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BRONCHOSCOPY CONTRIBUTES TO THE CLINICAL MANAGEMENT OF INDIGENOUS CHILDREN NEWLY DIAGNOSED WITH BRONCHIECTASIS

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Abbreviated title:

FB/BAL in the management of children with bronchiectasis
Key words not in the title:
chronic suppurative lung disease, eosinophilia, foreign body, strongyloides

Abbreviations:
BAL  bronchoalveolar lavage
chRCT chest high-resolution computed tomography
CSLD chronic suppurative lung disease
CFU colony-forming units
CF  cystic fibrosis
FB  flexible bronchoscopy
IQR interquartile range
ABSTRACT

Background

Some pediatric centres perform flexible bronchoscopy (FB) routinely when bronchiectasis is suspected. However, there are no published data evaluating this practice.

Objective

To evaluate the contribution of FB and bronchoalveolar lavage (BAL) to the initial management of children newly diagnosed with non-cystic fibrosis (CF) bronchiectasis.

Method

We examined FB and BAL data collected prospectively in 56 children aged 0.8-9.8 years during initial investigations for bronchiectasis. Investigations contributed to management if any of the following were identified: (1) airway obstruction requiring additional intervention, (2) lower airway eosinophilia (BAL eosinophils >2.5%), or (3) BAL fluid culture >10^4 colony-forming units/mL of a respiratory bacterial pathogen requiring change from usual empiric antibiotics.

Results

Of the 56 children undergoing FB, there were 25 occasions in 23 children where these procedures altered empiric treatment. Lower airway eosinophilia was identified in 19 (34%) children, BAL microbiology results led to antibiotic changes in 5 (9%) and an unsuspected foreign body was found in another (2%). Strongyloides serology was performed in 38 children, including 12 of the 19 with airway eosinophilia, and was positive in 5 of these 12 children (42%).

Conclusion

Contrary to some expert recommendations that FB should only be performed when bronchiectasis is localized, our data suggest that FB with BAL should at least be included in the initial investigations of Indigenous children with non-CF bronchiectasis.
INTRODUCTION

Non-cystic fibrosis (CF) bronchiectasis is recognized increasingly as an important chronic respiratory disorder affecting children and adults in both developing and affluent countries.\(^1,2\) When left untreated, bronchiectasis is associated with infection, persistent airway inflammation and deteriorating lung function. Recent evidence however, suggests that effective management of bronchiectasis in children can improve or, at least, preserve lung function.\(^3,4\)

Bronchiectasis has several different etiologies. In affluent regions predisposing disorders, such as primary immune deficiency, are found commonly.\(^2,4\) However, in a developing world setting and amongst some Indigenous populations in affluent countries, recurrent respiratory tract infections remain the most commonly recognized factor associated with bronchiectasis in children.\(^5,6\)

Irrespective of the likely etiology, flexible bronchoscopy (FB) is recommended by some to exclude a foreign body or obstructive lesion.\(^2,7\) In addition, bronchoalveolar lavage (BAL) performed during FB allows collection of airway specimens for microbiologic analyses and examination of inflammatory cell types. There is increasing evidence to support the use of airway cellularity in guiding clinical management, particularly if airway eosinophilia is present.\(^8-10\) However, FB is an invasive procedure, adds to the cost and demand for health services and may not be easily accessible (particularly for those living in rural regions). Furthermore, some authorities only recommend FB when bronchiectasis affects a single lobe and a foreign body needs to be excluded.\(^11\) Although Australian and New Zealand guidelines recommend FB as a standard investigation for children with bronchiectasis,\(^2\) there are no data published to support this. Given the contrary\(^2,11\) recommendations, we examined the contribution of FB and BAL to the initial clinical management of children in our settings undergoing investigations for bronchiectasis and chronic suppurative lung disease (CSLD).
MATERIALS AND METHODS

Study participants

Fifty-six consecutive children (32 males), aged 0.8-9.8 (median 2.2) years, undergoing chest high-resolution computed tomography (cHRCT) scans and FB at the Royal Darwin Hospital, Northern Territory, Australia between November 2007 and December 2009 to evaluate persistent respiratory symptoms and suspected bronchiectasis were recruited prospectively. Clinical and socio-demographic data (Table 1) were obtained from the parent/guardian and medical records using standardized data collection forms. Although the children were in a stable clinical state at the time of their investigations 26 were receiving prophylactic antibiotics for their respiratory symptoms and another 4 had received antibiotics within the previous 2-weeks for chronic suppurative otitis media, a common co-morbidity in our setting. Routine investigations for all children included a full blood count, serum concentrations of the major immunoglobulin classes, antibody responses to tetanus protein and pneumococcal polysaccharide vaccine antigens and a sweat test. As purulent nasal discharge is very common amongst children in our setting, nasal cilia biopsies were not performed, meaning rare cases of primary ciliary dyskinesia could not be excluded. Written informed consent was obtained for all procedures. The human research ethics committee of the Northern Territory Department of Health and Families and Menzies School of Health Research approved the study (#0763).

cHRCT scans, bronchoscopy and BAL

cHRCT scans were performed under general anesthesia, followed immediately by FB (3.8 mm external diameter) as described previously. Radiographic diagnosis of bronchiectasis was made by the attending pediatric respiratory physician (AC) or pediatrician (PB) using standard published criteria (inside bronchial diameter-to-adjacent artery ratio > 1). BAL followed European
Respiratory Society guidelines and was obtained from the most abnormal lobe identified by FB or cHRCT scans.\textsuperscript{13} Two aliquots of sterile normal saline (1 ml/kg, max 10ml for the first and 2ml/kg, maximum 20mL, for the second aliquot) were instilled into the lobe and suctioned immediately into a mucus trap. The first aliquot was used for microbiologic analysis, the second for cytology. Specimens were placed on ice and sent immediately to the Laboratory for processing. Total and differential cell counts were performed on unfiltered BAL. A hemocytometer determined total cell counts. Cytoslides were prepared with a Cytospin 4 (Thermo Scientific), loading approximately $5 \times 10^{4}$ cells per slide and stained with Quick Dip (Fronine, Australia). The macrophage, neutrophil, lymphocyte and eosinophil percentages were calculated from a total count of 300 cells.

Routine microbiologic investigations for respiratory bacterial pathogens, including culture for \textit{Haemophilus influenzae}, \textit{Streptococcus pneumoniae}, \textit{Moraxella catarrhalis}, \textit{Staphylococcus aureus}, \textit{Pseudomonas aeruginosa} and \textit{Klebsiella pneumoniae}, and staining and culture for mycobacterial and fungal pathogens, were performed by the Diagnostic Laboratory at the Royal Darwin Hospital. In addition, identification and quantification of \textit{H. influenzae}, \textit{S. pneumoniae} and \textit{M. catarrhalis} were performed by our research laboratory by published methods and the diagnostic threshold for a lower airway infection set at $>10^{4}$ colony-forming units (CFU)/mL of BAL.\textsuperscript{12}

**Definition of FB and BAL data altering clinical management**

We defined \textit{a priori} that data obtained from FB and BAL contributed to clinical management if any of the following were met: (1) identification of unsuspected airway obstruction (eg foreign body or airway lesion requiring additional intervention), (2) lower airway eosinophilia (BAL eosinophils $>2.5\%$) prompting treatment with inhaled corticosteroids, or (3) respiratory bacterial pathogens $>10^{4}$ CFU/mL requiring a change in therapy. Locally, oral amoxicillin-clavulanate or parenteral...
Ceftriaxone are used by pediatricians empirically to treat children with either chronic suppurative lung disease or bronchiectasis.

Statistical analyses

As the data lacked a normal distribution, medians and their inter-quartile range (IQR) were used for descriptive data, and non-parametric methods, including chi-square tests for dichotomous outcomes, Mann-Whitney U tests for continuous variables and Spearman’s r for correlation were employed for analyses. The sensitivity, specificity, negative and positive predictive values of a history of current wheeze (within the last 12-months) and peripheral blood eosinophilia (>1.5 x 10^9/L) for airway eosinophilia (>2.5%) were also calculated. A two-tailed P-value <0.05 was considered significant. Graph Pad Prism Software (California, USA) was used for most statistical calculations.
RESULTS

Clinical diagnosis

Bronchiectasis (cHRCT-diagnosis) was identified in 52 of the 56 (93%) children (Table 1). The 4 remaining children had CSLD and as the Australian and New Zealand guidelines advocate that children with CSLD are managed similarly to those with bronchiectasis, the entire cohort is described below.

Findings from FB and BAL that altered clinical management

We identified 25 occasions where FB and BAL altered clinical management in 23 (41%) children with two children meeting two criteria (airway eosinophilia and either P. aeruginosa or K. pneumoniae). An unsuspected foreign body (chicken bone) in the left main stem bronchus was removed from a 5-year old Indigenous girl, but who then did not proceed to BAL. This particular child had at least a 3-year history of cough, had been hospitalized for pneumonia on 3 previous occasions and the cHRCT scan showed evidence of bronchiectasis in the left lower and right upper and lower lobes.

The mean BAL return was 47%. Lower airway infection (>$10^4$ CFU/mL) was diagnosed in 25/55 (45%) children. Lower airway infection rates were not significantly different between children taking (13/26; 50%) or not taking (12/29; 41%; P=0.52) antibiotics at the time of FB. Major pathogens included H. influenzae (n=16), S. pneumoniae (n=10) and M. catarrhalis (n=9) in 20 children. However, 5 (9%) required changes to their initial empiric antibiotic treatments as either P. aeruginosa (n=4) or K. pneumoniae (n=1) were identified in BAL fluid cultures. The 4 children identified with P. aeruginosa infection were aged 0.8-2.5 years and had bronchiectatic changes
involving 2-4 lobes. Neither mycobacterial nor fungal pathogens were isolated from any child in the
study.

**Airway differential count**

BAL fluid eosinophilia (>2.5%) was the most common indication for changing clinical
management. Nineteen children (34%) were identified with airway eosinophilia (Figure 1). The
median (IQR) eosinophil percentage in BAL fluid was 1.3% (0.3-5.0). Median (IQR) values for
neutrophils were 14.3% (6.7-47), lymphocytes 6.0% (2-12) and macrophages 66% (38-83), while
the median (IQR) total cell count was 46 (25-80) x10^4 per ml of BAL fluid. The percentage of
airway eosinophils was significantly correlated with the number of peripheral blood eosinophils,
r= 0.49, P=0.0002 (Figure 2). Absolute airway eosinophil counts also correlated with number of
peripheral blood eosinophils (r = 0.6886, P=<0.0001). However, a current history of wheeze and
peripheral blood eosinophilia (>1.5 x10^9/L) were both unreliable predictors of airway eosinophilia
(Table 2). Similarly, airway cellularity was not significantly different between children who were, or
were not, receiving antibiotics at the time of FB [median (IQR) total cell counts, 44 (27-75) vs 47
(25-84) x 10^4 per mL of BAL fluid, P=0.87; neutrophil 10.6 (3.8-28.2)% vs 16.6 (8.2-51.2)%
P=0.15; and eosinophil 1.3 (0.2-3.1)% vs 1.3 (0.3-5.9)% P=0.55 respectively].

After finding lower airway eosinophilia in 7 of the first 18 participants, the next 38 children (12 with
airway eosinophilia) had strongyloides serology performed at the regional reference laboratory
(PathWest Laboratory Medicine WA, Australia, IgG by EIA > 0.45 absorbance units). Five
Indigenous children had positive strongyloides serology, which was accompanied by airway
eosinophilia (Figure 2) and each child received anti-helminthic therapy. Strongyloides serology was
either negative (n=6) or equivocal (n=1) in the remaining 7 children with airway eosinophilia.
Similarly, children without airway eosinophilia at BAL had negative strongyloides serology, except for one child with an airway eosinophil differential percentage of 2.3% who had equivocal serological results. Of the 5 children already receiving inhaled corticosteroids, 2 had airway eosinophilia, including one child who was seropositive for strongyloides.
DISCUSSION

This is the first study to prospectively evaluate the contribution of FB with BAL to the initial management of children with non-CF bronchiectasis or CSLD. In 41% of the 56 children studied, we found that FB with BAL led to a change in management by identifying lower airway eosinophilia and antibiotic-resistant respiratory pathogens and helped discover an unexpected inhaled foreign body. If we had included any respiratory infection instead of infection requiring a change from empiric antibiotics, and removal of mucous plugs during bronchoscopy as therapeutic interventions the yield of FB could have been even higher.

Airway eosinophilia is associated with several respiratory disorders and in adults with bronchiectasis, there is evidence of eosinophil activation. However, to our knowledge airway eosinophilia has not been reported previously in children with bronchiectasis. Published data on airway cellularity in children with bronchiectasis are limited, and to date, only neutrophilia has been described. The importance of finding eosinophilia is that sustained (>6-months) systemic and lower airway eosinophilia can be associated with end-organ damage. Also airway eosinophilia is used to help guide corticosteroid therapy in eosinophil-associated airway diseases. Even using a conservative cut-off of 2.5% as an indication to commence inhaled corticosteroids while waiting to investigate the underlying cause, we found that 34% (19 children) had clinically important airway eosinophilia. Importantly, both current wheeze and circulating eosinophilia were poor predictors of airway eosinophilia in these children. A sputum eosinophil count of 2-3% is considered the threshold for predicting a positive therapeutic outcome from inhaled corticosteroids. However, the threshold used for BAL specimens should be lower as direct comparisons between paired BAL and sputum samples indicate that BAL specimens have lower eosinophil counts than found in sputum, which may reflect dilution and sampling from peripheral...
rather than central airways. The upper threshold of BAL eosinophil values in pediatric controls (age range 0.16-14.5 years) is between 0% and 1.19% (75th percentile). Published studies have used thresholds as low as 1.1% to define airway eosinophilia or as high as 2% to define eosinophilic pneumonia. However, in the absence of robust clinical data from randomized controlled trials using BAL, we chose a conservative threshold for therapeutic intervention. Our data suggest that airway cellularity to detect eosinophilia should be considered when investigating children for bronchiectasis. However, we do not advocate bronchoscopy is undertaken merely to detect airway eosinophilia particularly in selected situations where other simple, non-invasive means of detecting airway eosinophilia (such as exhaled nitric oxide measurement in children aged > 4 years) are available.

In endemic regions parasitic infections are a common cause of circulating eosinophilia and may also result in respiratory symptoms. Strongyloides stercoralis is an intestinal nematode endemic to Northern and Central Australia and as part of its life cycle migrates to the lungs and airways. Helminths with a similar respiratory phase including Ancylostoma (hook worm) and Ascaris are now uncommon in Australian Indigenous communities. While infection can be associated with asymptomatic chronic disease, strongyloidiasis can also lead to significant morbidity and even mortality in Indigenous Australians. Although we were unable to test all children, our data suggest that infection with S. stercoralis may contribute to the airway inflammatory profile of some Indigenous children with bronchiectasis. Any contribution to airway inflammation potentially contributes to airway injury and bronchiectasis and should be investigated and treated when present. As this was a cross-sectional study, it is unknown whether the peripheral blood and lower airway eosinophilia observed was chronic or transient and if it responded to anti-helminthic or corticosteroid therapy. Our data also suggest that strongyloidiasis does not fully explain the high
prevalence of lower airway eosinophilia seen in this cohort. Allergic bronchopulmonary aspergillosis (ABPA) is another recognized cause of airway eosinophilia. We did not test for Aspergillus-specific IgE, but Aspergillus was not detected in the BAL of any of these children. Furthermore, Aspergillus is very rare in children with non-CF bronchiectasis (none in 113 children), although it is well described in adults with bronchiectasis. The value of BAL for diagnosing respiratory infection in the pediatric setting is widely recognized. Non-typeable H. influenzae, S. pneumoniae and M. catarrhalis are the most commonly detected pathogens in children with bronchiectasis and this forms the basis for the choice of the initial empiric antibiotic therapy for respiratory exacerbations. However, when children with CSLD and bronchiectasis are deteriorating despite therapy, BAL cultures can help identify pathogens, such as P. aeruginosa, which require different antibiotics for adequate treatment. Similarly, exclusion of anatomical airway lesions and obstruction is also important as bronchiectasis and long-term pulmonary complications may occur in 25-60% of patients when the diagnosis of foreign body airway aspiration is delayed ≥30-days. If obtainable, sputum cultures are an alternative to those obtained by BAL from older children, particularly as a means of monitoring treatment. However, studies using sputum induction in children are restricted largely to subjects who are at least 6-years of age when it can be performed safely and successfully. The median age of children in this study was 2.2-years, with only 4 children over the age of 6 years and it was therefore not feasible to include sputum culture in this study. As spontaneous sputum expectoration in young children is unusual, clinicians often have to rely upon FB when seeking suitable lower airway specimens.

The present study has several important limitations. In addition to its cross-sectional nature, only a limited number of investigations were performed to detect underlying causes of airway eosinophilia. We could not define ‘therapeutic response’ to the multitude of interventions given once the
diagnosis was made. Although it is current ‘best practice’ to treat clinically important airway
eosinophilia, there are no randomized controlled trial data in children on when and how airway
eosinophilia should be managed. Also, as this study was conducted predominantly in Indigenous
children from remote communities in Northern Australia, the findings, especially of airway
eosinophilia, may not be directly applicable to other children with bronchiectasis, either in Australia
or elsewhere. Another potential limitation is that although 81% of children of children in this study
had multi-lobed bronchiectasis (33% with 3 or more lobes affected), we sampled from a single lobe,
as is current practice in our setting. Studies in children with CF have shown that while airway
inflammation can involve both lungs, the distribution of bacteria between both lungs and within
lobes from the same lung is often uneven.\textsuperscript{31,32} It is possible therefore that a similar situation may
exist in children with non-CF bronchiectasis and future consideration should perhaps be given to
multi-lobe sampling, particularly in children with extensive bronchiectasis. Regardless, this study
highlights the value of bronchoscopy in providing detailed, individualized data which can direct
therapy, a finding which is applicable globally.

There is accumulating evidence that with early diagnosis and intensive therapy, bronchiectasis can
be stabilized and lung function preserved.\textsuperscript{3,4} While the contribution of FB and BAL to the
management of children with bronchiectasis or CSLD may seem self-evident, this study is the first
to provide evidence to support this recommendation.\textsuperscript{2} It also, raises important questions over the
etiology and consequences of lower airway eosinophilia in children with bronchiectasis, which will
require additional research.
ACKNOWLEDGMENTS

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Conflict of interest: All the authors have no conflict of interest to disclose.
REFERENCES


FIGURE LEGENDS

Figure 1.
Distribution of eosinophils (a) and neutrophils (b) as a percentage of total airway leukocytes in bronchoalveolar lavage fluid from 55 children with bronchiectasis or chronic suppurative lung disease. The lower limit for clinically important airway eosinophilia (2.5%) is represented by the dashed line. The y axis is a split scale. Cytoslides of BAL show eosinophilia with neutrophilia (c) original x400 and neutrophilia (d) original x200.

Figure 2.
Scatter plot of eosinophil percentages in bronchoalveolar lavage fluid and absolute eosinophil counts in peripheral blood (n=54), r=0.49, P=0.0002. Open circles identify children with positive strongyloides serology (enzyme immunoassay >0.45 absorbance units). Thresholds for circulating and airway eosinophilia are shown by the dashed lines.\textsuperscript{17,20,21}
FLEXIBLE BRONCHOSCOPY AND BAL CONTRIBUTES TO THE MANAGEMENT OF CHILDREN WITH BRONCHIECTASIS.

BRONCHOSCOPY CONTRIBUTES TO THE CLINICAL MANAGEMENT OF INDIGENOUS CHILDREN NEWLY DIAGNOSED WITH BRONCHIECTASIS

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ABSTRACT

Background

Some pediatric centres perform flexible bronchoscopy (FB) routinely when bronchiectasis is suspected. However, there are no published data evaluating this practice.

Objective

To evaluate the contribution of FB and bronchoalveolar lavage (BAL) to the initial management of children newly diagnosed with non-cystic fibrosis (CF) bronchiectasis.

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We examined FB and BAL data collected prospectively in 56 children aged 0.8-9.8 years during initial investigations for bronchiectasis. Investigations contributed to management if any of the following were identified: (1) airway obstruction requiring additional intervention, (2) lower airway eosinophilia (BAL eosinophils >2.5%), or (3) BAL fluid culture >10^4 colony-forming units/mL of a respiratory bacterial pathogen requiring change from usual empiric antibiotics.

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INTRODUCTION

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Irrespective of the likely etiology, flexible bronchoscopy (FB) is recommended by some to exclude a foreign body or obstructive lesion.\(^2,7\) In addition, bronchoalveolar lavage (BAL) performed during FB allows collection of airway specimens for microbiologic analyses and examination of inflammatory cell types. There is increasing evidence to support the use of airway cellularity in guiding clinical management, particularly if airway eosinophilia is present.\(^8-10\) However, FB is an invasive procedure, adds to the cost and demand for health services and may not be easily accessible (particularly for those living in rural regions). Furthermore, some authorities only recommend FB when bronchiectasis affects a single lobe and a foreign body needs to be excluded.\(^11\) Although Australian and New Zealand guidelines recommend FB as a standard investigation for children with bronchiectasis,\(^2\) there are no data published to support this. Given the contrary\(^2,11\) recommendations, we examined the contribution of FB and BAL to the initial clinical management of children in our settings undergoing investigations for bronchiectasis and chronic suppurative lung disease (CSLD).
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cHRCT scans were performed under general anesthesia, followed immediately by FB (3.8 mm external diameter) as described previously. Radiographic diagnosis of bronchiectasis was made by the attending pediatric respiratory physician (AC) or pediatrician (PB) using standard published
criteria (inside bronchial diameter-to-adjacent artery ratio > 1). BAL followed European Respiratory Society guidelines and was obtained from the most abnormal lobe identified by FB or cHRCT scans. Two aliquots of sterile normal saline (1 ml/kg, max 10ml for the first and 2ml/kg, maximum 20mL, for the second aliquot) were instilled into the lobe and suctioned immediately into a mucus trap. The mean BAL return was 47%. The first aliquot was used for microbiologic analysis, the second for cytology. Specimens were placed on ice and sent immediately to the Laboratory for processing. Total and differential cell counts were performed on unfiltered BAL. A hemocytometer determined total cell counts. Cytoslides were prepared with a Cytospin 4 (Thermo Scientific), loading approximately 5x10^4 cells per slide and stained with Quick Dip (Fronine, Australia). The macrophage, neutrophil, lymphocyte and eosinophil percentages were calculated from a total count of 300 cells.

Routine microbiologic investigations for respiratory bacterial pathogens, including culture for \textit{Haemophilus influenzae}, \textit{Streptococcus pneumoniae}, \textit{Moraxella catarrhalis}, \textit{Staphylococcus aureus}, \textit{Pseudomonas aeruginosa} and \textit{Klebsiella pneumoniae}, and staining and culture for mycobacterial and fungal pathogens, were performed by the Diagnostic Laboratory at the Royal Darwin Hospital. In addition, identification and quantification of \textit{H. influenzae}, \textit{S. pneumoniae} and \textit{M. catarrhalis} were performed by our research laboratory by published methods and the diagnostic threshold for a lower airway infection set at >10^4 colony-forming units (CFU)/mL of BAL.

**Definition of FB and BAL data altering clinical management**

We defined \textit{a priori} that data obtained from FB and BAL contributed to clinical management if any of the following were met: (1) identification of unsuspected airway obstruction (eg foreign body or airway lesion requiring additional intervention), (2) lower airway eosinophilia (BAL eosinophils
>2.5%) prompting treatment with inhaled corticosteroids, or (3) respiratory bacterial pathogens >10^4 CFU/mL requiring a change in therapy. Locally, oral amoxicillin-clavulanate or parenteral ceftriaxone are used by pediatricians empirically to treat children with either chronic suppurative lung disease or bronchiectasis.²

**Statistical analyses**

As the data lacked a normal distribution, medians and their inter-quartile range (IQR) were used for descriptive data, and non-parametric methods, including chi-square tests for dichotomous outcomes, Mann-Whitney U tests for continuous variables and Spearman’s r for correlation were employed for analyses. The sensitivity, specificity, negative and positive predictive values of a history of current wheeze (within the last 12-months) and peripheral blood eosinophilia (>1.5 x 10^9/L) for airway eosinophilia (>2.5%) were also calculated. A two-tailed P-value <0.05 was considered significant. Graph Pad Prism Software (California, USA) was used for most statistical calculations.
RESULTS

Clinical diagnosis

Bronchiectasis (cHRCT-diagnosis) was identified in 52 of the 56 (93%) children (Table 1). The 4 remaining children had CSLD, and as the Australian and New Zealand guidelines advocate that children with CSLD are managed similarly to those with bronchiectasis, the entire cohort is described below.

Findings from FB and BAL that altered clinical management

We identified 25 occasions where FB and BAL altered clinical management in 23 (41%) children with two children meeting two criteria (airway eosinophilia and either P. aeruginosa or K. pneumoniae). An unsuspected foreign body (chicken bone) in the left main stem bronchus was removed from a 5-year old Indigenous girl, but who then did not proceed to BAL. This particular child had at least a 3-year history of cough, had been hospitalized for pneumonia on 3 previous occasions and the cHRCT scan showed evidence of bronchiectasis in the left lower and right upper and lower lobes.

The mean BAL return was 47%. Lower airway infection (>10^4 CFU/mL) was diagnosed in 25/55 (45%) children. Lower airway infection rates were not significantly different between children taking (13/26; 50%) or not taking (12/29; 41%; P=0.52) antibiotics at the time of FB. Major pathogens included H. influenzae (n=16), S. pneumoniae (n=10) and M. catarrhalis (n=9) in 20 children. However, 5 (9%) required changes to their initial empiric antibiotic treatments as either P. aeruginosa (n=4) or K. pneumoniae (n=1) were identified in BAL fluid cultures. The 4 children identified with P. aeruginosa infection were aged 0.8-2.5 years and had bronchiectatic changes
involving 2-4 lobes. Neither mycobacterial nor fungal pathogens were isolated from any child in the study.

**Airway differential count**

BAL fluid eosinophilia (>2.5%) was the most common indication for changing clinical management. Nineteen children (34%) were identified with airway eosinophilia (Figure 1). The median (IQR) eosinophil percentage in BAL fluid was 1.3% (0.3-5.0). Median (IQR) values for neutrophils were 14.3% (6.7-47), lymphocytes 6.0% (2-12) and macrophages 66% (38-83), while the median (IQR) total cell count was 46 (25-80) x10^4 per ml of BAL fluid. The percentage of airway eosinophils was significantly correlated with the number of peripheral blood eosinophils, r= 0.49, P=0.0002 (Figure 2). Absolute airway eosinophil counts also correlated with number of peripheral blood eosinophils (r = 0.6886, P=<0.0001). However, a current history of wheeze and peripheral blood eosinophilia (>1.5 x10^9/L) were both unreliable predictors of airway eosinophilia (Table 2). Similarly, airway cellularity was not significantly different between children who were, or were not, receiving antibiotics at the time of FB [median (IQR) total cell counts, 0.44 (0.27-0.75) vs 0.47 (0.25-0.84) x 10^4 per mL of BAL fluid, P=0.87; neutrophil 10.6 (3.8-28.2)% vs 16.6 (8.2-51.2)% P=0.15; and eosinophil 1.3 (0.2-3.1)% vs 1.3 (0.3-5.9)% P=0.55 respectively].

After finding lower airway eosinophilia in 7 of the first 18 participants, the next 38 children (12 with airway eosinophilia) had strongyloides serology performed at the regional reference laboratory (PathWest Laboratory Medicine WA, Australia, IgG by EIA > 0.45 absorbance units). Five Indigenous children had positive strongyloides serology, which was accompanied by airway eosinophilia (Figure 2) and each child received anti-helminthic therapy. Strongyloides serology was either negative (n=6) or equivocal (n=1) in the remaining 7 children with airway eosinophilia.
Similarly, children without airway eosinophilia at BAL had negative strongyloides serology, except for one child with an airway eosinophil differential percentage of 2.3% who had equivocal serological results. Of the 5 children already receiving inhaled corticosteroids, 2 had airway eosinophilia, including one child who was seropositive for strongyloides.
DISCUSSION

This is the first study to prospectively evaluate the contribution of FB with BAL to the initial management of children with non-CF bronchiectasis or CSLD. In 41% of the 56 children studied, we found that FB with BAL led to a change in management by identifying lower airway eosinophilia and antibiotic-resistant respiratory pathogens and helped discover an unexpected inhaled foreign body. If we had included any respiratory infection instead of infection requiring a change from empiric antibiotics, and removal of mucous plugs during bronchoscopy as a therapeutic intervention, the yield of FB could have been even higher.

Airway eosinophilia is associated with several respiratory disorders and in adults with bronchiectasis, there is evidence of eosinophil activation. However, to our knowledge airway eosinophilia has not been reported previously in children with bronchiectasis. Published data on airway cellularity in children with bronchiectasis are limited, and to date, only neutrophilia has been described. The importance of finding eosinophilia is that sustained (>6-months) systemic and lower airway eosinophilia can be associated with end-organ damage. Also airway eosinophilia is used to help guide corticosteroid therapy in eosinophil-associated airway diseases. Even using a conservative cut-off of 2.5% as an indication to commence inhaled corticosteroids while waiting to investigate the underlying cause, we found that 34% (19 children) had clinically important airway eosinophilia. Importantly, both current wheeze and circulating eosinophilia were poor predictors of airway eosinophilia in these children. A sputum eosinophil count of 2-3% is considered the threshold for predicting a positive therapeutic outcome from inhaled corticosteroids. However, the threshold used for BAL specimens should be lower as direct comparisons between paired BAL and sputum samples indicate that BAL specimens have lower eosinophil counts than found in sputum, which may reflect dilution and sampling from peripheral...
rather than central airways.\textsuperscript{14} The upper threshold of BAL eosinophil values in pediatric controls (age range 0.16-14.5 years) is between 0\% and 1.19\% (75\textsuperscript{th} percentile).\textsuperscript{22,23} Published studies have used thresholds as low as 1.1\% to define airway eosinophilia or as high as 2\% to define eosinophilic pneumonia.\textsuperscript{22,24} However, in the absence of robust clinical data from randomized controlled trials using BAL, we chose a conservative threshold for therapeutic intervention. Our data suggest that airway cellularity to detect eosinophilia should be considered when investigating children for bronchiectasis. However, we do not advocate bronchoscopy is undertaken merely to detect airway eosinophilia particularly in selected situations where other simple, non-invasive means of detecting airway eosinophilia (such as exhaled nitric oxide measurement in children aged $> 4$ years) are available.

Several disorders are associated with peripheral blood and airway eosinophilia. In endemic regions parasitic infections are a common cause of circulating eosinophilia and may also result in respiratory symptoms.\textsuperscript{25} Strongyloides stercoralis is an intestinal nematode endemic to Northern and Central Australia\textsuperscript{26} and as part of its life cycle migrates to the lungs and airways. Helminths with a similar respiratory phase including Ancylostoma (hook worm) and Ascaris are now uncommon in Australian Indigenous communities.\textsuperscript{27} While infection can be associated with asymptomatic chronic disease, strongyloidiasis can also lead to significant morbidity and even mortality in Indigenous Australians.\textsuperscript{28} Although we were unable to test all children, our data suggest that infection with S. stercoralis may contribute to the airway inflammatory profile of some Indigenous children with bronchiectasis. Any contribution to airway inflammation potentially contributes to airway injury and bronchiectasis and should be investigated and treated when present, in our cohort. As this was a cross-sectional study, it is unknown whether the peripheral blood and lower airway eosinophilia observed was chronic or transient and if it responded to anti-helminthic or corticosteroid therapy.
Nevertheless, our data also suggest that strongyloidiasis does not fully explain the high prevalence of lower airway eosinophilia seen in this cohort. Moreover, other helminths that migrate through the lung as part of their life cycle are now uncommon in Australia. Allergic bronchopulmonary aspergilliosis (ABPA) is another recognized cause of airway eosinophilia. We did not test for Aspergillus-specific IgE, but Aspergillus was not detected in the BAL of any of these children. Furthermore, Aspergillus is very rare in children with non-CF bronchiectasis (none in 113 children), although it is well described in adults with bronchiectasis. Thus, the etiology of our novel finding of clinically important airway eosinophilia remains unknown, but requires further study as it may contribute to airway injury and severity of bronchiectasis.

The value of BAL for diagnosing respiratory infection in the pediatric setting is widely recognized. Non-typeable H. influenzae, S. pneumoniae and M. catarrhalis are the most commonly detected pathogens in children with bronchiectasis and this forms the basis for the choice of the initial empiric antibiotic therapy for respiratory exacerbations. However, when children with CSLD and bronchiectasis are deteriorating despite therapy, BAL cultures can help identify pathogens, such as P. aeruginosa, which require different antibiotics for adequate treatment. Similarly, exclusion of anatomical airway lesions and obstruction is also important as bronchiectasis and long-term pulmonary complications may occur in 25-60% of patients when the diagnosis of foreign body airway aspiration is delayed ≥30-days. If obtainable, sputum cultures are an alternative to those obtained by BAL from older children, particularly as a means of monitoring treatment. However, studies using sputum induction in children are restricted largely to subjects who are at least 6-years of age when it can be performed safely and successfully. The median age of children in this study was 2.2-years, with only 4 children over the age of 6 years and it was therefore not feasible to
include sputum culture in this study. As spontaneous sputum expectoration in young children is unusual, clinicians often have to rely upon FB when seeking suitable lower airway specimens.

The present study has several important limitations. In addition to its cross-sectional nature, only a limited number of investigations were performed to detect underlying causes of airway eosinophilia. We could not define ‘therapeutic response’ to the multitude of interventions given once the diagnosis was made. Although it is current ‘best practice’ to treat clinically important airway eosinophilia, there are no randomized controlled trial data in children on when and how airway eosinophilia should be managed. Also, as this study was conducted predominantly in Indigenous children from remote communities in Northern Australia, the findings, especially of airway eosinophilia, may not be directly applicable to other children with bronchiectasis, either in Australia or elsewhere. Another potential limitation is that although 81% of children of children in this study had multi-lobed bronchiectasis (33% with 3 or more lobes affected), we sampled from a single lobe, as is current practice in our setting. Studies in children with CF have shown that while airway inflammation can involve both lungs, the distribution of bacteria between both lungs and within lobes from the same lung is often uneven. It is possible therefore that a similar situation may exist in children with non-CF bronchiectasis and future consideration should perhaps be given to multi-lobe sampling, particularly in children with extensive bronchiectasis. This study does, however, Regardless, this study highlights the value of bronchoscopy in providing detailed, individualized data which can direct therapy, a finding which is applicable globally.

There is accumulating evidence that with early diagnosis and intensive therapy, bronchiectasis can be stabilized and lung function preserved. While the contribution of FB and BAL to the management of children with bronchiectasis or CSLD may seem self-evident, this study is the first
to provide evidence to support this recommendation. It also, raises important questions over the etiology and consequences of lower airway eosinophilia in children with bronchiectasis, which will require additional research.

ACKNOWLEDGMENTS

We thank the families who participated in this study. We thank Dr Brian Spain and the anaesthetic staff, Radiology and Pathology Departments of Royal Darwin Hospital for their support.

Conflict of interest: All the authors have no conflict of interest to disclose.
REFERENCES


FIGURE LEGENDS

Figure 1.
Distribution of eosinophils (a) and neutrophils (b) as a percentage of total airway leukocytes in bronchoalveolar lavage fluid from 55 children with bronchiectasis or chronic suppurative lung disease. The lower limit for clinically important airway eosinophilia (2.5%) is represented by the dashed line. The y axis is a split scale. Cytoslides of BAL show eosinophilia with neutrophilia (c) original x400 and neutrophilia (d) original x200.

Figure 2.
Scatter plot of eosinophil percentages in bronchoalveolar lavage fluid and absolute eosinophil counts in peripheral blood (n=54), r=0.49, P=0.0002. Open circles identify children with positive strongyloides serology (enzyme immunoassay >0.45 absorbance units). Thresholds for circulating and airway eosinophilia are shown by the dashed lines\textsuperscript{17,20,21}.
Table 1: Sociodemographic, clinical and radiographic characteristics of 56 children at the time of flexible bronchoscopy and bronchoalveolar lavage.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (range) age (years)</th>
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<tbody>
<tr>
<td>Median (range) age (years)</td>
<td>2.2 (0.8-9.8)</td>
</tr>
<tr>
<td>Males</td>
<td>32 (57%)</td>
</tr>
<tr>
<td>Indigenous Australian</td>
<td>52 (93%)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>41 (75%)</td>
</tr>
<tr>
<td>Current nasal discharge</td>
<td>33 (60%)</td>
</tr>
<tr>
<td>History of wheezing</td>
<td>29 (53%)</td>
</tr>
<tr>
<td>Previous</td>
<td>26 (47%)</td>
</tr>
<tr>
<td>Current (within the last 12-months)</td>
<td>17 (31%)</td>
</tr>
<tr>
<td>Respiratory hospitalizations &gt;2</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>Current antibiotic use*</td>
<td>26 (46%)</td>
</tr>
<tr>
<td>Current inhaled corticosteroids</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>≥ 2 doses conjugate pneumococcal vaccine</td>
<td>53 (95%)</td>
</tr>
<tr>
<td>CT scan evidence of bronchiectasis †</td>
<td>52 (93%)</td>
</tr>
<tr>
<td>No. of lobes involved:</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>2</td>
<td>25 (48%)</td>
</tr>
<tr>
<td>3</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>4</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>5</td>
<td>2 (4%)</td>
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</tbody>
</table>

CT, computed tomographic; * azithromycin 20, roxithromycin 1, trimethoprim-sulfamethoxazole 1, amoxicillin 4; † 51/52 were Indigenous Australian children, remaining 4 had chronic supplicative lung disease.
Figure 1. Distribution of eosinophils (a) and neutrophils (b) as a percentage of total airway leukocytes in bronchoalveolar lavage fluid from 55 children with bronchiectasis or chronic suppurative lung disease. The lower limit for clinically important airway eosinophilia (2.5%) is represented by the dashed line. The y axis is a split scale. Cytoslides of BAL show eosinophilia with neutrophilia (c) original x400 and neutrophilia (d) original x200.
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Table 2: Current wheeze and peripheral blood eosinophilia as predictors of airway eosinophilia

<table>
<thead>
<tr>
<th></th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Wheeze</td>
<td>28 (11, 54)</td>
<td>59 (39, 76)</td>
<td>29 (11, 56)</td>
<td>56 (38, 74)</td>
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<tr>
<td>(in last 12-mths)</td>
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<tr>
<td>Blood eosinophilia</td>
<td>73 (39, 93)</td>
<td>74 (59, 86)</td>
<td>42 (21, 66)</td>
<td>91 (75, 98)</td>
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<td>(1.5x10^9/L)</td>
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PPUL-11-0337_ResponseToReviewers_Appendix2, showing a slice of HRCT scan which was reported by local radiologist as "no bronchiectasis". However, this CT was interpreted as having bronchiectasis in LLL and borderline bronchiectatic changes in RLL by the paediatric pulmonologist, taking into account the child’s clinical history as well. This highlights the disparity of opinions on CT reporting by adult-based radiologist compared to paediatric specialists.

This image is a supplement to the the response to Reviewer 2, comment 2 only and is not for publication.