Does failed chronic wet cough response to antibiotics predict bronchiectasis?

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ABSTRACT

Aim To determine whether a child with chronic wet cough and poor response to at least 4 weeks of oral antibiotics is more likely to have bronchiectasis.

Methods All chest multi-detector computerised tomography (MDCT) scans at a single paediatric tertiary hospital from April 2010 to August 2012 were reviewed retrospectively so as to identify those ordered by respiratory physicians for assessment of children with a chronic wet cough. Information regarding age, sex, ethnicity, indication for imaging and the response to at least 4 weeks of antibiotics before having the scan were recorded from their charts. The data were analysed using simple and multiple logistic regression.

Results Of the 144 (87 males) eligible children, 106 (65 males, 30 Indigenous) aged 10–199 months had MDCT scan evidence of bronchiectasis. Antibiotic data were available for 129 children. Among the 105 children with persistent cough despite at least 4 weeks of antibiotics, 88 (83.8%) had bronchiectasis, while of the 24 children whose cough resolved after antibiotics, only six (25.0%) received this diagnosis (adjusted OR 20.9; 95% CI 5.36 to 81.8). Being Indigenous was also independently associated with radiographic evidence of bronchiectasis (adjusted OR 5.86; 95% CI 1.20 to 28.5).

Conclusions Further investigations including a MDCT scan should be considered in a child with a chronic wet cough that persists following 4 weeks of oral antibiotics. However, while reducing the likelihood of underlying bronchiectasis, responding well to a single prolonged course of antibiotics does not exclude this diagnosis completely.

INTRODUCTION

Chronic cough in children is associated with a high burden of illness, including doctor visits and parental stress.1 It is integral to a wide variety of diagnoses ranging from a simple non-specific dry cough following an uncomplicated acute respiratory infection to potentially more serious causes, such as pertussis, a foreign body in the airway and tuberculosis. A chronic wet cough is an important symptom of endobronchial infection shared by a spectrum of disorders, including protracted bacterial bronchitis (PBB), chronic suppurrative lung disease (CSLD) and bronchiectasis.2–4 In a clinical setting, parental reporting of a wet cough, unlike wheeze,5 shows close agreement with a clinician’s cough assessment and bronchoscopic findings.6

The recommendation that children with a chronic (>4 weeks) wet cough should undergo a careful clinical review6,7 is based upon several key points. First, bronchoalveolar lavage studies in children with chronic wet cough have found evidence of lower airway bacterial infection and inflammation, which in children with PBB will respond to a course of antibiotics.6–12 Second, a recent retrospective study10 described a significant correlation between duration of wet cough and severity of the radiographic findings on high resolution CT (HRCT) scans and the degree of inflammation determined by neutrophil percentage in bronchoalveolar lavage fluid. In adult non-smokers newly diagnosed with bronchiectasis, the duration of productive cough had a significant negative correlation (r = −0.51) with airway obstruction measured on spirometry.13 Third, available data suggest that early diagnosis and management of bronchiectasis in children can prevent, reduce and even occasionally reverse long-term morbidity.14 Thus, we15 and others10 have advocated that children with chronic wet cough should be evaluated carefully for an underlying aetiology.

In a recent randomised controlled trial on cough pathways, the algorithm used for children with chronic wet cough without additional symptoms or signs (ie, isolated wet cough) was that they received 2 weeks of antibiotics. If, despite this treatment, the wet cough remained, the course of antibiotics was extended for another 2 weeks. However, in those children whose wet cough failed to resolve after 4 weeks of continuous antibiotic treatment, further specialist evaluation was recommended. This approach is consistent with guidelines developed for...
identifying cases of bronchiectasis, which also suggest a chronic wet cough unresponsive to treatment should be investigated further. Nevertheless, there are no published data to help support these recommendations of an empirical trial of antibiotics before embarking on further investigations. This is important as assessments may include CT scans, which in children involve a small, but increased risk of cancer from high radiation doses. Furthermore, CT scans add to the cost and demands for health services and may not be readily accessible, especially for those living in remote and rural communities.

We therefore report the outcomes of 144 children with chronic wet cough who received 4 weeks of antibiotic treatment targeted against respiratory bacteria commonly associated with PBB, CSLD and bronchiectasis, and who underwent a multi-detector CT scan (MDCT) of the chest. Our primary question was: in children who have chronic wet cough, does a poor response to at least 4 weeks of oral antibiotics predict an increased risk of bronchiectasis on a MDCT scan of the chest? We hypothesised that children with a chronic wet cough who did not improve after 4 weeks of oral antibiotics will have an increased likelihood of bronchiectasis being detected on a chest CT scan.

METHODS

Study population and protocol

Children with a chronic wet cough (duration >4 weeks) and referred to the Department of Respiratory Medicine at the Royal Children’s Hospital, Brisbane, Australia follow a standardised management pathway. This includes prescribing up to 4 weeks of oral antibiotics (amoxicillin-clavulanate) before undergoing more intensive investigations, such as bronchoscopy and MDCT scans of the chest. We therefore evaluated retrospectively all MDCT scans of the chest undertaken at this tertiary paediatric centre between April 2010 and August 2012. The scans were identified retrospectively on the hospital’s radiology software system (IMPAX Client V.6,4.0.2380, AGFA, Mortsel, Belgium). The request form and/or chart of each child were reviewed for eligibility based upon a priori defined inclusion/exclusion criteria. These were: presence of chronic wet cough (duration >4 weeks) and having completed at least 4 weeks of oral antibiotics directed against likely respiratory bacterial pathogens associated with PBB, CSLD and bronchiectasis. Exclusion criteria were cystic fibrosis (CF), asthma, a known case of bronchiectasis and scans requested by oncology, surgical, intensive care and trauma teams.

Clinical data were extracted from the medical charts with particular attention paid to the indication for the CT scan, exposure to tobacco smoke and history of antibiotic treatment, including its duration and the child’s response to this course of antibiotics before the CT scan was performed. A poor response to antibiotics was defined as persistence of the wet cough after 4 weeks of oral antibiotics based upon the clinical judgment of the child’s treating respiratory physician. For the purpose of this study Indigenous status for children was ascribed by parents or caregivers as Australian Aboriginal, Torres Strait Islander, Maori or Pacific Islander. The Children’s Health Queensland Hospital and Health Service Human Research Ethics Committee approved the study.

Radiology

MDCT scans with high resolution reconstruction were performed with a 64-slice scanner (Aquilon, Toshiba Medical Systems; Tochigi, Japan). All children had inspiratory and expiratory scans. CT imaging protocols were different for children in different weight ranges. Tube parameters were 120 KVp and current (in mA) and pitch variable, determined by rotational and z-axis modulation. Dose modulation in the Toshiba Aquilon 64 is calculated by achieving a SD of noise in an image. The SD was set at 10 for these examinations. For inspiratory films only limited scans were done, with 2 mm thickness and intervals of 10 mm for children weighing up to 10 kg, intervals of 20 mm for those weighing 11–25 kg and 30 mm intervals thereafter for those above 25 kg in weight. A scan time of 0.5 s was used. The scans were conducted under general anaesthesia in children unable to cooperate with the procedure.

Images were viewed online using IMPAX Client software under 3× magnification. As reported previously, the maximum diameter of the pulmonary artery and the inner luminal diameter of the adjacent bronchus were measured using electronic callipers. In the context of a chronic wet cough, bronchiectasis was diagnosed when the broncho-arterial ratio was larger than 0.8 with or without peribronchial thickening or lack of bronchial tapering.

Of the 1013 scans retrieved, full chart reviews were undertaken on 163 children (figure 1). The scans from 19 children were excluded following chart review because of CF (two patients), a previous diagnosis of bronchiectasis (16 patients) and a scan done after an episode of severe croup. The remaining 144 scans were reviewed independently by two of the authors (VG and AC). A consensus was reached, in the eight scans where disagreement occurred.

Statistical analysis

Data with a normal distribution were expressed as means±SD and, when skewed, medians and range were used. The association between recorded clinical responses to oral antibiotic treatment in children with subsequent MDCT scan evidence of bronchiectasis as a binary outcome was examined by simple logistic regression, while multivariate logistic regression adjusted for potential confounding from demographic and clinical features. All statistical analyses were performed on STATA V11.0 software.

RESULTS

The median age of the 144 (87 males) study children was 56.9 months; median duration of persistent wet cough was 12 months (range 1.5–144) months. Co-morbidities included...
congenital heart disease ($n=11$), chronic neonatal lung disease ($n=5$), primary ciliary dyskinesia ($n=4$), previous tracheo-oesophageal fistula and tracheostomy ($n=1$), cerebral palsy ($n=5$), various genetic syndromes ($n=7$) and inflammatory bowel disease ($n=1$). Antibiotic data were recorded in the charts of 129 children. Each child received at least 4 weeks of oral antibiotics before undergoing a chest CT scan.

Overall, 106 (74%) had evidence of bronchiectasis on their MDCT scans. Univariate analysis found significant differences between groups for responses to antibiotics and Indigenous ethnicity and the presence of bronchiectasis, which remained significant following multivariate analysis (table 1). As expected, digital clubbing was seen only in those patients with radiographic evidence of bronchiectasis. There was also weak evidence for a chronic wet cough of more than 12-month duration being associated with an increased risk of underlying bronchiectasis. While a poor response of an isolated chronic wet cough to antibiotics as a predictor of bronchiectasis on MDCT scans had a sensitivity of 93.6% (95% CI 86.1 to 97.4), the specificity was only 51.4% (95% CI 34.3 to 68.3). Positive and negative predictive values were 83.8% (95% CI 75.3 to 90.3) and 75.0% (95% CI 53.2 to 90.2), respectively. The positive and negative likelihood ratio were 1.93 (95% CI 1.4 to 2.7) and 0.12 (95% CI 0.1 to 0.3), respectively.

**DISCUSSION**

In our retrospective review of 144 children with chronic wet cough, those who did not respond to at least 4 weeks of oral antibiotics were at significantly greater risk of having radiographic changes of bronchiectasis than children whose chronic wet cough responded to this treatment. Being Indigenous was the only other factor independently associated with bronchiectasis, which is consistent with findings from other studies.21 22

The burden of bronchiectasis unrelated to CF is large and under-recognised.23 In a recent multicentre study using a standardised algorithm to manage chronic cough in 346 children, 9% had radiographic evidence of bronchiectasis.24 The importance of an early diagnosis and commencement of appropriate treatment for bronchiectasis has long been recognised25 26 and can result in improved short and medium term clinical outcomes,14 27 including complete resolution of bronchiectasis in some children.28 Although guidelines suggest further investigations for children with a chronic wet cough not responding to treatment,2 16 there are no data on when such investigations should begin and what constitutes an adequate trial of antibiotic therapy.7 Our data suggest that children should be evaluated if the cough does not respond to 4 weeks of antibiotics. We chose 4 weeks based upon studies of PBB, which indicate that the wet cough should resolve within 2 weeks of appropriate antibiotic treatment,21 6 there are no data on when such investigations does not lead to a resolution in symptoms in children with isolated chronic wet cough. This approach is also consistent with a view held widely that a longer course of antibiotics and daily physiotherapy are often required in children with CSLD and bronchiectasis.7

We included children with co-morbidities in this study, representing a real-life clinical approach as it is not prudent to subject every child with chronic cough to a CT scan, even with conditions such as tracheo-oesophageal fistula. Doing so would lead to overinvestigations and the associated adverse effects of radiation.17 Further, although numbers were small, the presence of co-morbidity was not a significant predictor of presence of bronchiectasis (table 1). Interestingly, more than one-quarter of children had been treated for asthma, which highlights the importance of considering alternative diagnoses and management when children fail asthma therapy.

Our study does have several limitations that need to be considered. It is limited by its retrospective nature, unequal numbers in the two groups, and the missing antibiotic data from 15 children. Furthermore, its results may not be able to be generalised to other settings as the children were referred to tertiary paediatric respiratory physicians and the 12-month median duration of wet cough suggests they were a high-risk group of patients. The limitations of using adult radiology criteria to diagnose bronchiectasis are well recognised by paediatricians.19 Thus, we used a definition of bronchiectasis based upon radiology findings in the presence of clinical symptoms consistent

**Table 1 Summary of univariate and multivariate analyses of children undergoing multi-detector contrast tomography chest scans because of a chronic (>4 weeks) wet cough**

<table>
<thead>
<tr>
<th></th>
<th>Bronchiectasis N=106*</th>
<th>No bronchiectasis N=38*</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate (n=122) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>65:41</td>
<td>22:16</td>
<td>1.15 (0.54 to 2.44)</td>
<td>1.16 (0.35 to 3.82)</td>
</tr>
<tr>
<td>Indigenous†</td>
<td>30/106 (28.3%)</td>
<td>3/37 (8.1%)</td>
<td>4.47 (1.27 to 15.67)</td>
<td>5.86 (1.21 to 28.5)</td>
</tr>
<tr>
<td>Age ≥5 years</td>
<td>50/106 (46.2%)</td>
<td>18/38 (47.3%)</td>
<td>1.00 (0.47 to 2.08)</td>
<td>1.79 (0.58 to 5.46)</td>
</tr>
<tr>
<td>Cough ≥12 months</td>
<td>55/101 (54.4%)</td>
<td>15/37 (40.5%)</td>
<td>1.75 (0.82 to 3.77)</td>
<td>3.01 (0.97 to 9.31)</td>
</tr>
<tr>
<td>Tobacco smoke exposure‡</td>
<td>37/65 (56.9%)</td>
<td>7/20 (35.0%)</td>
<td>2.45 (0.86 to 6.95)</td>
<td>N/A</td>
</tr>
<tr>
<td>Prior asthma medications</td>
<td>23/103 (24.2%)</td>
<td>15/38 (39.4%)</td>
<td>0.44 (0.2 to 0.98)</td>
<td>0.37 (0.11 to 1.32)</td>
</tr>
<tr>
<td>Previous pneumonia</td>
<td>31/105 (29.5%)</td>
<td>8/38 (21%)</td>
<td>1.57 (0.65 to 3.80)</td>
<td>2.39 (0.69 to 8.23)</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>4/105 (3.8%)</td>
<td>1/38 (2.6%)</td>
<td>0.99 (0.96 to 1.01)</td>
<td>0.98 (0.95 to 1.01)</td>
</tr>
<tr>
<td>Other co-morbidities</td>
<td>25/105 (21.9%)</td>
<td>9/38 (23.6%)</td>
<td>1.00 (0.42 to 2.40)</td>
<td>1.05 (0.29 to 3.73)</td>
</tr>
<tr>
<td>Clubbing</td>
<td>12/105 (11.4%)</td>
<td>0/38 (0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wheeze on presentation</td>
<td>14/105 (13.3%)</td>
<td>5/38 (13.1%)</td>
<td>1.01 (0.34 to 3.04)</td>
<td>0.7 (0.16 to 3.04)</td>
</tr>
<tr>
<td>Crackles on presentation</td>
<td>23/105 (21.9%)</td>
<td>4/38 (10.5%)</td>
<td>2.38 (0.77 to 7.41)</td>
<td>1.58 (0.33 to 7.63)</td>
</tr>
<tr>
<td>Poor response to antibiotics</td>
<td>88/91 (93.6%)</td>
<td>17/35 (48.5%)</td>
<td>15.52 (5.38 to 44.8)</td>
<td>20.94 (5.36 to 81.8)</td>
</tr>
</tbody>
</table>

*Data were not recorded completely in the medical charts for some variables and hence the denominator may differ between variables.
†Indigenous=Aboriginal, Torres Strait Islander, Maori and Pacific Islander children.
‡Tobacco smoke exposure was not included in the multivariate model as this information was available in only 60% of study children.

15 children. Furthermore, its results may not be able to be generalised to other settings as the children were referred to tertiary paediatric respiratory physicians and the 12-month median duration of wet cough suggests they were a high-risk group of patients. The limitations of using adult radiology criteria to diagnose bronchiectasis are well recognised by paediatricians.19 Thus, we used a definition of bronchiectasis based upon radiology findings in the presence of clinical symptoms consistent
with this diagnosis. Also, we used HRCT reconstructed images from a MDCT scan as several studies\(^{29-30}\) have shown that a conventional HRCT scan (without MDCT) is less sensitive at detecting bronchiectasis than one using MDCT technology, probably as a result of the fewer slices taken for a HRCT scan. It is worth questioning why 24 patients had a chest CT scan even though their cough resolved after antibiotics. Of these 24 children, 11 had recurrent PBB, six had other co-morbidities, four had in addition recurrent pneumonia and one had proven aspiration. For three patients, it was not clearly documented in the charts why they had a CT scan even after their cough resolved with antibiotics. While this could simply reflect a difference in practice between respiratory paediatricians, it also highlights that even amongst the children in whom wet cough responds to antibiotics, there is a proportion, who in presence of other potential risk factors, such as prolonged wet cough symptoms or digital clubbing can still have bronchiectasis detected by CT scan. Another limitation is that because of the children’s young age antibiotic therapy could not be determined by sputum culture results. However, we have shown previously that the common pathogens detected in the lower airways of children (Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis) would be expected in our community to be susceptible to amoxicillin-clavulanate.\(^{12\ 18\ 31}\) Finally, although we have a standardised approach in our clinic to manage chronic wet cough, it is possible we did not capture all eligible cases as some children who failed to respond to antibiotics might not have undergone a chest CT scan.

We therefore recommend that a child whose chronic wet cough persists despite 4 weeks of oral antibiotic therapy undergo careful clinical review and consideration of a chest CT scan to detect underlying bronchiectasis, which requires more intensive management. This investigation should be undertaken in experienced paediatric units using child-specific protocols. However, a good clinical response to at least 4 weeks of antibiotics still does not exclude completely the possibility of bronchiectasis and consequently these children still require further follow-up and investigations should their chronic wet cough become recurrent or if other symptoms and signs suggestive of bronchiectasis develop. A larger prospective study with predefined criteria for further investigation of chronic wet cough is now needed to confirm our findings.

**Contributors** VG contributed to the study design, data collection, data analysis, data interpretation and writing of the manuscript. ABC contributed to the study design and review of the manuscript. VG wrote the first draft of the manuscript. Each author has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

**Funding** Supported by grants from Australian National Health and Medical Research Council (NHMRC) project grant (number 1019834), NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant number 1040830), NHMRC grant 545216 (fellowship to ABC) and the Children’s Health Foundation Queensland. None of the authors received any honorarium, grant, or other form of payment to produce the manuscript.

**Competing interests** None.

**Ethics approval** Ethics approval was granted by the Children’s Health Queensland Hospital and Health Service Human Research Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Arch Dis Child* 2014 99: 522-525 originally published online February 12, 2014
doi: 10.1136/archdischild-2013-304793

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