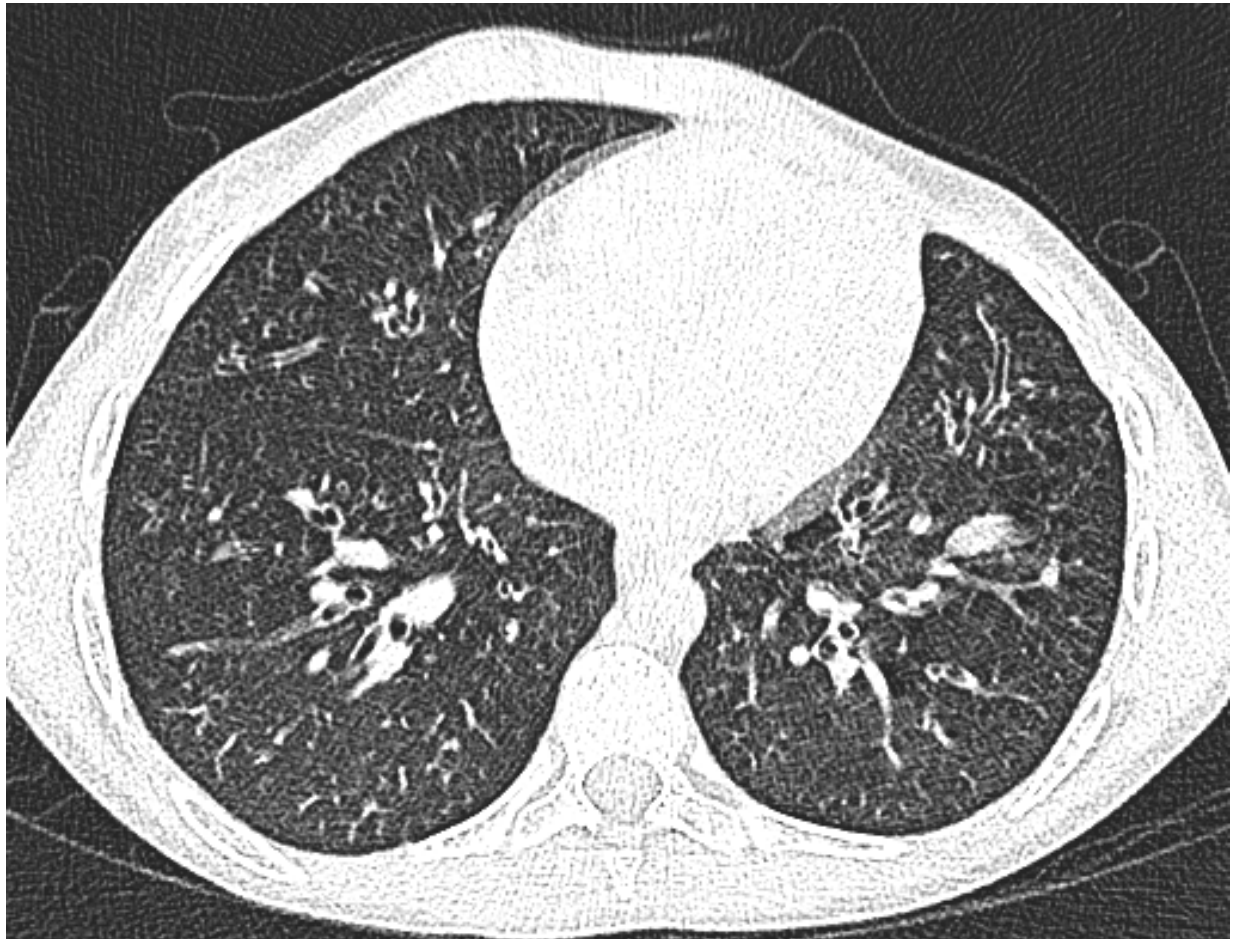
Bronchiectasis:

An African Perspective on Diagnostic Approach



A/Prof Diane Gray

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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

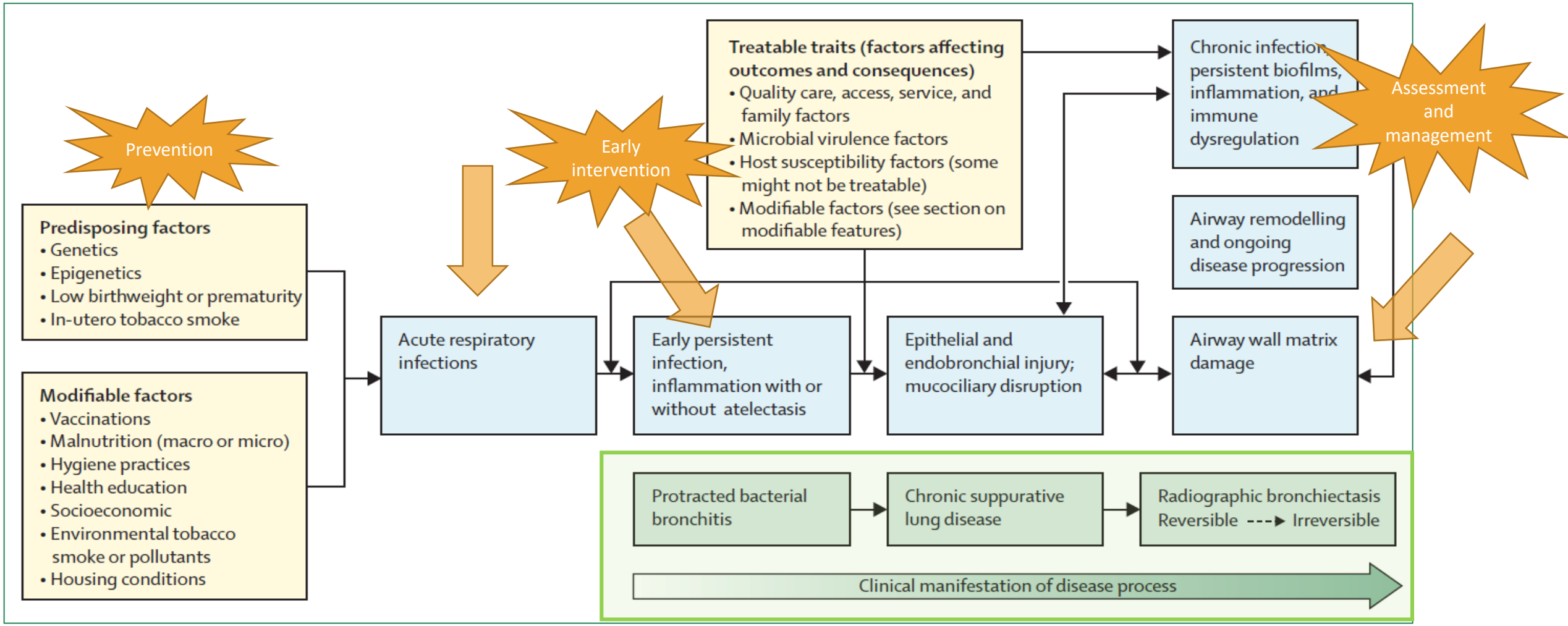
- In an area with limited data – we have near none
- Limited access to chest CT scan - disease defining tool
- Limited access to diagnostics (e.g. test for PCD, CF) and management (microbiology, lung function) tools
- High prevalence of risk factors for bronchiectasis –lower respiratory tract infections, 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

Reference	Pub. year	Country	Region	Population	Era	Time (years)	Male: female	Age (years)	Data source	Given or extrapolated[h] BE cases (*n*)	Chest high resolution computer tomography (*n*)	Median age at diagnosis (years)	Given or rate extrapolated[b] population denominator (*n*)	Alternative[b] population denominator estimate (*n*)	Given or extrapolated[i] average annual incidence
Affluent countries															
Saynajakangas et al. (35)	1998	Finland	National	Non-specific	1983–1992	10	31:16	<14	Hospital admissions (ICD8 518; ICD9 494)	47	na	na	**959,184**[a]	944,253[c] (1983–1992avg)	0.5
Dawson and Bakalinova ( )	1997	UAE	Al in	Arabic	1994–1995	1	na	1–13	Pediatric hospital clinic	12	na	na	**90,000**	nr	13.3[j]
Laverty et a (37)	2008	UK	All cou ries	Non-specific	2006–2007	1	na	<16	Electronic registry	23	na	na	na	**11,644,416**[c] (2006[j])	0.20[j]
Zaid et al. 8)	2010	Republic of Ireland	Nati al	Non-specific	2006	1	na	<18[a]	Pediatrician surveillance	24[h]	24	na	na	**1,040,623**[c] (2006)	2.3
Simpson t al. (34)	2014	NZ	Natio l	Non-specific	2009–2013	5	na	<15	Hospital admissions (ICD10 J47)	681	na	na	**908,000**	1,000,160[c] (2013)	15.0
Disadva taged populations															
Flynn (19	1994	Fiji	Suva	Native Fijian	1985–1989	4	na	5–14	Hospital admissions (ICD9 494)	25	na	na	**89,285**[a]	78,960[d] (1994)	7.0[j]
Singleto et al. (16)	2000	USA	Alaska (YK Delta)	Alaskan natives	1980–1990	10	na	<14[a]	Statewide registry and hospitalizations	~91[h]	28[+]	na	na	6,500[e] (1990)	~140[j]
Edwards 18)	2003	NZ	Auckla d	TOTAL Pacific Island Maori Europeans Other	1998–2000	3	36:24	1–17	Hospital admissions	60 33 15 8 4	60	8.0	**354,000**[a] 60,180 63,720 173,460 56,640	307,600[f] 57,000 50,600 167,000 33,000 (2001)	5.7[j] 18.3 7.9 1.5 2.4
Chang et l. (8)	2003	Australia	Centra	Indigenous	2000–2002	2	31:34	≤15	Hospital admissions (ICD10 J47) + medical record review	65	59	5.4	**4,422**[a]	nr	735.0[j]
Twiss et a (20)	2005	NZ	Natio l	TOTAL Pacific Island Maori European Other	2001–2002	2	28:37	≤15	Pediatrician surveillance	63 32 19 18 3	63	5.2	**851,351**[a] *89,887* *197,916* *600,000* *62,500*	877,200[f] *100,000* *216,100* *652,600* *69,000* (2001)	3.7 17.8 4.8 1.5 2.4
O'Grady et (39)	2010	Australia	NT	Indigenous	1999–2004	5	7:3	<1	Hospital admissions (ICD10 J47)	10	na	0.7	**9,295**	nr	118
Das and Kovesi (17)	2014	Canada	Qikiqtani, Nunavut	Indigenous	1998–2011	13	na	<17	Medical record review	17	17	5.6	**8,415**[a]	nr	15.5[j]
Janu et al. (40)	2014	Australia	Central Qld	Indigenous	2007–2011	5	4:3	<2	Hospital admissions (ICD10 J47) + medical record review	7	7	0.5	**341**[a]	nr	410



Chang, Bush, Grimwood Lancet 2018

Early intervention halts or reverses process and improves outcome

Tracheomalacia
Foreign body

Primary ciliary dyskinesia

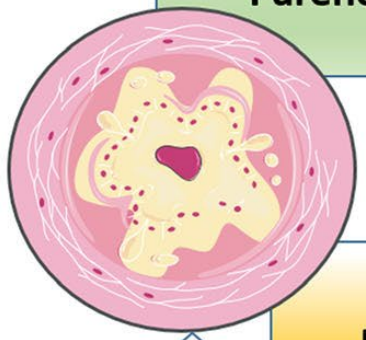
Immune deficiency

Severe pneumonia

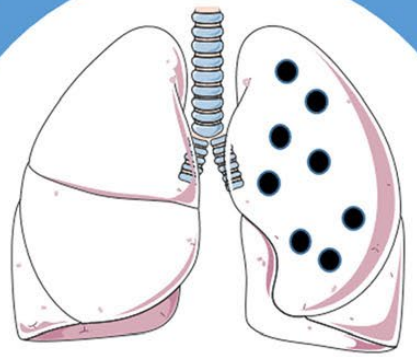
Mucus inspissation, retention and plugging

- Anatomical distortion
- Lung injury – Bronchi & Parenchyma

- Impaired mucociliary clearance
- Innate & adaptive immune deficits

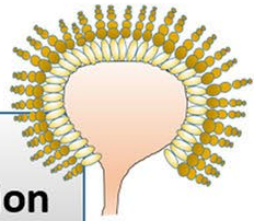


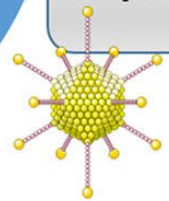
Structural Bronchiectasis

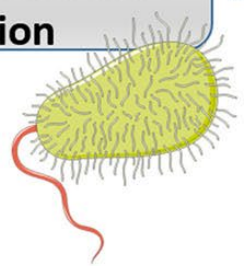


Cole's vicious cycle hypothesis

Microorganism acquisition, colonisation & infection

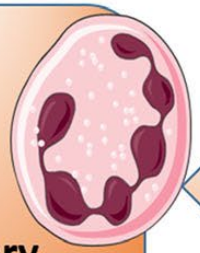






- Loss of cilia & mucociliary function
- Destruction of the bronchial wall
- Mucus retention

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



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

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

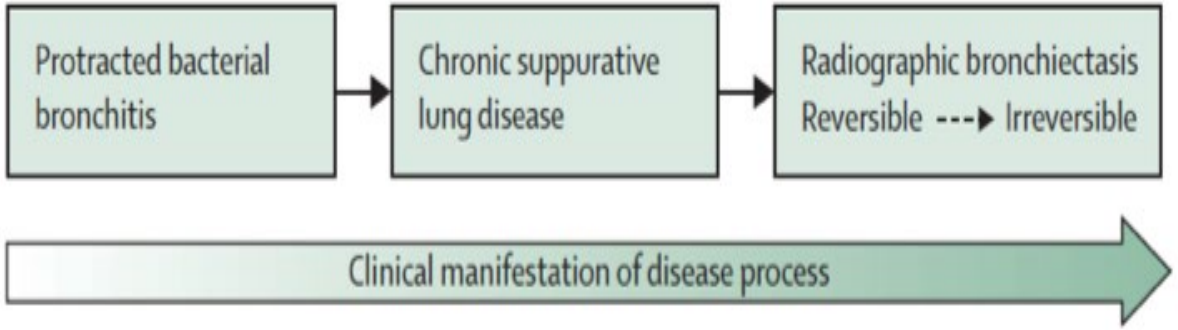
Wurzel Chest 2016; 150: 1101; Goyal *Arch Dis Child* 2014; 99: 522; Chang *Lancet* 2018; 392: 866

Defining Bronchiectasis

- clinical syndrome (persistent/ recurrent wet cough) AND
- HRCT scan: paediatric BAR* (abnormal when >0·80)

Chang, Bush, Grimwood Lancet 2018

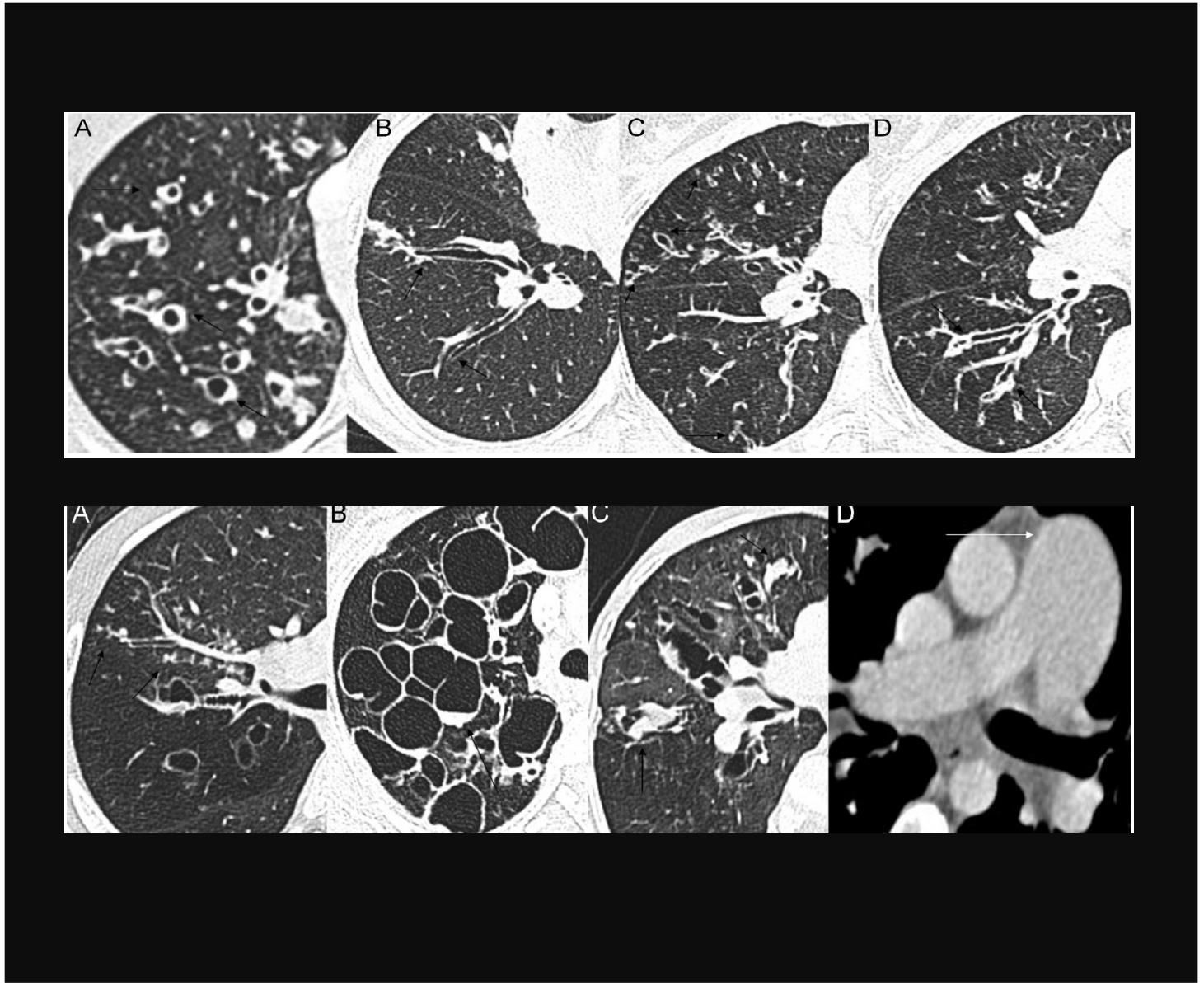
*BAR: broncho-arterial ratio: inner bronchus and outer artery radius



- 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 → BE
  - 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

Countries	Post Infectious %	Immune deficiency %	Primary ciliary dyskinesia %	Congenital abnormality %	Aspiration %	Idiopathic %
High income[1]	4-35	10-34	1-24	1-15	4-22	2-55
Social disadvantage high income[2]	22-94	3-12	0	0-1	4-10	0-54
Low- mid- income[3]	10-40	4-19	3-26	3-10	2-9	14-53

[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

McCallum Front Pediatr 2017. 5:27

- ➢ History, symptoms and signs important to assessing aetiology
- ➢ Comorbidities important

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
- Poycystic kidney disease and other renal disease

Changing epidemiology

Table 2 Underlying etiologies for non-CF patients

	Historical Cohort 1987–2001	Recent Cohort 2002–2019	*p* value
Idiopathic	42 (37.8)	20 (19.2)	0.03
Postinfectious	33 (29.7)	27 (26)	0.43
Immunodeficiencies	17 (15.3)	18 (17.3)	0.69
PCD	7 (6.3)	34 (32.7)	0.001
Asthma	5 (4.5)	3 (2.9)	0.72
Foreign body aspirations	4 (3.6)	0	NA
Others	3 (2.7)	3 (2.9)	0.64
Esophageal atresia-tracheoesophageal fistula	3 (2.7)	1 (0.9)	
Cardiac diseases	0	2 (2)	

Values in parentheses are percentages
NA not applicable

Eralp et al. BMC Pulmonary Medicine (2020) 20:172

- 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)

Post Infectious	Immune deficiency	Primary ciliary dyskinesia	Congenital abnormality	Aspiration	Idiopathic
21 (37.5%)	Total: 19 (33.9%) Primary: 3 (5.4%) Acquired (HIV): 16 (28.6%)	0 (0%)	4 (7.0%)	8 (14.3%)	2 (3.6%)

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

	HIV infected (n=16)	HIV exposed uninfected (n=6)	HIV unexposed and Uninfected (n= 31)
Bronchiectasis caused by Tuberculosis only	11 (69%)	0 (0%)	6 (19%)
Bronchiectasis caused by Tuberculosis co-infection	3 (19%)	1 (17%)	3 (10%)
Bronchiectasis caused by Non Tuberculosis infection	2 (12%)	5 (83%)	22 (71%)

Dr Muntanga Mapani, MPhil research 2020, unpublished

HIV and bronchiectasis in children

- Chronic radiological change (CRC) is common in children living with HIV (CLWH): bronchiectasis and decreased attenuation *Norton 2001, du Plessis 2011, Desai CID 2017*
  - 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

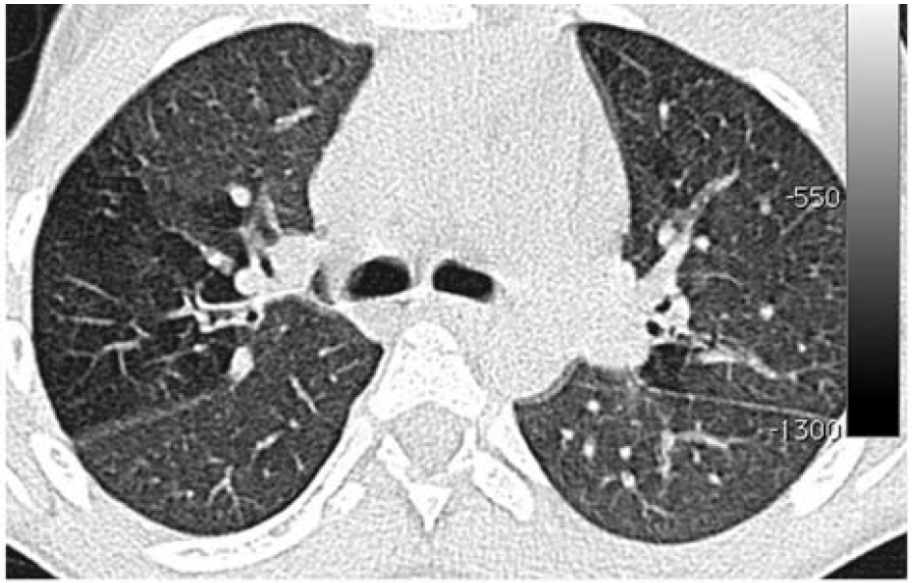
  Berman Ped Pulm 2007, Pitcher Thorax 2015
- May also be due to HIV-mediated defects in innate immunity and accompanying airway neutrophilic inflammation

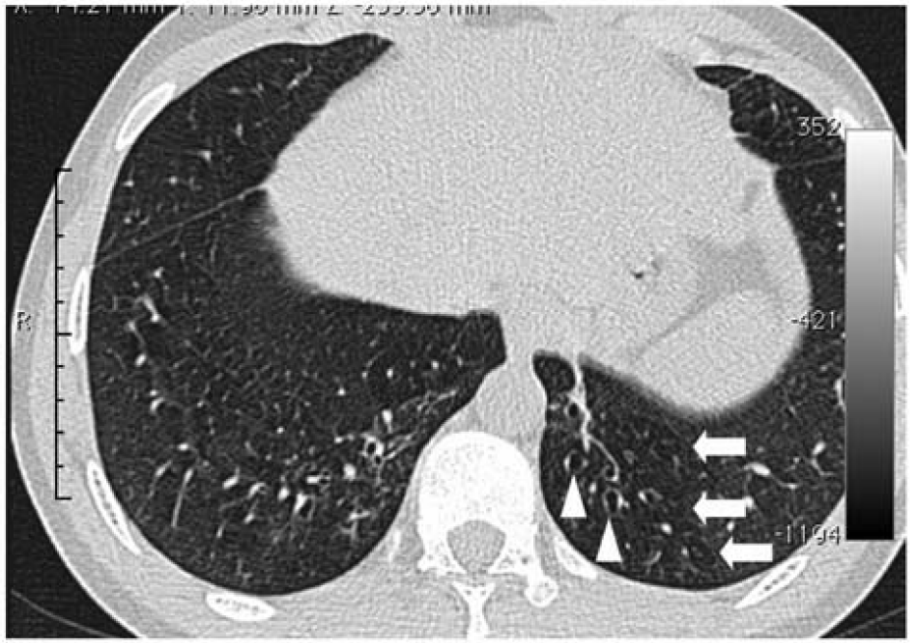
  Masekela IJTLD 2012, Ped Pulm 2015

Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection

Rashida A. Ferrand,[1,2,3] Sujal R. Desai,[4] Charlotte Hopkins,[3] Caroline M. Elston,[5] Susan J. Copley,[6] Kusum Nathoo,[7] Chiratidzo E. Ndhlovu,[8] Shungu Munyati,[2] Richard D. Barker,[5] Robert F. Miller,[1,9] Tsitsi Bandason,[2] Athol U. Wells,[10] and Elizabeth L. Corbett[1,2,11]

HIV/AIDS • CID 2012:55 (1 July) •





Bronchiectasis and bronchiolitis obliterans in youth living with HIV (YLWH)

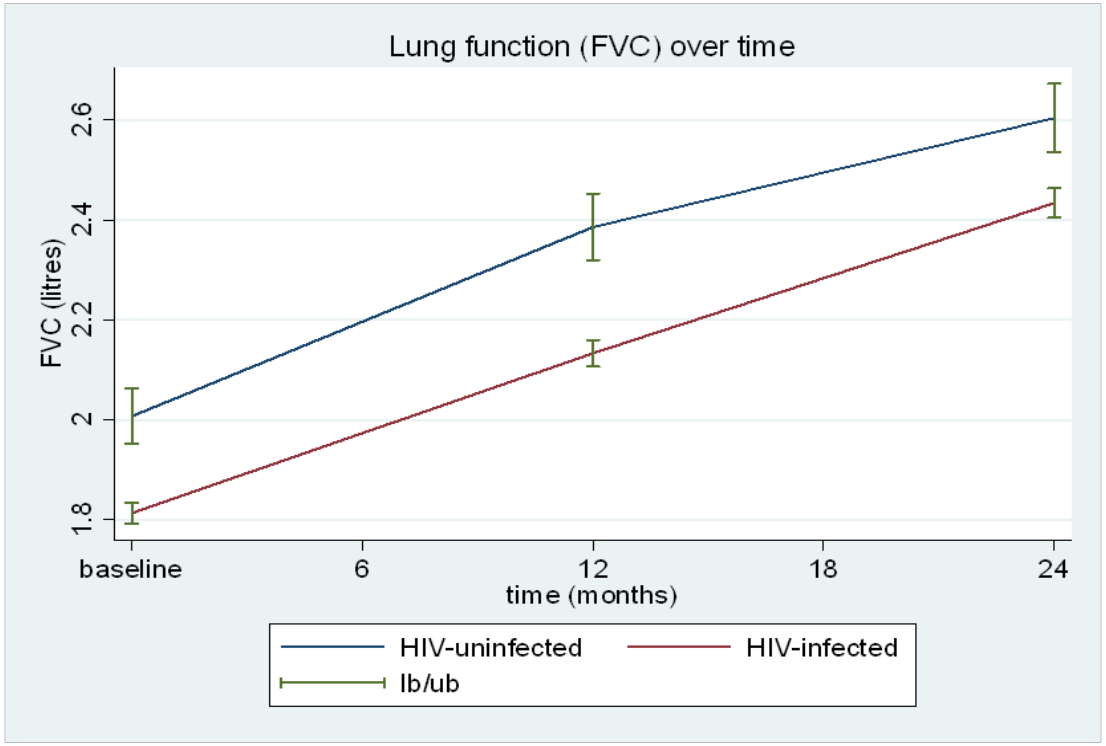
- 100/116 (86%) YLWH, 14.6 ± 2.4 yrs, had chronic lung disease*
- Symptoms: Chronic cough 66%, recurrent LRTI 21%, abnormal chest X-ray 47%, clubbing 10%
- CT scan in 52 YLWH (excluded if active TB – 23%)
  - 55% BO 43% bronchiectasis

* Cough 3 months, recurrent LRTI, mod effort intolerance OR hypoxia

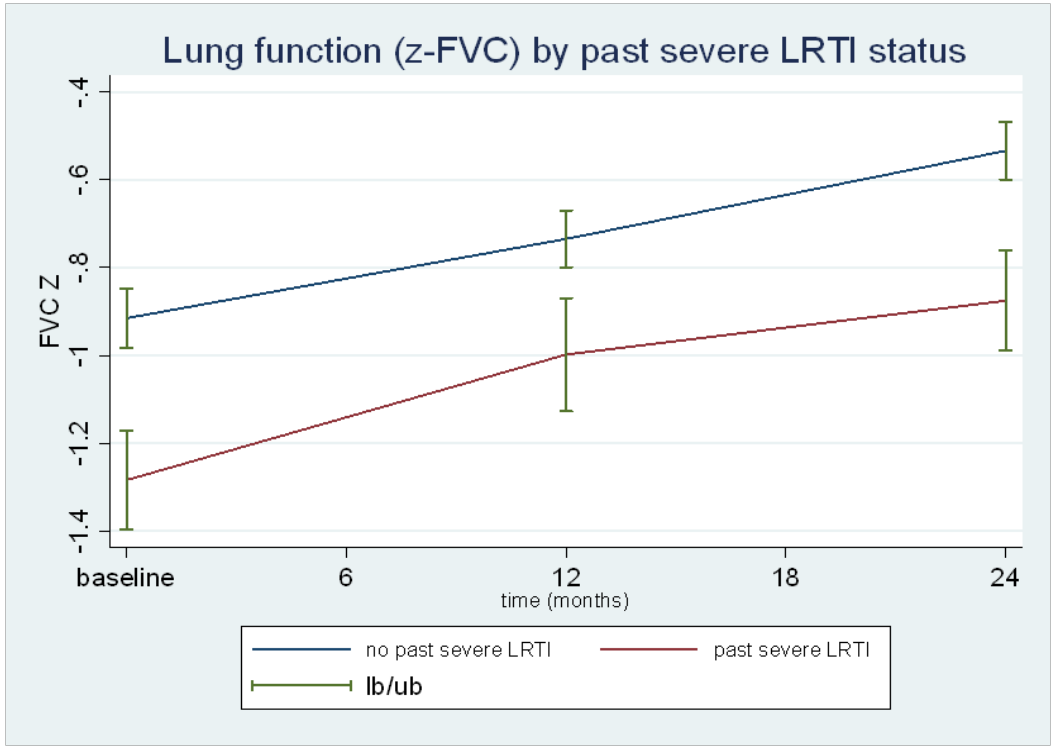
HIV - Longitudinal spirometry findings

Cape Town Adolescent Antiretroviral Cohort

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 **BEFORE IRREVERSIBLE AIRWAY DAMAGE**

Thorough investigation for underlying aetiology

Assessment of baseline severity

Assessment of other risk factors and co-morbidities

Plan management

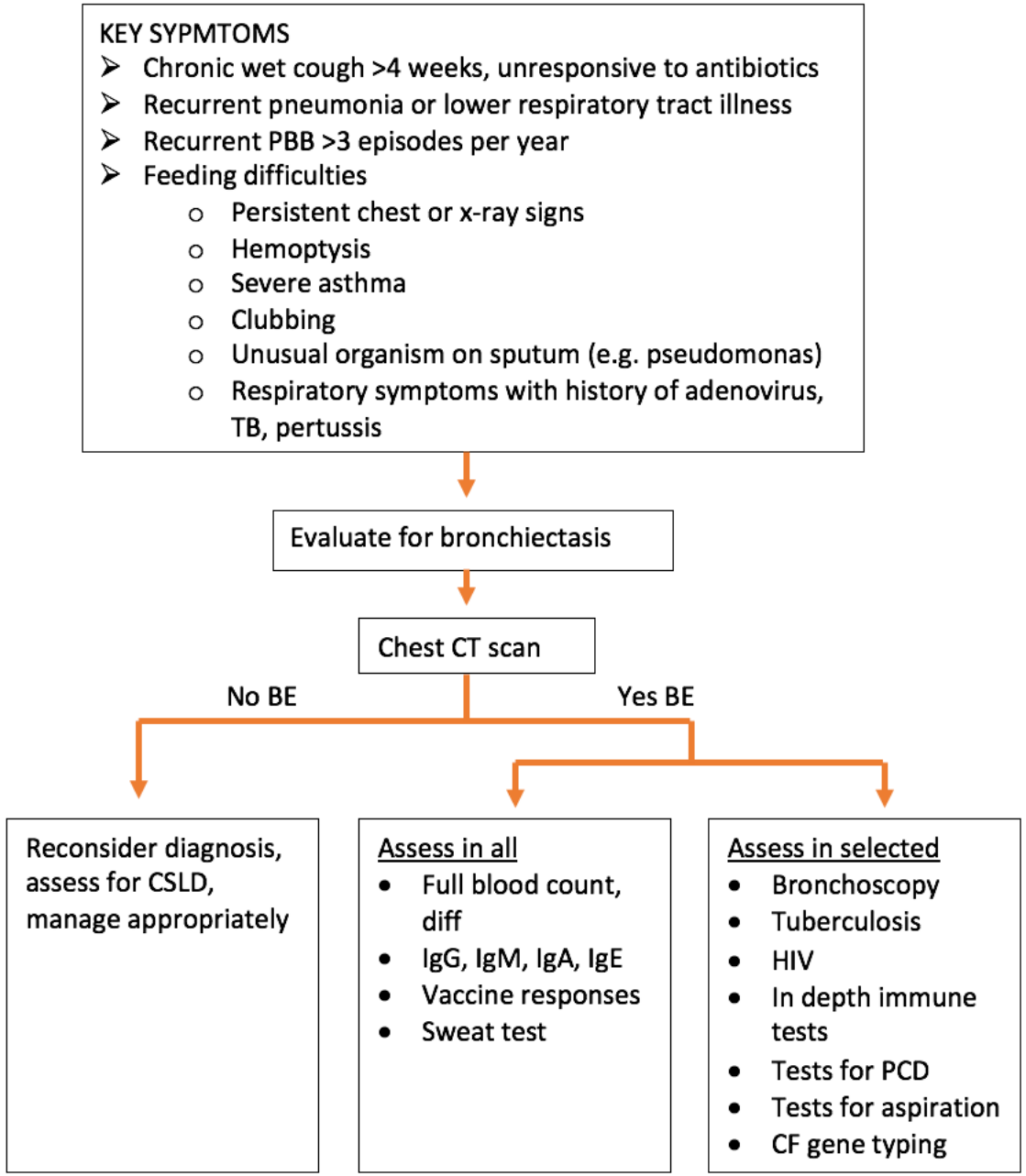
Improve quality of life

Prevent or reduce exacerbation frequency

Preserve lung function

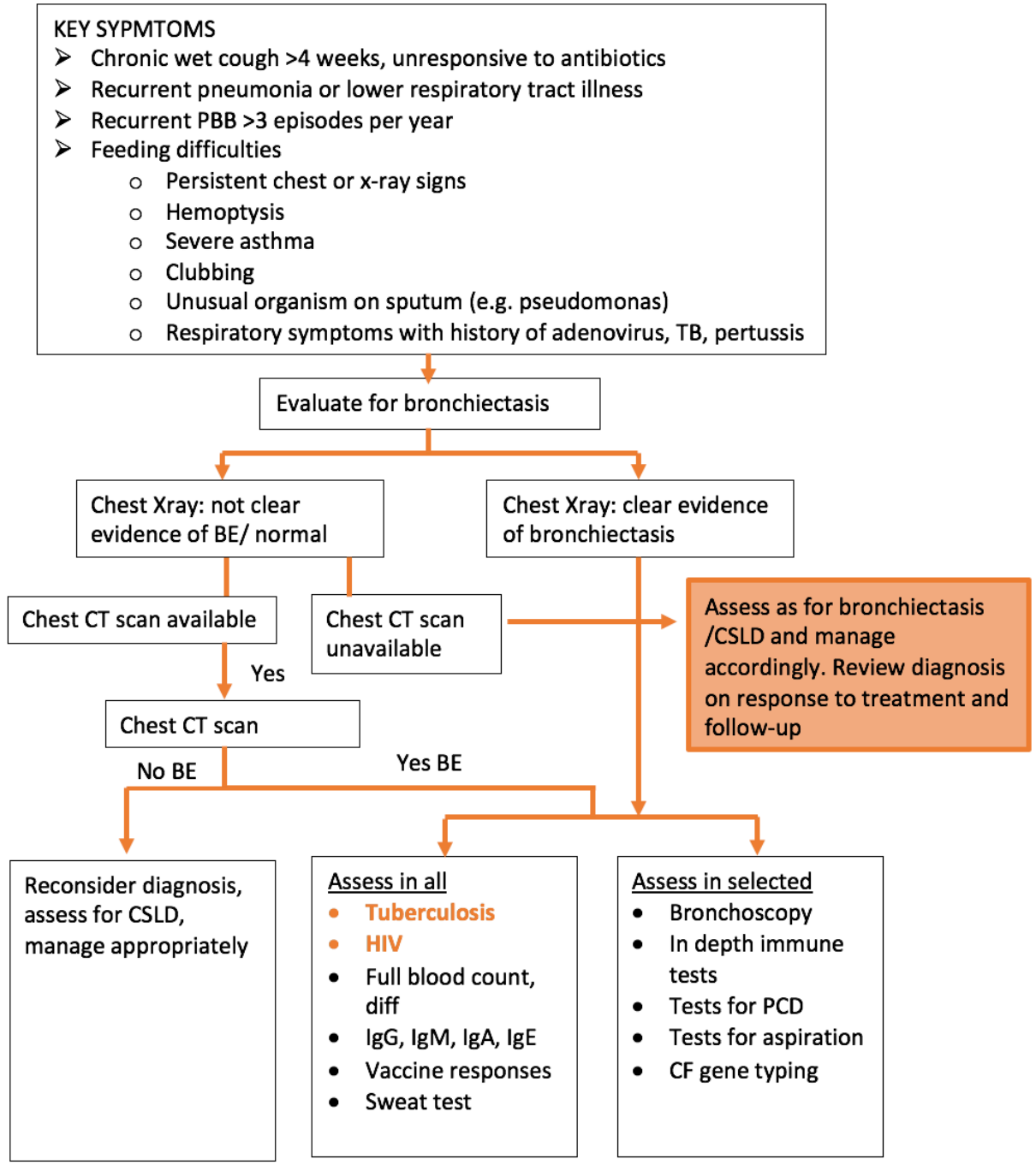
Approach to diagnosis

Chang, Bush, Grimwood
Lancet 2018



Approach to diagnosis – limited CT access

Adapted from Chang, Bush, Grimwood Lancet 2018



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 oesphageal 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)

Conclusion

- 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

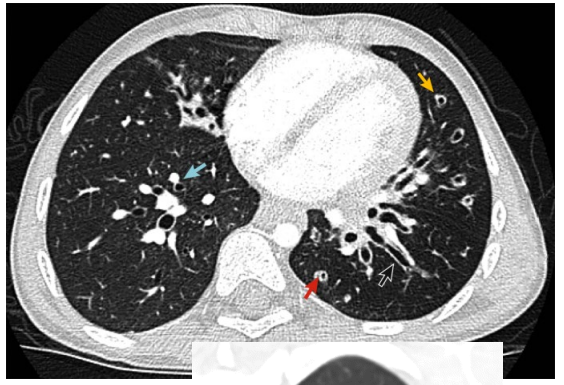
University Hospital Leuven, Belgium

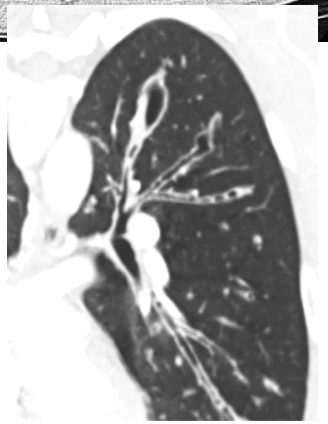
CI

- 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





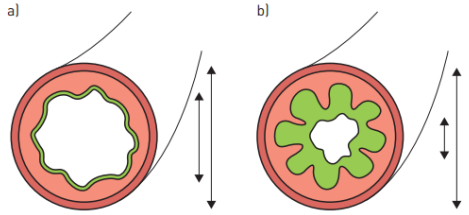


FIGURE 1 a) A healthy small airway and b) an inflamed airway with a thickened wall at full inspiration. On inspiration, the mucosa of the healthy airway is only slightly folded. The inflamed airway has larger folds compared with the normal airway. Mucus fills up the gaps between the mucosal folds. On chest CT, the folds and mucus will be interpreted as a thickened airway wall. This figure also illustrates why the outer diameter is a more robust parameter for diagnosing and quantifying bronchiectasis because in contrast to the inner diameter, it is not influenced by the presence of mucus in the lumen. Image provided by, and reproduced and modified with the kind permission of, M. Meerburg (Amsterdam, The Netherlands).

The radiological diagnosis of bronchiectasis: What’s in a name? Tiddens H et al Eur Respir Rev 2020

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

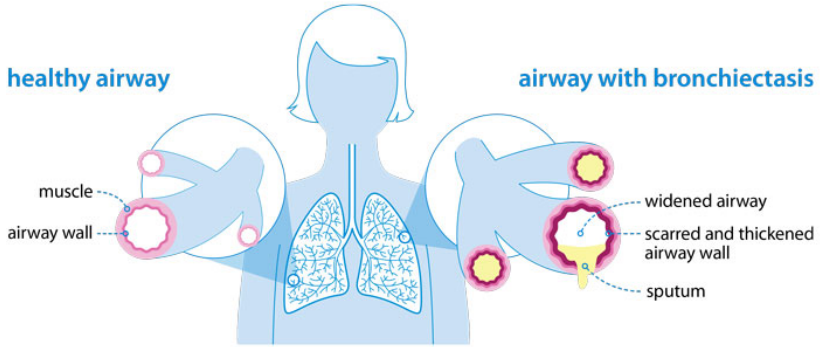
1. Management
    - 1.1 Airway mucus clearance
        - 1.1.1 Medication
        - 1.1.2 ACT
    - 1.2 ICS, SABA
    - 1.3 Antibiotic therapy
    - 1.4 Anti-inflammatory treatment
    - 1.5 Surgery

2. Follow-up/Qol/Prognosis

1. Management of non-CF bronchiectasis

Aims at

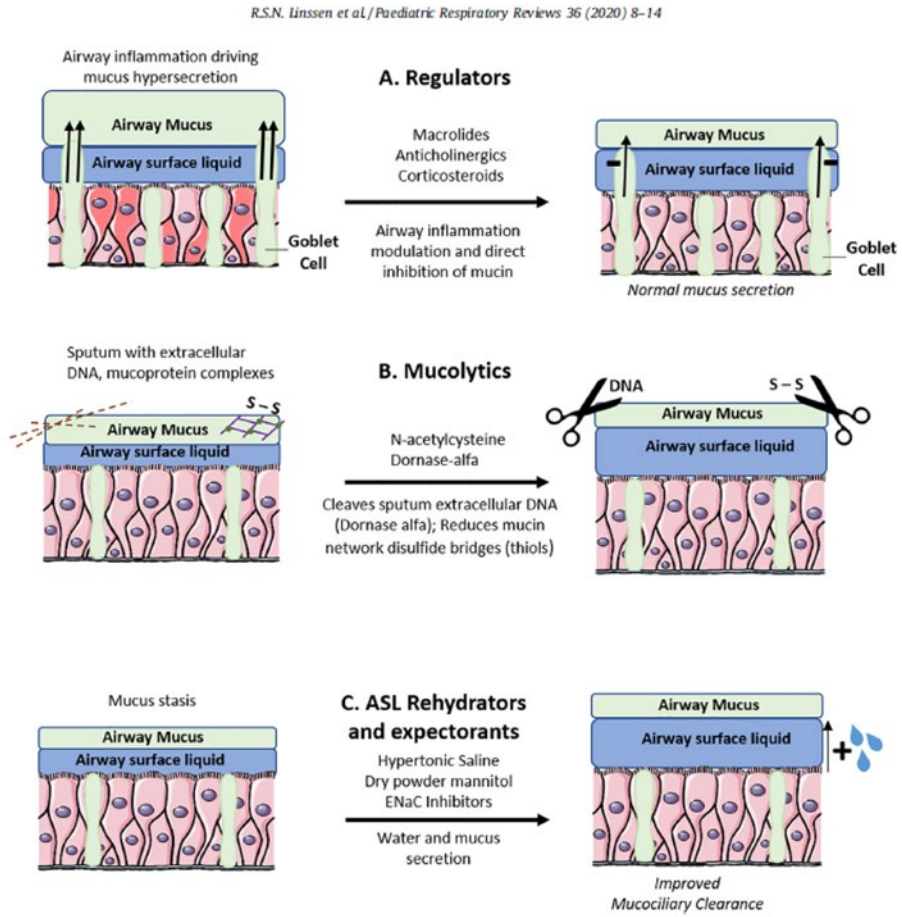
- Improving persistent/recurrent wet cough
- Reducing pulmonary exacerbations (Pex)
- Preserving lung function
- Slow/prevent progression of bronchiectasis
- Improving Qol
- Treat etiology if known
- Adress comorbidity



El Boustany et al Pediatric Pulmonology 2019; 54:487-496

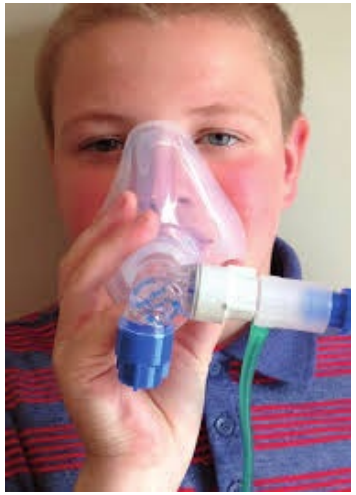
1.1.1 Airway clearance: medication

- 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 200S, 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)

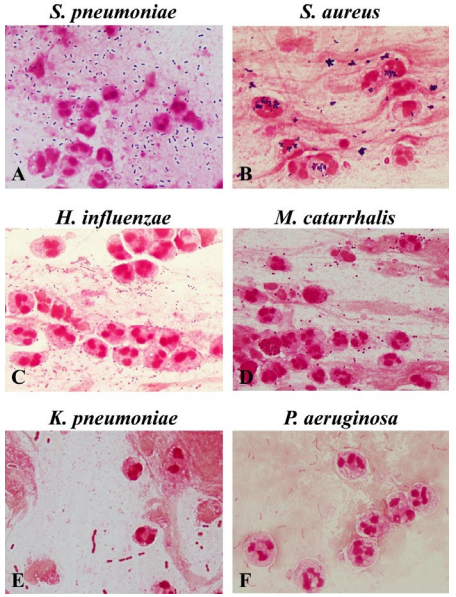
- Overal ACT are safe and improve sputum expectoration
- Lack of RCT's in children with non CF bronchiectasis *(Snijders D et al 2015)*
  - Many studies in adults, almost none in children (*Poeta M et al 2020 Review)*
  - Improve sputum expectoration and decrease sputum volume
  - Cochrane review in 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 likes VEST, cough assist etc
  - Positive pressure/oscillating devices can be helpful: PEP mask, flutter
  - Autogenic drainage, active cycle of breathing, assisted cough techniques ..



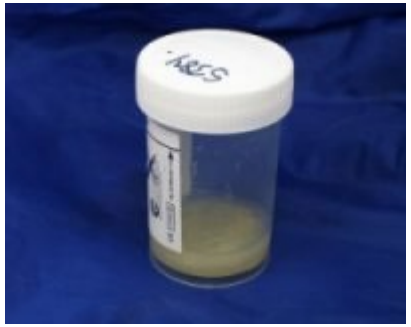
1.2 Asthma medication? ICS and SABA/LABA

- Largely overused in this context
- Most likely only usefull 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 sputumculture
- 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)

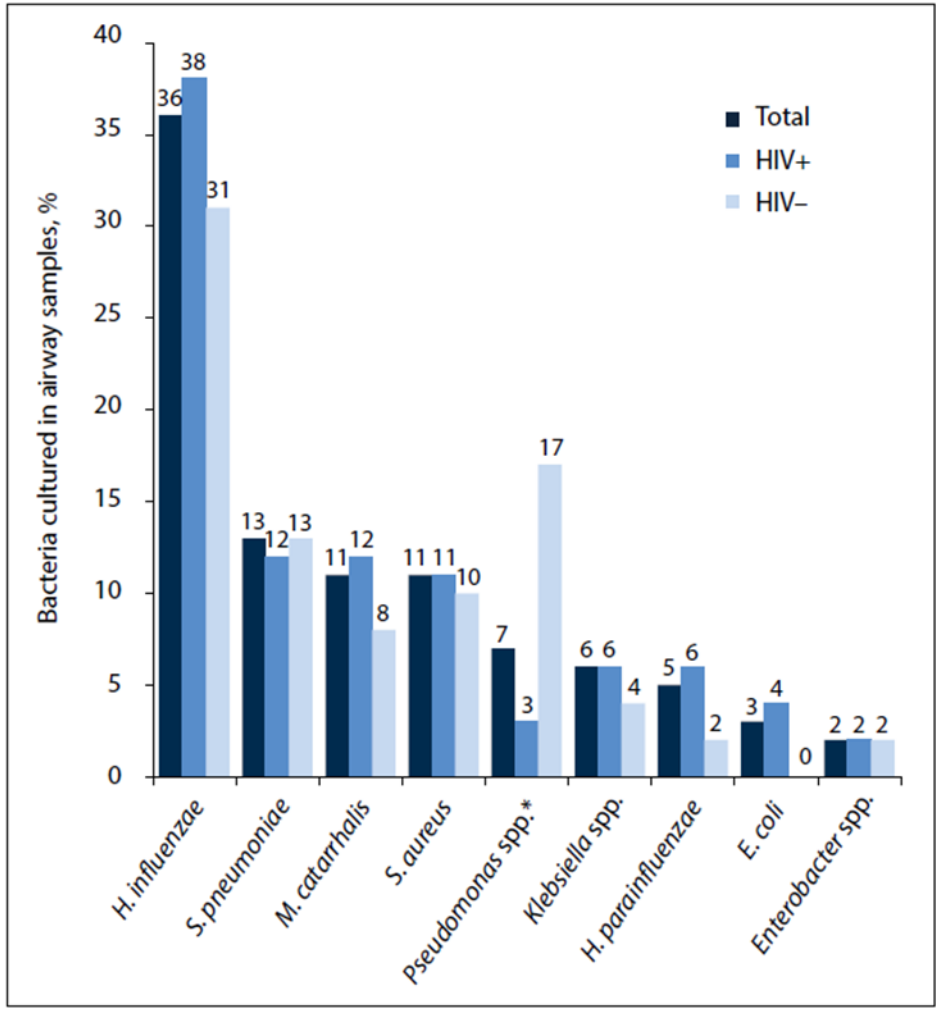


*Fig. 1. Types and percentages of bacteria cultured in airway samples. (*Difference is not statistically significant when the denominator is patients and not samples. HIV+ = HIV-infected; HIV– = HIV-uninfected.)*

South African data: Expectorated/induced sputum
N= 66 (79% HIV infected)
Verwey et al 2017

Amoxyclav in treatment of chronic wet cough (>3 weeks) in children

Table 1 Subject characteristics at baseline

	Treatment group (n=25)	Placebo group (n=25)	p Value
Age in years, mean (SD)	1.75 (0.9, 4.6)	2.8 (0.95, 5.25)	0.34
Men, n (%)	14 (56)	12 (48)	0.58
Cough duration in weeks, median (IQR)	15.0 (8.5–59)	11.0 (4.0–28)	0.18
Smoke exposure, n (%)	8 (32)	7 (28)	0.75
VCD score, median (IQR)	3.0 (2.0–3.0)	2.5 (2.0–3.0)	0.55
CXR abnormal, n (%)	9 (41%) (n=22)	6 (30%) (n=20)	0.56
BAL data	n=19	n=18	
Total cell count ($\times 10^9$/litre), median (IQR)	426.0 (196.0–632.0)	261.0 (185.5–467.5)	0.45
% Neutrophil, median (IQR)	38.5 (13.0–58.0)	34.5 (8.0–66.0)	0.81
Significant bacterial culture, n (%)	13 (68)	14 (78)	0.78

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

Marchant et al Thorax 2012

Amoxyclav (14 days) in treatment of chronic wet cough (>3 weeks) in children

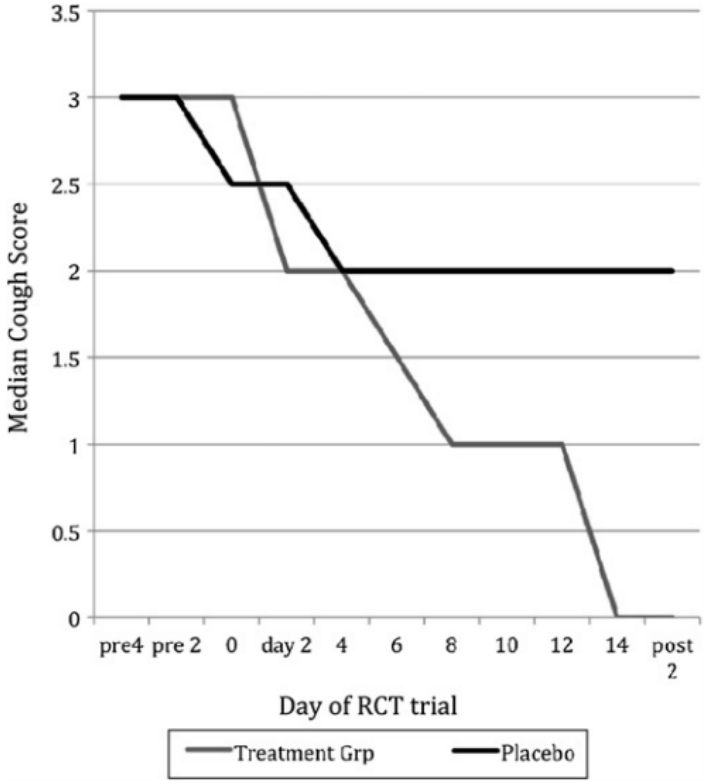


Figure 3 Median verbal category cough scores[17] prior to commencement of study medications (pre), at baseline (day −1), treatment days (days 1−14), and after completion of the study (post). Dotted line = amoxycillin clavulanate group; Continuous line = placebo group. RCT, randomised controlled trial.

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

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

*Placebo group had access to antibiotics after day 14.
†End-treatment minus baseline VCD score.
VCD, verbal descriptive category score.[17]

Marchant et al Thorax 2012

Acute Pex in non CF BX: amoxyclav or azithromycin for 21 days?

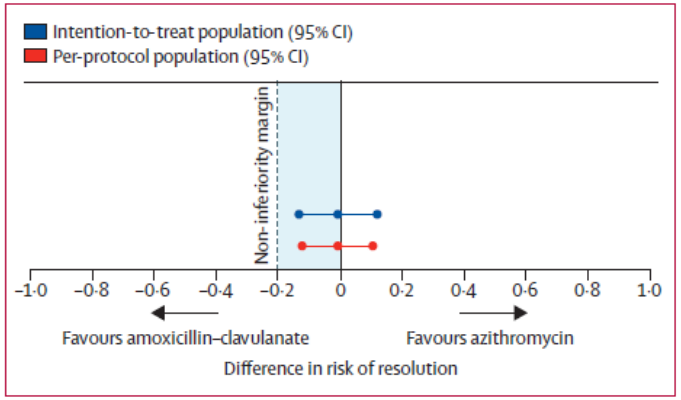


Figure 2: **Risk difference for resolution of exacerbations with azithromycin versus amoxicillin–clavulanate**

	Amoxicillin–clavulanate group (n=97)	Azithromycin group (n=82)	p value
Per-protocol analyses			
Time to resolution (days)	10 (6–15)	14 (8–16)	0·014
Time to next exacerbation (days)*	85 (30–180)	91 (38–180)	0·81
Intention-to-treat analyses			
Time to resolution (days)	10 (6–15)	14 (7–16)	0·013
Time to next exacerbation (days)*	75 (26–180)	90·5 (37–180)	0·52

Data are median (IQR). *Data were censored at 180 days.

Table 2: **Time to resolution and to next exacerbation**

Implications of all the available evidence

Although azithromycin is non-inferior to amoxicillin-clavulanate for treating non-severe acute exacerbations of bronchiectasis in children, the exacerbation might take significantly longer to resolve, and the risk of inducing macrolide resistance should be considered. Although azithromycin might be used cautiously for some patients, such as those with penicillin hypersensitivity or for whom less frequent dosing might improve adherence, amoxicillin–clavulanate remains the first choice empirical antibiotic.

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

	Start of treatment (day 1)					End of treatment (day 14)				
	Placebo (n=47), n (%)	Amoxicillin–clavulanate (n=39)		Azithromycin (n=42)		Placebo (n=47), n (%)	Amoxicillin–clavulanate (n=39)		Azithromycin (n=42)	
		n (%)	p value*	n (%)	p value*		n (%)	p value*	n (%)	p value*
Streptococcus pneumoniae	11 (23%)	4 (10%)	0·11	7 (17%)	0·43	6 (13%)	1 (3%)	0·085	3 (7%)	0·38
Azithromycin-resistant	4 (36%)†	1 (25%)†	0·68	1 (14%)†	0·31	2 (33%)†	0	0·50	3 (100%)†	0·058
Penicillin-resistant	2 (18%)†	0	0·36	0	0·23	2 (33%)†	0	0·50	1 (33%)†	1·0
Haemophilus influenzae	13 (28%)	4 (10%)	0·044	5 (12%)	0·065	6 (13%)	0	0·021	2 (5%)	0·19
Azithromycin-resistant	0	0	NA	0	NA	0	0	NA	0	NA
Ampicillin-resistant	3 (23%)†	1 (25%)†	0·94	0	0·24	1 (17%)†	0	NA	0	0·54
Moraxella catarrhalis	14 (30%)	12 (31%)	0·92	18 (43%)	0·20	15 (32%)	6 (15%)	0·076	1 (2%)	<0·0001
β-lactamase positive	14 (100%)†	12 (100%)†	0·37	17 (94%)†	NA	15 (100%)†	6 (100%)†	NA	1 (100%)†	NA
Staphylococcus aureus	8 (17%)	7 (18%)	0·91	5 (12%)	0·50	15 (32%)	5 (13%)	0·037	3 (7%)	0·0040
Azithromycin-resistant	3 (38%)†	2 (29%)†	0·71	1 (20%)†	0·51	3 (20%)†	2 (40%)†	0·37	2 (67%)†	0·010
Meticillin-resistant	1 (13%)†	3 (43%)†	0·19	2 (40%)†	0·25	2 (13%)†	2 (40%)†	0·20	0	0·50
Any of the above pathogens	32 (68%)	20 (51%)	0·11	22 (52%)	0·13	32 (68%)	11 (28%)	<0·0001	8 (19%)	<0·0001
Azithromycin-resistant (any)	7 (22%)†	3 (15%)†	0·54	2 (9%)†	0·22	5 (16%)†	2 (18%)†	0·84	5 (63%)†	0·0060

Data are n (%) of children with paired nasal swabs (on days 1 and 14 of treatment), unless otherwise specified. NA=not applicable. *Versus placebo group at the same timepoint. †Percentages are the proportion of isolates with the specified resistance out of the total number of isolates of that species.

Table 4: **Nasal swab bacteriology on days 1 and 14 of study medication**

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 resolution1·50 [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

Goyal et al Lancet 2019

1. 4 Anti –inflammatory therapy: Macrolides

- Excellent tissue penetration
- Broad efficacy againts 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
  - Inhbiti adherence of micro –organisms
  - Inhibit bacterial virulence and toxin production
- Azitromycin
  - Does not inhibit CYP3A4
  - Prolongued 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

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

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.

El Boustany et al Pediatric Pulmonology 2019; 54:487-496

Metanalysis of macrolides in non CF bronchiectasis

Table 1

Characteristics of randomized clinical trials included in the meta-analysis.

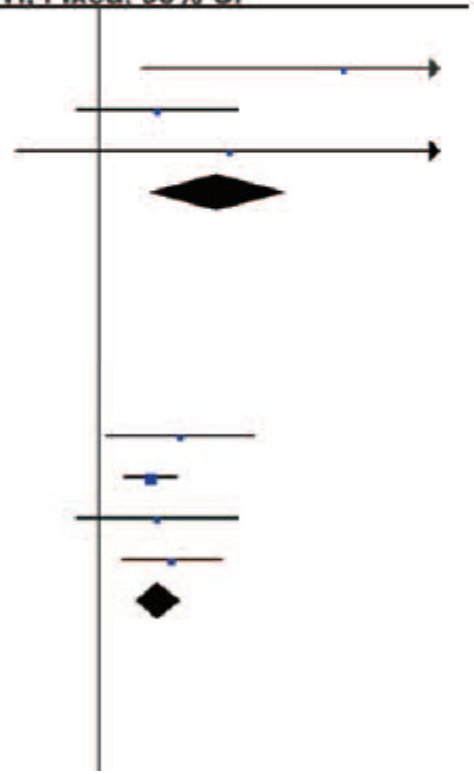
Study period	Location	Study design	Total Sample (T/C)(F/M)	Age range	Diagnosis criteria	Exacerbation history and bronchiectasis states	Macrolides dose and frequency	Therapy duration Follow-up duration
Koh Y.Y 1995.10–1996.2	Korea	DB,RCT	25 (13/12) (11/14)	10–18	Clinical features and CT	Stable bronchiectasis, incresed AR	Roxithromycin 4mg/kg twice daily	12 weeks 12 weeks
Tsang KW 1996.10–1997.4	China	DB,RCT	21 (11/10) (16/5)	35–75	HRCT	Stable idiopathic bronchiectasis	Erythromycin 500 mg twice daily	8 weeks 8 weeks
Cymbala AA 2005	America	Open label, crossover, RCT	22 (11/11) (NR)	≥18years	HRCT	NR	Azithromycin 500 mg twice weekly	6 months 6 months
JF Liu 2007.6–2010.6	China	DB,RCT	43 (22/21) (20/23)	18-65	Meeting the criti-eria of O'Donnell	Stable bronchiectasis	Roxithromycin 150 mg once daily	6 months 18 months
Wong C 2008.2–2009.10	New Zealand	DB,RCT	141 (71/70) (98/43)	≥18years	HRCT	Stable bronchiectasis, ≧1 exacerbation in the past year	Azithromycin 500 mg thrice weekly	6 months 12 months
Masekela R 2009.1–2011.6	South Africa	DB,RCT	31 (17/14) (13/18)	6-18	HRCT	Bronchiectasis associated with HIV	Erythromycin, <15 kg 125 mg, >15 kg 250 mg per day	52 weeks 52 weeks
Valery PC 2008.12–2010.12	Australia	DB,RCT	89 (45/44) (47/42)	1–8	HRCT	Stable bronchiectasis, ≧1 exacerbation in the past year	Azithromycin 30 mg/kg once a week	12–24 months 12–24 months
Serisier DJ 2008.10–2011.12	Australia	DB,RCT	117 (59/58) (71/46)	20-85	HRCT	Stable bronchiectasis, ≧2 exacerbations in the past year	Erythromycin 400 mg twice dialy	48 weeks 52 weeks
Altenburg J 2008.4–2010.9	Nether-land	DB,RCT	83 (43/40) (53/30)	≥18years	HRCT or plain bronchography	Stable bronchiectasis, ≧3 LRTIs in the past year	Azithromycin 250 mg once daily	52 weeks 52 weeks
De Diego 2005.1–2005.12	Spain	Open label, RCT	30 (16/14) (16/14)	≥18years	Clinic data and HRCT	Stable bronchiectasis	Azithromycin 250 mg thrice weekly	3months 3months

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

Donghai Wang et al 2019

Macrolides and Pex

Study or Subgroup	microlide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.6.1 children							
Koh Y.Y 1997	13	13	0	13	0.3%	27.00 [1.77, 411.40]	1997
Valery PC 2013	9	45	4	44	2.3%	2.20 [0.73, 6.62]	2013
Masekela R 2013	3	17	0	14	0.3%	5.83 [0.33, 104.22]	2013
Subtotal (95% CI)		**75**		**71**	**2.9%**	**5.03 [2.02, 12.50]**	
Total events	25		4				
Heterogeneity: Chi² = 3.63, df = 2 (P = 0.16); I² = 45%							
Test for overall effect: Z = 3.47 (P = 0.0005)							
1.6.3 Azithromycin							
Cymbala AA 2005	9	11	3	11	1.7%	3.00 [1.10, 8.19]	2005
Wong C 2012	49	71	24	70	13.6%	2.01 [1.40, 2.88]	2012
Valery PC 2013	9	45	4	44	2.3%	2.20 [0.73, 6.62]	2013
Altenburg J 2013	23	43	8	40	4.6%	2.67 [1.36, 5.28]	2013
Subtotal (95% CI)		**170**		**165**	**22.2%**	**2.25 [1.67, 3.02]**	
Total events	90		39				
Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 5.35 (P < 0.00001)							



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

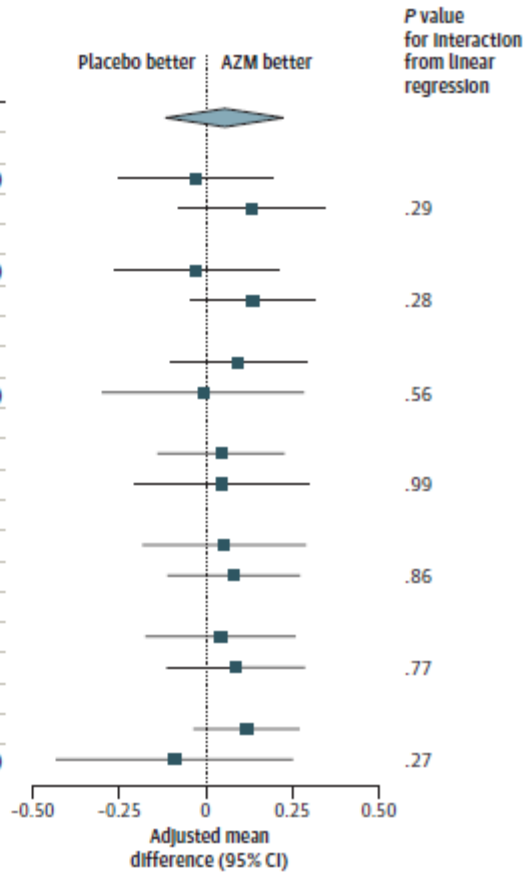
Ferrand RA et al 2020

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

Subgroup	Placebo Patients, No	Placebo Mean (SD)	AZM Patients, No	AZM Mean (SD)	AMD (95% CI)	*P* value for interaction from linear regression
Overall association	146	-1.95 (0.91)	162	-1.90 (0.90)	0.06 (-0.10 to 0.21)	
Sex						
Female	73	-1.99 (0.90)	73	-2.00 (0.89)	-0.03 (-0.25 to 0.19)	
Male	73	-1.91 (0.93)	89	-1.82 (0.89)	0.13 (-0.08 to 0.34)	.29
Age						
<15.28 y	64	-1.75 (0.94)	95	-1.91 (0.99)	-0.03 (-0.26 to 0.21)	
≥15.28 y	82	-2.10 (0.87)	67	-1.89 (0.75)	0.14 (-0.04 to 0.32)	.28
FEV_1 *z* score						
≥-2	81	-1.55 (0.64)	88	-1.46 (0.63)	0.09 (-0.10 to 0.29)	
<-2	65	-2.45 (0.97)	74	-2.42 (0.89)	-0.01 (-0.30 to 0.29)	.56
HIV viral load						
<1000 copies/mL	82	-1.84 (0.77)	96	-1.79 (0.84)	0.04 (-0.14 to 0.23)	
≥1000 copies/mL	64	-2.09 (1.06)	64	-2.07 (0.95)	0.05 (-0.21 to 0.30)	.99
Weight-for-age *z* score						
≥-2	76	-1.84 (0.95)	67	-1.76 (0.90)	0.05 (-0.18 to 0.29)	
<-2	70	-2.07 (0.86)	95	-2.00 (0.88)	0.08 (-0.11 to 0.27)	.86
Height-for-age *z* score						
≥-2	81	-1.84 (0.90)	71	-1.79 (0.83)	0.04 (-0.17 to 0.26)	
<-2	65	-2.08 (0.92)	91	-1.99 (0.94)	0.09 (-0.11 to 0.29)	.77
Site						
Zimbabwe	108	-1.92 (0.82)	111	-1.84 (0.81)	0.12 (-0.03 to 0.27)	
Malawi	38	-2.04 (1.15)	51	-2.02 (1.05)	-0.09 (-0.43 to 0.25)	.27

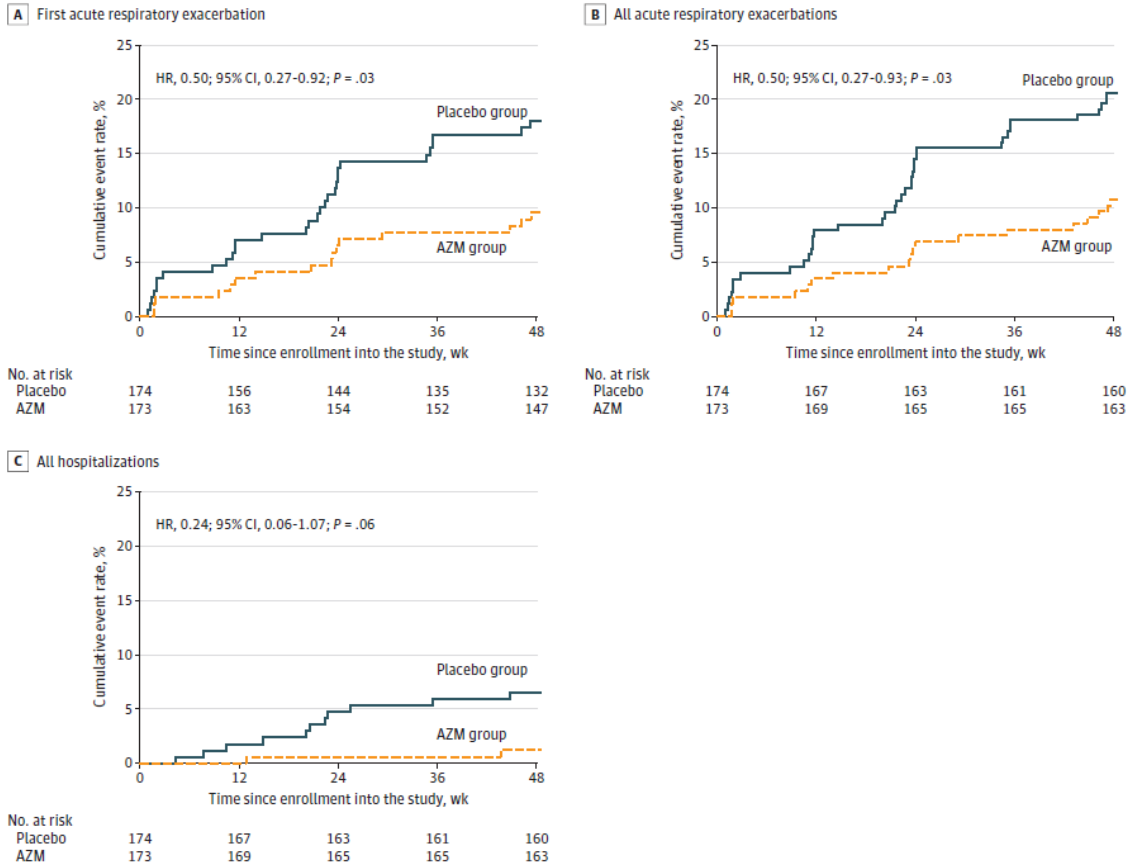


AZM indicates azithromycin; and FEV_1, forced expiratory volume in 1 second.

Ferrand RA et al 2020

Secondary outcomes

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



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

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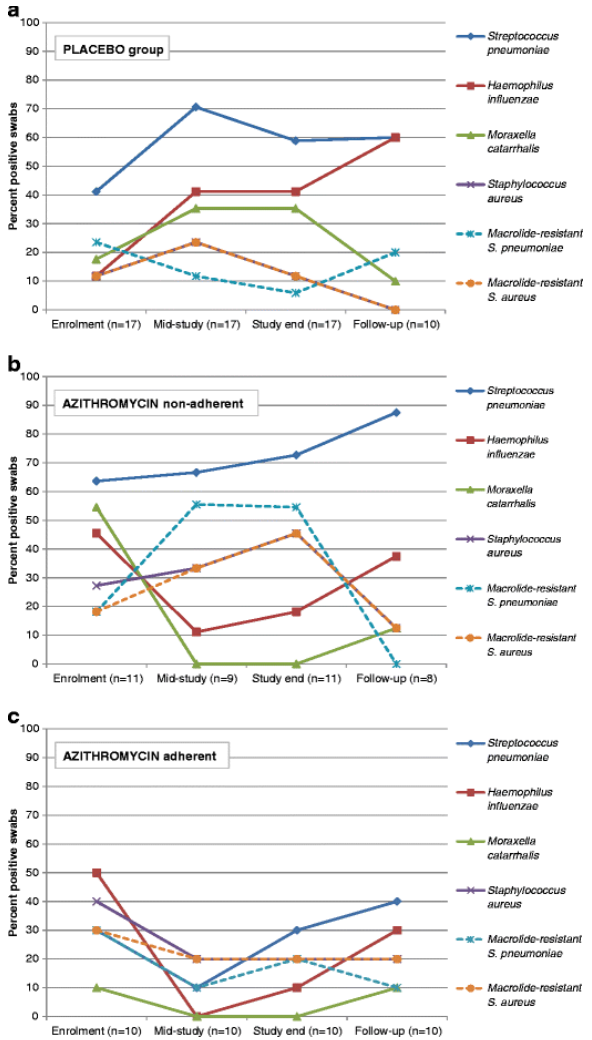
Adverse effects of long term macrolides

- 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 compaired to erythro

Carriage and resistentence with long term AZM therapy

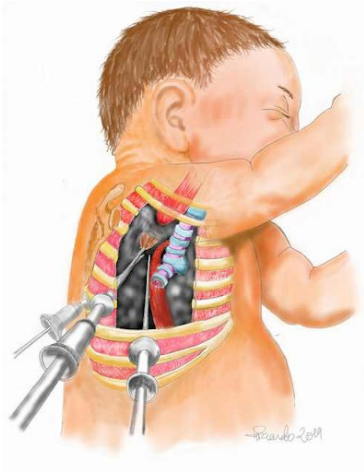
- RCT weekly AZT for 24 months with 12 months FU *(Valery et al 2013)*
- Australia (n= 38) and New Zealand (n=40)
- AZM *versus* Placebo
  - Lower carriage of *H influenzae* and *M cattharalis*
  - More macrolide resistent *S aureus* and *S pneumoniae*
    - Recovery of *S pneumonae* R not of *S aureus*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



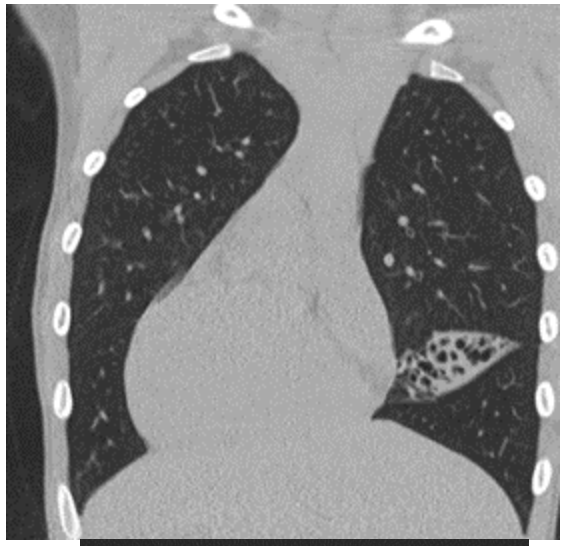
Hare et al 2015

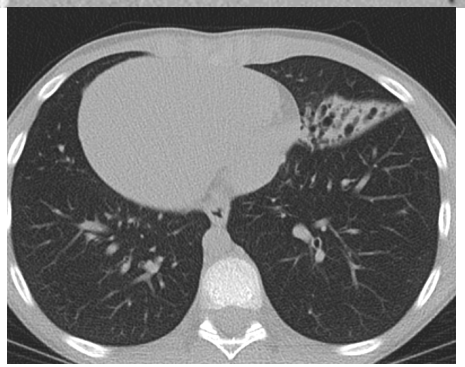
1.5 Surgery (Lobectomy, segmentectomy)

- Only indicated in case of localised disease and insuffucient respons 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 !





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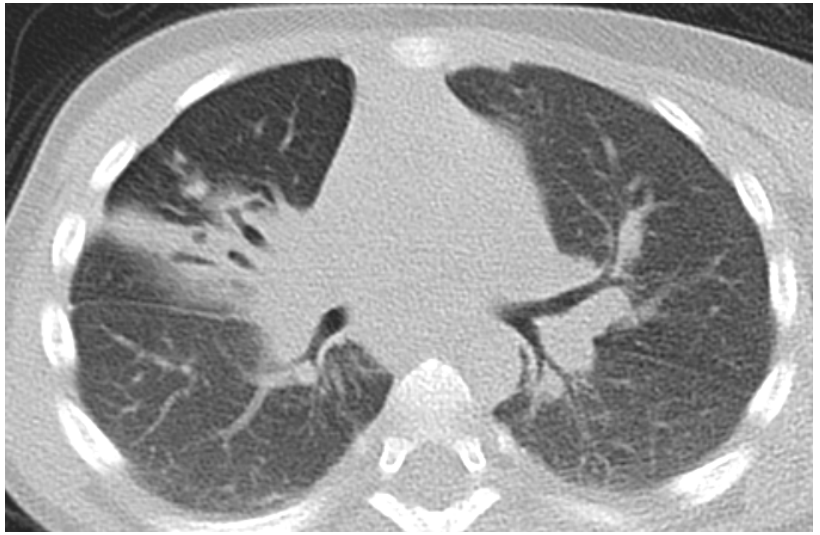
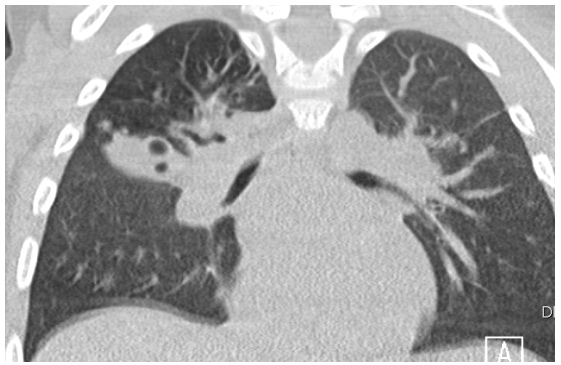
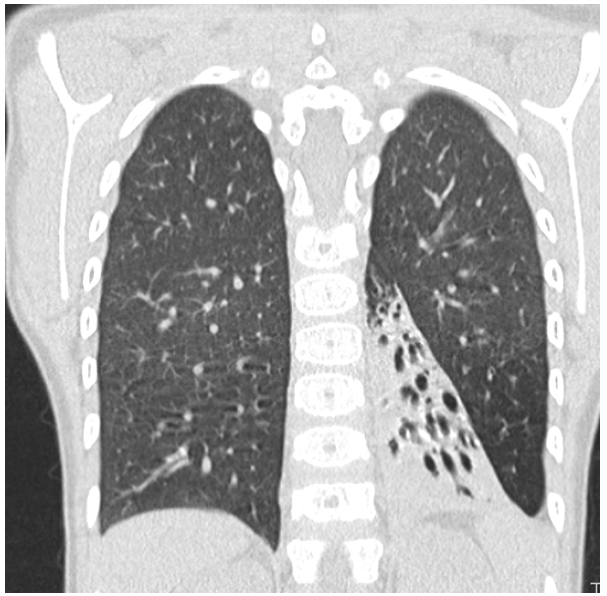
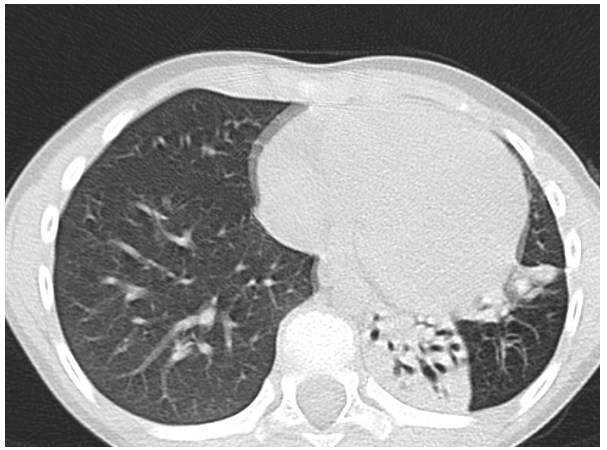




SPAD and chronic aspiration





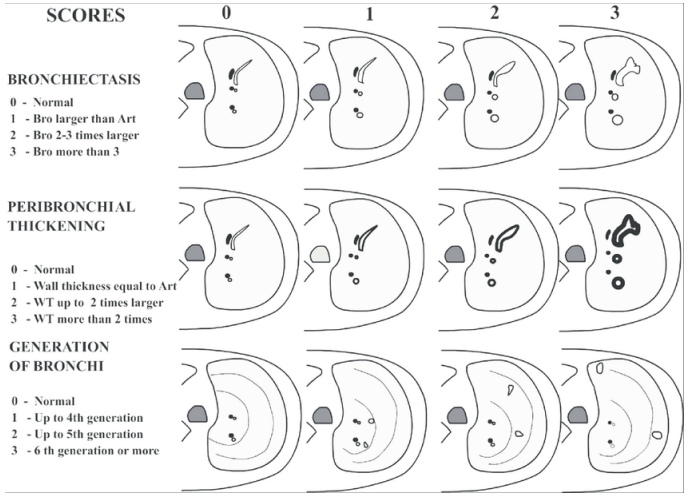
Humoral immunodef R/ SCIGG

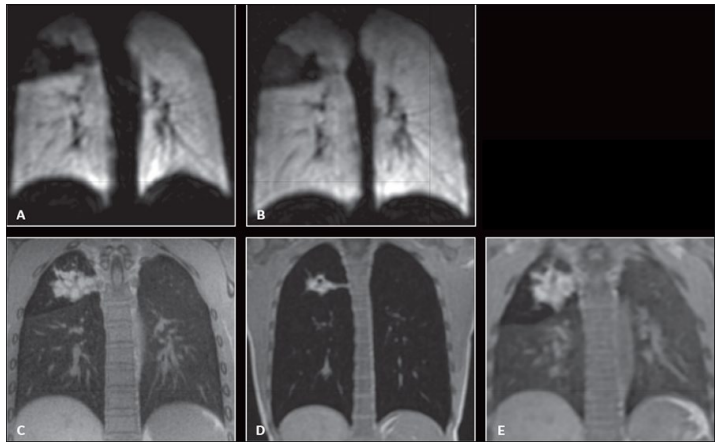
2.1 Follow-up

- 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 2 Comparison of physical characteristics, pulmonary functions, respiratory, and peripheral muscle strength in patients with CF and non-CF bronchiectasis and typically developing children and adolescents

Variables	CF (n = 20) Mean ± SD	Non-CF bronchiectasis (n = 20) Mean ± SD	Typically developing (n = 20) Mean ± SD	χ^2	*P*
Age, y	11.40 ± 3.15	12.90 ± 2.71	12.05 ± 3.18	2.47	.291
Sex (male/female)	11/9	7/13	12/8	2.80	.247
Height, z score	−0.90 ± 1.33	−0.76 ± 1.09	0.69 ± 1.09	14.74	.001*
Weight, z score	−0.84 ± 0.99	−0.76 ± 1.10	0.46 ± 1.13	4.44	.109
BMI, z score	−0.41 ± 0.88	−0.47 ± 1.19	0.17 ± 1.11	5.10	.078
FEV_1 (%)	84.45 ± 23.00	76.35 ± 19.59	93.80 ± 11.94	7.08	.029*
FEV_1, z score	−1.18 ± 1.69	−1.96 ± 2.34	−0.30 ± 1.92	12.61	.002*
MIP, cmH_2O	92.95 ± 21.12	81.65 ± 25.75	94.85 ± 14.67	4.37	.112
%MIP	103.68 ± 31.41	94.38 ± 30.68	94.67 ± 22.52	3.11	.211
MEP, cmH_2O	101.25 ± 19.93	94.55 ± 22.95	103.05 ± 27.87	2.58	.275
%MEP	91.95 ± 22.23	83.63 ± 25.99	94.01 ± 30.95	0.40	.523

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2.2 Disease severity/impact on Qol

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

	CF (n = 20)	Non-CF bronchiectasis (n = 20)	Typically developing (n = 20)		
Pediatrics	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	χ^2	*P*
Global function	348.90 ± 40.92	353.95 ± 35.56	376.05 ± 25.13	7.83	**.020***
Upper extremity physical function	90.85 ± 10.70	93.25 ± 6.94	95.95 ± 5.19	3.07	.214
Sports/physical function	82.65 ± 13.26	82.05 ± 15.88	92.95 ± 8.13	9.59	**.008***
Transfers/basic mobility	97.85 ± 6.92	97.80 ± 4.14	99.10 ± 1.97	1.42	.491
Pain/comfort	77.55 ± 19.68	80.85 ± 17.71	88.05 ± 15.17	4.25	.119
Happiness	82.75 ± 16.81	83.25 ± 17.11	86.75 ± 15.49	0.86	.650
Expectations	87.30 ± 10.17	88.50 ± 8.99	93.95 ± 6.35	7.74	**.021***
Adolescents					
Global function	356.18 ± 43.03	346.37 ± 41.88	386.07 ± 12.11	8.59	**.014***
Upper extremity physical function	94.36 ± 7.77	91.00 ± 10.21	98.00 ± 2.60	5.20	.074
Sports/physical function	81.72 ± 18.54	80.56 ± 16.50	92.00 ± 7.51	4.53	.103
Transfers/basic mobility	99.27 ± 1.84	98.00 ± 3.84	100.00 ± 0.00	6.56	**.037***
Pain/comfort	80.81 ± 23.78	76.81 ± 22.36	96.07 ± 8.19	9.95	**.007***
Happiness	77.72 ± 24.93	74.68 ± 20.85	84.28 ± 16.39	1.24	.537
Expectations	83.00 ± 17.14	85.93 ± 10.48	96.50 ± 3.08	10.39	**.006***

Abbreviation: CF, cystic fibrosis.
*$P < .05$, the Kruskal-Wallis Test.

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2.2 Qol in children with non CF bronchiectasis

TABLE 1 | Summary of studies and their findings of quality of life (QOL) in children with non-cystic fibrosis bronchiectasis (NCFB).

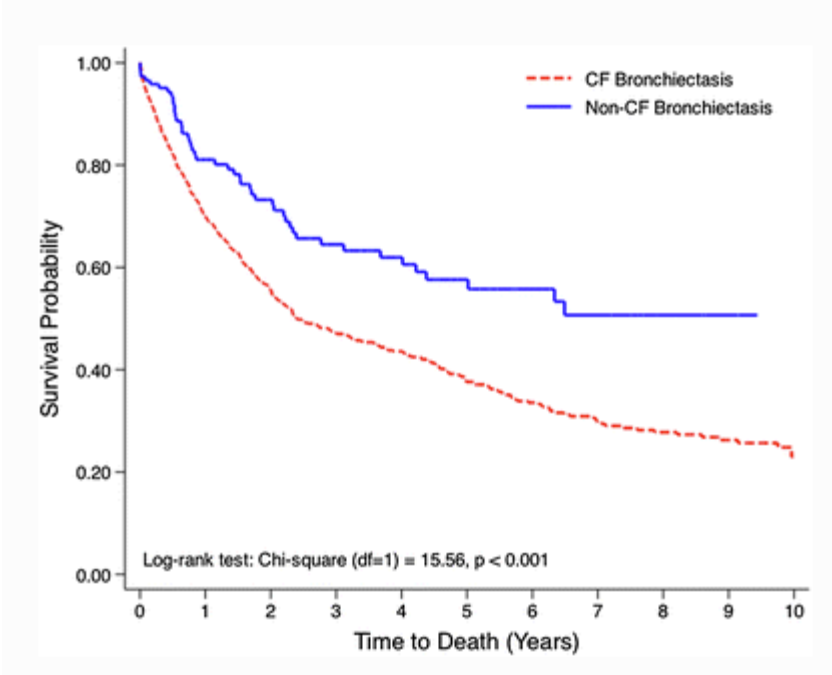
Country, year	Number	Type of study	Age (years)	Questionnaire	Findings
Australia, 2010	69	Cross-sectional	Median (IQR): 7 (3, 8, 10.9)	PC-QOL, DASS21	Parents of young children were more likely to report an impaired QOL Radiological extent, baseline lung function, underlying etiology, and chronic upper airway disease did not influence the burden of disease scores
Malaysia, 2014	60 (CF = 10; others = 50)	Cross-sectional	Median (range): 1.3 (0.3–11)	PC-QOL, DASS21	Mental health of parents 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
Turkey, 2014	76	Case–control	11.7 (±2.6)	CDI, STAI-C, PedsQL-P, PedsQL-C	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, FEV_1/FVC% predicted, dyspnea, and wheezing severity were the significant factors associated with a worse QOL Patients reported worse physical QOL
Turkey, 2014	42	Cross-sectional	12.7 (±2.3)	SF-36, SGRQ	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, HRCT score, and socioeconomic status
UK, 2010	78 PCD	Cross-sectional		SF-36, SGRQ	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

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

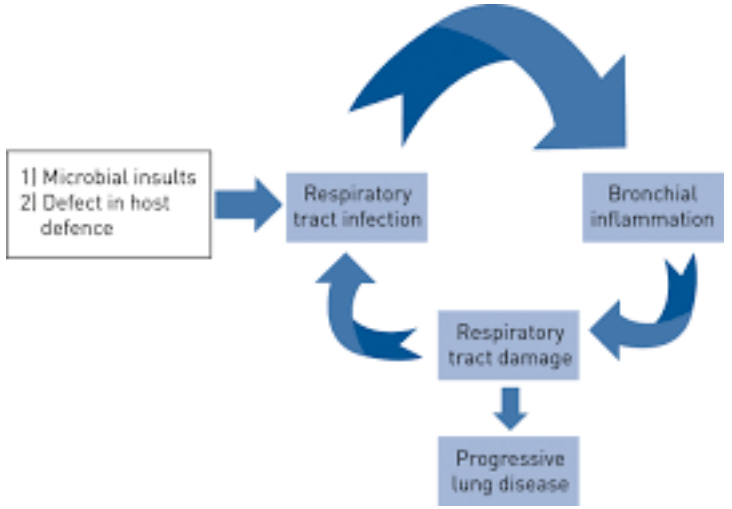
2.3 Prognosis

- 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)*

Characteristics	Participants, No. (%)	
	AZM group (n = 173)	Placebo group (n = 174)
Demographic characteristics		
Age, median (IQR), y	14.7 (12.6-16.8)	15.8 (13.0-18.1)
Female	80 (46.2)	90 (51.7)
Currently in school[a]	146 (84.4)	139 (79.9)
HIV characteristics		
Age at diagnosis, median (IQR), y	7.2 (3.5-9.9)	8.3 (5.2-11.1)
Cotrimoxazole prophylaxis	157 (90.7)	156 (89.7)
Duration taking antiretroviral therapy, median (IQR), y	5.9 (3.8-9.0)	6.4 (3.9-8.2)
HIV viral load $\log_{10}$ copies/mL, median (IQR)[a]	2.5 (1.6-4.0)	2.7 (1.7-4.1)
HIV viral load <1000 copies/mL[a]	100 (58.5)	94 (54.0)
CD4 cell count/mm^3, median (IQR)	601 (417-784)	550 (325-779)
Lung function characteristics, mean (SD)		
FEV_1 *z* score	−2.01 (0.76)	−2.00 (0.74)
FEV_1, L	1.59 (0.50)	1.71 (0.53)
FEV_1, %	73.3 (10.3)	73.6 (10.2)
FVC *z* score[a]	−1.77 (0.97)	−1.71 (0.89)
FVC, L	1.89 (0.59)	2.04 (0.63)
FVC, %[a]	77.8 (12.0)	78.4 (11.0)
FEV_1:FVC ratio *z* score[a]	−0.66 (1.14)	−0.74 (1.13)
FEV_1:FVC ratio[a]	0.85 (0.08)	0.84 (0.08)
Clinical characteristics		
Weight-for-age *z* score, mean (SD)	−2.23 (1.43)	−2.07 (1.50)
Underweight[b]	98 (56.7)	83 (47.7)
Height-for-age *z* score, mean (SD)	−2.16 (1.18)	−2.04 (1.24)
Stunted[b]	95 (54.9)	80 (46.0)
History of tuberculosis	58 (33.5)	39 (22.4)
Admitted for chest problems in last year	3 (1.7)	3 (1.7)
Current cough	13 (7.5)	18 (10.3)
Coughing up sputum[c]	7 (4.0)	17 (9.8)
Shortness of breath	5 (2.9)	1 (0.6)
Respiratory rate, mean (SD), breaths/min	22.2 (3.0)	22.6 (3.2)
Abnormal respiratory rate[d]	67 (38.7)	85 (48.9)
Oxygen saturation, mean (SD), %[a]	96.7 (3.0)	96.7 (2.4)
Oxygen saturation <92%	6 (3.5%)	11 (6.3%)
Heart rate, mean (SD), beats/min[a]	87.6 (12.5)	85.6 (11.6)
Abnormal heart rate[d]	6 (3.5%)	8 (4.6%)
Shuttle walk duration, mean (SD), min:s[a]	10:26 (1:56)	10:49 (2:03)

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.

	CF (n = 49)	Non-CF (n = 53)	Control (n = 88)	*p* value		
				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	<0.0001	<0.0001	NS
FEV_1 (% Predicted) *	70.9 ± 20.5	68.7 ± 21.5	99.1 ± 12.4	<0.0001	<0.0001	NS
FVC (L) *	2.8 ± 1.0	2.7 ±1.1	3.5 ± 1.3	<0.005	<0.005	NS
FVC (% Pred) *	82.9 ± 18.5	79.9 ± 20.6	102.2 ± 12.0	<0.0001	<0.0001	NS
peak $\dot{V}O_2$ (mL/min)	1915.5 ± 702.0	1740 ± 568	2111.0 ± 748.3	NS	0.007	NS
peak $\dot{V}O_2$ (%Pred)	92.9 ± 21.9	87.7 ± 19.0	101.6 ± 19.7	0.049	<0.0001	NS
peak $\dot{V}O_2$/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]	<0.01	<0.01	NS
Peak HR (beats/min)	180 [167–192[	182 [172–190]	182 [175–191]	NS	NS	NS
Peak HR (%pred)	89 [85–96]	92[87–96]	94 [92–97]	0.001	NS	NS
Lowest $\dot{V}E/\dot{V}CO_2$	31.4 ± 4.1	31.7 ± 4.1	27.2 ± 2.8	<0.0001	0.008	NS
$\dot{V}O_2$/peakHR (mL/min/beat)	10.8 ± 3.9	9.6 ± 3.0	11.6 ± 4.3	NS	0.010	NS
$\dot{V}O_2$/peakHR (%Pred)	100.6 ± 21.8	92.6 ± 18.3	108.0 ± 20.5	NS	<0.0001	0.046
peak$\dot{V}E$ (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	<0.0001	<0.0001	NS
SpO_2 (%) (pre)	98.3 ± 1.8**	98.7 ± 2.3***	99.5 ± 0.86	0.001	0.032	NS
$SpO_{2\ at\ peakVO2}$ (%) (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%)	<0.0001	<0.0001	NS
CT score	9.23±5.9	9.10±5.1		NA	NA	NS

REF??

Intervention	Main results	Comments
Positive expiratory pressure mask[44]	Significant improvement of pre- *versus* post- treatment regional lung ventilation. No change of pre- *versus* post-treatment FEV_1.	8-week trial in 6 children No comparison group not undergoing airway clearance techniques.
Supervised physiotherapy[45]	Significant thoracic gas volume decrease and FEV_1 improvement *versus* unsupervised controls.	1-month trial in 24 children. No comparison group not undergoing airway clearance techniques.
Inspiratory-threshold loading device and cough training[46]	Significantly improved pulmonary function and respiratory muscle strength in treated *versus* untreated subjects.	8-week trial (abstract).
Postural drainage, percussion and vibration *versus* high-frequency chest wall oscillation[47]	Significantly improved pulmonary function, no desaturation and no differences between methods. Both methods efficient, chest wall oscillation more comfortable.	Controlled randomized crossover study of 2 methods in 24 children with primary ciliary dyskinesia. Efficiency and comfort measured subjectively. Short study period.

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

Poeta M et al 2020 Review