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Bronchiectasis in children in a high HIV and tuberculosis prevalence setting

P Juggernath,[1] MB BCh; **K Mopeli,**[1] FC Paed (SA), MMed (Paed); **R Masekela,**[2] FC Paed (SA), PhD; **Z Dangor,**[1,3] FC Paed (SA), PhD; **A Goga,**[4,5] FC Paed (SA), PhD; **D M Gray,**[6] FC Paed (SA), PhD; **C Verwey,**[1,3] FC Paed (SA), PhD

[1] *Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Department of Paediatrics and Child Health, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa*
[3] *South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, University of the Witwatersrand, Johannesburg, South Africa*
[4] *South African Medical Research Council HIV and other Infectious Diseases Research Unit, Johannesburg, South Africa*
[5] *Department of Paediatrics and Child Health, Faculty of Heath Sciences, University of Pretoria, South Africa*
[6] *Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa*

Corresponding author: *C Verwey (charl.verwey@wits.ac.za)*

Background. Bronchiectasis, a chronic suppurative lung condition, is a largely neglected disease, especially in low- to middle-income countries (LMICs), from which there is a paucity of data. Post-infectious causes are more common in LMICs, while in high-income countries, inborn errors of immunity (IEIs), recurrent aspiration, primary ciliary dyskinesia (PCD) and cystic fibrosis are more common. Children living with HIV (CLWH), especially those who are untreated, are at increased risk of bronchiectasis. Data on risk factors, diagnosis and follow-up of children with bronchiectasis are required to inform clinical practice and policy.
Objectives. To describe the demographics, medical history, aetiology, clinical characteristics and results of special investigations in children with bronchiectasis.
Methods. We undertook a retrospective descriptive study of children aged <16 years with chest computed tomography (CT) scan-confirmed bronchiectasis in Johannesburg, South Africa, over a 10-year period. Demographics, medical history, aetiology, clinical characteristics and results of special investigations were described and compared according to HIV status.
Results. A total of 91 participants (51% male, 98% black African) with a median (interquartile range) age of 7 (3 - 12) years were included in the study. Compared with HIV-uninfected children, CLWH were older at presentation (median 10 (6 - 13) years v. 4 (3 - 9) years; $p<0.01$), and more likely to be stunted ($p<0.01$), to have clubbing ($p<0.01$) and hepatosplenomegaly ($p=0.03$), and to have multilobar involvement on the chest CT scan ($p<0.01$). All children had a cause identified, and the majority (86%) of these were presumed to be post-infectious, based on a previous history of a severe lower respiratory tract infection. This group included all 38 CLWH. Only a small proportion of the participants had IEIs, secondary immune deficiencies or PCD.
Conclusion. A post-infectious cause for bronchiectasis was the most common aetiology described in children from an LMIC in Africa, especially CLWH. With improved access to diagnostic techniques, the aetiology of bronchiectasis in LMICs is likely to change.
Keywords. Bronchiectasis, chronic suppurative lung disease, paediatrics, children living with HIV.

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Study synopsis
What the study adds. In this retrospective descriptive study of children aged <16 years with chest computed tomography scan-confirmed bronchiectasis in Johannesburg, South Africa (SA), over a 10-year period, we report that a post-infectious cause for bronchiectasis was the most commonly described, and that HIV was an important contributor. A large proportion of children with bronchiectasis in low- and middle-income countries such as SA do not benefit from an extensive work-up for the non-infectious causes of bronchiectasis.
Implications of the findings. With improved access to diagnostic techniques, including improvements in early diagnosis and access to treatment for children living with HIV, the aetiology of bronchiectasis is likely to change in the coming years.

Bronchiectasis, a chronic suppurative lung condition, is characterised by irreversible bronchial dilation and excessive airway mucus production.[1] Clinically, children with bronchiectasis may have a chronic wet or productive cough, exertional dyspnoea, respiratory exacerbations, poor growth, digital clubbing and chest deformity.[2,3] The diagnosis is confirmed radiologically by identifying bronchial dilation on a chest computed tomography (CT) scan.[2-4]

Largely a neglected disease, bronchiectasis has a prevalence ranging from 67 to 566 per 100 000 globally, with variability between and within countries (including indigenous populations in high-income countries (HICs)).[5-7] Post-infectious causes are more common in low- and middle-income countries (LMICs), while in HICs, inborn errors of immunity (IEIs), recurrent aspiration, primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) feature more commonly.[2,8] Access to improved diagnostics

Table 1. Characteristics of children with bronchiectasis, subdivided by HIV status

Variable	Total (*N*=91),* *n* (%)†	HIV infected (*n*=38), *n* (%)†	HIV uninfected (*n*=50), *n* (%)†	*p*-value
Female	45/91 (49.5)	23/38 (60.5)	21/50 (42.0)	0.09
Black African	89/91 (97.8)	37/38 (97.4)	49/50 (98.0)	0.85
Age (years), median (IQR); range	7 (3 - 12); 0 - 16	10 (6 - 13); 1 - 16	4 (3 - 9); 0.2 - 14	0.01
Relevant history				
HIV positive	38/91 (41.8)	38/38 (100)	0/50 (0)	n/a
On ART	34/38 (89.5)	34/38 (89.5)	n/a	n/a
Home oxygen	10/91 (11.0)	5/38 (13.2)	5/50 (10.0)	0.64
Cough	83/91 (91.2)	35/38 (92.1)	45/50 (90.0)	0.73
Wet cough	65/69 (71.4)	26/27 (96.3)	39/39 (100)	0.50
Exertional dyspnoea	16/89 (17.6)	10/36 (27.8)	6/05 (12.0)	0.06
Previous chest infections	78/91 (85.7)	38/38 (100)	40/50 (80)	<0.01
Previously treated TB	67/89 (73.6)	31/38 (81.6)	35/49 (71.4)	0.27
Anthropometry				
Weight (kg), median (IQR); range	16 (11.5 - 23.5); 3 - 69	20 (15 - 28); 5 - 40	14 (10 - 18.5); 3 - 69	<0.01
Height (cm), mean (SD); range	109.7 (24.09); 53 - 156	117.4 (21.5); 64 - 149	101.8 (23.8); 53 - 156	<0.01
Underweight	56/82 (61.5)	21/37 (67.6)	34/49 (69.4)	0.92
Stunted	49/82 (53.9)	30/35 (85.7)	17/42 (40.5)	<0.01
General examination				
Room air oxygen saturation (%), median (IQR); range	93 (88 - 96); 60 - 100	93 (87 - 96); 60 - 99	93.5 (89 - 96); 76 - 100	0.60
Digital clubbing	67/91 (73.6)	34/38 (89.5)	31/50 (62.0)	<0.01
Oedema	5/90 (5.5)	3/38 (7.9)	1/49 (2.0)	0.20
Otitis media	1/91 (1.1)	1/37 (2.7)	0/50 (0)	0.24
Respiratory				
Hyperinflation	27/91 (29.6)	13/38 (34.2)	14/50 (28.0)	0.53
Crackles	81/89 (89.0)	35/38 (92.1)	44/48 (91.7)	0.94
Bronchial breathing	20/88 (22.7)	11/38 (28.9)	9/50 (18.0)	0.17
Cardiovascular				
Displaced apex beat	4/91 (4.4)	1/38 (2.6)	2/50 (4.0)	0.73
Right ventricular hypertrophy	14/90 (15.3)	8/38 (21.1)	6/49 (12.2)	0.28
Abnormal heart sounds	27/91 (29.7)	14/38 (36.8)	13/50 (26.0)	0.45
Audible murmur	4/91 (4.4)	1/38 (2.6)	3/50 (6.0)	0.27
Pulmonary hypertension – clinical	19/91 (20.9)	12/38 (31.6)	7/50 (14.0)	0.05
Abdominal				
Hepatomegaly	23/90 (25.3)	14/38 (36.8)	8/49 (16.3)	0.03

IQR = interquartile range; n/a = not applicable; ART = antiretroviral therapy; TB = tuberculosis; SD = standard deviation.
*Three patients did not have known HIV status. Denominators vary owing to the variation in available data for specific data captured.
†Except where otherwise indicated.

and consequent earlier recognition of underlying susceptibility to recurrent respiratory infections may contribute to the differing aetiology between settings.[9]

In LMICs, recurrent lower respiratory tract infection (LRTI) in early childhood, especially cases requiring hospitalisation, is a risk factor for developing bronchiectasis.[10] Inadequate vaccination against common respiratory pathogens, inhaled environmental pollutants, and poverty, associated with overcrowding, poor water supply, macro- and micro-malnutrition, and limited access to healthcare and antibiotics, are further risk factors for developing bronchiectasis.[3,11] Children living with HIV (CLWH), especially those who are untreated, are at increased risk of recurrent and severe LRTIs, including pulmonary tuberculosis (PTB),[12] which increase the likelihood of airway damage and eventual bronchiectasis.[13-16]

Data on risk factors, diagnosis and follow-up of children with bronchiectasis are required to inform local clinical practice and policy. There are very limited data in South Africa (SA), or in LMICs generally, on the prevalence, investigational pathways, management and outcomes of children with bronchiectasis, despite a high prevalence of known risk factors for chronic respiratory disease. Available data are predominantly from high-risk populations, such as cohorts of CLWH, with 43% of adolescents with perinatally acquired HIV in Malawi and Zimbabwe being reported to have high-resolution chest CT scan-confirmed bronchiectasis, but data are limited on all causes of bronchiectasis.[14,17]

We therefore aimed to describe the clinical characteristics, aetiology and risk factors for disease severity in children with CT-confirmed bronchiectasis attending the paediatric pulmonology service at Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, SA, over a 10-year period.

Methods

Study design

We undertook a retrospective descriptive study of children aged <16 years with chest CT scan-confirmed bronchiectasis, attending the paediatric pulmonology specialist clinic at CHBAH over a 10-year period from February 2011 to December 2020.

This study forms part of the Bronchiectasis in African Children: Prevalence, Aetiology, and Clinical outcome (BACPAC) study, a multisite, observational clinical cohort study with the aim of establishing a national SA paediatric bronchiectasis registry. Study participating sites are CHBAH (Johannesburg), Inkosi Albert Luthuli Central Hospital (Durban), Red Cross War Memorial Children's Hospital (Cape Town), and Steve Biko Academic Hospital (Pretoria).

Study setting

CHBAH is a tertiary referral hospital for southern Johannesburg, Gauteng Province. The paediatric pulmonology clinic is set in the paediatric outpatient department and receives referrals from the paediatric in-house services and primary and secondary hospitals in the drainage area, as well as from neighbouring provinces. In-house referrals are received from one of four acute general paediatric wards or other subspecialty services, for example the haematology-oncology unit and the infectious diseases unit, which also runs the hospital's paediatric HIV clinic.

In children with CT-confirmed bronchiectasis, investigations to determine the aetiology of the bronchiectasis are undertaken but are dependent on the availability of resources. Over the course of the study, diagnostic capabilities improved with the addition of more specialised tests, for example nasociliary brushings and transmission electron microscopy (TEM) for the diagnosis of PCD since May 2019, and improved ability to investigate for IEIs, as experience and knowledge of the condition have improved. Sweat tests for CF are conducted off-site at another Johannesburg hospital.

Study definitions

For the purpose of this study, children were enrolled if they had characteristic radiographic features of bronchiectasis on a chest CT scan.[1,4,18,19] The diagnosis of CT-confirmed bronchiectasis was made after a paediatric pulmonologist or a radiologist who provided a CT scan report reviewed the CT scans. Radiographic features of bronchiectasis on the chest CT scan include an increased bronchoarterial ratio (the diameter of the bronchi divided by the diameter of the accompanying airway) of >1 - 1.5 in adults, with a proposed cut-off value of 0.8 in children.[1,4,5,20] Corroborating features include one or more dilated bronchi, the signet ring sign, non-tapering of the bronchi as they branch towards the periphery, presence of visible bronchi adjacent to the mediastinal pleura or within the outer 1 - 2 cm of the lung fields, bronchial wall thickening, and mucus plugging or impaction.

Underweight was defined as a weight for age less than the –2 *z*-score and stunting as a height for age less than the –2 *z*-score. Confirmed tuberculosis (TB) was defined as either microscopically or culture-positive TB, or a positive Xpert MTB/RIF assay.

Clinical and risk factor information

Data were collected from the paediatric pulmonology database and patient records and entered into a RedCAP (Research Electronic Data Capture, Vanderbilt University, 2022) database developed by BACPAC investigators and hosted by the University of the Witwatersrand. The following variables were captured: demographic data, past medical history, current clinical features, and findings on radiological investigations, sputum microbiology, blood investigations and pulmonary function tests. Data reported were from the initial time of presentation to the paediatric pulmonology specialist clinic.

Statistical analysis

Demographics, medical history, aetiology, clinical characteristics and results of special investigations were described using standard summary statistics, and data were presented as means and standard deviations (SDs) for normally distributed and medians and interquartile ranges (IQRs) for non-normally distributed continuous variables, and as proportions and percentages for categorical variables. Data were compared based on sex, HIV status and nutritional status. Comparisons between these groups were made using Student's *t*-test for continuous variables with normal distribution and the Mann-Whitney *U*-test for those without normal distribution, and the χ^2 or Fisher's exact test for categorical variables. Differences were considered statistically significant when the *p*-value was <0.05.

Ethical considerations

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M190529).

Results

Characteristics of cohort

A total of 91 children (51% male, 98% black African) with a median (IQR) age of 7 (3 - 12) years were included in the study (Table 1). Thirty-eight (42%) were HIV positive, of whom 90% were on antiretroviral therapy at the time of bronchiectasis diagnosis.

The majority (86%) of the participants had a history of previous chest infections, and 67/89 (74%) had previously been treated for PTB; 5 (7%) of these had confirmed PTB.

At first presentation, 83 children (91%) were coughing; 65/69 (71%) reported a productive cough. Sixteen of 89 (18%) reported exertional dyspnoea and 5/91 (6%) wheezing. On clinical examination, 56/82 (62%) were underweight for age and 49/82 (54%) were stunted. The majority, 67/91 (74%), had digital clubbing and almost a third, 27/91 (30%), had features of hyperinflation. Predominant auscultatory findings were crackles in 81/89 (89%) and bronchial breathing in 20/88 (23%). The median (IQR) room air oxygen saturation was 93% (88 - 96%). Almost a quarter of the participants, 19/91 (21%), had clinical evidence of pulmonary hypertension.

CLWH tended to be older at first presentation than those who were uninfected (median (IQR) 10 (6 - 13) years v. 4 (3 - 9) years; $p<0.01$) and were more likely to be stunted ($p<0.01$) and to have clubbing ($p<0.01$) and hepatosplenomegaly ($p=0.03$) (Table 1). There were no differences between male and female children with bronchiectasis (data not shown). Children who were underweight for age were more likely than those of normal weight to have clinical right ventricular hypertrophy and hepatomegaly (data not shown).

Investigations

The majority of the children (96%) had chest radiographs available for review, of which 51% had changes suggestive of multilobar bronchiectasis, 27% had changes predominantly in the right hemithorax, and 21% had changes predominantly in the left hemithorax (Table 2). Chest CT revealed that 38% of children had bilateral changes suggestive of bronchiectasis, and in those with unilateral disease, 37% had right hemithorax and 26% left hemithorax involvement. CLWH had more multilobar involvement on chest CT than those who were HIV uninfected ($p<0.01$) (Table 2). There were no differences between male and female children with bronchiectasis (data not shown).

Only 21/89 children (23%) had upper gastrointestinal contrast studies performed, with abnormal anatomy reported in one case and aspiration in one. Fourteen children had radionucleotide-milk scans or videofluoroscopy performed, with reflux reported in four cases and aspiration in one.

Sputum or bronchoalveolar lavage specimens were sent for analysis at the time of diagnosis in the majority of cases (81%), with 69% ($n=52/75$) having a positive culture; just over half of these (56%) cultured multiple organisms. *Haemophilus influenzae* (34%) was the most commonly cultured organism. There were no differences between CLWH and those who were HIV uninfected.

Investigations for CF, including faecal elastase, sweat conductivity testing and CF gene analysis, were performed in 30% of the participants, with no results being suggestive of CF, while nasociliary brushings with TEM were done in 13/90 children (14%), of whom five (38%) were confirmed with PCD, all class 1 defects.

Lung function tests (spirometry) were only performed on 20% of patients at the time of diagnosis; almost a quarter (22%) displayed normal pulmonary function, while 44% displayed mixed obstructive/restrictive pulmonary function, 28% restrictive lung disease, and only one obstructive lung disease alone. The mean (SD) forced vital capacity (FVC) *z*-score was –2.46 (2.32) and the mean forced expiratory volume in 1 second (FEV_1) *z*-score –2.9 (2.14), with an FEV_1/FVC ratio of 0.79 (0.17), an FEV_1/FVC *z*-score of –1.46 (1.85), and a forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) *z*-score of –3.09 (1.60). These findings were similar for the CLWH and those who were HIV uninfected.

Bronchoscopy was performed on just over half (53%) of the children, of whom two showed abnormal anatomy, one a right upper lobe tracheal bronchus and one narrowing of the left main bronchus.

Aetiology of bronchiectasis

Discernible causes of bronchiectasis are summarised in Table 3. All the children had a cause identified. The majority (86%) of these were presumed to be post-infectious based on a history of a severe LRTI. This was the most likely cause in all 38 CLWH. Only a small proportion (4%) had IEIs, which included two cases of common variable immune deficiency and one case each of agammaglobulinaemia and hypergammaglobulinaemia. Secondary immune deficiencies, excluding HIV, accounted for bronchiectasis in a further four children, including two with malignancies, receiving immunosuppressive therapy, one with nephrotic syndrome, and one with microdeletion of *22q11* (CATCH-22) and tetralogy of Fallot. Five children (6%) were diagnosed with PCD.

Discussion

In this study we reported data from an LMIC setting in Africa describing 91 children (median age 7 years) with bronchiectasis, and compared CLWH with those who were HIV uninfected.

A presumed post-infectious cause for bronchiectasis was the most common aetiology described, with the majority of children having previously been treated for a severe LRTI, including all 38 children who were HIV infected. Furthermore, CLWH were older at diagnosis of bronchiectasis, which could explain the differences in basic growth parameters between the two groups, but they were also more likely to be stunted, to display digital clubbing, and to have hepatomegaly. Lastly, CLWH were more likely to present with multilobar disease on chest CT scan.

A post-infectious aetiology has been reported as one of the leading causes of bronchiectasis, especially in LMICs.[3,20] Severe or recurrent chest infections, PTB and HIV have been documented as significant risk factors in the development of bronchiectasis.[13-15,21] More than two-thirds (60 - 90%) of CLWH globally reside in sub-Saharan Africa, and the World Health Organization reports that 12% of newly diagnosed PTB cases in children aged <15 years occur in Africa, providing a large potential reservoir of children with an increased incidence of bronchiectasis.[21-23] CLWH are also more likely to develop LRTI, to have more recurrent LRTIs and to have more severe LRTI, which is likely to explain the increased presence of multilobar lung involvement in CLWH.[12] Ferrand *et al.*[14] reported that 43% of their cohort of highly active antiretroviral therapy (HAART)-naive adolescents living with HIV (ALWH) in Zimbabwe

Table 2. Investigations in children with bronchiectasis, subdivided by HIV status

Variable	Total (*N*=91),* *n* (%)†	HIV infected (*n*=38), *n* (%)†	HIV uninfected (*n*=50), *n* (%)†	*p*-value
Imaging				
Chest X-ray done	87/91 (95.6)	37/38 (97.4)	47/50 (94.0)	0.45
Multilobar involvement	42/83 (50.6)	19/34 (55.9)	23/47 (48.9)	0.38
Location of findings of bronchiectasis on CT chest	91/91 (100)	38/38 (100)	50/50 (100)	n/a
Multilobar involvement	63/91 (69.2)	32/38 (84.2)	29/50 (58.0)	<0.01
Mainly left lung involvement	23/91 (26.1)	9/36 (25.0)	14/47 (2.6)	0.40
Mainly right lung involvement	32/91 (36.6)	11/36 (30.5)	18/47 (36.7)	0.31
Bilateral lung involvement	33/91 (37.5)	16/36 (44.4)	17/47 (34.7)	0.30
Contrast studies				
Upper gastrointestinal study done	21/89 (23.1)	5/36 (13.9)	16/50 (32.0)	0.05
Abnormal anatomy	1/21 (4.8)	1/5 (20.0)	0/16 (0)	0.07
Aspiration	1/21 (4.8)	1/5 (20.0)	0/16 (0)	0.07
Reflux	12/21 (57.1)	2/5 (40.0)	10/16 (62.5)	0.38
Milk scan/videofluoroscopy done	14/89 (15.4)	0/37 (0)	14/49 (28.6)	n/a
Aspiration	1/14 (7.1)	0/38 (0)	1/14 (7.1)	n/a
Reflux	4/14 (28.6)	0/38 (0)	4/14 (28.6)	n/a
Sputum				
Sputum/BAL sent	74/91 (81.3)	30/37 (79.0)	43/50 (86.0)	0.38
Microscopy sent	74/91 (81.3)	29/37 (78.4)	44/49 (89.8)	0.14
Culture sent	75/91 (82.4)	29/37 (78.4)	45/50 (90.0)	0.13
Positive culture	52/75 (69.3)	20/29 (69)	32/45 (71.1)	0.84
Multiple organisms	29/52 (55.7)	12/20 (60.0)	17/32 (53.1)	0.90
Fungal culture sent	13/88 (13.2)	6/36 (16.7)	7/49 (14.3)	0.76
Positive fungal culture	5/13 (38.5)	1/6 (16.7)	4/7 (57.1)	0.39
TB work-up				
TB microscopy positive	3/75 (3.3)	1/28 (3.6)	2/45 (4.4)	0.86
TB culture positive	4/75 (4.4)	1/28 (3.6)	3/45 (6.7)	0.57
Xpert MTB/RIF assay positive	2/76 (2.6)	0/28 (0)	2/45 (4.4)	0.26
CF work-up				
Faecal elastase done	22/91 (24.2)	1/38 (2.6)	20/50 (40.0)	n/a
Faecal elastase <100 µg/g	0/22 (0)	0/1 (0)	0/20 (0)	n/a
Sweat test (conductivity) done	27/91 (29.7)	1/38 (2.6)	27/50 (54.0)	n/a
Sweat conductivity >80 mmol/L	0/27 (0)	0/1 (0)	0/27 (0)	n/a
CF gene done	16/91 (17.6)	0/38 (0)	15/50 (30.0)	n/a
CF gene positive	0/16 (0)	0 (0)	0/17 (0)	n/a
Lung function				
Spirometry done	18/91 (19.8)	8/38 (21.1)	10/50 (20.0)	0.90
FVC z-score, mean (SD); range	−2.46 (2.33); −5.23 - 2.19	−2.44 (2.87); −5.23 - 2.19	−2.48 (1.99); −5.21 - 0.43	0.98
FEV_1 z-score, mean (SD); range	−2.93 (2.14); −5.73 - 1.79	−2.62 (2.62); −5.73 - 1.79	−3.19 (1.80); 4.85 - 0.16	0.65
FEV_1/FVC, mean (SD); range	0.78 (017); 0.44 - 0.98	0.81 (0.16); 0.51 - 0.93	0.76 (0.18); 0.44 - 0.98	0.61
FEF_{25-75} z-score, mean (SD); range	−3.09 (1.60); −6.12 - 0.31	−2.94 (1.53); −5.18 - 1.55	−3.21 (1.78); −6.12 - 0.31	0.77
Other tests				
Nasal brushing done	13/90 (14.4)	0/37 (0)	9/50 (18.0)	<0.01
PCD confirmed	5/13 (38.5)	0/5 (0)	5/5 (100)	n/a
Lung biopsy done	2/87 (2.2)	1/36 (2.8)	1/48 (2.1)	0.84
Bronchoscopy done	48/89 (52.8)	15/36 (41.7)	30/50 (60.0)	0.09
Abnormal anatomy	2/48 (4.2)	1/15 (6.7)	1/30 (3.3)	0.61

CT = computed tomography; n/a = not applicable; BAL = bronchoalveolar lavage; TB = tuberculosis; CF = cystic fibrosis; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FEF_{25-75} = forced expiratory flow between 25% and 75% of FVC; SD = standard deviation; PCD = primary ciliary dyskinesia.

*Three patients did not have known HIV status. Denominators vary owing to the variation in available data for specific data captured.

†Except where otherwise indicated.

Table 3. Aetiology of bronchiectasis in children

Underlying aetiology	Total (*N*=91), *n* (%)	HIV infected (*n*=38), *n* (%)	HIV uninfected (*n*=50), *n* (%)	*p*-value
Post-infectious (presumed)	78 (85.7)	38 (100)	40 (80)	<0.01
Primary ciliary dyskinesia	5 (5.5)	0	5 (10)	0.06
Cystic fibrosis	0	0	0	n/a
Inborn error of immunity	4 (4.4)	0	4 (8.0)	0.09
Secondary immune deficiency (excluding HIV)	4 (4.4)	1 (2.6)	3 (6.0)	0.47
Aspiration	2 (2.2)	1 (2.6)	1 (2.0)	<0.01

had bronchiectasis. The increased availability and early use of HAART and sulfamethoxazole-trimethoprim prophylaxis have significantly reduced the number and severity of LRTIs in CLWH, as has the availability of multiple vaccines against childhood LRTI, for example measles, pertussis and BCG, as well as the more recently introduced pneumococcal conjugate vaccine.[24-26] The burden of paediatric bronchiectasis in CLWH now lies with those patients with perinatally acquired HIV diagnosed later in childhood.

Although older age at diagnosis of bronchiectasis in CLWH could account for the differences in growth parameters between the two groups, the increased burden of stunting, digital clubbing and hepatomegaly is more likely to be due to the potential presence of multiple chronic disease processes in CLWH and delayed initiation of ARVs, and has been well described in previous studies.[27,28] More than half of the children in our cohort were underweight for age and a similar proportion were also stunted, with a significantly higher prevalence of stunting in CLWH (86% v. 41%; $p<0.01$).

Malnutrition, a condition much more prevalent in Africa and LMICs than in HICs, has been implicated as a risk factor in the development of bronchiectasis and chronic lung disease.[29] Furthermore, CLWH, and those with a prior history of PTB, are at increased risk of developing malnutrition, and bronchiectasis itself may also lead to a catabolic state in children, resulting in a higher energy demand that cannot be sustained, leading to malnutrition.

The most common symptom in our cohort was a chronic productive cough (71%), with 18% also experiencing exertional dyspnoea. This finding is similar to those in studies describing CLWH from Zimbabwe and Malawi, as well as studies performed in HICs, denoting that irrespective of the underlying aetiology and socioeconomic background, the symptomatology of bronchiectasis is similar in children whether HIV infected or uninfected.[5,14,16] The majority of our cohort had digital clubbing and crackles on chest auscultation, and 38% had radiological changes of bronchiectasis on both hemithoraces on the chest CT scan. These findings are similar to those in studies from Africa and globally, and are valuable pointers for referral from primary settings for investigation.[14,16,30,31]

Surveillance of airway-colonising organisms is essential for all patients with bronchiectasis. The majority of the children in our study had a positive culture on sputum/bronchoalveolar lavage, with more than half of the children (56%) culturing multiple organisms and *H. influenzae* (34%) being the most common organism cultured. This finding is similar to those of multiple studies investigating the sputum of children with bronchiectasis unrelated to CF.[15,32]

Only a small proportion of our cohort were worked up for CF, PCD and IEI, with 10% being confirmed with either PCD or IEI. Although the proportion of children with underlying causes for bronchiectasis, other than post-infectious, is relatively small, this finding clearly demonstrates that all cases of bronchiectasis in childhood warrant full aetiological investigation, as a definitive diagnosis affects the management of the bronchiectasis. In a study from Turkey, it was reported that with increased access to further investigations, an increased number of children with an identified cause for the bronchiectasis, other than post-infectious, can be found, with increased cases of PCD and a decreased number of idiopathic cases.[9] In our study, additional significant aetiological results were found in the small number of patients who did undergo full investigation. This finding suggests that we have much more to learn regarding the aetiology of bronchiectasis in our setting, and an increased proportion of other causes may be uncovered if all cases are thoroughly investigated. However, in LMICs, nasociliary brushings and TEM for the diagnosis of PCD, and any testing modality for the diagnosis of CF, are not readily available outside of specialist centres, and IEI investigations are costly, leaving many cases of bronchiectasis deemed post-infectious or idiopathic.[17]

Spirometry was only performed on 20% of patients, with 44% displaying a mixed obstructive/restrictive picture. Attia *et al.*[13] reported that 45% of ALWH, of whom 43% had bronchiectasis on the chest CT scan, had abnormal FEV_1, while Chang *et al.*[30] reported that children with bronchiectasis from LMICs had lower FEV_1 and FVC than those from HICs.

There are notable limitations to our study. Firstly, it was a retrospective observational study, with all the inherent shortcomings of a study of this type, including incomplete data capturing. Furthermore, it was a single-centre study with a strict definition of CT scan confirmation of bronchiectasis. In resource-limited settings, this definition may miss many children, and an alternative LMIC-based approach previously proposed by this group may be more appropriate.[17] The CF data presented in this study may be misleading, as there is a dedicated CF centre in Johannesburg to which children may have been referred directly from the drainage area of our hospital, and it is therefore possible that cases of CF were missed. Children were investigated based on the tests that were available at their time of presentation and attendance at the clinic, with children who presented in the later years having more extensive testing to identify causes of bronchiectasis than those in the earlier years. At the time of enrolment into the study, the majority of CLWH had not been investigated any further to look for

additional contributing causes of their bronchiectasis, which could inadvertently have led to underdiagnosis of certain aetiologies of bronchiectasis in this subgroup. At the time of enrolment, further data on the immunological status of the CLWH, including their viral load, CD4 count and antiretroviral status, were not available. These data could have better described the CLWH population.

The strength of the study is that we describe in detail children with chest CT scan-confirmed bronchiectasis, thereby ensuring minimal possible misdiagnosis of the clinical syndrome, providing novel data from an LMIC in Africa.

Conclusion

A post-infectious cause was the most common aetiology described in children with bronchiectasis from an LMIC in Africa, especially in CLWH. With improved access to diagnostic techniques and improvements in early diagnosis and management of childhood HIV, the aetiology of bronchiectasis in LMICs is likely to change in the coming years, to more closely resemble that in HICs.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (CV) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.

Declaration. The research for this study was done in partial fulfilment of the requirements for PJ's MMed (Paed) degree at the University of the Witwatersrand.

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Author contributions. PJ and CV conceptualised this project, analysed the data, wrote the manuscript and approved the final version. ZD, KM, DMG, AG and RM reviewed and revised the manuscript and approved the final version. CV, DMG, AG and RM conceptualised and implemented the BACPAC group and database on which this study is based.

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