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The clinical presentation, etiology, and disease progression of children with post-infectious bronchiolitis obliterans in Cape Town, South Africa

Aamir Yassin[1], Diane M Gray[1], Leah Githinji[1], Marco Zampoli[1], Aneesa Vanker[1]

[1]Department of Paediatrics and Child Health and South African Medical Research Council (SAMRC) Unit on a child and Adolescent Health, University of Cape Town, South Africa.

***Corresponding author:**
Aneesa Vanker
Department of Paediatrics and Child Health and South African Medical Research Council (SAMRC) Unit on a child and Adolescent Health, University of Cape Town, South Africa.

Aneesa.vanker@uct.ac.za

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ABSTRACT

Objectives: We describe the clinical spectrum, etiology, and progression of children with post-infectious bronchiolitis obliterans (PIBO) from a low- and middle-income setting for which there is limited literature.

Materials and Methods: A cross-sectional, retrospective, and descriptive study between November 2019 and October 2020 of all PIBO patients aged 6 months to 15 years managed at pediatric pulmonology service in Cape Town, South Africa.

Results: Fifty-one patients with PIBO were enrolled; 78% were males, median age of 60 months (IQR 33–107). Median age at disease presentation was 6 months (IQR 3–12), 80% presented with cough; 94% required hospital admission, 92% needed supplemental oxygen therapy and 75% needed ventilatory support. Reported cigarette smoke exposure was high (47%). Adenovirus infection was the most common etiology (64%). Chest radiographic findings included lung hyperinflation (43 [84.3%]) and bronchiectasis (23 [45%]). Twenty-seven patients had spirometry and showed mixed (41% [n = 8]) or obstructive (27% [n = 12]) pattern with mean (standard deviation) forced expiratory volume in 1s (FEV_1) z-score −3.3 (± 1.4), forced vital capacity (FVC) z-scores −2.4 (± 1.6), and FEV_1/FVC z-score −3.1 (± 2.4). Systemic corticosteroids were used during initial presentation in 47 patients (92%). Forty-four patients (86%) required two or more subsequent hospital admissions. Improvement of symptoms was reported in 82% of patients with a mean follow-up period of 5 years. Cough (43% [n = 22]) and wheeze (39% [n = 20)]) were the most common reported current symptoms.

Conclusion: PIBO is a recognized cause of pediatric obstructive lung disease in South African settings, with adenovirus pneumonia being the most common preceding illness. Symptoms of airway obstruction persist over time, but improvement was observed with treatment including corticosteroids.

Keywords: Children, Chronic obstructive airways disease, Post-infectious bronchiolitis obliterans, South Africa

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality in adults worldwide[1,2] with increasing evidence of COPD originating in early-life in the form of childhood chronic obstructive airway diseases (COAD).[3] There is limited literature on the etiology, spectrum, and outcome of childhood COAD especially from low- and middle-income countries (LMIC) settings. Causes of COAD in children and adolescents include environmental, genetic, and infectious factors.[4] Bronchiolitis obliterans (BO) is a relatively rare cause of COAD

in children[5,6] and post-infectious BO (PIBO) following respiratory tract infections, commonly adenovirus (Adv), is the most common cause.[5,6] Although the incidence and prevalence of PIBO vary, it has been reported commonly in southern hemisphere countries where the burden of viral infections is high (Chile, Argentina, Brazil, New Zealand and Australia).[6-8] Data from Africa are however lacking.

Fischer *et al*. described clinical and radiological criteria used in conjunction to diagnose PIBO which include: (1) History of an acute and severe bronchiolitis/viral pneumonia in a previously healthy child in the first 3 years of life; (2) evidence of persistent airway obstruction after the acute event, identified by physical examination and/or spirometry (3) chest radiograph findings of obstructive lung disease such as hyperinflation, atelectasis, airway wall thickening and bronchiectasis; (4) mosaic pattern and air trapping on chest computed tomography (CT); and (5) exclusion of other chronic lung diseases that progress with permanent respiratory symptoms, including tuberculosis, cystic fibrosis, bronchopulmonary dysplasia, immunodeficiencies, severe asthma, and alpha-1-antitrypsin deficiency.[6] However, a limitation of this classification is the reliance on CT as a diagnostic aid which is often not easily accessible or available in LMIC. Alternative approaches for recognizing fixed lower airway obstruction using a combination of physical examination, spirometry and chest radiographs must therefore be applied in LMIC settings to diagnose PIBO. PIBO in children runs a chronic course with periods of pulmonary exacerbations and variable degrees of airflow reversibility.[6]

In this study, we aimed to describe the clinical spectrum, etiology, and disease course of children with PIBO at Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary pediatric referral center, in Cape Town, South Africa. This is one of the first studies from a Southern African setting where the burden of lower respiratory tract infections (LRTI) remains high and the sequels of LRTI have not been well-described.

MATERIALS AND METHODS

Study population

This was a cross-sectional, retrospective, and descriptive study that recruited children aged 6 months to 15 years with PIBO seen in the pulmonology service at RCWMCH over a period of 1 year (November 2019 to October 2020). Inclusion criteria were similar to the Fischer criteria[6] except for the requirement of CT evidence of PIBO because CT scan was not routinely done in our setting due to resource constraints and because of technical need for controlled ventilation which can only be achieved under general anesthetic, especially in young children. The inclusion criteria were: (1) Symptoms of wheeze/cough/tachypnea for ≥3 months with onset following early childhood pneumonia, (2) evidence of persistent airway obstruction after the acute event, identified by physical examination and/or spirometry (forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] < lower limit of normal [LLN] [−1.64 z-score] using Global Lung Initiative equation[9] as reference), (3) chest radiograph findings of obstructive lung disease such as hyperinflation, atelectasis, airway wall thickening and bronchiectasis; and/or if available (4) mosaic pattern and air trapping on chest CT. Patients with asthma, cystic fibrosis, large airway obstruction, and uncorrected congenital heart disease were excluded from the study, as well as children with regional lung pathology without clinical or radiological evidence of bilateral lower airway obstruction.

Data collection and analysis

Data were collected using a pre-defined clinical research form which included: (1) Demographic data and description of cohort at the time of recruitment in the study (age, sex, growth parameters, current symptoms and signs, spirometry, and radiological findings); and (2) data that described the initial presentation (initial pneumonia episode, identified etiologies, and treatment course) of the cases and their clinical follow-up which was retrieved from the medical records. The laboratory records for viral antibody rapid tests, viral polymerase chain reaction results, and microbiological culture from nasopharyngeal aspirate, sputum, tracheal aspirate, or bronchoalveolar lavage samples were reviewed to identify the likely etiology. The medical records of two follow-up visits (the first follow-up visit after initial presentation and the last before the time of recruitment) were used to collect data about patients progression which included: the duration of follow up in respiratory unit, growth parameter change, spirometry change, and frequency of respiratory exacerbations after diagnosis (defined as increased shortness of breath, cough, or wheeze requiring clinic/hospital visits and adjustment of treatment or hospitalization).

Data were analyzed using Statistical Package for the Social Science software (IBM®SPSS® Statistics version 26). Categorical variables were summarized and presented as frequencies with proportions whereas continuous variables were summarized as means with standard deviation if normally distributed (partial oxygen saturation, duration of intensive care unit (ICU) stay, and duration of ventilator support), or as medians with interquartile range if not normally distributed (age, growth parameters, duration of hospital stay, and spirometry results).

The Pearson Chi-square test or Fischer exact test, as appropriate, was calculated to compare categorical variables. The independent samples *t*-test was used to compare continuous variables, and the probability value (*P*-value) was set at 0.05 for a 95% confidence interval (CI 95%).

Ethical considerations

Ethical approval was obtained by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 647/2019) and the RCWMCH Research Review Committee. Informed consent was obtained from caregivers and assent from children >8 years before enrolment into the study.

RESULTS

Participants' demographics and assessment at study enrollment

Fifty-one patients were enrolled, which was 16% of all patients seen in the clinic over the study period (*n* = 318); 40 (78.4%) were males [Table 1]. The median age was 60 months (IQR 30–107). Clinical assessment was conducted on all patients at the time of study enrolment. The median height-for-age was −0.22 (IQR −1.16–0.44) z-score, weight-for-age was −0.3 (IQR −0.18–0.64) z-score, and body mass index (BMI) 0.15 (IQR −0.88–1.12). Current symptoms were cough among 43.1% (*n* = 22) of patients and shortness of breath among 35.3% (*n* = 18) of patients. Signs of chronic respiratory disease, namely, digital clubbing and chest wall deformity were present in seven (13.7%) and 17 (33.3%) patients, respectively. Chest hyperinflation was common (*n* = 28 [54.9%]) and six (11%) children were tachypnoeic at rest. The mean oxygen saturation in room air was 97.6% (standard deviation [SD] ± 2.8). A third of children had wheeze (16 [31.4%]) and/or crackles (17 [33%]) on auscultation. Three patients (5.9%) had pulmonary hypertension confirmed by echocardiography; however, there were no features of cor pulmonale among them.

Table 1: Patients demographic, anthropometric, clinical, and lung function data at time of recruitment (*n*=51).

Male, *n* (%)	40 (78.4%)
Female, *n* (%)	11 (21.6)
Age (months), median (IQR)	60 (33.107)
Weight-for-age (z-score)	−0.03 (−0.18.0.64)
Height-for-age (z-score)	−0.22 (−1.16.0.44)
Body mass index (z-score)	0.15 (−0.88.1.12)
Household exposure to smoke, *n* (%)	24 (47)
Cough, *n* (%)	22 (43.1)
Short of breath	18 (35.3)
Finger clubbing	7 (13.7)
Chest deformity	17 (33.3)
Chest recessions	13 (25.5)
Tachypnea	6 (11.8)
Chest hyperinflation	28 (54.9)
Decreased air entry	30 (58.8)
Wheeze	16 (31.4)
Crackles	17 (33)
Spirometry, *n* (%)	29 (57)
FEV_1* z-score, mean (SD)	−3.3 (±1.4)
$FVC_†$ z-score	−2.4 (±1.6)
FEV_1/FVC ratio z-score	−3.1 (±2.4)

n: Number of patients, SD: Standard deviation, IQR: Interquartile range, *Forced expiratory volume in 1 s, †Forced vital capacity, FVC: Forced vital capacity

Table 2: Radiological findings among patients in the study.

Imaging modality	Proportion *n* (%)
Chest X-ray	51 (100)
Abnormal chest X-ray finding	47 (92.2)
Lung hyperinflation	43 (84.3)
Bronchial wall thickening	37 (72.5)
Atelectasis	7 (13.7)
Bronchiectasis	23 (45.1)
Chest CT* scan	14 (27.5)
Abnormal CT scan finding	14 (100)
Mosaic perfusion pattern	9 (64.3)
Vascular attenuation	10 (71.4)
Air trapping	11 (78.6)
Bronchial wall thickening	9 (64.3)
Bronchiectasis	7 (50)
Mucus plugging	6 (42.9)

*Computerized topography; *n*: Number of patients.

Spirometry results were available for 29 patients, of them 27 (93%) had decreased lung function when compared to age-appropriate norms. Obstructed pattern (FEV_1/FVC < LLN) was reported in 8 (27%) patients, mixed pattern (FEV_1/FVC < LLN; FVC < LLN) in 12 (41%), restricted pattern (FVC < LLN) in 7 (24%), and normal spirometry in 2 (7%) patients. Bronchodilator responsiveness could be elicited in 5 (17%) patients. Fourteen (28%) patients were <3 years of age and unable to perform spirometry; and data were missing in 8 (16%) patients.

Forty-seven (92%) chest radiographs at the time of recruitment were abnormal [Table 2]. Lung hyperinflation was the most common abnormal chest radiographic finding (43 [84.3%]) and chronic changes suggestive of bronchiectasis (persistent increased bronchovascular markings, tram track opacities, ring shadow at terminal bronchi, and/or air fluid level) was found in 23 (45.1%). Chest CT scan was performed in 14 (27.5%). Abnormal findings were air trapping (11/14 [78.6%]), mosaic perfusion (9/14 [64.3%]), bronchiectasis (7/14 [50.0%]), and mucus plugging (6/14 [42.9%]) [Figure 1].

Retrospective data and patients progression

Initial pneumonia episode

All participants had a history of LRTI at the onset of symptoms. The median patient's age at the time of precipitating respiratory infection was 6 months (IQR 3–12, range 1–120 months). Most patients (*n* = 48 [94%]) required hospital admission with median duration of hospital stay of 13 days (IQR 5–27).

All of the admitted patients had radiographic evidence of pneumonia. Thirty-nine patients (76.5%) were admitted to ICU with mean duration of ICU admission of 4.6 (SD ± 7.6) days. Ventilatory support was required in 38 (74.5%) patients. Continuous positive airway pressure was the most common form that was used, either alone (in 15 [29.4%] patients) or in combination with other forms of ventilatory support (21 [41.1%] patients). The mean duration of ventilatory support was 6.1 (SD ± 6.6) days, [Table 3]. Eight patients (15.7%) required prolonged oxygen therapy and were discharged home on domiciliary oxygen therapy.

Identified etiologies

Viral etiologies were detected among 40 (78.4%) patients. The most common isolated viruses were Adv (in 33 [64.7%] patients), rhinovirus (13 [25.5%]), and respiratory syncytial virus (7 [13.7%]), [Table 3]. More than one virus was isolated in 17/40 (42.5%) patients. The most common combination of viruses found was Adv and rhinovirus, which were isolated alone (2/17 [11.8%]) or in combination with other viruses (9/17 [52.9%]).

Table 3: Characteristics of initial pneumonia episode, hospital course, and viral etiology among patients with PIBO (*n*=51).

Median age at initial pneumonia episode, median months (min, max)	6 (1.120)
Duration of index admission (days), median (Min, Max)	13 (0.98)
Duration of ICU* admissions (days), median (Min, Max)	2 (0.41)
Duration on ventilatory support (days), median (IQR)	5 (0–8)
Highest ventilatory support required, *n* (%)	
HFNO†	1 (2.0)
CPAP††	25 (49)
CV§	8 (15.7)
HFOV§§	4 (7.8)
Virus results	
Viruses detected via different sampling techniques	40 (76.9)
Adenovirus	33 (64.7)
Rhinovirus	13 (25.5)
Respiratory syncytial virus	7 (13.7)
Parainfluenza virus	4 (7.8)
Influenza virus	2 (3.9)
Bocavirus	4 (7.8)
Enterovirus	4 (7.8)
Metapneumovirus	1 (2)
More than one virus detected	17 (32.7)
Average period of follow-up (months), median (min, max)	60 (2,161)
Change in height over period of follow up (z-score), mean (SD)	0.22(±1.05)
Change in BMI over period of follow up (z-score), mean (SD)	−0.11 (±1.0)

Data presented as number (percentage) unless otherwise stated.
*ICU: Intensive care unit, †HFNO: High flow nasal oxygen, ††CPAP: Continuous positive airway pressure, §CV: Conventional ventilation, §§HFOV: High frequency oscillation ventilation.
IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, PIBO: Post-infectious bronchiolitis obliterans

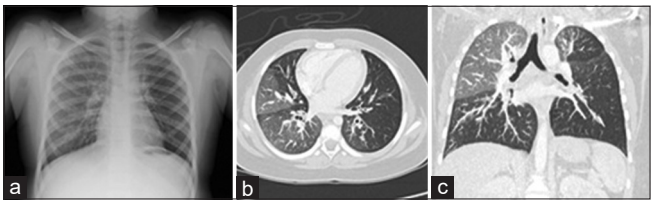

Figure 1: Radiological findings in patient with post-infectious bronchiolitis obliterans. (a) Plain chest X-ray showing lung hyperinflation, bronchial wall thickening, relative hyper lucency of left lung; (b) and (c): Chest computerized topography scan showing mosaic perfusion pattern, vascular attenuation, and air trapping.

Human immunodeficiency virus (HIV) antibodies rapid test results were available for 46 (90.2%) patients of which one was HIV-infected.

Management course

During the initial pneumonia, 50 (98%) patients were treated with antibiotics and bronchodilators, 47 (92.2%) patients received corticosteroids as an anti-inflammatory agent, and 43 (84.3%) patients received azithromycin as immune modulator. Methylprednisolone pulse doses were used early during the course of the disease in 34 (82.9%) patients.

Patients progression

The median duration of follow-up in the pulmonology service was 53 months (range 2–161). The median number of annual respiratory exacerbations was one (range 0–5) with 44 (86%) requiring at least one hospital admission during follow-up and 29 (56.9%) with more than 3 admissions.

Height-for-age z-score was stable during follow-up, median z-score of 0.25 (IQR −0.2–0.71), with no significant difference between patients who did not receive corticosteroids and those who did ($P = 0.6$). BMI was also stable over the period of follow-up, median z-score of 0.00 (IQR −0.64–0.34), with no significant difference between those who did not receive corticosteroid treatment and those who did ($P = 0.39$).

The median change in FEV_1 z-score over the period of follow-up for 23 patients who had spirometry was −0.07 z-score (IQR −0.96–0.05) with improvement of spirometry z-scores in 7 (30.4%) patients and decline in 12 (52.2%) patients. Children with higher BMI at time of recruitment were associated with better FEV_1/FVC z-score (95% confidence

interval (CI) [0.20–1.73]); lower FEV_1/FVC z-scores were significantly associated with younger age at precipitating pneumonia (95% CI [−0.09−−0.01]) and recurrent hospital admissions (95% CI [−1.21−−0.10]). Patient sex, type of virus isolated, duration of ICU admission, number of injectable steroid cycles, and number of respiratory exacerbations were not significantly associated with change in FEV_1/FVC z-score.

Improvement of symptoms over time of follow-up was reported among majority of patients, cough 42 (82%), short of breath 43 (84%), and wheez (86%) patients.

DISCUSSION

In this study, the majority of patients with PIBO presented in infancy with pneumonia that caused the PIBO. The initial pneumonia was frequently severe requiring ICU admission; however a quarter of patients had a mild illness. Immune modulators (corticosteroids and azithromycin) were the mainstay of management. Recurrent wheeze, cough, low lung function, and evidence of air trapping on radiological investigations were present in most children on follow-up. Symptoms improved but persisted over time. Lung function impairment was associated with younger age at first presentation and recurrent hospital admissions. Children with higher BMI at initial presentation had higher FEV_1/FVC z-score in later life.

The median age of first presentation in our cohort was 6 months, with 75% <1 year age. This is younger compared to previous reports which describe the mean age to be 12 months (SD ± 10) for disease onset,[10] and another study with median age of 15 months (IQR 6–23.5).[11] The incidence of pneumonia in early life is very high in this population, LRTI incidence of 0.49 episodes per child year in the 1st year of life reported in recent local epidemiological data.[12] This may partially explain the younger age of presentation in our cohort.

Cough and wheeze were the most common presenting symptoms at the initial pneumonia among our patients, which is consistent with other reports[10,11,13,14] and other causes of cough and wheeze like bronchial asthma were excluded at the time of presentation. Interestingly in our study, median duration of hospitalization was shorter when compared to previous reports,[14] and in some cases, children did not require hospital admission.

Adenovirus is recognized as a key risk factor for PIBO.[10,15] Adenovirus, without identification of serotypes, was the most commonly identified etiology in our study and the commonest virus detected in patients who required ventilatory support, as found in other studies.[8,13,16] Identifying adenovirus serotypes may be useful for prognosis of lung injury. The common adenovirus (Adv) serotypes reported with PIBO are AV3, AV11, and AV7 which were associated with severe forms of lung injury.[13] Similar to the study by Castro-Rodriguez *et al*., we found that more than 50% of patients with PIBO following adenovirus-pneumonia required ICU admission during their initial presentation.[10] Studies have shown that the host's immunological responses to the infecting agent direct the progression and the severity of the viral infection, which vary according to the infecting virus.[17]

While histopathological diagnosis was previously required to confirm PIBO, this is no longer appropriate or feasible. Clinical symptoms and lung function are suggestive, but not specific for BO. Radiological features are additionally useful in the diagnosis of BO and include mosaic attenuation on CT chest.[6,17] BO is a spectrum of COAD that results from severe peripheral airway injury[18] and is characterized by partial or complete obstruction of the respiratory bronchiole by inflammatory or fibrous tissues.[19] Bronchiectasis is an important complication of PIBO[20] and we found it a common comorbidity, in 45% of the cohort. Given our limited access to chest CT scans, this is likely underreported and should be a consideration in the ongoing management of children with PIBO.

Different therapies have been tried to treat PIBO but no proven effective treatment has been identified.[21] Systemic and inhaled corticosteroids aim to control the inflammatory element of the disease and as rescue treatment during respiratory exacerbations.[6] Clinical improvement has been reported in children with PIBO with high dose pulse corticosteroid therapy[22] which is similar to our study results, while prolonged oral corticosteroid therapy has shown less effective results.[23] Robust randomized control trials are needed to adequately establish the most effective treatments for PIBO.

Despite ongoing lung growth during follow-up, lung function remained reduced as evidenced by low z-scores which may indicate slower rate of lung growth compared to healthy children.[8] Consistent with other reports, we found low rates of bronchodilator response which could be explained by the lower airway obstruction due to peribronchial inflammation and fibrosis.[14] This may have been impacted by current chronic medication such as inhaled corticosteroids as bronchial hyperresponsiveness in children with PIBO has been described.[20] Spirometry is limited in its ability to assess small airway obstruction and more comprehensive lung function like forced oscillation technique may better assess disease and long-term response to treatment.[21,23] However, lung function impairment associated with younger age at first presentation and recurrent hospital admissions highlights the significant impact of these early life insults on lung health.[12] Children with higher BMI early in the course of the disease had higher FEV_1/FVC z-score in late childhood. The role that nutrition may play in longitudinal outcomes for patients with PIBO requires further exploration.

This study's strength is that it addresses an important respiratory health issue, in a high burden setting, where data are lacking. We reviewed a relatively large number of children with PIBO with mean follow-up of 5 years and had access to microbiological data in most children. The major limitation is the retrospective part of clinical data which relies on clinical note taking for exposure and outcome assessment and temporal nature of events is difficult to assess, and the relatively small number of CT scans done among our cohort. Although CT scan is the gold standard for diagnosis of PIBO, we propose that this should not be the case in settings where access high quality CT scans in young children are not available. Alternative clinical, radiographic, and spirometry findings demonstrating persistent small airway disease in the correct context should be sufficient to diagnose PIBO and initiate appropriate treatment without delay.

CONCLUSION

We report a group of children with PIBO, and the first in a Southern African setting. Our findings were similar to reports from areas with high prevalence of PIBO, though our cohort was younger at initial presentation. Adenovirus is most common cause of PIBO in our setting. Early recognition, monitoring, and intervention following acute adenovirus infection in at risk patients are important.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

Dr. Marco Zampoli is on the editorial board of the Journal.

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