Non-Cystic Fibrosis Bronchiectasis in Children

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Doctorate of Medicine (M.D.)

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The Charles Darwin University in September 2011

Institute of Advanced Studies
Declaration by author

I hereby declare that the work herein, now submitted as a thesis for the degree of Doctor of Philosophy of the Charles Darwin University, is the result of my own investigations, and all references to ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree, and is not being currently submitted in candidature for another degree.

Nitin Kapur
Statement of contributions to jointly authored works contained in the thesis


Drs Kapur and Karadag contributed to review outline and concept. Dr Kapur contributed by undertaking literature search. Drs Kapur and Karadag contributed to the drafting of the article.


Drs. Kapur, Masters, Masel and Chang contributed to the study concept and design. Ms Watson contributed by performing HRCT reconstruction from raw data. Drs. Kapur and Masel performed bronchial and arterial diameter measurements. Drs Kapur and Chang contributed to the analysis and interpretation of the data. Drs. Kapur, Masters, Chang, Masel and Ms Watson contributed to the drafting of the article.


Drs. Kapur, Masters and Chang contributed to the study concept and design. Dr Kapur collected all the data. Drs Kapur and Newcombe contributed to the analysis and interpretation of the data. Drs. Kapur, Newcombe, Masters and Chang contributed to the drafting of the article.

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Drs. Kapur, Grimwood, Masters and Chang contributed to the study concept and design. Dr Kapur collected all the data. Drs Kapur and Grimwood contributed to the analysis and interpretation of the data. Drs. Kapur, Grimwood, Masters, Morris and Chang contributed to the drafting of the article.


Drs. Kapur, Masters and Chang contributed to the study concept and design. Dr Kapur collected all the data. Drs Kapur and Chang contributed to the analysis and interpretation of the data. Drs. Kapur, Masters and Chang contributed to the drafting of the article.

Drs. Kapur, Masters, Morris and Chang contributed to the study concept and design. Mr. Galligan contributed in serum IL6, precalcitonin and amyloid A measurements. Drs Kapur, Masters and Chang contributed to data collection. Dr. Kapur, Dr. Chang and Mr. Ware contributed to the analysis and interpretation of the data. Drs. Kapur, Masters, Chang, Morris and Mr. Ware and Mr. Galligan contributed to the drafting of the article.


Drs. Kapur, Masters and Chang contributed to the study concept and design. Dr Mackay contributed in nasopharyngeal aspirate polymerase chain reaction (PCR) for respiratory viruses. Dr Kapur collected all the data. Drs Kapur and Chang contributed to the analysis and interpretation of the data. Drs. Kapur, Masters, Sloots, Mackay and Chang contributed to the drafting of the article. This work has been submitted to Thorax and awaits editorial decision.


Dr Chang was responsible for independent review of studies identified, independent data extraction and assessment of quality of studies independently. Dr Kapur was also responsible for independent review of studies identified, independent data extraction and assessment of quality of studies independently as well as the meta-analysis, literature
review and writing of manuscript. Drs Bell and Kolbe were responsible for reviewing the manuscript and the statistics.


Dr Chang was responsible for independent review of studies identified and assessment of quality of studies independently. Dr Kapur was also responsible for independent review of studies identified and assessment of quality of studies independently as well as the literature review and writing of manuscript.
List of Publications relevant to the Thesis


Presentation by the candidate relevant to the thesis

1. Presenting at the 2011 Queensland Royal Australian College of Physicians (RACP) Paediatric Advanced Trainee Presentations, Brisbane Powerhouse, breakfast session in October 2011; Oral Presentation on Defining Exacerbations in Non-Cystic Fibrosis Bronchiectasis.

2. Presented at the Queensland Children’s Medical Research Institute’s (QCMRI) Annual Student Expo in August 2011 and was awarded the “Best Oral Presentation” award as well as the “Student Researcher of the Year” award.


6. To present at the TSANZ ASM, Perth 2011; Poster presentation: Role of Respiratory Viruses in Exacerbations of Non-Cystic Fibrosis Bronchiectasis in Children.


8. APSR ASM, Manila 2010; Oral presentation: Bronchoarterial ratio on High Resolution CT scan of the chest in children without pulmonary pathology—Need to redefine bronchial dilatation.

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Abstract

Introduction

Non Cystic-Fibrosis (CF) bronchiectasis is recognised as an important cause of chronic respiratory morbidity in developing countries and in Indigenous people of affluent countries. Over the last decade, it is also increasingly diagnosed and recognised as an important cause of respiratory illness in the non-Indigenous populations of affluent countries. Yet it is a neglected condition with gaps in knowledge in major clinical issues pertaining to its diagnosis, management and outcome, especially in regard to pulmonary exacerbations.

Aims

The specific aims of this thesis were:

1. To determine the range of bronchial to accompanying arterial diameter ratio in children undergoing multi-detector Computed Tomography (MDCT) of the chest for non-pulmonary conditions.
2. To examine the burden of disease and psychological influences (anxiety, depression, stress) in parents of children with bronchiectasis and to assess the magnitude of changes in these parameters with pulmonary exacerbations.
3. To study the determinants of changes in the lung function and growth parameters in children with bronchiectasis over a three and five year period.
4. To describe the microbiologic and cellular constituents of BAL fluid at the time of diagnosing bronchiectasis.
5. To ascertain the clinical and investigational features of pulmonary exacerbations in bronchiectasis.
6. To formulate a robust, clinically relevant, repeatable and easy to use definition of pulmonary exacerbation in children with bronchiectasis.
7. To identify and determine the point prevalence of respiratory viruses associated with pulmonary exacerbations in children with bronchiectasis.

8. To perform systematic reviews using Cochrane methodology to evaluate the efficacy of inhaled corticosteroids (ICS) and non-steroid anti inflammatory drugs (NSAIDs) in children and adults with bronchiectasis.

Methods

Broncho-arterial ratio study

Children undergoing MDCT chest for non-pulmonary conditions were prospectively identified. Airway and vessel diameters were measured in the upper and lower lobes of both lungs. Mean broncho-arterial (BA) ratio was calculated and its correlation with age assessed.

Prospective bronchiectasis cohort study

A cohort of 69 children with non-CF bronchiectasis was prospectively followed for 900 child-months. The changes in clinical, systemic and lung function parameters with exacerbations were statistically evaluated to formulate a definition of a pulmonary exacerbation. The parents completed two questionnaires [parent-proxy cough-specific QOL (PC-QOL) and Depression, Anxiety and Stress scale (DASS)] in stable and exacerbation states. Polymerase chain reaction (PCR) for respiratory viruses was performed on nasopharyngeal-aspirates collected during exacerbations.

Longitudinal lung function study

Children with ≥3-years of lung function data were retrospectively reviewed. Changes in annual anthropometry and spirometry at year-3 and year-5 from baseline were analysed. The impact of gender, age, aetiology, baseline FEV₁, exacerbation frequency, extent of radiological changes, socio-economic status, environmental tobacco smoke exposure and period of diagnosis was evaluated.

Bronchoalveolar lavage (BAL) fluid study
Microbiology and cellularity of BAL fluid was analysed retrospectively at diagnosis of bronchiectasis.

Results

The mean (SD) BA ratio on HRCT chest of children with non-pulmonary conditions was 0.626 (0.068), significantly lower than that in adults. Pulmonary exacerbations caused significant worsening in the burden of disease and parental depression, anxiety and stress in children with non-CF bronchiectasis. In this group, wet cough and cough severity (score ≥2) over 72-hours were the best predictors of an exacerbation with area under the curve (AUC) of 0.85 (95% CI 0.79-0.92) and 0.84 (95% CI 0.77-0.91) respectively. Sputum colour, chest pain, dyspnoea, haemoptysis and chest signs were significant though minor criteria. Inclusion of serum C-reactive protein, amyloid-A and IL-6 to the definition improved its specificity. Respiratory viruses were associated with 48% of exacerbations, with human rhinovirus being the most common virus implicated. Lung function and anthropometric parameters remained stable over a 3 and 5 year follow-up period once appropriate therapy was initiated. At diagnosis, 68% children had positive BAL fluid cultures for respiratory bacterial pathogens with *Haemophilus influenzae* being the most common. In contrast, *Pseudomonas aeruginosa* was rare, while mycobacterial and fungal species were absent.

Conclusions

In the paediatric age-group, the airway is significantly smaller than the adjoining vessel. Using the radiological criteria of BA ratio greater than one to define bronchial dilatation, as is done in adults, would under estimate the presence and extent of bronchiectasis leading to delayed and missed diagnosis. There is a significant burden of disease on parents of children with bronchiectasis that gets worse with exacerbations. Pulmonary exacerbation in children with non-CF bronchiectasis can be validly predicted using a standardised assessment of clinical features, with additional systemic markers improving predictive values. Respiratory
viruses are commonly found during pulmonary exacerbations of children with bronchiectasis. Spirometric and anthropometric parameters in children with non-CF bronchiectasis remain stable over a 3-5 year follow-up. BAL fluid microbiology of children with bronchiectasis differs from adults with rates of *P. aeruginosa*, mycobacterial and fungal species being substantially lower.

**Keywords:**

Biomarkers, bronchoalveolar lavage, bronchiectasis, bronchoarterial ratio, burden, definition, exacerbation, HRCT chest, quality of life, viruses, microbiology, spirometry
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BA</td>
<td>Broncho-arterial</td>
</tr>
<tr>
<td>BAL</td>
<td>Bronchoalveolar Lavage</td>
</tr>
<tr>
<td>BE</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BO</td>
<td>Bronchiolitis obliterans</td>
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<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony Forming Units</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DASS</td>
<td>Depression Anxiety and Stress</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusing capacity of the lung for carbon monoxide</td>
</tr>
<tr>
<td>ETS</td>
<td>Environmental Tobacco Smoke</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>Forced expiratory flow midexpiratory phase</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in the first second</td>
</tr>
<tr>
<td>FTT</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>HBoV</td>
<td>Human bocavirus</td>
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<tr>
<td>HCoV</td>
<td>Human coronavirus</td>
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<tr>
<td>HEV</td>
<td>Human enterovirus</td>
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<tr>
<td>hMPV</td>
<td>Human Metapneumovirus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HPIV</td>
<td>Human parainfluenza virus</td>
</tr>
<tr>
<td>HRCT</td>
<td>High Resolution computerised tomography</td>
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<tr>
<td>HRQOL</td>
<td>Health related quality of life</td>
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<tr>
<td>HRV</td>
<td>Human rhinovirus</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>High sensitivity C-reactive protein</td>
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<tr>
<td>ICS</td>
<td>Inhaled Corticosteroids</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IOS</td>
<td>Impulse Oscillometry System</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MDCT</td>
<td>Multi-detector computerised tomography</td>
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<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
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<tr>
<td>MPI</td>
<td>Myocardial Performance Index</td>
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<tr>
<td>NPA</td>
<td>Nasopharyngeal aspirate</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>NSAID</td>
<td>Non Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>NTM</td>
<td>Non-tuberculous Mycobacterium</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
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<tr>
<td>OR</td>
<td>Odd’s Ratio</td>
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<tr>
<td>PCD</td>
<td>Primary Ciliary Dyskinesia</td>
</tr>
<tr>
<td>PC-QOL</td>
<td>Parent proxy cough specific quality of life</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>PCT</td>
<td>Procalcitonin</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
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<tr>
<td>RSV</td>
<td>Respiratory Syncytial virus</td>
</tr>
<tr>
<td>SAA</td>
<td>Serum Amyloid A</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>TCC</td>
<td>Total cell count</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis factor</td>
</tr>
<tr>
<td>UIP</td>
<td>Usual Interstitial Pneumonitis</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>USD</td>
<td>United States dollar</td>
</tr>
<tr>
<td>WCC</td>
<td>White Cell Count</td>
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</table>
Introduction and Literature Review

1.1 An overview of bronchiectasis

Bronchiectasis is a pathological state of the conducting airways manifested by radiological evidence of bronchial dilatation and clinically by chronic productive cough.\textsuperscript{1,2} The hallmarks of bronchiectasis are stasis of infected airway secretions; reduced airway mucus clearance; and regional or diffuse airway wall dilatation, thickening and destruction with loss of airway structural integrity.\textsuperscript{3-5} Such damage is the result of a vicious cycle of inflammation and infection arising from a number of causes either inherited or acquired.\textsuperscript{6} Bronchiectasis is associated with a prolonged neutrophilic inflammatory and secretory response within the airways, producing a “wet” sounding cough in young children\textsuperscript{7} and mucopurulent sputum expectoration in older children. When bronchiectasis is localised, it can produce recurrent cough and infectious exacerbations, or it may be diffuse, resulting in additional generalised
airway obstruction and destruction that may eventually lead to respiratory failure.\textsuperscript{1} Though pathological changes of bronchiectasis are usually considered irreversible, recent data suggests that there is a potential for reversibility of radiological changes in some children if appropriate treatment is offered in a timely manner.\textsuperscript{8,9}

Bronchiectasis is diagnosed by characteristic airway features seen on high-resolution computerised tomographic (HRCT) scans of the chest.\textsuperscript{10-12} The most important cause of clinically significant bronchiectasis in North America, Europe and Australia is Cystic Fibrosis (CF).\textsuperscript{1} Other causes of bronchiectasis, unrelated to CF, constitute a diverse and important yet neglected group of disorders that come under the umbrella of non-CF bronchiectasis. The focus of this dissertation is non-CF bronchiectasis and all references to bronchiectasis imply non-CF bronchiectasis, unless otherwise specified.

1.2 Burden of disease

1.2.1 Epidemiology and Prevalence

Improved hygiene and nutrition, better vaccine coverage and early institution of antibiotic therapy have all been instrumental in the decline of bronchiectasis prevalence in the developed countries, making it an “orphan disease”.\textsuperscript{13,14} It continues to be an important cause of respiratory morbidity in developing countries\textsuperscript{15-22} and Indigenous and socially disadvantaged populations of the affluent countries.\textsuperscript{8,23-26} In the last decade though, there has been renewed clinical and research interest\textsuperscript{8,27,28} and increasing incidence\textsuperscript{29,30} of this ignored condition in the developed world as well.
In the later part of last century, the prevalence of bronchiectasis was reported to be declining in the affluent world with a reported decline in incidence from 48/10,000 people in 1940 to 10/10,000 people in 1960.\textsuperscript{31} Similarly, in a longitudinal report from Finland,\textsuperscript{32} Saynajakangas and colleagues reported a decline in bronchiectasis treated in hospital from 143 admissions per million inhabitants in 1972 to 87 admissions per million inhabitants in 1992. The admissions, new occurrences and the days in hospital all decreased, at annual rates of 1.3, 4.2 and 5.7\%, respectively. Thus, where the number of new occurrences was 50 per million persons in 1977, it was 27 per million in 1992. These trends have been attributed to effective treatment of pulmonary infections, vaccination against measles and the reduction in tuberculosis.

More recently though, the rate of bronchiectasis-associated hospitalisation\textsuperscript{29} and mortality\textsuperscript{30} in adults has been increasing. The bronchiectasis hospitalisation data from 12 states in the United States from 1993 to 2006\textsuperscript{29} suggested that the age-adjusted rate increased significantly, with an average annual percentage increase of 2.4\% among men and 3.0\% among women. The median cost for inpatient care was US$ 7,827 (range, US$ 13-543,914). Further, between 2001 and 2007, 5745 bronchiectasis related deaths were registered in England and Wales.\textsuperscript{30} When standardised to the 2007 population, this showed an increase in absolute numbers from 797 (2001) to 908 (2007), a rise in mortality of 3\% per year. In a recent study from Japan,\textsuperscript{33} of the 1,409 adults (aged 23-86 years) on whom CT chest was performed as part of a health-screening program at a single health promotion centre, 129 (9.1\%) were diagnosed with bronchiectasis. It has been estimated that there are at least 110,000 adults in the United States with this condition.\textsuperscript{34} In addition, there is overlap with chronic
obstructive pulmonary disease (COPD), with two studies reporting an incidence of bronchiectasis in COPD as being 29% \(^\text{35}\) and 50%, \(^\text{36}\) respectively.

Longitudinal data on prevalence of bronchiectasis in children is limited to single-point estimates of paediatric prevalence from the affluent countries. These range from 1 in 6000 in the Auckland paediatric population \(^\text{25}\) to 1 in 5800 in the British paediatric population. \(^\text{8}\) The incidence of bronchiectasis has been reported to be 3.7/100,000 per year in under 15 years old children in the New Zealand cohort with calculated prevalence of 1 in 3000 children overall (twice that of CF) and 1 in 625 in children of Pacific Island ethnicity. \(^\text{26}\) The same study reported the incidence of bronchiectasis to be three times higher in Maori and twelve times higher in Pacific children compared with those of European ethnicity. Similarly, the Indigenous children from Central Australia have a much higher reported prevalence of 4.9 per 1000, \(^\text{24}\) which is similar to the rates reported from the Alaska paediatric population. \(^\text{23}\) Singleton and colleagues \(^\text{23}\) also reported that the prevalence of bronchiectasis in Alaska native children had been relatively stable for those born between the 1940s and 1980s, with a prevalence of approximately 11.0 per 1,000 persons among those born during the 1940s and 1950s, to 20.5 per 1,000 persons among persons born during the 1960s. Although similar data on incidence and prevalence is not available from the developing world, data from Indigenous and socially deprived population of the affluent world may be used as proxy. Even if we use the somewhat moderate estimate of prevalence such as 1 in 3000 children in the developing world, the burden of disease is potentially substantial.
In spite of the high prevalence of bronchiectasis in children and adults as described above, it remains a neglected condition. Further, it is likely that even these estimates are falsely low since a significant number of these children with chronic cough are misdiagnosed as “asthma” and do not reach a diagnostic conclusion either due to lack of facilities for CT scan of the chest in the non-affluent world, or just delay in referral of these “chronic coughers” to a respiratory specialist. This is reflected by demographic data suggesting that the age at diagnosis of bronchiectasis is significantly later than the age at initiation of symptoms. In a cohort of 105 children with bronchiectasis from Italy, the median age at diagnosis was 7 years though the children were symptomatic from the median age of 6 months. Similar delay in diagnosis have been reported in the British cohort of 93 children who were symptomatic from the first year of life but the diagnosis was made at more than 7 years of age. Epidemiological studies are needed to determine the incidence and prevalence of paediatric bronchiectasis in these regions. Also, data pertaining to the health related cost of managing children with bronchiectasis is needed. Further, there is no bronchiectasis related paediatric mortality data available from the affluent or developing world. The epidemiology of bronchiectasis is discussed in greater detail in Chapter 1B.

1.2.2 Pulmonary morbidity in bronchiectasis

Bronchiectasis is predominantly a disease of the lungs with pulmonary symptomatology constituting the major portion of disease burden, though it may have non-pulmonary co-morbidities associated with it. When the disease is localised to a single or few lobes, infectious exacerbations and recurrent cough are the major features and cause significant morbidity. Exacerbations may require hospitalisation.
resulting in increased health care cost and worsen the pulmonary morbidity. As the pulmonary involvement becomes more diffuse and severe, additional features of airflow limitation may develop. This may result in increasing symptoms, exercise limitation and eventually hypercapnic respiratory failure. Haemoptysis,\textsuperscript{15,18} chest deformity\textsuperscript{38} and chronic respiratory failure\textsuperscript{19,20} have all been commonly reported in some cohorts of children with bronchiectasis. The clinical features of bronchiectasis are discussed in detail in section 1.4.3 and chapter 1B; and the role of pulmonary exacerbation in worsening pulmonary morbidity in section 1.5.

While the best monitoring tool for pulmonary disease in bronchiectasis is yet undetermined, pulmonary function measurements and HRCT are the most objective parameters.\textsuperscript{3} While HRCT may be useful tool in following disease progression,\textsuperscript{39} the radiation (and reported increased cancer risk)\textsuperscript{40,41} associated with repeat scanning limits its use in children. As we considered it unethical to subject children to additional radiation for research purposes, repeated HRCT scans was not performed in studies within this thesis and will not be discussed as a tool for monitoring disease progression. However, the use of HRCT as a diagnostic tool in bronchiectasis is discussed in section 1.4.2.

Spirometry is generally considered insensitive in detecting early structural lung damage and disease progression\textsuperscript{42} though it still one of the most objective tools for monitoring the severity of bronchiectasis and is a commonly used measure in interventional trials.\textsuperscript{43,44} Moreover, low forced expiratory volume in the first second (FEV\textsubscript{1}) is one of the important predictor of poor quality of life in adults with bronchiectasis.\textsuperscript{45} Spirometric values may be normal in children with bronchiectasis,
but when an abnormality is present, it is classically obstructive in the earlier stages and later becomes a mixed obstructive and restrictive process. Banjar in a Saudi Arabian cohort reported lung function abnormality in 88% of the children with bronchiectasis (22% obstructed, 18% restrictive & 48% both). Similarly, the mean FEV₁ in a Turkish cohort was 63.3% of predicted and 68% of predicted in a Tunisian cohort. Among those with obstructive changes on spirometry, 45% to 70% have some component of airway reversibility with bronchodilators. Lung function abnormalities have been less prominent in cohorts from the affluent world. In a study of 105 children with bronchiectasis from Italy, Santamaria and colleagues reported the median FEV₁ to be 95% of predicted. Similarly, Twiss et al. reported a nearly normal lung function indices in 65 children with bronchiectasis from New Zealand. The use of conventional lung function measurements while non-invasive, is limited by their inability to achieve meaningful results in younger/uncooperative children. Respiratory impedance measurements by impulse oscillometry system (IOS) can potentially be used as a lung function parameter in younger children due to it being a simpler technique along with tidal breathing measurements, though there use is still limited to research settings.

In spite of its potential significance, paediatric data on longitudinal lung function is minimal with no information on factors that predict change in lung function over time. In 61 adults with bronchiectasis, King et al. have recently reported a progressive decline in FEV₁ and diffusing capacity of the lung for carbon monoxide (DLCO) over a 7 year follow-up. Adult data suggests that with early and intensive treatment, FEV₁ decline can be prevented. Other reported predictors of FEV₁ decline in adults with bronchiectasis are chronic colonization with Pseudomonas aeruginosa, frequency of severe exacerbations and systemic inflammatory markers.
Prior to commencement of studies in this thesis, there were no paediatric papers on the longitudinal pattern of FEV₁ in children with bronchiectasis. Hence a study was undertaken to evaluate the determinants of changes in the lung function and growth parameters in children with bronchiectasis over a three and five year period. The 2 papers that were published before paper 4.1 reported contradictory results and neither examined for multiple factors associated with respiratory function change. The British study (59 children over 2-yrs, 31 children over 4-yrs) found that with intensive treatment, lung function improves but does not necessary normalise. In contrast, the New Zealand study of 44 children over 4.5-yrs found that FEV₁ declined at 1.9% per annum. Further, no information was available on the factors that govern nutritional and/or lung function decline, if any, in children with bronchiectasis. Specifically, the impact of modern pulmonary treatment regimens, which are largely based on CF regimens, has not been well established on lung function parameters in childhood bronchiectasis.

Since paper 4.1 was published, a further study from the same group in New Zealand reported a mean FEV₁ decline of 1.6% predicted per year in 66 children with bronchiectasis, with reduced lung function associated with male gender, chronic Haemophilus influenzae infection, longevity of disease, and Maori and Pacific Island ethnicity.

1.2.3 Bronchiectasis and nutrition

In 1949, Field suggested that “Good nutrition and home conditions probably give the child a better chance of more complete recovery from lung damaging disease.” Poor nutrition (both macro and micro-nutrient) is known to effect childhood morbidity and mortality by affecting the innate and adaptive immune function and leads to the
malnutrition-infection-malnutrition cycle.\textsuperscript{57} Appropriate nutrition is important for both reduction of acute respiratory infections\textsuperscript{58,59} as well as maintaining good lung function in chronic suppurative lung disease\textsuperscript{60,61} though data on malnutrition specifically preceding bronchiectasis are limited and inconsistent. In bronchiectasis related to CF, optimal nutrition is important for reducing pulmonary decline.\textsuperscript{60,61} Low Body Mass Index (BMI) is known to increase long term mortality in adults with bronchiectasis,\textsuperscript{62} though its role in predicting the clinical course in paediatric disease is uncertain. Bronchiectasis itself predisposes to malnutrition as a result of chronic pulmonary infection causing diminished appetite and reduced caloric intake, and it is a common feature in bronchiectasis cohorts from under-privileged populations. Failure to thrive (FTT) was reported in 46\% of the 204 children with bronchiectasis in the Turkish cohort,\textsuperscript{21} and 75\% of the 65 children with bronchiectasis in the Indigenous population.\textsuperscript{24} In central Australia, children with bronchiectasis were three times more likely to have had malnutrition in early childhood before the diagnosis of bronchiectasis.\textsuperscript{63} In the 1960's, Clark reported similar prevalence of malnutrition in bronchiectasis with nearly half the children below the 10\textsuperscript{th} centile for height and weight.\textsuperscript{64} In contrast, malnutrition has been reported less frequently from the Alaskan cohort,\textsuperscript{23} and more recently from the affluent countries.\textsuperscript{52,65} High prevalence of breast feeding among the Alaskan native mothers\textsuperscript{66} and early detection and management among the affluent countries could be one of the reasons for this trend. A British study published before paper 4.1 reported normal anthropometric parameters in their cohort of 59 children with bronchiectasis.\textsuperscript{52} The growth was also normal over the follow-up period of 4 years.

1.2.4 Psychological burden of disease in bronchiectasis
Outcomes of children with bronchiectasis have traditionally been assessed with parameters such as pulmonary function and radiological extent\(^3\) though their correlation with clinical severity may be poor.\(^{24,67}\) Moreover, even the clinical measurements of disease do not always convey the true burden of illness for the child and family.\(^{68}\) Juniper therefore stated that “assessment of health-related quality of life should be an essential component of all clinical evaluations”.\(^{68}\)

In paediatric cohorts with chronic respiratory illness (asthma, CF, chronic cough), upper airway disease such as sinusitis/ otitis,\(^{69}\) recurrent doctor visits\(^{70}\) and high frequency of cough\(^{71}\) all serve to increase the burden of disease. Though bronchiectasis specific data from paediatric cohorts are missing, factors that govern quality of life (QOL) in adults with bronchiectasis include \textit{Pseudomonas aeruginosa} infection,\(^{72}\) dyspnoea, sputum production\(^{45}\) and frequency of exacerbation.\(^{73}\) Since chronic cough is an important and common feature of bronchiectasis, cough specific QOL parameters have been used in bronchiectasis cohorts.\(^{74}\) Factors such as exacerbations that make the cough worse are therefore likely to increase the burden of disease though there is no direct data available. Given the lack of data, a study (chapter 3, aim 2 of thesis) was undertaken to address this gap.

In addition to affecting the child, the family, and particularly the primary caregiver may face considerable burden due to the chronic illness,\(^{70,75}\) causing stress, anxiety and depression.\(^{76}\) These are important since maternal depression is an important factor in non-adherence to therapy and morbidity.\(^{77,78}\) In adults with bronchiectasis, elevated scores for anxiety and/or depression have been described in up to a third of patients.\(^{79}\)

Knowledge of the issues of burden of illness and psycho-morbidity are important for holistic patient/ family centred care which looks beyond treatment of the primary illness to maximize favourable outcomes. Addressing these psychological aspects are
likely to improve health, function and minimise the burden of illness.\textsuperscript{80} The lack of data on the burden of disease in bronchiectasis in children is an important gap in clinical knowledge on bronchiectasis.

1.2.5 Cardiac and other co-morbidities in bronchiectasis

Besides causing significant pulmonary morbidity, bronchiectasis has considerable non-pulmonary co-morbidities as well. The effect on growth and the psychological effects have already been addressed in section 1.2.3 and section 1.2.4.

Cardiac dysfunction, though uncommon in children with bronchiectasis, is an important cause of morbidity especially in adults with severe lung disease. In 15 adults with bronchiectasis, HRCT scores were strongly correlated with pulmonary artery pressure (regression $R = 0.59$, P value $= 0.001$),\textsuperscript{81} with nearly a third reporting echocardiographic features of pulmonary hypertension. Further, in 25 adults with bronchiectasis, the myocardial performance index (MPI), a sensitive parameter of both systolic and diastolic ventricular function, was significantly lower than age matched controls signifying early cardiac dysfunction in this cohort.\textsuperscript{82} The effect on children is more subtle with study on 21 children with bronchiectasis reporting normal left ventricular systemic function on echocardiography though some children had abnormal diastolic function that correlated with clinical disease severity.\textsuperscript{83} In addition, exercise capacity was decreased in most children.

Hypertrophic osteoarthropathy (clubbing, periostosis and arthritis-like features) is a common feature of bronchiectasis\textsuperscript{15,17,18,20} with reported incidence ranging from 5% to 50%. It has also shown to correlate with the radiological severity of the disease.\textsuperscript{38} Systemic amyloidosis has also been reported as a complication of bronchiectasis\textsuperscript{84-86}
causing renal failure in a few cases. Other reported co-morbid conditions associated with bronchiectasis are scoliosis, chronic middle ear disease, gastroesophageal reflux, social problems and developmental delay.¹

1.3 Pathology and Pathophysiology of bronchiectasis

1.3.1 Pathology and pathophysiology

Bronchiectasis is the end result of chronic airway inflammation and infection with resultant anatomical distortion and dilatation of the bronchi. The pathological features include neutrophilic inflammation, intra-luminal accumulations of secretions and obliteration of distal airway all causing alterations in sub-segmental bronchial structures.² There are additional changes ranging from peribronchial inflammation and fibrosis, distal atelectasis and pleural adhesions.¹ The initial trigger for the bronchiectasis process is unknown, though based on animal models, inadequate mucus clearance and persistent infection are considered necessary prerequisites.⁸⁷ It is well known that the lung is continuously exposed to inhaled pathogens and environmental pollutants. Persistence of microorganisms in the airways because of impaired mucus clearance or other host defence mechanisms may lead to a vicious circle of unrelenting inflammatory reaction and progressive lung damage.⁶ Cole proposed that an environmental insult often on a background of genetic susceptibility and impaired mucociliary clearance results in persistence of microbes in the sino-bronchial tree and microbial colonisation. The microbial infection causes chronic inflammation resulting in tissue damage and impaired mucociliary motility. In turn this leads to more infection with a cycle of inflammation causing progressive lung damage.
The current view is that the two factors required for the initiation and progression of bronchiectasis are persistent infection and a defect in host defence. This is supported by evidence of increased neutrophils and pro-inflammatory mediators in the airways and endobronchial biopsy of adults with bronchiectasis.\textsuperscript{88} Their bronchoalveolar lavage (BAL) fluid contains increased levels of inflammatory mediators such as neutrophil elastase, myeloperoxidase, tumour necrosis factor (TNF) $\alpha$ and interleukin 8 (IL-8).\textsuperscript{89} Dilatation of the bronchus is believed to result from a combination of factors including atelectasis induced negative intrapleural pressure on the wall of the bronchus already weakened by these lytic enzymes.\textsuperscript{14,90}

This inflammatory cycle is not only triggered but also sustained by concomitant infection with bacterial and viral agents. \textit{Pseudomonas aeruginosa} infection in particular is associated with increased morbidity in adult cohorts,\textsuperscript{91} though it is less prevalent in paediatric cohorts. More recently, non-tuberculous mycobacterium (NTM) and aspergillus related lung disease have been implicated in the pathogenesis of bronchiectasis in adults though there is no published data on the prevalence and significance of NTM in paediatric bronchiectasis.\textsuperscript{10,91,92} Data in adults with bronchiectasis reported high prevalence of NTM from the sputum of screened patients.\textsuperscript{93-95} One British cohort of 100 adults with bronchiectasis reported the prevalence of NTM to be 2%,\textsuperscript{94} and another cohort of 98 adults from a different centre in United Kingdom reported a prevalence of 10%.\textsuperscript{93} In 91 adults with bronchiectasis seen over 6 years in Hong Kong,\textsuperscript{95} a positive mycobacteria culture was obtained in 12 (13%) cases. NTM infection in bronchiectasis has also been reported to be associated with aspergillus-related lung disease in adults.\textsuperscript{92}
Despite the central role of infection and inflammation in the pathogenesis of bronchiectasis, there are few published paediatric studies on the lower airway microbiology and cellularity in bronchiectasis and on the organisms implicated in early disease progression. Most data are from older children with well established disease capable of providing sputum. Cross-sectional studies conducted in outpatient clinics or during an exacerbation report 40-67% of children with bronchiectasis have respiratory bacterial pathogens in their sputum and that Haemophilus influenzae and Streptococcus pneumoniae are the most commonly identified bacteria. As contamination of respiratory specimens by oropharyngeal flora is a concern, BAL fluid samples are the gold standard for evaluating lower airway microorganisms and inflammation in adults as well as in young children unable to expectorate sputum. The few available studies using BAL techniques to collect lower airway specimens from children with bronchiectasis have important limitations. Specifically, they have either been conducted in special populations, such as Indigenous children from remote communities in northern Australia where results may not be applicable to other bronchiectasis patients or BAL culture results have been combined with those from sputum cultures rather than being presented separately. Given the lack of data, a study (chapter 5, aim 4 of thesis) was undertaken to address this gap. Knowing the type of airway infection and inflammation in early bronchiectasis would not only help in the understanding of the pathogenesis of this chronic condition but would also have important management implications by facilitating appropriate anti-inflammatory and antibiotic therapy. Isolation of these micro-organisms from the lower airways early in the disease does not directly implicate them as the “disease initiator” but may link them to disease progression, specially since presence of certain organisms such as Pseudomonas aeruginosa predict higher morbidity in
Moreover, those with more severe bronchiectasis (earlier diagnosis, lower FEV$_1$ and varicose-cystic bronchiectasis) are more likely to be colonised with pathogens$^{100}$ and have more intense inflammation than those not colonised. $^{89}$ In this section, the pathophysiology of bronchiectasis has only been briefly described since this was not one of the main objectives of this thesis.

1.3.2 Aetiological risk factors of bronchiectasis

Bronchiectasis is the end result of a variety of airway insults and predisposing conditions that culminate in airway injury, recurrent or persistent airway infection and destruction. $^{101}$ Many paediatric case series, from both the affluent and the developing countries, have described in detail the underlying aetiology of bronchiectasis. As most patients are usually diagnosed with bronchiectasis after several years of symptoms, it is often difficult to prove causality in development of this condition. $^{14}$ A common feature of most patients is the impaired local and/or systemic host defences to infection. $^{102,103}$ In the non-Indigenous populations of affluent countries, primary immunodeficiency remains the most common cause accounting for 20% to 40% of the paediatric bronchiectasis. $^{8,27,28,104}$ Nikolaizik and Warner $^{104}$ reported 27% of the 41 children with bronchiectasis had underlying immunodeficiency. Post-infectious causes are more common in the Indigenous populations with up to 90% of bronchiectasis being attributed to previous infections. $^{23,24}$ Similarly, in non-affluent countries, bronchiectasis consequent to previous infections are more common, causing 17%$^{17}$ to 30%$^{15,18}$ of cases. Karadag et al. $^{15}$ reported significant past infection in 30% of their cohort, of which 8% had measles, 3% had varicella and 2% had tuberculosis. Primary ciliary dyskinesia (PCD) is also commonly reported as the predominant underlying cause of bronchiectasis in the affluent countries (15% to
24%\cite{27,28,104}, though it is rare in the developing countries and Indigenous populations (0% to 10%).\cite{15,18,20,22} In addition to the known causes of bronchiectasis, nearly a 30-50% have no apparent underlying cause found. Knowing the underlying aetiology in bronchiectasis is also important since it guides appropriate management\cite{27} and could facilitate improved outcomes. The aetiological risk factors for bronchiectasis are discussed in greater details in chapter 1B.

1.4 Diagnosis of bronchiectasis

1.4.1 What is the history of bronchiectasis diagnosis?

The histopathology of bronchiectasis was first described by Laennec in 1819\cite{105} though most studies on pathology of bronchiectasis were reported between 1930 and 1960 due to access to significant quantities of lung specimens at this time. Whitwell\cite{106} studied 200 consecutive operative lung specimens with bronchiectasis and demonstrated marked inflammation of the bronchial wall, principally in the smaller airways. Bronchial dilatation was characterised by deficiency/loss of elastin and more advanced disease by destruction of muscle and cartilage. There was variable bronchial wall fibrosis, atelectasis and peri bronchial pneumonic change. The diagnosis of bronchiectasis continued to be made based on pathology till Jean Athnanse introduced contrast bronchography in 1922, which allowed for images of the destructive changes seen in bronchiectasis. In the 1950's, Lynne Reid linked bronchography with pathologic specimens.\cite{107} Reid categorised bronchiectasis as having three main phenotypes: 1) tubular characterised by smooth dilation of the bronchi; 2) varicose where the bronchi are dilated with multiple indentations; and 3) cystic in which dilated bronchi terminate in blind ending sacs.\cite{108} Currently the gold standard of
diagnosing bronchiectasis is through data obtained from HRCT scan of the chest\textsuperscript{10-12} as discussed in the next section.

1.4.2 Radiological diagnosis

Plain chest radiographs are relatively insensitive in diagnosing bronchiectasis. In a study of 27 patients by Currie et al., the diagnosis of bronchiectasis by chest radiograph was present in only 40\% of those with proven bronchographic bronchiectasis.\textsuperscript{109} HRCT of the chest is now the gold standard for diagnosing bronchiectasis in which one of the key markers is increased bronchoarterial (BA) ratio.\textsuperscript{1,15} Other radiological features of bronchiectasis include peribronchial thickening, mucus plugging, failure of airway to taper normally while progressing to lung periphery, air trapping and sacculations.\textsuperscript{12,10,111} HRCT does not distinguish the aetiologies of bronchiectasis\textsuperscript{112} though adult studies have reported certain characteristic features in CF, allergic bronchopulmonary aspergillosis, and atypical mycobacteria infection.\textsuperscript{113} The advent of multi-detector CT (MDCT) scan has further enhanced this imaging capability by providing more comprehensive and precise information.\textsuperscript{114,115} However, the radiological definition of airway dilatation and bronchiectasis in children has substantial limitations\textsuperscript{7} since most criteria are still adult based.\textsuperscript{9} Since HRCT features in adults may not necessarily be equivalent to those in children as lung morphology changes with aging,\textsuperscript{116,117} the lack of paediatric criteria is an important knowledge gap in this area. Moreover, the adult criteria have been predominantly based on a study on 6 adults by Naidich and colleagues\textsuperscript{4} with bronchiectasis nearly three decades ago, whereby airways were considered dilated if their internal diameter was larger than the outer diameter of the adjacent pulmonary vessel i.e. the BA ratio of more than 1.\textsuperscript{5} However numerous subsequent studies on
asymptomatic adults have reported a much lower BA ratio, especially in younger adults.\textsuperscript{118-120} As BA ratio has been shown to increase with age,\textsuperscript{118} application of adult definitions to paediatric cohorts could underestimate the presence and extent of bronchiectasis. This issue has previously been raised by Eastham and colleagues\textsuperscript{8} who suggested that there is a group of children with chronic supplicative lung disease who do not have radiological features of bronchiectasis. This has important implications in terms of late and/or missed diagnosis of clinical syndrome of bronchiectasis in children, resulting in delayed initiation of treatment and increased morbidity. Another issue with CT diagnosis of bronchiectasis includes the need of two HRCT scans to truly fulfil the criteria of “irreversible dilatation”, something that may be unethical in children if done purely for diagnostic purposes, considering the increased risk of cancer due to the radiation.\textsuperscript{41} Also, CT scans performed in different clinical states such as in exacerbation may yield different results when compared with a so called “stable state”, both of which are difficult to define. This concern was raised by Gaillard et al.,\textsuperscript{9} who suggested that early bronchial dilatation might be reversible once appropriate treatment is initiated. In the Liverpool group,\textsuperscript{9} bronchial dilatation resolved completely in 6 of the 21 children with bronchiectasis post-medical treatment. Early diagnosis is important to a better clinical outcome in chronic respiratory disease such as CF\textsuperscript{121} and COPD.\textsuperscript{122} Ellerman and Bisgaard\textsuperscript{123} showed, in their cohort of people with primary ciliary dyskinesia, that adults who were diagnosed later had significantly worse lung function. Though direct evidence of such correlation in bronchiectasis is missing, establishment of appropriate therapy has been shown to stabilise lung function in children with bronchiectasis.\textsuperscript{52,65} Also, data suggests that radiological bronchiectasis can resolve with treatment,\textsuperscript{8,9} making timely diagnosis even more significant. A paediatric radiological definition of bronchiectasis
is therefore highly relevant in the context of detecting early changes on HRCT in children where changes may be subtle and often missed by using adult-based criteria. This issue is addressed in chapter 2 (Aim 1 of thesis).

1.4.3 Clinical features of bronchiectasis

The clinical case definition of bronchiectasis is imprecise and diagnosis based solely on clinical features may be inaccurate. Diagnosis of bronchiectasis should be suspected when a child has a chronic moist-sounding cough, exertional dyspnoea, recurrent wheezing and chest infections, haemoptysis, growth failure, digital clubbing, and/or chest wall deformity. Children with bronchiectasis typically have a preceding history of recurrent pulmonary infections and chronic cough. The cough associated with bronchiectasis is chronic in nature, is “wet” in character and may be associated with expectoration of purulent sputum in older children. The significance of sputum colour stems from the adult data suggesting high correlation between sputum colour and bacterial colonisation (5% in mucoid sputum; 43.5% in mucopurulent sputum; 86.4% in purulent sputum; p<0.0001) as well as severe radiological bronchiectasis and worse lung function parameters. Li et al. reported recurrent chest infection in 77% and chronic cough in 35% of their cohort. Clubbing, chest deformity and FTT are usually rare in cohorts from the affluent world, with less than 5% children showing features of FTT in the British cohort. Karadag et al. reported cough (81%), dyspnoea (49%), and wheeze (47%) as the most common presenting feature in their Turkish cohort, with clubbing present in 41% of the population. Similar features have been reported from Korea, Saudi Arabia, Tunisia and New Zealand though none of the studies have tried to differentiate the clinical features as baseline or in exacerbation. Digital clubbing and chest deformities,
markers of disease severity\(^3\), are common in the underprivileged population with 21%\(^1\) to 52%\(^2\) children reported to have clubbing. Haemoptysis (10% to 40%)\(^15,18\) and chronic respiratory failure (21% in Tunisian cohort\(^19\) and 23% in Saudi Arabian cohort\(^20\)) were a common feature in this population, though they have been relatively uncommon in the affluent populations. The clinical features of bronchiectasis are discussed in greater detail in chapter 1B.

As in other chronic pulmonary conditions such as asthma, CF and chronic obstructive pulmonary disease (COPD), children and adults with bronchiectasis have recurrent acute pulmonary exacerbations that impact the short and long term morbidity.\(^37,65,73,123\) Acute pulmonary exacerbations in bronchiectasis is discussed in detail under the following section.

### 1.5 Respiratory exacerbations of bronchiectasis

The importance of exacerbations (clinically and for research) is accepted for chronic respiratory disease such as asthma,\(^126-128\) CF\(^129,130\) and COPD.\(^131-135\) Recurrent acute pulmonary exacerbations form part of the disease progression in most children with bronchiectasis resulting in increased morbidity, hospital admission,\(^37\) health care cost and the burden of disease. Recurrent exacerbations may lead to progressive deterioration of lung function\(^123\) and is also one of the strongest predictors of poor quality of life in adults with bronchiectasis.\(^73\) Moreover, frequency of pulmonary exacerbations is being increasingly used as an outcome measure in many therapeutic trials on bronchiectasis and is a good clinical marker of disease severity and control.\(^44,136\) Despite its known significance, there are significant gaps in the knowledge and research pertaining to exacerbations in bronchiectasis. This includes
the lack of a standardised definition; minimal data on clinical features, effect on lung function, precipitants and the effect on the burden of disease.

1.5.1 Clinical features of an exacerbation in bronchiectasis

Though data on the overall clinical features of bronchiectasis is available from large case series, none of the published studies have carefully determined the clinical features associated with respiratory exacerbations of bronchiectasis in children. A significant contributory factor to this systematic lack of data is due to there being no standard definition of an exacerbation, as discussed in section 1.5.2. Increase in cough, sputum volume, increased sputum purulence, increased dyspnoea, deterioration in spirometry or chest signs have all been reported in adult studies as features of exacerbation. However, adult features of bronchiectasis differ significantly from paediatric cohorts since young children usually do not expectorate. None of the adult studies have considered cough character, specially a “wet” cough, as a feature of bronchiectasis exacerbation, a factor of immense significance in paediatric chronic suppurative lung disease. Presence of wet cough indicates presence of excessive airway mucus and therefore may be a proxy indicator of ongoing lower airway inflammation in the non-expectorating paediatric population. Moreover, whereas adult bronchiectasis is considered a disease of chronic cough and sputum production, clinical experience had suggested that children with bronchiectasis may be minimally symptomatic once stabilised on appropriate management, though at the time of starting this thesis, direct evidence to this was missing. Further, no information is available on clinical features that may predict exacerbation severity, treatment success or failure with oral or intravenous antibiotics or factors precipitating an exacerbation.
1.5.2 **What is the definition of exacerbation in paediatric bronchiectasis?**

Despite the significance of exacerbations in bronchiectasis, there is a lack of a standardised definition in the paediatric and adult literature with varying definitions across studies including in CF as highlighted by Mogayzel et al. In the current literature, definitions of exacerbations include changes in sputum and selected potential biomarkers and hospitalisations. As symptoms of bronchiectasis share features, and often co-exist, with COPD, the definition of exacerbation in COPD in adults by Anthonisen et al. has been extrapolated to bronchiectasis studies. These features included increased dyspnoea, sputum purulence and sputum volume. Anthonisen further graded these exacerbations into type 1 (all three cardinal symptoms), type 2 (two cardinal symptoms) and type 3 (one cardinal symptom plus one of the following: an upper respiratory tract infection in the past 5 days, fever without other cause, increased wheezing or cough, or an increase in heart rate or respiratory rate by 20% compared with baseline readings). Despite the fact that this is a non-validated definition, this definition has come into common use in COPD and even bronchiectasis. Moreover, extrapolation of an adult COPD definition on to paediatric bronchiectasis is even more inappropriate considering the notable differences the clinical and pathophysiological features in the two populations. Sputum-based criteria used in adults, as in the Anthonisen’s criteria, have low sensitivity and limited applicability in paediatrics non-expectorating population. Clinical scores alone (such as those used in CF) lack specificity. The need for therapeutic interventions and/or hospitalisation is arguably variable (as it is subjective) and limited to severe exacerbations. There are no studies on sputum or plasma biomarkers of exacerbation in children with bronchiectasis.
1.5.2.a Potential biomarkers of exacerbation

The fact that exacerbation in bronchiectasis remains a clinical diagnosis and the
difficulties inherent in assessing airway inflammatory markers in clinical practice
have led to the idea that systemic biomarkers (blood and/or lung function parameters)
may have clinical utility in diagnosis of an exacerbation of bronchiectasis, akin to
COPD exacerbation. In adults, serum procalcitonin (PCT) and amyloid A (SAA) show promise. PCT is a more specific and sensitive marker of bacterial infections that has been increasingly used in clinical practice. In the absence of infection, PCT, a precursor peptide from the hormone calcitonin, is restricted to predominantly the C-cells of the thyroid, where it is cleaved to form calcitonin and stored in secretory granules. In contrast, bacterial infection leads to a constitutive release of PCT from all parenchymal tissues of the body, causing increased serum levels. This up regulated calcitonin gene expression is thought to be mediated by the microbial toxins themselves, or via the cytokines of the cell mediated or antibody host response. Its sensitivity for defining a bacterial infection is further increased by the down regulation of calcitonin gene expression by cytokines related to a viral infection. Data from adult cohorts with bronchiectasis suggests that in spite of some correlation of severity of exacerbation with PCT, overall it has not been a useful marker of exacerbation when compared to CRP and is generally low in bronchiectasis.

SAA is an acute-phase protein induced by inflammatory mediators, including IL-6, IL-1β, and TNF-α. SAA is secreted from the liver as the predominant apolipoprotein associated with plasma high-density lipoprotein cholesterol. The human SAA gene family is comprised of four members: SAA1 and SAA2 are induced during inflammation or in response to tissue injury; SAA3 is a pseudogene; and SAA4 is
constitutively expressed. SAA has been found to be more sensitive than C-reactive protein (CRP) in acute exacerbation of COPD in adults with SAA levels of 7.7 mg/L in stable state compared to 57.6 mg/L during an acute exacerbation; p<0.01.

1.5.2.b Spirometry during exacerbations

Acute fall in lung function parameters, especially FEV₁, have long been clinically assumed to reflect deterioration in clinical state such as exacerbation, though direct data proving this in lacking in paediatric bronchiectasis. Further, its use in defining an exacerbation is limited in paediatric cohorts due to the reasons discussed in section 1.2.2. In COPD, FEV₁ declines with an acute exacerbation and improves with its treatment. Because in published literature, none of the systemic biomarkers and/or lung function parameters clearly distinguish an exacerbation from the stable state in bronchiectasis, it is imperative that a definition of exacerbation be a combination of clinical and investigational parameters. The usefulness of combining clinical and investigational parameters has been well established in COPD exacerbations, a condition much better researched. A standardised definition of pulmonary exacerbation is clinically important for treatment and as outcome for research studies. This would improve the quality of individual intervention trials and enhance comparison of results between studies and meta-analyses. An easy to use definition with both clinical and objective markers will advance the field of bronchiectasis, a relatively under-researched area.

1.5.3 Pathogenesis of acute pulmonary exacerbation in bronchiectasis

Bronchiectasis is considered a result of inflammatory and infectious damage to the airways. Acceleration of the same inflammatory and infectious process by various triggers is thought to be the underlying feature of an exacerbation. There are
multiple factors stepping up this inflammatory cascade, all of which can lead to further airway destruction and progression of disease, akin to the “Cole’s vicious circle hypothesis” described for the pathogenesis of bronchiectasis itself. Factors that can trigger these changes are discussed in the section 1.5.4. Inflammatory surges seen in exacerbation, play a role in clinical deterioration as well as lung function decline, though this has been well studied and described only in COPD.\textsuperscript{157} Sputum purulence, a surrogate marker of level of airway infection and inflammation,\textsuperscript{125,158} increases during exacerbations and decreases with treatment.\textsuperscript{159} Those with less purulent sputum in the non-acute state have a longer period before their next exacerbation.\textsuperscript{159}

Several groups have shown an alteration in inflammatory profile after treatment of an exacerbation, indirectly demonstrating the role of inflammation in the pathogenesis of an exacerbation. Courtney et al.\textsuperscript{139} in 18 adults with bronchiectasis reported that sputum cell count, IL-8, neutrophil elastase and IL-10 all reduced with treatment of an exacerbation. Ip and colleagues reported increased sputum neutrophil chemotactic activity and elastolytic activity during an exacerbation of bronchiectasis.\textsuperscript{160} Watt and colleagues\textsuperscript{161} also showed that concentrations of TNF α, IL-8 and neutrophil elastase in sputum supernatant were significantly reduced at day 14 of antibiotic therapy compared with initiation of treatment. The increase in inflammatory mediators during an exacerbation may result in an increase in bronchial wall thickness, luminal exudates and expiratory flow limitation; all of which contribute in the clinical spectrum of exacerbation. This inflammatory-clinical severity correlation is best researched in COPD with no direct evidence available in bronchiectasis.\textsuperscript{153,157}
1.5.4 What precipitates an exacerbation in bronchiectasis?

Triggers of bronchiectasis exacerbations have not been studied. In other chronic respiratory diseases\textsuperscript{162} (such as asthma,\textsuperscript{128,163} CF\textsuperscript{164,165} and COPD\textsuperscript{166-168}) respiratory tract infections, especially with respiratory viruses, are common precipitants of exacerbations. However, it is unknown what proportion of bronchiectasis exacerbations are triggered by an infection and if so, the type of infection. It is also unknown how often viral infections trigger an exacerbation. Other probable precipitants of exacerbation include pollution (environmental or occupational)\textsuperscript{140,153,169} tobacco smoke,\textsuperscript{170} biomass combustion,\textsuperscript{171} poor nutrition and overcrowding, though none of these have been directly implicated in bronchiectasis exacerbation. Despite the importance of viral precipitants of exacerbation and huge health care cost associated with it, there is no published prospective data. Knowing the prevalence of viral triggers of exacerbation in bronchiectasis would not only be an important epidemiological exercise as previously well documented in COPD;\textsuperscript{166,168} it could also potentially lead to understanding new patho-physiological mechanisms relevant for bronchiectasis, as Johnston et al. has shown for asthma.\textsuperscript{163,172} This data could also help in the judicious use of antibiotics and new anti-viral agents (such as neuraminidase inhibitors and monoclonal antibodies), as they become increasingly available.\textsuperscript{173} Further, virological data would also help in clarifying the role of vaccines such as the influenza vaccine in bronchiectasis.\textsuperscript{101}

Despite the importance of infection, other factors may provoke exacerbation. In the absence of data from children or adults with bronchiectasis, comparison with COPD is made. In a study of 1016 patients with severe COPD, infection was the proven cause in only 51\% of exacerbations, with heart failure accounting for 26\% and no
aetiology for the rest. \(^{174}\) Epidemiological studies have identified more exacerbations during periods of increased pollution. \(^{175}\) Increases in black smoke particulate matter, sulphur dioxide, ozone and nitrogen dioxide are associated with increases in respiratory symptoms, admissions for exacerbation, and COPD associated mortality. \(^{175}\) Pollutants have been shown to be pro-inflammatory in animal models. \(^{176}\) Studies in bronchiectasis are required to better characterise the infective and non-infective triggers of exacerbation.

1.5.5 How does acute pulmonary exacerbation affect the burden of disease in bronchiectasis?

In addition to the paucity of quantitative studies addressing the burden of disease on parents of children with bronchiectasis, there are no studies that have looked at acute changes in these parameters with pulmonary exacerbations. Recurrent exacerbations (in the preceding year) in adults have been reported to predict poor QOL in stable bronchiectasis \(^{73}\) though similar paediatric data and data on acute effects of exacerbation on burden of disease is unavailable. Further, in 15 adults with bronchiectasis, Courtney et al. reported a significant improvement in QOL scores after treatment of pulmonary exacerbations. \(^{139}\) Similar improvements have also been reported with treatment in adolescents with CF. \(^{177}\) It is therefore intuitive but conjectural, that QOL and burden of disease may acutely worsen during an exacerbation. Worsening in clinical symptoms such as dyspnoea and sputum production are associated with worsening QOL in adults with chronic respiratory illnesses. \(^{45,178}\) Acute events such as pulmonary exacerbations that aggravate symptoms are therefore likely to worsen the quality of life, though there is no direct evidence, specially in paediatric cohorts. Another challenge in assessing the effect of
exacerbation on burden of disease is quantifying clinically significant change in the QOL parameters.179

1.6 Why is this thesis about bronchiectasis in children?

Current literature has shown that bronchiectasis is increasingly being recognised as an important cause of respiratory morbidity in children of developed and developing countries. The above data summarises some of the current clinical gaps in paediatric bronchiectasis and highlights some differences between children and adults with bronchiectasis. This thesis addresses some of the major current gaps in the clinical knowledge in bronchiectasis particularly in relation to acute pulmonary exacerbations as discussed in this review (section 1.1 -1.5) through the following aims and hypothesis.

1.6.1 Hypothesis and Aims

The overarching aim of the thesis is to address some of the major current gaps in the clinical knowledge in paediatric bronchiectasis particularly pertaining to exacerbation.

The major hypothesis of this thesis is that children with bronchiectasis have different characteristics to adults including pulmonary exacerbations that can be defined by using a combination of clinical and investigational parameters.
Aims

The specific aims of the thesis are:

1. To determine the range of bronchial to accompanying arterial diameter ratio in children undergoing MDCT chest for non-pulmonary conditions.

2. To examine the burden of disease and psychological influences (anxiety, depression, stress) in parents of children with bronchiectasis and to assess the magnitude of changes in these parameters with pulmonary exacerbations.

3. To study the determinants of changes in the lung function and growth parameters in children with bronchiectasis over a three and five year period.

4. To describe the microbiologic and cellular constituents of BAL fluid at the time of diagnosing bronchiectasis and to evaluate the potential factors determining the risk of infection by lower respiratory pathogens.

5. To ascertain the clinical and investigational features of pulmonary exacerbations in bronchiectasis.

6. To formulate a robust, clinically relevant, repeatable and easy to use definition of pulmonary exacerbation in children with bronchiectasis.

7. To identify and determine the point prevalence of respiratory viruses (including newly-identified viruses) associated with pulmonary exacerbations in children with bronchiectasis.

8. To perform systematic reviews using Cochrane methodology to evaluate the efficacy of inhaled corticosteroids (ICS) in stable state bronchiectasis and in reducing the severity and frequency of acute respiratory exacerbations and long term pulmonary decline; and to assess the role of non steroid anti-inflammatory drugs (NSAIDs) on symptom control and natural history of the disease in children and adults with bronchiectasis.
1.7 Thesis Design

Studies were performed to address the specific thesis aims and in so doing address some of the gaps in knowledge previously outlined. In chapter 2, we have challenged the radiological definition of bronchial dilatation that forms the key to diagnosing bronchiectasis. This study is an essential step in understanding the differences in radiological features of bronchiectasis in children from adults through redefining the paediatric criteria for bronchiectasis.

Chapter 3 describes the burden of illness for parents of children with bronchiectasis is described and the presence of symptoms of depression, anxiety and stress in the parents is also evaluated. This is the first study to measure the parent perceived quality of life in a paediatric cohort of bronchiectasis and report how pulmonary exacerbations affect the burden of disease.

Chapter 4 evaluates the effect of disease on the growth and lung function parameters of children with bronchiectasis and the factors that determine the change in these parameters over the 3 to 5 year follow-up period. Since both anthropometric and lung function parameters could be used as outcome variables of chronic disease in paediatric cohorts, this study significantly adds to the knowledge on long term morbidity of bronchiectasis in children, specially after treatment is instituted.

Chapter 5 describes the role of lower airway infection and inflammation in early bronchiectasis by a retrospective analysis of BAL fluid in children with bronchiectasis. It also studies the factors that may predict infection of the airway with lower respiratory pathogens.
Chapter 6 forms the pilot study to determine the clinical features associated with a pulmonary exacerbation in a retrospective cohort of children with bronchiectasis. The data obtained from this study formed the basis of designing the prospective study to define an exacerbation in bronchiectasis, described in chapter 7.

Chapter 7 evaluates the various clinical, investigational and statistical steps undertaken to formulate a robust, clinically relevant, repeatable and easy to use definition of pulmonary exacerbation in children with bronchiectasis.

As part of the same prospective cohort which was followed up for over two years, we also looked at the respiratory viruses associated with a pulmonary exacerbation of bronchiectasis, the details of which constitute chapter 8. This is the first study to report role of viruses in triggering a pulmonary exacerbation in bronchiectasis.

One of the major clinical gaps on long term management of bronchiectasis and associated pulmonary exacerbations is the lack of randomised controlled trials (RCT) on role of preventer therapy. We therefore performed two Cochrane reviews of currently available RCT’s, the first addressing the role ICS in bronchiectasis and the second measuring the effect of NSAID in bronchiectasis. Both these Cochrane reviews constitute chapter 9.

The final chapter (chapter 10) summarises and discusses the thesis findings, relates it to other current work and discusses future research directions.
1.8 Summary of Chapter 1

Bronchiectasis is a well recognised, important and yet under-researched chronic respiratory illness that results in physical and psychological morbidity in children. It affects children in both affluent and developing countries. A review on the differences between these settings have been summarised in the paper that follows this chapter as chapter 1B.

This thesis addresses some of the major clinical gaps in our knowledge and understanding of bronchiectasis in children. Addressing these gaps will potentially lead to improving the clinical management of children with bronchiectasis. Specifically, the studies in this thesis explore and highlight the differences between children and adults with respect to radiologic evaluation, airway microbiology and cellularity, lung function data over 5 years and exacerbation data.
1B

Differences and similarities in non-cystic fibrosis bronchiectasis between developing and affluent countries
Bronchoarterial ratio on High Resolution CT scan of the chest in children without pulmonary pathology—
Need to redefine bronchial dilatation
2.2 Summary of Chapter 2

In this chapter we have challenged the current radiological definition of bronchial dilatation in children since adult criteria are still being extrapolated into paediatric clinical practice. Since bronchial dilatation is the hallmark of bronchiectasis, our study also reviewed the radiological definition of bronchiectasis in children.

We prospectively identified 41 children who were undergoing MDCT of the chest for non-pulmonary conditions, most commonly as part of oncological work-up. We calculated the mean BA ratio for each child and reported our paediatric normative data. We concluded that the BA ratio in children is significantly lower than 1 [Mean (SD) 0.626 (0.068)], the cut-off usually taken to define bronchial dilatation in adults. This ratio in children was also significantly lower than similar normative data available from adults. We did not find any correlation with age in our cohort. Our study has highlighted the need to re-define the criteria for bronchial dilatation in children.
The burden of disease in paediatric non-cystic fibrosis bronchiectasis
3.4 Summary of Chapter 3

In this chapter we reported the burden of disease in a cohort of 69 children with bronchiectasis followed prospectively over 900 child-months. Burden was measured by parent-proxy cough-specific QOL (PC-QOL) and Depression, Anxiety and Stress scale (DASS) in stable and exacerbation states. We ascertained that there was a significant burden of disease, especially during exacerbation, on parents of children with bronchiectasis. We reported that factors such as radiological extent, lung function and underlying etiology did not affect the burden.
Longitudinal growth and lung function in paediatric non-CF bronchiectasis — what influences lung function stability?
4.3 Summary of Chapter 4

At the time of commencement of studies for this thesis, the longitudinal lung function data in children with bronchiectasis were unavailable. It was also unclear if lung function parameters in this group continue to decline as had been reported in CF cohorts. Moreover there was no published data on effect of disease on anthropometric parameters. In this chapter we described the lung function and anthropometric parameters in 52 children with bronchiectasis over a 3 year period and over 5 years in 25 children. We concluded that lung function and anthropometric parameters are stable in this group over 3-5 years once appropriate treatment is initiated. We also established that severe exacerbations are associated with accelerated lung function decline.
Lower airway microbiology and cellularity in children with newly diagnosed non-CF bronchiectasis
5.2 Summary of Chapter 5

It is well known that infection and inflammation form key elements in the pathogenesis and progression of bronchiectasis though data is very limited in paediatric population. In this chapter we described the lower airway microbiology and cellularity at diagnosis of bronchiectasis in a retrospective review of BAL fluid in 113 children. We found that 68% children had infection with respiratory bacterial pathogens at diagnosis with *Haemophilus influenzae* being the most common pathogen. Respiratory viruses were identified in 12% children. *Pseudomonas aeruginosa* was rare while mycobacterial and fungal infection were absent. Children also had marked airway neutrophilia, especially with higher bacterial loads.
Exacerbations in non cystic fibrosis bronchiectasis: Clinical features and investigations
6.2 Summary of Chapter 6

In this chapter we described the clinical features of 115 paediatric pulmonologist defined exacerbations in a retrospective cohort of 30 children with bronchiectasis. We also studied the factors that predict failure of treatment with oral antibiotics. In the absence of available data, this study was done as a “pilot” project to gather information for designing our larger prospective cohort study on defining an exacerbation in bronchiectasis (described in chapter 7). We reported that increase in frequency of cough and a change in its character were the most common symptoms associated with an exacerbation. Nearly a third of the exacerbations failed to resolve with oral antibiotics and required hospital admission. Those on prophylactic antibiotics were more likely to fail oral antibiotic therapy for acute exacerbation.
7

Defining Pulmonary Exacerbation in Children with Non-Cystic Fibrosis Bronchiectasis
7.3 Summary of Chapter 7

The lack of a validated definition of pulmonary exacerbation in paediatric bronchiectasis is a limitation for clinical practice and research. This chapter described the process of prospectively formulating a robust, clinically relevant, repeatable and easy to use definition of pulmonary exacerbation in children with bronchiectasis. In 69 children with bronchiectasis who were followed for 6-30 months; changes in clinical, systemic and lung function parameters from 81 exacerbations were statistically evaluated using conditional logistic regression, receiver operating characteristic (ROC), sensitivity, specificity and positive (PPV) and negative predictive values (NPV) to formulate a definition of a pulmonary exacerbation.

The results presented in this chapter have described three options for definition of an exacerbation useful for different clinical (primary vs. tertiary care) and research settings. These three options were formed by combination of major (wet cough and cough severity), minor clinical (sputum colour, chest pain, dyspnoea, haemoptysis and chest signs) and investigatory (serum C-reactive protein, amyloid-A and IL-6) criterion. Our final combined model consisted of one major with one investigatory criterion (PPV 91%, NPV 72%); two major criteria (PPV 79%, NPV 91%); or one major and two minor criteria (PPV 79%, NPV 94%).
Role of Respiratory Viruses in Exacerbations of Non-Cystic Fibrosis Bronchiectasis in Children
8.3 Summary of Chapter 8

In this chapter, we described prospectively the role of respiratory viruses (including newly-identified viruses) in pulmonary exacerbations in 69 children with bronchiectasis followed for 900 child-months. We reported that respiratory viruses were detected on nasopharyngeal aspirate during 48% of the exacerbations, with human rhinovirus-A being the most common virus detected. We also reported that virus-positive exacerbations were more likely to require hospitalisation and have fever, hypoxia, chest signs and raised C-reactive protein when compared with virus-negative exacerbations.
Role of preventer anti-inflammatory therapy in bronchiectasis
9.3 Cochrane review update

An update of the Cochrane review contained within chapter 9.1 has been completed. The review was updated with searches until October 2010. No new studies were eligible for inclusion and there were no changes made to the authors’ conclusions.

An update of the Cochrane review contained within chapter 9.2 has been completed. The review was updated with searches until January 2010. No new studies were eligible and there were no changes made to the authors’ conclusions.

9.4 Summary of Chapter 9

At the time of commencement of studies for this thesis, many Cochrane reviews on possible interventions were available. However the role of preventer therapy (ICS and NSAID’s) in bronchiectasis especially on exacerbation frequency was unclear. As the major aim of our thesis was to fill clinical knowledge gaps specially pertaining to exacerbation, the available evidence from management perspective was evaluated and systematically reviewed. As Cochrane methodology is currently the most accepted method of performing systematic reviews, this method was chosen to review the evidence. In section 9.1, we evaluated the efficacy of ICS in children and adults with bronchiectasis during stable bronchiectasis; and for reducing the severity and frequency of acute respiratory exacerbations and long term pulmonary decline. As asthma-like symptoms are common in people with bronchiectasis, the routine use of inhaled corticosteroids was considered as potentially beneficial in reducing exacerbations, symptoms and pulmonary decline. The review found that there was insufficient evidence for the routine use of ICS in people with bronchiectasis. While ICS may be beneficial in a subgroup of people with bronchiectasis, its use had to be
balanced with adverse effects that include a potential increase in commensal bacterial
density in the sputum. This review was completely rewritten, reanalysed with new
conclusions added, from a previous review by Ram and colleagues\textsuperscript{181} that had
included only two trials on a total of 54 patients.

In section 9.2, we assessed the role of NSAIDs on symptom control and natural
history of the disease in children and adults with bronchiectasis. No randomised
controlled trials that assessed the use of oral NSAIDs in bronchiectasis were found.
Thus the routine use of NSAIDs in bronchiectasis could not be recommended.
Conclusion

10.1 Discussion

Bronchiectasis is recognised as an important cause of chronic respiratory morbidity in developing countries\textsuperscript{15-21} and in Indigenous people of affluent countries.\textsuperscript{23,24} Over the last decade, it is also increasingly diagnosed and recognised as an important cause of respiratory illness in the non-Indigenous populations of affluent countries.\textsuperscript{8,25,26,28} In undertaking the studies for this thesis, the major gaps in the knowledge about bronchiectasis, especially pertaining to pulmonary exacerbations, were glaring.

Adult-based radiological criteria have been used to define and detect bronchiectasis in children although they had never been critically evaluated. Bronchiectasis was considered a disease of unrelenting deterioration in lung function akin to CF lung
disease with role of early intervention unclear in overall outcome. There was no standardised definition of exacerbation in children or adults leading to inconsistent outcomes both clinically and in research. Further, there was no data available on the clinical features, investigational outcomes, burden of disease and precipitants of an exacerbation.

The work presented in this thesis has shown that, in the paediatric population, the criteria to define bronchial dilatation and therefore bronchiectasis should not be the same as used in adults. It has described the significant disease burden for parents of children with bronchiectasis that is increased during a pulmonary exacerbation. It has also highlighted that growth and lung function can be stabilised in this cohort once appropriate therapy is instituted. Further, the formulation of a standardised, statistically robust, clinically useful and easy to use definition of an acute pulmonary exacerbation in paediatric bronchiectasis, is a significant advancement in paediatric respiratory research knowledge. The studies within this thesis have further described the infectious precipitants of exacerbations and its effect on lung functions and burden of disease.

The key to improve outcomes in many chronic respiratory and non-respiratory conditions is early diagnosis and management. This need for early diagnosis forms the basis of the concept of disease screening, and the model of secondary and tertiary prevention. Early diagnosis has not only improved outcomes in many oncological and neonatal metabolic diseases; it has also been reported to reduce pulmonary morbidity in CF, COPD and PCD. Radiological features of bronchiectasis might improve and even resolve once properly managed. Similarly, as discussed in chapter 4,
establishment of appropriate therapy has been shown to stabilise lung function in children with bronchiectasis. For these reasons it is important that the diagnosis of bronchiectasis is made early and then managed appropriately to preserve the potential of disease reversibility. It is in this context that chapter 2 of our thesis becomes relevant. A children-specific radiological definition of bronchiectasis is important in detecting early bronchiectasis changes in children, where changes may be subtle and often missed if adult-based criteria are used. Our new cut-off to define bronchial dilatation, as discussed in chapter 2, helps in improving the sensitivity of HRCT for detecting bronchiectasis, since children are likely to have less severe bronchiectasis compared to adults. This will in turn help in early diagnosis and management, especially in those with clinical features of chronic pulmonary suppuration.

The need for early detection becomes even more pertinent in light of our findings that even at the time of initial diagnosis; the majority of children with bronchiectasis had infection with respiratory pathogens and significant airway neutrophilia, as discussed in chapter 5. Early treatment of this infection and inflammation with appropriate antibiotics and anti-inflammatory agents may be a key to prevent disease progression in this group. In this study we also demonstrated that Pseudomonas aeruginosa, fungal agents and NTM are not important pathogens in paediatric bronchiectasis, a significant difference from adult bronchiectasis data. Whereas empirical antimicrobial treatment in adults with bronchiectasis constitutes anti-Pseudomonal therapy, that the suggestion of the use of empirical antibiotic therapy in paediatric bronchiectasis to cover H. influenzae, S. pneumoniae and M. catarrhalis is confirmed.
It is well accepted that quality of life assessment is an important component of any medical review. The family of the child may also face considerable burden due to the chronic illness, causing stress, anxiety and depression. Thus chapter 3 explored this important area and showed that there is a significant burden of illness, especially during pulmonary exacerbation, on parents of children with bronchiectasis. These findings suggest that management of bronchiectasis, especially during pulmonary exacerbation, could be substantially improved. Appropriate counselling to understand the burden of individual parents and alleviate it, where possible, would significantly improve care for this patient group. General medical literature, available both to paediatricians and general practitioners, needs to explain the features of pulmonary exacerbation, so that doctors are cognizant to the psychologically vulnerable period in this group.

In keeping with our broad hypothesis of formulating a standardised definition of pulmonary exacerbation in children with bronchiectasis using clinical and investigational parameters, we have found that exacerbation could be defined by using a combination of clinical features with additional systemic markers improving predictive values. Our final combined model consisted of three options suitable for different settings ranging from tertiary clinical, community and research based settings. Presence of a “wet” cough and a significant frequency of cough (defined by median cough score $\geq 2$) were major criteria each having high sensitivity and specificity in defining an exacerbation. We conclude that a child with bronchiectasis with a frequent wet cough is likely to be in exacerbation. This is especially important since many doctors (including general paediatricians) tend to ignore an ongoing wet cough in children with bronchiectasis thus delaying antibiotic therapy in the absence
of fever or chest signs. This finding also indicates that even though bronchiectasis in adults is considered to be a disease of chronic cough and purulent sputum production, children with bronchiectasis may be minimally symptomatic or even asymptomatic for prolonged periods once stabilised on appropriate ongoing management. What constitutes appropriate management is still debatable, but many of these exacerbations do require intravenous antibiotics when oral antibiotics fail, as discussed in chapter 6.

Systemic and airway inflammation are important features of bronchiectasis in adults\(^ {184}\) and lead to considerable co-morbidity associated with the condition. In the perfect model, airway inflammation by direct sampling should be measured with every exacerbation. This is impractical (as young children often do not expectorate sputum), costly and invasive in the paediatric population as bronchoscopy under anaesthesia is usually required. Systemic surrogates of airway inflammation may act as “biomarkers” of disease severity and might help in differentiating stable from exacerbation state. This has been well researched in COPD\(^ {134,144-147}\) though data from bronchiectasis is limited. The limitation of such a surrogate is that inflammation and infection in bronchiectasis is predominantly endobronchial, and the systemic “spillover” may only occur in severe lung disease or during an exacerbation. We report that serum CRP, amyloid A and IL6 improve the ability to detect an exacerbation by improving the specificity though none were in itself robust enough to predict an exacerbation, since none had individual area under the curve (AUC) of ROC > 0.8, considered as an acceptable standard.\(^ {185}\) So, we cannot label any of these systemic markers as “biomarkers” of exacerbation in bronchiectasis. Their role remains important though in conjunction with the clinical features mentioned above, especially in research and tertiary clinical practice, where outcome arguably should be
more specific and their addition may improve the predictive value in defining an exacerbation. This would possibly reduce over diagnosis (and thus over-treatment including in-patient hospital stay), as well as facilitate standardised outcomes for clinical studies and trials.

The role of exacerbation in the short term and long term morbidity in children with bronchiectasis was also discussed in chapters 3, 4, 6 and 8. Chapter 4 described that with each exacerbation requiring hospital admission, the FEV₁ fell by 1.6%, thereby making exacerbation the only factor that was associated with lung function decline in our group. These figures are comparable to CF studies that have also reported lung function decline with exacerbations. Also in Chapter 3 it is reported that pulmonary exacerbations are associated with significant worsening in burden of disease on parents (parental depression, anxiety and stress scores) with in the cohort; 38-50% had scores reflecting abnormal depression, anxiety and stress during an exacerbation. This further highlights the need for prevention, early detection and aggressive management of pulmonary exacerbation, research on which to date has been limited. The use of the derived definition of exacerbation in interventional trials would improve consistency of outcomes and would make the studies more comparable and results more applicable to a larger population.

Data from chronic respiratory conditions such as asthma, CF and COPD and clinical experience in children with bronchiectasis have suggested that respiratory tract infections, especially with respiratory viruses, are common precipitants of an exacerbation. Yet at the time of thesis design, triggers (infectious or non-infectious) of bronchiectasis exacerbation had not been studied. In our retrospective analysis of
exacerbations described in chapter 6, 21% of upper airway samples were positive for respiratory viruses. From the described prospective cohort followed over 900 child months, it is concluded that nearly half of respiratory exacerbations were associated with detection of respiratory viruses in the nasopharyngeal aspirates, with human rhinovirus being the most common virus detected. Systemic features such as fever and chest signs were uncommon in virus-negative exacerbations. These findings suggest that withholding antibiotic therapy during exacerbation in the absence of systemic features such as fever, a practice still followed by many general practitioners and paediatricians, is likely unjustified and deprives the child of benefit from antibiotic therapy. Using antibiotics for all the exacerbations on the other hand, may lead to overuse of antibiotics. The role of antibiotics in virus-positive exacerbation in unknown, especially when concurrent bacterial data were not obtained in the study.

There is limited data on the role of long term preventer therapy in reducing exacerbation rate in bronchiectasis in children. Adult data suggests that long term antibiotic therapy is usually beneficial in reducing the rate of exacerbation.\textsuperscript{187} Murray and colleagues in a recent RCT reported significant reduction in rate of exacerbation in 65 adults treated with nebulised gentamycin over 12 months compared to placebo.\textsuperscript{44} Similar benefit has also been reported with use of azithromycin.\textsuperscript{137,188} The evidence on role of ICS in prevention of exacerbation was reviewed using Cochrane methodology in chapter 9. It was concluded that there was no difference in the exacerbation frequency during short term (< 6 months) or long term use of ICS, though there was only one study included in each of these groups. The role of oral NSAID in exacerbation prevention was also presented and found no relevant trials that had systematically addressed this issue.
10.2 Limitations of the thesis

The limitations of this thesis are stated within each chapter and primarily pertain to the methodology, especially regarding the retrospective nature of some components of the thesis. The data for the longitudinal lung function study (chapter 4), lower airway microbiology study (chapter 5) and clinical features of exacerbation study (chapter 6) were retrospectively collected. For formulating a definition of exacerbation (chapter 7) and studying its viral triggers and effect of exacerbation on burden of disease, we chose the paediatric-pulmonologist defined exacerbations, where children required additional treatment, as the gold standard. This is consistent with other studies defining pulmonary exacerbations as 'use of rescue medications' (corticosteroids for asthma\textsuperscript{127} and antibiotics for COPD.)\textsuperscript{189} The paucity of data in this area precluded any better reference standard. Nevertheless, in an ideal world, the definition should be subjected to a RCT whereby use of the definition improves clinical outcomes. Moreover, we have only partially validated the derived definitions. The validity of our derivations of exacerbations is supported by objective data and high repeatability of the factors (Kappa >0.75). Post treatment data further supports the validity and robustness of our definition. However the use of these definitions should be ideally further validated by a different group in a different centre.

Some aspects of the thesis results may have been strengthened by increased patient numbers. This is particularly evident in sub-group analysis of the exacerbation definition in children with baseline wet cough (chapter 7) and 5 year follow up data in the longitudinal lung function study (chapter 5). The findings in chapter 8 would have been strengthened if viral data during stable clinical state or recovery phase were available. Johnston et al. detected a virus (by PCR) among 12% of children with
In the absence of stable state data from our cohort, causality of viral agents in inducing an exacerbation cannot be concluded. Also, we did not have bacterial data to study if some or all of the effect could be explained by bacterial co-infection.

Finally, the Cochrane review of role of NSAID in bronchiectasis did not have any studies available. Further, in the Cochrane on ICS in bronchiectasis, no paediatric data was available. The data on effect of ICS on exacerbation frequency was limited to only one study each in short term and long term effects. Further, data extraction was limited to only one to 4 studies for the outcomes examined. The small sample size (max 101) for the meta-analysis was also a significant limitation. The major contributor to the benefit of ICS was from a non-placebo controlled study.

10.3 Conclusion

This thesis has proposed new criteria to define radiological bronchiectasis in children that would assist earlier diagnosis of bronchiectasis. This is based on the lower BA ratio in children, confirming that children differ from adults. The studies have further suggested that once appropriate therapy is initiated, the lung function and growth in children could be stabilised. The role of infection and inflammation early in disease progression, as proposed by Cole it his vicious cycle hypothesis, has been supported by this thesis. In addition, the findings within the thesis have highlighted the major differences in the microbiological flora between children and adults. It has also been successful in formulating a clinically relevant and easy to use definition of exacerbation in children with bronchiectasis. It has described that "wet" character of cough and significant frequency of cough are the strongest predictors of exacerbation in children with bronchiectasis, with systemic biomarkers such as SAA, IL6 and CRP.
improving overall diagnosis. It has clearly highlighted the importance of exacerbations not only in worsening lung functions and clinical state, but also in increasing the burden of disease. Further, it has shown a clear association between pulmonary exacerbation and respiratory viruses in bronchiectasis and in the process described several newly-identified viruses such as Human parainfluenza-virus 4 (HPIV-4), Human coronaviruses (HCoV) and Human bocavirus (HBoV) not previously reported in bronchiectasis. This thesis has also reviewed the available literature and shown that additional evidence is needed to clarify the role of ICS and NSAID’s in bronchiectasis, especially in children.

10.4 Future projects and Further Research Work

Further work on bronchiectasis, particularly the identification, underlying mechanisms and management of exacerbations in bronchiectasis is clearly needed. Further studies could also be planned based on the new radiological definition of bronchiectasis proposed in this thesis. Suggested work could include:

(I) Further validation of the various definitions of exacerbation

The definition of acute pulmonary exacerbation suggested in this thesis is only partially validated. This definition needs to be prospectively validated in a new cohort of children with bronchiectasis, preferably in a different centre. The definition also needs to be validated in an older cohort of children with bronchiectasis where symptom might be more severe and major criteria of “wet cough” may have to be replaced with “increase in wet cough”. Once the definition is validated, it can then be used to answer the following questions:

a) What is the epidemiology and prevalence of exacerbation in bronchiectasis?
b) What is the duration of antibiotic therapy required for treatment of exacerbation?

c) What are the factors that define treatment response or failure?

d) What are the factors that precipitate an exacerbation in bronchiectasis?

e) What is the difference in time to next exacerbation between children treated with oral vs. intravenous antibiotics?

f) What are the short term and long term effect of exacerbations on the radiological and lung function parameters?

g) Could this definition (or a modification of it) be validated in CF cohorts?

(II) Role of respiratory viruses in precipitating exacerbation in bronchiectasis

Though our prospective study did explore the association of respiratory viruses with exacerbations in bronchiectasis, the lack of viral data during stable clinical state was a limitation. Time sequenced cohort studies during stable state, exacerbations and recovery periods are needed to determine the role of viral infections and their interaction with bacteria. This prospective study should also collect bacterial data to explore the virus-bacterial interaction in precipitating an exacerbation in bronchiectasis.

(III) Prospective follow-up lung function study in bronchiectasis

A well designed prospective follow-up study is required to define the long term effect of modern treatment regimens on lung function in children with bronchiectasis. This prospective study would also explore factors affecting the lung function over a relatively long follow-up period. These factors could include frequency of exacerbations, lower airway microbiology, use of prophylactic antibiotics etc.
(IV) Novel and non-invasive biomarkers of exacerbation in bronchiectasis

In this thesis we have explored many novel systemic biomarkers to define an exacerbation such as PCT, SAA, IL6 and fibrinogen, though none were in itself robust enough to define an exacerbation. Moreover measuring serum bio-markers requires a venipuncture, which may be considered a semi-invasive process, especially in children. Non-invasive markers of disease severity and clinical state such as exhaled matrix metalloproteinase (MMP)\textsuperscript{190,191} and nitric oxide\textsuperscript{192} should be explored in future studies to define an exacerbation and grade its severity, specially in conjunction with our definition of exacerbation.

(V) Defining child-specific QOL instrument in bronchiectasis

The burden of illness in childhood bronchiectasis was described within this thesis and the effect of exacerbation uncovered. We used the parent-proxy cough-specific QOL (PC-QOL) questionnaire to ascertain the burden of disease in our cohort. Though cough specific QOL questionnaire such as the Leicester Cough Questionnaire have been validated in adults with bronchiectasis,\textsuperscript{24} no bronchiectasis specific QOL tool is available in children. In adults, the St George’s Respiratory Questionnaire (SGRQ) is often used\textsuperscript{73} but a similar child specific QOL tool for future paediatric research, particularly interventional studies, would be of significant value.

(VI) RCT’s on role of inhaled hyperosmolar agents in prevention and management of pulmonary exacerbations

Therapies shown to be effective in cystic fibrosis are often provided to patients with bronchiectasis, without definitive evidence of benefit. Hypertonic saline inhalation is known to accelerate tracheobronchial clearance in many conditions, probably by
inducing a liquid flux into the airway surface, which alters mucus rheology in a way favourable to mucociliary clearance. Inhaled dry powder mannitol has a similar effect\(^{193}\) though role of these agents in prevention and acute management of exacerbations in bronchiectasis have never been explored. This is important especially since these agents have minimal adverse effects, are easily available and are relatively inexpensive.

10.5 Summary

In this final chapter the overall findings of the thesis are presented, conclusions drawn and recommendations for future research outlined. Overall the work of this thesis has shown that the radiological definition of bronchiectasis in children are not the same as adults and a standardised definition of pulmonary exacerbation in children could be formulated using a combination of clinical and systemic biomarkers. The thesis results provide indisputable support to our hypothesis that paediatric bronchiectasis is different to that described in adults, in terms of clinical and investigational features. The new definition of radiological bronchiectasis and pulmonary exacerbation proposed in this thesis has brought attention to a condition which has long been ignored, and would certainly standardise many future research studies and clinical protocols. Continuing research aimed at utilizing the definition of exacerbation to formulate “Best Management Practice Guidelines” for paediatric bronchiectasis is essential in improving our understanding of this important cause of chronic respiratory morbidity.
References (Introduction & Conclusion)


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