Bronchiectasis:

An African Perspective on Diagnostic Approach

A/Prof Diane Gray
Division Paediatric Pulmonology | Red Cross War Memorial Children’s Hospital | University of Cape Town | South Africa
Conflict of interest

• Research grant: The Wellcome Trust (intermediate fellowship)
Talk overview

- Highlight some of the key concepts in paediatric bronchiectasis and chronic suppurative lung disease
- Discuss the pathogenesis in relation to a framework for approaching case recognition and assessment
- Present some of the African experience in children with chronic suppurative lung disease
- Ideas of a way forward for improving our prevention and care of childhood bronchiectasis
African challenges with bronchiectasis

- In an area with limited data – we have near none
- Limited access to chest CT scan - disease defining tool
- Limited access to diagnostics (e.g. test for PCD, CF) and management (microbiology, lung function) tools
- High prevalence of risk factors for bronchiectasis – lower respiratory tract infections, tuberculosis, HIV, social disadvantage
Bronchiectasis is not a rare disease

- Paediatric estimated prevalence 0.2 to 735 per 100,000 population
- Higher in socially disadvantaged communities
- No prevalence data from Africa (or S. America) McCallum Frontiers Ped 2017
- Trend in increasing hospital admissions for bronchiectasis and mortality
- Associated: age, sex, SES, severity, co-morbidities Quint ERJ 2016, Seitz Chest 2010

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pub. year</th>
<th>Country</th>
<th>Region</th>
<th>Population</th>
<th>Era</th>
<th>Time (years)</th>
<th>Male: female</th>
<th>Age (years)</th>
<th>Data source</th>
<th>Given or extrapolated BE cases (n)</th>
<th>Chest high resolution computer tomography (n)</th>
<th>Median age at diagnosis (years)</th>
<th>Given or rate of BE extrapolated population denominator (n)</th>
<th>Given or rate of extraplated average annual incidence</th>
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<td>Zaid et al. (48)</td>
<td>2010</td>
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<td>2006</td>
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<td>USA</td>
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<td>&lt;14</td>
<td>Statewide registry and hospitalizations</td>
<td>29*</td>
<td>29</td>
<td>29</td>
<td>6,500* (1990)</td>
<td>-140</td>
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<td>Edward (50)</td>
<td>2003</td>
<td>NZ</td>
<td>Auckland</td>
<td>TOTAL New Zealand</td>
<td>1998-2000</td>
<td>3</td>
<td>38:24</td>
<td>1-17</td>
<td>Hospital admissions (ICD 484)</td>
<td>60</td>
<td>53</td>
<td>19</td>
<td>50,308*</td>
<td>51,700</td>
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<td>Chang (51)</td>
<td>2003</td>
<td>Australia</td>
<td>Central</td>
<td>Indigenous</td>
<td>2000-2002</td>
<td>3</td>
<td>31:34</td>
<td>&lt;15</td>
<td>Hospital admissions (ICD10 J47 + medical record review)</td>
<td>65</td>
<td>59</td>
<td>5.4</td>
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<td>Takas et al. (52)</td>
<td>2005</td>
<td>NZ</td>
<td>National</td>
<td>TOTAL New Zealand</td>
<td>2001-2002</td>
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<td>O’Grady et al. (53)</td>
<td>2010</td>
<td>Australia</td>
<td>NT</td>
<td>Indigenous</td>
<td>1909-2004</td>
<td>5</td>
<td>7:3</td>
<td>&lt;1</td>
<td>Hospital admissions (ICD10 J47)</td>
<td>10</td>
<td>na</td>
<td>0.7</td>
<td>1,909</td>
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<tr>
<td>Das and Kowser (54)</td>
<td>2014</td>
<td>Canada</td>
<td>Central, Rural</td>
<td>Indigenous</td>
<td>1998-2011</td>
<td>13</td>
<td>na</td>
<td>&lt;17</td>
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<td>17</td>
<td>5.6</td>
<td>8,416*</td>
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<td>Janu et al. (55)</td>
<td>2014</td>
<td>Australia</td>
<td>Central</td>
<td>Indigenous</td>
<td>2007-2011</td>
<td>5</td>
<td>4:3</td>
<td>&lt;2</td>
<td>Hospital admissions (ICD10 J47 + medical record review)</td>
<td>7</td>
<td>7</td>
<td>0.5</td>
<td>341*</td>
<td>nr</td>
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</tbody>
</table>
Early intervention halts or reverses process and improves outcome
Tracheomalacia
Foreign body

Anatomical distortion
- Lung injury – Bronchi & Parenchyma

Structural Bronchiectasis
- Loss of cilia & mucociliary function
- Destruction of the bronchial wall
- Mucus retention

Tracheomalacia
Foreign body

Mucus inspissation, retention and plugging

Primary ciliary dyskinesia
- Impaired mucociliary clearance
- Innate & adaptive immune deficits

Microorganism acquisition, colonisation & infection

Cole’s vicious cycle hypothesis

Chronic infection
- Exacerbations
- Inflammation
- Clinical symptoms
- Changes in pulmonary physiology

Neutrophil-mediated inflammation & neutrophil derived proteases (e.g. NE)

Severe pneumonia

Immune deficiency

Diagram acknowledgement: Chandrasekaran BMC Med 2018
Clinical symptoms of Bronchiectasis

**Key Symptoms***
- **Chronic wet or productive cough**
  - failure to respond to 4 weeks of oral antibiotics (OR 20.9, 95% CI 5.4–81.8) of CT bronchiectasis
- Abnormal chest x-ray
- Recurrent pneumonia
- Feeding difficulties
- Recurrent (>3 episodes per year) protracted bacterial bronchitis
  - OR 11.5, 95% CI 2.3–56.0) and a wet or productive of CT bronchiectasis

*associated with CT confirmed bronchiectasis

**Other signs and symptoms**
- Clubbing
- Wheeze
- Chest pain
- Haemoptysis
- Failure to thrive
- Effort intolerance
- Chest deformity
- Crackles

*Wurzel Chest 2016; 150: 1101; Goyal Arch Dis Child 2014; 99: 522; Chang Lancet 2018; 392: 866*
Defining Bronchiectasis

- Clinical syndrome (persistent/recurrent wet cough) AND
- HRCT scan: paediatric BAR* (abnormal when >0.80)

Chang, Bush, Grimwood Lancet 2018

*BAR: broncho-arterial ratio: inner bronchus and outer artery radius

- Chronic suppurative lung disease (CSLD): clinical syndrome WITHOUT chest HRCT findings
- Protracted bacterial bronchitis (PBB): chronic wet or productive cough (>4-8 weeks), in an otherwise well child, that responds to 2 weeks of an appropriate antibiotic
- ? Clinical syndrome and no HRCT findings
  - Clinical syndrome and obvious BE chest X-ray findings
  - Clinical syndrome and unclear/non-specific chest X-ray findings

Possible BE
Chest CT scan

1. Increased broncho-arterial ratio (BAR), A
2. Lack of bronchial tapering/tramline, B
3. Presence of bronchial structure in periphery, C
4. Bronchial wall thickening, D
5. Mucus plugging
6. Mosaic perfusion (air-trapping)
Aetiology matters – global variation

<table>
<thead>
<tr>
<th>Countries</th>
<th>Post Infectious %</th>
<th>Immune deficiency %</th>
<th>Primary ciliary dyskinesia %</th>
<th>Congenital abnormality %</th>
<th>Aspiration %</th>
<th>Idiopathic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income ¹</td>
<td>4-35</td>
<td>10-34</td>
<td>1-24</td>
<td>1-15</td>
<td>4-22</td>
<td>2-55</td>
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<td>Social disadvantage high income ²</td>
<td>22-94</td>
<td>3-12</td>
<td>0</td>
<td>0-1</td>
<td>4-10</td>
<td>0-54</td>
</tr>
<tr>
<td>Low- mid- income ³</td>
<td>10-40</td>
<td>4-19</td>
<td>3-26</td>
<td>3-10</td>
<td>2-9</td>
<td>14-53</td>
</tr>
</tbody>
</table>

¹ 6 studies UK, Aus, Ire, Italy ² 7 studies, Alaska, NZ, Aus, Can ³ 13 studies; Turkey, South Korea, Taiwan, Saudi Arabia, Tunisia, India

Other causes:
Concomitant disease/syndrome:
- Asthma or airway hyperresponsiveness
- Prematurity
- Non-post inf Bronchiolitis obliterans
- Allergic bronchopulmonary aspergillosis
- Interstitial or connective tissue disease
- Inflammatory bowel disease
- Marfan syndrome
- Yellow Nail syndrome
- Pycostic kidney disease and other renal disease

History, symptoms and signs important to assessing aetiology
Comorbidities important
Changing epidemiology

• Aetiology:
  • Less: idiopathic, post-infectious and post TB
  • More: PCD, Immunodeficiency

  ➢ Increased case detection
  ➢ Better understanding of and investigation for underlying causes
  ➢ Improved prevention and management of LRTI
  ➢ Decreased TB prevalence
South African experience

- 56 children with bronchiectasis (BE), general respiratory clinic at tertiary hospital, Cape town
- 17.5% of clinic patients
- BE defined as clinical symptoms with radiographic evidence of BE (chest X-ray or HRCT)
- Mean age at diagnosis: 24 months (range 7 to 120 months)

<table>
<thead>
<tr>
<th>Post Infectious</th>
<th>Immune deficiency</th>
<th>Primary ciliary dyskinesia</th>
<th>Congenital abnormality</th>
<th>Aspiration</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 (37.5%)</td>
<td>Total: 19 (33.9%)</td>
<td>4 (7.0%)</td>
<td>8 (14.3%)</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary: 3 (5.4%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acquired (HIV): 16</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(28.6%)</td>
<td></td>
<td></td>
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</table>

Dr Muntanga Mapani, MPhil research 2020, unpublished
Previous infections related to bronchiectasis

- All 57 children had a history of severe or recurrent lower respiratory tract infections prior to bronchiectasis diagnosis
- The commonest infectious causes in the HIV-uninfected children: adenovirus (64%, many in setting of multiple co-infections)
- The commonest infectious cause in HIV-infected children: tuberculosis (88%)

Table: Previous tuberculosis infection and bronchiectasis in children by HIV status

<table>
<thead>
<tr>
<th></th>
<th>HIV infected (n=16)</th>
<th>HIV exposed uninfected (n=6)</th>
<th>HIV unexposed and Uninfected (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis caused by Tuberculosis only</td>
<td>11 (69%)</td>
<td>0 (0%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Bronchiectasis caused by Tuberculosis co-infection</td>
<td>3 (19%)</td>
<td>1 (17%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bronchiectasis caused by Non Tuberculosis infection</td>
<td>2 (12%)</td>
<td>5 (83%)</td>
<td>22 (71%)</td>
</tr>
</tbody>
</table>
HIV and bronchiectasis in children

- Chronic radiological change (CRC) is common in children living with HIV (CLWH): bronchiectasis and decreased attenuation. 
  
  
  • South African children spanning the ART rollout: 85% with CRC and 50% with extensive diffuse changes; 30% of severe disease due to TB. ART associated with improved radiological change. 
  
  Pitcher Ped Pulm Pitcher Thorax

- Bronchiectasis common in CLWH – 6% in American cohort (Berman Ped Pulm 2007), higher in Sub-Saharan African adolescents – up to 50% (Ferrand CID 2012, Mwalukomo 2016)

- Risk factors for bronchiectasis in HIV: recurrent LRTI, severe immune suppression and LIP, tuberculosis 
  
  Berman Ped Pulm 2007, Pitcher Thorax 2015

- May also be due to HIV-mediated defects in innate immunity and accompanying airway neutrophilic inflammation
  
  Masekela IJTD 2012, Ped Pulm 2015
Bronchiectasis and bronchiolitis obliterans in youth living with HIV (YLWH)

- 100/116 (86%) YLWH, 14.6 ± 2.4 yrs, had chronic lung disease*
- Symptoms: Chronic cough 66%, recurrent LRTI 21%, abnormal chest X-ray 47%, clubbing 10%
- CT scan in 52 YLWH (excluded if active TB – 23%)
  - 55% BO 43% bronchiectasis

* Cough 3 months, recurrent LRTI, mod effort intolerance OR hypoxia
Forced vital capacity over 2 years in HIV infected (red) and uninfected (blue) adolescents

Forced vital capacity over 2 years in HIV infected adolescents with past LRTI (red) and no past LRTI (blue)

Githinji L et al, CID April 2019
Diagnostic Approach

- Identify children at risk for bronchiectasis with early referral and diagnosis

- Thorough investigation for underlying aetiology

- Assessment of baseline severity

- Assessment of other risk factors and co-morbidities

- Plan management
  - Improve quality of life
  - Prevent or reduce exacerbation frequency
  - Preserve lung function

BEFORE IRREVERSIBLE AIRWAY DAMAGE
Approach to diagnosis

Chang, Bush, Grimwood
Lancet 2018

KEY SYMPTOMS
- Chronic wet cough >4 weeks, unresponsive to antibiotics
- Recurrent pneumonia or lower respiratory tract illness
- Recurrent PBB >3 episodes per year
- Feeding difficulties
  - Persistent chest or x-ray signs
  - Hemoptysis
  - Severe asthma
  - Clubbing
  - Unusual organism on sputum (e.g. pseudomonas)
  - Respiratory symptoms with history of adenovirus, TB, pertussis

Evaluate for bronchiectasis

Chest CT scan

No BE

Yes BE

Reconsider diagnosis, assess for CSLD, manage appropriately

Assess in all
- Full blood count, diff
- IgG, IgM, IgA, IgE
- Vaccine responses
- Sweat test

Assess in selected
- Bronchoscopy
- Tuberculosis
- HIV
- In depth immune tests
- Tests for PCD
- Tests for aspiration
- CF gene typing
Approach to diagnosis – limited CT access

Adapted from Chang, Bush, Grimwood Lancet 2018

KEY SYMPTOMS
- Chronic wet cough >4 weeks, unresponsive to antibiotics
- Recurrent pneumonia or lower respiratory tract illness
- Recurrent PBB >3 episodes per year
- Feeding difficulties
  - Persistent chest or x-ray signs
  - Hemoptysis
  - Severe asthma
  - Clubbing
  - Unusual organism on sputum (e.g. pseudomonas)
  - Respiratory symptoms with history of adenovirus, TB, pertussis

Evaluate for bronchiectasis

- Chest Xray: not clear evidence of BE/normal
- Chest Xray: clear evidence of bronchiectasis
- Chest CT scan available
  - Yes
  - Chest CT scan unavailable

- Chest CT scan
  - No BE
  - Yes BE

Reconsider diagnosis, assess for CSLD, manage appropriately

Assess in all
- Tuberculosis
- HIV
- Full blood count, diff
- IgG, IgM, IgA, IgE
- Vaccine responses
- Sweat test

Assess in selected
- Bronchoscopy
- In depth immune tests
- Tests for PCD
- Tests for aspiration
- CF gene typing

Assess as for bronchiectasis /CSLD and manage accordingly. Review diagnosis on response to treatment and follow-up
Assessment of baseline severity

- Sputum
- Lung function
- Nutritional status
- Immunisation
Assessment of co-morbidities and exacerbators

- Air pollution
- Psychosocial
- Previous history: prematurity, tracheoesophageal fistula, asthma, chronic obstructive airway disease
- Neurodevelopmental delay, muscle weakness – aspiration risk
- Gastro oesophageal reflux disease
Way forward for tackling bronchiectasis in Africa

• Better understand the burden of disease through robustly assessing prevalence, aetiology and clinical outcomes in African children
  • Align definitions and diagnostic approach
  • Advocating for improved access to diagnostics

• Better understand relative risk factors for bronchiectasis, particularly in areas with high TB and HIV prevalence

• Better phenotype disease sub-groups, so that management (and research) can be better targeted

• Well designed studies to assess barriers to and impact of earlier diagnosis and current proposed management strategies
BACPAC Study – Bronchiectasis in African Children: Prevalence, Aetiology and Clinical outcome

- Collaborative initiative between 7 paediatric pulmonology services in South Africa.
- **Phase 1** – Establishment of a clinical registry of all children age 0-18 years known with bronchiectasis from any cause
- **Phase 2** – Prospective enrolment of children with chronic wet cough (>4 weeks) despite antibiotic treatment
- Current: 2 of 7 sites have started data collection with 118 children on the registry
- 2021 aim: to establish registry across all sites, to encourage work with colleagues for a PAN African registry. This registry aligns with EMBARC approach and hopes to contribute in time to international registry data.

- Principal investigators: Ameena Goga (UP), Diane Gray (UCT), Charl Verwey (WITS), Refiloe Masekela (UKZN)
- Co-investigators: Pierre Goussard (US), Fiona Kritzinger (Private), Gabaza Tiva (UL), Lore Van Bruwaene (US), Aneesa Vanker (UCT), Meryline Ndlovu (UKZN)
• Bronchiectasis is an important and largely preventable cause of chronic lung disease in children
• Untreated it can lead to a lifelong trajectory of worsening severity and premature death in adulthood
• Early intervention can improve outcome, case detection can be assisted through identification of key symptoms
• Diagnosis of bronchiectasis relies on clinical symptoms and radiological (currently HRCT) confirmation – *but diagnostic assessment and intervention can be actioned without HRCT*
• It is a very heterogeneous disease that requires better phenotyping to improve treatments and outcome
Non-CF bronchiectasis in children

Management

M Proesmans MD, PhD
Pediatric Pulmonology
University Hospital Leuven, Belgium
• I have no conflicts of interest to declare for this talk
Non-CF bronchiectasis in children

• Heterogenous disorder
• Many etiologies
• Diagnosis relies on evaluation of anatomical changes on chest CT
  • ‘Signet ring sign’: enlarged internal bronchial diameter relative to the adjacent artery
    • Airway/arterial ratio: > 1 or > 0.8?
  • Lack of bronchial tapering towards the periphery
  • Airway is clearly visible towards periphery
  • Airway has irregular wall
Non-CF bronchiectasis in children

Has been covered in part 1
• Etiology
• Epidemiology
• Pathogenesis
• Clinical features
• Diagnostic work-up

Will be covered in part 2
1. Management
   1.1 Airway mucus clearance
      1.1.1 Medication
      1.1.2 ACT
   1.2 ICS, SABA
   1.3 Antibiotic therapy
   1.4 Anti-inflammatory treatment
   1.5 Surgery

2. Follow-up/QoL/Prognosis
1. Management of non-CF bronchiectasis

**Aims at**

- Improving persistent/recurrent wet cough
- Reducing pulmonary exacerbations (Pex)
- Preserving lung function
- Slow/prevent progression of bronchiectasis
- Improving Qol
- Treat etiology if known
- Adress comorbidity
1.1.1 Airway clearance: medication

- Inhaled muco active drugs (CF drugs ..)
  - Hypertonic saline
    - No data in children
    - In adults positive effects on sputum properties and lung function (Kellet F et al 2011; Nicolson CH et al 2012)
  - Mannitol
    - Increases mucus clearance and improves sputum properties in adults (Daviskas E 1999, Daviskas E 2005, Daviskas E 2010)
    - No improvement in pulmonary function or symptoms (Bilton D 2013)
    - No data in children
  - rhDNAse
    - Only case reports in children
    - Meta analysis in adults: ineffective and potentially harmful (Tarrants BJ et al 2017)
1.1.2 Airway clearance techniques (ACT)

- Overall ACT are safe and improve sputum expectoration
- Lack of RCT’s in children with non CF bronchiectasis ([Snijders D et al 2015](#))
  - Many studies in adults, almost none in children ([Poeta M et al 2020 Review](#))
  - Improve sputum expectoration and decrease sputum volume
  - Cochrane review in adults and children (2015)
    - Safe
    - Potentially beneficial for sputum expectoration; lung function; QoL
    - Role in treatment of acute exacerbations not clear
    - Additional studies are needed

- Which techniques?
  - Individually assess
  - No added value proven of expensive aids like VEST, cough assist etc
  - Positive pressure/oscillating devices can be helpful: PEP mask, flutter
  - Autogenic drainage, active cycle of breathing, assisted cough techniques ..
1.2 Asthma medication? ICS and SABA/LABA

• Largely overused in this context
• Most likely only useful in children with asthma co-diagnosis
  • Although studies in adults show some benefit ..
1.3 Antibiotic therapy

• To treat acute exacerbations
  • If possible guided by sputum culture

• On long term basis
  • To prevent Pex and reduce lung function decline
  • Cochrane review in adults and children (2015)
    • Risk for Pex reduced by 50%
    • Risk of Emergence of drug resistant bacteria 30%
    • AB studies were oral/inhaled and a large variation (not including TMP/SMX)
  • Several small studies on inhaled AB suggest some benefit but are insufficient to recommend their use
1.3 Antibiotic therapy

- Most isolated bacteria
  - *H influenzae*, *S pneumoniae*, *M catarrhalis* (90% beta lactamase +ve)
  - *(P aeruginosa)*

- AB choices
  - Amoxyclav, cefuroxim, macrolides
  - Cotrimoxazole (! high Moraxella resistance)

South African data: Expectorated/induced sputum
N= 66 (79% HIV infected)
Verwey et al 2017
Amoxycilav in treatment of chronic wet cough (>3 weeks) in children

Table 1  Subject characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=25)</th>
<th>Placebo group (n=25)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>1.75 (0.9, 4.6)</td>
<td>2.8 (0.95, 5.25)</td>
<td>0.34</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (56)</td>
<td>12 (48)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cough duration in weeks, median (IQR)</td>
<td>15.0 (8.5–59)</td>
<td>11.0 (4.0–28)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoke exposure, n (%)</td>
<td>8 (32)</td>
<td>7 (28)</td>
<td>0.75</td>
</tr>
<tr>
<td>VCD score, median (IQR)</td>
<td>3.0 (2.0–3.0)</td>
<td>2.5 (2.0–3.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>CXR abnormal, n (%)</td>
<td>9 (41%) (n=22)</td>
<td>6 (30%) (n=20)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

BAL data

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=19)</th>
<th>Placebo group (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell count (×10³/litre), median (IQR)</td>
<td>426.0 (196.0–632.0)</td>
<td>261.0 (185.5–467.5)</td>
</tr>
<tr>
<td>% Neutrophil, median (IQR)</td>
<td>38.5 (13.0–58.0)</td>
<td>34.5 (8.0–66.0)</td>
</tr>
<tr>
<td>Significant bacterial culture, n (%)</td>
<td>13 (68)</td>
<td>14 (78)</td>
</tr>
</tbody>
</table>

BAL, bronchoalveolar lavage; CXR, chest x-ray; VCD, verbal descriptive category score.17

Marchant et al Thorax 2012
Amoxycillin (14 days) in treatment of chronic wet cough (>3 weeks) in children

Figure 3 Median verbal category cough scores prior to commencement of study medications (pre), at baseline (day −1), treatment days (days 1–14), and after completion of the study (post). Dotted line = amoxycillin clavulanate group; Continuous line = placebo group. RCT, randomised controlled trial.

Table 2 Verbal category descriptive cough scores and cough resolution post intervention

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n = 25)</th>
<th>Placebo group (n = 25)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough resolution, n (%)</td>
<td>12 (48)</td>
<td>4 (16)</td>
<td>0.015</td>
</tr>
<tr>
<td>VCD score at end of treatment, median (IQR)</td>
<td>0.5 (0.0−2.0)</td>
<td>2.25 (1.15−2.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>VCD score at end of study on day 28, median (IQR)</td>
<td>0.0 (0.0−1.5)</td>
<td>1.0 (0.0−2.4)</td>
<td>0.17*</td>
</tr>
<tr>
<td>Change† in VCD score, median (IQR)</td>
<td>1.5 (0.0−2.5)</td>
<td>0.5 (−0.4−1.0)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Placebo group had access to antibiotics after day 14.
†End-treatment minus baseline VCD score.
VCD, verbal descriptive category score.
Acute Pex in non CF BX: amoxyclav or azithromycin for 21 days?

Goyal et al Lancet 2018
Acute Pex in non CF Bx:
placebo, amoxyclav or azithromycin for 14 days?

• Non-CF Bx median age 6 years; non severe exacerbations
• Azithro maintenance excluded
• Between 4-10% long term use of other AB

Goyal et al Lancet 2019
Acute Pex in non CF Bx: placebo, amocyclav or azithromycin for 14 days?

- Exacerbation resolution by day 14
  - Placebo group: 29 (43%)
  - Amoxicillin–clavulanate group: 41 (65%) (RR for resolution 1·50 [95% CI 1·08–2·09] vs placebo, p=0·015; NNT 5 [95% CI 3–20]).
  - Azithro group: 41 (61%) (RR for resolution 1·41 [1·01–1·97] vs placebo, p=0·042; NNT 6 [3–79]).

- The median duration of exacerbation:
  - Placebo group (10 days [IQR 6–12])
  - Amoxicillin–clavulanate group (7 days [6–10], p=0·018),
  - Azithromycin group (8 days [5–12], p=0·24).

- The median time to next exacerbation after resolution was similar in all three groups

- CONCLUSION: amoxyclav remains the first choice for treatment of exacerbations
1.4 Anti-inflammatory therapy: Macrolides

- Excellent tissue penetration
- Broad efficacy against many respiratory pathogens
  - Prevent bacterial replication; mainly bacteriostatic
- Inhibit biofilm formation
- Reduce mucus secretion
- Anti-inflammatory properties (all 14 and 15 membered macrolides)
  - Inhibit neutrophil migration
  - Inhibit pro-inflammatory cytokines
  - Inhibit adherence of microorganisms
  - Inhibit bacterial virulence and toxin production
- Azitromycin
  - Does not inhibit CYP3A4
  - Prolonged half life
  - Accumulation in phagocytes
Macrolides in pediatric non CF bronchiectasis

**TABLE 3** Summary of clinical trials of the use of macrolide therapy in pediatric non-cystic fibrosis bronchiectasis

<table>
<thead>
<tr>
<th>Study/design</th>
<th>Number of subjects</th>
<th>Macrolide dosage</th>
<th>Length of follow up</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kho et al/RDBPCT&lt;sup&gt;83&lt;/sup&gt;</td>
<td>25</td>
<td>Roxithromycin 4 mg/kg, Twice daily</td>
<td>3 months</td>
<td>↓AHR, ↓Sputum purulence, No difference in PFTs</td>
</tr>
<tr>
<td>Yalcin et al/RCT&lt;sup&gt;84&lt;/sup&gt;</td>
<td>34</td>
<td>Clarithromycin 15 mg/kg, Once daily</td>
<td>3 months</td>
<td>↓Sputum production, ↑FEF (25-75%), ↓IL-8 Levels, total cell count, neutrophil ratios in BAL</td>
</tr>
<tr>
<td>Valerie et al/RDBCT&lt;sup&gt;85&lt;/sup&gt;</td>
<td>89</td>
<td>Azithromycin 30 mg/kg, Once a week</td>
<td>12-24 months</td>
<td>↓Pulmonary exacerbations by 50%, Improved weight-for age Z-scores, ↓Non-pulmonary illnesses</td>
</tr>
</tbody>
</table>

AHR, airway hyper responsiveness; BAL, bronchoalveolar lavage; FEF (25-75%), forced expiratory flow; PFTs, pulmonary function tests; RCT, randomized controlled trial; RDBPCT, randomized double-blind Placebo controlled trial.
# Metanalysis of macrolides in non CF bronchiectasis

## Table 1

<table>
<thead>
<tr>
<th>Study period</th>
<th>Location</th>
<th>Study design</th>
<th>Total Sample (M/F)</th>
<th>Age range</th>
<th>Diagnosis criteria</th>
<th>Exacerbation history and bronchiectasis states</th>
<th>Macrolides dose and frequency</th>
<th>Therapy duration Follow-up duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koreh Y.Y</td>
<td>Korea</td>
<td>DB.RCT</td>
<td>25 (19/16)</td>
<td>10–18</td>
<td>Stable bronchiectasis, increased AR</td>
<td>Roithromycin 4mg/kg twice daily</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Chang M</td>
<td>China</td>
<td>DB.RCT</td>
<td>21 (14/7)</td>
<td>35–70</td>
<td>Acute exacerbation bronchiectasis</td>
<td>Erythromycin 250 mg twice daily</td>
<td>8 weeks</td>
<td></td>
</tr>
<tr>
<td>Cymbala AA</td>
<td>America</td>
<td>Open label, crossover, RCT</td>
<td>22 (11/11)</td>
<td>≥18 years</td>
<td>HRCT</td>
<td>NR</td>
<td>Azithromycin 500 mg twice weekly</td>
<td>6 months</td>
</tr>
<tr>
<td>JF Liu</td>
<td>China</td>
<td>DB.RCT</td>
<td>43 (22/21)</td>
<td>18–65</td>
<td>Stable bronchiectasis</td>
<td>Roithromycin 150 mg once daily</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Wang G</td>
<td>New Zealand</td>
<td>DB.RCT</td>
<td>141 (71/70)</td>
<td>≥18 years</td>
<td>Stable bronchiectasis: ≥1 exacerbation in the past</td>
<td>Azithromycin 500 mg thrice weekly</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Maseela R</td>
<td>South Africa</td>
<td>DB.RCT</td>
<td>31 (17/14)</td>
<td>6–18</td>
<td>HRCT</td>
<td>Bronchiectasis associated with HIV</td>
<td>Erythromycin, &lt;15 kg 125 mg, &gt;15 kg 250 mg per day</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Valery PC</td>
<td>Australia</td>
<td>DB.RCT</td>
<td>89 (45/44)</td>
<td>1–8</td>
<td>HRCT</td>
<td>Stable bronchiectasis: ≥1 exacerbation in the past</td>
<td>Azithromycin 250 mg once daily</td>
<td>12–24 months</td>
</tr>
<tr>
<td>Sentier DJ</td>
<td>Australia</td>
<td>DB.RCT</td>
<td>117 (59/58)</td>
<td>20–85</td>
<td>HRCT</td>
<td>Pyelonephritis</td>
<td>Erythromycin, 400 mg twice daily</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Altenburg J</td>
<td>Netherland</td>
<td>DB.RCT</td>
<td>63 (43/20)</td>
<td>≥18 years</td>
<td>HRCT or plain bronchiectasis</td>
<td>Azithromycin 250 mg thrice weekly</td>
<td>52 weeks</td>
<td></td>
</tr>
<tr>
<td>De Diego</td>
<td>Spain</td>
<td>Open label, RCT</td>
<td>30 (16/14)</td>
<td>≥18 years</td>
<td>Bronchiectasis</td>
<td>Azithromycin 250 mg thrice weekly</td>
<td>3 months</td>
<td></td>
</tr>
</tbody>
</table>

AR = airway responsiveness; C = control group; DB = double blinded; F = female; HIV = human immunodeficiency virus; HRCT = high Resolution CT; LRTI = lower respiratory tract infection; M = male; NR = not reported; RCT = randomized controlled trial; T = treat group.
Macrolides and Pex

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>microlide</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.6.1 children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koh Y.Y 1997</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Valery PC 2013</td>
<td>9</td>
<td>45</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Masekela R 2013</td>
<td>3</td>
<td>17</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>75</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>25</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 3.63, df = 2 (P = 0.16); I² = 45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Z = 3.47 (P = 0.0005)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.6.3 Azithromycin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>microlide</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Cymbala AA 2005</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Wong C 2012</td>
<td>49</td>
<td>71</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>Valery PC 2013</td>
<td>9</td>
<td>45</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Allenburg J 2013</td>
<td>23</td>
<td>43</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>170</td>
<td>165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>90</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 0.93, df = 3 (P = 0.82); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Z = 5.35 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Donghai Wang et al 2019
BREATHE RCT

• Effect of once weekly AZM /placebo for 48 weeks
• Zimbabwe and Malawi
• In children with HIV associated chronic lung disease
  • 6-19 years old
  • HIV mother to child transmission
  • ART for at least 6 months
  • Diagnosis of HIV associated CLD with FEV z score < -z score (at start -1.64 z score) and lack of SABA reversibility
• Primary outcome: FEV1 z score at 48 weeks
• Secondary outcomes:
  • N of ARE, time to first ARE, death, all cause hospitalisation, infections, weight z score

Ferrand RA et al 2020
BREATHE RCT

• Primary outcome: FEV1 z score not different

![Figure 3. Intervention Effect (Adjusted Mean Difference [AMD]) for the Primary Outcome Overall and by Subgroups](image)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo Patients, N</th>
<th>Mean (SD)</th>
<th>AZM Patients, N</th>
<th>Mean (SD)</th>
<th>AMD (95% CI)</th>
<th>Placebo better</th>
<th>AZM better</th>
<th>$P$ value for interaction from linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall association</td>
<td>146</td>
<td>-1.95 (0.91)</td>
<td>162</td>
<td>-1.90 (0.90)</td>
<td>0.05 (-0.19 to 0.23)</td>
<td></td>
<td></td>
<td>.29</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>73</td>
<td>-1.99 (0.90)</td>
<td>73</td>
<td>-2.00 (0.89)</td>
<td>-0.01 (-0.25 to 0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>-1.91 (0.93)</td>
<td>89</td>
<td>-1.82 (0.89)</td>
<td>0.09 (-0.09 to 0.37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15.25 y</td>
<td>64</td>
<td>-1.75 (0.94)</td>
<td>55</td>
<td>-1.91 (0.99)</td>
<td>-0.16 (-0.32 to 0.01)</td>
<td></td>
<td></td>
<td>.28</td>
</tr>
<tr>
<td>≥15.25 y</td>
<td>82</td>
<td>-2.10 (0.87)</td>
<td>67</td>
<td>-1.89 (0.75)</td>
<td>0.14 (-0.04 to 0.32)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>FEV1 z score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>81</td>
<td>-1.55 (0.64)</td>
<td>88</td>
<td>-1.46 (0.63)</td>
<td>0.09 (-0.10 to 0.29)</td>
<td></td>
<td></td>
<td>.96</td>
</tr>
<tr>
<td>&lt;2</td>
<td>65</td>
<td>-2.46 (0.97)</td>
<td>74</td>
<td>-2.42 (0.69)</td>
<td>-0.04 (-0.10 to 0.39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV viral load</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10000 copies/ml</td>
<td>83</td>
<td>-1.84 (0.77)</td>
<td>96</td>
<td>-1.79 (0.84)</td>
<td>.04 (-0.14 to 0.23)</td>
<td></td>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>≥10000 copies/ml</td>
<td>64</td>
<td>-2.09 (1.06)</td>
<td>64</td>
<td>-2.07 (0.95)</td>
<td>.05 (-0.21 to 0.30)</td>
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<tr>
<td>Weight-for age z score</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>76</td>
<td>-1.84 (0.95)</td>
<td>67</td>
<td>-1.76 (0.90)</td>
<td>.05 (-0.18 to 0.29)</td>
<td></td>
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<td>.86</td>
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<tr>
<td>&lt;2</td>
<td>70</td>
<td>-2.07 (0.86)</td>
<td>95</td>
<td>-2.00 (0.88)</td>
<td>.08 (-0.11 to 0.27)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Height-for age z score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>61</td>
<td>-1.84 (0.90)</td>
<td>71</td>
<td>-1.79 (0.83)</td>
<td>.04 (-0.17 to 0.25)</td>
<td></td>
<td></td>
<td>.77</td>
</tr>
<tr>
<td>&lt;2</td>
<td>65</td>
<td>-2.08 (0.92)</td>
<td>51</td>
<td>-1.99 (0.94)</td>
<td>.00 (-0.11 to 0.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>108</td>
<td>-1.92 (0.82)</td>
<td>111</td>
<td>-1.84 (0.81)</td>
<td>.12 (-0.03 to 0.27)</td>
<td></td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>Malawi</td>
<td>38</td>
<td>-2.04 (1.15)</td>
<td>51</td>
<td>-2.02 (1.05)</td>
<td>-0.09 (-0.41 to 0.25)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AZM indicates azithromycin, and FEV1, forced expiratory volume in 1 second.
Secondary outcomes

Figure 2. Cumulative Incidence of Time-to-Event Outcomes, Intention to Treat Analyses

A. First acute respiratory exacerbation
- HR, 0.50; 95% CI, 0.27-0.92; P = .03

B. All acute respiratory exacerbations
- HR, 0.50; 95% CI, 0.27-0.92; P = .03

C. All hospitalizations
- HR, 0.24; 95% CI, 0.06-1.07; P = .06

Graphs show data for first acute respiratory exacerbation (A), all acute respiratory exacerbations (B), and all-cause hospitalizations (C). AZM indicates azithromycin.

Ferrand RA et al 2020
Adverse effects of long term macrolides

• Macrolide resistance increases
  • Adult studies
    • *S pneumoniae*, oropharyngeal streptococci, *Moraxella, Hemophilus, S aureus* (*Embrace study, BAT trial, BLESS trial*)
    • However no effect on Pex; need for IV AB
  • Pediatric studies
    • Effect of macrolide use on *Moraxella* macrolide S is limited (*Hare 2019*)

• Changes in airway microbiota
  • More *P aeruginosa* with erytro (*Rogers 2019*)

• GI complaints
  • Less with azitro compared to erythro
Carriage and resistentence with long term AZM therapy

- RCT weekly AZT for 24 months with 12 months FU (Valery et al 2013)
- Australia (n= 38) and New Zealand (n=40)
- AZM versus Placebo
  - Lower carriage of *H influenzae* and *M cattharalis*
  - More macrolide resistant *S aureus* and *S pneumoniae*
    - Recovery of *S pneumoniae* R not of *S aureus* R
  - No isolation of *P aeruginosa*

*Hare et al 2015*
1.5 Surgery (Lobectomy, segmentectomy)

- Only indicated in case of localised disease and insufficient response to medical treatment
- Caution if underlying disease is progressive (such as PCD)
- Several pediatric studies available
  - Complete resolution of symptoms in 42-73% of children
  - However complications in 13-17% and mortality of 5.6% (Andrade C 2014, Sirmali M 2007)
Personal experience:
can make a big difference in well selected cases!

PCD

SPAD and chronic aspiration

Humoral immunodef R/ SCIGG
2.1 Follow-up

• AIM: stabilise/improve symptoms and lung disease

• Base line follow-up
  • History on cough, sputa, SOB, Pex
  • Therapy review (including adherence!)
  • Clinical exam
  • Spirometry (if old enough)
  • Oxygen sats
  • Comorbidities (and diagnostic clues)

• Radiology ?
  • CT scan? Scoring ? Every how many years? On indication ?
Chest CT (scoring) ?

- CT is superior to chest Xray and LF for assessment and monitoring pediatric bronchiectasis
- Low dose CT protocols have radiation doses comparable to chest Xray
- CT scoring systems developed for CF may not always be appropriate for other causes of bronchiectasis
- Pulmonary MRI (with hyperpolarized gas) can be performed in dedicated centers yield images comparable to CT

Murphy KP et al AJR 2016; Robinson P 2018
2.2 Disease severity/impact on Qol

<table>
<thead>
<tr>
<th>Variables</th>
<th>CF (n = 20)</th>
<th>Non-CF bronchiectasis (n = 20)</th>
<th>Typically developing (n = 20)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11.40 ± 3.15</td>
<td>12.90 ± 2.71</td>
<td>12.05 ± 3.18</td>
<td>2.47</td>
<td>.291</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/9</td>
<td>7/13</td>
<td>12/8</td>
<td>2.80</td>
<td>.247</td>
</tr>
<tr>
<td>Height, z score</td>
<td>-0.90 ± 1.33</td>
<td>-0.76 ± 1.09</td>
<td>0.69 ± 1.09</td>
<td>14.74</td>
<td>.001*</td>
</tr>
<tr>
<td>Weight, z score</td>
<td>-0.84 ± 0.99</td>
<td>-0.76 ± 1.10</td>
<td>0.46 ± 1.13</td>
<td>4.44</td>
<td>.109</td>
</tr>
<tr>
<td>BMI, z score</td>
<td>-0.41 ± 0.88</td>
<td>-0.47 ± 1.19</td>
<td>0.17 ± 1.11</td>
<td>5.10</td>
<td>.078</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>84.45 ± 23.00</td>
<td>76.35 ± 19.59</td>
<td>93.80 ± 11.94</td>
<td>7.08</td>
<td>.029*</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;3&lt;/sub&gt; z score</td>
<td>-1.18 ± 1.69</td>
<td>-1.96 ± 2.34</td>
<td>-0.30 ± 1.92</td>
<td>12.61</td>
<td>.002*</td>
</tr>
<tr>
<td>MIP, cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>92.95 ± 21.12</td>
<td>81.65 ± 25.75</td>
<td>94.85 ± 14.67</td>
<td>4.37</td>
<td>.112</td>
</tr>
<tr>
<td>%MIP</td>
<td>103.68 ± 31.41</td>
<td>94.38 ± 30.68</td>
<td>94.67 ± 22.52</td>
<td>3.11</td>
<td>.211</td>
</tr>
<tr>
<td>MEP, cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>101.25 ± 19.93</td>
<td>94.55 ± 22.95</td>
<td>103.05 ± 27.87</td>
<td>2.58</td>
<td>.275</td>
</tr>
<tr>
<td>%MEP</td>
<td>91.95 ± 22.23</td>
<td>83.63 ± 25.99</td>
<td>94.01 ± 30.95</td>
<td>0.40</td>
<td>.523</td>
</tr>
</tbody>
</table>

Ozipek M et al Pediatric Pulmonology 2020
Monocentric academic cross sectional study
### 2.2 Disease severity/impact on QoL

**Table 5** Pediatric Outcome Data Collection Instrument scores of CF, non-CF bronchiectasis, and typically developing children

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>CF (n = 20)</th>
<th>Non-CF bronchiectasis (n = 20)</th>
<th>Typically developing (n = 20)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global function</strong></td>
<td>348.90 ± 40.92</td>
<td>353.95 ± 35.56</td>
<td>376.05 ± 25.13</td>
<td>7.83</td>
<td>.020*</td>
</tr>
<tr>
<td><strong>Upper extremity physical function</strong></td>
<td>90.85 ± 10.70</td>
<td>93.25 ± 6.94</td>
<td>95.95 ± 5.19</td>
<td>3.07</td>
<td>.214</td>
</tr>
<tr>
<td><strong>Sports/physical function</strong></td>
<td>82.65 ± 13.26</td>
<td>82.05 ± 15.88</td>
<td>92.95 ± 8.13</td>
<td>9.59</td>
<td>.008*</td>
</tr>
<tr>
<td><strong>Transfers/basic mobility</strong></td>
<td>97.85 ± 6.92</td>
<td>97.80 ± 4.14</td>
<td>99.10 ± 1.97</td>
<td>1.42</td>
<td>.491</td>
</tr>
<tr>
<td><strong>Pain/comfort</strong></td>
<td>77.55 ± 19.68</td>
<td>80.85 ± 17.71</td>
<td>88.05 ± 15.17</td>
<td>4.25</td>
<td>.119</td>
</tr>
<tr>
<td><strong>Happiness</strong></td>
<td>82.75 ± 16.81</td>
<td>83.25 ± 17.11</td>
<td>86.75 ± 15.49</td>
<td>0.86</td>
<td>.650</td>
</tr>
<tr>
<td><strong>Expectations</strong></td>
<td>87.30 ± 10.17</td>
<td>88.50 ± 8.99</td>
<td>93.95 ± 6.35</td>
<td>7.74</td>
<td>.021*</td>
</tr>
</tbody>
</table>

**Adolescents**

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>CF (n = 20)</th>
<th>Non-CF bronchiectasis (n = 20)</th>
<th>Typically developing (n = 20)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global function</strong></td>
<td>356.18 ± 43.03</td>
<td>346.37 ± 41.88</td>
<td>386.07 ± 12.11</td>
<td>8.59</td>
<td>.014*</td>
</tr>
<tr>
<td><strong>Upper extremity physical function</strong></td>
<td>94.96 ± 7.77</td>
<td>91.00 ± 10.21</td>
<td>98.00 ± 2.60</td>
<td>5.20</td>
<td>.074</td>
</tr>
<tr>
<td><strong>Sports/physical function</strong></td>
<td>81.72 ± 18.54</td>
<td>80.56 ± 16.50</td>
<td>92.00 ± 7.51</td>
<td>4.53</td>
<td>.103</td>
</tr>
<tr>
<td><strong>Transfers/basic mobility</strong></td>
<td>99.27 ± 1.84</td>
<td>98.00 ± 3.84</td>
<td>100.00 ± 0.00</td>
<td>6.56</td>
<td>.037*</td>
</tr>
<tr>
<td><strong>Pain/comfort</strong></td>
<td>80.81 ± 23.78</td>
<td>76.81 ± 22.36</td>
<td>96.07 ± 8.19</td>
<td>9.95</td>
<td>.007*</td>
</tr>
<tr>
<td><strong>Happiness</strong></td>
<td>77.72 ± 24.93</td>
<td>74.68 ± 20.85</td>
<td>84.28 ± 16.39</td>
<td>1.24</td>
<td>.537</td>
</tr>
<tr>
<td><strong>Expectations</strong></td>
<td>83.00 ± 17.14</td>
<td>85.93 ± 10.48</td>
<td>96.50 ± 3.08</td>
<td>10.39</td>
<td>.006*</td>
</tr>
</tbody>
</table>

Abbreviation: CF, cystic fibrosis.

*\( P < .05 \), the Kruskal-Wallis Test.
2.2 QoL in children with non CF bronchiectasis

<table>
<thead>
<tr>
<th>Country, year</th>
<th>Number</th>
<th>Type of study</th>
<th>Age (years)</th>
<th>Questionnaire</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia, 2010</td>
<td>60</td>
<td>Cross-sectional</td>
<td>Median (IQR): 7 (3, 8, 10.9)</td>
<td>PC-QOL, DASS21</td>
<td>Parents of young children were more likely to report an impaired QoL. Radiological extent, baseline lung function, underlying etiology, and chronic upper airway disease did not influence the burden of disease scores.</td>
</tr>
<tr>
<td>Malaysia, 2014</td>
<td>60 (CF = 10; others = 50)</td>
<td>Cross-sectional</td>
<td>Median (range): 1.3 (3.5–11)</td>
<td>PC-QOL, DASS21</td>
<td>Mental health of patients with children with CF were better than those with NCFB. Frequent exacerbations, frequent cough, age of diagnosis, and age of patients were not significantly associated with PC-QOL scores.</td>
</tr>
<tr>
<td>Turkey, 2014</td>
<td>76</td>
<td>Case–control</td>
<td>11.7 (±2.8)</td>
<td>CDI, STAI-C, PedsQL-P, PedsQL-C</td>
<td>Patients did not have depression and anxiety scores significantly different from controls. CDI and STAI-C scores negatively correlated with QoL scores. Parents reported worse QoL in physical, psychosocial, and total areas. Number of exacerbations and hospitalizations, FEV1/FVC%, predicted dyspnea, and wheezing severity were the significant factors associated with a worse QoL. Patients reported worse physical QoL.</td>
</tr>
<tr>
<td>Turkey, 2014</td>
<td>42</td>
<td>Cross-sectional</td>
<td>12.7 (±2.3)</td>
<td>SF-36, SGRQ</td>
<td>Symptom subscale of SGRQ correlated positively with low lung function and frequent antibiotic requirements. Inverse correlation between SGRQ symptom scores and the duration of regular follow-up. No correlation between SGRQ scores and current age, age at diagnosis, age at the beginning of the symptoms, height and weight Z-scores, etiology of NCFB, sputum microbiology, HPCT score, and socioeconomic status.</td>
</tr>
<tr>
<td>UK, 2010</td>
<td>78 PCD</td>
<td>Cross-sectional</td>
<td>SF-36, SGRQ</td>
<td></td>
<td>Patients with the highest treatment burden had worse QoL. Positive correlation between time since diagnosis and improvement in perceived QOL. No correlation between scores with age or age at diagnosis.</td>
</tr>
</tbody>
</table>

CDI, The Child Depression Inventory; STAI-C, State-Trait Anxiety Inventories for Children; PedsQL-P, Pediatric Quality of Life Inventory Parent Version; PedsQL-C, Pediatric Quality of Life Inventory Child Version; SF-36, Short Form-36; SGRQ, St George’s Respiratory Questionnaire; PCD, primary ciliary dyskinesia; CF, cystic fibrosis; DASS21, Depression Anxiety Stress Scale 21; PC-QOL, parent-cough specific quality of life questionnaire.

Review Nathan AM et al 2017
2.3 Prognosis

• Mortality: mostly adult data
  • Prospective study (Goeminne et al 2014)
    • N = 245 median age 68 years
    • 20% mortality over 5 years
    • Risk factors: numbers of lobes affected and associated COPD

• Survival on lung transplant list (Hayes D et al 2015)
  • Advanced non-CF bronchiectasis (mean age 39 years) lower mortality compared to CF (mean age 29 years)
Summary: non-CF bronchiectasis in children

• Treatment
  • Airway mucus clearance
  • Antibiotics
    • for acute Pex
    • As maintenance
  • Macrolide anti-inflammatory treatment
    • Reduce exacerbations
    • Azitromycin more effective than other macrolides
    • Risk of macrolide resistance
  • Surgery for rare/selected cases

• QoL/Prognosis
  • Depending on underlying disease/severity..
  • More studies needed
Extra
BREATHE RCT *(Ferrand RA et al 2020)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZM group (n = 173)</td>
<td>Placebo group (n = 174)</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>14.7 (12.6-16.8)</td>
<td>15.8 (13.0-18.1)</td>
</tr>
<tr>
<td>Female</td>
<td>80 (46.2)</td>
<td>90 (51.7)</td>
</tr>
<tr>
<td>Currently in school</td>
<td>146 (84.4)</td>
<td>139 (79.9)</td>
</tr>
<tr>
<td>HIV characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, median (IQR), y</td>
<td>7.2 (3.5-9.9)</td>
<td>8.3 (5.2-11.1)</td>
</tr>
<tr>
<td>Cotrimoxazole prophylaxis</td>
<td>157 (90.7)</td>
<td>156 (89.7)</td>
</tr>
<tr>
<td>Duration taking antiretroviral therapy, median (IQR), y</td>
<td>5.9 (3.8-9.0)</td>
<td>6.4 (3.9-8.2)</td>
</tr>
<tr>
<td>HIV viral load log10 copies/mL, median (IQR)a</td>
<td>2.5 (1.6-4.0)</td>
<td>2.7 (1.7-4.1)</td>
</tr>
<tr>
<td>HIV viral load &lt;1000 copies/mL</td>
<td>100 (58.5)</td>
<td>94 (54.0)</td>
</tr>
<tr>
<td>CD4 cell count/mm³, median (IQR)</td>
<td>601 (417-784)</td>
<td>550 (325-779)</td>
</tr>
<tr>
<td>Lung function characteristics, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ z score</td>
<td>-2.01 (0.76)</td>
<td>-2.00 (0.74)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.59 (0.50)</td>
<td>1.71 (0.53)</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>73.3 (10.3)</td>
<td>73.6 (10.2)</td>
</tr>
<tr>
<td>FVC z scorea</td>
<td>-1.77 (0.97)</td>
<td>-1.71 (0.89)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.89 (0.59)</td>
<td>2.04 (0.63)</td>
</tr>
<tr>
<td>FVC, %</td>
<td>77.8 (12.0)</td>
<td>78.4 (11.0)</td>
</tr>
<tr>
<td>FEV₁:FVC ratio z scorea</td>
<td>-0.66 (1.14)</td>
<td>-0.74 (1.13)</td>
</tr>
<tr>
<td>FEV₁:FVC ratio</td>
<td>0.85 (0.08)</td>
<td>0.84 (0.08)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight-for-age z score, mean (SD)</td>
<td>-2.23 (1.43)</td>
<td>-2.07 (1.50)</td>
</tr>
<tr>
<td>Underweightb</td>
<td>98 (56.7)</td>
<td>83 (47.7)</td>
</tr>
<tr>
<td>Height-for-age z score, mean (SD)</td>
<td>-2.16 (1.18)</td>
<td>-2.04 (1.24)</td>
</tr>
<tr>
<td>Stuntedc</td>
<td>95 (54.9)</td>
<td>80 (46.0)</td>
</tr>
<tr>
<td>History of tuberculosis</td>
<td>58 (33.5)</td>
<td>39 (22.4)</td>
</tr>
<tr>
<td>Admitted for chest problems in last year</td>
<td>3 (1.7)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Current cough</td>
<td>13 (7.5)</td>
<td>18 (10.3)</td>
</tr>
<tr>
<td>Coughing up sputum</td>
<td>7 (4.0)</td>
<td>17 (9.8)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>5 (2.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Respiratory rate, mean (SD), breaths/min</td>
<td>22.2 (3.0)</td>
<td>22.6 (3.2)</td>
</tr>
<tr>
<td>Abnormal respiratory rate</td>
<td>67 (38.7)</td>
<td>85 (48.9)</td>
</tr>
<tr>
<td>Oxygen saturation, mean (SD), %c</td>
<td>96.7 (3.0)</td>
<td>96.7 (2.4)</td>
</tr>
<tr>
<td>Oxygen saturation &lt;92%</td>
<td>6 (3.5%)</td>
<td>11 (6.3%)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats/minα</td>
<td>87.6 (12.5)</td>
<td>85.6 (11.6)</td>
</tr>
<tr>
<td>Abnormal heart rateα</td>
<td>6 (3.5%)</td>
<td>8 (4.6%)</td>
</tr>
<tr>
<td>Shuttle walk duration, mean (SD), mins²</td>
<td>10.26 (1.56)</td>
<td>10.49 (2.03)</td>
</tr>
</tbody>
</table>
2. Prognosis?

• Little data

• Comparison to historical cohort (Eralp et al 2020, Turkey)
  • Less clubbing
  • Better LF
  • No decrease in exacerbations
Prognosis: exercise capacity (mean age 19 y)

Table 3. Cardiopulmonary parameters in CF and Non-CF bronchiectasis patients.

| Parameter                          | CF (n = 49) | Non-CF (n = 53) | Control (n = 88) | p value
|-----------------------------------|-------------|-----------------|-----------------|---------
<p>|                                   |             |                 |                 | Control vs CF | Control vs Non-CF | CF vs Non-CF |
| FEV(_1) (L/Sec) *              | 2.1 ± 0.83  | 2.0 ± 0.9       | 2.9 ± 1.03      | &lt;0.0001   | &lt;0.0001          | NS           |
| FEV(_1) (% Predicted) *        | 70.9 ± 20.5 | 68.7 ± 21.5     | 99.1 ± 12.4     | &lt;0.0001   | &lt;0.0001          | NS           |
| FVC (L) *                         | 2.8 ± 1.0   | 2.7 ± 1.1       | 3.5 ± 1.3       | &lt;0.005    | &lt;0.005           | NS           |
| FVC (% Pred) *                    | 82.9 ± 18.5 | 79.9 ± 20.6     | 102.2 ± 12.0    | &lt;0.0001   | &lt;0.0001          | NS           |
| Peak VO(_2) (mL/min)            | 1915.5 ± 702.0 | 1740 ± 568       | 2111.0 ± 748.3 | NS       | 0.007            | NS           |
| Peak VO(_2) (%Pred)             | 92.9 ± 21.9 | 87.7 ± 19.0     | 101.6 ± 19.7    | 0.049     | &lt;0.0001          | NS           |
| Peak VO(_2)/kg (mL/kg/min)      | 37.7 ± 10.3 | 35.3 ± 10.8     | 39.6 ± 8.9      | NS       | 0.035            | NS           |
| RER                               | 1.05 [0.98–1.13] | 1.03 [0.98–1.10] | 1.13 [1.03–1.20] | &lt;0.01     | &lt;0.01            | NS           |
| Peak HR (%pred)                   | 89 [85–96]  | 92 [87–96]      | 94 [92–97]      | 0.001     | NS               | NS           |
| Lowest VE/VCO(_2)              | 31.4 ± 4.1  | 31.7 ± 4.1      | 27.2 ± 2.8      | &lt;0.0001   | 0.008            | NS           |
| VO(_2)/peak HR (mL/min/beat)   | 10.8 ± 3.9  | 9.6 ± 3.0       | 11.6 ± 4.3      | NS       | 0.010            | NS           |
| VO(_2)/peakHR (%Pred)          | 100.6 ± 21.8 | 92.6 ± 18.3     | 108.0 ± 20.5    | NS       | &lt;0.0001          | 0.046        |
| peakVE (L/min)                    | 68.8 ± 27.4 | 60.2 ± 22.7     | 77.3 ± 31.1     | NS       | 0.002            | NS           |
| MVV (L/min)                       | 86.1 ± 35.4 | 81.6 ± 35.9     | 120.8 ± 42.9    | &lt;0.0001   | &lt;0.0001          | NS           |
| SpO(_2) (%) (pre)              | 98.3 ± 1.8** | 98.7 ± 2.3***   | 99.5 ± 0.86     | 0.001     | 0.032            | NS           |
| SpO(_2) (%) (post)             | 97.4 ± 4.0** | 97.7 ± 4.9***   | 99.3 ± 0.99     | 0.006     | 0.023            | NS           |
| Low Breathing Reserve n (%)       | 24 (49%)    | 23 (43%)        | 4 (5%)          | &lt;0.0001   | &lt;0.0001          | NS           |
| CT score                          | 9.23±5.9    | 9.10±5.1        | NA              | NA       | NA               | NS           |</p>
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Main results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive expiratory pressure mask&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Significant improvement of pre-versus post-treatment regional lung ventilation.</td>
<td>8-week trial in 6 children</td>
</tr>
<tr>
<td></td>
<td>No change of pre- versus post-treatment FEV&lt;sub&gt;1&lt;/sub&gt;.</td>
<td>No comparison group not undergoing airway clearance techniques.</td>
</tr>
<tr>
<td>Supervised physiotherapy&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Significant thoracic gas volume decrease and FEV&lt;sub&gt;1&lt;/sub&gt; improvement versus unsupervised controls.</td>
<td>1-month trial in 24 children.</td>
</tr>
<tr>
<td></td>
<td>No comparison group not undergoing airway clearance techniques.</td>
<td></td>
</tr>
<tr>
<td>Inspiratory-threshold loading device and cough training&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Significantly improved pulmonary function and respiratory muscle strength in treated versus untreated subjects.</td>
<td>8-week trial (abstract).</td>
</tr>
<tr>
<td>Postural drainage, percussion and vibration versus high-frequency chest wall oscillation&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Significantly improved pulmonary function, no desaturation and no differences between methods. Both methods efficient, chest wall oscillation more comfortable.</td>
<td>Controlled randomized crossover study of 2 methods in 24 children with primary ciliary dyskinesia. Efficiency and comfort measured subjectively. Short study period.</td>
</tr>
</tbody>
</table>

Table 2. Key practice points for pulmonary rehabilitation programs and airways clearance techniques in children and adolescents with non-cystic fibrosis bronchiectasis.