The Clinical Spectrum, Aetiology and Disease Progression of Children with Post-infectious Bronchiolitis Obliterans at Tertiary Paediatric Pulmonology Service in Cape Town, South Africa

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Declaration

I, Aamir Yassin, hereby declare that this dissertation/thesis is based on my original work (except where acknowledgement indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Acknowledgment

Aamir Yassin conceived and designed the study; and substantially contributed to data acquisition, analysis and interpretation; drafting the dissertation and final approval of the version submitted. Aneesa Vanker substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Diane Gray substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Leah Githinji substantially contributed to study design and interpretation of data, revising the dissertation critically for intellectual content and final approval of the version to be submitted. Marco Zampoli substantially contributed to study design and interpretation of data.

Abstract

Introduction: There is limited literature on chronic obstructive airway disease in the paediatric age group. Post-infectious bronchiolitis obliterans (PIBO) is a cause of obstructive airway disease children, with limited data in African children.

Aim: To describe the clinical spectrum, aetiology, and disease progression of children with post-infectious bronchiolitis obliterans.

Methodology: This is a cross sectional descriptive study included all patients aged 6 months to 15 years with PIBO attending a tertiary paediatric pulmonology service in Cape Town, South Africa over period of one year (November 2019 to October 2020).

Results: Fifty-one patients with PIBO were enrolled, 78% were males, median age 60 months (IQR 33-107). The median age at disease presentation was 6 months (IQR 3-12), 80% initially presented with cough. Ninety-four percent of patients required hospital admission, 76% were admitted to ICU, 92% required supplemental oxygen therapy and 75% required ventilatory support. Reported cigarette smoke exposure was high (47%). Adenovirus was the most common cause of initial infection 59%. Lung hyperinflation (84%) and air trapping (78%) were the most common current chest radiographic findings; bronchiectasis in 45% of patients. Spirometry showed mixed (41.4%) or obstructive (27%) patterns, mean (SD) FEV_1 z-score -3.3(±1.4), FVC z-scores -2.4(±1.6) and FEV_1/FVC z-score -3.1(±2.4). Corticosteroids were used during initial presentation in 92% of patients. Seventy six percent of patients required two or more hospital admissions. Cough (43%) and wheeze (39%) were the commonest reported current symptoms. Lung function impairment was associated with younger age at first presentation and recurrent hospital admissions. Children with higher BMI at presentation had higher FEV_1/FVC z-score in later life. Improvement of symptoms over time was reported among 82% of patients.

Conclusion: PIBO is a relatively common cause of chronic lung disease in South African children, with adenovirus being the commonest preceding illness. Symptoms of airway obstruction persist over time, but showed improvement with treatment, which included corticosteroids.

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Adv	Adenovirus
ATS	American Thoracic Society
BO	Bronchiolitis Obliterans
BOOP	Bronchiolitis Obliterans Organising Pneumonia
COAD	Chronic Obstructive Airway Disease
COP	Cryptogenic Organizing Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CXR	Chest Radiograph
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume In The First Second
FVC	Forced Vital Capacity
HRCT	High Resolution Computerized Topography
PCD	Primary Ciliary Dyskinesia
PIBO	Post-Infectious Bronchiolitis Obliterans
RCWMCH	Red Cross War Memorial Children's Hospital
RSV	Respiratory Syncytial Virus
RV	Residual Volume
6 MWT	6 Minutes Walk Test

Chapter 1 Introduction and literature review

1.1 Background

Chronic obstructive pulmonary disease is one of the five leading causes of mortality in adult worldwide.(1, 2) Childhood chronic obstructive airway disease (COAD) can be a cause of chronic obstructive pulmonary disease in adult. There is limited literature on the aetiology, spectrum and outcome of childhood COAD especially from high burden settings. Causes of COAD in children and adolescents include environmental, genetic and infective factors.(3) Bronchiolitis obliterans (BO) is considered a relatively rare cause of COAD in children. Viral lower respiratory tract infection is the most common cause of Post infectious BO (PIBO).(4, 5) Although the prevalence of PIBO is not known, it has been reported mostly from the southern hemisphere where the burden of viral infections is high (Chile, Argentina, Brazil, New Zealand and Australia).(5-7) The data form South Africa is lacking.

Pathophysiology and clinical features:

The pathological features of BO are characterized by neutrophilic inflammation, bronchial remodelling and small airway fibrosis.(3) The clinical and pathological description of BO was first reported by Lange 1901 who described chronic inflammation caused by injury of small airway that lead to air flow limitation. BO is characterized by partial or complete airway obstruction of the respiratory bronchiole by inflammatory or fibrous tissues.(8) Kurland and Michelson have related these changes to epithelial cell injury that lead to functional or structural disturbances followed by accumulation of inflammatory exudate, cellular and vascular proliferation that lead to the development of intraluminal polyps (Masson body). The progression of circumferential scarring of the affected airways leads to the narrowing and eventually occlusion of the airways.(9)

According to the histopathological characteristics, two main types of BO have been described: 1) proliferative BO: characterized by airway obstruction by polyp and/or granulation tissue in the lumen of bronchiole; 2) constrictive BO: characterized by peribronchial inflammation and fibrosis without involvement of distal lung parenchyma.(3,10,11) The term BO organising pneumonia (BOOP) is used to describe the form of proliferative BO in which intraluminal polyps involve the respiratory bronchiole, alveolar duct and alveolar space as well as involvement of distal lung parenchyma.(10) The term cryptogenic organizing pneumonia (COP) is preferred to BOOP according to the American Thoracic Society/European Respiratory Society (ATS/ ERS) consensus as it avoids the confusion with other form of BO.

Post-infectious BO (PIBO) is the second histological type which is reported following viral infections such as influenza, parainfluenza, measles, respiratory syncytial virus (RSV), varicella, and more commonly adenovirus (Adv) which is associated with severe lung injury. Although the prevalence of PIBO is not known, it has been reported mostly from southern hemisphere where the burden of these viral infections are high (Chile, Argentina, Brazil, New Zealand and Australia).(5-7) A study from Argentina by Colom et al. described adenovirus infection as significant risk factor for development of PIBO (OR = 49; 95% CI = 12 – 199).(7) The common adenovirus serotypes reported with PIBO are Ad3, Ad7 and Ad7; and are associated with severe forms of lung injury and PIBO.(5) Similarly, a northern hemisphere case series, from China, also reported adenovirus infection as the most common cause of PIBO.(12) However, data from Africa and South Africa is lacking.

The confirmation of a diagnosis of PIBO requires histopathological testing which is not possible for all patients. Fischer and his group (5) describe criteria to diagnose PIBO which include: 1) history of an acute and severe bronchiolitis/viral pneumonia in previously healthy children during their first three years of life; 2) evidence of persistent airway obstruction after the acute event, identified either by physical examination and/or by lung function tests; 3) chest radiograph findings of obstructive lung disease such as hyperinflation, atelectasis, airway wall thickening and bronchiectasis; 4) mosaic pattern and air trapping in chest computed tomography; 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.

The host's immunological responses to the infecting agent directs the progression and the severity of the viral infection. Diaz and his group demonstrated the difference of immune response to different viruses. They studied the different effect of RSV and Adv on the mononuclear cytokine response and showed that adenovirus induced Th-1 cellular immune responses that persist during the presence of the virus which may explain the severity of the immune response and the outcome of the infection.(13)

Interestingly, genetic factors have also been associated with the hosts response to adenoviral infection. Children who developed PIBO were noted to be deficient in mannose-binding lectin (MBL). This arises from polymorphisms in the coding and non-coding region on the *MBL2* gene and has been associated with more frequent and severe respiratory infections. Children with MBL insufficiency were more prone to develop PIBO than healthy controls, demonstrating the importance of innate immune defence factors in the development of this condition.(14)

Radiological features:

The radiological picture of lower airway obstruction is important to diagnose BO. Chest radiograph (CXR), high resolution computerized topography (HRCT) and lung ventilation/perfusion scan (V/Q scan) are the commonly used techniques. The CXR radiological findings are non-specific of BO and include peri-bronchial thickening; air trapping which manifests as generalized or localized over-inflation of lungs, flattening of diaphragms and increased retrosternal air; bronchiectasis and atelectasis. Chest radiograph is used as the primary imaging modality for BO and for follow up of the clinical course of the disease.(5,15) Unilateral hyperlucent lung following Adv infection is known as Swyer-James or MacLeod syndrome. The V/Q scan shows lobar or segmental matched ventilation-perfusion defects which can be used as an objective assessment for lung damage and disease severity. This may be more accurate in detecting lung damage than the CXR but less than the CT scan.(16)

HRCT scan is a non-invasive, effective and more sensitive diagnostic tool to detect airway and lung parenchymal abnormalities. The most important radiological finding is well demarcated mosaic hypoperfusion which is caused by vascular shunting from malfunctioning hypo-ventilated lung segments to the normal segments due to vasoconstriction secondary to tissue hypoxia; bronchiectasis; air trapping; bronchial wall thickening; atelectasis and mucus plugging.(5,17,18) Imaging during both inspiratory and expiratory phase is important to demonstrate air trapping but doubles the radiation dose. The low dose protocol is developed to reduce the radiation exposure which is an important consideration when using HRCT in children.(5,8) Different techniques have been tried to reduce radiation exposure of CT scans; including using CT densitovolumetry whereby a helical CT performed during single breath holding, measures the emphysematous (non-functional) lung area and correlates this to the lung function (19); Xenon ventilation CT with dual-source dual -energy technique accurately demonstrated impaired regional ventilation in children with BO without additional radiation.(20)

Pulmonary function test (PFT)

Pulmonary function test (PFT) is important for diagnosis and follow up of children with BO. PFT usually shows a fixed obstructive picture with air trapping and minimal degree of reversibility that slowly improves over time.(15, 21) Oscillometry in young children shows increased resistance and decreased compliance with minimal response to bronchodilator and it can change according to the disease course.(21) The reduction of forced expiratory volume in the first second (FEV_1), the ratio between FEV_1 to forced vital capacity (FEV_1/FVC ratio) and forced expiratory flow at 50-75 % of FVC (FEV_{50-75}) indicates the degree of airway obstruction. Air trapping with consequent increased residual volume (RV) can give a mixed or restrictive spirometric picture on PFT with reduction of FVC despite normal lung volumes.(22) Spirometry is not sensitive to small airway disease and tests better able to assess this should be considered in diagnosis and follow-up where possible.(23) Decline in PFT demonstrated by mild reduction of FVC and significant reduction of FEV_1, FEV_1/FVC ratio and FEV50-75 are the common findings that are seen in school children with BO.(15,18) Interestingly, a systematic review has found that early-life viral infections including respiratory syncytial virus, also results in abnormal pulmonary function testing and in particular an obstructive pattern.(24)

Colom et al. followed the PFT of children with BO for 12 years and noticed although an improvement of FVC and FEV_1 values with growth, Z scores were still reduced indicative of slower rate of lung development compared to healthy children.

Improvement in FVC may exceed FEV_1, possibly explained by dysynaptic growth, whereby there is unequal growth of lung parenchyma and airways.(21) Exercise testing including cardiopulmonary exercise test (CPET) and 6 minute walk test (6MWT), are used as prognostic measures and for follow up of patients with BO. Although less sensitive, the 6MWT is easy to perform making it more feasible than CPET which requires specialised equipment.(5,21) In patients with BO, distance walked during a 6MWT and estimated oxygen consumption during CPET is less than that in healthy individuals.(21)

Treatment and prognosis

While different therapies have been tried for the treatment of PIBO, no proven effective treatment has been identified.(25) Inhaled bronchodilators (short and long acting forms) have been used to treat wheeze in bronchodilator responsive patients and during the respiratory exacerbations.(6,16) Inhaled corticosteroids are used for variable durations as anti-inflammatory agents to control the airway inflammation.(25) High dose corticosteroids have been used for severe obstructive events with evidence of efficacy especially in hypoxic patients. Intravenous high-dose pulsed corticosteroids are used as an alternative to prolonged oral high-dose pulse corticosteroid with minimal adverse effects.(26) Hydroxychloroquine has been used for its anti-inflammatory effect alternatively or in combination with systemic or inhaled corticosteroid.(5) The use of intravenous immunoglobulins in the management of PIBO has also been reported.(25) Antibiotic therapy has been used both for acute respiratory exacerbations and in some cases for prophylactic therapy. Azithromycin, an aminoglycoside, has been used for its anti-inflammatory effects and as an immune modulator.(5) Oxygen is an important supplementary treatment especially in hypoxic patients. After the initial insult some patients my require prolonged oxygen therapy but most are able to be weaned off with time and clinical improvement.(15) Lung rehabilitation and respiratory muscle exercise together with good nutritional support has been shown to have a positive impact on respiratory muscle strength.(5, 15) Lung transplantation may be indicated for advanced forms of the disease and respiratory failure.(15)

The prognosis of PIBO in paediatric populations is variable, dependent on aetiology, age of onset and severity.(5, 9) Studies from South America have described high mortality in young children during the acute Adv infection and lower mortality but high morbidity with established PIBO.(5) This variabilty was also reported in children with severe disease during the first year of life who developed respiratory failure requiring prolonged oxygen therapy (upto 6 months) but subsequently improved clinically and were weaned from oxygen.(27) Understanding the clinical spectrum and disease progression of PIBO in South African children will help improve the standard management of this disease in children and in turn hopefully lead to better respiratory health in later childhood and adulthood.

Motivation/purpose of the study

This research aimed to describe the clinical spectrum, aetiology and disease progression of children with post-infectious bronchiolitis obliterans (PIBO) in a tertiary paediatric pulmonology service in Cape Town.

This study addresses an important area in respiratory health where the data is lacking and motivates further studies in this area.

1.2 Ethical considerations

Ethical approval was obtained by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC REF:647/2019) and the Red Cross War Memorial Children's Hospital (RCWMCH) Research Review Committee (RXH:RCC 212:WC_201910_027). Informed consent was obtained from caregivers and assent from children >8years before enrolment of patients into the study.

1.3 Author guidelines of the Journal for which the paper has been formatted

Paediatric pulmonology journal has been chosen for publication of this study. It is a monthly peer-reviewed medical journal covering paediatric pulmonology and listed in the citation index of the Institute for Scientific Information (ISI) (ISSN: 8755-6863 (print), 1099-0496 (web)).

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Original Research Articles should follow the standard structure of abstract, introduction, methods, results, discussion, and references, and may include up to six tables and/or images when appropriate. Original Research Articles should be limited to 3,500 words (not including the abstract or references). The abstract should not exceed 250 words, and references should be limited to 40. There should be no more than 6 figures/tables in any combination. The Methods section must state that the paper has IRB approval or explain why the study is exempt.

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All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

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Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.

Book with authors

Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.

Book with editors

Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.

Chapter from a book

Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.

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Chapter 2 Publication ready report

Original research article

The Clinical Spectrum, Aetiology and Disease Progression of Children with Post-infectious Bronchiolitis obliterans at Tertiary Paediatric Pulmonology Service in Cape Town, South Africa

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Abbreviated title: Post-infective Bronchiolitis Obliterans in Children.

ABSTRACT

Introduction: There is limited literature on chronic obstructive airway disease in the paediatric age group. Post-infectious bronchiolitis obliterans (PIBO) is a cause of obstructive airway disease children, with limited data in African children.

Aim: To describe the clinical spectrum, aetiology, and disease progression of children with post-infectious bronchiolitis obliterans.

Methodology: This is a cross sectional descriptive study included all patients aged 6 months to 15 years with PIBO attending a tertiary paediatric pulmonology service in Cape Town, South Africa over period of one year (November 2019 to October 2020).

Results: Fifty-one patients with PIBO were enrolled, 78% were males, median age 60 months (IQR 33-107). The median age at disease presentation was 6 months (IQR 3-12), 80% initially presented with cough. Ninety-four percent of patients required hospital admission, 76% were admitted to ICU, 92% required supplemental oxygen therapy and 75% required ventilatory support. Reported cigarette smoke exposure was high (47%). Adenovirus was the most common cause of initial infection 59%. Lung hyperinflation (84%) and air trapping (78%) were the most common current chest radiographic findings; bronchiectasis in 45% of patients. Spirometry showed mixed (41.4%) or obstructive (27%) patterns, mean (SD) FEV_1 z-score -3.3(±1.4), FVC z-scores -2.4(±1.6) and FEV_1/FVC z-score -3.1(±2.4). Corticosteroids were used during initial presentation in 92% of patients. Seventy six percent of patients required two or more hospital admissions. Cough (43%) and wheeze (39%) were the commonest reported current symptoms. Lung function impairment was associated with younger age at first presentation and recurrent hospital admissions. Children with higher BMI at presentation had

higher FEV_1/FVC z-score in later life. Improvement of symptoms over time was reported among 82% of patients.

Conclusion: PIBO is a relatively common cause of chronic lung disease in South African children, with adenovirus being the commonest preceding illness. Symptoms of airway obstruction persist over time, but showed improvement with treatment, which included corticosteroids.

INTRODUCTION:

Chronic obstructive pulmonary disease is one of the five leading causes of mortality in adult worldwide[1,2], with a substantial portion of disease arising from early life.[3] Childhood chronic obstructive airway disease (COAD) can be a cause of chronic obstructive pulmonary disease in adult. There is limited literature on the aetiology, spectrum and outcome of childhood COAD especially from high burden settings. Causes of COAD in children and adolescents include environmental, genetic and infective factors.[4] Bronchiolitis obliterans (BO) is considered a relatively rare cause of COAD in children. Viral lower respiratory tract infection is the most common cause of Post infectious BO (PIBO).[5,6] Although the prevalence of post-infectious BO (PIBO) is not known, it has been reported mostly from the southern hemisphere where the burden of viral infections is high (Chile, Argentina, Brazil, New Zealand and Australia).[6-8] The data form South Africa are lacking.

PIBO in children runs a chronic course with periods of pulmonary exacerbations and variable degree of airflow reversibility.[6] The gold-standard of PIBO diagnosis is histopathological testing which is not possible for most patients. Fischer et al. described criteria to diagnose PIBO which include: 1) history of an acute and severe bronchiolitis/viral pneumonia in a previously healthy child in the first three years of life; 2) evidence of persistent airway obstruction after the acute event, identified by physical examination and/or lung function tests; 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; 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]

In this study we aimed to describe the clinical spectrum, aetiology and disease progression of children with chronic airway obstruction due to PIBO at Red Cross War

Memorial Children's Hospital (RCWMCH), a tertiary facility providing paediatric services with a full range of sub-specialties including pulmonology, in Cape Town, South Africa.

METHODOLOGY

This was a cross sectional descriptive study of all children seen between November 2019 to October 2020 in the pulmonology service at RCWMCH with chronic airway obstruction and included all patients aged 6 months to 15 years, who consented to participate. Chronic airway obstruction was defined as persistent symptoms of wheeze/cough/tachypnoea for ≥ 3months, and obstructive pattern of lung function (FEV_1/FVC <LLN (5% or -1.64 z-score) using Global Lung Initiative (GLI) equation as reference) with no significant bronchodilator response (≥12% post-bronchodilator increase in FEV1 or FVC), or chest x-ray signs of bilateral lower airway hyperinflation. Patients with atopic asthma, cystic fibrosis, large airway obstruction and uncorrected congenital heart disease were excluded, as well as children with unilateral or single lobe bronchiectasis without clinical or radiological evidence of lower airway obstruction. Two chest x-rays were included in analysis, one at the time of first diagnosis and another during follow-up.

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

Data collection and analysis: The data was collected using a pre-defined clinical research form (Addendum A, suppl.) which included the patient's current clinical status (symptoms, clinical signs, radiological finding and lung function) and historical data retrieved from the patient's records (presentation history, workup, management, hospital admissions and clinical course). Data was analysed using statistical package for social science software (IBM®SPSS® Statistics version 26). Count (percent), mean (SD) and/or median (IQR 25%-75%) were used to describe: 1) the occurrence of the symptoms, examination finding, radiological examination finding and lung function test, 2) the exposure factors that may have led to the development of

PIBO. 3) the clinical course and outcomes (lung function, respiratory symptoms, respiratory rate, growth parameters, exacerbation frequency and number of clinic/hospital unscheduled visits) of children included in the study.

STUDY RESULTS

Fifty-one patients with study defined chronic airway obstruction were enrolled, 16% of patients seen in the clinic over that period. All had a history of initial lower respiratory tract infections (LRTI). Participant demographics are included in table 1. Of the 51 patients enrolled, 40 (78.4 %) were males. The median age was 60 months (IQR 30-107). The median weight-for-age z score was -0.03 (IQR -0.18-0.64). Household exposure to cigarette smoke was reported in 24 (47%) patients, table 1.

1. *Initial presentation and hospital course*

The age at the precipitating respiratory infection were ranging between 1-120 months, median six months (IQR 3.0-12.0). The most common presenting symptom was cough 41 (80.4%) patients. The majority of patients (n=48 (94%)) required hospital admission for LRTI at initial presentation, with 44 (86%) patients requiring at least one further admission during follow up; 29 (56.9%) patients had more than 3 admissions. The median duration of index admission was 13 days (IQR 5-27). Thirty-nine patients (76.5%) were admitted to ICU, the mean duration of ICU admission was 4.6 (SD±7.6) days. Ventilatory support was required in 38 (74.5%) patients, Continuous Positive Airway Pressure (CPAP) was the commonest form. The mean duration of ventilatory support was 6.1 (SD±6.6) days, table 2. Eight patients (15.7%) required prolonged oxygen therapy after discharge from hospital.

Viral etiologies were detected among 40(78.4%) patients. The common detected viruses were adenovirus (Adv) 33 (64.7%) patients, rhinovirus 13 (25.5%), and respiratory syncytial virus (RSV) 7 (13.7%), table 2. More than one virus was isolated in over 40% of cases [17/40 (42.5%)], the commonest combination of viruses found were Adv and rhinovirus which have been isolated alone [2/17 (11.8)] or in combination with other viruses [9/17(52.9%)]. The samples were collected using nasopharyngeal aspirate (NPA), tracheal aspirates (TA), and bronchoalveolar lavage (BAL). NPA was the most successful sample to detect Adv [n= 30/37 (81%)] followed by BAL [n= 5/7 (71.4%)], and TA [n= 6/9 (66.7%)].

HIV results was available for 46 (90.2%) patients, with only one positive result. Immunoglobulin level assay was done for 23 (45.1%) patients, low level of immunoglobulin IgA and IgG was reported in one (2%) patient.

2. *Assessment at study enrollment*

2.1 Clinical findings

Clinical assessment was conducted on all patients at the time of study enrolment. The median duration of follow-up in pulmonology service was 53 months (min 2, max 161). Current symptoms were cough in 22 (43.1%) patients, shortness of breath 18 (35.3%), and wheezing 20 (39.2%) patients, table 3. Signs of chronic respiratory disease were present: clubbing in seven (13.7%) patients and chest deformities in 17 (33.3%) of patients. 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% (SD±2.8). A third of children had wheeze [16 (31.4%)] and/or crackles [17 (33%)] on auscultation. Pulmonary hypertension was detected in 3 (5.9%) patients without features of right ventricular failure, table 3.

The median number for annual respiratory exacerbations was one exacerbation (min 0, max 5). The assessment of symptoms progression by physicians during the period of follow up were documented on clinical notes and reported improvement of all symptoms among 42 (82%) patients.

Height-for-age z-score (HAZ) was stable during follow-up, median z-score 0.25 (IQR -0.2 to 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

0.00 (IQR -0.64 to 0.34), with no significant difference between those who did not receive corticosteroid treatment and those who did (p=0.39).

2.2 Pharmacological treatment received

During the initial presentation, 50 (98%) patients were treated with antibiotics and bronchodilator, 47 (92.2%) patients received corticosteroids as anti-inflammatory agent.

After the initial presentation and during their course of illness and follow up, 43 patients (84.3%) received Azithromycin as immune modulator, 50 patients (98%) received inhaled short acting inhaled β_2 agonist (SABA), seven patients (13.7%) received long acting β_2 agonist in combination with inhaled steroid, and two patients received oral theophylline as oral bronchodilator therapy. Anti-inflammatory agents (corticosteroids and/or chloroquine) were used by 50 (98%) patients, table 3. Chloroquine was used with corticosteroids by two (3.9%) patients, and as a single anti-inflammatory agent by one patient (2%). At least 1 cycle of intravenous corticosteroid (methylprednisolone) was used in 20 (39%) patients, median 2 cycles (IQR 1-3). Subsequent courses of oral or inhaled corticosteroid were used as detailed in table 3. Inhaled corticosteroid was used by 43(84.3%) patients with 38(74.5%) patients required treatment for more than 1 years.

2.3 Radiological findings

At follow-up 47 (92%) chest radiographs were abnormal as assessed by a paediatric radiologist. Lung hyperinflation was the most common abnormal chest radiographic finding [43 (84.3%)] and chronic changes suggestive of bronchiectasis was found in 23(45.1%). Chest CT scan was performed in 14 (27.5%) patients. 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%)]. Mostly the current chest radiograph findings were consistent with the previous radiological findings apart from new features consistent with bronchiectasis which were more apparent in the current radiological examination. Radiological study for gastro-esophageal reflux done for 26 (51%) patients, of them 14 (53.8%) had a positive nuclear isotope study (milk scan) for gastro-esophageal reflux. (Table 4)

2.3 Lung function testing

Spirometry was conducted in 29(57%) patients, of which 27(93%) had decreased lung function when compared to age-appropriate norms. Obstructed pattern was reported in eight (27%) patients, mixed pattern (FEV_1/FVC <LLN; FVC <LLN) in 12 (41.4%), restricted pattern (FVC<LLN) in seven (24.1%), and normal spirometry in two (6.9%) patients. The mean FEV_1 z-score -3.3(±1.4), FVC z-scores -2.4(±1.6) and FEV_1/FVC z-score -3.1(±2.4). Bronchodilator responsiveness could be elicited in five (9.8%) patients. The median change in FEV_1 over the period of follow up was 0.29 z-score (IQR -0.72 to 0.45) with improvement of spirometry z scores in 12(23.5 %) patients. Children with higher BMI were associated with better FEV_1/FVC z-score [95%CI (0.20 to1.73)]; younger children at first presentation and those with recurrent hospital admissions have significantly lower ratios [95% CI (-0.09 to -0.01), (-1.21 to -0.10)]. The statistical correlation between patient sex, type of virus isolated, duration of ICU admission, number of injectable steroid cycles, and number of respiratory exacerbations were not significantly affecting the progression of FEV_1/FVC z-core.

DISCUSSION:

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

The age of first presentation in our cohort was early, the first year of life in the majority of cases. This is earlier 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] A possible explanation maybe the high incidence of LRTI in early-life with recent local epidemiological data showing an LRTI incidence of 0.49 episodes per child year in the first year of life.[12] Further, we speculate that an increased awareness of this condition may have led to earlier recognition.

Cough and wheeze were the commonest presenting symptoms at the initial illness among our cohort, which is consistent with other reports.[9,10,11,13] 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 recognised as a key risk factor for PIBO.[10.15] Adenovirus, without identification of serotypes, was the commonest identified aetiology among our study group and the commonest virus detected in patients who required ventilatory support, as found in other studies.[8,9,16] Although identifying adenovirus serotypes would have been useful, this is a limitation of this study as this was not available in our research setting. Similar to the study by Castro-Rodriguez et al., we found that more than 50% of patients who subsequently developed PIBO following adenoviral pneumonia have required ICU admission during their initial presentation.[10] Adenoviral infection has also been associated with longer hospitalization[15], the same effect is seen in our cohort with mean duration of hospitalization with and without adenovirus infection of 22 day and 11 days respectively (P=0.24). The host immunological responses to infecting agent directs the progression and the severity of the viral infection which vary according to the infecting virus.[17] Studies on the effect of respiratory syncytial virus (RSV) and adenovirus on the mononuclear cytokine response have showed that adenovirus induced Th-1 cellular immune responses persist during the presence of the virus and could in part explain the severity of the immune response and the outcome of the infection.[17]

While histopathological diagnosis confirms PIBO, this is often not appropriate nor 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] Bronchiectasis is an important complication of PIBO[19] and we found it to be common, found in 45% of the cohort. Given we had limited access to chest CT scan, this is likely an under report and should be a consideration in the ongoing management of children with PIBO.

Despite ongoing lung growth during follow-up, lung function remained reduced as evidenced by low z-scores. We report an improvement in spirometry in the majority of participants during follow-up (average increase 0.3 z-score FEV_1), but still low. Consistent with other reports we found low rates of bronchodilator response. This may have been impacted by current chronic medication such as inhaled corticosteroids as bronchial hyperresponsiveness in children with PIBO has been described.[19] Spirometry is limited in its ability to assess small airway obstruction and more comprehensive lung function may better assess disease and long-term response to treatment.[21,22] 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. Children with higher BMI at presentation had higher FEV_1/FVC z-score in later life. The role that nutrition may play in longitudinal outcomes requires further exploration. There are currently no published studies that we are aware of, assessing longitudinal lung function outcomes in children with PIBO.

Different therapies have been tried to treat PIBO but no proven effective treatment has been identified.[22] Systemic and inhaled corticosteroids aim to control the inflammatory element of the disease and as rescue treatment during respiratory exacerbations.[6] In children with BO clinical improvement with high dose pulse corticosteroid therapy has been shown[24] and less effective results with prolonged oral corticosteroid therapy.[21] Hydroxychloroquine is used for its anti-inflammatory effect alternatively or in combination with systemic or inhaled corticosteroid and demonstrated mixed results.[6] In our study although we report an improvement with high-dose pulse corticosteroid therapy, this may not have been the cause of improvement. Robust randomized control trials are needed to adequately establish the most effective treatments for PIBO.

A strength of this study is that it addresses an important area in respiratory health in a high burden setting where data are lacking. We were able to review a relatively large cohort of children with mean follow-up time of 5 years. We had access to microbiological data in the vast majority of children. The major limitation of our study is the retrospective collection of clinical data which relies on clinical note taking for exposure and outcome assessment and temporal nature of events are difficult to assess, and the relatively small number of CT scan done among our cohort. However, we were fortunate to have access to a database of investigations and all patients notes covering follow-up period, as well as current status being assessed by clinical examination and caregiver/patient interview.

We enrolled 51 patients in our study which is one of the largest described cohorts of children with PIBO, and one of the first in a Southern African setting. Our study showed similar results of international literature from area with high prevalence of PIBO. The large number of adenovirus cases in our study flags the importance of virus isolation and early intervention in cases with prolonged symptoms and when PIBO is suspected.

CONCLUSION:

We describe the clinical findings, treatment and outcomes of PIBO in a low-middle income setting from which there is limited data. PIBO is the most common form of BO in LMIC with adenovirus being the commonest aetiology. Increasing awareness of the disease may lead to earlier diagnosis and intervention, potentially contributing to improved outcomes. We report improvement in symptoms over time in a cohort whose majority received corticosteroids and azithromycin. Well-designed studies are needed to assess the true efficacy of these treatments, optimal dosing, and indications for treatment. It is likely that better phenotyping of PIBO, including immunological, clinical, and physiological presentations, will be necessary to better inform management strategies.

ACKNOWLEDGEMENTS:

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TABLES AND FIGURES

Table 1: Demographic data and anthropometry (n=51).

		Male	Female	Total
Sex, n (%)		40 (78.4%)	11 (21.6%)	51 (100%)
Age (months)	Median (IQR)	60 (31,109)	86 (46,100)	60 (33,107)
Weight-for-age (z-score)		-0.15 (-0.9,0.7)	0.00 (-0.76,0.5)	-0.03 (-0.18,0.64)
Height-for-age (z-score)		-0.21 (-0.82,0.37)	-0.33 (-1.23,0.8)	-0.22 (-1.16,0.44)
Body mass index (z-score)		-0.08 (-0.89,1.23)	0.28 (-0.83,0.91)	0.15 (-0.88,1.12)
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)
Household exposure to smoke n (%)		19 (37.3%)	5 (9.8%)	24 (47%)

Table 2: The initial presentation, hospital course and identified organisms among patients in the study (n=51).

Basics	
Age at first respiratory symptom (months), median (min, max)	6 (1,120)
Average time of follow-up (months), median (min, max)	60 (2,161)
Tachypnoea	19 (37.3%)
Cough	41(80.4%)
SOB	27 (52.9%)
Wheezing	27 (52.9%)
Cyanosis	1 (2.0%)
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	
HFNO	1 (2.0%)
CPAP	25 (49%)
CV	8 (15.7%)
HFOV	4 (7.8%)
Viral 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%)

ICU: Intensive Care Unit; CPAP: Continuous Positive Pressure Ventilation; CV: Conventional ventilation; HFNO: High Flow Nasal Oxygen; HFOV: High frequency Oscillation ventilation.

Table 3: The current clinical assessment, exacerbation frequency, and medications received (n=51).

Symptoms, n (%)	
Cough	22 (43.1%)
Short of breath	18 (35.3)
Wheeze	20 (39.2%)
Signs, n (%)	
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%)
Frequency of annual exacerbation, mean (SD)	1.08 (±1.1)
Anti-inflammatory treatment received, n (%)	
Chloroquine	3 (20%)
Corticosteroids†	49 (96%)
Injectable Corticosteroids cycles received, n (%)	
One cycle	6 (11.8%)
Tow cycles	4 (7.8%)
Three cycles	9 (17.6%)
Four cycles	1 (2.0%)

†Oral, injectable, and inhaled forms have been used alone or in combinations.

Tables 4: Radiological findings and lung function.

	Male, n (%)	Female, n (%)	Total ,n (%)
CXR			51 (100%)
Abnormal CXR finding	37 (72.5%)	10 (19.6%)	47 (92.2%)
Lung Hyperinflation	34 (66.7%)	9 (17.6%)	43 (84.3%)
Bronchial wall thickening	30 (58.8%)	7 (13.7%)	37 (72.5%)
Atelectasis	6 (11.8%)	1(2.0%)	7 (13.7%)
Bronchiectasis	17 (33.3%)	6 (11.8%)	23 (45.1%)
Chest CT scan			14 (27.5%)
Abnormal CT scan finding	10 (71.4%)	4 (28.6%)	14 (100%)
Mosaic Perfusion Pattern	6 (42.9%)	3 (21.4%)	9 (64.3%)
Vascular attenuation	7 (50%)	3 (21.4%)	10 (71.4%)
Air Trapping	7 (50%)	4 (28.6%)	11 (78.6%)
Bronchial wall thickening	6 (42.9%)	3 (21.4%)	9 (64.3%)
Bronchiectasis	5 (35.7%)	2 (14.3%)	7 (50%)
Mucus bulging	5 (35.7%)	1 (7.1%)	6 (42.9%)
GORD work-up			26 (51%)
Milk scan	20 (77%)	6 (23%)	26 (100%)
Gastro-oesophageal reflux	11 (42.3%)	3 (11.5%)	14 (53.8%)
Lung function testing (spirometry)			29 (57%)
FEV1 z-score, mean (SD)			-3.3 (±1.4)
FVC z-score			-2.4 (±1.6)
FEV1/FVC ratio z-score			-3.1 (±2.4)

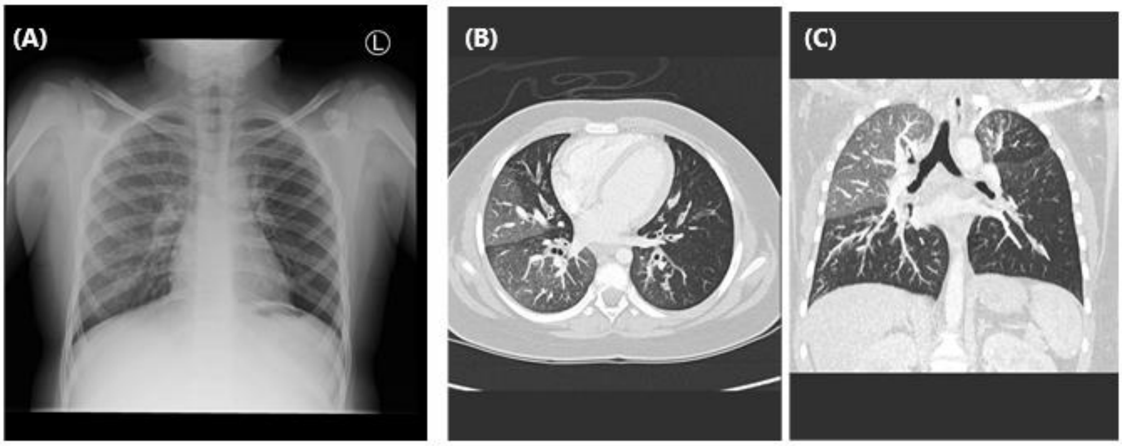

Figure 1: Radiological finding in patient with PIBO.

(A): Plain chest x-ray showing lungs hyperinflation, bronchial wall thickening and bronchiectasis; (B) and (C): Chest CT scan showing mosaic perfusion pattern, vascular attenuation, air trapping and bronchiectasis.

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APPENDICIES

Addendum A : Clinical Research Form

1.0 Patient details:

1.1 Patient number: ____________________

1.2 Name: ___________________________

1.3 Date of birth: ______________________

1.4 Sex: _____________________________

2.0 Symptoms history (from current assessment):

2.1 Cough: Y / N

2.1.1 Frequency: a) daily b) intermittently

2.1.2 Timing : a) morning b) evening c) other________

2.1.3 Character:

a) wet/productive b) dry c) brassy d) other_______

2.2 Short of breath: Y / N

2.2.1 Frequency: a) daily b) weekly c) intermittently

2.2.2 Relation to activity:

a) at rest b) with minimal exercise c) with severe exercise

2.3 Chest tightness: Y / N

2.4 Wheezing: Y / N

2.4.1 Frequency: a) daily b) weekly c) intermittently

2.4.2 Timing: a) morning b) evening c) other_________

2.4.3 Relation to activity:

a) at rest b) with daily activity c) with severe exercise

3.0 Clinical examination:

3.1 General examination:

3.1.1 Pallor: Y / N

3.1.2 Cyanosis: Y / N

3.1.3 Clubbing: Y / N

3.2 Growth parameters:

3.2.1 Weight for age: _______ z-score

3.2.2 Height for age: _______ z-score

3.2.3 Weight for Height: _______ z-score

3.2.4 BMI : _______ z-score

3.3 Respiratory signs:

3.3.1 Chest deformity: Y / N

3.3.1.1 Pectus carinatum Y/ N

3.3.1.2 Pectus excavatum Y / N

3.3.1.3 Harrison's sulcus Y / N

3.3.2 Chest Recessions Y/ N

3.3.3 Respiratory rate ________ CPM

3.3.3.1 Tachypnoeic Y/ N

3.3.4 Oxygen saturations

3.3.4.1 At rest ___________ %

3.3.4.2 6 min walk ________%

3.3.5 Hyperinflated chest Y / N

3.3.6 Chest auscultation

3.3.6.1 Air entry Normal / Diminished Side:_________

3.3.6.2 Wheeze Y/ N

3.3.6.2.1 Zone: Right Upper, Mid, Lower; Left Upper, Mid, Lower

3.3.6.3 Crackles Y / N

3.3.6.3.1 Zone: Right Upper, Mid, Lower; Left Upper, Mid, Lower

3.4 Cardiac signs:

3.4.1 Pulse rate:_______ ppm

3.4.2 Blood pressure _________ mmHg

3.4.3 Abnormal heart examination finding Y / N

3.4.3.1 Pulmonary hypertension Y / N

3.4.3.2 Right sided cardiac failure Y / N

3.4.3.3 Congestive cardiac failure Y / N

3.4.3.4 Murmur Y / N

Description:___________________

3.4.3.5 Rhythm Y / N

4.0 Radiological examination:

4.1 Chest x-ray now or within past 3 months (not associated with lower respiratory tract illness): Y/N

4.1.1 Date: ____________

4.1.2 Abnormal finding Y / N

4.1.2.1 Hyperinflated lungs Y / N

4.1.2.2 Atelectasis Y / N

4.1.2.3 Bronchiectasis Y / N

4.1.2.4 Bronchial wall thickening

4.2 Chest CT scan : Y / N

4.2.1 Date________________

4.2.2 Abnormal finding Y / N

4.2.2.1 Mosaic perfusion pattern Y / N

4.2.2.2 Vascular attenuation Y / N

4.2.2.3 Air trapping Y / N

4.2.2.4 Bronchial wall thickening Y / N

4.2.2.5 Bronchiectasis Y / N

4.2.2.6 Mucus plugging Y / N

4.3 Contrast studies: Y / N

4.3.1 Milk scan Y /N

4.3.1.1 Date: ________________

4.3.1.2 Gastro-oesophageal reflux Y / N

4.3.1.3 Abnormal gastric emptying Y / N

4.3.2 Barium swallow Y / N

4.3.2.1 Date: ______________

4.3.2.2 Aspiration Y / N

4.3.2.3 Gastro-oesophageal reflux Y/ N

4.3.3 Lung perfusion scan Y / N

4.3.3.1 Date: _______________

4.3.3.2 Ventilation/perfusion defect Y /N

4.3.3.2.1 Site: a) Right lung b)Left lung c)Bilateral

5.0 Lung function:

5.1 Forced oscillation technique (FOT) Y/ N

5.1.1 Resistance 5 and 7Hz

5.1.2 Reactance 5 and 7 Hz

5.1.3 Resonant frequency ________

5.2 Spirometry Y / N

5.2.1 Date of test: ______________

5.2.2 Height at test : ____________ cm

5.2.3 Pre-bronchodilator

5.2.3.1 FEV1 _______________L

5.2.3.2 FVC _______________L

5.2.3.3 FEV1/FVC ______________ %

5.2.4 Post bronchodilator

5.2.4.1 FEV1 _______________L

5.2.4.2 FVC _______________L

5.2.4.3 FEV1/FVC ______________ %

5.3 6 Minutes Walk Test: Y / N

5.3.1 Distance walked ___________ m

5.3.2 SpO2 before the test __________%

5.3.3 SpO2 after the test ____________%

6.0 Initial presentation (from clinical records):

6.1 Source of referral:

6.1.1 General pulmonology clinic Y / N

6.1.2 In-patients general paediatric wards Y / N

6.1.3 Medical emergency Y / N

6.1.4 Paediatric intensive care unit (PICU) Y /N

6.2 Age at first respiratory symptom: ___________ month

6.3 Symptoms at presentation:

6.3.1 Just tachypnoea Y / N

6.3.2 Cough Y / N

6.3.3 Difficulty of breath Y/ N

6.3.4 Wheezing Y / N

6.3.5 Cyanosis Y / N

6.4 Previous ventilatory support required Y /N

6.4.1 Type of ventilatory support :
CPAP / ET intubation and ventilation / Conventional and high frequency oscillation

6.4.2 Nitric oxide used Y / N

6.4.3 Duration on ventilatory support: ____________ hours

6.5 Supplemental oxygen needed Y/ N

6.5.1 During first presentation Y / N

6.5.2 After first presentation Y / N

6.5.3 Maximum oxygen requirement : ___________ L/min

6.6 Home supplemental oxygen required Y / N

6.6.1 Oxygen flow required: __________ L/min

6.7 Environmental factors:

6.7.1 Exposure to Cigarette smoke at home Y / N

6.7.1.1 The smoker at home : mother / father / both parents / other:_________

6.7.2 The type of cooking fuel used in the patient's home

Gas / coal / wood / electricity / other: ____________

6.8 Laboratory Investigations

6.8.1 Inflammatory markers:

6.8.1.1 FBC Y / N

6.8.1.1.1 White cell count ______________

6.8.1.1.2 Polymorph nuclear cell _________

6.8.1.1.3 Lymphocyte _______________

6.8.1.1.4 Haemoglobin _______________

6.8.1.1.5 Platelets count ______________

6.8.1.2 CRP : ___________

6.8.2 Immunological test : Y / N

6.8.2.1 Immunoglobulins: Y /N

6.8.2.1.1 IgA :________

6.8.2.1.2 IgM : _______

6.8.2.1.3 IgG : ________

6.8.2.1.4 IgE: _________

6.8.2.2 CD4 count : Y / N count : _________

6.8.2.3 Vaccine response : Y / N

6.8.2.3.1 H. Influenza : ________

6.8.2.3.2 Pertussis: _________

6.8.2.3.3 Diphtheria: _________

6.8.2.4 HIV screen: positive / negative

6.8.3 Microbiology:

6.8.3.1 Nasopharyngeal aspirate Y/N

6.8.3.1.1 Virus Y / N specify ________________

6.8.3.1.2 Bacteria Y / N specify ________________

6.8.3.1.3 Other ____________

6.8.3.2 Tracheal aspirate Y / N

6.8.3.2.1 Virus Y / N specify ________________

6.8.3.2.2 Bacteria Y / N specify ________________

6.8.3.2.3 Other ____________

6.8.3.3 Bronchoalveolar lavage Y / N

6.8.3.3.1 Virus Y / N specify ________________

6.8.3.3.2 Bacteria Y / N specify ________________

6.8.3.3.3 Other ____________

6.8.3.4 Blood culture Y / N

6.8.3.4.1 Positive Y / N specify _________________

6.8.3.5 HIV-PCR Y / N

6.8.3.5.1 Positive Y / N

6.8.3.6 Sputum for AFB Y / N

6.8.3.6.1 Positive Y / N

6.8.3.7 TB Gene Xpert. Y / N

6.8.3.7.1 Positive Y / N

6.8.4 Sweat test. Y / N

6.8.4.1 Na: __________

6.8.4.2 Cl: ___________

6.8.4.3 Na/Cl: ___________

6.8.5 Nasal scraping and electron microscopy Y / N

6.8.5.1 Positive Y / N

6.8.6 Other test _________________

6.9 Hospital admission: Y / N

6.9.1 Duration of index admission: ____________days

6.9.2 ICU admission Y / N

6.9.2.1 Duration: _____________ days

6.9.3 Total number of hospital admissions: ___________

6.9.4 Total number of ICU admissions: _____________

6.10 Treatment:

6.10.1 Antibiotics Y / N

6.10.1.1 Indication :

6.10.1.1.1 Treatment of infection Y / N

6.10.1.1.1.1 Antibiotic duration _______________

6.10.1.1.2 Prophylaxis of infections Y / N

6.10.1.1.2.1 Type __________________________

6.10.1.1.2.2 Compliance: good/ fair / poor

6.10.1.1.2.3 Duration _____________________

6.10.1.1.3 Immune modulator Y / N

6.10.1.1.3.1 Type __________________________

6.10.1.1.3.2 Compliance: good/ fair / poor

6.10.1.1.3.3 Duration ______________________

6.10.2 Inhaled bronchodilators Y / N

6.10.2.1 Short acting B agonist Y / /N

6.10.2.1.1 Type __________________________

6.10.2.1.2 Compliance: good/ fair / poor

6.10.2.1.3 Duration ______________________

6.10.2.2 Anticholinergics. Y / N

6.10.2.2.1 Type __________________________

6.10.2.2.2 Compliance: good/ fair / poor

6.10.2.2.3 Duration _______________________

6.10.3 Anti-inflammatory agent Y / N

6.10.3.1 Systemic corticosteroid Y / N

6.10.3.1.1 Oral Y / N

6.10.3.1.1.1 Therapeutic use

6.10.3.1.1.1.1 Pulse dose Y / N

6.10.3.1.1.1.2 Number of cycles______

6.10.3.1.1.1.3 Duration of treatment___

6.10.3.1.1.2 Maintenance dose Y / N

6.10.3.1.1.2.1 Regimen daily dose / weekly dose

6.10.3.1.1.2.2 Compliance: good/ fair / poor

6.10.3.1.1.2.3 Duration of treatment___

6.10.3.1.2 Injectable Y / N

6.10.3.1.2.1 Type ___________________________

6.10.3.1.2.2 Number of cycles _______________

6.10.3.1.3 Inhaled corticosteroid Y / N

6.10.3.1.3.1 Type ___________________________

6.10.3.1.3.2 Dose ___________________________

6.10.3.1.3.3 Compliance: good/ fair / poor

6.10.3.1.3.4 Duration of treatment ____________

7.0 Interval progress:

7.1 Number of Exacerbations (increase severity or frequency of short of breath, cough and/or wheeze requiring clinic/hospital review and adjustment of treatment): _________

7.2 Symptom progression:

7.2.1 Cough: improved / not improved / worsen.

7.2.2 Short of breath: improved / not improved / worsen.

7.2.3 Wheezing: improved / not improved / worsen.

7.2.4 Chest tightness: improved / not improved / worsen.

7.3 Follow up of Growth parameters: change of z-score over time:

7.3.1 Weight for age: _________________z -score

7.3.2 Height for age: _________________z -score

7.3.3 Weight for Height: _________________z -score

7.3.4 BMI : _________________z -score

7.4 Spirometry changes over time: ________________z-score