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

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for the Doctor of Philosophy (PhD) in Paediatrics,
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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 aswell as oral antibiotic use. However, low adherence suggests poor acceptability.

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LIST OF ABBREVIATIONS

ABPA	Allergic broncho-pulmonary aspergillosis
ADA	Adenosine deaminase defiency
AIDS	Acquired immunodeficiency syndrome
α1AT	Alpha one antitrypsin deficiency
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANOVA	Analysis of variance
ATS	American Thoracic Society
BAL	Broncho-alveolar lavage
BD	Twice daily
BMT	Bone marrow transplant
BO	Bronchiolitis obliterans
BPD	Broncho-pulmonary dysplasia
BTPS	Body temperature and pressure, saturated.
BX	Non-cystic fibrosis bronchiectasis
CR1	Component of the complement pathway
C3bl	Component of the complement pathway
CD 4+	Cluster of differentiation 4 (predominantly Helper T Cells and macrophages)
CD 45	Cluster of differentiation 44 (predominantly expressed by T lymphocytes)
CD 8	Cluster of differentiation 8 (predominantly Cytotoxic T cells)
CDSR	Cochrane Database Systematic Review
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony forming unit
CGD	Chronic granulomatous disease
CI	Confidence interval (all 95% unless specified otherwise)
CMAD	Count mean aerodynamic diameter
CMV	Cytomegalovirus
CNLD	Chronic neonatal lung disease
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Disease Questionnaire
CT	Computer tomography scan
CVID	Common variable immunodeficiency
D_LCO	Carbon monoxide transfer coefficient
DNA	Deoxyribose nucleic acid
DTT	Dithiothreitol
EBV	Ebstein barr virus
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EPP	Equal pressure point
ERS	European Respiratory Society
FBA	Foreign body aspiration
$FEF_{25-75\%}$	Maximum mid expiratory flow
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
g	Gram
GORD	Gastro-oesophageal reflux disease

GSD	Geometric standard deviation
H_20_2	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
IgG_1	Immunoglobulin class G subclass 1
IgG_2	Immunoglobulin class G subclass 2
IgG_3	Immunoglobulin class G subclass 3
IgG_4	Immunoglobulin class G subclass 4
$IgG_{SC}D$	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
O_2^-	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

Pari	Company name (nebuliser manufacturer)
Patm	Atmospheric pressure
Pbr	Intra-bronchial pressure
PCD	Primary ciliary dyskinesia
PCP	Pneumocystis jeroveci pneumonia
PD	Pharmacodynamics
PEP	Positive expiratory pressure
PET	Positron emission tomography
PFT	Pulmonary (or lung) function testing
pg	pico-gram
PG_{E2}	Prostaglandin E2
pH	The log of the hydrogen ion (H^+) concentration (acidity level)
PICU	Paediatric intensive care unit
PID	Primary immunodeficiency
PK	Pharmacokinetics
pKA	The negative logarithm of the acid dissociation constant, Ka.
Ppl	Pleural pressure
PSU	Paediatric Surveillance Unit
QoL	Quality of life
r	Rho correlation
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RR	Relative risk
RSV	Respiratory syncytial virus
RV	Residual volume
S.aureus	Staphylococcus aureus
S.pneumoniae	Streptococcus pneumoniae
SARS	Severe acute respiratory syndrome
SCID	Severe combined immunodeficiency
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGRQ	St George Respiratory Questionnaire
SLE	Systemic lupus erythematosus
SNZ	Statistics New Zealand
SPECT	Single photon emission computed tomography
TDS	Thrice daily
TGF-β	Transforming growth factor – beta
T_i	Inspiratory time
TIMP	tissue inhibitors of metalloproteinases
T-K curve	Time-Kill curve
TLC	Total lung capacity
TNFα	Tumour necrosis factor – alpha
TOBI	Brand name for tobramycin solution for inhalation
TSI	Tobramycin solution for inhalation (TOBI™)
T_{tot}	Duration of one respiratory cycle
µg	micro-gram
UK	United Kingdom
USA	United States of America
Vd	Volume of distribution
VSD	Ventricular septal defect
XLA	X-linked agammaglobulinaemia