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CHILDHOOD BRONCHIECTASIS: NATIONAL INCIDENCE, DISEASE PROGRESSION AND AN EVALUATION OF INHALED ANTIBIOTIC THERAPY

JACOB TWISS

ABSTRACT

**Background:** Bronchiectasis is a chronic suppurative lung disease, defined by dilatation of bronchial airways, resulting in significant morbidity, mortality, and healthcare expenditure. It continues to affect large numbers of people worldwide, particularly indigenous or disadvantaged communities. The goals of this thesis were to determine childhood bronchiectasis occurrence in New Zealand, define its progression, and evaluate a potential new therapy; inhaled antibiotics.

**Methods:** Firstly, a single-centre retrospective study described the prevalence, aetiology and severity of childhood bronchiectasis in Auckland. Secondly, a two year prospective multi-centre study described the incidence, aetiology and severity of new cases of bronchiectasis in New Zealand. Thirdly, disease progression was estimated through retrospective linear mixed-model analyses of pulmonary function and compared to peers with cystic fibrosis. Fourthly, an evaluation of inhaled gentamicin pharmacokinetics was made through a single-dose open-label study. Finally, a randomised double-blinded placebo-controlled two-period community-based crossover trial of inhaled antibiotics was conducted.

**Results:** Children identified had severe, extensive bronchiectasis with an Auckland prevalence of 1:3000 and a national incidence of 3.7:100,000 per year. Compared with New Zealand children of European ethnicity, the incidence was 12 times higher in Pasifika and 3 times higher in Maori. Pneumonia, poverty, immunodeficiency, aspiration and recent immunosuppressive therapy were the most important aetiologies. Children with bronchiectasis had more severe obstructive lung disease than peers with cystic fibrosis (FEV$_1$ intercept at ten years age 63% versus 77% predicted, p<0.001) but declined more slowly (-0.9% versus -2.5% predicted per annum, p=0.02). Inhaled gentamicin (80mg) safely achieved target concentrations within sputum (mean 697 μg/g). Despite low adherence, inhaled gentamicin was well tolerated, resulted in reduced symptoms, decreased *Haemophilus influenzae* density (-2.7 log$_{10}$ cfu/ml, p<0.001), decreased airway inflammation (neutrophils, IL-1β, IL-8, TNFα) and reduced oral antibiotic use (OR 0.19, p<0.001). No significant change in spirometry or hospitalisation rates occurred over the three months.

**Conclusion:** Childhood bronchiectasis has a high and increasing prevalence in New Zealand, especially in Pasifika and Maori. Children have extensive, progressive disease despite ‘standard’ management. Inhaled gentamicin is well tolerated, achieves effective concentrations, improves symptoms, reduces bacterial load and airway inflammation as well as oral antibiotic use. However, low adherence suggests poor acceptability.
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ABPA</td>
<td>Allergic broncho-pulmonary aspergillosis</td>
</tr>
<tr>
<td>ADA</td>
<td>Adenosine deaminase deficiency</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>α1AT</td>
<td>Alpha one antitrypsin deficiency</td>
</tr>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>AML</td>
<td>Acute myeloid leukaemia</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BAL</td>
<td>Broncho-alveolar lavage</td>
</tr>
<tr>
<td>BD</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BMT</td>
<td>Bone marrow transplant</td>
</tr>
<tr>
<td>BO</td>
<td>Bronchiolitis obliterans</td>
</tr>
<tr>
<td>BPD</td>
<td>Broncho-pulmonary dysplasia</td>
</tr>
<tr>
<td>BTPS</td>
<td>Body temperature and pressure, saturated.</td>
</tr>
<tr>
<td>BX</td>
<td>Non-cystic fibrosis bronchiectasis</td>
</tr>
<tr>
<td>CRI</td>
<td>Component of the complement pathway</td>
</tr>
<tr>
<td>C3bl</td>
<td>Component of the complement pathway</td>
</tr>
<tr>
<td>CD 4+</td>
<td>Cluster of differentiation 4 (predominantly Helper T Cells and macrophages)</td>
</tr>
<tr>
<td>CD 45</td>
<td>Cluster of differentiation 44 (predominantly expressed by T lymphocytes)</td>
</tr>
<tr>
<td>CD 8</td>
<td>Cluster of differentiation 8 (predominantly Cytotoxic T cells)</td>
</tr>
<tr>
<td>CDSR</td>
<td>Cochrane Database Systematic Review</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance regulator</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony forming unit</td>
</tr>
<tr>
<td>CGD</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval (all 95% unless specified otherwise)</td>
</tr>
<tr>
<td>CMAD</td>
<td>Count mean aerodynamic diameter</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNLD</td>
<td>Chronic neonatal lung disease</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CO2</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRQ</td>
<td>Chronic Respiratory Disease Questionnaire</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography scan</td>
</tr>
<tr>
<td>CVID</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>D1CO</td>
<td>Carbon monoxide transfer coefficient</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribose nucleic acid</td>
</tr>
<tr>
<td>DTT</td>
<td>Dithiothreitol</td>
</tr>
<tr>
<td>EBV</td>
<td>Ebstein barr virus</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<tr>
<td>EPP</td>
<td>Equal pressure point</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FBA</td>
<td>Foreign body aspiration</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>Maximum mid expiratory flow</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal reflux disease</td>
</tr>
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</table>
GSD  Geometric standard deviation
H₂O₂  Hydrogen peroxide
H.influenzae  Haemophilus influenzae
HIV  Human immunodeficiency virus
HRCT  High resolution computer tomography chest scan
Ig  Immunoglobulin
IgA  Immunoglobulin class A
IgAD  Immunoglobulin class A deficiency
IgG  Immunoglobulin class G
IgG₁  Immunoglobulin class G subclass 1
IgG₂  Immunoglobulin class G subclass 2
IgG₃  Immunoglobulin class G subclass 3
IgG₄  Immunoglobulin class G subclass 4
IgG₅D  Immunoglobulin class G subclass deficiency
IL  Interleukin
IL-1β  Interleukin one beta
IL-10  Interleukin ten
IL-6  Interleukin six
IL-8  Interleukin eight
IVIG  Intravenous immunoglobulin therapy
l  litre
LIP  Lymphocytic interstitial pneumonitis
LRTI  Lower respiratory tract infection
LTB₄  Leukotriene beta four
M.catarrhalis  Moraxella catarrhalis
MDI  Metered dose inhaler
MEF  Mid-expiratory flow
MEFV  Mid-expiratory flow volume
mg  Milligram
MIC  Minimum inhibitory concentration
ml  Millilitre
MMAD  Mass median aerodynamic diameter
MMD  Mass median diameter
MMEF  Maximum mid expiratory flow
mmol  One thousandth of a mole
MMP  Matrix metalloproteinases
mol  Mole
mosm  Osmoles per millilitre
MPO  Myeloperoxidase
MRC  Medical Research Council, United Kingdom
NAG  N-acetyl-B-D-Glucosaminidase
NCCLS  National Committee for Clinical Laboratory Standards
NR  Not reported
NZ  New Zealand
NZDEP  New Zealand deprivation score or decile
NZPSU  New Zealand Paediatric Surveillance Unit
O₂⁻  Oxygen radical
OECD  Organisation for economic co-operation and development
OR  Odds ratio
osm  Osmolar (osmoles per litre)
P.aeruginosa  Pseudomonas aeruginosa
Palv  Intra-alveolar pressure
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pari</td>
<td>Company name (nebuliser manufacturer)</td>
</tr>
<tr>
<td>Patm</td>
<td>Atmospheric pressure</td>
</tr>
<tr>
<td>Pbr</td>
<td>Intra-bronchial pressure</td>
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<tr>
<td>PCD</td>
<td>Primary ciliary dyskinesia</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis jiroveci pneumonia</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PEP</td>
<td>Positive expiratory pressure</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary (or lung) function testing</td>
</tr>
<tr>
<td>pg</td>
<td>pico-gram</td>
</tr>
<tr>
<td>PG&lt;sub&gt;E2&lt;/sub&gt;</td>
<td>Prostaglandin E2</td>
</tr>
<tr>
<td>pH</td>
<td>The log of the hydrogen ion (H&lt;sup&gt;+&lt;/sup&gt;) concentration (acidity level)</td>
</tr>
<tr>
<td>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>PID</td>
<td>Primary immunodeficiency</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>pKA</td>
<td>The negative logarithm of the acid dissociation constant, Ka.</td>
</tr>
<tr>
<td>Ppl</td>
<td>Pleural pressure</td>
</tr>
<tr>
<td>PSU</td>
<td>Paediatric Surveillance Unit</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>r</td>
<td>Rho correlation</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SCID</td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>SDS-PAGE</td>
<td>Sodium dodecyl sulfate polyacrylamide gel electrophoresis</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George Respiratory Questionnaire</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>SNZ</td>
<td>Statistics New Zealand</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>TDS</td>
<td>Thrice daily</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming growth factor – beta</td>
</tr>
<tr>
<td>T&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Inspiratory time</td>
</tr>
<tr>
<td>TIMP</td>
<td>tissue inhibitors of metalloproteinases</td>
</tr>
<tr>
<td>T-K curve</td>
<td>Time-Kill curve</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour necrosis factor – alpha</td>
</tr>
<tr>
<td>TOBI</td>
<td>Brand name for tobramycin solution for inhalation</td>
</tr>
<tr>
<td>TSI</td>
<td>Tobramycin solution for inhalation (TOBI™)</td>
</tr>
<tr>
<td>T&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>Duration of one respiratory cycle</td>
</tr>
<tr>
<td>µg</td>
<td>micro-gram</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>Vd</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>VSD</td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>XLA</td>
<td>X-linked agammaglobulinaemia</td>
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