irreversible airway dilatation with cystic formation as determined by HRCT (at the severe end of the spectrum). Increasing evidence suggests that progression of airway damage can be limited by intensive treatment, even in those predestined to have bronchiectasis (eg immune deficiency). Treatment is aimed at achieving a cure in those at the milder end of the spectrum to limiting further deterioration in those with severe ‘irreversible’ radiological bronchiectasis.

INTRODUCTION
When a child has chronic productive cough, digital clubbing, chest wall deformity, adventitial chest signs, and dilated airways on high resolution computerised tomography chest (HRCT) scan, almost all clinicians would recognise that the child has bronchiectasis. However, in our current era with improved clinical care, access to health and diagnostic modalities most children are
diagnosed at an earlier stage in disease progression and most do not have the this classical presentation with radiological changes of severe bronchiectasis as described many decades ago.1,2 The vicious circle hypothesis, currently accepted as the most coherent explanation of bronchiectasis formation in the absence of interstitial lung disease, suggests that impaired host defence leads to bacterial (and likely biofilm colonisation) of conducting airways. This induces inflammation resulting in damage to the airways and further impairment of mucociliary clearance. In many cases of bronchiectasis, a period of many months, years or even decades may precede the development of sufficient damage to appear as classical ‘bronchiectasis’ on a HRCT scan. The rate of damage progression is likely dependent on a number of factors: whether there is an underlying problem such as cystic fibrosis (CF), the type of the pathogenic colonisation/infection,3 the frequency of exacerbations,4 access to healthcare, and the efficacy of, and adherence to, therapeutic interventions. In cystic fibrosis, for example, the appearance of bronchiectasis on HRCT scans has been greatly delayed with more aggressive anti-microbial therapy and strategies designed to enhance mucociliary clearance.

It is increasingly recognised that many (if not most) severe chronic lung can be largely prevented and attention has focused on possible interventions in childhood.5–7 It is highly likely that some, if not most, cases of non-CF bronchiectasis can be prevented through intervention designed to improve airway clearance and eliminate bacteria (with associated inflammatory ‘soup’ and possibly biofilms) from the airways and that this approach would be most successful if initiated in childhood.8,9 In this paper, we discuss the limitations of current diagnostic criteria, precursors of bronchiectasis and the evidence (albeit limited) on why children with protracted bronchitis, suppurative lung disease and bronchiectasis require vigilant medical follow-up and appropriate therapies.

**Diagnosis labelling**

As noted above, the current paradigm suggests that there is a spectrum of disease associated with the presence and/or persistence of pathogenic bacteria in the lower airways. In these children the cough is associated with bacterial infection and/or colonisation of the conducting airways. This ranges from being transient (after a viral lower respiratory tract infection) through to the patient with severe bronchiectasis described previously. A common thread is the presence of bacteria suggesting that this is a spectrum of disease in which the manifestations can vary markedly between and within individuals over time. Prior to the ‘diagnosis’ of ‘idiopathic bronchiectasis’ being made on the basis of a HRCT scan, the patient (children and adults) may have been labelled as having recurrent viral infections, asthma, and/or chronic bronchitis.10–12 Yet it is likely the same disease process that caused them to be ‘chesty’ (with wet cough) from childhood. In two relatively large series (n = 103–150), most (60–80%) adults newly diagnosed with bronchiectasis (on HRCT) had chronic wet cough or productive cough since childhood.13,14

Unfortunately the subject of how bronchiectasis evolves has received relatively little attention over the past 40 years. The high case numbers of bronchiectasis described in the 1940 s and 1950 s2 with a seeming resurgence described from the 1990 s15–17 suggests two possibilities. Either it was under-recognised in the intervening years, when there was a co-existing strong focus on asthma, or that the widespread use of oral antibiotics in early childhood to treat ‘viral respiratory tract infections’ also treated developing persistent bacterial bronchitis (PBB) and/or pneumonitis. Eradicating bacteria prior to the formation of biofilms is theoretically easier than after the biofilms have become established and in the same way many pneumonias were probably inadvertently treated so many cases of bacterial bronchitis were probably inadvertently prevented. We speculate that the reappearance of an old disease may in part be the unintended consequence of an appropriate attempt to reduce antibiotic prescribing for acute viral respiratory tract infections. The terminology used is also confusing as it suggests that there are different diseases rather than a spectrum of clinical phenotypes with a common underlying problem. The use of some of the diagnostic terms is discussed in next section and has been summarised in a previous review.9

### Bronchiectasis

Classically, bronchiectasis is a radiological or pathological diagnosis characterised by irreversible bronchial dilatation. Currently this is most commonly diagnosed by HRCT which has replaced bronchograms. The key features of bronchiectasis on HRCT scans are (a) one or more ‘dilated’ bronchi defined as the internal luminal diameters of the airways exceeding the diameter of the adjacent vessel, (b) non-tapering of the bronchi and (c) presence of visible bronchi adjacent to the mediastinal pleura or within the outer 1–2 cm of the lung fields. However, bronchiectasis (radiological diagnosis) may be reported by radiologists in patients with interstitial lung diseases (such as pulmonary fibrosis) where traction on the airways causes bronchial dilatation. Traction bronchiectasis in the absence of chronic productive or wet cough will not be considered further in this paper. In children, cough is wet rather than productive, as young children usually do not expectorate,9 and following treatment the cough often temporarily resolves.4

### Chronic Suppurative Lung Disease (CSLD)

CSLD describes a clinical syndrome where there are symptoms of chronic endobronchial suppurration with or without HRCT evidence of radiological bronchiectasis. The presenting symptoms are identical to bronchiectasis; a prolonged moist or productive cough, exertional dyspnoea, features of reactive airway disease, growth failure, recurrent chest infections and/or wet cough responsive to antibiotics. Physical signs include clubbing, chest wall deformity, adventitious sounds and/or hyperinflation.1 Haemoptyisis is rare in children. However, absence of symptoms (other than wet cough) and signs do not reliably exclude either bronchiectasis or CSLD. Lung abscess and empyema (previously included as CSLD) have distinct radiological characteristics, are not discussed here and in our era should not be considered as within the CSLD category.

### Protracted bacterial bronchitis (PBB)

Most children have a productive or wet cough for several years before a diagnosis is made.1 Pathobiological studies18–20 and clinical observations suggest many patients have bronchitis initially that, untreated, gradually evolves into bronchiectasis.9,10 The entity of PBB has been described in children where a wet cough completely resolves following antibiotic treatment.5,11 Many of these children were previously misdiagnosed with asthma and had responded poorly to asthma therapies. In some settings these children would have been classified as having ‘difficult or severe asthma’.9,10 This is also likely relevant to adults. From a recent study, 40% of newly referred adults (and who had a CT scan) with ‘difficult asthma’ were found to have bronchiectasis.31

### Limitations of definitions

The definitions of bronchiectasis, CSLD and PBB have limitations as their associated symptoms and signs overlap and lack specificity. Whether these conditions are different or reflect part of
a spectrum of disease severity remains undetermined. However, we believe absolute reliance on a radiology-based definition is also unsatisfactory for the following reasons:

1. It is unknown when the radiological changes consistent with bronchiectasis occur in the context of a patient with symptoms of CSLD/bronchiectasis. Adult-based studies have shown that bronchography (the previous gold standard for diagnosis of bronchiectasis) is superior to HRCT scans especially in mild disease. Furthermore recent studies have shown that contiguous 1-mm slices are superior in diagnostic terms compared to conventional HRCT images (1 mm slice every 10 mm). Hill et al reported that the contiguous 1-mm slices protocol (using multidetector CT scan) demonstrated 40 extra lobes with bronchiectasis not identified on conventional HRCT in 53 adults. False negative results are more likely to occur when the disease is mild and localised. As children are likely to have less severe bronchiectasis than adults, it is possible that the HRCT in a sub-group of children with clinical symptoms of bronchiectasis may still have insufficient sensitivity to detect early signs of this disorder. In addition it is more difficult to obtain appropriate full inspiratory scans in young children.

2. A significant number of children have clinical characteristics of bronchiectasis but their HRCT scans do not meet the criteria for radiological bronchiectasis (Figure 1). HRCT findings of bronchiectasis were derived from adult studies and may not be applicable to children as airways and morphologic changes in the lung occur with maturation and aging. One of the key HRCT signs of bronchiectasis is increased broncho-arterial ratio (defined as the diameter of the bronchial lumen divided by the diameter of its accompanying artery) of > 1-1.5. However this ratio is influenced by age and we argue that a lower broncho-arterial ratio should be used in children to diagnose bronchiectasis. Extrapolation of this line suggests that the cut-off should be at 0.4-0.5 in infancy. Indeed the broncho-arterial ratio in young children (0-5 years) without CSLD symptoms was 0.49 to 0.58. A study based on multi-detector CT chest scans in 41 children (aged < 18 years) without pulmonary symptoms described that broncho-arterial ratio of ≥ 0.8 should be considered abnormal.

3. To fulfil the criteria of ‘irreversible dilatation’ at least two HRCT scans are required. Performing more than one HRCT scan purely for diagnostic reasons (as opposed to required for management reasons) in some settings is highly impractical and unnecessarily increases cancer risk from CTs in children and adolescents. HRCT scans performed in different clinical states, such as during an acute pulmonary exacerbation, immediately following treatment or when clinically stable, may yield different results. While HRCT scans are ideally performed in a ‘non-acute state’, this is sometimes difficult to define. A ‘non-exacerbation state’ is not necessarily the same as post-treatment state. Clinicians have realised that this is a significant limitation. The Liverpool group described bronchial dilatation resolving completely in 6 of 21 children with radiologically defined bronchiectasis when HRCT scans were repeated immediately following intensive medical therapy. We and others have observed that radiological ‘bronchiectasis’ can resolve following appropriate treatment though this is unlikely in more advanced distortion of the conducting airways. Also, Field eluded to this pre-bronchiectatic state back in the 1940’s.

The above reasons had lead some clinicians, particularly paediatricians, to use the term CSLD. Clinically these conditions overlap and the eventual diagnosis is evident only with further investigations and time. While the principles of managing all three conditions are the same, there are few published intervention studies, especially for CSLD. Until further evidence is available, we believe recognising the continuum of a pathogenic process is important given the:

(i) spectrum of disease,
(ii) increasing evidence that early diagnosis and treatment improves outcomes and reduces pulmonary decline,
(iii) difficulties surrounding robust definitions outlined above, and
(iv) increasing recognition that ‘bronchiectasis’ may be reversible, at least in the milder cases.

These issues and diagnostic categories were raised in a previous review and guidelines. Similarly, the categories were recently endorsed by the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation in their position statement.

This places the focus on the unifying driver of symptoms and progressive damage which is infection (or colonisation) of the airways with pathogenic bacteria (with likely biofilm formation).

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![Figure 1](image1.jpg) HRCT of the lower lobes of a child aged 3 years and 7 months during routine investigation for a chronic wet cough that was found to be related to common variable immunodeficiency. The HRCT shows borderline bronchiectasis. Most respiratory paediatricians considered bronchiectasis was present in this HRCT scan but two paediatric radiologists reported absence of abnormal airway dilatation (and thus absence of bronchiectasis). Following treatment (immunoglobulin replacement, intravenous antibiotics and airway clearance), the cough cleared after 2 weeks. Child is currently well (now aged 5.5 years), cough free and has no abnormality spirometry.
and places the clinical manifestation in this context. While there is currently no evidence on the detection of biofilm in the airways (other than for CF and diffuse panbronchiolitis), it is however likely important in the pathophysiology of chronic lower airway infections and contributes to the difficulty in eradicating infection once established. In the mucosa of ears (which is arguably relevant to lower airways), the importance of biofilms in chronic otitis media has been described. In this paradigm, bronchiectasis is viewed as a radiological or pathological sign resulting from a long standing process in the same way that a myocardial infarction is an event in some patients with ischemic heart disease. As with ischemic heart disease the paradigm of persistent bacterial bronchitis is a description of a process which can have a clinical expression from asymptomatic, minimal symptoms to life threatening severe impairment of function or premature death. Moreover with appropriate intervention progression can be arrested or even reversed.

Precursors of bronchiectasis and lung function abnormality

Aetiological associations and risk factors for bronchiectasis are discussed by Kapur and Karadag in this series. Other potential precursors of airway dysfunction, CSLD and bronchiectasis are further briefly discussed below.

While low birth weight and pre-existing small lungs are predictors of future lung function parameters, there is increasing evidence that early events in life are equally important determinants of adult pulmonary dysfunction in human and animal studies. Harding et al showed that later size and structure of lungs in sheep born preterm (but not requiring respiratory support) were dependent on post-natal growth rather than being low-weight at birth. This is plausible as lung growth continues at least through the first two years of life and, in the lung parenchyma, this occurs by increasing alveolar number as opposed to increasing alveolar size. Events such as respiratory infections and persistent neutrophilic inflammation (eg PBB when not treated) during this critical period of lung development may lead to long term pulmonary effects. Reviews on the biology of persistent airway neutrophilia and its potential damaging effects are available elsewhere.

In recent years, large epidemiological data from the COPD literature have shown that in addition to tobacco smoking, the antecedence of these chronic respiratory diseases occurs in childhood. While bronchiectasis is not COPD, both diseases share some common features when advanced (chronic productive cough, fixed airflow limitation). Two studies have also described the high prevalence (29-50%) of bronchiectasis in adults with COPD. Whether or not these adults had bronchiectasis before being labelled as having COPD is unknown ie the temporal relationship between the two diseases is unknown. Similarly there is a substantial overlap between bronchiectasis with asthma and COPD. In bronchiectasis-specific literature, recurrent hospitalisations for respiratory infections and prematurity have been shown to be independent significant risk factors for the later development of bronchiectasis in children. It would appear that childhood respiratory disease and risk factors are relevant for the development of adult respiratory disease, epidemiological studies documenting this relationship are reviewed below.

Nine years follow-up data on community based samples of 20-44-yr-old subjects from 29 centres that participated in the ‘European Community Respiratory Health Survey’ described that significant respiratory infections in the first 5-years of life were associated with a lower FEV\(_1\) (adjusted difference of -144mls, 95\%CI -211 to -78 for hospitalised episode) even when excluding ‘ever asthmatics’ and ‘current wheezers’. Dharmage and colleagues further documented that the impact of early infections was more significant in subjects exposed to maternal or active smoking. From the same cohort, Svanes et al reported that early life disadvantage (maternal and paternal asthma, severe respiratory infections before aged 5-years, maternal smoking) were significantly associated with adult development of COPD. Longitudinal data from the Newcastle Thousand Families cohort likewise described that childhood respiratory infections contributed significantly to future adult lung function. Other important factors from this study were birth weight, breast feeding (for >4 weeks), asthma and smoking. A study from Scotland described that respiratory disease in early life was associated with a higher risk in adulthood of chronic productive cough, dyspnoea and doctor diagnosis of asthma, bronchitis or emphysema (adjusted odds ratios ranging from 1.40 to 6.95 for these outcomes). These recent epidemiological studies support older data showing that childhood pneumonia was related to poor lung function in adults with no history of wheeze. While recall bias is always an issue in the design of studies described here, the findings from several large studies are at least consistent and supported by animal work and bronchiectasis-specific literature.

Can CSLD and bronchiectasis be prevented?

Bronchiectasis causes an accelerated lung function decline and premature death in adults. In Indigenous Australian adults (a group that generally receive sub-optimal treatment) the mortality of a hospital-based cohort of 61 adults (mean age of 42±15-yr) was 11.5% within 12-months. Elsewhere, mortality rates in adults with bronchiectasis vary widely from 4-yr survival of 58% (Turkey), 75% survival at 8-8 yrs (Finland) to 81% survival at 14-yrs (Scotland). In the past, surgical interventions to reduce the severe symptoms of bronchiectasis were common practice. Currently lobectomies or pneumonectomies for children with bronchiectasis are rarely appropriate in affluent countries but remain a common and important treatment option in less affluent countries. The fact that the natural history of bronchiectasis and mortality has altered with improvements in health and the environment suggests that with the implementation of other preventative factors, the progression of bronchiectasis could be ameliorated in the majority of children. Furthermore, there is evidence demonstrating:

(a) The effect that exacerbations and/or delayed treatment is associated with lung function decline,
(b) Children at risk of bronchiectasis can have normal lungs with early diagnosis and appropriate management, and
(c) Appropriate treatment reduces exacerbations of bronchiectasis.

(a) Exacerbations and/or delayed treatment is associated with lung function decline,

Increased mortality risk is associated with the degree of lung function impairment. Determinants of accelerated lung function decline in adults with bronchiectasis are frequency of hospitalised exacerbations, increased systemic inflammatory markers and colonization with P. aeruginosa. Available longitudinal FEV\(_1\) data in children with non-CF bronchiectasis are inconsistent but support that early and intensive treatment improves lung function in children with reduced FEV\(_1\) at diagnosis and prevents deterioration in the following 2-5 year period. One London-based retrospective study (31 children over 4-yrs) found that with intensive treatment lung function improved but did not necessarily normalize. In contrast, an Auckland (New Zealand) study (44 children over 4.5yrs) described a decline of FEV\(_1\) of 1.9% per year.
A Brisbane (Australia) retrospective study (52 children over 3-yrs, 25 over 5-yrs) found that children with normal lung function at diagnosis maintained normal lung function at 5-yrs, but those with low lung function at diagnosis were likely to have low lung function at 5-yrs, although improved. The Brisbane study also found that the only significant predictor of FEV₁ decline (over 3-yrs) was frequency of hospitalized exacerbations. With each exacerbation, the FEV₁%predicted decreased by 1.95% (p = 0.048) adjusted for time. The other two published cohorts did not examine exacerbations as a determinant of lung function decline. Thus, interventions that reduce exacerbations are likely to be important for later adult lung dysfunction. Furthermore, adult data has shown that recurrent exacerbations is one of the strongest predictors of poor QOL. Data on asthma exacerbations in child and adulthood mirrors these findings. O’Byrne and colleagues described that exacerbations requiring hospitalisation or emergency treatment were associated with accelerated lung function (FEV₁) decline in subjects not on preventative therapy. It could be argued that children with exacerbations were predestined to have lung function decline anyway, however what evidence there is suggests that children at risk of development of CSLD should receive appropriate therapies to improve immediate symptoms and minimise future lung dysfunction.

(b) People at risk of bronchiectasis can have normal lung function with early appropriate management.

There is increasing evidence that intensive treatment of children either at risk of, or who have, bronchiectasis prevents poor lung function in adulthood. In two heterogeneous cohort studies, primary immunodeficiency (as the prescribed aetiology) did not relate to any marker of bronchiectasis severity or to future lung function decline. With respect to primary ciliary dyskinesia (PCD) and primary immunodeficiency, three studies described that delayed diagnosis was associated with more severe disease. A large (n = 182) Australian study of adults newly diagnosed with bronchiectasis has shown that the decline in FEV₁ correlates (r = 0.51) with the duration of chronic wet cough, the most common symptom. For each additional year of cough, FEV₁%predicted declined 0.51% in non-smokers. In children with ‘right middle lobe syndrome’, Priftis and colleagues found a positive correlation to duration of the deterioration of symptoms prior to presentation with development of bronchiectasis (p = 0.03). Duration of symptoms also correlated with an unfavorable clinical outcome.

(c) Appropriate treatment reduces respiratory exacerbations.

Appropriate therapy improves prognosis and reduces respiratory exacerbations. The frequency of exacerbations is higher in those with more severe disease and unmanaged CSLD/bronchiectasis. In a Turkish study of 111 children, ‘intensive medical treatment’ (prompt antibiotic use, physiotherapy, bronchodilators) reduced exacerbation rates from 6.5 ± 4 to 2.9 ± 2.9 per year. Exacerbation frequency per year is directly related to bronchial wall thickening on HRCT scans and severe bronchial wall thickness was the most adverse prognostic determinant in a study using serial chest HRCT scans. While there is little randomised controlled trial (RCT) data on therapies that reduce exacerbations, available data in adults suggest that standard therapies used for CSLD and bronchiectasis (eg pneumococcal vaccination, antibiotics) reduce respiratory exacerbations. A cohort study described improvement in lung function and reduction in exacerbation frequency by 50-67% when regular azithromycin was given to adults with bronchiectasis. Whether this reduction is related to azithromycin’s anti-microbial effect or the immune-modulatory influences remain to be defined.

EXACERBATIONS

Despite the known importance of exacerbations in most chronic respiratory diseases (e.g. asthma, COPD) data are scarce for the triggers, definitions, associated clinical features and evidence for treatment of bronchiectasis in both children and adults. A review of exacerbations in people with bronchiectasis is available elsewhere. Whether viruses and other non-bacterial respiratory pathogens such as Mycoplasma and Chlamydia spp. trigger bronchiectasis exacerbations has never been examined. A Brisbane retrospective study found that 34% of exacerbations were preceded by an upper respiratory illness. However, a systematic study utilising modern, sensitive molecular techniques and inclusive of the more recently described viruses (e.g., human metapneumovirus, human coronaviruses (HCoV NL63 and HKU1), human bocaviruses and polyomaviruses, rhinovirus C) have not been undertaken. Clearly this is required as one of the first steps in understanding triggers of respiratory exacerbations in children with bronchiectasis.

CONCLUSION

Recent studies have indicated that in a significant proportion of children with chronic cough referred to secondary care, the cough is attributable to infection (or colonisation) of the airways with pathogenic respiratory organisms. The clinical manifestations of this bacterial bronchitis are variable being influenced by factors such as age, extent of infection and the degree of damage to the airways. Symptoms may be limited to a cough, typically a moist cough (protracted bacterial bronchitis), while in older children and those with significant damage to the conducting airways (bronchiectasis), expectoration of sputum and more persistent cough occurs. Absent or ineffective treatment regimes lead to progressive damage that can ultimately lead to severe pulmonary impairment.

Many unanswered questions remain. In this article we have highlighted the current limitations of dependence on radiological diagnoses of childhood bronchiectasis. We also presented the evidence why early diagnosis, active and close monitoring, and intensive treatment are advocated in children with protracted bronchitis, CSLD and bronchiectasis. Clearly further studies are required to delineate appropriate diagnostic labelling, pathogenesis questions as well as clinical trials that address prevention and treatment issues.

RESEARCH DIRECTIONS

Childhood bronchiectasis

- The direct measurement of neutrophilic inflammation in the airways of children.
- Prospective studies determining factors governing lung function decline and exacerbations.
- The role of viruses and Chlamydia species in respiratory exacerbations and persistence of symptoms.
- To determine whether chronic nasopharyngeal carriage of pathogenic bacteria contribute to CSLD or bronchiectasis.
- The roles of bacteria-virus interaction, biofilms and other non respiratory bacteria in the pathophysiology of non-CF bronchiectasis.
- Evidence based studies examining the role of early therapy in the prevention and/or progression of bronchiectasis.
PRACTICE POINTS

Childhood bronchiectasis

- Diagnosis by radiological techniques in children were extrapolated from adult studies and have substantial limitations.
- Early diagnosis and appropriate management likely prevent disease progression.
- Protracted bronchitis and chronic suppurative lung disease (CSLD) are likely precursors of bronchiectasis, if left untreated.
- Children with conditions at risk of bronchiectasis should be vigilantly monitored and appropriately treated when wet cough is present to reduce the likelihood of developing CSLD and bronchiectasis.

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