Surgery for bronchiectasis in children living with HIV: A case series from a low- to middle-income country

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Background. Bronchiectasis (BE) in children living with HIV (CLWH) remains a significant cause of morbidity and mortality, especially in tuberculosis (TB)-endemic low- and middle-income countries. Treatment modalities for BE in CLWH currently focus mainly on prevention of infections and management of symptoms, while surgical management is indicated for a select group. In contrast, surgical management in non-cystic fibrosis BE is well established.
Objectives. To describe the indications for and complications of surgical resection for BE in CLWH, and to identify variables influencing outcome.
Methods. A retrospective medical records review was conducted of all CLWH aged ≤14 years who underwent surgical resection for BE at Tygerberg Hospital, Cape Town, South Africa, between 1 January 2007 and 30 September 2014. The variables collected included immune status, antiretroviral treatment (ART), previous treatment for TB, operative and postoperative complications, and postoperative symptom relief.
Results. Twelve CLWH on ART with symptomatic BE underwent surgical resection. The mean age was 7 years and the mean CD4 count 970 cells/μL. Indications for surgery included recurrent infections, chronic cough and persistent lobar collapse. The most common procedures were left lower lobe lobectomy (42%), left pneumonectomy (17%) and right bilobectomy (17%). Complications were limited to persistent pneumothorax after surgery in one child. There were no deaths. Ten children (83%) showed significant improvement of symptoms at follow-up.
Conclusion. Surgical resection for BE in CLWH can be performed safely with a low complication rate, resulting in significant improvement of symptoms postoperatively.
Keywords. Bronchiectasis, childhood thoracic surgery, HIV-related chronic lung disease, lobectomy.

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Study synopsis
What the study adds. Bronchiectasis (BE) in children living with HIV (CLWH) is a significant cause of morbidity and mortality. Current treatment focuses on preventing infections and managing symptoms, while surgical management is rarely considered. A retrospective medical records review of 12 children aged ≤14 years in South Africa found that surgical resection for BE can be performed with a low complication rate, resulting in significant improvement of symptoms postoperatively. Variables influencing outcome include immune status, antiretroviral treatment and previous treatment for tuberculosis.
Implications of the findings. This study demonstrates that surgery for BE can be performed safely in CLWH, with significant improvement of respiratory symptoms postoperatively.

Bronchiectasis (BE) is defined as the irreversible destruction of the bronchial wall and surrounding tissues. It is caused by an initial infectious process that initiates a persistent inflammatory response resulting in impaired mucociliary clearance, complicated by acute or chronic infections causing permanent damage to the bronchial wall and subsequently to the lung parenchyma.[1,2]

HIV-related lung disease has been responsible for an increase in chronic lung disease (CLD), including BE, especially in the pre-antiretroviral therapy (ART) era.[1] In 2017, the prevalence of HIV infection in South Africa (SA) was 12.6% (7 million people),[3] while Western Cape Province had a prevalence of 6.6% in 2015/16.[4] Furthermore, SA remains among the countries with the

highest incidence of tuberculosis (TB) (615 per 100 000 population in 2019).[5]

BE is a common cause of morbidity and mortality in children living with HIV (CLWH), specifically those in early adolescence.[6,7]

Subsequent to the early use of ART in children, the prevalence of BE decreased in industrialised countries, but it remains common in the high HIV prevalence countries of sub-Saharan Africa.[2] This situation can be explained by the late diagnosis of HIV infection in children, poorly managed lower respiratory tract infections (LRTIs), and a high prevalence of TB.[8] It has been reported that CLD, including BE, is common in adolescents living with HIV (ALWH) who were only recently diagnosed with HIV infection.[9] Even after initiating ART in CLWH with BE, lung function does not improve and patients remain symptomatic.[10]

Studies conducted in Zimbabwe and Malawi among older children and adolescents with perinatally acquired HIV showed that 50% had chest radiographic features consistent with BE.[11,12] Two-thirds of children in the African studies had been on ART for at least a median duration of 20 months and had a median CD4 count >350 cells/μL.[13]

Risk factors for developing BE in CLWH are severe immunosuppression (blood lymphocyte CD4 percentage <15%), pulmonary TB (PTB), and persistent and/or recurrent pneumonia, mostly caused by multiple organisms.[1,8] In CLWH, both neutrophil-driven airway inflammation and an exaggerated local and systemic immunological response to bacterial and fungal pathogens contribute to BE.[10]

Despite HIV-associated BE being one of the most common causes of non-cystic fibrosis (non-CF) BE, there are no published guidelines on the standard of care with regard to medical and surgical management.[14]

Reports of surgical treatment for non-CF BE in children demonstrate that it is a safe procedure with acceptable morbidity and negligible mortality, leading to significant improvements in symptoms and quality of life.[15,16] There are only case reports of single cases of HIV-related BE in which surgical management of BE in adults or children has been described.[2,17,18]

The aim of this study was to report on the surgical management of BE in a series of CLWH and to determine morbidity and mortality following thoracic surgery in these chronically ill children.

Methods

This was a retrospective study of a case series of CLWH who underwent surgical resection for BE between 1 January 2007 and 30 September 2014. The study was conducted at Tygerberg Hospital, a tertiary care hospital in Western Cape Province, SA, a region with a high prevalence of both HIV and TB.

All CLWH aged ≤14 years with surgically resectable BE were included in the case series. Surgical resection of the BE was only considered if the child had unilateral BE and relatively preserved lung function and remained symptomatic after ART and medical management of the BE were optimised. Symptomatic was defined as one or more of the following conditions: a chronic cough (defined as lasting 3 - 4 weeks)[19] with copious sputum production, recurrent pneumonia (defined as two episodes of pneumonia in 1 year or three episodes over any time frame), or recurrent LRTI (more than eight per year)[20] and failure to thrive. These symptoms had to persist after optimising ART.

Standard medical management of BE in the paediatric pulmonology unit includes optimising nutrition, physiotherapy, appropriate immunisations and exclusion of PTB, in addition to the use of macrolide antibiotics as an immune modulator. All the children in the study were managed by a team of healthcare providers in the context of a dedicated HIV or ARV clinic. Standard practice includes that children are admitted preoperatively for intensive chest physiotherapy, pulmonary hygiene and preoperative evaluation before thoracotomy.

The children were therefore carefully assessed prior to surgery. The assessment included an immunological work-up, cardiac echocardiography, fibreoptic bronchoscopy and chest computed tomography (CT). The paediatric pulmonologist and cardiothoracic surgeons discussed the children with BE to ensure that they were optimally managed and met the inclusion criteria.

The immunological work-up of the children was central to consideration for surgery. The clinical immune status, CD4 count (percentage and absolute values) and viral load were assessed. All the children were on ART and clinically considered fit for surgery.

Chest CT findings were used to evaluate the severity and distribution of BE and to determine the resectability of affected lung tissue.

Bronchial blockers and selective bronchial intubation were used during thoracotomy in cases where they were possible.

As recommended by studies in children with non-CF BE, all affected lung tissue was resected.[16] A posterolateral thoracotomy was performed in all children, either in the 4th or 5th intercostal space. Anatomical pulmonary, lobar or segmental resection was done. Intercostal drains were placed prior to closure of the chest. All resected specimens were sent for histopathological evaluation.

Postoperatively, the children were admitted to the intensive care unit (ICU) for optimal analgesia and monitoring. The chest drains were monitored for drainage and air leaks and removed when indicated. Complications were recorded during the intra- and postoperative periods. All the children received prophylactic TB treatment with rifampicin, isoniazid and pyrazinamide for 3 months postoperatively.

Lung tissue was sent for histological examination and reviewed by one paediatric pathologist.

The children were subsequently reviewed at the paediatric pulmonology outpatient clinic 6 weeks after surgery and then as required at monthly intervals for at least 1 year after surgery. They and their caregivers were questioned regarding symptoms according to the following categories: symptom free, improved symptoms, no change, or worsening of symptoms. They were asked about chronic cough, night-time coughing, admission to hospital and oral antibiotic use.

The patient data were collected from the medical records on a clinical research form and transcribed to a database where all patient identifiers were removed. Ethical permission was received from the Human Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University (ref. no. S13/10/212).

Results

Twelve CLWH underwent surgical resection for BE during the study period (Table 1). The mean (standard deviation (SD)) age was 7 (3.3) years, and the male-to-female ratio was 1:1. All the children were receiving ART. The median (interquartile range) duration of ART before surgery was 31 (12.3 - 47.8) days.

According to World Health Organization immunological staging, the absolute CD4 count (cells/μL) was used to classify immunosuppression in children aged >5 years, while the CD4 percentage was used in children aged 0 - 59 months.[21] Seven children had non-significant immunosuppression, 3 had mild immunosuppression, 1 had advanced immunosuppression, and 1 had severe immunosuppression. The viral load was measured in 11 of the 12 children. The results showed that 7 children had a viral load that was lower than detectable (log_{10} <1.3). Of the remaining children, 1 had a viral load between log_{10} 1.3 and 2, 2 a viral load between log_{10} 2 and 3, and 1 a viral load between log_{10} 3 and 4.

The indications for surgery were recurrent infections in 75% (*n*=9), chronic cough with sputum production in 33% (*n*=4), and persistent lobar collapse in 17% (*n*=2). More than one of the conditions was present in 3 children (Table 2).

Prior to referral to our unit, 92% of the children received TB treatment, despite the fact that TB was confirmed by *Mycobacterium tuberculosis* (MTB) culture in only 17%. Seven children had negative MTB cultures prior to surgery. One child was diagnosed with culture-proven drug-susceptible TB on bronchoalveolar lavage (BAL) during work-up, despite receiving a four-drug anti-TB regimen during the 6 months prior to surgery.

From the BAL performed prior to surgery, the following organisms were cultured: *Haemophilus influenzae* (*n*=5), *Streptococcus pneumoniae* (*n*=2), beta-haemolytic *Streptococcus* (*n*=1), MTB (*n*=1) and *Candida* species (*n*=1).

Chest CT scans were done in 11 cases (92%). The results demonstrated BE in the right lower lobe (*n*=1), left lower lobe (*n*=6), right upper lobe (*n*=1), and combined right middle and lower lobe (*n*=2). Two patients suffered total destruction of the left lung, and 2 had bilateral BE with one lung minimally involved.

The following surgical procedures were performed: left lower lobe lobectomy (*n*=5; 42%), right lower lobe lobectomy (*n*=1; 8%), right upper lobe lobectomy (*n*=1; 8%), right bilobectomy (*n*=2; 17%), left lobectomy and segmentectomy (*n*=1; 8%), and left pneumonectomy (*n*=2; 17%) (Table 2). None of the health workers involved with the surgery sustained needle-stick or splash incidents during the surgery.

Intercostal drains were removed 2 - 6 days postoperatively (median 3.5 days). The mean (SD) duration of ICU stay was 2.3 (0.87) days. The children were discharged home postoperatively at a mean of 5.7 (1.92) days. The mean total hospital stay, including the pre- and postoperative periods, was 12.6 (5.23) days (Table 3).

The intra- and postoperative morbidity rate was low, with only one child (8%) developing a persistent pneumothorax requiring replacement of an intercostal drain. No children had re-operations, and there was no operative mortality.

The histological reports confirmed BE in 75% (*n*=9) of the children. In one child the histological features were those of CLD with extensive fibrosis, and in another child reactive lymphoid hyperplasia was reported. The histology report for one child was unavailable. There was no histological or microbiological confirmation of TB on the resection samples.

At follow-up, the children and their caregivers were questioned regarding symptoms. One child was lost to follow-up. Six children (50%) were completely symptom free, and 4 (33%) reported improved symptoms. The improved symptoms included reduced coughing, especially night-time coughing. One child reported no change in symptoms, and none reported worsening of symptoms. There were no hospital admissions for LRTIs in this cohort during the year after surgery. Two children received oral antibiotics for episodes of LRTI as home therapy. Chest radiographs were available for 11 of the patients at 1 year after surgery. In 7 cases the radiographs were normal except for the post-surgical appearance, and 4 showed volume loss with mediastinal shift to the side of the surgical resection.

The outcome of surgical management of these children shows that 83% either had no symptoms or had improved symptoms at follow-up.

Table 1. Demographics and clinical characteristics

	Patient no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Age	13y3m	5y10m	1y10m	7y2m	4y2m	7y6m	3y9m	8y2m	6y4m	11y2m	11y1m	8y7m
WHO immunological staging[19]	Advanced	Mild	Severe	Mild	Not significant	Not significant	Mild	Not significant	Not significant	Not significant	Not significant	Not significant
CD4 count (cells/μL)	263	378	691	422	2 362	561	996	1 471	676	648	1 434	1 748
CD4%	14	13.6	11	27.8	32.3	19	24	25.4	31.55	14.47	44.5	32.5
Viral load	Unknown	1 300 copies/mL log10 3.11	310 copies/mL log10 2.49	LDL	LDL	LDL	688 copies/mL log10 2.84	LDL	LDL	LDL	LDL	log10 1.89
Duration of ART	1y2m	3y5m	1y1m	7m	8m	3y	2y2m	5y8m	3y3m	10m	6y4m	7 - 8y
TB diagnosis proven	No	No	No	No	Yes	No	Yes	No	No	No	No	No
TB Rx received	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

WHO = World Health Organization; LDL = lower than detectable limit; ART = antiretroviral treatment; TB = tuberculosis; Rx = treatment.

Table 2. Bronchiectasis and surgical interventions

	Patient no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Affected segments	RLL	LLL	LLL	RUL	LLL	RML, RLL	LLL, lingula	LLL	LLL	RML, RLL	Left lung	Left lung
Indications for surgery	Recurrent infections	Recurrent infections	Recurrent infections	Recurrent infections	Persistent LLL collapse	Persistent RLL collapse	Symptoms, recurrent infections	Symptoms, recurrent infections	Symptoms, recurrent infections	Symptoms	Recurrent infections	Recurrent infections and FTT
Resection	RLL lobectomy	LLL lobectomy	LLL lobectomy	RUL lobectomy	LLL lobectomy	Bilobectomy, RML and RLL	LLL and lingula	LLL lobectomy	LLL lobectomy	Bilobectomy, RML and RLL	L pneumonectomy	L pneumonectomy
ICU stay (days)	3	2	2	4	1	2	2	1	2	3	3	2
Hospital stay (days)	26	12	14	15	14	14	7	8	15	10	9	7
Discharged after surgery (days)	8	10	4	6	3	5	5	7	4	6	5	5
Operative morbidity	None	None	None	None	None	None	Additional ICD	None	None	None	None	None
Operative mortality	No	No	No	No	No	No	No	No	No	No	No	No
Histology	BE	Report lost	Follicular BE	CLD with extensive fibrosis	Reactive lymphoid hyperplasia	Follicular BE	BE of LLL and lingula	BE	BE	BE	BE and aspergilloma	BE
Follow-up symptoms	Improved symptoms	No symptoms	No change in symptoms	Improved symptoms	No symptoms	Lost to follow-up	Improved symptoms	Improved symptoms	No symptoms	No symptoms	No symptoms	No symptoms

RLL = right lower lobe; LLL = left lower lobe; RUL = right upper lobe; RML = right middle lobe; FTT = failure to thrive; L = left; ICU = intensive care unit; ICD = intercostal drain; BE = bronchiectasis; CLD = chronic lung disease.

Discussion

The incidence of acute pulmonary infections in patients with HIV has been declining because of the use of co-trimoxazole prophylaxis and ART, but CLD remains an important complication among older CLWH and ALWH.[11] Adolescents with delayed diagnosis of perinatally acquired HIV have a particularly high burden of chronic respiratory disease.[11-13,22]

All of the CLWH in the present study were not diagnosed at birth, emphasising the significance of early ART in preventing permanent lung damage.

The lungs are particularly susceptible to infection in individuals living with HIV, leading to recurring and severe LRTIs, an elevated risk of TB, susceptibility to opportunistic organisms, and immune dysregulation by HIV, resulting in inflammation and a modified lung microbiome.[23] All of the patients in this cohort had a history of recurrent infections for which ART only started later in life, which would have increased their risk of developing BE. These factors serve as potential precursors to BE.[6,24-27] Among older children and adolescents in Zimbabwe with perinatally acquired HIV, CLD was prevalent (86%), and high-resolution CT scans confirmed bronchiectasis in 33% (n=28/84) to 43% (n=24/56) of cases.[28] Additionally, a history of severe LRTIs and PTB was linked to a 4 - 5-fold increased risk of bronchiectasis in this well-controlled group receiving ART.[29]

The results of the present study confirm that surgical removal of bronchiectatic lobes and lungs in CLWH established on ART can be performed safely without short- or long-term morbidity or mortality, provided the children are carefully evaluated preoperatively. The surgery resulted in an improvement in the chronic symptoms associated with BE in 83% of these CLWH, with only 2 of the 12 children (17%) unable to report an improvement of symptoms.

In our series, 7 of the children (58%) had an undetectable viral load with immune reconstitution preoperatively. This is likely to be why the findings of this study differ from

Table 3. Summary of patient data

Age (years), mean (SD)	**7.488 (3.340)**
CD4 count (cells/μL), mean (SD)	970 (646)
CD4%, mean (SD)	17 (5.72)
Duration of ARVs (months), median (IQR)	31 (12.3 - 47.8) AUTHOR: check cf. Table 1
ICU stay (days), mean (SD)	2.3 (0.87)
Hospital stay (days), mean (SD)	12.6 (5.23)
Discharge after surgery (days), mean (SD)	5.7 (1.92)

SD = standard deviation; ARVs = antiretrovirals.

other studies that reported higher morbidity and mortality rates in CLWH requiring general surgery when compared with HIV-uninfected children.[30] Karpelowsky *et al.*[30] reported on 84 CLWH, among whom postoperative complications occurred in 38% and were associated with young age (odds ratio (OR) 4.3; 95% confidence interval (CI) 1.6 - 11.9) and a major surgical procedure (OR 6.8; 95% CI 1.6 - 31.4), but not with malnutrition or degree of immunosuppression. The same group reported that children who were born to HIV-infected mothers but were not themselves infected (HIV-exposed children) also had an increased risk of developing postoperative complications.[31] The risk of complications was, however, lower than the complication rate in CLWH. In our study, the children had all received ART, allowing for reconstitution of their immune systems, which was probably the reason why few had infection-related complications. There are no known case series of CLWH who were established on ART and required thoracic surgery for comparison.

CLWH with CLD are at high risk for MTB infection, especially in TB-endemic countries. Eleven of the children in our study received TB treatment prior to referral to the paediatric pulmonology unit, despite the fact that only 2 children had confirmation of TB with culture.

Empirical TB treatment remains common practice in low- and middle-income settings where there is a high incidence of PTB. Clinical and radiological signs, together with a high index of suspicion, often result in initiation of empirical anti-TB treatment in CLWH. There is considerable overlap in the symptoms caused by PTB and those caused by HIV-related lung disease, especially BE,[7] resulting in overdiagnosis of PTB, as can be seen in this case series, where 92% of the children were treated for TB while the diagnosis was only proven in 16%. Ascribing a cause to the BE can therefore be complicated. In a study reporting on pneumonectomy in children, TB was present in 13%.[32] In our study, we cultured MTB in 16%. It is for this reason that all children received 3 months' standard anti-TB treatment postoperatively to prevent activation of latent TB.

Postoperative anti-TB treatment depends on the bacillus status of the patient at the time of surgery. Previously susceptible bacteria need 3 - 4 months, and drug-resistant bacteria require 6 - 8 months. An 18-month window seems to be needed following the conversion. Double-blind randomised multicentre trials are not the exclusive sources of reasonable knowledge in the vast field of TB, especially as the outcomes are also deeply influenced by non-medical factors.[33,34]

The use of anti-TB treatment after BE in CLWH needs to be studied, as routine anti-TB treatment in children with normal immunity is not advocated. Our cohort was a select cohort, but none of the patients had histological evidence of current or previous TB.

Although surgical resection of diseased lung has been done in children of all ages without an increased risk of morbidity and mortality, an increased risk of complications has been reported in children undergoing pneumonectomy.[32] These authors recommend careful assessment of these patients prior to surgery. In the present study we followed this recommendation, but in addition ensured that ART had been established, to reduce postoperative complications and to reduce the risk of accidental transmission of HIV to the surgeon.

The main limitation of this retrospective study is the small number of children included, although the study was conducted in an area with a high HIV prevalence. As HIV care for mothers and their infants improves, fewer children are becoming HIV infected, making it less likely to find children with HIV-related lung disease. Objective evidence of the degree of improvement, especially in the absence of lung function testing during follow-up, further limits the study.

Conclusion

This study showed that the ultimate goal of a symptom-free child with a decreased risk of LRTI can be achieved with very low morbidity and mortality in symptomatic CLWH by selective resection of bronchiectatic lung. Surgical management requires special preoperative care, with treatment of immunosuppression, including ART, diagnosis and management of associated infections, and meticulous perioperative care.

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Author contributions. This was a joint work by all the listed authors.

Data availability. The data that support the findings of this study are available on request from the corresponding author (PG). The data are not publicly available owing to privacy or ethical restrictions.

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Conflicts of interest. None.

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