ATOPY AND AQUIRED IMMUNE DEFICIENCY – ISSUES OF CONTROL OF TWO EXTREMES OF A SPECTRUM OF PAEDIATRIC RESPIRATORY DISORDERS WITH AN IMMUNOLOGICAL BASIS

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Published work submitted to the University of Pretoria for the degree of Doctor of Science in Medicine

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DECLARATION

I, the undersigned, declare that the work contained in this presentation of publications is my original work, as set forth in the statements which precede the published articles.

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RJ GREEN

I certify that on this ..... day of ..... 2013, Robin John Green signed this declaration in my presence.

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COMMISSIONER OF OATHS

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DEDICATION

To my wife Dee, who has been my inspiration

INTRODUCTION

The author has an intimate personal knowledge of the atopic conditions and their implications, as described in this submission. He grew up with eczema, allergic rhinitis and asthma. General practitioners and many specialists failed to recognise the conditions and the correct therapy remained elusive. He had been the victim of the 'allergic march' and its attendant complications, including a profound impact on quality of life. His own personal journey made him determined to investigate and ideally put a stop to the mismanagement of atopic conditions in children in South Africa.

The author graduated from Medical School at the University of the Witwatersrand and specialised at that institution in Paediatrics. In the early years research was conducted in collaboration with David Luyt (now at the Leicester Royal Infirmary). His PhD thesis was completed with Professor Alan Rothberg as supervisor. In later times collaboration with Professor David Price from Aberdeen University led too some of the epidemiological work of this submission.

In 2005 he joined the Department of Paediatrics at the University of Pretoria as Professor of Paediatric Pulmonology and Critical Care. It is here that some of the later studies in clinical assessment of asthma control and his new interest, in human immunodeficiency virus (HIV)-related pulmonary disease, took place.

With regard to an interest in asthma and allergic rhinitis and the control of these conditions the author was a co-founder of the National Asthma Education Programme in South Africa in 1994, together with Dr's David Luyt and Mike Greenblatt. He is also co-founder, with David Luyt, of the Allergic Rhinitis Working Group in 1995. His PhD thesis focused on aspects of 'Inflammatory airway disease' and looked at issue of quality of life and cost of these two conditions.

Over the last 10 years he has presented his research work at international and local congresses.

In later years the author has become involved in research into the pulmonary complications of HIV infection in children. He joined the University of Pretoria at a time when acute lower respiratory tract infections were claiming a significant number of lives and a policy was in place around the country not to admit HIV-infected children to the Paediatric Intensive Care, as it was believed that the prognosis from these conditions in children was dismal. The author felt that this was unethical and proceeded to change the policy and then set about investigating strategies to reverse the poor outcome of these infants. His research efforts have managed to remove acute severe pneumonia, in HIV-infected infants, as a major cause of mortality in these children. Another clinical problem area was end stage lung disease in HIV-infected children. Historical failure to recognise and correctly manage episodes of pneumonia in these children would result in bronchiectasis. This condition too, was badly managed. Through the research efforts of a PhD candidate in his team, he was able to uncover the epidemiological and immunological mechanisms at work in this condition. This knowledge has resulted in a clinic where these children are now treated and their quality of life improved.

The author has been fascinated by the fact that both atopic conditions, which have their origin in an excess of T-cell mediated immunity (T-helper 2 skewing), and HIV-related conditions, which have their origin in deficiency of T-cell immunity (T-helper cell suppression), are both found in the South African population. In fact, these conditions are the commonest chronic diseases found in this country and often occur in the same child. The health and economic implications of these problems have become important for researchers to address and the author has contributed to a clarity of understanding of a way to manage both disorders to improve the life, quality and span, in affected children, both individually and as a society.

SUMMARY

Twenty publications are submitted. All deal with the issues of control of two ends of the spectrum of immune-mediated respiratory disorders in children, namely atopic (asthma and allergic rhinitis) and HIV-related lung disease.

This submission summarises the research by the author into this spectrum of lung diseases of children in South Africa, highlighting the diversity of conditions that are not only clinically important, but also common. Understanding of all conditions is required to improve the health of children in this region. Management of chronic conditions requires two major end points - adequate and timely diagnosis and - management to control the condition. The author has a passion for improving the quality of life of children and firmly believes that the research findings will, and have, led to transformation in management of both these common disorders.

This document follows the progression of the authors research work and highlights how interesting and important is the scope of two disorders which could be thought to have a central origin, namely in the T-cell. T-cells form the basis of cellular immunity and an excess of T-helper 2 cell activity promotes atopy, whilst the human immunodeficiency (HI) virus infects T-helper cells and promotes cellular immune deficiency and its attendant clinical disorders. The author's research work is not based on the immunological basis of these conditions but does deal with the clinical implications and especially aspects relating to control of these two extremes of a clinical spectrum of disorders. To take the clarity of two diseases at the end of a spectrum to its natural conclusion these extremes are defined in aetiology or pathophysiological differences (excess versus suppression of the immune system), occurring in the affluent and poor alike versus just the poor, control being required to improve quality of life versus to save lives and finally that management requires anti-inflammatory therapy versus antibiotic and anti-infective therapy.

For the eight publications based on atopic respiratory disease in children the themes are firstly that children with asthma and chronic rhinitis are diagnosed late, that most individuals with these conditions are not well controlled and finally that the reasons for lack of control are becoming obvious.

For the first time, the significant lack of asthma and allergic rhinitis control in South Africa is documented. These studies suggest that, like surveys from the rest of the world, asthma control is seriously under-estimated and neglected in all asthmatics in South Africa, in both the privileged and the under-privileged. The research also defines reasons for poor asthma and allergic rhinitis control in this region. As in many studies published from around the world it is now evident that poor asthma and allergic rhinitis control cannot be blamed on any one source. A multitude of reasons underlie this phenomenon and each of the subsequent papers in this section illustrates attempts at defining these principles. The three most important reasons for poor control are probably that most asthmatics are managed in the wrong hands (by doctors who don't understand adequate control and who aren't empowered to use the correct therapy), that control may actually be a pipe dream and practically difficult to do or even impossible to achieve and lastly that the allergic basis of asthma is over emphasised and may not in fact determine all asthma.

The subsequent papers summarise research work in the field of HV infection in children and exposes the opposite end of a spectrum of Paediatric respiratory disease and highlight research into the conditions common in HIV-infected children. Eleven papers are presented. For the diseases associated with the HI virus the major complications of inadequate diagnosis and prevention in children are acute pneumonia (especially severe pneumonia) and bronchiectasis. Bronchiolitis is not common in HIV infected children, despite epidemics of this condition in non-infected children. Passive smoking does not aggrevate or worsen disease progression in children. The complications of HIV related diseases in children require the same principles of adequate diagnosis and control as would apply to the chronic atopic conditions.

Once the author delved into the disorders at the other end of the clinical spectrum, namely those associated with immune deficiency secondary to HIV-infection he faced the question of a possible relationship between the conditions. One submission explores that relationship.

This research has a unique perspective, conferred by the fact that these two conditions do not occur to the same extent anywhere else in the world. Atopic respiratory conditions and HIV-related lung diseases occur side by side in abundance in this region. This perspective has created a clarity for research to address the two most important aims in clinical medicine, namely to diagnose correctly and then to manage the condition so that control is achieved. These must be universal principles of the successful practice of medicine.

CONTENTS

LIST OF PUBLISHED SUBMISSIONS

DECLARATION

This submission deals with twenty publications. For Paper 1 I, together with the co-author, had the idea to define delay to diagnosis of asthma in a group of South African children. Together we collected and analysed the patient data and wrote the paper. Similarly we initiated Paper 2, collected the data and wrote the paper.

I, as Chairman of the National Asthma Education Programme (NAEP), was the initiator of the project that led to Paper 3. In collaboration with the co-authors and the NAEP we collected the data from the rural health clinics through a team of asthma nurses, working with the NAEP.

For Paper 4, data was collected throughout the country and analysed by myself. I wrote the paper. Once again the co-authors made contributions to study and questionnaire design.

I was the originator of the research project that led to Paper 5 and coordinated data collection and analysis. The publication was written by myself as first author. The co-authors contributed to study and questionnaire design and to randomisation strategies.

I was a principle investigator on the project (The Asthma Control Study, South Africa) that led to publication of Paper 6. The publication was written primarily by myself with input from all the authors. I was the corresponding author.

I was the project leader and initiator of the study that led to Paper 7. I led the team that collected the data points and I wrote the paper. The second author on the paper contributed significantly to the written paper, while the other co-authors helped in data collection. Paper 8 was the result of research activity by a Fellow in my Department. I was the senior author on the publication and led the research team.

The latter publications reflect mainly the research work of the Department of Paediatrics at the University of Pretoria (where the author heads the research team) into the respiratory tract infections of children with human immunodeficiency virus (HIV) infection.

Paper 9 deal with issues relating to research work of a PhD student in my Department. I was the PhD supervisor and senior and corresponding author on the publication.

For Paper 10 I was one of the team that analysed data and specifically the radiological data for patients. The first author wrote the paper under my guidance.

I was senior and corresponding author on Papers 11 and 12. They deal with issues relating to research work of a PhD student in my Department. I was the PhD supervisor and senior and corresponding author on each publication.

For paper 13 I contributed to analysis of clinical and radiological data and was the primary author on the paper. For Paper 14 the idea was mine. Data was collected by the first author, as a Fellow in my Department. I wrote the paper.

The idea for the research, leading to Paper 15, was initiated by myself. The paper was written by myself. Papers 16 - 19 resulted from research work conducted toward a successful PhD degree by the first author. I am the PhD supervisor. I was senior author on all four papers.

I was the senior author on Paper 20 and wrote the paper.

ABSTRACT

Management of chronic conditions requires two major end points - adequate and timely diagnosis and - management to control the condition.

As the authors interest in control of asthma and other atopic conditions began, control of atopic respiratory conditions, asthma and allergic rhinitis, began to define the authors research ideas. Paper 1 and 2 followed from an attempt to determine reasons for poor asthma and allergic rhinitis control and explored the patients presenting to the authors own private practice. One reason uncovered was that of delay in asthma diagnosis. Whilst the missed opportunities to diagnose asthma are evident at all ages, this problem stems from childhood where a great number of children are ill defined in terms of recurrent asthma symptoms and consequently are poorly treated. When asthma is not diagnosed, inappropriate therapy is likely to follow and quite clearly significant morbidity is likely to ensue. The study is an audit of a single practice but a large number of well-defined asthmatics are in fact analysed. A similar methodology was employed for Paper 2. Paper 2 suggests that allergic rhinitis is, like asthma, incompletely diagnosed in childhood and clearly this phenomenon leads to poor overall control of, not only the nasal disease, but also of the co-existing asthma.

In subsequent years the author was provided with the opportunity, as Chairman of the National Asthma Education Programme, to investigate asthma control in rural South Africans. Paper 3 attempts to define asthma control in the poorest arm of South Africa's population, namely rural asthmatics. This group of individuals would normally have difficulty accessing asthma services and therapies and many of the drugs suggested in guidelines would be unavailable. A similar, but interestingly no worse, scenario of asthma control exists in this population group. This paper reflects data collected on a small number of individuals but is representative of most rural areas in the country. It is certainly possible that these small numbers are not representative of all rural asthmatics, but based on results from the larger national survey (Paper 5) it is clear that a

picture of poor asthma control is emerging in South Africa, study methodologies aside. This study was the first to tie South Africa to the world in suggesting that asthma control has been seriously neglected as a public health concern. In South Africa this issue is often explained away by talk of more pressing health concerns of infectious diseases; HIV and tuberculosis. The current prevalence of asthma of 20% in South Africa necessitates a revision of priority definition to include asthma as an important public health issue.

At this time the author noted that South African children were burdened by the two respiratory disorders that might define opposite ends of the spectrum of immunologically mediated conditions. Research into the latter disease profile would occupy his later career.

Nasal disease forms part of the spectrum of the ‘united airway’ concept and is no less important a cause of impaired quality of life than asthma. Many persons with asthma have allergic rhinitis and uncontrolled nasal disease makes asthma control less likely. Paper 4 is a survey of allergic rhinitis morbidity in a group of patients who might expect complete resolution to normal life. This paper is the first South African study to address allergic rhinitis morbidity and seek out the prevalence of poor control in this common condition. Once again it is a patient survey and not linked to objective measures of allergic rhinitis control. However such measures are ill-defined and seldom used in practice. Volunteer bias is unlikely in this large sample.

The submission that resulted in Paper 5 is a survey of known asthmatics in the general population of the country. This assessment was initiated because the absolute, population-based evidence, of poor asthma control in the urban population of South Africa, was lacking. The author had already reported on asthma control in rural South Africans and hence this study was necessary. This is the group of individuals who pay for health services through insurance. This population would define individuals who might expect the best care from health practitioners and therapies that are readily available. The study suggests

that, as with surveys from the rest of the world, asthma control is seriously under-estimated and neglected in this group of individuals. A limitation of this research paper is that some volunteer bias may have been possible. However, since the doctor groups that selected patients were selected by randomisation, it is unlikely that this phenomenon makes the results unreliable. In addition the questionnaire has a symptom-based bias and is not linked to objective evidence of lack of asthma control. Such surveys have been widely published from around the world and this data in South Africa had not been collected prior to this study.

Some years after publishing the early findings of poor asthma control a follow-up study was conducted. Paper 6 is the most recent survey of asthma control in South Africa. The aim of this study was to compare assessments of asthma control as reported by patients and their doctors. The article suggests that doctors over-estimate control of asthma but also reveals that asthma control is best achieved by specialist private pulmonologists for their patients and is also best achieved when a combination inhaled corticosteroid and long-acting beta-agonist are used in combination in a single inhaler. These findings need to be translated into care of South African asthmatics and need careful implementation if our goal is truly asthma control.

For the individual asthmatic patient control means achieving the ‘goals of asthma management’. Paper 7 illustrates an attempt to define asthma control more clearly and precisely in the individual patient. This study illustrates clearly the overriding theme of this research work that asthma control cannot be defined simply, nor measured by single variables or testing. It seems reasonable to suggest that only by stressing the importance of multiple measures of asthma control will change occur in this disease and its present significant load on morbidity. An alternative thought is that measuring asthma control may in fact be an elusive pipe dream with the current tools available. This study was adequately powered to compare assessment tools and has been published in a major international journal. It is hoped that this paper will

focus world wide and South African attention on the problems of failing to measure asthma control in individuals with asthma and in addition failing to properly quantify asthma control.

Paper 8 continues to explore the thought that has been germinating in Africa for some time, that not all children with asthma in Africa are atopic and that proof of atopy is absent in many families. This too should be considered a pilot study.

Papers 6, 7 and 8 offer potential reasons for the poor control of atopic respiratory disorders in children, namely that most practitioners looking after individuals with asthma are not knowledgeable to do so or are not empowered to use the optimal therapy, that in fact aiming for asthma control may be difficult or impossible to measure and that the allergic basis of these conditions, especially asthma, has been overestimated and requiring proof of allergy is limiting diagnostic possibilities for many asthmatics.

The following papers summarise research work in the field of HIV infection in children and exposes the opposite end of a spectrum of Paediatric respiratory disease and highlight research into the conditions associated with immune suppression in children. Eleven papers are presented. This work began when the author joined the Department of Paediatrics and Child Health in 2005. A similar role for lack of adequate diagnosis and management that exists for the atopic disorders, occurs in HIV-related respiratory conditions in children. The two most important complications of this latter state are acute pneumonia and bronchiectasis.

Acute pneumonia reflects a failure of HIV prevention policies and admission to hospital is a frequent event for children with pneumonia. Auditing the costs of admission of children with pneumonia (Paper 9) has revealed that the case fatality rate for HIV-associated acute pneumonia is 14% in a general ward and 46% in a paediatric intensive care unit (PICU). The actual bed costs are R1388.23 for an HIV-infected child in a ward but R3060.00 in a PICU. That is

three times higher than an HIV-uninfected child. Controlling this process is critical to the health economy of a country facing a significant burden from HIV.

A particularly severe form of acute pneumonia in HIV-infected infants has been common in the author's hospital and region. This is known as Pneumocystis pneumonia (PCP). Paper 10 describes the first intervention, conducted by the author to reduce the very high mortality from this condition, which was occurring. In this paper the role of oral corticosteroids for PCP in children, was proven to be beneficial. As a result of this study corticosteroids have been routinely introduced to the management of children with PCP across the world.

Paper 11 highlights case study lessons that have been learnt in the management of children with unusual presenting symptoms. Paper 11 describes Cytomegalovirus (CMV)-associated immune reconstitution syndrome in children, previously only reported twice in the literature.

Paper 12 is a final study highlighting our improvement in mortality for PCP when combining strategies of management. With regard to severe pneumonia in HIV-infected children the author has been experimenting with strategies to reduce mortality in PCP. This is the culmination of the authors research work and endeavours to improve mortality for a previously fatal condition. Through the use of lung protective ventilation and addition of oral steroids and ganciclovir mortality has been reduced from 90% to 30%. These activities have led to describing PCP as a new pulmonary syndrome with multiple overlapping aetiologies.

Paper 13 describes the cytokine and chemokine profiles of infants with severe (hypoxic) pneumonia and demonstrates these patterns for the first time. The study was adequately powered to provide meaningful data.

Bronchiolitis is a disease of infancy and presents as the first episode of wheeze in HIV-uninfected children. Paper 14 was initiated because bronchiolitis in HIV-

infected children had not been studied and the research has uncovered that bronchiolitis occurs at a different age in HIV-infected children. The mean age of bronchiolitis in HIV-infected children is 8 months as opposed to the HIV-uninfected children where the mean age is 5.8 months. In addition there appears to be a significantly lower incidence of bronchiolitis in HIV-infected children. This conclusion is most interesting and is the subject of ongoing study in the authors research unit.

Paper 15 reflects on an interesting phenomenon in HIV-infected children, that passive environmental cigarette smoke exposure seems not to affect disease progression. This phenomenon has not previously been reported in children. This study is an exploratory study that deserves follow-up.

The other result of HIV disease not identified and adequately managed is bronchiectasis. Bronchiectasis in Africa is increasingly commonly linked to HIV-related lung disease and Papers 16 - 19 highlight the research work. Paper 18 documents a failure of a cost-effective anti-inflammatory, immunomodulating therapy, namely erythromycin, to prevent exacerbations of bronchiectasis. The study may be limited in sample size but it appears unlikely even a much larger study would document benefit. Paper 19 addresses the issue of the differential diagnosis of immune deficiency related bronchiectasis, namely cystic fibrosis, because as this paper suggests this disease occurs in black South African children.

The author has contributed to the understanding of, but more importantly, reduction in morbidity and mortality, from the lung diseases in children infected with the human immunodeficiency virus. The author is most proud of this contribution to medicine.

The study that led to Paper 20 was conducted to explore the possibility that the two immunologically based respiratory conditions that the author had an interest in might have common pathophysiological mechanisms. Results in Paper 20

have revealed a significantly elevated IgE in the study population of HIV-infected children. Previous studies, in adults infected with HIV, have shown a relationship between IgE and the staging of the disease. However, as a result of this study there does not appear to be any correlation, between IgE level, and the stage of HIV infection, in children. There was interestingly, also no increase in the T-helper 2 mediated cytokines in relation to the elevated IgE. This demonstrates that the elevation in IgE is not related to atopy but probably reflects a polyclonal hyperglobulinaemia related to T cell depletion in HIV. In a previous study of children with HIV infection, no increase in skin prick test positivity, was documented; confirming that atopy is not responsible for the elevated IgE.

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Clinical characteristics of childhood asthmatics in Johannesburg

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Objectives. To describe the clinical features of Caucasian childhood asthmatics in Johannesburg in order to compare these with a similar population of black asthmatic children resident in Soweto.

Design. In a prospective study, a history was obtained by means of an investigator-administered questionnaire.

Main outcome measures. Presenting asthma symptoms, precipitants of symptoms, concomitant diagnoses, individual and family background of allergy and 'delay to diagnosis' of asthma (age at symptom onset subtracted from age at diagnosis) from history and allergen sensitivity as assessed by skin-prick tests (SPTs).

Results. Of the 468 (297 boys) asthmatics studied, 456 (97.4%) presented with cough, 362 (77.3%) with wheeze, 286 (61.1%) with a tight chest and 277 (59.2%) with breathlessness. Cough as sole symptom occurred in 102 (21.8%) while only 8 (1.7%) wheezed and did not cough. Commonest symptom triggers were upper respiratory tract infections and activity/exercise. An individual atopic background was common — allergic rhinitis in 413 (88.2%) — as was a family history of atopy, present in 390 (83.3%). Prolonged symptomatic periods occurred in most patients before asthma was diagnosed (among children diagnosed after the age of 4 years, 50% had been symptomatic for more than 3 years). 'Delay to diagnosis' was not influenced by presenting symptoms or by previous hospitalisation for asthma. Other respiratory diagnoses of bronchitis and pneumonia were common, possibly because of misdiagnosis. Commonest allergens on SPT were corn pollen, Bermuda and 5-grass mix, and standardised mites. Aside from wheat, food allergy was uncommon.

Conclusions. Cough was the commonest presenting symptom despite its still being regarded as a less classic symptom of asthma that may account for misdiagnosis and a high frequency of other respiratory diagnoses. Associated allergy, especially allergic rhinitis, occurred frequently. Many aspects of presentation in whites were similar to those in Soweto children, although the latter had a more frequent concomitant diagnosis of tuberculosis, and recognised dust and cold weather as more frequent triggers. Differences might be influenced by the care-giving situation.

S Afr Med J 1997; **87:** 878-882.

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Recent international epidemiological studies have reported increases in the prevalence of asthma.[1-5] In South Africa there is a paucity of epidemiological information available as only a few prevalence studies have been conducted.[6] However, despite this lack of evidence from community-based prevalence estimates, physicians working in asthma clinics have noted increases in the numbers of children attending these clinics. Furthermore, asthma is frequently missed — symptoms being attributed to other chest conditions like bronchitis or tuberculosis — and hence inappropriately treated. The gravity with which both local and international experts regard both underdiagnosis and undertreatment is reflected in the number of consensus statements published to date.[7-15]

The prevalence and management components of asthma have therefore been well researched and described, but failure to attribute symptoms or symptom complexes is the reason for misdiagnosis of asthma and it is in this area that there is a relative paucity of information. We recently described the clinical characteristics of black asthmatic children from Soweto attending the asthma clinic at Baragwanath Hospital.[16] This study was undertaken to describe the presenting clinical features in a similarly aged primarily Caucasian population of childhood asthmatics living in the suburbs of Johannesburg, and to compare their symptom presentation with that of the Soweto children.

Subjects and methods

We prospectively studied 468 children (297 boys) from the suburbs of greater Johannesburg, excluding Soweto, referred to a specialist paediatric asthma and allergy practice over the 12-month period starting in October 1994. The subjects studied were clearly a select group, as they were referred specifically for suspected or confirmed allergic disease. The population sample was therefore a convenience and not a random sample.

The diagnosis of asthma was ascertained from the initial parental history and from subsequent response to anti-asthma treatment. Confirmatory factors such as a history or clinical evidence of other atopic conditions (allergic rhinitis and eczema) were also considered. Patients over 7 years old who were able to perform repeatable pulmonary function tests (peak flow rates and spirometry) underwent these and, where necessary, airway reversibility was assessed to confirm the diagnosis.

The clinical data were recorded at each patient's initial clinic visit by means of an investigator-conducted questionnaire. The questionnaire recorded demographic data such as address, age and sex; the patient's respiratory history, including presenting symptoms (cough, wheeze, breathlessness, tight chest) and their precipitants (upper respiratory tract infections, exercise/activity, food or drink, dust, grass/pollens, animals, birds, cold weather); previous respiratory diagnoses (tuberculosis, haemoptysis, bronchiolitis, pneumonia, bronchitis); other atopic conditions (hay fever, conjunctivitis, eczema, food allergy) in the child and a family history of atopy in first-degree relatives.

The questionnaire also determined the age of onset of symptoms and the age at which asthma had been diagnosed. If asthma had not yet been diagnosed, the current age was regarded as the age of diagnosis. The 'delay to diagnosis' was therefore computed by subtracting the age at symptom onset from the age at diagnosis.

Skin-prick tests (SPTs) were performed in 107 patients where indicated. Only children over 4 years old were tested. Children referred after previous allergy tests (either SPTs or the radio-allergosorbent test) were not retested and their results were not included in the analysis. We used the Hollister-Stier allergen extracts (Bayer Miles) with 0.5% phenol as negative control and with 1% histamine as positive control. The allergen extracts used were: corn culture Zea Mays (pollen), Bermuda grass, 5-grass mix, tree mix, mould mix (*Alternaria tenuis, Aspergillus* mix, *Hormodendrium cladosporioides, Penicillium* mix), dog-hair dander, cat-hair dander, feather mix, standardised mite *Dermatophagoides pteronyssinus*, cow's milk, whole-grain soybean, peanut mix, whole egg, fish mix and wheat. Reactions were measured according to wheal size at 10 minutes, and a wheal 2 mm greater than the negative control was regarded as a positive reaction.

Results

Johannesburg patients

Of the 468 patients seen, 297 (63.4%) were boys, which gave a male/female ratio of 1.74:1. Patients ranged in age from 1 month to 18 years.

The rates of presenting symptoms were as follows: cough in 456 (97.4%) patients, wheeze in 362 (77.3%), a tight chest in 286 (61.1%) and breathlessness in 277 (59.2%). Cough and wheeze together were reported in 354 (75.6%), cough only in 102 (21.8%), wheeze only in 8 (1.7%) and neither in 4 (0.8%) patients (Fig. 1).

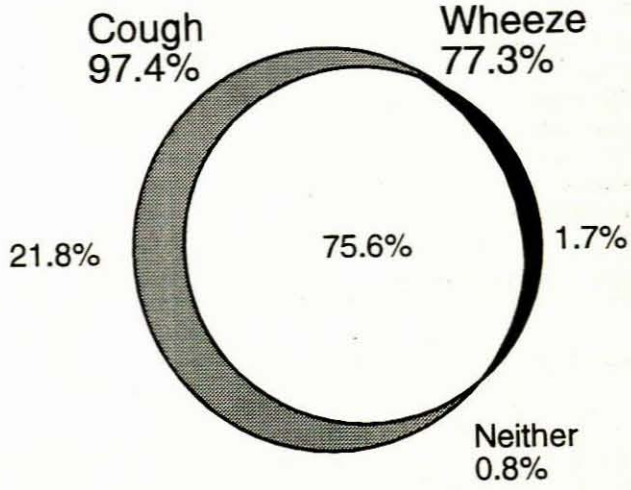

Fig. 1. Presenting symptoms in the asthmatic children.

Precipitants of both cough and wheeze are shown in Table I. Previous respiratory conditions were reported in 5 (1.0%) patients for tuberculosis, 2 (0.4%) for haemoptysis, 183 (39.1%) for bronchitis, 151 (32.2%) for pneumonia and 50 (10.6%) for bronchiolitis.

Other atopic conditions were prevalent with the patient's asthma as follows: 413 (88.2%) had allergic rhinitis, 165 (34.8%) had a history of current or previous eczema, 43 (10.6%) had conjunctivitis, and drug allergy and bee allergy were reported in 4.3% and 1.9%, respectively. A family history of atopy (asthma, allergic rhinitis or eczema) was present in 390 (83.3%) patients.

Table I. Rates at which precipitants triggered the symptoms of cough and wheeze

Precipitating factor (patient perceived)	Symptom: Cough (*N* = 456) No.	(%)	Wheeze (*N* = 362) No.	(%)
Upper respiratory tract infections	328	(71.9)	239	(66.0)
Exercise or activity	298	(65.3)	214	(59.1)
Food or drink	108	(23.6)	81	(22.3)
Dust	60	(13.1)	39	(10.7)
Grass or pollens	19	(4.1)	46	(12.7)
Animals	22	(4.8)	49	(13.5)
Birds	2	(0.4)	3	(0.8)
Cold weather	48	(10.5)	20	(5.5)

Parents were able to recall accurately the age of symptom onset and the age at asthma diagnosis in 299 children. Table II illustrates the computed 'delay to diagnosis' in these patients. The results are expressed in 6-monthly age groups at age of diagnosis as *possible* duration of delay will clearly be influenced by the patient's age. 'Delay to diagnosis' was not influenced by either presenting symptoms or whether the patient had been admitted to hospital with respiratory problems. As only 8 subjects presented with wheeze without cough, comparison between wheeze and cough was not possible as the wheeze sample size was too small. Therefore when the influence of presenting symptoms was assessed, patients presenting with either wheeze or cough (not both) were compared with those who presented with both symptoms. The mean (SD) 'delay to diagnosis' in these respective groups was 18.21 (23.76) and 21.12 (18.96) months; for subjects with and without a previous history of admission it was 19.30 (24.39) and 18.70 (21.58), respectively.

The results of the SPTs are shown in Table III. One hundred and seven children (62 boys) were tested with the commonly used standard eight aero-allergens. In addition to asthma, 97 of these had allergic rhinitis, 36 had a history of eczema, 2 of conjunctivitis and 1 of food allergy. Subsequently, the test was expanded to include the mould mix and the six food allergens.

Table III. Results of skin-prick tests

Allergen	No. tested	No. (%) positive	
Inhalant allergens			
Corn pollen	107	47	(43.9)
Bermuda grass	107	48	(44.8)
5-grass mix	107	43	(40.2)
Tree mix	107	30	(28.0)
Mould mix	62	33	(53.2)
Dog-hair dander	107	31	(29.0)
Cat-hair dander	107	37	(34.6)
Feather mix	107	17	(15.9)
Standardised mite	107	44	(41.1)
Food allergens			
Cow's milk	55	3	(5.4)
Whole-grain soybean	55	7	(12.7)
Peanut mix	55	10	(18.2)
Whole egg	58	4	(6.9)
Fish mix	53	8	(15.1)
Wheat	56	17	(30.4)

Discussion

This study examines the clinical features of childhood asthma in white children to compare these with a like group of black children from Soweto. The presenting symptoms of a disease will be influenced not only by the disease *per se* but also by the way in which the symptom complex is perceived by the patient, his or her parents and the attending doctors. The patients' socio-economic and cultural backgrounds will impact more on the latter than the former, although these will also influence the disease itself. Living conditions in many areas of Soweto are very different from those of suburban Johannesburg and these are likely to influence respiratory conditions, as are the socio-

Table II. Delay to diagnosis of asthma (No. (%))

Age at diagnosis (mo.)		Delay in months: No delay	< 6	7 - 12	13 - 24	25 - 36	36+
0 - 6	(*N* = 17)	12 (70)	5 (30)				
7 - 12	(*N* = 33)	10 (30)	14 (42)	9 (27)			
13 - 18	(*N* = 26)	3 (12)	5 (19)	12 (46)	6 (23)		
19 - 24	(*N* = 33)	14 (42)	8 (24)	2 (6)	9 (27)		
25 - 30	(*N* = 22)	5 (23)	2 (9)	0 (0)	10 (45)	5 (23)	
31 - 36	(*N* = 31)	8 (26)	3 (10)	3 (10)	9 (29)	8 (26)	
37 - 48	(*N* = 46)	8 (17)	2 (4)	5 (11)	11 (24)	17 (37)	3 (6)
49 - 60	(*N* = 27)	4 (15)	2 (7)	6 (22)	5 (18)	4 (15)	10 (37)
61 - 72	(*N* = 24)	6 (25)	4 (17)	2 (8)	1 (4)	1 (4)	10 (42)
73 - 84	(*N* = 10)	0 (0)	2 (20)	1 (10)	1 (10)	1 (10)	5 (50)
84+	(*N* = 30)	0 (0)	0 (0)	5 (17)	3 (10)	3 (10)	19 (63)
All	(*N* = 299)	70 (23.4)	45 (15.1)	45 (15.0)	64 (21.4)	39 (13.0)	47 (15.7)

economic status of the family; a poorer family might, for example, present to the doctor much later with more advanced or severe disease because of lack of funds for travel or medical fees. Therefore the clinical presentation of a disease, although generally similar from population to population and country to country, is specific to each community. It is therefore appropriate to study the disease in the communities in which we work.

The gender distribution of asthma showed a male preponderance; more than 60% of the study population were boys. A greater proportion of male asthmatics was also seen in the children from Soweto, a finding in keeping with international experience.[17]

The commonest presenting symptom was a chronic or recurrent cough, which was reported in all but 12 of the 456 children studied — 8 of these presented with wheeze only and 4 with neither wheeze nor cough. Furthermore, cough was the sole presenting symptom in more than 1 in 5 of the subjects. Wheeze occurred less commonly than cough in 3 out of 4 children, mostly in combination with cough. These figures mirror almost precisely those of the Soweto children where cough was reported in 93.6%, wheeze in 76.3%, cough and wheeze in 73.2% and cough alone in 20.4%. Like the Baragwanath study, this survey again refutes the misconception that cough is a 'less classic' presenting symptom in asthma than wheeze — indeed it would seem to be the most classic presenting symptom for asthma. Therefore in paediatric patients, the absence of wheeze does not exclude the diagnosis of asthma, as 1 in 5 of them will never wheeze.

Failure to recognise the presenting symptom complex of asthma as asthma has resulted in misdiagnosis and consequent undertreatment. In this study we showed that in most patients there was a period in which symptoms were present before the diagnosis of asthma was made. This period had to be shorter in the younger children, whereas some of the older children had been symptomatic for prolonged periods before their asthma was recognised. Indeed, of the 91 children who were diagnosed when older than 4 years, half had been symptomatic for more than 3 years, and this has also been reported from the UK.[18] The importance of recognising cough as the commonest presenting symptom has been discussed. Because so few patients presented with wheeze only, it was not possible to compare the two symptoms (cough and wheeze) in isolation and their influence on the 'delay to diagnosis'. However, presentation with cough and wheeze, whether alone or together, did not influence the 'delay to diagnosis'; neither did previous hospitalisation for chest problems. The study also highlights the common occurrence of a productive cough in asthma given that of those experiencing symptoms of cough, 45.3% reported the cough to be productive of mucus. This suggests that the classically described dry or non-productive cough is not necessarily the only type of cough to occur in asthma.

A high proportion of children had experienced previous respiratory problems or had had previous respiratory diagnoses — nearly 40% had had bronchitis and one-third pneumonia. These may be alternative diagnoses for persistent or recurrent symptoms which were not recognised as asthma. In the study at Baragwanath Hospital, a smaller proportion had had bronchitis (21.5%) and pneumonia (16.5%) but many more — 34 versus 5 in this study — had had tuberculosis. This is possibly because of a greater tendency to diagnose tuberculosis in black children with persistent or chronic respiratory symptoms than in white children. Hence, as mentioned above, the environment in which the patient's symptom complex presents may well influence the manner in which it is perceived by patients and doctors and therefore how it is managed.

Upper respiratory tract infections and exercise/activity were most frequently reported as trigger factors for both cough and wheeze. Similar observations have been reported in other studies as well as among the Soweto children. The rates at which various trigger factors precipitate symptoms are thought to be reflective of the environment under study. Interesting differences between Soweto and Johannesburg included the following: cold weather was a frequent trigger in Soweto (64.6%) but an infrequent trigger in Johannesburg (10.5% for cough and 5.5% for wheeze); and dust which was ascribed to symptoms in 38.6% of children in Soweto was regarded as a trigger in only 13.1% of Johannesburg children for cough and 10.7% for wheeze. The poorer living conditions in Soweto, with greater exposure to cold and to the dusty untarred roads, may explain these differences despite the similar climates of these two neighbouring cities. Similar prevalences were reported in these two communities for the remaining triggers, although food was implicated slightly more commonly in Soweto. The questionnaire did not detail specific foods and was therefore not able to differentiate between the two communities in respect of diet.

Moulds were the commonest allergens, with SPT positivity occurring in more than 50% of the patients tested. In the Baragwanath study, the mould extracts used were *Candida albicans* and *Aspergillus fumigatus*. As these differ from the mould mix used in this study a direct comparison was not possible. However, it is important to note that mould sensitivity was much less common in the children from Soweto, with SPT positivity rates of 16.5% and 9.9% for *A. fumigatus* and *C. albicans*, respectively. Moulds thrive in cold moist surroundings, and the difference in sensitivity between the two communities must reflect differences in living conditions, as the climate is the same. Possibly the more affluent Johannesburg homes are better insulated, thereby retaining moisture and allowing mould to grow while the indoor environments in Soweto are less well insulated and drier, and thus inhibit mould growth. Corn pollen, Bermuda grass and 5-grass mix and house-dust mite were the next most common allergens to cause SPT positivity, as the positivity rate was greater than 40% in all subjects. The Soweto children displayed almost identical responses and, in that study as in this, it must be concluded that high allergenicity to pollen and grass is evidence that the major components of the highveld's vegetation are natural grasses and cultivated cereals. The high rate of house-dust mite SPT positivity is more difficult to explain, as these creatures thrive in warm humid conditions and not in the colder drier climes experienced on the highveld. Acquiring sensitivity at the coast is more likely in these children as most had at some time spent holidays at the coast but only 9 had at any one time lived at the coast. Most of the Soweto children had not visited the coast. Sensitivity to dog-hair and cat-hair danders were, as with the children studied by Mercer and Van Niekerk,[19] more common than among the Soweto children, reflecting the frequency with which the respective communities keep household pets.

Aside from sensitivity to wheat, the rates of SPT positivity to food allergens were much lower than those to the inhalant allergens. It is interesting to note that milk sensitivity occurred least commonly, even though it is the one food which parents most frequently implicate as being responsible for food-induced symptoms. In addition, soya, the milk these children use after discontinuation of cow's milk, caused twice as many positive reactions as the latter. Sensitivity to peanuts, eggs and fish was also infrequent.

Conclusion

This study has allowed us to compare asthma presentation in two different ethnic communities from neighbouring cities. The similarities in presentation are striking, in particular the high prevalence of cough as the commonest presenting symptom. A disturbing finding was the misdiagnosis or failure to diagnose asthma and the high frequency with which other diagnoses are made, leading to unnecessary and costly treatment. In addition, three studies have now reported irreversible reduction in lung function parameters if there is delay in asthma diagnosis and treatment.[20-22] A survey of this nature highlights the manner of asthma presentation to the practising physician and will hopefully result in earlier diagnosis with the introduction of the correct medicines.

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Halothane hepatitis in a South African population — frequency and the influence of gender and ethnicity

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Aim. To review post-anaesthetic hepatitis in a South African population, given that halothane use is restricted in other countries because of the high mortality and morbidity of its associated type II (idiosyncratic) hepatitis, even though it is still widely used in South Africa.

Study design. Descriptive, retrospective analysis.

Patients and methods. Hepatitis cases that occurred after inhalational anaesthetic use were identified by means of a computer search of Groote Schuur Hospital records, 1980 - 1994. Cases of hepatitis caused by circulatory failure and viral hepatitis were excluded.

Results. Twenty-six episodes occurred in 22 patients (mean age 49.05 years, range 32 - 65 years), of whom 15 were women. This gave an estimated incidence of 3.53/100 000 anaesthetics (95% confidence interval 2.06 - 5.0/100 000). All had pyrexia (mean 38.7 ± 0.72°C), malaise, anorexia or nausea and vomiting, with onset a mean of 4.27 ± 3.5 days after exposure. Jaundice occurred in 86%, rash in 13.6%; 17 patients (77%) were obese. Alanine and aspartate aminotransferase levels were raised 47.49 ± 61.8 and 55.9 ± 54.5 times the upper limit of normal. Seven patients died and 1 underwent liver transplantation. Hepatitis occurred after the first exposure in only 2 patients (9%). Men and women had a similar risk, but the estimated relative risk for whites v. black or coloured patients was 3.33 (95% confidence interval 1.45 - 7.23; $P = 0.003$) controlling for gender. Awareness of the condition was suboptimal, and in 3 patients re-exposure to halothane occurred after an initial episode of typical halothane hepatitis.

Conclusion. Halothane hepatitis remains a major cause of morbidity and mortality in South Africa. It is more common in whites, but there was no gender-related excess risk.

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Clinical presentation of chronic non-infectious rhinitis in children

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Chronic rhinitis is one of the commonest conditions affecting humans and there is evidence that its prevalence (and especially that of allergic rhinitis) is increasing. Although common, it is poorly recognised by doctors, parents and patients, particularly in children.

Aims. This study surveyed children with chronic non-infectious rhinitis to describe their presenting symptoms, differences in presentation between preschool and school-aged children and the prevalence of complications.

Subjects and methods. We prospectively surveyed patients with a diagnosis of chronic rhinitis that was subsequently confirmed by response to therapy. Symptoms of rhinitis were assessed via an interview-conducted questionnaire.

Results. 567 children (357 boys), with a mean age (± SD) of 5.3 ± 3.6 years, were studied over 14 months. Three hundred and fourteen were preschool children. Symptoms of a blocked or a runny nose were reported in 85% of patients, both symptoms occurring simultaneously in 59.9%. A blocked nose occurred more frequently in school-aged children, while a runny nose was commoner in preschool children. Sneeze and itch occurred less frequently in 56.1% and 33.6%, respectively. Complicating recurrent ear infections were reported in 46.9% of patients, more frequently in preschool children ($P = 0.01$); almost one-third (32.02%) had had grommets inserted. Learning problems, possibly secondary to somnolence as a result of poor sleep induced by sleep apnoea (snoring was reported in 58.4%), were reported in 24.1% of school-going children.

Conclusion. As chronic rhinitis in South Africa commonly manifests with a blocked nose, patients display a high prevalence of associated complications. Doctors need to be aware of the presenting symptoms to diagnose and treat chronic non-infectious rhinitis earlier to prevent these complications.

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Chronic rhinitis is one of the commonest chronic diseases experienced by humans.[1] Depending on the community under study, it has been variably described as affecting between 4.5%[2] and 38.3%[3] of the population. It is estimated that at least 25 - 30 million in the USA suffer from allergic rhinitis and that it alone accounts for an astounding 2.5% of all doctor visits for all disease.[4] It occurs in 75% of children with asthma, which itself is a very common condition.[5] In southern Africa it is estimated to affect 20% of children.[6]

Although chronic (non-infectious) rhinitis is very common, and recent evidence suggests that the prevalence may even be increasing,[7-9] it remains poorly recognised and treated. Possible explanations may be that despite being a troublesome disease, it is often not taken seriously enough by patients, their parents and doctors[6] or that diagnosis relies on a symptom complex that may be difficult to recognise because it varies in severity.[10] For example, surveys of 'normal' subjects thought not to suffer from rhinitis have shown that 40% had experienced nasal symptoms the previous day.[11] This failure to recognise chronic, especially allergic, rhinitis occurs more frequently in children, especially young children; the rhinitic symptoms are frequently attributed to recurrent viral infectious rhinitis and these 'colds' are themselves common in this age group. The mean frequency of the common cold in children 2 - 6 years of age is 6 per year.[10]

In this prospective survey of children in whom chronic rhinitis was diagnosed, we describe their presenting symptoms, differences in presentation between preschool (< 5 years old) and school-aged children, and the prevalence of complications.

Subjects and methods

We prospectively studied 567 children consecutively attending an allergy practice during the 14-month period from October 1994 to November 1995. Subjects were included in the analysis if, at their initial visit, they were diagnosed as having chronic non-infectious rhinitis and if, at follow-up, they were shown to have responded to topical (anti-inflammatory) treatment.

Chronic rhinitis was diagnosed if symptoms attributable to the nose were present for more than 1 hour on most days[10] in the year. This category of conditions encompassed allergic rhinitis but also in some cases chronic rhinitis of irritant or idiopathic cause (vasomotor rhinitis). Response to medical anti-inflammatory treatment was important to exclude tumours, anatomical disorders and systemic disease with nasal symptoms. In the diagnosis of allergic rhinitis, confirmatory factors such as a history or clinical evidence of other allergic conditions (e.g. asthma), a family history of atopy as well as previous allergy skin-prick tests were also considered in the diagnosis. Allergic rhinitis was diagnosed in patients with chronic symptoms of rhinitis with an allergic diathesis proven by skin-prick test sensitivity (2 mm greater than negative control) to one or more relevant common allergens or by positive Phadiatop, elevated IgE levels for age or a positive radio-allergosorbent test (RAST) (again, to the relevant common allergen). The study population was not stratified by aetiology of chronic rhinitis; however, allergic rhinitis was by far the commonest cause.

Therapy consisted mainly of topical corticosteroids, with or without antihistamines. Allergen avoidance, although attempted, and specific immunotherapy (where indicated) were successful in a minority of patients. Where allergic rhinitis was present, only patients with perennial symptoms were included.

Clinical data were recorded at the patient's initial visit by means of a questionnaire. The questionnaire interview was personally conducted by the two investigators (RG and DL). Questions were derived from texts that described the presenting symptoms of chronic rhinitis[12-14] in an attempt to make the questionnaire as inclusive and complete as possible. The questionnaire recorded patient demographic data such as sex and age. The nasal symptoms and complications of chronic rhinitis enquired about included principal nasal symptoms (blocked nose, runny nose, sneezing and itching), associated symptoms (recurrent epistaxis, snoring, restless sleep, excessive tiredness during the day, irritability in the afternoon, post-nasal drip, frequent stomach aches, frequent sore throats, halitosis and frequent or persistent 'colds'), associated signs of oedematous nasal mucosa, the 'allergic facies' (rings or bags under eyes, constant rubbing of the nose, mouth breathing) and, lastly, related problems such as learning difficulties or problems at school, recurrent ear problems, recurrent tonsillitis, tonsillectomy, adenoidectomy, grommets, sinus headaches and sinus operation. A history of other allergic conditions (asthma, eczema) in the patient and a family background of atopy (asthma, allergic rhinitis or eczema) in first-degree relatives were also elicited.

As patients with chronic rhinitis have been classified into two categories, 'blockers' (predominantly blocked nose) and 'runners' (predominantly runny nose),[10,15] we assessed the relative frequency of either or both of these principal symptoms in our patients.

Statistical analysis was performed by means of the Z-test, given the large sample size, for comparison of individual symptoms. Statistical significance was established at the 5% significance level. In addition the two groups (preschool and school-aged children) were compared as a whole for each complex of symptoms. In this case a contingency table analysis was performed by means of the chi-square test. A *P*-value was obtained by comparing the test statistic to a critical value for each of the contingency tables.

Results

Of the 567 children studied, 314 (55.4%) were ≤ 5 years of age. There were 357 boys, giving a ratio of boys to girls of almost 2:1. The gender ratios were similar for preschool (≤ 5 years) and school-aged children as 192/314 (61.1%) of the former and 165/253 (65.2%) of the latter were boys. The mean (± SD) age of all children was 5.3 ± 3.6 years with a range of 1 month to 19 years.

In addition to chronic rhinitis, a history of asthma was recorded in 414 patients (73.0%), of eczema in 221 (39.0%), and of conjunctivitis in 44 (7.7%), and a family history of atopy in 414 (73.0%). The prevalence of asthma was similar in the two age groups, as 237 (75.5%) preschool children and 177 (70%) school-aged children were diagnosed asthmatics.

The frequency of the nasal symptoms of a blocked and/or runny nose are shown in Fig. 1. In the two age groups the presence of both symptoms was reported with similar frequency, occurring in 190/314 (60.5%) preschool children and 149/253 (58.9%) school-aged children. A runny nose alone was reported more commonly in the younger age group, affecting 24.5% of the preschool children and 10.3% of school-aged children ($P < 0.001$) while prevalences were reversed in respect of a blocked nose — 11.1% and 26.5%, respectively ($P < 0.001$). A runny nose was therefore the commonest single symptom affecting preschool children (85.0%) whereas a blocked nose occurred most frequently in the older school-going children (85.3%). The other two symptoms diagnostic of rhinitis — sneezing and an itchy nose — occurred less frequently in this study population. The respective prevalences for the study population as a whole and the younger and older children were: 289/567 (51.0%), 147/314 (46.8%) and 142/253 (56.1%) for sneezing, and 171/567 (30.2%), 86/314 (27.4%) and 85/253 (33.6%) for an itchy nose (Table I).

The prevalences of other symptoms and signs of chronic rhinitis are shown in Table II, and the prevalences of problems associated with rhinitis are shown in Table III. The appearance of the nasal mucosa was useful in diagnosis in terms of boggy and wetness of the turbinates but not colour. The classic textbook description of pale or pale grey mucosa (especially for allergic rhinitis) was not found in most patients and this description has now been dropped from much of the literature. Statistical analysis of the combination of factors in each of the three groups revealed that both primary symptoms (Table IV) and certain associated problems differed in the preschool and school-going groups ($P < 0.0005$ and $P < 0.001$, respectively, for primary and associated symptoms). No statistically significant difference was detected for associated signs ($P > 0.50$); in respect of related problems a significant difference was once again detected ($P < 0.001$) (Table V).

Discussion

This study describes the presenting symptoms of chronic rhinitis in children, emphasising the relative frequencies of individual symptoms that constitute the symptom complex of chronic (non-infectious) rhinitis. Although the association of most of these symptoms with chronic rhinitis is well described and well recognised,[12-14] this paper describes the frequencies with which they occur, thereby highlighting their importance to the clinician in identifying chronic rhinitis. Furthermore, the South African climate is sufficiently warm much of the year to produce a longer-lasting pollen season than colder northern climates.[16,17] Symptoms are therefore more chronic where associated with allergic rhinitis and, if not treated, possibly more likely to result in the complications of chronic rhinitis. This paper also describes the prevalences of complications and surgical interventions for these complications.

The onset of allergic rhinitis is classically described at between 5 and 10 years of age, with a peak occurring between 10 and 20 years.[14,18,19] Chronic rhinitis is frequently due to atopy and therefore also peaks in this age group; however, rhinitis may occur at any age. Our survey was

Table I. Primary symptoms of allergic rhinitis

Primary symptom	Age group: All children (*N* = 567)	Preschool children (*N* = 314)	School-aged children (*N* = 253)	*P*-value†
Runny nose only	103 (18.2%)	77 (24.5%)	26 (10.3%)	< 0.001*
Blocked nose only	102 (18.0%)	35 (11.1%)	67 (26.5%)	< 0.001*
Both symptoms	339 (59.8%)	190 (60.5%)	149 (58.9%)	0.348
Sneezing	289 (51.0%)	147 (46.8%)	142 (56.1%)	0.014*
Itching	171 (30.2%)	86 (27.4%)	85 (33.6%)	0.055

* Statistically significant at the 5% significance level.
† Z-test.

Table II. Prevalences of associated symptoms and signs of allergic rhinitis

Symptom	Age group: All children (*N* = 567)	Preschool children (*N* = 314)	School-aged children (*N* = 253)	*P*-value†
Associated symptoms				
Recurrent epistaxis	107 (18.87%)	32 (10.19%)	75 (29.64%)	< 0.001*
Snoring	331 (58.38%)	187 (59.55%)	144 (56.92%)	0.263
Restless sleeper	359 (63.32%)	209 (66.56%)	150 (59.29%)	0.037
Daytime tiredness	262 (46.21%)	130 (41.40%)	132 (52.17%)	0.005*
Irritable	211 (37.21%)	120 (38.22%)	91 (35.97%)	0.291
Post-nasal drip	402 (70.90%)	201 (64.01%)	201 (79.45%)	< 0.001*
Stomach ache	221 (38.98%)	98 (31.21%)	123 (48.62%)	< 0.001*
Sore throats	264 (46.56%)	119 (37.90%)	145 (57.31%)	< 0.001*
Halitosis	219 (38.62%)	99 (31.53%)	120 (47.43%)	< 0.001*
Frequent colds	347 (61.20%)	212 (67.52%)	135 (53.36%)	< 0.001*
Associated signs				
Allergic shiners	349 (61.55%)	159 (50.64%)	190 (75.10%)	< 0.001*
Allergic salute	380 (67.02%)	187 (59.55%)	193 (76.28%)	< 0.001*
Mouth breathing	323 (56.97%)	154 (49.04%)	169 (66.80%)	< 0.001*

* Statistically significant at the 5% significance level.
† Z-test.

Table III. Prevalence of problems related to allergic rhinitis

Symptom	Age group: All children (*N* = 567)	Preschool children (*N* = 314)	School-aged children (*N* = 253)	*P*-value†
Learning problems	61 (10.76%)	–	61 (24.11%)	
Ear problems	266 (46.91%)	161 (51.27%)	105 (41.50%)	0.010*
Grommets	175 (22.05%)	44 (14.01%)	81 (32.02%)	< 0.001*
Recurrent tonsillitis	210 (37.04%)	101 (32.17%)	109 (43.08%)	0.004*
Tonsillectomy	129 (22.75%)	48 (15.29%)	81 (32.02%)	< 0.001*
Adenoidectomy	107 (18.87%)	37 (11.78%)	70 (27.67%)	< 0.001*
Sinus headaches	121 (21.34%)	32 (10.19%)	89 (35.18%)	< 0.001*
Sinus washout	39 (6.88%)	17 (5.41%)	22 (8.70%)	0.062

* Statistically significant at the 5% significance level.
† Z-test.

Table IV. Statistical comparison of primary symptoms for grouped data

Primary symptom	Preschool children (observed, expected, chi-square)			School-aged children (observed, expected, chi-square)			All
Runny nose only	77	54.9	8.9	26	48.1	10.2	103
Blocked nose only	35	54.4	6.9	67	47.6	7.9	102
Both symptoms	190	180.6	0.5	149	158.4	0.6	339
Sneezing	147	154.0	0.3	142	135.0	0.4	289
Itching	86	91.1	0.3	85	79.9	0.3	171
Total	535	535	16.89	469	469	19.26	1 004
	Chi-square = 36.16		Critical value = 9.488		*P*-value < 0.0005		

Table V. Statistical comparison of symptom complexes for grouped data

Symptom	Preschool children (observed, expected, chi-square)			School-aged children (observed, expected, chi-square)			All
Associated symptoms							
Recurrent epistaxis	32	55.3	9.8	75	51.7	10.5	107
Snoring	187	171.0	1.5	144	160.0	1.6	331
Restless sleeper	209	185.5	3.0	150	173.5	3.2	359
Daytime tiredness	130	135.4	0.2	132	126.6	0.2	262
Irritable	120	109.0	1.1	91	102.0	1.2	211
Port-nasal drip	201	207.7	0.2	201	194.3	0.2	402
Stomach ache	98	114.2	2.3	123	106.8	2.5	221
Sore throats	119	136.4	2.2	145	127.6	2.4	264
Halitosis	99	113.2	1.8	120	105.8	1.9	219
Frequent colds	212	179.3	6.0	135	167.7	6.4	347
Total	1 407	1 407	28.1	1 316	1 316	30.0	2 723
	Chi-square = 58.08		Critical value = 16.919		*P*-value < 0.0005		
Associated signs							
Allergic shiners	159	165.9	0.3	190	183.1	0.3	349
Allergic salute	187	180.6	0.2	193	199.4	0.2	380
Mouth breathing	154	153.5	0.0	169	169.5	0.0	323
Total	500	500	0.51	552	552	0.46	1 052
	Chi-square = 0.98		Critical value = 5.991		*P*-value > 0.50		
Related problems							
Learning problems	0	25.4	25.4	61	35.6	18.1	61
Ear problems	161	110.6	22.9	105	155.4	16.3	266
Grommets	44	52.0	1.2	81	73.0	0.9	125
Recurrent tonsillitis	101	87.3	2.1	109	122.7	1.5	210
Tonsillectomy	48	53.6	0.6	81	75.4	0.4	129
Adenoidectomy	37	44.5	1.3	70	62.5	0.9	107
Sinus headaches	32	50.3	6.7	89	70.7	4.7	121
Sinus washout	17	16.2	0.0	22	22.8	0.0	39
Total	440	439.9	60.2	618	618.1	42.89	1 058
	Chi-square = 103.13		Critical value = 12.592		*P*-value < 0.001		

conducted in a paediatric practice and teenagers are therefore likely to be under-represented, with a consequent underestimation of the numbers of older children and adolescents presenting with chronic rhinitis. However, we did observe an almost equal distribution between children younger and older than 5 years; in fact, in contrast to these observations, there was a slightly higher presentation rate in preschool children. Chronic (including allergic) rhinitis has been observed in the newborn period,[20] and this, rather than eczema, was reported by Orgel *et al*.[21] to be the earliest manifestation of allergy. Doctors need to be aware of this early age of onset and the possiblity of making the diagnosis of chronic rhinitis in very young children. The high rate of frequent or persistent 'colds', particularly in preschool children, can be seen as a failure to recognise chronic (non-infectious) rhinitis.

Mygind *et al*.[15] divided patients presenting with chronic rhinitis into 'runners' and 'blockers' and noted that patients with seasonal allergic rhinitis are more commonly 'runners' while those with perennial non-allergic rhinitis were more commonly 'blockers'. These symptoms reflect the pathogenesis of rhinitis. Rhinorrhoea is the result of glandular activity and leakage of plasma while nasal blockage results from a decrease in the tone of the capacitance vessels and tissue oedema.[13] The latter is thought to reflect more chronic changes in the nasal mucosa. We have shown that these two symptoms occurred with equal frequency, although a runny nose was slightly more common in younger children. As mentioned above, the South African climate results in 'seasonal' allergic symptoms almost year-long. Consequently, patients with allergic rhinitis tend to be prone to the more chronic symptoms, particularly the older children in whom the disease is likely to have been present for a longer period of time. Our observations are therefore not in conflict with those of Mygind *et al*.[15] but reflect rather the unique clinical presentation of allergic rhinitis as a result of our climate.

Nasal congestion with obstruction is the major mechanism for the development of complications associated with chronic rhinitis. As discussed above, because obstruction is more chronic in South Africa, chronic rhinitis would be expected to be associated with high prevalences of these complications. Recurrent middle ear infections were reported in just under half of our patients, a higher prevalence than described in previous reports.[22,23] The higher prevalence in younger children is in keeping with previous

observations. Previous use of grommets was also reported frequently. Nearly 1 in 5 patients reported sinus headaches, although among the older children these were reported to occur in more than one-third. The lower prevalence in preschool children possibly reflects the inability to vocalise such a symptom at this age, and the fact that many of the sinuses are not yet fully aerated and are therefore not prone to congestion. A recent study in children attending an allergy clinic with rhinitis showed computed tomographic evidence of sinusitis in 63%.[24]

Increased upper airway resistance from nasal congestion is recognised as the mechanism that produces sleep disturbances associated with allergic rhinitis. Patients experience obstructive sleep apnoea and significantly more micro-arousals.[25,26] This disturbed or restless poor-quality sleep produces chronic fatigue which, in children, manifests in daytime tiredness and irritability and learning problems at school.[27] This study showed that nearly two-thirds of children snored at night, reflecting upper airway obstruction; many of these children continued to snore despite having had their adenoids and tonsils removed. Daytime tiredness and irritability were also frequently reported, but by far the most worrying aspect of this component of the disease syndrome was the high prevalence of reported perceived learning difficulties at school. Nearly 1 in 4 of the school-aged children had had some form of learning problem.

Nasal congestion is responsible for the typical 'allergic' or adenoidal facies and mannerisms associated with chronic rhinitis. The infra-orbital dark circles or bags ('allergic shiners') are probably related to venous plexus engorgement. The venous plexus of the mid-face drains into the nose. The 'allergic gape' or continuous open-mouth breathing is a result of nasal blockage as is the 'allergic salute', which is a frequent upward rubbing of the nose in an attempt to relieve the obstruction.[14,15] These features were frequently reported among our patients. Therefore, patients with chronic rhinitis can often be recognised by their typical facial characteristics. These may not be specific to allergic rhinitis.

Other symptoms associated with chronic rhinitis which were reported frequently are post-nasal drip and its associated sore throats, stomach aches and halitosis. The irritation of the mucosa by the post-nasal drip is responsible for the sore throats and stomach aches, and its presence in the throat produces halitosis.[13]

Conclusion

In this survey of symptoms, clinical manifestations and complications of chronic non-infectious rhinitis in children we have described the frequency with which these occur. The study highlights the chronic nature of symptoms, including those of allergic rhinitis, because of the warm South African climate with its almost year-long pollen season. As symptoms tend to be chronic, with nasal congestion the main manifestation of this chronicity, complications are most commonly associated with nasal congestion and therefore high prevalences of complications were noted. Of special concern is the high frequency with which learning problems were associated with allergic rhinitis. If 1 in 5 children has chronic rhinitis and 1 in 4 of these has learning problems secondary to his or her rhinitis, then 1 in 20 children — more than 1 per class — will be struggling at school because of a blocked nose. Doctors therefore need to be aware of the magnitude of the problem and to be familiar with the manifestations of chronic rhinitis to ensure that children are appropriately and timeously treated to avoid complications. This study is the first to describe a difference in both the presentation and complications of chronic rhinitis through its categorisation of preschool and school-aged children.

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Asthma management and perceptions in rural South Africa

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Background: Many First World countries have endeavored to measure the impact of asthma on individuals with asthma and, in addition to this quality of life evaluation, have attempted to define the quality of care for this common chronic illness.

Objective: The primary objective of this research probe was to assist the National Asthma Program in South Africa with the formulation and delivery of its outreach program to rural asthmatic patients.

Methods: A discussion/questionnaire document was compiled by Partners in Research from established literature. All interviews were conducted in either the clinics, hospitals, or respondents' homes. Both adult asthmatic patients and parents of pediatric asthmatic patients were interviewed. Interviewing took place at seven rural health clinics across South Africa. Each interview included extensive demographic details, questions on asthma definition, symptoms and symptom triggers, family history, age at diagnosis, frequency of symptoms, and treatment.

Results: Thirty-five adult asthmatic patients and 27 parents of pediatric asthmatic patients were interviewed. Of the adults, 40% reported wheezing at least once a week (despite diagnosis and treatment) and 19% of children reported similar symptom exacerbations. Fifty-one percent of adults and 56% of children were awakened at least once a week by cough or wheeze. Quality of life measurement reflected that, on average, 37% of responders were frightened during an acute asthma attack, and 68% of parents reported fearing the death of their asthmatic children. Fifty-one percent of adults and 33% of children had been hospitalized at least once for asthma. Although respondents claimed regular training in use of inhaler device, only 43% of adults completed each step correctly.

Conclusions: There is a great deal of fear and ignorance surrounding asthma and, therefore, there is a real need for a greater level of patient education even in the rural areas of South Africa. In rural South Africa, attention should be paid to nurses, because they play a greater role than doctors in management and education of asthma.

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INTRODUCTION

Research is proceeding at unprecedented speed in all areas of asthma and, yet, we live with a disease that escalates in prevalence and severity, despite a greater understanding of the pathophysiology and therapy. In the domain of patient education, many countries, including South Africa now, have a national body attempting to correct the deficiencies in asthma care. Deficiencies may arise at many levels, from poor doctor knowledge of asthma to limited governmental funding for asthma. Many First World countries have endeavored to measure the impact of asthma on individuals with the disease and, in addition to this quality of life evaluation, have attempted to define the quality of care for this common chronic illness.[1–4] It is only through understanding of the fundamental deficiencies (or strengths) of a health network that change can be planned and measured against.

The primary objective of this research probe was to assist the National Asthma Education Program in South Africa with the formulation and delivery of its outreach program to rural asthmatic patients. This was done by establishing from patients (and health care providers) attitudes toward the condition and its treatment, knowledge with regard to asthma and its treatment, present asthma therapy, knowledge gaps and needs, and needs in dissemination of information.

Subjects and Methods

A discussion guide and questionnaire document was compiled by Partners in Research from established literature. On finalization of this document, one pilot interview was completed to revise key elements. All interviewers were comprehensively briefed on content and expectation. Interviewers were medically competent, and familiarity with terminology and ethos allowed for spontaneity and digression where appropriate. All interviews were conducted in either the clinics, hospitals, or respondents' homes. Interviews were tape-recorded for later transcription and analysis. All respondents received a monetary incentive. Both adult asthmatic patients and parents of pediatric asthmatic patients were interviewed. Interviewing took place at seven rural health clinics across South Africa: Mugodeni Grace Health Center, Letaba; Letlhabile Primary Health Care Clinic, Brits; Ocean View Clinic, Ocean View; Kwamashu Poly Clinic, Kwamashu; Montshiwa Clinic, Ratshidi; Botlokwa Health Center, Dwarsrivier; and Voortrekker Hospital, Potgietersrus). The term "rural

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Table 1. Commonly Reported Emotions and Consequences of Asthma

	Adults (n = 35)	%	Children (n = 27)	%	Total (n = 62)	%
During an Acute Attack						
Afraid/Frightened	18	51	5	19	23	37
Anxious	4	11	–	–	–	–
Worried	–	–	13	48	–	–
Confused	4	11	–	–	–	–
Sleepy	3	9	–	–	–	–
Frustrated	3	9	4	15	7	11
Miserable	3	9	–	–	–	–
Fear of death	–	–	4	15	–	–
Depressed	–	–	4	15	–	–
General						
Fear of death	28	80	14	52	42	68
Will have it forever	3	9	3	11	6	10
Can't lead a normal life	–	–	2	7	–	–
Impact on Lifestyle						
None	11	31	12	44	23	37
No smoking at home	3	9	7	26	10	16
Keep home, dust free	7	20	2	7	9	15
Impact on Work						
Don't work	22	63	–	–	–	–
None	5	14	–	–	–	–
Keeping away from smokers	2	6	–	–	–	–
Impact on School						
None	–	–	13	48	–	–
No sport	–	–	4	15	–	–

health clinic" is applied to a primary health care clinic situated well outside an urban environment, and provides health care support to a largely underprivileged community.

Each interview included extensive demographic details; questions on asthma definition, symptoms, and symptom triggers; family history; age at diagnosis; frequency of symptoms, and treatment.

RESULTS

All results are expressed separately and then jointly (percentage noted is rounded to the nearest full number) for the 35 adult asthmatic patients and 27 parents of pediatric asthmatic patients. No stratification by clinic was performed in view of the small numbers. Ages of patients are as follows: <1 year, 1 of 27; 1 to 3 years, 2 of 27; 4 to 8 years, 15 of 27; 9 to 12 years, 9 of 27; and 13 to 20 years, 1 of 35; 21 to 30 years, 10 of 35; 35 to 49 years, 12 of 35; and 50 years +, 12 of 35.

Sex stratification was 11 of 35 (31%) male adults and 17 of 27 (63%) male children. The patients' native languages were Pedi, 9 of 35; Tswana, 8 of 35; Zulu, 5 of 35; Shangaan, 5 of 35; Afrikaans, 5 of 35; English, 3 of 35; and Ndabele, 1 of 35. There were traditional Africans, colored, and white patients. Education levels reflected no schooling in 21%, completed primary school in 16%, some high school training in 21%, and matriculation in 5%. Symptoms of asthma were recorded as wheeze at least once a week, 14 of 35 adults (40%) and 5 of 27 children (19%; total 31%); cough at least once a week, 16 of 35 adults (46%) and 10 of 27 children (37%; total 42%); and awakened at night at least once a week by cough or wheeze, 18 of 35 adults (51%) and 15 of 27 children (56%; total 53%).

Patients did not distinguish clearly between factors involved in asthma etiology and factors which trigger an attack. The main factors identified were smoke pollution in 84% and cigarette smoke in 86%. A family history of asthma was noted in 41% of respondents. Control of asthma as reflected by frequency of symptom exacerbations was at least *once a week* in 4 of 35 adults (11%) and 4 of 27 children (15%; total 13%); *every month* in 14 of 35 adults (40%) and 4 of 27 children (15%; total 29%); within *6 month*s in 6 of 35 adults (17%) and 6 of 27 children (22%; total 19%); *seldom* in 2 of 35 adults (2%) and 2 of 27 children (7%; total 7%); and *never* in zero of 35 adults but 2 of 27 children (7%). Symptoms of attacks of asthma/loss of control were *difficulty breathing* in 22 of 35 adults (63%) and 13 of 27 children (48%; total 57%); *tight chest* in 18 of 35 adults (51%) and 6 of 27 children (22%); *wheeze* in 5 of 35 adults (14%) and 13 of 27 children (48%; total 29%); *cough* in 5 of 35 adults (14%) and 4 of 27 children (15%; total 15%). Only 4 of 35 adults (11%) reported chest pain.

Frequency of action taken to prevent exacerbations or attacks of asthma were recorded as: take treatment regularly in 19 of 35 adults (54%) and 12 of 27 children (44%; total 50%); no action taken in zero of 35 adults but 4 of 27 children (15%); activity restrictions in zero of 35 adults but 3 of 27 children (11%); and environmental control in 11 of 35 adults (31%) and 9 of 27 children (33%; total 32%).

Environmental control included avoidance of dust and smoke. Treatment used by respondents for an exacerbation or asthma attack are recorded as follows: using medication in 29 of 35 adults (83%) and 18 of 27 children (67%; total 76%); consult clinic for medication in 12 of 35 adults (34%) and 8 of 27 children (30%; total 32%); consult doctor in 6 of 35 adults only (17%), and consult nurse in 5 of 35 adults only (14%). Quality of life measures are recorded in Table 1.

When asked to rate (1 = low/5 = high) the impact that asthma had had on their or their child's quality of life, the majority of those sampled reported a significant (5 of 5) impact: 21 of 35 adults and 17 of 27 children. Delay to diagnosis of asthma from initial symptom presentation was: diagnosis made at *first visit* in 7 of 35 adults (20%) and 9 of 27 children (33%; total 26%); *1 to*

2 months in 3 of 35 adults (9%) and 3 of 27 children (11%; total 18%); up to *1 year* in 13 of 35 adults (37%) and 8 of 27 children (30%; total 34%); *1 to 2 years* in 3 of 35 adults (9%) and 6 of 27 children (22%; total 15%); *4 to 5 years* in 2 of 35 adults (6%) and zero of 27 children. Seven of 35 adults (20%) and 1 of 27 children (8%; total 13%) did not know when asthma was diagnosed. Many markers are available for assessing the success of asthma management; the most reliable are shown in Table 2.

Ninety-six percent of children and 91% of adult respondents were treated in state hospital or clinics. Only five respondents admitted having being treated by a traditional healer (witch doctor/sangoma who uses herbal and nonmedicinal therapies). Current medication usage is listed in Table 3, bearing in mind that this is the therapy used in the same group of patients reporting frequency of symptom exacerbation and quality-of-life disturbance. All patients described regular use of β_2-agonists or theophylline, but beclomethasone, 100 μg to 300 μg/day, was used regularly in 54% of adults and 83% of children given this therapy (only 34% of adults and 31% children were given beclomethasone). Although respondents claimed regular training in use of inhaler device, only 43% of adults completed each step correctly when asked to demonstrate usage to the interviewer.

Finally, with regard to the role of health personnel, patients rated the role of the nurse as being more important than that of the doctor (80% of adults and 90% of parents of children during an acute attack) and most respondents (69% of adults and 78% of parents) obtained their information regarding asthma from the nurses.

CONCLUSION

There is a great deal of fear and ignorance surrounding asthma, and therefore, there is a real need for a greater level of patient education. This study highlights this need in the rural areas of South Africa. Nurses currently play a far greater role than doctors in management and education of asthma, particularly in rural clinics. Glaring errors in asthma therapy usage are noted, both in limitation of available drugs, incorrect dosage formats, and prophylactic therapy. Use of the inhaled prophylactic therapy in only 30% of patients despite 77.4% indicating the impact of asthma on their quality of life (5 on a scale 1 to 5) highlights this mismanagement and, in addition, suggests that isolated symptom reporting is a poor indication of overall well-being or disease control.

It is obvious that failure to relate the concerns and quality of life implications of asthmatic patients in rural areas to overall success of therapy needs urgent review, although it is encouraging to note that skills exist in these regions. Urgent and correct education of medical staff regarding asthma is required.

Two major observations are evident from this study. First, in the domain of asthma symptoms and their consequences, an interesting comparison is made to the Lifestyle Study[5], which showed asthma-related school absences in 38% of children in the previous 3 months (an average of 3 days away from school was recorded). The same study described the feelings of an asthmatic child when experiencing an attack of asthma. In general, 63% were frightened and 28% were embarrassed (n = 773). This was especially true when at school or work with 63% and 56% reporting fright and embarrassment, respectively. The children in our study were not asked about the consequences of troublesome asthma symptoms at night where the Lifestyle Study reported that 74 of 276 young children felt sleepy in lessons. Our study, however, reported that less than half of children (48.2%) reported no impact of asthma on school performance. Second, with regard to patient-perceived quality of care, both patients and we as observers observe that there is less than optimal care in the form of care-

Table 2. Frequency and Extent of Hospitalization and Missed School/Work Days for Asthma-Related Reasons

Factor	Adults	% of total	% of subgroup	Children	% of total	% of subgroup	Total	%
Hospitalization ever	18/35		51	9/27		33	27/62	44
Number in last year								
1	8/18	30	44	5/9	19	56		
2	3/18	9	17	2/9	7	22		
3	4/18	11	22	2/9	7	22		
4	1/18	3	6	–	–	–		
>4	2/18	6	11	–	–	–		
Number of days								
1–3	4/18	11	22	5/9	19	56		
4–8	10/18	29	56	2/9	7	22		
>1 week	3/18	9	17	2/9	7	22		
Number of days off work/ school in the last year								
<1 week	4/9			14/16				
>1 week	2/9			2/16				

takers, medication, and education on delivery device utilization.

When studying urban children in both Johannesburg and Baragwanath Hospitals, Jensen et al[6] commented that, "the education of asthmatic patients and their families has been neglected in South Africa and we have fallen behind the rest of the world where well-structured and organized education program have been operational for some time." This study confirms this challenge and includes the rural community in the need. This is the first study of its kind in truly rural communities and highlights the importance of an education program reaching into all communities, not just the readily accessible. However, studies in urban Cape Town[7,8] have reported similar prevalence of asthma symptoms in children and similar attitudes to the disease. Although there have been previous reports suggesting that asthma is a rare condition in rural South Africans,[9] this scenario appears to be changing and it is the impression of health care workers in rural South Africa that asthma is now increasing in these areas. Van Niekerk and colleagues[9] have also commented that terms to describe wheeze and asthma are not present in many African languages, but this too is changing as the disease becomes more prevalent in these communities and, in addition, we believe that the interview-based questionnaire was able to overcome these perceived difficulties. Most studies of this nature conclude with similar recommendations to accept the quality of life issues raised by patients as well as improve the quality of care provided.

Policy makers and government are often quick to defend themselves against reports suggesting a suboptimal quality of care, especially for chronic illness, by extending financial restriction on improved care, and especially on education funding. However, there is good evidence that investment in education, in fact, lowers cost, not only in a First World or urban setting, but in poorer communities, too. An asthma treatment and teaching program conducted in Düsseldorf, Germany revealed the true, hidden costs of asthma.[10] In this study, the authors demonstrated that intensified training can result in cost saving; not only in medicines but also in indirect costs of many factors including those such as loss of income. In this study evaluation was made on the cost-effectiveness of the structured Asthma Teaching and Training Program assessing whether the monetary benefits outweighed the costs of the intervention program. The Asthma Teaching and Training Program was performed on an inpatient basis, lasting a full week from Monday to Friday, in the general ward. It must be stressed that well asthmatic patients were admitted for education only, conducted by a special nurse educator on all aspects of asthma. In the cost analysis, time lost from work while participating in the program was included in the costs. In the year after the program, hospitalizations were reduced by 50%, as were days absent from work. Unscheduled physician visits were reduced from 3.3 per patient per month to 1.0, and the number of attacks of asthma decreased from 4.8 to 1.0 per patient per year. These differences were all highly significant. It is important to note that these savings were achieved without more medication being used. Overall this teaching program showed a benefit to cost ratio of all costs (including lost productivity, etc) of 5.0 and one of 2.7 when only medical costs were considered. The savings achieved by a simple training program were therefore highly significant.

In affluent children in California, an educational program produced savings of US$180 per child per year in asthma costs, despite investing in education.[11] However, in low income areas of New York, for children admitted to hospital for asthma in the previous year, intervention through education resulted in an average saving over the following year of US$11 for every dollar spent on delivery of health education.

The National Asthma Education Program in South Africa is actively engaged in education of all asthmatic patients, urban and rural, and is probably the most active educational program in South Africa that does not have government funding. Asthma is not a rare condition. It deserves input from all health players, from doctors to managed health care organizations to government if we are to truly impact on the significant morbidity of this condition. Death from asthma is high in the colored population of the Western Cape,[13] and education is most important in overcoming this problem.

Table 3. Current Medication Usage for the Group of Patients

Medication	Adults (n = 35)	%	Children (n = 27)	%	Total (n = 62)	%
Salbutamol, Fenoterol MDI	24	69	5	19	29	47
Beclomethasone generic MDI	13	37	6	22	19	31
Salbutamol tablets/syrup	8	23	10	37	18	29
Theophylline SR	7	20	6	22	13	21
Prednisone	5	14	–	–	–	–

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ORIGINAL RESEARCH

Concerns of patients with allergic rhinitis: the Allergic Rhinitis Care Programme in South Africa

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Abstract

Background: The major reason for treating chronic rhinitis is to improve quality of life. Although primary symptoms cause morbidity in their own right, these symptoms are significantly aggravated by the impact of cognitive dysfunction and quality of life.

Objective: The Allergic Rhinitis Care Programme was initiated by the South African Allergic Rhinitis Working Group. An important task of this programme was to document health-related quality of life impairment amongst allergic rhinitis patients in South Africa.

Methods: A questionnaire, appropriate to South Africa, was distributed to patients. The questionnaire inquired about symptoms, quality of life, complications, trigger factors, associated allergic conditions, medication preference, medication adherence and concerns about the condition.

Results: 1181 people completed the questionnaire and returned the survey. Nasal congestion was identified as a common and frequent problem, while seasonality of symptoms was uncommon. Symptoms affected sleep in 76.6% of sufferers, and in at least a third this was every night. Over 1000 respondents felt miserable due to allergic rhinitis (85.2%). 63.1% indicated that they always followed instructions for taking rhinitis medication. A variety of perceived concerns around having and being treated for allergic rhinitis were identified, suggesting multiple reasons for non-adherence.

Conclusions: We report symptom frequency and quality of life impairment for respondents who identify themselves as having allergic rhinitis. Since allergic rhinitis is, in the main, a doctor-diagnosed condition, this would suggest a significant problem with inappropriate, insufficient or incorrect therapy.

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Keywords allergic rhinitis, quality of life, nasal congestion, non-adherence

Introduction

Rhinitis is not a life-threatening condition, and although this has perhaps trivialised its status, it places greater emphasis on patient well-being as an outcome measure. In fact, the major reason for treating chronic rhinitis is to improve quality of life.[1] As a disease, it has major ramifications in terms of associated morbidity and cost. Although primary symptoms (rhinorrhoea, nasal congestion, sneezing and itch) cause morbidity in their own right, these symptoms are significantly aggravated by associated problems of ear and sinus disease, as well as the impact of cognitive dysfunction and quality of life.[2-6]

The South African Allergic Rhinitis Working Group (SAARWG) was convened by interested allergists, pediatricians, Ear Nose and Throat (ENT) Surgeons, and General Practitioners (GPs). In 1996, the group met to discuss and publish guidelines for the diagnosis and management of allergic rhinitis in South Africa.[7] International Guidelines[8] had recently been published, but at this first meeting, and subsequently, a need was expressed to document the problems and concerns of patients with allergic rhinitis in South Africa. The Allergic Rhinitis Care Programme was born. An important task of this programme was to document

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Table 1. Symptoms of allergic rhinitis (n=1181) (%).

Symptom	More than once a week	More than once a month	Occasionally	Seasonally (eg. in spring)	Never
Nasal congestion	612 (51.8)	170 (14.4)	155 (13.1)	129 (10.9)	14 (1.2)
Runny nose	491 (41.6)	184 (15.6)	225 (19.1)	146 (12.4)	56 (4.7)
Sneezing	558 (47.3)	170 (14.4)	199 (16.9)	152 (12.9)	57 (4.8)
Itching in the nose	458 (38.8)	185 (15.7)	222 (18.8)	135 (11.4)	57 (4.8)

NB: Some responses missing hence totals not 100%

impairment in health-related quality of life amongst allergic rhinitis patients in South Africa. Subsequent to this study the SAARWG has prioritised patient education as a critical factor in the success of managing allergic rhinitis.

This study was deemed necessary to document the effects of diagnosis and pharmacological treatment on patient well-being and resolution of symptoms in patients with allergic rhinitis. The impact of these two factors alone requires documentation in devising patient education strategies. In addition, the concerns of patients with persistent allergic rhinitis needed quantification.

Methods

The members of the South African Allergic Rhinitis Working Group (Allergists, Paediatricians, Otorhinolaryngologists and GPs with an interest in allergic rhinitis) were asked to submit questions, based on experience and evidence, that they felt would best uncover the concerns of patients with regard to allergic rhinitis. A 20-question questionnaire, appropriate to South Africa, was compiled. These questions were tested for their ability to demonstrate reliability in a workshop of 50 volunteers with allergic rhinitis accompanied by two expert clinicians. The questionnaire was reduced to 11 questions in this way (see Appendix 1 at www.thepcrj.org). The pilot study revealed that the language was understandable by all patients (including those with limited formal education, and patients from different racial groups) and the question results correlated well with objective observer assessment of rhinitis control. The questionnaire inquired about symptoms, quality of life, complications, trigger factors, associated allergic conditions, medication preference, medication adherence and concerns about the condition. Respondents were asked about perceived concerns around having, and being treated for, allergic rhinitis.

Patient recruitment

General Practitioners (GPs), ENT surgeons and Pharmacists (in South Africa) were randomly identified from the Medical Association database. These individuals were approached to recruit patients. Twenty of each group were identified in each of five major centres (Johannesburg, Pretoria, Durban, Cape Town and Bloemfontein). They invited all their patients known to have allergic rhinitis to complete the questionnaire. All patients had to have a clinical history of chronic nasal symptoms (nasal blockage, rhinorrhoea, sneezing or itch) together with a positive allergy test (skin prick test or RAST) to common aero-allergens. Other causes of chronic rhinitis had to be excluded in the judgement of the clinician. The questionnaire was titled 'Questionnaire for allergic rhinitis sufferers'. The survey was, however, targeted to selected patients and not a random population sample. All respondents completed written informed consent, and ethics approval (from the Medicines Control Council South Africa) was obtained for the study.

Table 2. Do allergic rhinitis symptoms affect the quality of your sleep? (n=1181) (%).

Affect sleep quality	904 (76.6)
- Every night	439 (37.2)
- Less than once a week	348 (29.5)
- Less than once a month	177 (15.0)

In an attempt to identify the impact of allergic rhinitis on quality of life, two questions were asked; 'Do these symptoms affect the quality of your sleep?'; and 'Does rhinitis make you feel miserable?' In an attempt to document the extent of non-adherence to chronic medication, a number of questions were posed – for example; 'Do you always follow instructions for taking rhinitis medication?'

Results

One thousand two hundred patients were approached to participate between October 2002 and September 2003. All patients were employed and had medical insurance. 1181 patients (521 male) ranging in age from 5 – 67 years (mean 32 years, SD 15.12) completed the questionnaire and returned the survey. Parents of children were asked to complete the questionnaire on behalf of children unable to do so. The number of 'proxy' responses from children was less

Table 3. Triggering factors (n=1181) (%).

Factor	Not at all	Very little	Moderately	Quite a lot	A great deal
Smoky atmosphere	84 (7.1)	118 (10.0)	228 (19.3)	280 (23.7)	327 (27.7)
Air pollution	49 (4.2)	107 (9.1)	255 (21.6)	347 (29.4)	282 (23.9)
Changes in weather	72 (6.1)	112 (9.5)	224 (19.0)	319 (27.0)	322 (27.3)
Pets	212 (18.0)	198 (16.8)	205 (17.4)	166 (14.1)	176 (14.9)
Pollen	72 (6.1)	101 (8.6)	172 (14.6)	318 (26.9)	341 (28.9)
Food	373 (31.6)	198 (16.8)	191 (16.2)	82 (6.9)	71 (6.0)
Emotional upset	370 (31.3)	179 (15.2)	179 (15.2)	112 (9.5)	81 (6.9)

NB: Some responses missing hence totals not 100%

than 20. This was a response rate of 98%. One third (34%) of questionnaires were returned from GPs, one third (31.5%) from pharmacies, and one third (34.5%) from ENT surgeons. There was no significant difference in response rate between these groups.

Table 1 documents the response of individuals to specific questions and their frequency. Nasal congestion is identified as a common and frequent problem, while seasonality of symptoms was uncommon.

Symptoms affected sleep in 76.6% of sufferers, and for at least a third this was every night (Table 2). Over one thousand respondents felt miserable due to allergic rhinitis (85.2%).

Associated conditions of sinusitis, asthma and eczema were reported frequently. The description of headaches around the nose, cheeks and/or forehead was identified as 'sinus-related headaches' in 76.2% of patients at least occasionally. Three-hundred-and-six patients (25.9%) had symptoms more than once a week, 226 (19.1%) had symptoms more than once a month, and only 135 (11.4%) never had sinus symptoms. In terms of symptoms and a possible previous doctor-diagnosis of asthma, 58.3% of respondents identified a history of asthma (coughing, wheezing and chest tightness), and 46.0% a past history of present or past eczema (itchy skin and rash).

Table 3 reflects the results of questions on triggering/exacerbating factors and their frequency. Pollen, a smokey atmosphere, air pollution and changes in weather were frequent exacerbating factors. Pet exposure was not considered a major factor.

Sixty-three percent indicated that they always followed instructions for taking medication. Reasons given for non-adherence are documented in Table 4. Table 5 attempts to document patient preference for medication.

Finally, the responses to questions about perceived concerns around having, and being treated for, allergic rhinitis are documented in Table 6. Again, a variety of responses are noted.

Table 4. Reasons for non-adherence (n=1181) (%).

Forget to take my medicines	351 (29.7)
Worry about side effects	551 (46.7)
Do not like the method	90 (7.6)
Take what I need	693 (58.7)
Taking medicine is admitting defeat	104 (8.8)
Cannot afford medicine	271 (23.0)
Stop taking medicine when better	737 (62.4)

Table 5. Medication preference (n=1181) (%).

Route	
Nose spray	449 (40.5)
Tablets	614 (55.4)
Both	45 (4.1)

Table 6. Concerns about rhinitis (n=1181) (%)

It may last life-long	898 (76.0)
Effects of the medicine	686 (58.1)
Passing rhinitis on to children	491 (41.6)
Feeling self-conscious	602 (51.0)
Social activities restricted	627 (53.1)

Discussion

This study has a number of significant limitations. Firstly, the

questionnaire has not been validated nor translated into multiple languages. The quality of life questionnaire developed by Juniper[9] would be a useful follow-up tool. Secondly, the questionnaire is also not specific to a quality of life study, but is an attempt to document multiple concerns of South Africans with allergic rhinitis.

This study is part of an ongoing survey of health needs of South Africans with allergic diseases, since these conditions often are considered low priority when compared to more serious infectious diseases.

Allergic rhinitis in South Africa is a common problem and is most often a persistent disease.[10-12] This is borne out by this study in which patients note seasonality of symptoms in only 10.9% – 12.9% of cases. Persistent disease may contribute to symptom severity and quality of life impairment. The ISAAC Study conducted in 1998 revealed a prevalence of allergic rhinitis of 16% in Cape Town school children.[12] This prevalence has increased in recent surveys.[13]

This study is important in its documentation of the problems that may be experienced by patients with allergic rhinitis. Almost half of the patients in South Africa have symptoms at least once a week, and over one third have sleep disruption every night due to allergic rhinitis. The persistence of allergic rhinitis in South Africa is due, at least in part, to the climate of the country.[14] It is not surprising, therefore, that pollen is identified as a trigger factor in at least 70.4% of respondents. Using the two broad questions of sleep and 'feeling miserable' it appears that allergic rhinitis significantly affects quality of life. Despite the lack of specificity of these questions for this condition it should be remembered that these individuals identify these as problems as a consequence of their disease. This fact needs to be borne in mind by clinicians treating patients with allergic rhinitis. Bousquet *et al* reported that more than 80% of patients had impaired daily activities if they had moderate or severe allergic rhinitis, and even 40% of patients with mild disease report impairment.[1]

This study also documents the reasons for non-adherence to therapy and suggests that the phenomenon of non-adherence may, as with asthma, have a differential diagnosis. Not all patients fail to adhere to their therapy for a single reason and this must be borne in mind by clinicians treating such patients. This may provide education bodies with the tools to sort out this complex problem and permit the development of questionnaires that attempt to document non-adherence in a non-punitive manner and permit patients to indicate their concerns to busy doctors.

The survey also highlights the individual preference for route of therapy administration – and with the present availability of anti-inflammatory oral anti-histamines, careful patient selection and understanding of guidelines[15] is mandatory. One size definitely does not fit all in terms of treating allergic rhinitis. Patients have many concerns about allergic rhinitis and clearly there is an opportunity now to address these issues – including the education of medical personnel, as well as education and support for patients. Ultimately, the doctor-patient interaction needs to be strengthened in order for the disease not to impact negatively on quality of life.

The finding that 63.1% of patients indicated that they always followed instructions regarding taking rhinitis medication is surprising. This may reflect the sampled group (those attending medical care). Not surprisingly, a range of responses is noted with regard to reasons for non-adherence. The denominator for non-adherence is left as the study total, since some individuals clearly indicated total adherence in one question but still answered specific questions on non-adherence.

What is particularly worrying about this survey is the symptom frequency and quality of life impairment reported by the respondents who identify themselves as having allergic rhinitis. Since allergic rhinitis is, in the main, a doctor-diagnosed condition, this would suggest a significant problem with inappropriate, insufficient or incorrect therapy. Another possibility is, of course, non-adherence to therapy for a chronic condition. Either scenario suggests a role for better doctor-patient interaction regarding the therapy of this condition. Both patient and medical intervention, through education, are urgently required.

Furthermore, this study suggests that education on diagnosis and pharmacological treatment alone are insufficient to reduce the burden of allergic rhinitis. Treatment (in the broadest sense) should be instituted to reverse the effects of allergic rhinitis, and the selection of medication is of critical importance since non-adherence and poor patient understanding may detract from a successful outcome.

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Conflict of interest declaration

The authors declare that they have no conflict of interest in connection with this study.

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ORIGINAL RESEARCH

Perceptions, impact and management of asthma in South Africa: a patient questionnaire study

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Abstract

Introduction: A number of studies from around the world have indicated that asthma morbidity is still unacceptably high. In the AIRE study over one-third of children and half of the adults reported daytime symptoms at least once a week. This study was conducted to understand the impact (including the impact on health-related quality of life) of asthma on South African asthmatics.

Materials and methods: General Practitioners (GPs) and pharmacists in South Africa were randomly identified from the Medical Association database. These individuals were approached and asked to recruit asthmatic patients to complete a questionnaire. The questionnaire inquired about symptoms, quality of life, complications, trigger factors, associated allergic conditions, medication used, medication preference, medication adherence and concerns about the condition.

Results: 3347 respondents returned their demographic data but only 710 met the criteria for analysis, ie. had asthma and were presently on controller medication. Symptom analysis revealed that 21.4% of respondents were coughing on most days, 25.6% were wheezing on most days, and 22.8% were experiencing night-time symptoms on most days. Symptoms were exacerbated by exercise in 56.9%, while nocturnal wakening due to asthma occurred in 36.9% more than four times per week. Only 35.1% of respondents had not missed school or work in the preceding year. 45.4% of individuals worry about side effects of asthma therapy.

Conclusion: This study indicates that there is under-treatment, inappropriate treatment and/or lack of patient education for asthma patients in South Africa. The data support the notion that poor therapy and/or poor patient adherence has an enormous impact on the health-related quality of life of South Africa's asthmatics.

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Keywords Asthma

See Appendix A at www.thepcrj.org for Questionnaire for asthma sufferers

Introduction

Asthma is one of the commonest chronic diseases, affecting at least 1 in 10 people. It knows no prejudice, affecting people from all social, cultural and ethnic backgrounds – unlike tuberculosis, which one would expect to encounter in less privileged societies, and coronary artery disease, which is a disease of affluence. Therefore, no matter where the health-care giver (ie. doctor, nurse or pharmacist) practises he or she will see patients with asthma every day. This interaction with asthmatic patients is often limited – even in a medical setting – to the medical or clinical effects, and treatment, of the disease. These are very well known. Less well known, and certainly seldom discussed, are the quality of life, social, and psychological consequences of asthma as a chronic illness.

Some of these issues were highlighted in an important study from the UK in 1992; known as the Lifestyle Study,[1] it

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was one of the first large studies to focus on quality of life, which has now become an important concept in the assessment of chronic illnesses. The Lifestyle Study revealed a significant impact of asthma (even so-called "treated" asthma) on the lives of individuals with the condition. Further asthma-related quality of life studies and assessments of asthma control followed.[2-5] They reflect a dismal picture of asthma control around the world.[6] Such social or psychological impact goes beyond the disease itself. Poor sleep will produce a tired child who is unable to concentrate in class; this, in addition to school absence, has a dramatic impact on the academic potential of children with asthma.[7] Two further UK studies on asthma-related school absences showed that 60% of children had taken days off due to episodes of wheeze in the past year.[8,9] In their study of 284 children, Anderson and colleagues[8] reported that in the 30 (12%) most severely affected children, each child lost, on average, 30 days schooling each year – giving a total of 900 days of schooling missed. The emotional impact of asthma on the child and family were likewise considerable, with fear and embarrassment common emotions when experiencing an attack. These and other emotional effects have a direct bearing on the family of the asthmatic, due to limited activity and tensions and the eventual impact on other aspects of quality of life.

In addition to these consequences of asthma, a number of studies from around the world have indicated that asthma morbidity is still unacceptably high. The Asthma Insights and Reality in Europe (AIRE) survey assessed the level of asthma control, among current asthmatics in Western Europe, from the patient's perspective.[2] Over one-third of children and half of the adults reported daytime symptoms at least once a week. Furthermore, 28.0% of children and 30.5% of adults experienced asthma-related sleep disturbances at least once a week. Patient perception of asthma control did not match symptom severity, since approximately 50% of those reporting severe persistent symptoms considered their asthma to be completely or well controlled. In addition, it should be remembered that this social cost of asthma, or impact on health-related quality of life, will eventually have a direct monetary cost, adding to the cost of medication and consultations. Subsequent and recent studies have revealed that between 49%[10] and 53%[11] of asthmatics in Europe and Canada, respectively, have uncontrolled asthma.

The aim of this study, therefore, was to understand the impact (including the health-related quality of life impact) of asthma on South African asthmatics, following documentation of these parameters in South Africa's rural asthma patients.[12] There is a need to understand the complexities of asthma control in this country and to determine the burden of asthma morbidity.

Materials and methods

Questionnaire (see Appendix A at www.thepcrj.org)

A questionnaire, appropriate to South Africa, was compiled and subjected to pilot testing amongst a group of patients attending the authors' allergy clinics and practices. A list of 100 possible questions was reduced to the current questionnaire after discussion between a group of 25 asthmatics, 10 doctors and 10 pharmacists. Questions were retained if more than 80% of subjects felt the question was relevant, understandable and meaningful. In addition, the question responses had to match objective assessment of asthma control and medication usage in the patients. The pilot study revealed that the language was understandable by all patients (including those with limited formal education and patients from different racial groups) and the question results correlated well with objective observer assessment of asthma control. The questionnaire (see Appendix A at www.thepcrj.org) inquired about symptoms, quality of life, complications, trigger factors, associated allergic conditions, medication used, medication preference, medication adherence and concerns about the condition. Respondents were asked about perceived concerns around having, and being treated for, asthma.

Patient recruitment

General Practitioners (GPs) and pharmacists were randomly identified from the South African Medical Association database and were approached to recruit patients. The study was conducted between October 2002 and October 2004. Twenty of each group were identified in each of five major centres (Johannesburg, Pretoria, Durban, Cape Town and Bloemfontein). Each site was selected by a random number generator of practice numbers. The GPs and pharmacists invited patients, whom they believed had asthma, to complete the questionnaire. No attempt was made to define asthma or asthma severity in these patients. The questionnaire was entitled 'Questionnaire for asthma sufferers'. No attempt was made to select specific patients of disease type or severity. The survey was, however, targeted to patients and was not a random population sample. All respondents completed written informed consent, and ethics approval (from the Medicines Control Council South Africa) was obtained for the study. Despite a large number of responses to the survey, only asthmatic patients presently on controller medication were analysed.

Results

3347 patients (2340 female) ranging in age from 5 – 67 years (mean 32 years) completed the questionnaire and returned the survey. Parents of children were asked to complete the questionnaire on behalf of children unable to do so. The number of 'proxy' responses was less than 50. There was a

Table 1. Asthma symptom frequency amongst respondents [n (number out of 710), %].

Symptom	Every day		Most days		More than once a week		More than once a month		Never		Not answered	
Coughing	135	19.0	152	21.4	121	17.0	160	22.5	60	8.5	82	11.6
Wheezing	134	18.9	182	25.6	148	20.9	142	20.0	43	6.1	61	8.6
Night-time symptoms	159	22.4	162	22.8	124	17.5	159	22.4	45	6.3	61	8.6

Table 2. Asthma attacks per month [n, %].

	0-2		2-4		More than 4	
At night	218	30.7	136	19.2	262	36.9
After exercise / activity	148	20.9	118	16.6	284	40.0

response rate of 83%. Two thirds (69%) of questionnaires were returned from GPs. There was no significant difference in response rate between these groups.

3347 respondents returned their demographic data but only 710 met the criteria for analysis, ie. had asthma and were presently on controller medication. There was a fairly uniform spread across the provinces of South Africa. There were no particular trends revealed by sex or age differences. Although the individual drugs used by these patients were noted, no relationship between type, dose or duration, and the measures of asthma control questioned, was seen. Many patients were not able to recall their exact drug dosage.

Symptom analysis revealed that most patients still had symptoms of asthma; 21.4% were coughing on most days, 25.6% were wheezing on most days, and 22.8% were experiencing night-time symptoms on most days (see Table 1). Symptoms were exacerbated by exercise in 56.9% and by sport in 60.6%, probably reflecting similar patient groups. Daily activities caused symptom exacerbation in 46.2% (with 6.5% not answering this question). Nocturnal wakening due to asthma occurred frequently with 22.4% of respondents having nocturnal symptoms every day and 31.9% of respondents being woken more than four times per month due to asthma attacks (see Table 2).

Trigger factors for exacerbations and "attacks" are listed by the frequency with which they produced symptoms, in Table 3. 23.8% of respondents believed that air pollution caused symptoms every day, 28.3% on most days, and 4.4% seldom/never. Food as a trigger factor was generally reported as being uncommon, with respondents claiming a relationship (at most) more than once a month but less than once a week in 17.5%; this was the least common trigger factor reported, with a prevalence in the range of that for "emotional upset".

The vast majority of patients had associated "allergic" diseases – hay fever in 81.4%, blocked nose in 62.3% and eczema in 44.9%. 16.9% of responders did not answer the question on eczema, possibly because they didn't understand the condition.

With regard to quality of life, certain pertinent responses were received. Table 4 demonstrates the number of patients missing school or work due to disease, and the length of time off. Only 35.1% of respondents had not missed school or work in the preceding year; 26.3% had missed 1-3 days while

Table 3. Frequency with which common exposures result in symptom exacerbations [n, %].

Symptom	Every day		Most days		More than once a week		More than once a month		Never	
Smoky atmosphere	205	28.9	184	25.9	134	18.9	73	10.3	41	5.8
Air pollution	169	23.8	201	28.3	161	22.7	58	8.2	31	4.4
Weather	204	28.7	219	30.9	132	18.6	67	9.4	64	9.0
Pets	80	11.3	76	10.7	132	18.6	104	14.7	160	22.5
Pollen	116	16.3	148	20.9	118	16.6	100	14.1	81	11.4
Food	45	6.3	53	7.5%	121	17.0	124	17.5	203	28.6
Emotional upset	146	20.6	130	18.3	124	17.5	118	16.6	94	13.2

Table 4. Number of work and school days lost in the last year as a result of asthma [n, %].

No time	128	35.1
1 - 3 days off	96	26.3
4 - 7 days off	64	4.5
1 - 2 weeks off	39	10.7
2 - 4 weeks off	28	7.7
More than 5 weeks	3	0.8
Not worked - asthma	7	1.9

10.7% had missed 1-2 weeks. 15.9% of responders had been admitted to hospital in the previous year. Patients reported a doctor call-out, visit to the doctor, or visit to casualty, in 13.9%, 27.3% and 24.8% of cases, respectively.

With regard to the use of prescribed inhaled medication, a number of general questions were asked. Patient-listed reasons for non-adherence and concern about taking medication for asthma are shown in Table 5. 45.4% of individuals were worried about the side effects of asthma therapy and 321 (45.2%) of respondents admitted to stopping controller medication when feeling better.

Finally, the group was asked about home use of peak flow meters; 35.9% used one at home, and another 14.4% used their meter together with a diary card.

Table 5. Patient-listed reasons for non-adherence and concern about taking medication for asthma [n, %].

	n	%
I sometimes forget to take my medicine	202	28.5
I sometimes forget how many doses I have taken	98	13.8
I worry about side effects of the medicine	322	45.4
I have difficulty using my inhaler	46	6.5
I am not sure I am getting the right amount of medicine	132	18.6
I don't know how to take my medicine properly	28	3.9
I do not like the method of taking my medicine	59	8.3
I take what I think I know I need	300	42.3
I feel that taking medicine is admitting defeat	73	10.3
I am embarrassed to take my medicine in front of other people	199	28.0
I cannot afford to pay for my medicine	203	28.6
I sometimes stop taking my medicine when I feel better	321	45.2
I prefer not to take my my medicine unless I feel it is absolutely necessary	282	39.7
I worry that feel I might be taking too much medicine	181	25.5
I am saving my medicine for bad attacks	122	17.2

Discussion

This study has a number of significant limitations. Firstly, the questionnaire has not been validated nor translated into multiple languages. The complexity of some of the questions – such as that directed at symptom causation, with a matrix of symptom frequency and patient-perceived causation of symptoms (see Appendix A at www.thepcrj.org) – may have posed problems for patients in terms of their understanding and responding. For this question specifically, 73 patients (10.3%) did not answer the question on whether or not a smokey atmosphere caused symptoms. Secondly, the questionnaire is not specifically one relating to a quality of life study but is an attempt to document asthma control in South Africans. Employing other validated, international quality of life questionnaires, would be a useful follow-up tool. Thirdly, some questions were deliberately not defined in order to assess what patients understand, perceive, and do, independent of the medical label. One such example is the definition of an 'asthma attack'. Not all respondents answered every question and some results reflect missing data points – hence not all totals add up to 100%. Clearly the label of 'asthma' should be investigated and defined; however, this study reflects the real-world experience of patients who are labelled 'asthmatic' and then left to experience ongoing morbidity, without either review of the diagnosis or attempts at education. Finally, this study is part of an ongoing survey of health needs of South Africans with allergic diseases; these conditions often take a back seat to more serious infectious diseases.

This study does not stratify respondents by socio-economic status and the responses may mask trends in certain populations. However, the source of data from the questionnaires was standardised – i.e. the pharmacies and doctors – and therefore it is unlikely that large "unusual" groups would skew the findings. The number of individuals who were labelled as asthmatic by their doctor who thought they had asthma but were not using anti-inflammatory therapy raises a concern. Clearly asthma diagnosis may not always be correct (and this fact was not tested nor investigated) and some of these patients may have mild persistent asthma by definition. However, the large number and significant level of ongoing symptoms in those receiving controller therapy suggests that possible under-management of asthma is a major problem.

The decision not to report drug type and dosage and to compare it to symptom control is based on two reasons; firstly, many patients could not recall their drug dosage, and secondly the drug and dosage prescribed or taken is clearly inadequate.

The primary finding of this study is the number of patients with active symptoms despite diagnosis and therapy – 21.4% coughing on most days, 25.6% wheezing on most days, and 22.8% experiencing night-time symptoms on most days. For this reason, and also given the excessively high number of patients who have symptoms triggered by either exercise or daily activity, there is a clear case to be made for there being under-treatment, inappropriate treatment, and/or lack of patient education in the asthmatic population studied. Most asthma guidelines state that a normal and physically active life is a goal of asthma management.[13-15]

A significant number of patients are missing school or work due to asthma. The response rate of 51% for this question reflects a large number of women who are not formally employed. As a gross estimate of quality of life, the rate of hospital admission and crisis control visits were recorded; there was an unacceptably high rate of asthma exacerbations requiring emergency care (though it is encouraging to note that peak flow usage is being introduced.) The rate of symptom exacerbation, as well as the rate of acute attacks, crisis consultations with the doctor, and/or hospitalisation rates, not only supports the notion of poor therapy – or possibly poor adherence – but also suggests an enormous impact on the health-related quality of life of South Africa's asthmatics. This cannot be solely due to poor adherence; it strongly suggests a failure on behalf of the medical fraternity to educate patients completely.

There are some interesting reflections on the well-known asthma triggers. Common factors included triggers such as smokey atmosphere, weather change, pets and environmental pollution. Food was not identified as a major trigger factor, thereby supporting a common belief.

When comparing this survey to other studies, particularly the study of asthma control in rural South Africa,[12] similar findings are seen. In that group of 35 asthmatics, 19 (31%) had wheeze at least once a week, 26 (42%) cough at least once a week and 33 (53%) were being woken by symptoms at least once a week. This latter figure of 53% is similar to the figure in this study of 62.7%. The number of South African asthmatics in this study who do report complete asthma control is remarkably similar to the average of 6% quoted for world surveys.[2-6] The Lifestyle study[1] noted that 60% of children had taken days off school due to episodes of wheeze in the past year. Our study demonstrates a similar figure (64.9%) for both children and adults absent from daily activities due to asthma. As in the study by Anderson and colleagues,[8] days lost translate into significant costs to educational needs and to the economy.

Conclusion

The limitations of this study aside, it seems obvious that the need for asthma control has been under-recognised and poorly attended to in South Africa. The National Asthma Education Programme of South Africa now has a clear mandate to upgrade education of both doctors and patients. Luckily there are moves afoot in this arena and the mere publication of asthma guidelines is now recognised as being insufficient to address this problem.

Conflict of interest declaration

No conflict of interest to declare.

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Appendix 1. The Asthma CARE Programme

Date of Birth ____ ____ ____ **Patient Identifying Number** _____
Day Month Year

Please complete this questionnaire and return it by the date indicated in the newsletter to:
The Asthma CARE Programme, Private Bag X6, Fairland.
The answers you give will be kept fully confidential. This will help us to send you relevant information specifically designed to help your condition as you describe it. Thank you.

QUESTIONNAIRE FOR ASTHMA SUFFERERS

1. Which of the following asthma symptoms do you experience, and how often?

Symptom	Everyday	Most days	More than once a week	Never
Coughing				
Wheezing (noisy breathing)				
Night-time symptoms (experiencing coughing, wheezing or tightness of chest in bed)				

2. When and how often do you experience asthma attacks per month?

When	0-2 times	3-4 times	More than 4 times
At night			
After exercise / activity			

3. Have asthma symptoms prevented you from doing activities such as:

a. Exercise Yes [ ] No [ ]
b. Sports Yes [ ] No [ ]
c. Daily activities (e.g.climbing stairs] Yes [ ] No [ ]

4. Do you feel self-conscious about your asthma? Yes [ ] No [ ]

5. How often has your asthma prevented you from working or caused you to take time off school (Total in the past 12 months)

Lost no time off work / school	
Lost 1 – 3 days off work / school	
Lost 4 – 7 days off work / school	
Lost 1 – 2 weeks off work / school	
Lost 2 – 4 weeks off work / school	
Lost more than 5 weeks off work / school	
I have not worked because of asthma	

6. How many times in the past year have you .....

Been admitted to hospital with a bad attack of asthma	
Called a GP to your home because of back attack of asthma	
Attended your GP in his/her rooms because of your asthma	
Attended a hospital out-patient clinic because of your asthma	

Continued ...

Appendix 1. The Asthma CARE Programme continued

7. To what extent would you say your asthma is affected by each of the following factors? (PLEASE TICK ONLY ONE BLOCK FOR EACH FACTOR)

Factor	Not at all	Very little	Moderately	Quite a lot	A great deal
Smoky atmosphere (e.g. in a pub)					
Being in an area affected by air pollution					
Changes in weather (e.g. cold air)					
Pets					
Pollen					
Food					
Emotional upset					
OTHER: Please specify					

8. Do you suffer from any of the following?

a. Hayfever (symptoms include itchy eyes, runny nose, sneezing) Yes [ ] No [ ]
b. Regular blocked nose Yes [ ] No [ ]
c. Eczema (symptoms include itchy skin and rash) Yes [ ] No [ ]

9. Which medicines are you currently taking for asthma?

Name of medicine (brand name on pack)	Strength of medicine (shown on pack, e.g. 20 mcg, 100 mcg)	Number of puffs/tablets per day (e.g. 2,3)	For how long have you been using it? (e.g. 6 months, 1 year)
Airomir			
Atrovent			
Becloforte			
Becotide			
Becotide			
Clenil			
Duovent			
Flixotide			
Floradil			
Inflammide			
Lomudal			
Pulmicort			
Salbutin			
Seretide			
Symbicord			
Theo-Dur			
Uni-Dur			
Uniphyl			
Venteze			
Ventolin			
Zaditen			
OTHER: Please specify			

Continued ...

Appendix 1. The Asthma CARE Programme continued

10. Do you always follow the exact instructions for taking asthma medication? Yes [ ] No [ ]

11. Please tick whichever of the following statements you agree with:

I sometimes forget to take my medicine	
I sometimes forget how many doses I have taken	
I worry about side effects of the medicine	
I have difficulty using my inhaler	
I am not sure that I am getting the right amount of medicine	
I do not know how to take my medicine properly	
I do not like the method of taking my medicine	
I feel that taking medicine is admitting defeat	
I am embarrassed to take my medicine in front of other people	
I cannot afford to pay for my medicine	
I sometimes stop taking my medicine when I feel better	
I prefer not to take my medicine unless I feel it is absolutely necessary	
I worry that I might be taking too much medicine	
I am saving my medicine for bad attacks	

12. Who administers your medicine?

Yourself	
Your father / mother	
Other relatives	
Your teacher	
Other	

13. What concerns do you have about asthma?

	Yes	No
That it may last life-long		
That you may not outgrow your asthma		
The choice of devices		
The effects of the medicines		
Passing asthma on to your children		

14. Have you ever used .....

a. A peak flow meter Yes [ ] No [ ]
b. A peak flow diary card Yes [ ] No [ ]

Thank you for completing this questionnaire

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Comparison of doctor and patient assessments of asthma control

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KEYWORDS
Asthma;
Control;
ACT score

Summary
Introduction: The objective of asthma management is to control the condition. However, world-wide surveys reveal that only 5% of asthmatics are well controlled. One reason for this phenomenon is the fact that patients and doctors consistently over-estimate control. This study compared patient and doctor assessment of asthma control.
Methods: A random sample of asthmatics was identified by practitioners in South Africa. Patients completed an Asthma Control Test (ACT) and provided a list of medications currently being taken. The doctor also provided an assessment of control which was summarised into the categories - 'not controlled' and 'controlled' and listed all medications prescribed.
Results: The mean ACT score was 12.8 where doctors assessed the patients as being 'not controlled' and 20.7 where doctors assessed the patients as being 'controlled'. Half of the patients classified themselves as being 'not controlled' (ACT score <20, category 1), while doctors classified only 33% of patients as being 'not controlled'. Although only 7% of patients disagreed with the doctor's classification of 'not controlled', 29% disagreed with the doctor's assessment of being 'controlled'. There was a significant difference in ACT score between the sexes ($p < 0.0001$). Most therapeutic interventions (with the exception of combination products [ICS + LABA]) performed poorly with regard to level of control.
Conclusion: This study suggests that asthma still appears to be relatively poorly controlled in South Africa, although levels of patient control appear to have improved compared to previous surveys, and confirms that physicians and patients differ in their assessments of asthma control.

Introduction

Asthma is a common disease,[1] with considerable morbidity and appreciable mortality. The objective of management is to control the condition in order to enable the sufferer to live a life free from symptoms and exacerbations.[2,3]

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Some of the issues were highlighted in an important study in Britain in 1992. That study, known as the Lifestyle Study,[4] was one of the first large studies to focus on quality of life, which has now become an important concept in chronic illnesses. The Lifestyle Study revealed the significant impact of asthma (even so called ''treated'' asthma) on the lives of individuals with the condition. Further asthma-related quality of life studies and assessments of asthma control have been numerous.[5–9] They reflect a dismal picture of asthma control around the world with only 5% of asthmatics meeting the objective of control.[10] Reasons for this phenomenon are many but include the fact that ''patients and doctors consistently under-estimate severity and control''[10].

The Asthma Insights and Reality in Europe (AIRE) survey[5] assessed the level of asthma control, among current asthmatics in Western Europe, from the patient's perspective. Over one-third of children and half of the adults reported daytime symptoms at least once a week. Furthermore 28% of children and 30.5% of adults experienced asthma-related sleep disturbances at least once a week. Patient perception of asthma control did not match their symptoms severity, as approximately 50% of those reporting severe persistent symptoms considered their asthma to be completely or well controlled. Subsequent and recent studies have revealed that uncontrolled asthma occurred in between 49%[11] and 53%[12] of asthmatics in Europe and Canada respectively.

Many studies of this nature have suggested that patients and their doctors disagree as to the level of control of asthma with physicians consistently over-estimating control.[13] This has led to strategies relying on patient assessments of control in guiding therapy adjustments. In addition, the social cost of asthma and impact on health-related quality of life will have a direct monetary cost, adding to the cost of medication and consultations.

Many methods for assessing asthma control have been suggested (including patient questionnaires, spirometry, measures of airway hyper-responsiveness and exhaled nitric oxide), however, for the purposes of this study the 'gold standard' for assessing asthma control used was the ACT test. This test has been validated for this purpose.[14] The ACT was then compared to clinicians assessment, as would be done in the real world situation. Doctor assessment in determining asthma control is an imprecise science and despite recommendations in asthma guidelines there is little clear evidence for which questions or combination of questions actually determine control. There is evidence that a standardised questionnaire is better than conventional history taking. The GOAL Study authors attempted to resolve this problem with the Asthma Control Questionnaire.[15] In this study the authors used patient's symptoms and PEFR over time to assess control and found reasonable robust cut-points. Also quite interestingly, the positive and negative predictive values for assessment using the various cut-points did not change significantly when FEV_1 was omitted. This suggests that spirometry does not add significantly in determining asthma control.[15]

This study addresses comparisons between patient and doctor reported asthma control in South Africa in general, and with respect to different medical practice types (private versus public and generalist versus specialist). Documentation of the relationship between the level of control and medication being used was also noted.

The aim of this study was to compare the relative efficacy of patient perception obtained by means of a standardised questionnaire, the ACT, with that of the doctor's assessment of asthma control.

Methods

A random sample of asthmatics was identified by medical practitioners in multiple regions of South Africa. Doctors participating were selected from the Medical Association Data Base. Attempts were made to design the study so as to represent most medical practice types. This was performed in order to obtain data for patients from public and private medical facilities, and to include a range of doctor qualifications: Urban General Practitioner (GPU), Community Health Clinic (CHC), Academic Hospital Respiratory Clinic (RCH) and Specialist Private Pulmonologist (SPP). Each patient selected was a known asthmatic who was being seen for a routine follow-up visit. Patients presenting with acute asthma were excluded.

The study was conducted prospectively and both patients and doctors were informed that they were taking part in a clinical study. Patients completed a self-evaluation rating (ACT) as a measure of their level of asthma control and provided a list of medications currently being taken. The doctor also provided a blinded assessment of the same patient's level of control using the categories — 'not well controlled', 'well controlled' and 'totally controlled' and listed all medications prescribed. The categories 'well controlled' and 'totally controlled' were combined for ease of assessment. These categories will be referred to as 'not controlled' and 'controlled'. Doctors were not guided in the way they assessed control. Each practitioner was instructed to use his usual tools of assessment. These may have included history taking, examination, spirometry and/or measures of airway inflammation. The gender of the patient, their city of residence, the type of practice and the area in which the site fell, were also recorded.

The ACT score was analysed and in addition was coded into three sets of categories as described in the original study[14]: Category 1 (ACT score 1—19), Category 2 (ACT score 20—24) and Category 3 (ACT score 25). This facilitated comparison of the patient self-categorisation with the doctor's classification of 'not well controlled', 'well controlled' and 'totally controlled'. For ease of interpretation this paper generally discusses the analysis with Categories 2 and 3 combined as total asthma control may reflect too narrow an assessment band. Good (well or totally controlled) control may be an acceptable level of asthma control.

Medications listed were classified into standard groups.

Ethics Committee consent was obtained for this study and patient informed consent was obtained.

Statistical methodology

Association between the patient's self-assessed ACT score, and the doctor's assessment of control ('not well controlled', 'well controlled', and 'totally controlled') was tested using the Kruskal—Wallis analysis of variance test. Where a significant difference was found ($p < 0.05$), follow-

Table 1a Number of observations for patient assessed asthma control (ACT) (percentage) compared to doctor assessed level of control.

Doctor assessed control	Mean/Median[a]	ACT score			Total
		0–19	20–24	25	
Not controlled	12.8/12	391(92.9)	27(6.4)	3(0.7)	421
Well controlled	19.9/20	216(36.3)	357(60)	22(3.7)	595
Total control	22.6/24	34(13.1)	142(54.6)	84(32.3)	260
Total		641	526	89	1276

ACT = asthma control test.
[a] Mean/median reflects the mean/median of the ACT scores in the three groups of doctor assessed control (Not controlled, Well controlled and Total Control).

Table 1b Number of observations for patient assessed asthma control (ACT) (percentage) compared to doctor assessed level of control, combining well and total control.

Doctor assessed control	Mean/Median[a]	ACT score		Total
		0–19	20–25	
Not controlled	12.8/12	391(92.9)	30(7.1)	421
Controlled (well or total)	20.7/21	250(29.2)	605(70.8)	595
Total		641	635	1276

ACT = asthma control test.
[a] Mean/median reflects the mean/median of the ACT scores in the two groups of doctor assessed control (Not controlled and Controlled).

up Mann–Whitney *U* tests were performed, at a Bonferroni adjusted significance level.

Comparison of the measures of control and the grouped ACT categories was performed using a $\chi 2$ contingency table test and Cohen's Kappa.

The relationship between the patient and doctors assessment as to the level of control against demographic variables and medication types was determined using logistic regression. The demographic variables investigated were the combination of practice type, city of residence, and gender. Treatment types investigated were the type of medication, and, where a combined medication was prescribed, a test for differences between Salmeterol/Fluticasone and Formoterol/Budesonide. All interactions between these variables were investigated.

All analyses were performed using SPSS®.[16]

Results

Comparison of patient recorded asthma control (ACT) with doctor assessment of control

Significant association existed between the full ACT score and the doctor's assessment of control, with the median ACT scores increasing over the three categories of doctor assessments (overall and pair-wise tests, $p < 0.0001$). The mean ACT score was 12.8 where doctors assessed the patients as being 'not controlled' and 19.9 where doctors assessed the patients as being 'well controlled' (Table 1a). The mean ACT score was 20.7 when the ACT scores for 'well controlled' and 'total control' were added together as 'controlled' (Table 1b). Half of the patients classified themselves as being 'not controlled' (ACT score <20, category 1), while doctors classified only 33% of patients as being 'not controlled'. Although only 7% of patients disagreed with the doctor's classification of 'not controlled', 29.2% disagreed with the doctor's assessment of being 'controlled'.

Patient (ACT) and doctor assessed control by practice type, gender and medication use (logistic regression)

Assessments of asthma control (both by patient (ACT categories) and doctors) were significantly different between the practice types ($p < 0.0001$ for both patient and doctor). Specialist Private Pulmonologists (SPP) demonstrated the highest assessments of control. For those patients at an Academic Hospital Respiratory Clinic (RCH) the odds of being controlled were 0.303 for patient assessments and 0.225 for doctor assessments compared to being controlled if asthma was assessed by a Specialist Private Pulmonologist. There was also a significant gender difference ($p < 0.0001$) for patient assessments but not for doctor assessments ($p = 0.0618$). Median ACT score for females was 18, and for males 20. Overall 59.4% of males assessed their asthma control as being 'controlled' (20 or higher) versus only 43.7% of females. The practice type, gender and medication combinations are shown in Table 2 (patient assessment) and Table 3 (doctor assessment), which give the number of patients in each category, row percentage, *p* value, odds ratio (OR) and 95% confidence interval for the OR.

Table 2 Comparison of patient assessed level of asthma control over the medication groups as recorded by the doctor, after adjusting for practice type and sex (numbers of observations, row percentage, significance, odds ratio and the 95% confidence interval for the odds ratio).

	Patient assessed control (ACT category)					*p*	OR	95% confidence interval	
	1 (<20)	%	2 + 3 (20–25)	%	Total				
Practice						<0.0001			
GPU	69	46.3	80	53.7	149	0.0003	0.545	0.3925	0.7577
CHC	128	74.9	43	25.1	171	0.1808	0.765	0.5169	1.1325
RCH	257	61.0	164	39.0	421	<0.0001	0.303	0.1929	0.4746
SPP	182	35.0	338	65.0	520	–	–	–	–
Sex						<0.0001			
Male	199	40.8	289	59.2	488	<0.0001	1.665	1.3059	2.1232
Female	437	56.5	336	43.5	773	–	–	–	–
Medication group						0.0001			
no ICS	76	55.9	60	44.1	136	0.0002	0.534	0.3841	0.7424
ICS	327	60.1	217	39.9	544	0.0072	0.556	0.3621	0.8527
ICS/LABA separate	89	65.4	47	34.6	136	0.0001	0.389	0.2449	0.6177
Combined ICS/LABA	144	32.4	301	67.6	445	–	–	–	–
Total	636	50.4	625	49.6	1261				

Abbreviations: Community Health Clinic (CHC); Academic Hospital Respiratory Clinic (RCH); Urban General Practitioner (GPU); Specialist Private Pulmonologist (SPP), Inhaled corticosteroid (ICS) (without other drugs except SABA); Long-acting beta-agonist (LABA).

For both patient assessed and doctor assessed levels of control, there was a significant difference between the types of medication ($p < 0.0001$, $p = 0.0001$). For patient assessment (ACT score) the use of combined ICS/LABA was associated with significantly better scores than the other 3 groups (no ICS: $p = 0.0103$, ICS: $p = 0.0004$, separate: $p < 0.0001$) but the scores for the other medication groups did not differ significantly from each other. For doctor assessed control the reported use of combined ICS/LABA was associated with significantly better assessments than ICS/LABA separate ($p = <0.0001$), but did not differ significantly from the other two groups (no ICS: $p = 0.1084$, ICS: $p = 0.0504$). After controlling for the other factors, the odds, (chance of being controlled), for those patients on separate ICS/LABA was 0.34 that of being controlled when on combined ICS/LABA. Alternatively patients were 2.94 times more likely to be controlled if they were on combined ICS/LABA than on separate ICS/LABA, according to the doctors classification.

Table 3 Comparison of doctor assessed level of asthma control over the medication groups as recorded by the doctor, after adjusting for practice type and sex (numbers of observations, row percentage, significance, odds ratio and the 95th confidence interval for the odds ratio).

	Doctor assessed category				Total	*p*	OR	95% confidence interval	
	Not controlled		Controlled						
Practice						<0.0001			
GPU	49	32.9	100	67.1	149	0.0004	0.526	0.3682	0.7521
CHC	98	57.3	73	42.7	171	0.0072	0.558	0.3647	0.8538
RCH	169	40.1	252	59.9	421	<0.0001	0.225	0.1452	0.3497
SPP	103	19.8	417	80.2	520	–	–	–	–
Sex						0.0618			
Male	135	27.7	353	72.3	488	0.0618	1.282	0.9878	1.6631
Female	284	36.7	489	62.3	773	–	–	–	–
Medication group						0.0001			
no ICS	50	36.8	86	63.2	136	0.0573	0.701	0.4856	1.0111
ICS	213	39.2	331	60.8	544	0.1192	0.692	0.4351	1.0996
ICS/LABA separate	70	51.5	66	48.5	136	<0.0001	0.340	0.2115	0.5454
Combined ICS/LABA	86	19.3	359	80.7	445	–	–	–	–
Total	419	33.2	842	66.8	1261				

Abbreviations: Community Health Clinic (CHC); Academic Hospital Respiratory Clinic (RCH); Urban General Practitioner (GPU); Specialist Private Pulmonologist (SPP), Inhaled corticosteroid (ICS); Long-acting beta-agonist (LABA).

Use of ICS/LABA separate was associated with significantly worse assessment of control than ICS ($p = 0.0005$) and no ICS ($p = 0.0079$).

In addition the study could identify the level of agreement between patient and doctor disclosed medication use. Doctors and patients agreed in 91.9% of cases, but disagreed in 8.1% of cases. In addition no significant difference was found between the individual combination agents (fluticasone + salmeterol and budesonide + formoterol) for the ACT categorisation ($p = 0.8399$) or for the doctor assessed rating ($p = 0.3690$).

Discussion

A strength of this study is the relatively large number of patient and doctor pairs studied. This study suggests that asthma still appears to be poorly controlled in South Africa. A significant number of patients (50%) being treated for asthma identified their control, as measured by the ACT, as being 'uncontrolled'. However, this has significantly improved in contrast to a previous survey, where only 6–8% of treated asthmatics were considered to be well controlled.[9] This study also reveals that doctors and patients differ on individual assessments of asthma control. Doctors classified 39% of patients who assessed their own control as ACT category 1 ('not controlled') to be 'well and totally controlled'. This 'overestimation' is, however, well known from previous studies.[13] Chapman and colleagues found very similar disagreements with 59% of patients indicating uncontrolled asthma while physicians regard only 42% of patients as uncontrolled.[13] It should be remembered that because doctors were not guided in the way they assessed control, there is a possibility of classification errors which may influence the results.

Patients on the other hand seldom over-estimated control, in contrast to their doctor's assessment of their control. It is important to repeat this audit to determine whether the patient's knowledge of lack of control leads to a change in medication prescription and management strategies by doctors to achieve better control. This was not addressed in this study.

This study highlights some important issues with respect to level of care for asthmatics as well as therapy selection to achieve control. Specialist Private Pulmonologists appeared to perform better than all other groups of doctors in achieving asthma control in their patients, at least as indicated by patient ACT results.

The level of control can be expected to vary to a great extent between primary care and tertiary care.This finding may however, reflect the specific nature of the population group treated by this group of doctors. A number of confounding variables are possible including medication access and socio–economic factors. This may be especially true of the group of patients attending Academic Hospital Respiratory Clinics, and Community Health Clinics where medication access is limited. Increased consultation with pulmonologists should be made for those patients assessed as being uncontrolled, by themselves or by their general practitioner. This phenomenon should be borne in mind in planning health resources, even in resource-poor settings, if the goal of asthma management is to achieve control.

Secondly the gender discrepancies are interesting. No previous study has identified major differences between sexes with respect to asthma control.[17,18] In this study males appeared to be better controlled than females. Our study was not able to suggest a reason for this.

In general the study suggests that patients generally know what medication they are using. There is a good correlation between patient recall of their medication and that noted by their doctor. This phenomenon may have special relevance to asthma control as understanding should aid in adherence. Measures of adherence were not directly measured in this study but it was noted that the vast majority were prescribed ICS with which they were familiar. Interestingly only patients treated with a combination product (ICS + LABA) have significantly better asthma control. Lack of asthma control, as rated by the doctor, for the combination of ICS/LABA in separate containers is surprising and needs to be explored. Numerous studies have shown that combined ICS and LABA achieve better control.[19–21] Perhaps the lack of use of an ICS/LABA combination in the majority of patient's is a major factor in their lack of control. All other therapeutic combinations performed poorly at the level of asthma control. It should be remembered that this finding, whilst interesting, should ideally be substantiated by randomised clinical trial as the demographic data and severity of asthma of the patient population is not adjusted for.

Actual degree of asthma severity has not been elicited in this study and many overlapping factors may confound attempts to unravel the phenomenon of lack of control. However, it should be remembered that this is a large study of asthma control with many patient groups and practice types (from general practitioners to private pulmonologists) being represented. It is unlikely that only more severe asthmatics are being studied. Therefore, this study highlights an important observation about asthma control that should be noted and digested by all stakeholders in South Africa.

This study suggests one method of determining asthma control, namely ACT score. However what is still unclear is how measurement of asthma control is most effectively performed. Each of the conventional tools for doing this have both their proponents and detractors and evidence for and against reliability and validity.[11,22] Most previous studies have shown that clinician assessment of asthma control, without a specific objective tool perform poorly, and hence the need to find a more sensitive marker of control.[12] This study does not address the issue of verifying the asthma control assessments and the relevance of such assessment in the overall control of patients with asthma.

Conclusion

Asthma remains relatively poorly controlled in South Africa although the level of control has improved in contrast to that previously noted. Control is better achieved by Specialist Private Pulmonologists in contrast to all other practitioner groups. Patients have a different perception of their level of control than their doctor. Inexplicably males appear to be better controlled than females. Those patients on combination therapy of an ICS and LABA are best controlled whilst those not on a LABA in addition to an ICS are less well controlled.

With the recent publication of new asthma guidelines there is a certain degree of optimism that attempting to correct the deficiencies of asthma management of the past may finally be possible. Return to normal life is now the clear goal of asthma treatment.

This study suggests that physicians and patients may be capable of assessing asthma control with the various tools at their disposal but that action on this information to improve control is needed. This study demonstrates that there is an opportunity for intervention by doctors to control asthma better with education remaining a priority.

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Conflict of interest statement

Dr. Michael Greenblatt has participated on medical advisory boards, conducted continuing health education activities and/or industry-sponsored clinical research trials for the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline. Dr Jacky Galpin declares no conflict of interest. Ms Cindy Hill declares no conflict of interest. Dr Charles Feldman has participated on medical advisory boards, conducted continuing health education activities and/or industry-sponsored clinical research trials for the following companies: Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD and Pfizer. Dr Robin Green has participated on medical advisory boards, conducted continuing health education activities and/or industry-sponsored clinical research trials for the following companies: Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD and Pfizer.

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CHEST

Original Research

ASTHMA

Disagreement Among Common Measures of Asthma Control in Children

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Background: **Asthma is a worldwide problem. It cannot be prevented or cured, but it is possible, at least in principle, to control asthma with modern management. Control usually is assessed by history of symptoms, physical examination, and measurement of lung function. A practical problem is that these measures of control may not be in agreement. The aim of this study was to describe agreement among different measures of asthma control in children.**

Methods: **A prospective sequential sample of children aged 4 to 11 years with atopic asthma attending a routine follow-up evaluation were studied. Patients were assessed with the following four steps: (1) fraction of exhaled nitric oxide (FENO), (2) spirometry, (3) Childhood Asthma Control Test (cACT), and (4) conventional clinical assessment by a pediatrician. The outcome for each test was coded as controlled or uncontrolled asthma. Agreement among measures was examined by cross-tabulation and κ statistics.**

Results: **Eighty children were enrolled, and nine were excluded. Mean FENO in pediatrician-judged uncontrolled asthma was double that of controlled asthma (37 parts per billion vs 15 parts per billion, $P < .005$). There was disagreement among measures of control. Spirometric indices revealed some correlation, but of the unrelated comparisons, those that agreed with each other most often (69%) were clinical assessment by the pediatrician and the cACT. Worst agreement was noted for FENO and cACT (49.3%).**

Conclusion: **Overall, different measures to assess control of asthma showed a lack of agreement for all comparisons in this study.** ***CHEST 2013; 143(1):117–122***

Abbreviations: cACT = Childhood Asthma Control Test; $FEF_{25\%-75\%}$ = forced expiratory flow, midexpiratory phase; FENO = fraction of exhaled nitric oxide; PEFR = peak expiratory flow rate; ppb = parts per billion

Asthma is a problem throughout the world, and its prevalence appears to be increasing. Its cause is unknown; therefore, prevention is difficult. With the highly effective medications now available, it is possible, in principle, to control asthma, enabling almost every person with asthma to achieve a life free from symptoms and exacerbations with normal lung function.[1]

Current national and international guidelines advise that asthma be categorized at each patient visit as uncontrolled, partially controlled, or controlled and that it be managed accordingly.[2] A person with controlled asthma has no ongoing symptoms in any situation and seldom needs to use reliever therapy.[2] Categorization of control relies heavily on patient-reported symptoms, but because people with asthma are known to frequently underestimate the severity of their condition,[3] objective ways of corroborating patient history and physician assessment are sought.

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A number of objective methods to assess asthma control have been suggested in asthma guidelines. Use of standardized quality-of-life questionnaires, spirometry, and fraction of exhaled nitric oxide (FENO) are the most frequently used methods. The rationale for the FENO measurement is that because most patients are predominately atopic, the concentration of nitric oxide in exhaled air should mirror the level of asthma control; thus, FENO reflects the level of eosinophilic airway inflammation,[4] which is considered to mediate atopic asthma.[5]

Because asthma is a heterogenous condition with a number of phenotypic expressions, assessment of control in individual children may require asking patients and parents about ongoing symptoms and one or more objective tests to corroborate assessment of controlled or uncontrolled asthma. However, what combination of measures we should use is not clear in current guidelines, and the level of agreement among different measures is conflicting in different studies. The aim of the present study was to describe agreement among different measures of asthma control in children.

MATERIALS AND METHODS

Participants and Setting

Children with chronic asthma attending routine follow-up examinations were enrolled. Inclusion criteria were as follows: known asthma based on recurrent cough or wheezing that responds to a bronchodilator[6] (bronchodilator responsiveness determined by at least 12% reversibility of FEV_1 after administration of an inhaled bronchodilator); aged 4 to 11 years; atopic with at least one positive skin prick test (a panel of Bermuda grass, corn pollen, five-grass mix, mold mix, cat hair epithelium, dog hair dander, house dust mite [*Dermatophagoides pterynissinus*]) (ALK), with atopy manifesting as allergic rhinitis; ability to perform spirometry; and receiving therapy with inhaled corticosteroids for asthma and topical corticosteroids for allergic rhinitis. Children were excluded if they did not meet all inclusion criteria or were receiving oral corticosteroids, had significant other comorbid diseases, or could not perform all study measures.

Study sites were a public sector teaching hospital asthma clinic, which serves lower-income patients without medical insurance, and two pediatric private practices. The study was done in Gauteng province, South Africa, over 3 months during the summer rainfall season when grass pollen is the most prevalent aeroallergen. Written assent from children and consent from parents were obtained (University of Pretoria Ethics Committee approval 142-2006).

Study Sequence

Observations were made in a four-step sequence in the morning (9:00-11:00 AM).

Step 1: FENO was determined with a portable NIOX MINO (Aerocrine) device, following the manufacturer's recommended procedure. A single measurement was made in each patient. In 2006, Taylor[7] published a table plotting levels of FENO to asthma control outcomes. According to this publication, an FENO < 20 parts per billion (ppb) suggests adequate asthma control, whereas a value of > 35 ppb suggests poor asthma control. The range between 20 and 35 ppb is a gray zone where clinical interpretation is important. In this study, a cut point of FENO = 35 ppb was used to separate a child with well-controlled asthma (≤ 35 ppb) from a child with uncontrolled asthma (> 35 ppb). These cutoffs were advocated in a recent consensus statement.[8]

Step 2: Spirometry was done according to recommended procedure[9] with a portable spirometer (SpiroPro+; CareFusion Corporation). Results were expressed as a percentage of the predicted Polgar reference values and 10% downward adjustment in predicted values for nonwhite children.[10] For spirometry, $FEV_1 \geq 80\%$, force expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) ≥ 60%, peak expiratory flow rate (PEFR) ≥ 80% predicted, and $FEV_1/FVC \geq 80\%$ were regarded as controlled asthma. Spirometry was performed by a trained operator, and the equipment was calibrated daily.

Step 3: The childhood Asthma Control Test (cACT) was completed. The cACT is a standardized seven-item questionnaire about symptoms; four questions are answered by the child in relation to symptoms, and three are answered by the parent regarding symptoms in the past 4 weeks. The cACT has been validated against specialist-physician assessments and FEV_1.[11] A cACT score of ≤ 19 of 27 is regarded as inadequately controlled asthma.[11]

Step 4: Clinical assessment was conducted, without knowledge of the preceding results, by one of seven pediatricians with a special interest in asthma. Routine clinic procedures were used with a formal, but not validated protocol. Questions regarding daytime, nighttime, and exercise-induced symptoms; use of reliever bronchodilator medication; and exacerbations of asthma are routinely asked before performing a physical examination. On completion, the pediatrician categorized the asthma as controlled, uncontrolled, or acute attack, in which case the patient was excluded from the study.

Outcome Measures

Guidelines recommend a three-way categorization into controlled, partially controlled, and poorly controlled asthma. But for the purposes of this study, partially and poorly controlled asthma were both classified as uncontrolled asthma.

Statistical Analysis

nQuery Advisor 7.0 (Statistical Solutions) and Stata 10 (StataCorp LP) were used for computations. The parameters of clinical assessment by the pediatrician, spirometry (FEV_1, $FEF_{25\%-75\%}$, PEFR, FEV_1/FVC), cACT score, and FENO were assessed to depict well-controlled (0) and uncontrolled asthma (1). Interparameter agreement was assessed using McNemar test for symmetry, and the κ statistic was used to determine agreement (poor agreement, ≤ 0.4; moderate agreement, 0.4-0.75; excellent agreement, > 0.75).[12] Logistic regression was conducted using the method described by Hosmer and Lemeshow.[13]

RESULTS

Eighty children were enrolled. Nine were subsequently excluded because three could not complete all assessment steps and six were found by the pediatrician at step 4 to have an acute attack. Seventy-one

children (mean age, 8.4 years; median age, 9 years) completed the study, of whom 46 were boys aged 4 to 11 years (median, 8 years) and 25 girls aged 4 to 11 years (median, 9 years). All children were from lower- or middle-income families, and all were able to speak English. Sixty-one percent were black African children.

Each test individually revealed controlled or uncontrolled asthma, using the cut points described in the "Materials and Methods" section. Clinical assessment by the pediatrician revealed 41 controlled patients (57.7%); cACT, 41 (57.7%); FENO, 47 (66.2%); FEV_1, 52 (73.2%); $FEF_{25\%-75\%}$, 51 (71.8%); PEFR, 40 (56.3%); and FEV_1/FVC, 62 (87.3%).

To interrogate the ability of each test of asthma control to agree with the other measures, three associations were determined. The most comprehensible way to express the relationships for the FENO:clinical assessment by the pediatrician was a box plot (Fig 1). Mean FENO in uncontrolled asthma was more than double that of controlled asthma (37 ppb vs 15 ppb, $P < .005$).

Each test was then compared with every other test in a series of 2×2 tables. The results for the proportion of agreement of these comparisons, as reflected by the κ statistic (either both controlled or both uncontrolled) is shown in Figure 2.

The κ statistic ranged from 0.00 to 0.67 (median, 0.18), where ≤0.4 is interpreted as poor agreement (most comparisons in this study) and 0.4 to 0.75 is defined as moderate agreement. Only the comparisons of FEV_1 and PEFR and $FEF_{25\%-75\%}$ and FEV_1/FVC were moderately in agreement.

Finally, in a multivariate approach using logistic regression, all the measures of asthma control analyzed in this study were considered, and only FEV_1, cACT, and FENO were retained. To provide an equation by which the pediatrician could predict uncontrolled asthma, the latter (FEV_1, cACT, and FENO) were included in a logistic regression. The equation from the study data to predict uncontrolled asthma was $y = -2.132 + 1.423(FEV_1) + 1.713(cACT) + 1.826(FENO)$.

A specific patient's asthma will be predicted as uncontrolled when $y > -0.405$ ($P = e^y/(1 + e^y) > .4$ defines uncontrolled asthma). The latter cutoff gave the best diagnostic statistics for the prediction equation (sensitivity, 70%; specificity, 70.7%; positive predictive value, 63.6%; negative predictive value, 76%).

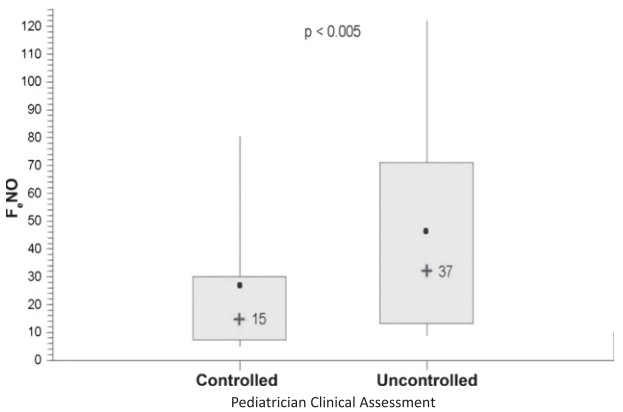

FIGURE 1. A boxplot of clinical assessment by the pediatrician. F_eNO = fraction of exhaled nitric oxide.

DISCUSSION

With respect to the aim of this study, overall agreement among testing methods to assess control of asthma was reached in 49.3% to 83.1% of assessments. Interparameter agreement using the κ statistic revealed poor (≤0.4) to moderate agreement (0.4-0.75) for all comparisons. Most tests were in poor agreement, and only the physiologic variables within spirometric assessment achieve moderate agreement.

When only a single measure of control is used, then 41 to 62 of the children with asthma (58%-87%) are classified as controlled. This finding may suggest that this cohort of children with asthma is not particularly well controlled; however, it is a typical finding of the degree of asthma control in similar studies.[14-16]

The apparent differences in mean values for FENO between the children with controlled and uncontrolled asthma as assessed by the pediatrician might appear to justify its value in measuring asthma control, but considerable overlap between the groups may render FENO insensitive for clinical use in individual children. The poorest agreement is between FENO and spirometry (κ ≤ 0.4). The best agreement is between the spirometric indices $FEF_{25\%-75\%}$ and FEV_1/FVC (κ = 0.4-0.75).

Asthma control assessment has been suggested in all asthma guidelines. All such guidelines stress the need for objective testing of control.

Since the mid-1990s, information on a disassociation between asthma symptoms and patient perceptions of these symptoms has been known. An early study revealed that a proportion of patients with asthma significantly underestimate disease severity and, thereby, may be at risk for increased mortality or morbidity.[3] The cACT aims to overcome some of the problems in history taking. It is now promoted as a validated measure and widely used in clinical settings and research studies.

Previous studies revealed a lack of agreement between cACT and specialist assessment of asthma control[11] and a conflicting association between cACT and FENO[16,17] and cACT and spirometry[15,16,18] for the assessment of asthma control. However, there is

	cACT	F_ENO	SPIROMETRY			
			FEV_1	FEF_{25-75}	PEFR	$\frac{FEV_1}{FVC}$
Clinical assessment by pediatrician	0.37	0.29	0.30	0.18	0.26	0.13
	cACT	0.00	0.24	0.18	0.03	0.00
		F_ENO	0.00	0.04	0.03	0.15
			FEV_1	0.35	0.43	0.21
				FEF_{25-75}	0.28	0.48
					PEFR	0.07

FIGURE 2. Proportion of observed agreement (κ statistic) among four criteria of disease control in 71 ambulatory children with asthma. Agreement is the sum of cases that are concordant for either uncontrolled or controlled asthma. cACT = Childhood Asthma Control Test; FEF_{25-75} = forced expiratory flow, midexpiratory phase; PEFR = peak expiratory flow rate. See Figure 1 legend for expansion of other abbreviation.

evidence that cACT may be an important predictor of future asthma exacerbations or asthma risk.[14] The current study supports that without additional measurements, the cACT may not uncover all children in whom asthma is uncontrolled. There is clear evidence[19,20] that the most significantly flawed area of assessment of asthma control is that involving physician-directed assessment either by asking questions or by examination.

Previous studies revealed discrepant results for spirometric correlation with asthma symptom history and quality of life. Wildhaber et al[21] found no significant correlation among FEV_1 ($r = -0.22$, $P = .34$), $FEF_{25\%-75\%}$ ($r = -0.27$, $P = .06$), and patient symptoms. Their study, however, was limited to an analysis of only 48 children with asthma. In a larger study, Fuhlbrigge et al[22] found that spirometry accurately predicts asthma symptoms and future risk of exacerbations. A potential explanation of these discrepancies relates to the actual questions used, and careful standardization of symptom history may resolve the effect differences.

FENO measurement by means of the NIOX MINO device has been validated for successful use in children.[23] What is less obvious from the literature is what FENO measurements mean when compared with other standard measures of asthma control. There is clear evidence that FENO is correlated with airway hyperresponsiveness and steroid response in many children with asthma.[24] A study by Jones et al[25] revealed that an FENO > 15 ppb has an 88% positive predictive value of loss of asthma control, but the negative predictive value is low (25%).

Many previous studies of FENO have documented disagreement between FENO and lung function testing.[26,27] This lack of correlation has also been revealed in the current study. Nitric oxide may not respond linearly to steroid therapy in some children, and this would need to be borne in mind if using FENO in the measurement of asthma control.[28]

Discrepancy in objective assessments of asthma control are obvious in the literature.[11,15-18] Although some studies find agreement among tools, others do not. In the study by Leung et al,[16] there was significant agreement between various questionnaires and objective testing (spirometry). However, other studies that have attempted to compare various control assessment questionnaires (eg, Asthma Control Test, Asthma Control Questionnaire) to the end points expected in various asthma guidelines (eg, Global Initiative for Asthma, National Asthma Education and Prevention Program, Joint Task Force Practice Parameter) have failed to find a correlation. In addition, when objective assessments of inflammation (FENO) are added to the assessments, no better agreement is reached.[17] Such studies find agreement when similar tools are compared (eg, between questionnaires) but not across different tool types.[17] One of the problems appears to be different population groups used, different inclusion criteria, and different definitions of control for nonobjective tests. Only when studies exactly replicate study groups with identical definitions will a clear answer to control assessments become obvious. It is obvious that small differences in measurement tools can lead to large differences in effect size and prevalence estimates.

The prediction equation suggested in the current study, which uses some of the measures of asthma control, provides some value. A sensitivity and specificity of about 70% can be debated as of value. However, what future studies of asthma control require is documentation of what variables in patient assessment are missing to create an equation that perfectly predicts controlled or uncontrolled asthma in an individual person with asthma. It seems likely that included in those missing variables would need to be documentation of the asthma phenotype for a particular patient. We may, however, never achieve perfect prediction or measurement of asthma control because of the complex nature of the disease.

The study is limited by the cross-sectional design. A longitudinal study to uncover the future risk element of uncontrolled asthma would be advantageous.

Conclusions

This study revealed significant disagreement among many of the testing methods used to assess asthma control. Assessment of multiple parameters, including biomarkers, physiologic measures, symptoms, and activity limitation, would probably be necessary to categorize asthma clinical status accurately.[29]

This study demonstrates that there is no easy answer to the measurement of asthma control. It seems likely that asthma control requires more than one end point in assessment and that both physician assessment and objective testing are required. However, to adjudicate asthma control, very careful definition of symptoms or testing cutpoints are required.

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Clinical Study

The Relationship between Maternal Atopy and Childhood Asthma in Pretoria, South Africa

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Introduction. Asthma is the commonest chronic condition of children. Diagnosis of this condition remains difficult. Many surrogate markers are used, such as documenting evidence of atopy. *Method*. A random sample of asthmatic children and their mothers attending the Children's Chest and Allergy Clinic at Steve Biko Academic Hospital were enrolled. Children were classified as having atopic or nonatopic asthma. Mothers completed a questionnaire to uncover atopic features. *Results*. Along with their mothers, 64 children with atopic asthma and 36 with nonatopic asthma were studied. The proportion of children with atopic asthma does not differ for mothers with and without a positive SPT ($P = 0.836$), a history of asthma ($P = 0.045$), symptoms suggestive of an allergic disease ($P = 1.000$), or who were considered to be allergic ($P = 0.806$). The odds ratio of a child having atopic asthma when having a mother with a doctor diagnosed history of asthma is 4.76, but the sensitivity is low (21.9%). *Conclusion*. The data demonstrates that all maternal allergic or asthmatic associations are poor predictors of childhood atopic asthma. Despite the increased risk of atopic asthma in a child to a mother that has a doctor diagnosis of asthma (OR 4.76 $P = 0.045$), this is a poor predictor of atopic asthma (sensitivity 21.9%).

1. Introduction

Asthma is one of the commonest childhood illnesses. Unfortunately, in some individuals, the diagnosis remains difficult, particularly in the preschool wheezer. This leads to widespread underdiagnosis, which negatively affects the quality of life of asthmatic children.

In an attempt to provide insight into the wheezy infant, much research has been conducted in order to provide markers, that may help predict and aid in the diagnosis of asthma in young individuals. Despite this, the epidemiology and disease expression of asthma and other allergic diseases still remain poorly understood. In the Northern Hemisphere, the relationship between asthma and atopy has been clearly shown [1, 2]. For this reason, the presence of atopy in children is often used as a surrogate marker to assist in making the diagnosis of asthma [2].

In the developing world and particularly in the South African context, the relationship between atopy and asthma may not be as clear [3]. Since 2005 the atopic status of asthmatic children attending the Steve Biko Academic Hospital Paediatric Asthma Clinic has been investigated. Results have demonstrated that only 49% of the children with asthma had one or more positive skin prick tests to common aeroallergens [4]. This is much lower than the atopic rate of asthmatics reported in the Northern Hemisphere [5]. This suggests that these children had a lower rate of an atopic diathesis than other groups reported, suggesting that using atopy as a diagnostic tool in our context may not be a perfect marker for asthma.

While the genetic basis for asthma remains unclear, the interaction between genetics and the environment is even more illusive [6]. The role of the environment has been postulated to explain the increase in the prevalence of asthma [7–11], as well as other allergic diseases. Some of these environmental factors include urbanisation, dietary changes, vitamin and micronutrient insufficiency, changes

in microbial burden, and industrial pollution. It is possible that these environmental factors play a greater role in the aetiology and expression of asthma and other allergic diseases in our context.

This study was performed to further investigate the relationship between maternal atopy and asthma. It has important implications because identification of atopy in relatives of asthmatic children may be unhelpful in the diagnosis of childhood asthma, especially in our setting, since fewer asthmatic patients are atopic. It is important to provide practitioners with diagnostic tools to aid in making a diagnosis, so as not to waste time asking questions that do not provide information.

In the context of this study, the following definitions are used.

Family history of allergy: family member with symptoms suggestive of an allergic disease or a known allergic disease, for example, allergic rhinitis, asthma, and food allergy.

Atopy: positive skin prick test to common aeroallergens and/or foods, in the context of an allergic disease [12].

Atopic asthmatic: asthmatic with a positive skin prick test.

Nonatopic asthmatic: asthmatic with a negative skin prick test.

"Allergic" mom: presence of a positive skin prick test, or a history of allergic symptoms or disease.

2. Objective

To determine if a maternal history of allergic disease or symptoms of such a disease and/or atopy is a useful predictor of the allergic basis of her child's asthma. This was performed by determining

(i) the association of atopy in mothers with atopic asthma in their children,

(ii) the association of asthma in mothers with atopic asthma in their children, and

(iii) the association of maternal history of allergic symptoms in mothers with atopic asthma in their children.

3. Methods

A random sample of children and their mothers attending the Children's Chest and Allergy Clinic at Steve Biko Academic Hospital, in Pretoria, South Africa, were enrolled. Children diagnosed with asthma and known to the clinic for longer than six months were considered. A diagnosis of asthma was made by all of the following [13]:

(1) a history of respiratory symptoms which respond to bronchodilators,

(2) a history of respiratory symptoms which respond to inhaled or oral corticosteroids, and

(3) airway hyper responsiveness, as demonstrated by reversible spirometry.

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria. Maternal consent and patient assent was obtained. Skin-prick testing (SPT) or ImmunoCAP (Thermofisher) test results, to common aeroallergens and foods, of the children were obtained from the child's hospital records.

Mothers completed a detailed questionnaire which included demographic details, birth history, occupation, habits, present environment, medical history, symptomatology of atopy, and a history of symptoms suggestive of allergic diseases. These were subdivided into skin, upper and lower respiratory tract symptoms, such as allergic rhinitis, sinusitis, eczema and asthma, as well as any history of proven asthma.

SPT using the Alk-Abelló allergen extracts (Laboratory Specialities) and negative (0.5% phenol) and positive (1% histamine) controls were performed on the mothers. The aero-allergen extracts used were Bermuda grass, corn pollen, 5 grass mix, tree mix, *Candida albicans*, *Aspergillus fumigatus*, cat-hair epithelium, dog-hair dander, feather mix, house-dust mix, and standardised *Dermatophagoides pteronyssinus*. Each extract was applied to the volar surface of the forearm with a sterile prick lancette. Reactions were read at 10 minutes, any wheal 3 mm or greater than the negative control was regarded as positive.

3.1. Statistical Analysis. The results were captured and the proportions were compared using the Fisher's-exact test. Test characteristics were evaluated for sensitivity, specificity, and predictive values using a standard two by two table. The outcome of interest was asthmatic children with a positive SPT (used to distinguish between atopic and nonatopic asthma).

4. Results

100 children and their parents were enrolled. All children were under 12 years old. The age range was 1–12 years (mean 6 years). Along with their mothers, 64 children with atopic asthma and 36 with nonatopic asthma were studied. The patients were not stratified according to race. The proportion of children with atopic asthma does not differ significantly for mothers with and without a positive SPT ($P = 0.836$; 0.625 (30/48) versus 0.654 (34/52)). The proportion of children with atopic asthma does not differ significantly for mothers with and without a history of doctor diagnosed asthma ($P = 0.045$; 0.875 (14/16) versus 0.595 (50/84)). The proportion of children with atopic asthma does not differ significantly for mothers with and without symptoms suggestive of an allergic disease ($P = 1.000$; 0.643 (45/70) versus 0.633 (19/30)). The proportion of children with atopic asthma does not differ significantly for mothers who were considered to be allergic (presence of a positive skin prick test, or a history of allergic symptoms) or not ($P = 0.806$; 0.649 (50/77) versus 0.608 (14/23)). The diagnostic variables (sensitivity, specificity, and predictive values) are reflected in Table 1.

Table 1: Descriptive statistics for the relationship between maternal allergy or asthma and children with atopic asthma.

Prevalence of maternal	Doctor diagnosed asthma	Skin prick test positive	Allergic symptoms	Allergic symptoms or SPT positive
Sensitivity	21.9%	46.9%	70.3%	78.1%
Specificity	94.4%	50%	30.7%	25%
ROC area	0.582	0.484	0.504	0.516
Positive predictive value (PPV)	87.5%	62.5%	64.3%	64.9%
Negative predictive value (NPV)	40.5%	34.6%	36.7%	39.1%

Table 2: Odds ratio of a child having atopic asthma when having a mother with or without the exposure variable.

	Skin prick test positive	Doctor diagnosed asthma	Allergic symptoms	Allergic symptoms or SPT positive
Odds ratio (OR)	0.882	4.76	1.04	1.19
95% CI	(0.36; 2.16)	(0.98; 45.3)	(0.38; 2.75)	(0.39; 3.42)

The relative risk (odds ratio) of a child having atopic asthma when having a mother with or without the exposure variable is reflected in Table 2.

5. Discussion

The data in Table 1 demonstrates that all maternal allergic or asthmatic associations are poor predictors of atopic asthma in their children. The descriptive statistics is low for all maternal factors. Only the association of maternal doctor diagnosed asthma reached statistical significance ($P = 0.045$) but this may have limited clinical significance.

Despite the increased risk of atopic asthma in a child of a mother that has a doctor diagnosis of asthma (OR 4.76 $P = 0.045$), a mother with a doctor diagnosis of asthma is, nevertheless, a poor predictor of a child with atopic asthma (sensitivity 21.9%). The false negative rate of this predictive test is high.

The findings in this study are important because the literature suggests that the most reliable way to demonstrate the inherited tendency of asthma is to demonstrate a positive family history of atopy. This is why atopy is used as a surrogate marker to aid in the diagnosis of childhood asthma. But it is clear here, that a history of maternal atopy or allergic diseases is not a good predictor of childhood asthma in our cohort of patients.

It has previously been suggested that the reason for the poor association between family history of allergic disease and childhood asthma may be due to lack of diagnosis of allergic diseases in family members [14]. This is because of underreporting of these symptoms by patients, or failure of doctors to recognise and diagnose allergic diseases. Parents should rather be asked about specific symptoms suggestive of asthma, allergic rhinitis, and other allergic diseases [14]. However, this study demonstrates that this cannot be the whole explanation for a poor family history, since mothers were specifically questioned on symptomatology suggestive of allergic diseases. Therefore adequate history taking is not a simple solution to a complex problem.

Perhaps the relationship between asthma and atopy has been overestimated in the first world [15]. Or perhaps this relationship, which we rely upon in everyday practice to aid in the diagnosis of childhood asthma, cannot be extrapolated to the third world. Other risk factors for asthma in our setting may have been neglected.

6. Conclusion

Atopic disease expression carries an inherited or genetic component [16]. Despite this, in our study, maternal atopy (positive SPT and an allergic disease process), or a history of symptoms suggestive of allergic diseases were not good predictors of atopic asthma in children. Even previously doctor diagnosed maternal asthma may not be a useful predictor of atopic asthma in her child. This supports previous local studies that have demonstrated that atopy occurs in fewer asthmatic children, at best in South Africa, than previously thought.

This raises questions about the uniform association between allergy and asthma, especially in Africa and suggests that asthma may be associated with other aetiological factors. Some environmental factors postulated are urbanisation, dietary changes, vitamin and micronutrient insufficiency, changes in microbial burden, and industrial pollution.

The data obtained are the result of a pilot study based on a limited number of patients. Also, reliance on maternal history to differentiate allergic from nonallergic mothers is another important limitation. These results should therefore be confirmed by further studies. Families should also be stratified according to race, to determine whether the results are influenced. The information obtained however, together with other local studies, has shown the emergence of a new picture of childhood asthma in the third world context. This is different to what was previously thought. Currently, the diagnosis of asthma in young children is aided by a family history of atopy or allergic diseases. But this may not be appropriate in the South African setting. There are many unanswered questions. This provides the motivation for further studies to be conducted among different ethnic

groups, especially in South Africa. This will hopefully shed more light on the complexity of the epidemiology and aetiology of childhood asthma in the third world.

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Costs of admission for paediatric pneumonia in a setting of human immunodeficiency virus infection

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SUMMARY

BACKGROUND: Pneumonia in South African children remains a major public health concern. The costs of hospital admission for pneumonia should be determined, especially where human immunodeficiency virus (HIV) infection is common.

OBJECTIVE: To determine the hospital costs of children (HIV-infected vs. non-HIV-infected) admitted for the management of pneumonia and compare them in the public and fee-for-service sectors.

METHODS: A retrospective review of paediatric admissions in 2007 was performed. Costs were determined for the public and fee-for-service sectors. Outcome measures included hospital mortality and comparative costs of admission.

RESULTS: There were 132 admissions in a public sector facility (67% HIV-infected), and 7882 in the fee-for-service sector (1.2% HIV-infected). Total mortality was respectively 25% in the public and 0.04% in the fee-for-service sectors. The mean cost for HIV-infected patients was respectively US$639.06 and US$10 540.04 in the public and fee-for-service sectors. For non-HIV-infected patients, the cost was respectively US$399.45 and US$3936.87. Length of stay for HIV-infected patients was longer by respectively 1.8 days and 5.7 days in the public sector among admissions to the ward and to the paediatric intensive care unit.

CONCLUSION: Admission for HIV-infected children with pneumonia costs significantly more in both sectors. Preventive strategies are needed.

KEY WORDS: HIV; pneumonia; cost

PNEUMONIA IN SOUTH AFRICA remains a major public health concern, with a number of children admitted to hospital each month with severe pneumonia. The cost of admission of a patient with community-acquired pneumonia (CAP) is seldom considered, although it is an important factor in calculating the cost-efficacy of preventive strategies such as vaccines.

CAP prevalence is unknown, but it is estimated that 2.1 million children aged <5 years die worldwide from pneumonia annually.[1] The prevalence of this condition is estimated to be 2–10 times greater in Africa and Asia than in the United States.[2] Together with diarrhoea and malnutrition, pneumonia ranks among the top three causes of death in developing countries.[3] Pneumonia accounts for nearly one fifth of childhood deaths worldwide, with the majority of the approximately 2 million deaths occurring in Africa and South-East Asia.[1,4]

The human immunodeficiency virus (HIV) and acquired immune-deficiency syndrome have had a significant impact on both the prevalence and severity of pneumonia.[5] In South Africa, there are approximately 80 000 new infections annually, with 30–40% of hospital admissions being HIV-related.[6] This results in a case-fatality rate of 15–28%.[7] The natural consequence of the HIV epidemic and the increase in the prevalence and severity of childhood pneumonia is therefore a rise in hospitalisation and a consequent increase in disease-related costs. Costs are dictated by, among others, increased number of admissions and utilisation of diagnostic and therapeutic services for more severe disease.

One prevention strategy that has been shown to be highly successful in the United States is routine childhood vaccination with pneumococcal conjugate vaccine. This vaccine did not form part of the South African government immunisation schedule at the time of the study, but vaccination against polio, hepatitis B, *Bordatella pertussis*, tetanus, diphtheria, *Haemophilus influenzae* B and measles had routinely been given to our patients. Local studies have shown the benefits of pneumococcal vaccine, with a reduction of invasive pneumococcal disease by between 65% and 85% in HIV-infected and non-HIV-infected children, respectively.[8] However, a cost-efficacy analysis of the benefits of such vaccines will dictate the real world impact on pneumonia.

The actual cost of a child admitted to hospital

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with pneumonia has never been determined in South Africa, and is an important pharmaco-economic factor in resource-poor settings. This expense is an important quantum when the cost of preventive strategies is calculated. This may impact cost-benefit calculations of routine pneumococcal 7-valent, 10-valent or 13-valent vaccines for children in South Africa.

The aim of the present study was to determine the total and individual costs of children admitted to hospital for the management of pneumonia. The study also set out to determine the cost differentials for HIV-infected and non-infected children and for children admitted to a general paediatric ward or a paediatric intensive care unit (PICU) in a public sector setting. A comparative analysis of the fee-for-service sector was performed. Mortality or discharge from the hospital was determined as the end point.

METHODS

Study design

This was a retrospective observational cross-sectional study. The study protocol was approved by the University of Pretoria ethics committee.

Each admission of children diagnosed with pneumonia to the Steve Biko Academic Hospital's paediatric pulmonology ward and PICU during the period 1 January 2007 to 31 December 2007 was reviewed. Pneumonia was defined, based on the World Health Organization definition of clinical severity, as severe pneumonia (cough, tachypnoea, rib and sternal recession) and very severe pneumonia (cough, tachypnoea, chest wall retraction, inability to drink, cyanosis). All children had pneumonic consolidation on chest radiograph. Admission to the PICU was based on the development of type 2 respiratory failure, assessed by arterial blood gas analysis. Patients with a diagnosis of bronchiolitis, tuberculosis or comorbid cardiac disease were excluded.

The direct costs of each admission, obtained from the hospital billing file, were calculated[9] based on hospital category code H2, for hospitalised patients partially subsidised by the state, as set out on the Uniform Patient Fee Schedule (UPFS). All aspects of public sector health care are subsidised, including facility fees, which reflects the overhead costs of providing the environment in which health care service is rendered (Level 3 tertiary hospital), and professional fees, which cover the costs of services provided by health care, laboratory and radiology professionals and antibiotics. Costs were calculated per patient per admission, and a median monthly cost per diagnosis per ward was calculated. All laboratory blood culture results and sputum results were also included. The present study was conducted before a routine policy of sampling for *Pneumocystis jirovecii* and cytomegalovirus was introduced. The outcome of these admissions was assessed as death in hospital or discharge home. Data were also obtained from the fee-for-service sector.[10] Data were compared for mortality and the average length and cost of hospitalisation in the ward and the PICU for the two health care sectors for both HIV-infected and non-infected children. To complete the analysis of the cost of severe pneumonia in children, all costs of strategies that may be deemed 'pneumonia preventive' were added. These costs may highlight what cost in savings (if any) could be achieved through preventing pneumonia in children.

Statistical analysis

An analysis of actual costs was compared for the different groups using the two-sample Wilcoxon rank-sum (Mann-Whitney) test. A 5% level of significance was considered statistically significant.

RESULTS

A total of 200 patients were admitted to the public sector facility for pneumonia during the study period; 68 were excluded as the diagnosis proved to be bronchiolitis ($n = 11$) or because HIV testing was not performed ($n = 57$). A total of 132 patients therefore qualified for data analysis: 86 were admitted to the paediatric pulmonary ward and 46 to the PICU. The male-to-female ratio was 1.45:1 (51:35) in the ward and 1:1.42 (19:27) in the PICU. Of these, 33 (25%) died: 12 in the ward and 21 in the PICU (Table 1). In the fee-for-service sector, 7882 patients were admitted: 7786 to the ward and 93 to the PICU. The male-to-female ratio was 1:0.8 (4423:3406) in the ward and 1:1.1 (24:26) in the PICU. Three patients (0.04%) died, all three in the PICU.

Table 2 (A and B) reflects the comparison of median costs for HIV-infected and non-HIV-infected children in both the ward and the PICU in the public sector. The costs of HIV testing were higher for HIV-infected than non-infected patients in the ward and the PICU ($P = 0.02$ and $P = 0.002$, respectively). This is because an HIV-DNA (polymerase chain reaction [PCR]) has to be performed on HIV-enzyme-linked immunosorbent assay (ELISA) positive children

Table 1 Overview of the patient profile and outcome of children admitted with pneumonia to a public service in South Africa, $N = 132$

	Ward *n/N* (%)	PICU *n/N* (%)
HIV-infected	58/86 (67)	31/46 (67)
Total deaths	12/86 (14)	21/46 (46)
HIV-infected deaths	12/58 (20.7)	17/31 (54.8)
Non-HIV-infected deaths	0/28 (0)	4/15 (26.7)
Length of stay, days, median [IQR]	7 [5–12]	6.5 [3–14]
HIV-infected length of stay	8 [4–12]	9 [5–18]
Non-HIV-infected length of stay	6.5 [5–8]	3 [2–7]

PICU = paediatric intensive care unit; HIV = human immunodeficiency virus; IQR = interquartile range.

Table 2 Median costs per patient (in US$)

Cost centre	HIV-infected	Non-HIV-infected	*P* value*
Public sector ward			
HIV testing	45.60	10.90	0.02
Blood culture	11.30	11.30	0.54
Sputum microbiology	28.80	28.80	0.18
Haematological testing	59.80	33.10	0.01
Hospital bed	173.50	139.50	0.23
Radiology	30.90	30.90	0.25
Antibiotics	0	0	0.20
Public sector PICU			
HIV test	45.60	10.90	0.002
Blood cultures	11.30	11.30	0.42
Sputum microbiology	28.80	28.80	0.54
Haematological testing	103.50	71.30	0.17
Hospital bed	382.50	127.50	0.01
Radiology	45.70	45.70	0.04
Antibiotics	0	0	0.11

*Statistical significance for comparison of HIV-infected patients with non-HIV-infected patients.
HIV = human immunodeficiency virus; PICU = paediatric intensive care unit.

aged <18 months to define HIV infection; 81% of our cohort required this test. HIV DNA (PCR) is ideally routinely conducted at postnatal follow-up. The mean cost of admission to the public sector ward was US$435.12 (for a mean of 8.67 days) and US$795.81 (for a mean of 9.35 days) to the PICU. The fee-for-service costs were US$1375.35 (for a mean of 5.6 days) and US$13 101.55 (for a mean of 10.5 days) for the ward and PICU, respectively. The public sector costs are therefore respectively 4.9 times (ward) and 1.3 times (PICU) lower than in the fee-for-service sector. In the public sector, antibiotics are included in the hospital bed costs, in accordance with the UPFS.

In the public sector, HIV-infected patients admitted to PICU had, on average, more haematological and blood culture tests performed than non-infected children and HIV-infected patients in the ward. The mean number of haematological investigations in the PICU was 16.03 haematological specimens and 1.67 blood culture specimens for HIV-infected patients, while 7.41 haematological specimens and 0.71 blood culture specimens were drawn from non-infected patients. In patients admitted to the ward, a mean of 6.41 haematological specimens and 0.83 blood culture specimens were collected in HIV-infected patients compared to 7.21 haematological specimens and 1.03 blood culture specimens in non-HIV-infected patients. HIV-infected patients had a greater number of positive cultures for bacteria than non-infected patients. This was noted in both the ward and the PICU. The mortality rate for the public sector was 25% (14% and 46% in the ward and PICU, respectively), but it was 0.04% (0% and 6% in the ward and PICU, respectively) in the fee-for-service sector. When all items deemed 'pneumonia preventive' are totalled, these amount to US$341.33–$1389.42 for HIV-infected children and US$229.91 for non-infected children (Table 3). The best-case scenario is one in which a child is born to a mother whose CD4 count is sufficiently high as not to warrant ongoing highly active antiretroviral therapy (HAART) throughout pregnancy and where the child is HIV-exposed but not infected. The worst-case scenario is where these criteria exist.

DISCUSSION

HIV-infected and non-infected children are still admitted to hospital and the PICU for management of severe pneumonia, and they cost the state a significant amount of money each year. During the study period, 132/1477 (8.9%) admissions to the public sector ward and 46/460 (10%) PICU admissions were diagnosed with pneumonia. The total number of non-HIV-infected children with severe and very severe pneumonia (28 in the ward and 15 in the PICU, respectively) during the study year (2007) suggests that, even in the absence of HIV infection, pneumonia is still a common condition among children. This is supported by figures from the fee-for-service sector, where even higher numbers (n = 7786) of non-HIV-infected children are admitted with a diagnosis of pneumonia. Pneumonia appears to cost less in the public sector than the fee-for-service sector in South Africa, but

Table 3 Costs (in US$) of pneumonia preventive strategies in children in South Africa

	HIV-infected		
Cost centre	Worst-case scenario	Best-case scenario	Non-HIV-infected
Antenatal ELISA	10.90	10.90	—
Maternal PMTCT best-case scenario (ARV at delivery)	—	1.11	—
Maternal PMTCT worst-case scenario (HAART/triple ARV × 9 months)	507.15	—	—
ELISA child	10.90	10.90	10.90
PMTCT child × 1 month	—	8.86	—
PCR at 6 weeks + 6 months	91.25	91.25	—
Worst-case scenario HAART/triple ARV × 1 year	550.21	—	—
PCV 7 × 3 doses	76.95	76.95	76.95
Infanrix Hexa (DTaP-HBV-IPV/HIB) × 4 doses	142.06	142.06	142.06
Total costs of preventive strategies	1389.42	341.33	229.91

ELISA = enzyme-linked immunosorbent assay; PMTCT = prevention of mother-to-child transmission; ARV = antiretroviral; HAART = highly active antiretroviral therapy; PCR = polymerase chain reaction; PCV = pneumococcal conjugate vaccine; DTaP = diphtheria, tetanus acellular pertussis vaccines; HBV = hepatitis B virus; IPV = inactivated poliovirus vaccine; HIB = *Haemophilus influenzae* type B.

this fact may be misleading, as all public health costs are heavily subsidised by the state. Fee-for-service costs may represent a truer quantum for this condition. Pneumonia mortality occurs irrespective of HIV status, and this has been well described.[11,12] However, what has emerged from this study is that once very severe pneumonia occurs and the patient requires admission to the PICU, the protective effect of not having HIV infection is mitigated and patients continue to die in the PICU. In the fee-for-service sector, deaths occurred only in non-HIV-infected patients admitted to the PICU. Reasons for this increasing mortality phenomenon are poorly understood, but immune compromise has been cited as a reason for hospital-acquired pneumonia.[13] The low mortality due to pneumonia in the fee-for-service sector probably reflects a less severely ill group of patients.

Not surprisingly, HIV-infected children admitted to hospital with pneumonia cost more, but this is seldom considered. The comparative costs of 'pneumonia preventive' strategies were US$1389.42 in HIV-infected (worst-case scenario) and US$341.33 (best-case scenario) and US$229.91 for non-HIV-infected patients (Table 3). This is important when calculating the true cost-benefit ratio of preventive strategies and in achieving the Millennium Developmental Goals for childhood mortality.[14] When the costs of pneumonia prevention strategies are weighed against the costs of admission and treatment of pneumonia, this calculation suggests that for every 1 dollar spent on prevention a cost saving of $1.70 and $17.10 may be realised for non-HIV-infected children in the public and fee-for-service sectors, respectively. For HIV-infected children, $1.90 and $30.90 would be saved for children classified as the best case scenario (maternal HIV but with high CD4 count) in the public and fee-for-service sectors, respectively. However, when the costs of prevention are balanced against treatment for HIV-infected children whose mothers also require HAART during pregnancy (worst case scenario), then savings would occur only for those children subject to preventive interventions in the fee-for-service sector ($7.60). In the public sector this balance would translate into a 50 cent loss for every dollar spent on prevention. In this setting, for pneumonia strategies to be cost-effective, one barrier is significant maternal AIDS. Prevention of pneumonia in children from this perspective would require an additional element of disease recognition and treatment in mothers for paediatric outcomes to be 'cost-effective'. This then becomes an ethical as well as a medical issue.

Blood culture and microbiology costs were not statistically significantly different between HIV-infected and non-infected children in the public sector, as all children undergo initial microbiological screening. Patients admitted to the PICU had significantly more haematological investigations performed, irrespective of HIV status, confirming that this population group had more severe disease. HIV-infected patients admitted to the PICU incurred higher hospital bed costs, as reflected by a longer duration of stay compared to non-HIV-infected patients in both sectors. The duration of hospitalisation was 1.8 days longer in the ward and 5.7 days longer in the public sector PICU. This was also reflected in the fee-for-service sector, where the duration of hospitalisation for HIV-infected children was 4.1 days longer in the ward and 11.1 days longer in the PICU. The pattern of organisms identified from blood culture among these children is similar to that described from other similar African settings.[15] Lack of positive yield on blood culture is a universally acknowledged phenomenon in childhood pneumonia.[16] The greater likelihood of culturing an organism from blood specimens in HIV-infected children has also been described previously.[16]

Study limitations

Study limitations include the small numbers of patients in the public sector analysis and the retrospective nature of the study. Some data, such as anthropometric measurements, were not recorded. The fee-for-service costs represent all children admitted to hospital for the whole country, but from a single funder. This might result in real bias if such patients represented a single economic group. This is not, however, the case. These limitations may be overcome by a more robust prospective and comparative study. However, it is unlikely that additional data would change the main conclusions: pneumonia is both common and costly in children and prevention strategies should be sought to reduce suffering and cost.

CONCLUSIONS

Children hospitalised for pneumonia represent a significant annual cost in the public and fee-for-service sectors, and HIV-infected children represent a greater cost burden. These costs need to be borne in mind when preventive campaigns are embarked upon. The public sector spends a significant amount on antiretroviral treatment for HIV-infected patients and treating the consequences of uncontained HIV disease. These costs are set to escalate unless authorities and medical personnel alike re-enforce preventive strategies such as reducing mother-to-child HIV transmission and promoting vaccines that prevent infectious diseases. An estimation of this has been demonstrated in this study. This should be coupled with reducing new infections in the parents of these children. Only when all preventive strategies are utilised in conjunction will the burden of pneumonia and its attendant costs fall. This study adds to mounting evidence that childhood pneumonia is a costly illness,[17] and that all efforts should be focused on preventing its occurrence.

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Adjunctive corticosteroid treatment of clinical *Pneumocystis jiroveci* pneumonia in infants less than 18 months of age – a randomised controlled trial

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Objectives. To determine the efficacy and safety of adjunctive corticosteroid therapy in clinical *Pneumocystis jiroveci* pneumonia (PCP) in infants exposed to HIV infection.

Design. Double-blind randomised placebo-controlled trial.

Methods. Infants with a clinical diagnosis of PCP, based on an 'atypical' pneumonia with: (*i*) hypoxia out of proportion to the clinical findings on auscultation; (*ii*) C-reactive protein count less than 10 mg/l; (*iii*) lactate dehydrogenase level above 500 IU/l; (*iv*) compatible chest radiograph findings; and (*v*) positive HIV enzyme-linked immunosorbert assay (ELISA) were included in the study.

Patients were randomised to receive either prednisone or placebo. The protocol provided for the addition of prednisone to the treatment at 48 hours if there was clinical deterioration or an independent indication for steroid therapy. Other treatment was carried out in accordance with established guidelines.

The primary study endpoint was in-hospital survival. Secondary outcome was time from admission to the first day of mean oxygen saturation above 90% in room air.

Results. One hundred patients were included, 47 in the prednisone and 53 in the placebo group. Patients in the prednisone group had a 43% better chance of survival than the placebo group (hazard ratio (HR) 0.57, 95% confidence interval (CI) 0.30 - 1.07, p=0.08). No significant differences could be demonstrated between groups with regard to other parameters of recovery.

Conclusions. In HIV-exposed infants with clinical PCP, adjunctive corticosteroid treatment does not appear to add benefit regarding time to recovery or oxygen independency, but early administration may improve survival. A large multicentred trial is needed to confirm these findings.

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Pneumocystis jiroveci pneumonia (PCP) is an important pathogen in HIV-infected infants with severe pneumonia.[1] PCP was found in 16 - 51% of HIV-positive African children who died from respiratory illness, being the most common cause of death in HIV-infected infants less than 6 months of age.[2] In a prospective South African study[3] to determine the cause of community-acquired pneumonia in infants, PCP was the AIDS-defining illness in 20% of HIV-infected children. The mortality rate was higher among those with PCP (47%) than in those without PCP (18%).

Given the rapid progression of disease and its high case-fatality rate,[3,4] specific antipneumocystis treatment (usually trimethoprim-sulfamethoxazole, and often adjunctive corticosteroids) is instituted on the basis of clinical suspicion. In developing countries, limited access to expensive diagnostic procedures further makes empirical PCP treatment of HIV-exposed (or HIV-infected) children with pneumonia imperative.[5]

It is also known that co-infection with viruses, particularly cytomegalovirus (CMV),[6] and bacterial pathogens is common, with similar clinical, radiographic and laboratory findings.[7]

Current recommendations for adjunctive corticosteroid therapy in cases of PCP,[8] based on a review of randomised trials in adults, may not be appropriate in infants.

Objective

The aim of the study was to determine the clinical relevance and safety of routine adjunctive corticosteroid therapy in cases of severe pneumonia clinically considered to be due to *P. jiroveci* in infants less than 18 months of age and exposed to HIV infection, in view of similar clinical, radiographic and laboratory findings (or co-infection) with CMV pneumonitis.

Methods

A double-blind randomised controlled trial was conducted among infants less than 18 months of age admitted with severe pneumonia clinically considered to be due to *P. jiroveci* at Pretoria Academic, Kalafong and Witbank hospitals. The study period was from 1 February 2005 to 31 March 2006. The admitting doctor enrolled the patients according to study protocol.

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A clinical diagnosis of PCP was made in patients with 'atypical' pneumonia with the following features: (*i*) hypoxia out of proportion to the clinical findings on auscultation; (*ii*) C-reactive protein (CRP) count less than 10 mg/l, or low; (*iii*) lactate dehydrogenase (LDH) level above 500 IU/l; (*iv*) bilateral perihilar interstitial infiltrates on chest radiograph (CXR), compatible with a diagnosis of PCP; and (*v*) positive HIV enzyme-linked immunosorbent assay (ELISA).

At the time of commencement of the study, specific antiretroviral treatment was not available in South Africa, and HIV polymerase chain reaction (PCR) testing was not performed routinely. HIV infection was not necessarily confirmed in all participants, and therefore patients with a positive ELISA test were deemed HIV-exposed rather than HIV-infected unless HIV PCR confirmed infection.

Suspected cases of PCP required prompt treatment regardless of confirmed HIV status. PCP is well described in HIV-negative patients, both immune-compromised and immune-competent, especially when less than 3 months of age.[9]

Ethical approval was obtained from the Research Ethics Committee of the University of Pretoria. The parent(s) or guardian gave informed written consent for participation in the study and for HIV testing. The sample size had to be restricted to 100 patients because of time and financial constraints.

A random number generator was used to determine the allocation to steroid or placebo treatment, which were provided in a double-blind fashion by the hospital pharmacists according to study number. Patients received either prednisone 2 mg/kg/day or placebo for 7 days. The protocol provided the addition of prednisone to the treatment at 48 hours if there was clinical deterioration or an independent indication for steroid therapy. Standard antibiotic regimens including co-trimoxazole were carried out in accordance with established guidelines.

The following baseline investigations were performed on admission.

1. CXR.
2. Full blood count, differential count and platelets, CRP, LDH, total protein and albumin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), CD4 count, blood culture and HIV ELISA. HIV PCR on a subset of patients followed only after the initiation of antiretroviral treatment as explained above.
3. Nasopharyngeal aspirates for respiratory viruses including CMV and PCP immunofluorescence were collected.
4. Induced sputum was collected for PCP PCR on a subset of patients.
5. A pp65 antigen for CMV in peripheral blood had to be omitted because of cost and lack of resources.

Daily monitoring included clinical examination, recording of temperatures, oxygen saturation and oxygen requirement, and development of new features. The number of days to achieve mean oxygen saturation above 90% in room air was recorded.

Where patients were still hospitalised on day 7, follow-up induced sputum and nasopharyngeal aspirates were collected.

The primary study endpoint was in-hospital survival. Secondary outcome was time from admission to the first day of mean oxygen saturation above 90% in room air. All findings were recorded on a standardised data collection sheet.

A senior registrar from the Radiology Department of the University of Pretoria evaluated the CXRs of participants in a systematic, standardised manner using adjusted scoring systems.[10,11] Scoring systems were adjusted in the following manner: (*i*) each lung field was divided into 4 equal quadrants; (*ii*) the left lower medial quadrant was excluded from the scoring because the heart often obscures the lung field in that quadrant; and (*iii*) each quadrant was then scored on a scale of 0 - 3, with a maximum score of 21 (0 = normal, 1 = subtle increased interstitial markings, 2 = prominent interstitial opacities, 3 = confluent interstitial and acinar opacities).

Data analysis

Cox proportional hazards regression was used for the statistical analysis. Intention to treat analysis (ITTA) was used as well as a treatment-only per protocol analysis (PPA); patients in the placebo group who received prednisone after randomisation were disregarded. The Cox proportional hazards assumptions were checked. The log-rank test was used to compare the survival curves between the treated and placebo groups. A p-value <0.05 was used to determine statistical significance.

Results

A total of 100 patients with a clinical diagnosis of PCP were included in this study. Respective outcomes for the prednisone and placebo groups, as well as those patients whose clinical condition warranted additional corticosteroid treatment, are depicted in Fig. 1.

Similar baseline clinical characteristics of the two groups are shown in Table I. The baseline investigations as well as CXR results reveal no significant difference between groups (Table II). The yield on the nasopharyngeal aspiration investigations

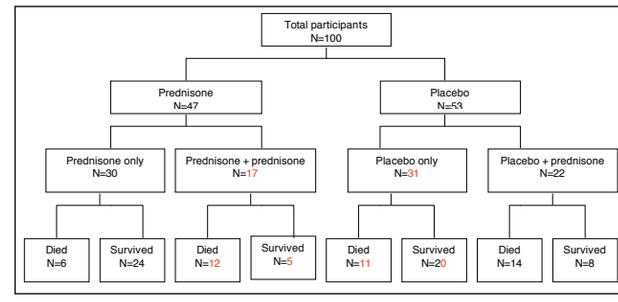

Fig. 1. Total participants and outcome.

Table I. Clinical characteristics of patients on admission

	Prednisone group (*N*=47)	Placebo group (*N*=53)
Mean age in months (SD)	3.4 (2.0)	3.2 (1.4)
Gender (*N* (%))		
Male	23 (49)	29 (55)
Female	24 (51)	24 (45)
HIV exposed (*N* (%))	46 (98)	51 (96)
Weight (kg) (mean (SD))	4.7 (1.0)	4.9 (1.2)
Weight for age (%) (mean (SD))	80 (20.3)	80 (18.1)
Weight for height (%) (mean (SD))	94(0.4)	100 (2.0)
Respiratory rate (bpm) (mean (SD))	77(14.0)	74 (13.0)
Peripheral oxygen saturation in room air (%) (mean (SD))	69 (15.8)	72 (13.8)

SD = standard deviation; bmp = breaths per minute.

was very low and a specific aetiology was proved in only a few cases.

Statistical analysis revealed no difference between groups in terms of age, severity of illness, duration of hospitalisation or co-morbid conditions. In terms of survival the ITTA and PPA results were similar (Table III). Fig. 2 demonstrates that patients in the prednisone group had a 43% better chance of survival (95% confidence interval (CI) 0.30 - 1.07, p=0.08).

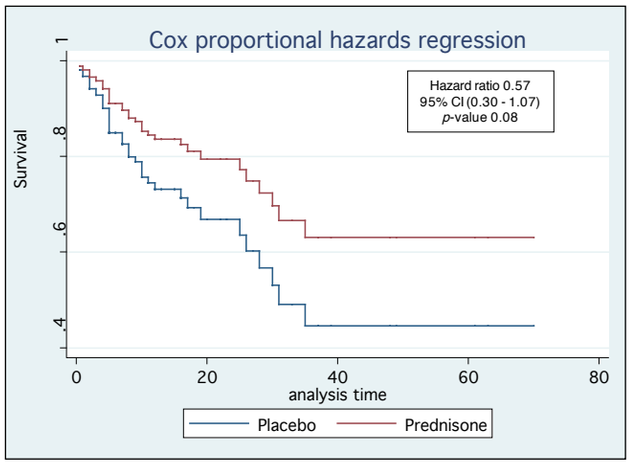

Fig. 2. Survival analysis adjusted for age and hospital.

Table II. Baseline investigations (mean (SD))

Investigation	Prednisone group (*N*=47)	Placebo group (*N*=53)
Haemoglobin (g/dl)	10.0 (1.7)	10.0 (1.7)
MCV (fl)	85.9 (7.5)	102.8 (12.1)
Platelets ($\times 10^9$/l)	313 (148)	311 (156)
White cell count ($\times 10^9$/l)	16.6 (7.6)	16.9 (10.5)
CD4 count		
Absolute count ($\times 10^6$/l)	988 (836.2)	973 (970)
Percentage	16.8 (11.2)	20 (13.3)
CRP (mg/l)	25 (87.8)	11.5 (21)
LDH (U/l)	934 (481)	905 (819)
AST (U/l)	95 (62)	83.7 (39)
ALT (U/l)	52 (52)	45 (66)
Total protein (g/l)	64 (11.9)	62 (14)
Albumin (g/l)	28 (6.01)	28 (4)
Globulin (g/l)	35 (11.2)	34 (13)
Blood culture no growth (*N* (%))	30 (64%)	35 (66%)
Nasopharyngeal aspirate for respiratory viruses (*N* (%))	(*N*=41)	(*N*=47)
RSV	1 (2%)	7 (15%)
CMV	1 (2%)	0
Adenovirus	0	1 (2%)
Influenza A	0	2 (4%)
Influenza B	0	0
Parainfluenza 3	0	1 (2%)
PCP IF positive (*N* (%))	3/39 (8%)	5/46 (11%)
PCP PCR sputum positive (*N* (%))	5/9 (56%)	3/6 (50%)
CXR findings	(*N*=42)	(*N*=48)
Bai and Boldt score (mean (SD))	8.6 (6.2)	8.7 (6.0)
Hyperinflation (*N* (%))	15 (36%)	10 (21%)
Infiltrate present (*N* (%))	40 (95%)	45 (93%)
Interstitial infiltrate (*N* (%))	40 (95%)	46 (95%)
Acinar infiltrate (*N* (%))	12 (28%)	15 (31%)

MCV = mean cell volume; CRP = C-reactive protein; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; RSV = respiratory syncytial virus; IF= immunofluorescence; PCR = polymerase chain reaction; CXR = chest radiograph.

Discussion

PCP is common among HIV-exposed infants with a high morbidity and mortality. Current recommendations for

Table III. Primary and secondary outcomes analyses

		HR	95% CI	*p*-value
Survival				
ITTA	Unadjusted	0.68	0.37 - 1.25	0.21
	Adjusted for age and hospital	0.57	0.30 - 1.07	0.08
PPA	Unadjusted	0.89	0.42 - 1.90	0.77
	Adjusted for age and hospital	0.58	1.25 - 1.38	0.22
Independent of oxygen				
ITTA	Unadjusted	0.86	0.50 - 1.48	0.58
	Adjusted for age and hospital	0.82	0.46 - 1.44	0.49
PPA	Unadjusted	0.58	0.31 - 1.07	0.08
	Adjusted for age and hospital	0.54	0.28 - 1.07	0.08
Subgroup analysis				
Survival	Unadjusted	0.40	0.15 - 1.12	0.82
	Adjusted for age and hospital	0.25	0.08 - 0.77	0.016
Independent of oxygen	Unadjusted	1.38	0.73 - 2.63	0.32
	Adjusted for age and hospital	1.22	0.69 - 2.17	0.48

ITTA = intention to treat analysis; PPA = per protocol analysis.

adjunctive corticosteroids in PCP are based on adult studies only and may not be appropriate in that these could worsen the outcome when co-infection with CMV is present in infants.The objective of this study was to determine the clinical relevance and safety of routine adjunctive corticosteroid therapy in cases of clinical PCP in infants.

There was no significant difference between the prednisone and placebo groups as a whole when comparing baseline characteristics or indicators of severity of illness. Adjunctive corticosteroid treatment had no impact on time to recovery or oxygen independency. Survival, however, seemed to be improved (hazard ratio (HR) 0.57, 95% CI 0.30 - 1.07, p=0.08), despite a large part of the placebo group receiving additional corticosteroids, as provided for per protocol.

When considering those patients who required additional corticosteroids more closely, two clinically distinct groups of patients can be identified. The first group presented with more severe and advanced disease – higher respiratory rates, lower peripheral oxygen saturation on admission and increased clinical severity of disease, which prompted the attending doctors to prescribe additional corticosteroids within 24 hours. These patients, both in the prednisone and placebo groups, often died within the first day or two after admission. In this group of patients adjunctive corticosteroid treatment did not seem to play a role.

In the clinically less ill group, however, retrospective subgroup analysis shows that corticosteroids did not significantly improve time to recovery or oxygen dependency, but survival did seem to be improved significantly (HR 0.25, 95% CI 0.08 - 0.77, p=0.016).

The lack of statistical significance may be due to our small study numbers, and is a limitation of the study. The study should be repeated in a large multicentre trial to confirm the findings.

Conclusion

In HIV-exposed infants with clinical PCP, adjunctive corticosteroid treatment does not appear to add benefit regarding time to recovery or oxygen independency, but early administration may improve survival. A large multicentre trial is needed to confirm these findings.

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Cytomegalovirus pneumonia occuring soon after starting highly active antiretroviral therapy in an infant

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A-2-month-old HIV-infected infant was ventilated for very severe *Pneumocystis jirovecii* pneumonia. After successful extubation, he was started on antiretroviral therapy. He developed a proven Cytomegalovirus infection, localising as pneumonia. This required repeated ventilation. He was extubated after six weeks and completed 32 days of ganciclovir.

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Introduction

Reports on immune reconstitution inflammatory syndrome (IRIS) in children following highly active antiretroviral therapy (HAART) are limited. Tuberculosis (TB) Bacillus Calmette-Guerin (BCG) IRIS is the most commonly reported disease. The prevalence of Cytomegalovirus (CMV) in patients with IRIS is unknown. We are reporting on the first case of proven CMV pneumonia IRIS occurring within four days of starting HAART. We hope this will increase awareness and also illustrate the need for guidelines on CMV IRIS in children.

Case report

Our patient, a 2-month-old boy, was admitted to the paediatric intensive care unit (PICU) with very severe pneumonia requiring respiratory support. His mother did not enrol in the prevention of mother-to-child transmission (PMTCT) programme. He was ventilated using a lung protection strategy with positive end expiratory pressure (PEEP) of 8 cm water, tidal volume of 6 ml/kg predicted for weight and with a fraction of inspired oxygen (FIO_2) of 0.60. Endotracheal aspirates were collected for *Pneumocystis jirovecii* immuno-flourescence, viral identification, bacterial and TB culture. Blood cultures, HIV DNA polymerase chain recation (PCR) (Ampliprep instrument real time qualitative PCR) and CMV viral load (Cobas Amplicor, Roche Diagnostics) were also performed.

The infant was treated with ampicillin and amikacin for five days, trimethoprim-sulfamethoxazole for 21 days, prednisone for 14 days and ganciclovir for five days. As per our protocol, ganciclovir was stopped when the CMV viral load revealed undetectable levels. His HIV DNA PCR was positive and he was worked up for HAART. HIV viral load, (Nuclisens instrument, BioMerieux Diagnostics) was included in the work up. The rest of the patient's pre-HAART results are demonstrated in Table 1. The infant was extubated after 11 days, and successfully weaned to nasal prong oxygen at a flow of 2l/min. Endotracheal aspirates and blood cultures performed two days before extubation were negative for bacterial growth. HAART was started on day 10. Four days after starting HAART, the child deteriorated clinically and radiologically and required re-ventilation. Repeat investigations demonstrated an increased CMV viral load. His CD4 count had also risen and his HIV viral load had fallen. This occurred in the absence of other infections (see Table 1 - post HAART). Ganciclovir was restarted; and 32 days later a repeat test of CMV viral load was undetectable. At no point was HAART stopped. The child was extubated after six weeks and weaned to nasal prong oxygen.

Table 1: Investigations performed before and after HAART was initiated

	Pre- HAART	Post-HAART
PJP IFA	**Positive**	**Negative**
CMV VL (log)	Undetectable	1,000,000 copies/ml (log 6)
CD4 count (%)	304x106/l (42.33%)	1,833x106/l (44.8%)
HIV VL (log)	4,800,000copies/ml (log 6.68)	19,000copies/ml (log 4.27)
ETA(bacteria)	Negative	Negative
ETA(viruses)	Negative	Negative
ETA(TB)	Negative	Negative

PJP IFA= *Pneumocystis jirovecii* immunoflourescence antibody, CMV VL= Cytomegalovirus viral load,
HIV VL= Human immunodeficiency virus viral load, ETA= Endotracheal aspirate, TB= Tuberculosis

HAART= Highly active antiretroviral therapy

Discussion

IRIS in children, especially infants, is infrequently reported in the literature. This may change, however, as more clinicians' implement the World Health Organization recommendation of 2008,[1] of starting infants who are HIV-infected on HAART irrespective of their immunological or clinical status. This

policy change was motivated by the study of Violari *et al.*[2] The challenge is the recognition and investigation of these infants and this may be an even a bigger challenge for the developing world with limited resources. The commonly reported organisms reported to cause IRIS are *Mycobacterium tuberculosis*, TB BCG, non tuberculous mycobacterium, skin manifestations of herpes zoster, impetigo and tinea capitis.[3-5] Only one case of CMV pneumonia IRIS has been reported.[5] In this case, the onset of symptoms occurred nine days after starting HAART. Our case suggests CMV pneumonia occurred four days after starting HAART. These two cases imply that the presentation of symptoms for CMV IRIS is earlier than other forms of IRIS.[6] We used a real time quantitative PCR to detect the presence of CMV on admission, and at the onset of deterioration of symptoms. Although there are no established cut points for CMV viral load, 1,000,000 copies/ml must be considered significant if symptoms recur after initial resolution. In addition, the viral load became undetectable 32 days after starting ganciclovir. At no point was HAART interrupted in our patient. The infant did not develop one of the established side effects of ganciclovir despite its addition to HAART.

Our patient met the case definition for IRIS, that is he demonstrated evidence of clinical response to HAART with a significant increase in CD4 count and more than 1 $\log_{10}$ decrease in his HIV viral load.[4] Even though the pathogenesis of IRIS is still poorly understood, it is postulated that during the recovery of the immune system, there is a rapid recovery of pathogen specific Th1 cells directed at extracellular pathogens, while the recovery of T regulatory cells lags behind.[4]

We present this case to alert physicians to be more vigilant in looking for unusual pathogens (especially CMV) in infants started on HAART and displaying symptoms suggestive of IRIS. In addition, we highlight the potential for CMV IRIS to occur earlier. We would encourage guidelines on HIV management in children, especially in resource-poor settings where the prevalence could be higher than presently reported, to explore CMV IRIS.

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Outcome of human immunodeficiency virus–exposed and –infected children admitted to a pediatric intensive care unit for respiratory failure*

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Objective: **Acute severe pneumonia with respiratory failure in human immunodeficiency virus-infected and -exposed infants carries a high mortality. *Pneumocystis jiroveci* is one cause, but other organisms have been suggested to play a role. Our objective is to describe the coinfections and treatment strategies in a cohort of human immunodeficiency virus-infected and -exposed infants with respiratory failure and acute respiratory distress syndrome, in an attempt to improve survival.**

Design: **Prospective intervention study.**

Setting: **Steve Biko Academic Hospital, Pretoria, South Africa.**

Patients: **Human immunodeficiency virus–exposed infants with respiratory failure and acute respiratory distress syndrome were recruited into the study.**

Interventions: **All infants were treated with routine therapy for *Pneumocystis jiroveci* and bacterial coinfection. However, in addition, all infants received ganciclovir from admission until the cytomegalovirus viral load result was demonstrated to be <log 4.**

Measurements: **Routine investigations included human immunodeficiency virus polymerase chain reaction, cytomegalovirus viral load, blood culture, C-reactive protein, and white cell count. Tracheal aspirates for *Pneumocystis jiroveci* detection, bacterial culture, tuberculosis culture, and viral identification were performed.**

Main Results: **Sixty-three patients met the recruitment criteria. The mortality rate was 30%. *Pneumocystis jiroveci* was positive in 33% of infants, while 38% had cytomegalovirus viral load ≥log 4. Only 7.9% of infants had a positive tuberculosis culture. Nineteen deaths occurred, 13 of which had a cytomegalovirus viral load ≥log 4. Bacterial coinfection and CD4 count were not predictors of mortality.**

Conclusions: **A case fatality rate of 30% is achievable if severe pneumonia with respiratory failure and acute respiratory distress syndrome is managed with a combination of antibiotics and ventilation strategies. Cytomegalovirus infection appears to be associated with an increased risk of death in this syndrome. This may, however, be a marker of as yet undefined pathology. (Pediatr Crit Care Med 2012; 13:516–519)**

Key Words: cytomegalovirus; ganciclovir; human immunodeficiency virus; mortality; pneumocystis syndrome

Within South Africa (as with many other countries) human immunodeficiency virus (HIV) infection is a significant cause of morbidity in women and their infants. In South Africa, 26% of pregnant women are HIV-infected, and in the absence of preventative therapy there is a 15%–30% risk of HIV infection in their infants (1, 2). Even children who are part of the Prevention of Maternal to Child Transmission program have an increased risk of HIV infection relative to those who are not exposed, although that risk is substantially reduced. Mortality in HIV-infected children results primarily from respiratory tract infections (3, 4).

In children (and especially HIV-infected children) with acute severe respiratory disease requiring endotracheal intubation and ventilation, a number of pathogens (including *Pneumocystis jiroveci* and cytomegalovirus [CMV]) have been isolated. Although there has been considerable focus on *P. jiroveci* as a cause of mortality (the term pneumocystis pneumonia [PCP] was retained when *Pneumocystis carinii* was taxonomically renamed jiroveci [5]), it would be important to consider the potential contribution of other pathogens, and in particular, the association of CMV infection, with mortality. CMV infection has been reported to affect nearly 90% of HIV-exposed infants (6) and especially HIV-exposed infants with severe pneumonia.

Admitting HIV-infected infants with severe pneumonia to an intensive care unit in a resource limited setting has created a number of ethical dilemmas for pediatricians, and these dilemmas are created by the historical poor outcome for these patients and the pressure on scarce resources (7).

Study Aim. To report on the pathogens identified in a cohort of HIV-exposed and -infected children admitted to a pediatric intensive care unit (PICU) with respiratory failure and acute respiratory distress syndrome (ARDS), and to explore the relationship between pathogens identified and patient outcomes.

MATERIALS AND METHODS

All HIV-exposed infants admitted to the PICU at the Steve Biko Academic Hospital, Pretoria, South Africa, with respiratory failure were recruited for enrollment into this study. Patients had to fit the diagnosis of ARDS as described by Bernard et al (8), the most important of which was hypoxic acute

*See also p. 597.

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lower respiratory tract infection with a partial pressure of oxygen in mm Hg over a fraction of inspired oxygen ratio of <200. Each infant was ventilated using a strategy of high positive end-expiratory pressure of 10–15 cm of water, tidal volume of 6–8 mL/kg, and a positive inspiratory pressure not exceeding 30 cm of water. Tidal volume was read from the ventilator display despite limitations of this technique (9, 10). None of the infants were offered high frequency oscillation ventilation due to unavailability of that modality. Total fluid intake was restricted to 60–80 mL/kg/day, and delivered medication was specifically included in the calculation of total fluid volume.

This prospective study of all consecutive admissions was conducted between January 2008 and December 2009. Children had their initial oxygenation index, Pediatric Risk of Mortality (PRISM), and Revised Pediatric Index of Mortality scores measured at admission to the PICU. Each child had a number of investigations performed at admission, and airway specimens were collected within 2 hrs of endotracheal intubation. Nonbronchoscopic bronchoalveolar lavage specimens were collected for *P. jiroveci* immunofluorescence antibody testing (performed using the Axis Shield diagnostics/UK Code FIPC200 available from Bioweb SA, Randburg, South Africa), bacterial microscopy culture and sensitivity, viral immunofluorescence antibody testing using the Chemicon/Millipore kit (Light Diagnostics, Billerica, MA), and tuberculosis microscopy culture and sensitivity (Wescor aerospray automatic stainer/US for auramine staining available from Nyala Technologies SA, Johannesburg, South Africa). Blood testing was conducted for white cell count (conducted using the automated hematology analyzer Advia 2120 [Siemens Diagnostics, Midrand, South Africa]). C-reactive protein was measured using an immunoturbidometric reaction (Beckman Coulter Synchron LX20 PRO, Beckman Coulter Incorporated, Fullerton, CA). CMV viral load polymerase chain reaction (PCR) was determined using a Toga lab on Cobas Amplicor instrument (Roche Diagnostics, Randburg, Gavleng, South Africa). An HIV deoxyribonucleic acid PCR was determined by means of a Amplicor HIV-1 DNA test, version 1.5 (Roche Diagnostics). A peripheral blood volume of 2 mL was collected for blood culture after careful cleansing of the arm. Blood was immediately injected into relevant blood culture bottles. Blood cultures positive for growth were plated onto agar and sensitivity measured using a Kirby–Bauer technique (Bactec 9240, Becton Dickinson, Sparks, MD).

Each infant was treated, at the time of presentation, with trimethoprim–sulphamethoxazole (20 mg/kg/day of the trimethoprim component and 100 mg/kg/day of the sulphamethoxazole component) and oral steroids (1–2 mg/kg/day). Ampicillin and amikacin were routinely added at the time of admission and administered for 5 days unless a resistant organism was cultured, in which case appropriate antibiotics were administered. This is in accordance with the national guideline, which in turn is based on the common organisms cultured in HIV-infected patients presenting with pneumonia (11). These initial antibacterial antibiotics were changed to meropenem if the patient deteriorated after 48 hrs of admission in order to treat the possibility of more resistant hospital-acquired organisms. Trimethoprim–sulphamethoxazole was continued for 21 days and oral steroids for 14 days.

In addition to these standards of therapy, all children received intravenous ganciclovir (10 mg/kg/day). There are currently no guidelines on what constitutes CMV disease in the setting of CMV viral isolation. For the purposes of this study, CMV infection status was defined as follows: CMV disease—CMV viral load >10,000 copies/mL (log >4); CMV infection—CMV viral load 0.1–10,000 copies/mL (log –1 to log 4); and CMV-uninfected—CMV viral load negative. The value of 10,000 copies/mL is extrapolated from transplant studies (12) and should be used together with clinical, radiological, and laboratory support for CMV disease. PCR holds promise as an alternative diagnostic method (13). Ganciclovir was continued until either CMV viral load was <10,000 copies/mL or for 3 wks after the onset of triple antiretroviral therapy.

Approval to conduct the study was obtained from the Human Ethics Committee of the University of Pretoria, and written informed consent was obtained from each parent with the help of a qualified PICU-trained nursing practitioner who was aware of the study.

In the case of infants who died, permission for postmortem examination was requested of each parent.

Statistical Methodology. The associations of mortality with individual exposure variables, on an ordinal scale, were assessed using Pearson's chi-square test, which was confirmed using Fisher's exact test, and for those exposure variables on a continuous scale, Student's two-sample *t* test was employed and was confirmed using Wilcoxon's rank sum test. Testing was done at the 0.05 level of significance, and those exposure variables significant at the liberal 0.15 level of significance were included into the multivariate logistic regression analysis. Stata 10 (eStataCorp LP, College Station, TX) was used for computations.

RESULTS

A total of 90 infants with HIV-related pneumonia, respiratory failure, and ARDS were admitted during the study period. Twenty-seven were excluded due to refusal of enrollment into the study. Sixty-three infants qualified for final analysis. The mean age was 3.7 months (range 2–9), median age 3 months. None of the infants in this study had received PCP (trimethoprim–sulphamethoxazole) prophylaxis, and none were on highly active antiretroviral therapy at the time of the study. The mean weight for age of the study population was 4.6 kg (z score = –2.7), which is moderately underweight for age. The median (range) for the oxygenation index, PRISM score, percentage-predicted death rate based on the PRISM score, and percentage-predicted mortality based on the Revised Pediatric Index of Mortality score were 16 (4.3–39.6), 10.0 (4.0–2.0), 6.1 (1.9–9.1), and 18.7 (13.4–52.6), respectively.

All study children were HIV-exposed; 53 (84%) were HIV-infected with a positive HIV DNA-PCR. Ten (16%) of the exposed infants were HIV-uninfected. Nineteen children (30%) died. Thirty-two percent of HIV-infected children died vs. 20% of HIV-uninfected infants (p = .709). Twenty-one (33%) of infants had *P. jiroveci* identified from a nonbronchoscopic bronchoalveolar lavage specimen. Thirty-five (55%) children had a positive CMV viral load; while 24 (38% of the total study group) had a CMV viral load in the range determined as CMV-disease.

The most important outcome in this study was deemed to be survival and therefore discharge from PICU. Each parameter or laboratory variable that might have reflected an infection on each patient at admission was analyzed for prediction of mortality. Blood culture was positive for bacterial organisms in five (7.9%) and eight (12.7%) of nonsurvivors and survivors, respectively. Pathogens cultured included coagulase negative *Staphylococcus* (n = 6), and one each of *Streptococcus pneumonia*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Enterococcus faecium*, and *Enterococcus faecalis*. Bacterial culture on nonbronchoscopic bronchoalveolar lavage yielded 19 pathogens, 6 (9.5%) and 13 (20.6%) in nonsurvivors and survivors, respectively. Pathogens included *Klebsiella pneumonia* (n = 4) and two each of extended-spectrum β-lactamase producing *K. pneumonia*, *S. aureus*, *S. maltophilia*, *Escherichia coli*, *and Enterobacter cloacae*. There was one culture of each of *S. pneumonia*, *P. aeruginosa*, *Acenitobacter baumanni*, *Proteus mirabilis*, and coagulase negative *Staphylococcus*. Nine respiratory viruses were isolated, one (1.6%) and eight (12.7%) from nonsurvivors and survivors, respectively. These included respiratory syncytial virus (n = 3), two each of adenovirus, parainfluenza virus 3, and influenza virus B. These bacterial cultures, viral isolates, together with neutropenia (11.1%), and elevated C-reactive protein (15.9%) were not contributors

to mortality (p = .508, p = 1.00, p = .256, p = .685, and p = .162, respectively).

Included into the multivariate logistic regression based on a 0.15 level of significance were CMV status (p = .002), CD4 percentage (p = .142), and tuberculosis (p = .078). From the logistic regression analysis, CMV status emerged as a significant risk factor of mortality (adjusted odds ratio = 6.5; p = .002; 95% confidence interval 1.98–21.23) (Table 2). Positive identification of *P. jiroveci* did not predict mortality *per se*, irrespective of the HIV status (p = .774). The risk of dying was higher in CMV-diseased infants (viral load log ≥4) (58%) (p = .002). Mortality in relation to interaction of *P. jiroveci* and CMV status is documented in Table 1. Mortality in this group of infants with a CMV viral load ≥4 occurs at a mean of 12.9 days. The average length of stay for all surviving infants was 14.1 days (confidence interval 10.4–17.9).

DISCUSSION

Within the context of this study and the methodology used, a number of organisms causing respiratory failure in HIV-infected and -exposed infants have been identified. The limitation of the methodology employed is acknowledged, and PCR testing for most of the organisms is now recognized as a gold standard (14–17). This was not available at the time of the study in our setting.

Within a setting of HIV-disease, mortality from respiratory failure in HIV-infected infants was 12% higher than those exposed but not infected. This was, however, not statistically significant. This may in part be due to the fact that this study is underpowered to detect this effect. What is clear, however, is that HIV-uninfected but exposed children contract PCP. This finding suggests that the immune dysregulation that creates a risk for PCP is present in HIV-exposed but not HIV-infected children. This has been demonstrated in a previous South African study (18). This finding was even more significant as none of the mothers were aware of their children's HIV exposure, and their children were consequently not offered prophylaxis against *P. jiroveci*. Pneumocystis prophylaxis, in HIV-exposed children, has been clearly shown to reduce mortality (19).

The overall mortality of patients was significantly higher than predicted using the PRISM score. Use of Revised Pediatric Index of Mortality scores, which specifically include HIV infection as a factor, substantially changes the predicted risk of mortality. In the context of our study and children with respiratory failure only, it appears that the PRISM score underpredicts mortality and the Revised Pediatric Index of Mortality score is a more realistic predictor of mortality, probably because HIV-infection is included as a "high-risk" diagnosis.

A case fatality rate of 30% has been achieved through a meticulous approach to management of the interaction between the host and infection in infants with respiratory failure. This has been demonstrated previously. In 2004, Cooper et al (20) documented that HIV-infected children admitted to a PICU in London had a 38% mortality when every effort is made to treat such children. The actual mortality of these infants beyond the PICU into the first year of life is a subject of an ongoing study. However, all of the patients in this study who were HIV-infected received antiretroviral therapy early in the course of their disease, and survival to 1 yr of age appeared to be better than reported in previous studies (21).

It appears that at least two major infectious diseases coexist in more severely ill patients with this form of pneumonia, namely *P. jiroveci* and CMV. The interaction of these two organisms in HIV-infected individuals has been suggested in previous reports (22, 23). CMV, in fact, appears to be associated with an increased risk of death in our study, with 79% of the deaths occurring in infants coinfected with CMV despite early treatment with ganciclovir. This CMV association with mortality in HIV-infected children has been documented in two recent publications. These report a case fatality rate of 28% (24) and 36% (25), respectively. The second study also reported a PICU mortality of 72% in the patients who were treated with trimethoprim–sulphamethoxazole and ventilated for suspected PCP but who did not respond to treatment. This cohort was not treated with ganciclovir. A possible explanation for the high mortality associated with CMV (and despite ganciclovir use) is the fact that the inflammatory response or pathological state induced by CMV disease may already be well-established at diagnosis and intervention is likely to be unsuccessful (26). Additional explanations may include poor activity of ganciclovir, drug interactions reducing ganciclovir efficacy and the possibility that CMV-infection is but a surrogate marker for another disease process. An explanation for this phenomenon still requires further study.

Despite reasonably small numbers of bacterial, other viral, and tuberculosis coinfections, these offending organisms must be contributing to respiratory failure with ARDS in these infants. Clearly the actual contribution is impossible to determine because the testing methodology of each of the tests employed is imperfect. It is well-known that few children with proven bacterial pneumonia have positive sputa or blood cultures (11). A follow-up study employing PCR for bacterial antigens would be advantageous.

Study Limitations. This study has a number of limitations. The major limitation of our study is the definition of CMV disease. Clearly use of a blood measure of viral load does not imply pulmonary disease. This fact has not escaped our attention, but short of lung biopsy actual proof of CMV infection has proven difficult in previous studies. In addition, the close correlation between CMV viral load and mortality must suggest that this test is identifying some disease process. Exactly what that disease is seems unclear from our study. Some additional limitations include failure to fully identify all potential pathogens through PCR and culture techniques. Such testing would enhance the diagnostic yield in our study but would of course not have changed our therapeutic strategy as all organisms, with the exception of tuberculosis, were

Table 1. Mortality as related to infection status

	Human Immunodeficiency Virus–Infected	Mortality (%)	Human Immunodeficiency Virus–Uninfected	Mortality (%)	Total Mortality (%)
PJP+/CMV+	10	5 (50)	2	2 (100)	7/12 (58.3)
PJP–/CMV+	19	8 (42)	3	0 (0)	8/22 (36.4)
PJP+/CMV–	9	0 (0)	0	0 (0)	0/8 (0)
PJP–/CMV–	15	4 (27)	5	0 (0)	4/21 (19.0)
Total	53	17 (32)	10	2 (20)	19/63 (30)

PJP, *Pneumocystis jiroveci*; CMV, cytomegalovirus.

empirically treated. An attempt was also made to get postmortem biopsies on the 19 deaths, but permission was denied by all the parents. This would have given us the opportunity to observe the histology of the lungs in order to determine whether fibrosis was the end-stage pathology of patients with this form of ARDS.

CONCLUSIONS

Respiratory failure in infants who are HIV-exposed or -infected has more than one etiology, and CMV coinfection appears to be associated with mortality. However, other explanations for this association are possible. Mortality of 30% was achieved through treating coinfection, ventilation in a controlled fashion, and liberal fluid restriction.

Decreasing 30% mortality will require interventions and research in the realm of CMV prevention and possibly better treatment.

It remains pertinent to point out that effective antenatal care with diagnosis and appropriate therapy of infected mothers can virtually eliminate the problems of HIV infection in young children.

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32 Cytokine Profile and Clinical Correlates in Immune Deficient (HIV-infected) Infants with Severe (hypoxic) Pneumonia

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RATIONALE: Severe pneumonia in infants who are HIV-infected is a common problem in many parts of the developing world, especially sub-Saharan Africa. What has been missing from previous studies of severe pneumonia in HIV-infected infants, however, is a description of the host inflammatory response and cytokine/chemokine profile that accompanies this disease. To describe the cytokine profiles associated with severe hypoxic pneumonia in HIV-infected infants.

METHODS: In a cohort of HIV-infected children diagnosed clinically with severe hypoxic pneumonia, paired serum and sputum cytokines were tested. A control group of HIV-infected children with bronchiectasis contributed matching controls.

RESULTS: A total of 100 infants (mean age 2.8 months) with a clinical diagnosis of severe hypoxic pneumonia were included in this study. IP-10 was markedly elevated in both sputum (mean 560.77pg/ml) and serum (mean 9091.14pg/ml), while IP-10 was elevated in serum (mean 39.55 pg/ml), with both these cytokines being significantly higher than in stable children with HIV-related bronchiectasis.

CONCLUSIONS: This study of HIV-infected infants with severe hypoxic pneumonia suggests that IL-10 and IP-10 are associated with more severe lung disease. However, further investigation of this association is required.

33 Atheroprotection Conferred by Immunization with 15-Mer Peptide Fragments From ApoB100

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RATIONALE: Native LDL vaccinations of atherosclerotic-prone mice (ApoE-/-) have yielded 50% athero-reduction when administered repeatedly at regular intervals over several months. Akin to allergy immunotherapy, the presumed mechanism of this atheroprotection is thought to be due to induction of tolerance to the suspected autoantigen, oxidized LDL. Here, we report the discovery of a novel peptide found in murine ApoB100 (the lipoprotein portion of LDL) and demonstrate its ability to confer atheroprotection.

METHODS: 15-mer peptide sequences spanning ApoB100 were synthesized and screened for their ability to bind tightly to MHC class II and cause T-cell proliferation after primary immunization. The candidate peptide (CP3) was used to vaccinate 5 female *ApoE*$^{-/-}$ using 50 micrograms of CP3/CFA subcutaneously in the inguinal area at 8 wks of age. Western diet was started at 10 wks of age. Repeated boosters with 25 micrograms of CP3/IFA were administered intraperitoneally at age 12, 16, 20 and 22 weeks. Mice were sacrificed at age 23 weeks and organs were harvested for analysis. PBS and irrelevant peptide were used as controls.

RESULTS: CP3 treated mice showed >50% reduction in lesion size by aortic pinning when compared to PBS ($p=0.003$) and irrelevant peptide controls ($p=0.004$). No differences were observed in the percentage of IFNg, IL-2, IL-10, IL-17A, or FoxP3 positive cells in spleen or lymph nodes by intracellular FACS staining.

CONCLUSIONS: CP3 is a novel peptide with T-cell specificity which affords atheroprotection to a similar degree as native LDL when used in a vaccination scheme.

34 Removal of Coagulation Factors by the Gamunex®-C Purification Process

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RATIONALE: Gamunex®-C is a highly purified human plasma-derived intravenous immunoglobulin (IVIG). Coagulation factors are natural components of the starting plasma used for IVIG manufacture and are removed during purification. Residual coagulation factor activity has been associated with an increased incidence of thromboembolic adverse events with a specific immunoglobulin product. The purpose of this study was to characterize the removal of coagulation factors during the manufacture of Gamunex®-C.

METHODS: Relevant fractionation and purification process intermediates from 30 Gamunex®-C batches were collected and analyzed for specific coagulation factors and procoagulant activity. The thrombin generation test (TGT) and the non-activated partial thromboplastin time (naPTT) are global coagulation methods that detect procoagulant activity. Samples were also assayed for specific clotting factors, including Factor XI (FXI), activated FXI (FXIa), and Factor XII (FXII).

RESULTS: The purification process effectively removes any detectable procoagulant activity from the product and reduces coagulation factor content (FXI and FXII) to levels just at or below the quantification limits of the respective methods. The caprylate treatment steps of the process are critical for procoagulant removal.

CONCLUSIONS: These data demonstrate consistent and robust removal of coagulation factors by the Gamunex®-C purification process and serve to identify the caprylate precipitation and caprylate incubation steps as critical for removal of procoagulant impurities. Overall, the entire purification process from Plasma Pool to Sterile Bulk reduces FXI and FXII content by at least 5000-fold relative to IgG concentration with removal to very low or non-quantifiable levels by the two caprylate steps.

35 Serum 25-Hydroxyvitamin D Is Associated with Positive Hepatitis B Vaccine Response

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RATIONALE: Vitamin D deficiency or insufficiency is a relatively common and significant public health problem. Previous lots of papers have shown the relationship between vitamin D and immune functions and .Recent paper showed vitamin D deficiency was associated with poor response to active hepatitis B immunization in patients with chronic kidney disease. According to previous report, we want to examine the associations between vitamin D levels and response to hepatitis B immunization in healthy adults in large sample size.

METHODS: We recruited 5025 male adult persons in one ship building company. We assessed the relationships between positive hepatitis B vaccine response and age, BMI(body mass index), hypertension, smoke, diabetes mellitus.

RESULTS: We found positive relations hepatitis B vaccine response and age ($P<0.01$), BMI($P=0.01$), smoke ($P<0.01$), diabetes mellitus ($p<0.01$). Hypertension was not associated with hapatitis B vaccine response ($p=0.54$).

CONCLUSIONS: Vitamin D levels are associated with poor response to hepatitis B immunization.

Acute viral bronchiolitis: aetiology and treatment implications in a population that may be HIV co-infected

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Introduction

Bronchiolitis is a disease where infection results in inflammation of the small airways and it occurs most commonly in children under 2 years of age.[1] Most authors and experts agree that the condition has a viral aetiology.[2] The commonest aetiology is respiratory syncitial virus (RSV) but parainfluenza virus (PIV) (especially type 3), influenza virus, adenovirus and some newer viruses have been identified.[3] Despite the viral nature of this condition, and overwhelming evidence that bacterial co-infection is an extremely rare event,[4,5] most general practitioners and even paediatricians in South Africa treat infants with bronchiolitis with an antibiotic. What is even more worrying is that the routine use of broad spectrum penicillins has made way for cephalosporins, macrolides and carbapenems. Recent guidelines have documented no additional benefit from routine antibiotic use in this condition.[6,7] There are, however, some studies pointing to bacterial super-infection in children with severe bronchiolitis.[8,9] One such study investigated 165 patients, with a median age of 1.6 months, and found that 70 (42.2%) had a bronchoalveolar lavage culture positive for bacteria. In 36 (21.8%), these were deemed to be co-infected, while 34 (20.6%) had low bacterial growth and were deemed 'possibly' co-infected. All children were, however, ventilated for severe bronchiolitis and those co-infected required longer intensive care stay. White cell count (WCC) and C-reactive protein (CRP) did not differentiate between the groups and did not help to identify bacterial co-infection.[8]

Another trend that has crept into specialist practice is performing a CRP measurement on a blood sample of children with bronchiolitis. CRP measurement has been widely shown to be neither a sensitive nor a specific measure of bacterial disease in children with pneumonia.[10-12] While most guidelines addressing pneumonia management in children suggest the routine use of antibiotics, those for bronchiolitis management discourage their use. Quite clearly failing to use clinical skills to differentiate between pneumonia and bronchiolitis contributes to poor treatment decision-making. Bronchiolitis is a disease of the peripheral airways and inflammation leads to air trapping with signs of hyperinflation such as the Hoover sign, loss of cardiac dullness and hepatoptosis. Pneumonia presents with fever, crepitations and signs of parenchymal consolidation. Some overlap of these conditions occurs but should then be defined clearly.

Bronchiolitis due to RSV is a disease of young infants in developed countries[13] but there is a suggestion of a later age of involvement in the developing world. The seasonality of bronchiolitis, although conventionally described as a winter disease, is not universally so in parts of South Africa.[14] In KwaZulu-Natal there is a greater tendency for bronchiolitis to occur throughout the year (Jeena P, personal communication). Risk factors for severe RSV-associated disease have been identified as gestational age less than 35 weeks at birth and chronological age less than 6 months, chronic lung disease in a child less than 2 years of age requiring medical therapy in the six months preceding admission for RSV bronchiolitis, children less than 2 years of age with cyanotic congenital heart disease or acyanotic congenital heart disease with a clinically significant shunt, and the presence of immunosuppression.[14]

The clinical diagnosis of viral pneumonia is made more frequently than that of bronchiolitis in HIV-infected children.[15] An altered host immune response after RSV infection may explain the difference in clinical presentation observed between HIV-infected and uninfected children, with HIV-infected children having more severe disease and more frequent bronchopneumonic changes. Other differences observed in this group of patients include the risk for developing RSV-associated severe lower respiratory tract infection that persists beyond the first 6 months of life and that the incidence of concurrent bacteraemia is more common in HIV-infected children.[15]

Bronchiolitis is frequently incorrectly managed with antibiotic therapy. Despite the evidence that bacterial co-infection occurs in children with more severe disease, predicting this in mild or moderate disease is unclear.[15]

The aim of this study is to document the viral nature of bronchiolitis in a cohort of bronchiolitics in Pretoria by describing the microbiological profile of children with bronchiolitis at Steve Biko Academic Hospital, assessing the rate of bacterial co-infection in bronchiolitis and seeking laboratory (biochemical; immunological) parameters that predict mixed (both viral and bacterial) infection.

Methods

This was a prospective longitudinal study of all children (under 2 years of age) admitted to Steve Biko (Pretoria) Academic Hospital with bronchiolitis during a two-year period (January 2006 – December 2007). Virological and bacteriological parameters were assessed. In an attempt to define bacterial co-infection, blood culture, CRP and white blood cell count were measured. All samples were collected only at study entry and not sequentially.

Complete blood count was determined using the automated haematology analyser Advia 2120 (Siemens Diagnostics, South Africa).

CRP was measured using an immunoturbidometric reaction (Beckman Coulter Synchron LX20 PRO, Beckman Coulter Incorporated, Fullerton, California, USA).

Blood cultures positive for growth were plated onto agar and sensitivity measured using a Kirby-Bauer technique (Bactec 9240, Becton Dickinson, Maryland, USA).

All children in this age group presenting to hospital with fast breathing, cough and noisy breathing in the period 1 January 2006 to 31 December 2007 were included. A chest radiograph was performed on every child. Children found to have pneumonic consolidation on chest X-ray (CXR) were excluded. These children were admitted to the paediatric short-stay ward. Immunofluorescence testing was done using Chemicon/ Millipore kit (Light Diagnostics) on nasopharyngeal aspirate samples for detection of respiratory viruses (parainfluenza 1, 2, and 3, influenza A and B, cytomegalovirus, adenovirus and RSV).

HIV testing was done using fourth generation HIV ELISA assays, Architect (Abbott Diagnostics) and Modular E170 (Roche Diagnostics). HIV DNA was extracted from 100 µl of whole blood using MagNa Pure LC DNA Isolation Kit III in a MagNa Pure instrument (Roche Diagnostics), then HIV polymerase chain reaction (PCR) was performed using an Amplicor HIV-1 DNA test, version 1.5 (Roche Diagnostics).

Children were managed by standard protocol which included oxygen by nasal prongs. No child was given an antibiotic.

Results

One hundred and six children with viral-proven bronchiolitis were identified in the two-year period. There were 52 males and 54 females with a male:female ratio of 1:1.04. The mean age for males was 6.2 months and for females 5.5 months.

The ages for children with bronchiolitis in whom RSV, parainfluenza virus, influenza virus and adenovirus were identified, are summarised in Table 1.There were five patients in whom two viruses were isolated.

Table 1: Summary statistics for age by viral isolate

Viral isolate	No. of positive results	Mean age in months (SD)	95% confidence interval
RSV	62	4.81 (4.28)	(3.72; 5.89)
Influenza virus	9	6.67 (3.97)	(3.62; 9.72)
Parainfluenza virus	26	6.37 (4.57)	(4.52; 8.21)
Adenovirus	14	6.71 (4.86)	(3.91; 9.52)
HIV	14	8.07 (3.85)	(5.85; 10.30)

At Steve Biko Academic Hospital, bronchiolitis shows a winter predominance (Figure 2) related to RSV and parainfluenza virus infections in particular.

A positive bacterial blood culture was found in 18 patients (16.98%). Fourteen of these were deemed to be contaminants as *Staphylococcus epidermidis* was isolated, and only four had a potential pathogen (one *Streptococcus pneumoniae*, one *Klebsiella pneumoniae*, one *Escherichia coli* and one *Staphylococcus aureus).* Among the patients tested only one was positive for both blood culture and CRP, while among the blood culture-negative patients 35 were CRP-positive, i.e. a very high false positive rate.

No correlation was found between CRP and white cell count (Figure 3) and between CRP and the neutrophil count (Figure 4) in either positive or negative blood culture groups.

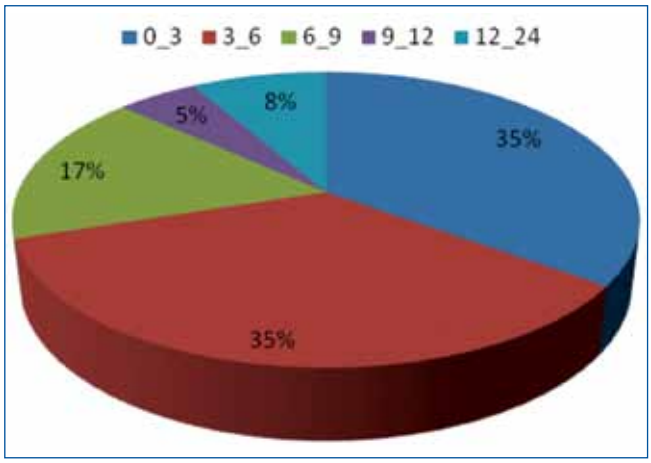

Figure 1: RSV age distribution (in months) for children with bronchiolitis at Steve Biko Academic Hospital (January 2006-December 2007)

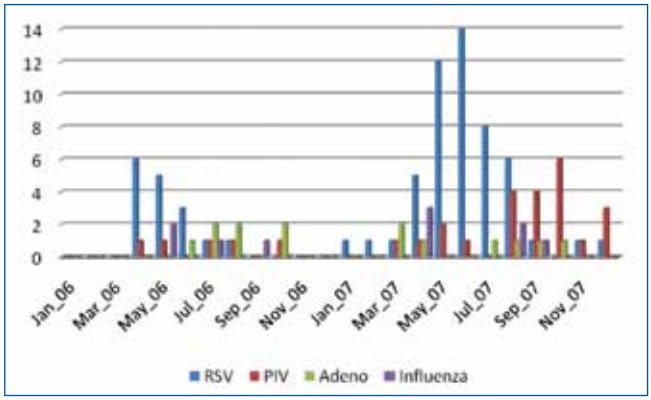

Figure 2: Number of viral isolates from children with bronchiolitis per month

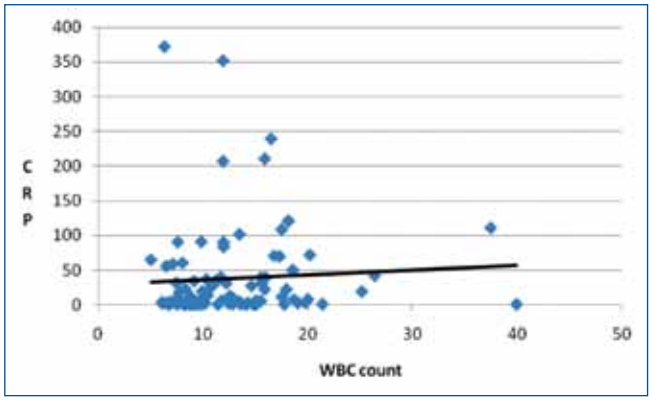

Figure 3: Correlation of CRP with white blood cell count in children with bronchiolitis, $R^2 = 0,0036$

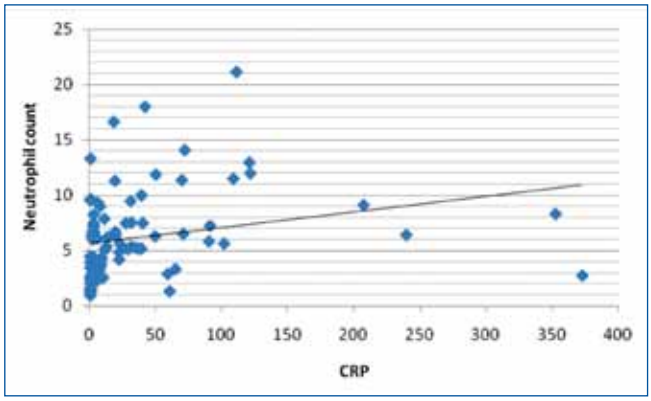

Figure 4: Correlation of neutrophil count with CRP in children with bronchiolitis, $R^2 = 0.055$

HIV was clinically suspected (presence of failure to thrive, hepatosplenomegaly, generalised lymphadenopathy or oral thrush) in 41 patients (38.7%) and then proven (positive HIV ELISA and PCR) in 14 patients (13.2%). The mean age of bronchiolitis in these children was 8 months, as opposed to the HIV-uninfected children where the mean age was 5.8 months. The HIV-infected bronchiolitics isolated the same viral organisms as the HIV-uninfected children, but the percentage composition was different (see Table 2).

Table 2: Proportion of positive viral isolates by HIV status

Isolate	HIV		Fisher's exact test
	Positive	Negative	p value
RSV	33% (5/15)	53.9% (14/26)	0.330
Influenza virus	6.67% (1/15)	11.54% (3/26)	1.000
Parainfluenza virus	40% (6/15)	26.9% (7/26)	0.492
Adenovirus	20% (3/15)	11.54% (3/26)	0.651

Due to the wide scatter of CRP values, geometric means along with their 95% confidence intervals are reported comparing HIV-positive and -negative patients in terms of their CRP values (Table 3), p value = 0.4736.

Table 3: Summary statistics for CRP by HIV status

HIV status	Geometric mean	95% confidence interval
Positive	18.44	(6.02; 56.43)
Negative	12.26	(6.49; 23.18)

Discussion

RSV bronchiolitis in children in Pretoria has a slightly older age distribution compared to that in developed countries. The mean age of bronchiolitis in HIV-infected children is higher than that of -uninfected children in keeping with the findings of earlier studies.[3] Both HIV-infected and HIV-uninfected children had determinants of bacterial co-infection that did not correlate with one another. Neither white blood cell count, % neutrophil count, CRP, nor blood culture of bacteria reliably suggest bacterial lung disease. We are unable to conclude from these variables what degree of bacterial pulmonary co-infection exists in viral bronchiolitis. However, none of the children in this study was treated with antibiotics and none suffered extended morbidity or mortality. We are therefore led to conclude that bacterial co-infection is both rare and inconsequential to true viral bronchiolitis. Since this study did not include children with a diagnosis of bronchopneumonia we limit our conclusions to bronchiolitis.

Since significant bacterial co-infection is rare in bronchiolitis, we recommend that the routine use of antibiotics for mild and moderately ill wheezy youngsters be discouraged. Bronchiolitis is a disease of viral origin (at least in our study of patients with mild to moderate disease) and whilst it is possible that bacterial co-infection occurs in children, especially those with more severe disease, the routine use of antibiotics is both inappropriate and potentially disastrous.

The under-representation of HIV-infected children in this study of bronchiolitis may have many explanations. Two of these may be that isolated viral bronchiolitis is uncommon in HIV-infected children and secondly that HIV infection confers a greater likelihood of more severe lung disease and bronchopneumonia. This study is unable to suggest a reason for this finding.

We suggest that there is an urgent need for South African bronchiolitis guidelines to manage this problem. Such guidelines must stress the differences between pneumonia (especially bronchopneumonia) and bronchiolitis. Routine antibiotic use is inappropriate in bronchiolitis. We would also encourage medical personnel to distinguish between bronchiolitis and bronchopneumonia as the inclusive diagnosis of bronchiolitis/bronchopneumonia in individual children is often interpreted as an excuse to use antibiotics. The routine use of bronchodilators and steroids, whilst a topic beyond the scope of this article, have also proven to be of limited value in this condition.[6]

Practitioners are urged to return to the evidence-based treatment of this very common condition. Misuse of antibiotics and CRP has both a cost, and also an implication for antimicrobial resistance. A number of limitations of this study are acknowledged. Firstly, the children treated for bronchiolitis were not followed clinically to determine long term morbidity and recurrence of disease and wheeze. It may be possible that bacterial co-infection may predict chronicity rather than severity of disease. Secondly, whilst this study attempted to test the value of the commonly employed diagnostic test, CRP, to predict bacterial disease, no attempt was made to determine if other diagnostic resources may have better discriminating ability. Such testing may have included serial CRP, procalcitonin (PCT) and cytokine assays (IL-1, 6). Again, although the evidence for the benefit of PCT is generally better than that of CRP, it is also not a useful screening test.[16] The limited ability of blood culture to determine bacterial pneumonia is noted.

Infection in the lung is often difficult to prove. The diagnostic tests used in this study are the routine tests commonly used at this facility. It might be possible that both viral and bacterial organisms have not been detected by these laboratory methods.

Conclusion

Bronchiolitis remains a viral disease. In our study, CRP does not correlate with white cell count or bacterial blood culture. It is therefore, no more useful than those tests in predicting bacterial co-infection. Routine use of antibiotics should be discouraged since their use is no longer a benign intervention. Serious sequelae of both adverse events and emerging microbiological resistance, both in targeted organisms and those not targeted for therapy (collateral damage), are potential areas of concern.

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Disease progression unrelated to passive environmental tobacco smoke exposure in HIV-infected children

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ABSTRACT

Background: Studies in adults have shown that smokers have a higher risk of death and a higher risk of developing AIDS. Other studies have shown an increased risk of smoking HIV-positive adults to infections. There is, however, no available data on HIV-related disease progression in environmental tobacco smoke exposed children.

Aim: The aim of this study was to determine if passive ETS exposure is a risk factor for HIV-related disease progression in children.

Methods: An observational, descriptive study of children attending the HIV Clinic at a District Hospital during October 2007.

Results: 127 children were enrolled. 47 (37%) were living in households where adults smoke. There was no difference between passive tobacco smoke exposed children and those not exposed for CD4 percentage (p=0.66) or HIV stage (p=0.70). HIV-infected children were no more likely to be admitted to hospital if caregivers smoked (p=0.70).

Conclusion: This study of HIV-infected children, did not reveal significant differences in objective measures of HIV status (CD4 count and HIV stage), nor increased rates of more severe illness (hospitalization) between children exposed to passive ETS and those not exposed. This is in contra-distinction to adult studies. The small sample size may limit comparison in this study.

Keywords: HIV-infected children, Passive environmental tobacco smoke

Running head: HIV status, environmental tobacco smoke exposure

Background

Cigarette smoking has been associated with increased morbidity and mortality in Human Immunodeficiency Virus (HIV)-infected adults.[1,2] In the Strategies for Management of Antiretroviral Therapy Clinical Trial, 40·5% of HIV-infected subjects were current smokers and 24·8% were former smokers.[1] The mortality of these individuals was higher in current smokers (hazard ratio (HR)=2·4; p<0·001) and there were more serious illnesses (major cardiovascular disease (HR=2·0; p=0·002), non-AIDS cancer (HR=1·8; P=0·008), and bacterial pneumonia (HR=2·3; p<0·001)), in smokers.[1]

In addition to the risks of cigarette smoking it seems that the prevalence of smoking is higher in HIV-infected individuals. This has been clearly shown for African HIV-infected individuals.[3,4]

Increased morbidity in smoking HIV-infected adults may take many forms. Importantly smoking increases the risk for secondary infection, including tuberculosis,[5] cardiovascular disease[1,6] and malignancy.[1,7]

Studies in adults have revealed that smokers on highly active anti-retroviral therapy (HAART) had poorer viral responses (HR=0·79; 95% confidence interval (CI)=0·67-0·93) and poorer immunologic responses (HR=0·85; 95%CI=0·73-0·99).[8] A greater risk of virological rebound (HR=1·39; 95%CI=1·06-1·69) and more frequent immunologic failure (HR=1·52; 95%CI=1·18-1·96) were also observed among smokers. There was a higher risk of death (HR=1·53; 95%CI=1·08-2·19) and a higher risk of developing AIDS (HR=1·36; 95%CI=1·07-1·72), but no significant difference between smokers and non-smokers in the risk of death due to AIDS. These authors concluded that 'some of the benefits provided by HAART are negated in cigarette smokers'.[8]

These findings may relate to research demonstrating that chronic exposure of mice and rats to cigarette smoke or nicotine inhibits T-cell responsiveness, which may account for the decreased antibody response to T-cell dependent antigens seen in these animals.[9]

Other studies have confirmed an increased risk of smoking adults to infections. Current smokers were more likely than never smokers to develop bacterial pneumonia (HR=1·57; 95%CI=1·14-2·15; p=0·006), oral candidiasis (HR=1·37; 95%CI=1·16-1·62; p=0·0002).[10] The AIDS dementia complex is also more likely in smoking HIV-infected adults (HR=1·80; 95%CI=1·11-2·90; p=0·02).[10]

These increased risks have led authors to call for incorporating advice on smoking cessation into HIV education programs and consultations.[11]

The natural progression of HIV in children differs from that of adults. Immaturity of the immune system leads to more rapid progression of HIV-related infection.[12] There are various factors that contribute to the rate of HIV progression in children. These include maternal viral load, genetic composition, immunological profile of the child and possibly some environmental factors.[13]

Despite a vast literature on the health effects of cigarette smoking on HIV-infected adults, there is no study demonstrating an effect of passive cigarette smoke exposure on the health of HIV-infected children.

Objective

The main objective of this research was to determine if passive environmental tobacco smoke (ETS) exposure is a risk factor for HIV progression and disease severity in children.

Methods

An observational, descriptive study of children attending the HIV Clinic at Tshwane District Hospital, Pretoria, South Africa during October 2007. A convenience sample of parents attending the clinic for routine follow-up of their children's disease was selected. Each attendee completed a questionnaire relating to their smoking habits and the HIV status of their children. Ethics approval was obtained from the Research Ethics Committee of the University of Pretoria and all subjects signed informed consent and assent where appropriate.

HIV infection was deemed to be present if HIV-enzyme linked immune-sorbent assay (ELISA) was positive in children older than 18 months of age. Children younger than 18 months required both a positive HIV ELISA and positive HIV polymerase chain reaction (PCR).

The World Health Organization (WHO) HIV clinical staging[14] was used to determine HIV stage of disease.

The Architect (Abbott Diagnostics) and MODULAR E170 (Roche Diagnostics), fourth generation HIV ELISA assays (detecting both p24 antigen and HIV antibodies simultaneously), were used for HIV serology. Qualitative HIV PCR was performed using Amplicor HIV-1 DNA assay, version 1·5 (Roche molecular systems). CD4 count measurements were performed on Epics instrument (Beckman Coulter Diagnostics) using a pan leukocyte gating (PLG) method.

Statistical Methods

Stata 10 (eStataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for computations**.** The two-sample t test with equal variances was performed for analysis of continuous variables while the Fischer exact test or Pearson Chi-square test was performed for analysis of categorical variables.

Results

Information was obtained from 127 accompanied HIV-infected children. Of these, 47 (37%) were living in households where adults smoke. There was not a significant difference in the mean age (at the time of the study) between ETS exposed and non-exposed children (4·6 months vs 4·9 months (p=0·66)). There was also not a significant difference for age of HIV diagnosis between ETS exposed and non-exposed children (p=0·50). 118 (93%) of the children were on HAART. At the time of the study the protocol for HAART was Stavudine, Lamivudine and Kaletra as first line therapy.

ETS exposed children had a 1·1% lower CD4 percentage than children who had no passive smoke exposure. This was not statistically significant (p=0·59) (Fig. 1).

There was not a significant relationship between cigarette smoke exposure and HIV-stage (p=0·70) (Table 1).

There was not a significant relationship between the number of cigarettes smoked daily by the caregivers and the CD4 count (p=0·9661), nor the HIV stage (p=0·4949), of the of the ETS exposed children.

Thirty two of the 127 children were hospitalized in the last month. This group included all of the children not on HAART and only 13 of the 32 children that were hospitalized in the last month had care-givers who smoked. The ETS and non-ETS groups did not differ with respect to hospitalization (OR=1·17; 95%CI=0·47-2·86; p=0·70) (Table 2).

The proportion of smokers amongst parents with secondary education does not differ significantly from those without secondary education (p=0·595; 38·2% vs 29·4%).

Conclusion

This is the first study reported of the effects of passive ETS exposure on the health of HIV-infected children.

The study reveals that rates of cigarette smoking are higher in parents of HIV-infected children than the South African national average.[15] This may support data available from other studies in Africa demonstrating that smoking was more common in HIV-infected adults.[3,4]

This study of 127 HIV-infected children attending an HIV treatment clinic did not reveal statistically significant differences in objective measures of HIV status (CD4 count and HIV stage) between children exposed to ETS and those not exposed. This is in contra-distinction to most adult studies.

In addition there is no apparent effect of ETS exposure on clinical disease severity as indicated by need for hospitalization. ETS exposure has been linked to greater risk of asthma exacerbations in asthmatic children[16] and it seems unlikely that this is not true of disease exacerbations in HIV-infected children. Either the study sample was too small to draw meaningful conclusions or the diseases associated with HIV-infection are of such a nature to render the additional effects of ETS insignificant.

Since most children were on HAART the effect of this form of therapy in relation to ETS exposure could not be assessed. Only a much larger study group would enable teasing out of the effect of cigarette smoke exposure on HIV-infected children prior to commencement of HAART or the possible effect of ETS exposure on efficacy of HAART.

The small sample size may limit comparison in this study. In addition the range of age in these children would mask some of the consequences of increasing age on HIV progression in individual patients. A large age-stratified study would be useful.

Conflict of Interest:

All authors disclose no financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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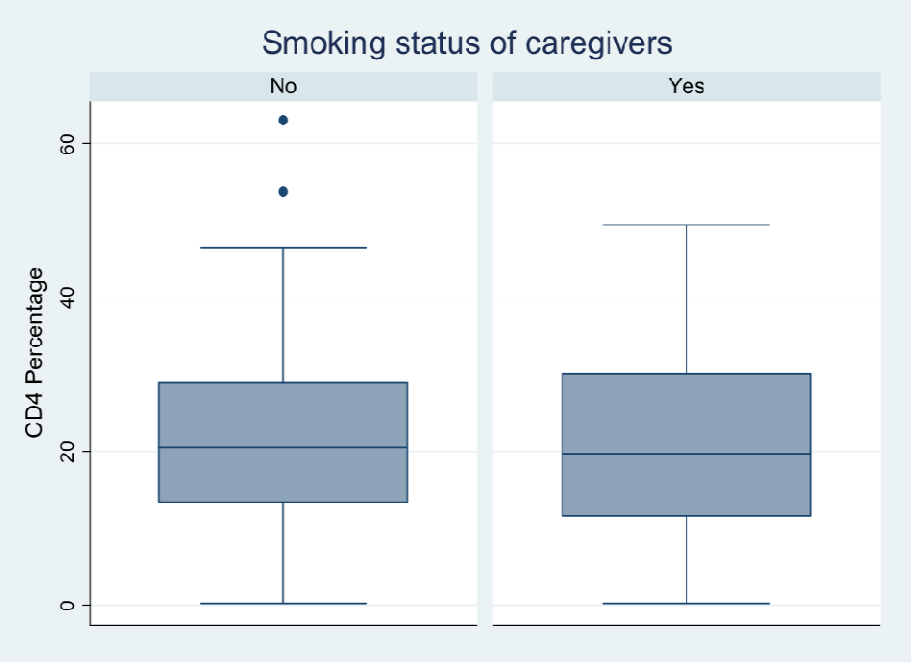

Figure 1: Box and whisker plots for smoking status of caregivers compared to CD4 percentage of their HIV-infected children

Table 1: Smoking status of caregivers versus HIV-stage of children, frequency (%).*

HIV Stage	Smoking		Total
	No	Yes	
1	8 (11·9)	2 (5·0)	10 (9·4)
2	7 (10·5)	5 (12·5)	12 (11·2)
3	38 (56·7)	23 (57·5)	61 (57·0)
4	14 (20·9)	10 (25·0)	24 (22·4)
	67 (100)	40 (100)	107 (100)

** Staging data unavailable on 20 children.*

Table 2: Smoking status of caregivers versus hospitalization of HIV-infected children, frequency (%)

	Hospitalization		Total
	Yes	No	
Smoking Yes	13 (27·1)	35 (72·9)	48 (100)
No	19 (24·1)	60 (76·0)	79 (100)
	32 (25·2)	95 (74·8)	

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HIV-related bronchiectasis in children: an emerging spectre in high tuberculosis burden areas

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SUMMARY

BACKGROUND: Human immunodeficiency virus (HIV) infected children have an eleven-fold risk of acute lower respiratory tract infection. This places HIV-infected children at risk of airway destruction and bronchiectasis.

OBJECTIVE: To study predisposing factors for the development of bronchiectasis in a developing world setting.

METHODS: Children with HIV-related bronchiectasis aged 6–14 years were enrolled. Data were collected on demographics, induced sputum for tuberculosis, respiratory viruses (respiratory syncytial virus), influenza A and B, parainfluenza 1–3, adenovirus and cytomegalovirus), bacteriology and cytokines. Spirometry was performed. Blood samples were obtained for HIV staging, immunoglobulins, immunoCAP®-specific immunoglobulin E (IgE) for common foods and aeroallergens and cytokines.

RESULTS: In all, 35 patients were enrolled in the study. Of 161 sputum samples, the predominant organisms cultured were *Haemophilus influenzae* and *parainfluenzae* (49%). The median forced expiratory volume in 1 second of all patients was 53%. Interleukin-8 was the predominant cytokine in sputum and serum. The median IgE level was 770 kU/l; however, this did not seem to be related to atopy; 36% were exposed to environmental tobacco smoke, with no correlation between exposure and CD4 count.

CONCLUSION: Children with HIV-related bronchiectasis are diagnosed after the age of 6 years and suffer significant morbidity. Immune stimulation mechanisms in these children are intact despite the level of immunosuppression.

KEY WORDS: human immunodeficiency virus; tuberculosis; bronchiectasis; paediatrics; cytokines

THE INCIDENCE of antenatal human immunodeficiency virus (HIV) infection has increased in South Africa, from 0.4% in 1991 to 29% in 2009.[1–3] This increase in maternal infection rates, coupled with a delay in the availability of highly active antiretroviral therapy (HAART) for effective prevention of mother-to-child transmission (PMTCT), has resulted in high vertical infection rates. Universal access to single-dose nevirapine (NVP) was made available in 2003 (South Africa Government Online, http://www.gov.za), and a combination of single-dose NVP, together with 6 weeks azidothymidine for PMTCT, in 2008.[4] Children born prior to 2003 therefore had a higher risk of vertically transmitted HIV and would therefore present with chronic manifestations of HIV.[5]

In a Rwandan study, HIV-infected children were three times more likely to die from respiratory tract infections.[6] Untreated HIV-infected children have an incidence rate of 11.1 per 100 child-years of acquiring acute lower respiratory tract infections (LTRIs); with HAART this decreases to 2.2/100 child-years.[7,8] Recurrent LRTIs place HIV-infected children at risk of airway destruction and subsequent bronchiectasis. The pathogens implicated in LRTIs in HIV-infected children are pneumococcus, *Haemophilus influenzae* and respiratory viruses.[9]

Childhood bronchiectasis has declined in affluent populations due to effective immunisation programmes, less overcrowding, access to medical care, better hygiene and nutrition, with reported rates of 0.49 per 100 000 population in Finland.[10,11] Certain groups in industrialised countries, such as the Alaskan natives of the Yokun Kuskokwim Delta, the New Zealand Maori and the Aborigines of Australia, have inordinately high bronchiectasis rates, ranging from 3.5 to 16/10 000.[12–14] Published data on bronchiectasis in developing countries suggest infectious causes, with post adenoviral bronchiolitis obliterans being a common cause of bronchiectasis in Brazil;[15] the high burden of infectious disease and tuberculosis (TB) account for the majority of cases.[16,17]

South Africa has one of the highest burdens of TB, with rates exceeding 500/100 000.[18] Although HIV

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and TB co-infection has been well documented,[19] the real co-infection rates are unfortunately unclear, as the radiological picture and tuberculin skin test can have a low diagnostic yield in HIV-infected children.[7,20,21] Lymphocytic interstitial pneumonitis (LIP) can also result in bronchiectasis in HIV-infected children.[8,22]

Bronchiectasis is an 'orphan' lung disease, as little research funding is devoted to this disease; this is even truer for HIV-related bronchiectasis.[23] Our objective was therefore to investigate possible predisposing and aggravating factors for bronchiectasis, to characterise local and systemic inflammatory markers and to document morbidity related to bronchiectasis in a cohort of HIV-infected children in a high TB burden area.

PATIENTS AND METHODS

Patients

We screened 56 children with HIV-related bronchiectasis attending the Paediatric Chest Clinic at the Steve Biko Academic Hospital, Pretoria, South Africa, from January to November 2009. Patients were enrolled if they were aged 6–18 years, were able to reliably perform lung function tests, and exhibited symptoms suggestive of bronchiectasis, namely chronic productive cough, clubbing or halitosis, and had radiological confirmation of bronchiectasis. Thirteen children aged <6 years were excluded from the study, and 43 subjects (77%) were eligible and screened. Another participant was excluded because the parents refused consent to participate, and seven were lost to follow-up. A final 35 children were included in the analysis.

Signed inform consent was obtained from the parents/guardians of all enrolled subjects. Assent was obtained from all children over the age of 7 years.

Clinical investigations

Information collected included age at HIV diagnosis, timing of initiation of HAART, exposure to environmental tobacco smoke (ETS) and biomass fuels (BMF), prior and current treatment for TB, and growth parameters (weight, height and body mass index [BMI, kg/m^2]). Lung function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC and forced inspiratory flow [$FEF_{25–75}$]) was measured using the ViasysSpiroPro Jaeger Spirometer (Jaeger, Hoechberg, Germany).

Laboratory investigations

Induced sputum samples were collected. One was analysed for bacterial pathogens, including *Mycobacterium tuberculosis* and respiratory viruses (respiratory syncytial virus, influenza A and B, parainfluenza 1–3, adenovirus and cytomegalovirus). Another sample (0.029–1.53 ml per patient) was assayed for sputum cytokines using the Bio-Plex® system (Bio-Rad Laboratories Inc, Hercules, CA, USA). The following analytes were measured: interleukin (IL) 1β, IL-1Ra, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF); results were expressed in pg/ml. Monthly sputum samples were sent for microbiological testing. Of these, 17.8% were collected during an exacerbation, defined as tachypnoea or dyspnoea, change in frequency of cough, increased sputum productivity, fever and chest pain.

Serum samples were collected for the following investigations: CD4+ lymphocytes, HIV viral load, C-reactive protein (CRP) and a panel of immunoglobulins (Ig): IgA, IgE, IgG and IgM. Other serum samples were sent for ImmunoCAP® RAST testing (radioallergosorbent test) for paediatric food mix (FX5), Phadiatop and *Aspergillus fumigatus* (Phadia AB, Uppsala, Sweden.)

Statistical analysis

Data analysis was performed using Stata Release 10 (Stata Corp LP, College Station, TX, USA) and statistical analyses using the Spearman correlation coefficient and the Wilcoxon rank sum test (Mann-Whitney test). Testing was performed at the 0.05 level of significance.

Ethics approval to conduct the study was granted by the Research Ethics Committee of the University of Pretoria, South Africa.

RESULTS

Thirty-five subjects were enrolled, with a male/female ratio of 57:43. Two patients died; both presented with severe bilateral lung disease and oxygen dependence. The diagnosis of HIV was made at a mean age of 6.9 years (range 6–11.1; Table 1). The median total and percentage CD4 count of the subjects was respectively 569 × 10^9 cells/l and 18.3%. The median HIV viral load was <25 copies/ml: 19 subjects were virologically suppressed, with viral loads <25 copies/ml, and 16 were non-suppressed (Table 2);

Table 1 Study group baseline characteristics

Parameter	Median	Range
FEV_1, % predicted	53	5–86
$FEF_{25–75}$, % predicted	52.0	11–165
CD 4 count, total × 10^9/l	569	54–1763
CD 4 count, %	18.3	1.68–35.6
HIV viral load, RNA copies/ml	<25*	<25–200 000
IgG, g/l	26	14.6–81.4
IgE, kU/l	770	54–1783
IgA, g/l	2.67	0.47–6.56
IgM, g/l	1.50	0.48–4.33
CRP, mg/l	9.2	0–401

FEV_1 = forced expiratory volume in 1 second; $FEF_{25–75}$ = forced inspiratory flow; HIV = human immunodeficiency virus; Ig = immunoglobulin; CRP = C-reactive protein.

Table 2 Comparison of subjects with and those without viral suppression

Variable, subjects	Suppressed* (*n* = 19)	Non-suppressed† (*n* = 15)	*P* value
C-reactive protein‡	25.4	55.15	0.407
FEV_1, l/min‡	54	46	0.195
IgE, kU/l‡	180.8	316.9	0.089
IgG, kU/l‡	27.7	34.9	0.257
Weight, kg‡	21.8	22.5	0.945
Height, cm‡	118.9	118.0	0.945
HAART, months‡	17.5	20.4	0.797
IL-4, pg/ml‡	0.5	0.4	0.242
Sputum IL-8, pg/ml	5 548.0	3 294.2	0.165
Serum IL-8, pg/ml‡	52 113	14 667	0.740
Serum IFN-γ, pg/ml‡	19.1	15.0	0.173

*Viral load >25 copies/ml.
†Viral load <25 copies/ml.
‡Mean values.
FEV_1 = forced expiratory volume in 1 second; Ig = immunoglobulin; HAART = highly active antiretroviral therapy; IL = interleukin; IFN-γ = interferon gamma.

all but one had received HAART at enrolment. The median number of months on HAART was 18 months (range 0–60). There were no statistically significant differences between the suppressed and non-suppressed individuals with respect to FEV_1, anthropometric parameters, months on HAART, IL-4, IL-8, IFN-γ or IgG. There was, however, a marginally significant difference between virologically suppressed and non-suppressed subjects with respect to IgE ($P = 0.089$). The mean BMI for the cohort was 15.3 kg/m^2 (range 12.1–23.2).

A total of 161 sputum cultures were performed over the 1-year follow-up period (multiple samples were collected from all 35 patients; Figure 1). At presentation, 42.8% of the subjects had a positive culture for a bacterial pathogen. The most common organisms were *H. influenzae* and *parainfluenzae*, which accounted for 49% of all cultures; 2% of cultures were identified as *Pseudomonas aeruginosa* and 1% as *Staphylococcus aureus*. Two subjects had mycobacteria other than tuberculosis (MOTT), namely *M. fortuitum* and *M. avium intracellulare*. Of the study population, 48.5% had previously received one course of anti-tuberculosis treatment, 21.2% two courses and 6% three courses. Only one subject had a positive viral identification on sputum (parainfluenza type 2).

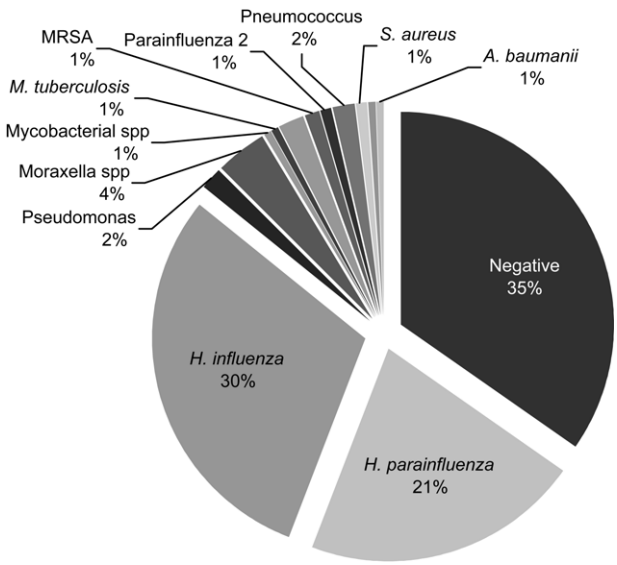

Figure 1 Cumulative data for patients (n = 35): infecting pathogens (n = 161). MRSA = methicillin-resistant *S. aureus*.

With respect to lung function, the median FEV_1 was 53% predicted (range 5–86), while the median $FEF_{25–75}$ was 52% predicted (range 11–165). Only eight children had a positive bronchodilator response, defined as a 15% increase in FEV_1 post-bronchodilator. When comparing the FEV_1 of those with positive or negative sputum culture at enrolment, the groups did not differ significantly ($P = 0.524$). There was also a lack of correlation between IgG and FEV_1 or $FEF_{25–75}$ (respectively $r = -0.049$ and $r = 0.02$).

Thirty-six per cent had been exposed to ETS, with at least one smoker among household contacts. The mean CD4 count for children exposed and non-exposed to ETS did not differ significantly ($P = 0.327$). With respect to FEV_1, there was also no statistically significant difference between ETS-exposed and non-exposed children ($P = 0.64$, 95% confidence interval [CI] 40.598–55.506). The two children who died were both exposed to ETS. BMF exposure to paraffin oil, coal stoves and other indoor coal fire heat sources was present in 40% of children.

The mean total IgE for the group was 770 kU/l, with only 10% of all children having a positive specific IgE on RAST testing for inhalants or foods. Total IgE and CD4 count were not correlated ($r = -0.02$, $P = 0.482$). IgG was the most significantly elevated immunoglobulin (median 26 g/dl). CRP levels were low, with a median value of 9.2 mg/l. There was a lack of correlation between CRP and serum cytokines IL-6 and IL-8 ($r = 0.259$ and $r = 0.324$, respectively).

Of the cytokines analysed in serum and sputum (Figure 2), IL-8 was the most significantly elevated, with median values of respectively 400 and 116 pg/ml. IFN-γ, a T-helper 1 (Th-1) cytokine, was also elevated. IL-1ra, an anti-inflammatory cytokine, was elevated in serum and sputum. There was no correlation between CD4% and HIV viral load and IL-8 ($r = -0.071$ and $r = -0.213$ respectively), or between Th2 cytokines IL-2, IL-4, IL-13 and IgE ($r = -0.22$, $r = -0.21$ and $r = 0.06$, respectively). There was, however, a positive correlation between IL-4 and HIV viral load ($r = 0.42$). There was no correlation between IL-1, IL-6, IL-8 and number of months on HAART ($r = 0.27$, $r = 0.287$, $r = 0.128$, respectively). The chemokine macrophage inflammatory protein-1 beta (MIP-1b) was elevated in serum as compared to sputum (47 vs. 1 pg/ml). Monocyte chemotactic protein-1 (MCP-1) was also elevated in serum, but to a lesser extent than MIP-1b (13 pg/ml).

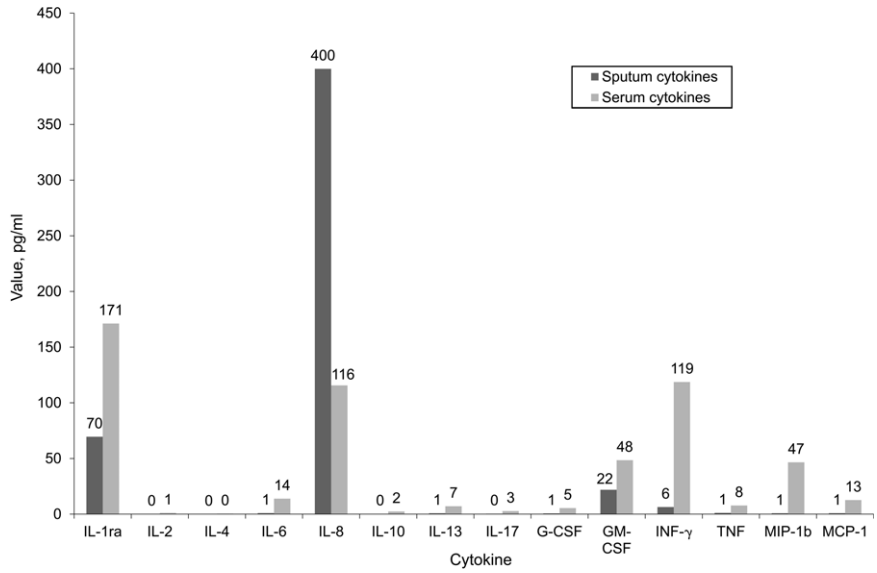

Figure 2 Sputum and serum cytokine values and ranges. IL = interleukin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony stimulating factor; IFN-γ = interferon gamma; TNF = tumour necrosis factor; MIP-1b = macrophage inflammatory protein-1 beta; MCP-1 = monocyte chemotactic protein-1.

GMCSF was elevated in both serum and sputum (48 and 22 pg/ml, respectively). Very low levels of IL-2, 4, 10, 13, G-CSF and TNF were present in both sputum and serum.

DISCUSSION

In our cohort of children with HIV-related bronchiectasis, the diagnosis of HIV infection is delayed, with the majority being diagnosed after the age of 6 years. It is presumed that the majority of these children had vertically transmitted HIV. This may demonstrate a failure of the PMTCT programme, as HIV-infected women and their newborn children are not offered HIV testing and subsequent follow-up. These children with HIV-related bronchiectasis were possibly of the 'slow-progressor' phenotype.

H. influenzae and *parainfluenzae* were the predominant organisms cultured. In South Africa, *H. influenza* Type B (Hib) vaccination has been universally available for all children since July 1999, with absolute cases of Hib decreasing by 65% in children aged <1 year from 1999–2000 to 2003–2004, while rates of non-typeable *H. influenzae* have increased, especially in HIV-infected children.[24] Although the Hib vaccine is less effective in HIV-infected children than in non-infected children; Madhi et al. found that the Hib vaccine reduced overall invasive Hib disease by 83% in all children.[25]

S. aureus was also not a major pathogen in our population. McNally et al. found that the risk of *S. aureus* nasal carriage (and therefore predicted sepsis) was 2.86 times higher in HIV-infected children presenting with acute pneumonia.[26] The presence of bacterial organisms did not seem to affect disease severity.

Seventy-five per cent of our study population had a prior diagnosis of TB, three of which were microbiologically confirmed. The difficulties of diagnosing TB in HIV-infected children are well documented, and in a high TB burden area there may be over-reliance on radiological diagnosis.[7,20,21] The limitations of this approach are that TB may have a similar radiological picture to bronchiectasis, and this may therefore explain how bronchiectasis may be missed. MOTT infections occur with bronchiectasis, which may be mislabelled as TB. Almost a quarter of children in our study received two courses of anti-tuberculosis treatment. This is not surprising, as current guidelines depend heavily on chest X-ray interpretations for TB diagnosis at the primary health care level.[27] LIP rates in our study population were low and therefore do not explain the bronchiectasis in our group.

The median FEV_1 in our study was 53% of predicted (range 5–86); this is in comparison to New Zealand children with non-cystic fibrosis (CF) related bronchiectasis, where Munro et al. reported a baseline predicted FEV_1 of 66%.[28] HIV-related bronchiectasis seems to cause accelerated lung function decline compared to other causes of non-CF-related bronchiectasis. Our cohort was undernourished, with a low BMI. The impact of nutrition on lung morbidity is well described in CF, where the lower the BMI, the higher is the morbidity from lung disease.[29] Whether this was due to increased metabolic demands from chronic lung disease, HIV infection or a surrogate marker for socio-economic status of the children is unclear.

There was a significantly elevated IgE in our study.

Previous studies in adults and children infected with HIV have shown a relationship between IgE and HIV stage.[30–35] We could not replicate this finding, and found no increase in the Th-2 mediated cytokines in relation to the elevated IgE. This confirms that IgE elevation is not related to atopy but probably reflects polyclonal hypergammaglobulinaemia related to T-cell depletion. There was a marginally significant difference in IgE levels between the subgroups with and without viral suppression; this was, however, not statistically significant, and may be related to the small sample size. In a previous study, we documented no increase in skin prick test positivity in HIV-infected children, confirming that atopy was not responsible for an elevated IgE.[36] The other potential explanation for elevated IgE is the presence of allergic bronchopulmonary aspergillosis, but this was ruled out. As with HIV-infected children with acute pneumonia,[37] we found elevated IgG levels, probably reflecting immune hyperstimulation related to HIV infection.

The predominant cytokine in our cohort was IL-8. This is similar to CF-related bronchiectasis, where oxidative stress results in increased IL-8 levels.[38,39] IL-8 is a marker of neutrophil-driven inflammation, where elevation may suggest that the disease process in HIV-related bronchiectasis is neutrophil-dependent. Whether the neutrophil driven inflammatory process in HIV-bronchiectasis is dependent on the innate or adaptive immune mechanisms requires further exploration. All potentially relevant cytokines related to inflammatory disease of this nature that represent Th 1-driven inflammation, including IL-1, IL-6, GM-CSF and IFN-γ, were elevated, reflecting an ability to mount immune responses against pathogens, although the levels did not correlate with HIV staging or use of HAART. We therefore postulate that the presence of an aggressive immune response against pathogens may trigger airway inflammation and subsequent bronchiectasis. Although in HIV infection the dominant abnormality is immunosuppression, the local and systemic immunological responses seem to be exaggerated. MIP-1b, which is mainly involved in the host response to bacterial, fungal, viral and parasitic pathogens and selectively attracts CD4 lymphocytes, was elevated in the serum and, to a lesser extent, in the sputum of our subjects. MIP-1b is also known to be a major suppressive factor of HIV produced by CD8+ cells, possibly suggesting that there is continuous immune stimulation systemically, and, to a lesser extent, in the lungs.

ETS exposure does not explain FEV_1 or CD4 count variability. An adult study by Feldman et al. reported a statistically significant difference in morbidity and mortality of smokers with HIV infection.[40] A previous study in our population of 121 HIV-infected children showed no difference in HIV staging in ETS exposed and non-exposed children, consistent with our current finding.[41] Kabali et al. also found no association between cigarette smoking and HIV disease progression.[42]

The limitations of our study were the small sample size and lack of objective measurements to quantify ETS exposure. Larger trials are needed to confirm these findings.

CONCLUSION

Children with HIV-related bronchiectasis have the diagnosis of HIV infection made at a median age of 6 years. In a high TB burden area, the differential diagnosis of an abnormal chest X-ray in children with chronic cough or previously treated TB should include bronchiectasis. Even in a setting of HIV-related bronchiectasis, local and systemic immune stimulation mechanisms appear to remain intact.

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Positron emission tomography in the prediction of inflammation in children with human immunodeficiency virus related bronchiectasis

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Abstract

There is a lack of objective tools to reliably diagnose exacerbations in bronchiectasis. *The primary aim of this study* was to assess the ability of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to detect sites of active inflammation in children with human immunodeficiency virus (HIV)-related bronchiectasis with or without exacerbations. The secondary aim was to assess whether ^{18}F-FDG-PET/CT results are in agreement with local and systemic inflammatory markers and markers of HIV disease activity. *Forty-one children* with HIV-related bronchiectasis underwent ^{18}F-FDG PET/CT. Data on the presence of a clinical exacerbation were recorded. Serum was collected for CD4 count, HIV viral load, C-reactive protein (CRP) and cytokines IL-8, INF-γ and TNF-α. Induced sputum samples were processed for microbiological culture and for IL-8, INF-γ and TNF-α. Mean age of all children was 8.2±2.2 years. *Twelve subjects showed* ^{18}F-FDG lung uptake while six of them had an exacerbation. There was no difference in the ^{18}F-FDG uptake in participants with or without an exacerbation (P=0.613). Fluorine-18-FDG-PET had a good correlation with the presence of consolidation (P=0.01, OR=6.67). The mean CRP was higher in the subjects with ^{18}F-FDG uptake when compared to those without uptake (51.96±95.12 vs. 13.26±19.87), although this difference was not significant (P=0.09). *In conclusion*, the ^{18}F-FDG-PET lung uptake technique could not reliably predict the presence of an exacerbation in children with HIV and bronchiectasis, and its diagnostic value was limited to identifying disease activity on the scan in acute pneumonia cases. Fluorine-18-FDG-PET had no significant correlation with CRP or with other inflammatory biomarkers and markers of HIV disease activity.

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Introduction

Non-cystic fibrosis (NCF) related bronchiectasis is regarded as an "orphan" lung disease [1, 2]. This is largely due to lower research and development activity for this condition. Rates of bronchiectasis have decreased dramatically in developed countries and reports in Finnish children under 15 years indicate a prevalence rate of 0.49 per 100,000 [1, 3-5]. These improvements have been largely attributed to immunization programs, better access to healthcare services and reduction in over-crowded living conditions [3, 6-8]. In developing countries the majority of reported cases of bronchiectasis are also post-infectious [9, 10]. In these communities the burden of respiratory diseases including tuberculosis (TB), coupled with poor access to healthcare services places children at risk for severe respiratory tract infections. South Africa has borne the brunt of the human immunodeficiency virus (HIV) pandemic, with reported ante-natal infection reaching 30% of the population in 2009 [11]. A large number of children with acquired HIV are therefore at high risk for respiratory tract infections [12]. The manifestation of multiple pulmonary infections, lymphocytic interstitial pneumonitis and tuberculosis are chronic lung damage and bronchiectasis.

The management of bronchiectasis involves aggressive antibiotic treatment of exacerbations, physiotherapy, together with optimal vaccinations to prevent further lung damage and improve quality of life [13, 14]. Current tools to assess disease severity and progression are clinical follow-up with treatment of exacerbations, lung function testing, sputum cultures, imaging and measurement of lung inflammatory biomarkers. All of these tools have their limitations and drawbacks. The definition of an exacerbation is based on the presence of new symptoms which in paediatric patients is limited by the quality of health information provided by the care-giver [14]. Spirometry cannot be performed in children below the age of six years. The current gold standard method

to assess lung inflammation includes analysis of airway neutrophils obtained from bronchoalveolar lavage [15, 16]. This has the drawback of being invasive and providing information only on specific lung segments. Sputum cultures are useful to guide antibiotic treatment but do not differentiate between chronic colonization and acute infection. Chest radiography is insensitive and provides gross anatomical localization of pathology, whilst high resolution computed tomography (HRCT) is the gold standard for diagnosing bronchiectasis and can be used for monitoring of structural lung changes. It does not however, provide any information on disease activity. There is also a concern of the patients' radiation burden from HRCT, especially if serial scanning is performed, making this an unattractive option with increased risk during regular follow-up.

There is a need for more reliable and objective tools that can be used to assess the degree of inflammation in order to guide management decisions and aid in the diagnosis of exacerbations in the context of HIV-related bronchiectasis.

Positron emission tomography with 2-[F-18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG-PET) is widely used in the diagnosis of oncological diseases based on high metabolic turnover of saccharides by tumour tissue. In the inflammatory response, neutrophils have an increased expression of glucose transport proteins and there is an up-regulation of the hexokinase activity [17]. Elevated ^{18}F-FDG accumulation in inflamed tissues is not only related to increased glucose metabolism in inflammatory cells, but also by macrophage proliferation and recruitment. This makes ^{18}F-FDG PET an attractive tool for the diagnosis and management of inflammatory pulmonary disease. The co-registration of PET and HCRT therefore has the benefit of both anatomical localisation of pathology with the assessment for disease activity.

There is currently lack of data on the role of PET-CT in children with non-CF related bronchiectasis, and especially in the context of HIV related bronchiectasis. The primary aim of this study was to evaluate the ability of ^{18}F-FDG- PET to detect sites of active inflammation in children with HIV related bronchiectasis with or without exacerbations. The secondary end-point was to assess whether ^{18}F-FDG- PET results agreed with local and systemic inflammatory biomarkers or HIV disease activity markers.

Patients, materials and methods

Patients

All HIV-infected children aged 6 to 18 years with HRCT confirmed bronchiectasis, during January 2009-March 2010, attended the Paediatric Chest and Allergy Clinic (Steve Biko Academic Hospital, Pretoria, South Africa) consented to participate in the study. Included participants exhibited symptoms that were suggestive of bronchiectasis, namely a chronic productive cough, clubbing or halitosis and had radiological confirmation of bronchiectasis. Testing HIV with a fourth generation HIV ELISA was performed as part of the work-up. Fifty-three participants were screened, 43 were eligible and enrolled, but two were lost during follow-up. Of the 41 participants, 24 (58%) were male. The median age was 8.2±2.2 years, age range was 6-14 years (Table 1).

Table 1. *Baseline characteristics of children with HIV-related bronchiectasis undergoing ^{18}F-FDG-PET (N=41).*

Characteristics	Mean ± SD
Age	8.2±2.2
Male sex	24 (58)
Presence of exacerbation	12 (29.2)
HAART (months)	17.61±17.86
CD 4%	19.34±9.89
HIV VL (copies/mL)	61.65± 254243.50
Bhalla score	13.94±4.32
CRP (mg/mL)	8.76±63.23
Serum	
IL-8¶ (pg/mL)	218.25±178560.20
TNF- α (pg/mL)	2.25±0.94
INF-γ (pg/mL)	204.88±349.80
Sputum	
IL-8 ¶ (pg/mL)	785±9352.06
TNF- α (pg/mL)	1.05±0.70
INF-γ (pg/mL)	15.98±21.50

¶: Geometric means reported; ( ): percentages in parenthesis; CRP- C reactive protein; IL-8- interleukin 8; HIV VL- HIV viral load; CD4%- percentage of cluster differentiation 4; TNF- α- tumour necrosis factor alpha; INF-γ- interferon gamma, SD: Standard deviation

Clinical evaluations

A respiratory exacerbation was characterised, if present at the time of the PET scan. The clinical definition of exacerbation was the presence of at least two of the following criteria: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on the chest X-ray. Pneumonia was diagnosed by the presence of symptoms suggestive of an exacerbation together with consolidation and air bronchograms on chest CT.

Two induced sputum samples were collected by a dedicated physiotherapist from each patient on the same day. One of the samples was sent for microbiological testing, which included microscopy where appropriate, culture, and antibiotic sensitivity, for bacterial pathogens, including *mycobacterium tuberculosis* as well as viral respiratory pathogens *respiratory syncytial virus*, *influenza* A and B, *parainfluenza* 1-3, *adenovirus* and *cytomegalovirus*. The presence of acid-fast bacilli in sputum with a culture of the mycobacteria confirmed the diagnosis of tuberculosis.

A second sputum sample was used for determination of sputum cytokines interleukin-8 (IL-8), interferon gamma (INF-γ) and tumour necrosis factor alpha (TNF-α). Serum and sputum cytokines were measured using the Bio-Plex® suspension bead array system (Bio-Rad Laboratories Inc, Hercules, CA, USA) which utilizes luminex® Xmap™ multiplex technology to enable simultaneous detection and quantitation of multiple different analytes in a single sample.

Venous blood (1.5mL) was collected and quantitatively analysed for: i) circulating concentration of CRP-acute phase reactant; ii) circulating CD4$^+$ T lymphocytes; iii) HIV-1 viral

loads; and iv) cytokines IL-8, INF-α and TNF-γ. Physicians who carried out the scan diagnosis were blinded to clinical data, morphological testing and special investigations.

^{18}F-FDG PET/CT scanning

Whole body ^{18}F-FDG PET scans were acquired on a PET-CT scanner (Biograph, Siemens) from the skull top to the pelvis after fasting for a minimum of 4h. Patients received a dose of ^{18}F-FDG based on their body weight using the following formula: ((body weight/10) +1))*37MBq with a minimum activity of 74MBq and a maximum of 370MBq. Images from PET/CT were acquired at 60min after intravenous injection of ^{18}F-FDG. This study measured the maximum standardised uptake value (SUVmax) in four zones of the lungs using whole body ^{18}F-FDG-PET.

Fluorine-18-FDG PET images were analyzed for the presence or absence of active 'lesion' sites by two experienced and blinded as above nuclear medicine physicians by consensus. Two blinded as above radiologists used the Bhalla scoring system to score the CT scans [18]. The Bhalla score is a qualitative CT scoring system to assess the severity of bronchiectasis, based on nine morphologic changes such as; peri-bronchial thickening, mucous plugging, abscesses or bronchiectatic sacculations, emphysema, bullae and consolidation or collapse. The Bhalla score is based on subtracting the value of the CT score from 25, with 25 indicating normal lungs and zero being severe bronchiectasis.

Ethics

The study protocol and informed consent had ethical approval from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria. All parents signed an informed consent and assent was obtained from each participant where applicable.

Statistical analysis

Statistical analysis was performed using Stata Release 10 (Statacorp LP, College Station, TX, USA). The Fisher exact test was used for analysis of categorical variables and the Mann-Whitney U test for non-parametric variables. Statistical significance was defined as P<0.05.

Results

The baseline characteristics of all participants are reflected in Table 1. There was positive tracer lung uptake on PET scans in 18 (46.9%) participants. Twelve participants (29.2%) had a clinical exacerbation at the time ^{18}F-FDG-PET was performed and 6 of them had positive uptake on ^{18}F-FDG-PET. There was no significant difference in the ^{18}F-FDG SUV of participants with exacerbation versus no exacerbation at PET scan (P=0.61). The sensitivity and specificity of PET to detect exacerbations were 50% and 59% respectively.

Of the 18 participants with tracer uptake, 9 had bilateral uptake, in segments in both the right and left lung. There was uptake in the left lower lobe in 7 of the 18 participants, rendering it the most common lobe having ^{18}F-FDG uptake in all participants.

Of the total study population there was consolidation on the CT scan in 12 participants. Of these participants, 3 had clinical exacerbation at the time of PET and 9 had positive ^{18}F-FDG uptake at the time of ^{18}F-FDG-PET, this was statistically significant (P=0.01) (Fig. 1). There was no difference in mean SUV between subjects with or without presence of a bacterial organism in culture (P=0.73). There was microbiological confirmation of mycobacterial infection in three patients with two having *mycobacterium tuberculosis* complex and another *mycobacterium avium intracellulare* infection at the time of the PET scan. All participants with active TB had positive uptake on ^{18}F-FDG-PET. The mean SUV were higher for the participants with consolidation as compared to those with TB (4.4vs2.5), although two of the TB positive participants had received two and three months of treatment respectively.

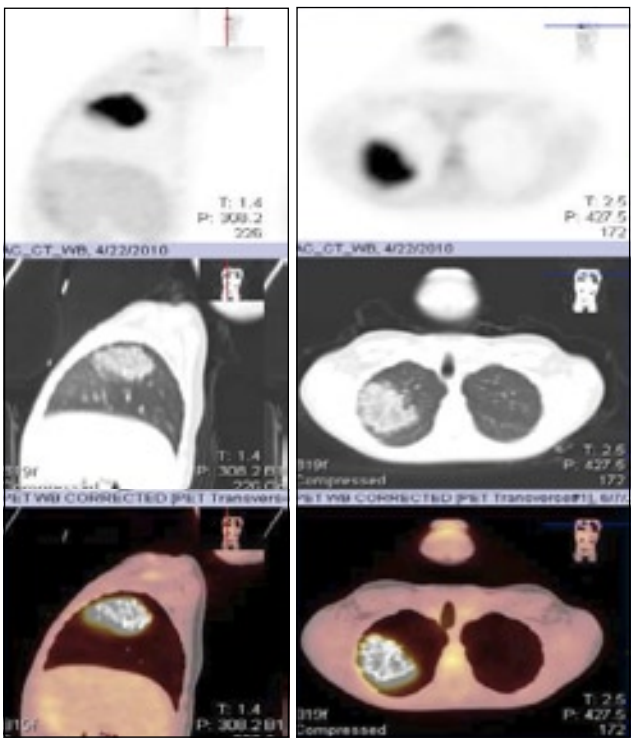

Figure 1. Transverse and axial views ^{18}F-FDG PET/CT of patient with consolidation and positive ^{18}F-FDG uptake in the right upper lobe (arrows).

All participants were on highly active antiretroviral treatment (HAART), 22 having HIV virological suppression with viral loads of <25 copies/mL. There was no significant difference between participants with: (i) positive ^{18}F-FDG uptake versus those with no uptake and number of months on HAART (P=0.37); (ii) positive ^{18}F-FDG uptake versus no uptake and CD4% (P=0.99); or (iii) positive ^{18}F-FDG uptake and no uptake and HIV viral load (P=0.23).

There was no significant difference in the Bhalla score when comparing participants with ^{18}F-FDG uptake 13.2±1.1 versus no ^{18}F-FDG uptake 14.9±0.8 (P=0.20). There was bronchiectasis in 116 lobes of the participants. The most affected lobes were the left lower lobe and the right lower lobe in 42 and 26 of all involved lobes, respectively.

In both serum and sputum, IL-8 was the prominently elevated cytokine (Table 2). There was no correlation between serum and sputum IL-8 and the Bhalla score (P=0.32 and P=0.37) respectively. As reflected in Table 2 there was not a significant difference in all other parameters except for INF-γ which was more elevated in the serum than in the sputum.

Table 2. *Inflammatory markers for children with HIV-related bronchiectasis with and without ^{18}F-FDG uptake on PET/CT*

Inflammatory marker	No ^{18}F-FDG uptake (-) N= 23	^{18}F-FDG uptake (+) N=18	P values for (+) vs (-)
CRP (mg/mL)	4.2±19.9	15.0± 95.1	0.11
Neutrophil (x10^9/L)*	4.2± 6.3	3.9 ±2.9	0.87
Sputum cytokines			
IL-8 (pg/mL)	l222.5±9203.0	1799.0±10341.0	0.62
TNF- α (pg/mL)	1.9±3.4	1.0±2.3	0.67
INF-γ (pg/mL)	2.1±23.1	18.4±19.3	0.39
Serum cytokines			
IL-8 (pg/mL)	113.3±4194.0	1205.3±549.0	0.32
TNF- α (pg/mL)	5.9±18.0	12.8±10.6	0.68
INF-γ (pg/mL)	118.7±431.6	150.0±181.7	0.50

*: neutrophils measured in serum; FDG: fluorodeoxyglucose; CRP: C reactive protein; IL-8: interleukin 8; TNF-α: tumour necrosis alpha; INF- γ: interferon gamma; Wilcoxon ranksum test done for comparing subjects with and without ^{18}F-FDG uptake.

Discussion

No difference in SUVmax values of sites of lung involvement were found between those with clinical exarcebation and those without. Hypothetically, this may relate, to the plethora of variables and their inter-individual contribution to ^{18}F-FDG uptake in such patients, to the lack of a gold standard as well as to an anamnestic effect by the care-giver or participants. Under inflammatory conditions, neutrophils and activated macrophages display a high ^{18}F-FDG uptake which is in part due to the up-regulated glucose transporter system and to an increase of affinity for deoxyglucose increased by various cytokines and growth factors [19, 20]. This mechanism might explain the positive correlation between the rate of ^{18}F-FDG uptake in the lung field and the number of neutrophils present in the bronchoalveolar lavage fluid [21]. Others with cell autoradiography have demonstrated that neutrophils are the predominant cells that take up ^{18}F-FDG in bronchoalveolar lavage fluid of CF participants [17]. A recent study with 20 CF participants found that the SUV above 3, could distinguish between foci of low or high tracer uptake intensity, and that scans showing high tracer uptake supported the clinical definition of exacerbation [22]. Contrary to this, there was no difference in the level of serum neutrophils between participants with or without ^{18}F-FDG uptake. This was also shown by others who showed a lack of uptake in subjects with CF bronchiectasis despite elevated sputum neutrophils [23]. Although cells are continually migrating to the inflammatory site**,** mucociliary clearance and cough are responsible for their removal from the lungs. We could not demonstrate elevation of serum neutrophils in subjects with ^{18}F-FDG uptake. This may be due to the fact that we measured serum neutrophils distant from the "inflammatory site" and therefore could not indicate local lung inflammatory milieu. The implication of this finding is that in HIV-related bronchiectasis, systemic neutrophils may not be as highly activated, despite seemingly adequate immune restoration by antiretroviral therapy and HIV virological suppression, as demonstrated by elevated level of neutrophils in our population. We also postulate that in the context of HIV, there is not only a quantitative defect in immune cells, but also a qualitative defect resulting in functionally ineffective neutrophils which may lack metabolic activity.

In line with previous studies, there was a correlation between ^{18}F-FDG uptake and the presence of consolidation on the CT scan [24]. This further emboldens the aspect that a PET study is more reliable in acute lobar pneumonia where there are sufficient numbers of neutrophils at the inflammatory site.

In our series, the majority of participants with positive ^{18}F-FDG uptake and consolidation did not fulfil the clinical criteria of an exarcebation. This may suggest that ^{18}F-FDG PET is more sensitive in assessing inflammation and thus superior than the clinical assessment for the detection of bronchiectasis inflammation and the presence of exacerbations.

In the current study systemic and pulmonary cytokines IL-8, TNF-γ and INF-α were elevated. IL-8 which is produced by neutrophils was the cytokine that was most significantly elevated in our study [25, 26]. Despite the presence of these cytokines in serum and sputum, we could not demonstrate significant uptake on the ^{18}F-FDG-PET scan. This may be explained by the fact that the majority of subjects in our study population had a positive culture of pathogens in their airways. The presence of colonizing organisms has been postulated to produce factors that suppress the respiratory burst of the neutrophils by affecting surface receptors or through the presence of substances capable of affecting neutrophil activity in mucus [27]. Others demonstrated a correlation between IL-8 and a modified Bhalla score [22], unlike our findings. This may relate to the fact that they had a much smaller study population (27 subjects) than the current study, and that their study population involved children with heterogeneous causes of bronchiectasis.

Importantly, in the series presented, the elevated CRP and the intensity of ^{18}F-FDG uptake were marginally statistically significant. This finding concurs with the ^{18}F-FDG studies which have been found to quantitatively delineate lung infection and inflammation in a diverse group of lung diseases including CF, pneumonia, pulmonary fibrosis and interstitial pneumonitis [17, 24, 28, 29].

The limitations of our study were the small sample size which may explain the lack of correlation of ^{18}F-FDG uptake with the inflammatory markers or could be because of a different explanation, like as another functioning mechanism at play. We also did not perform bronchoalveolar lavages to obtain sputum neutrophils.

There is a lack of a significant correlation of ^{18}F-FDG uptake and clinical analysis of exacerbations, although the presence of ^{18}F-FDG uptake in subjects without exacerbation suggests that ^{18}F-FDG may be more sensitive in assessing inflammation than currently available tools like systemic and sputum cytokines and acute phase reactants [22]. This study provides pilot data for a larger trial sufficiently powered to investigate the association of ^{18}F-FDG PET and inflammatory biomarkers.

In conclusion, ^{18}F-FDG-PET technique could not reliably predict the presence of an exacerbation in children with HIV, and its diagnostic value was limited to identifying disease activity on scan in acute pneumonia cases. Fluorine-18-FDG-PET had no significant correlation with CRP or with other inflammatory biomarkers and markers of HIV disease activity.

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The authors declare that they have no conflicts of interest.

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Research Article Open Access

Lack of Efficacy of an Immunomodulatory Macrolide in Childhood HIV-Related Bronchiectasis: A Randomised, Placebo-Controlled Trial

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Abstract

Background: The epidemic of human immunodeficiency virus (HIV)-1 infection has resulted in a large number of children suffering from respiratory morbidity in South Africa. One of the outcomes of recurrent chest infections and TB is HIV-related bronchiectasis.

Introduction: We conducted a randomised, double-blind, placebo-controlled trial to assess the efficacy of low dose erythromycin in reducing the number of pulmonary exacerbations.

Methods: We randomly assigned 31 HIV-infected children with radiologically confirmed bronchiectasis, to receive either erythromycin (17) or matching placebo (14) for a period of 52 weeks. The primary outcome was the number of exacerbations documented over the 52 weeks, in each study arm, after randomisation.

Results: There was no difference in the number of exacerbations in the participants receiving erythromycin versus those receiving placebo (2.14 ± 1.29 *vs.* 2.18 ± 1.59 per year; p=0.17). There was an improvement (although not statistically significant) in both FEV_1 % predicted and FVC % predicted (56.0% predicted ± 15.1 to 68.0% predicted ± 21.0 and 53.5% predicted ± 13.6 to 62.5% predicted ± 13.6; p=0.31) in the erythromycin and placebo arm, respectively. Erythromycin did not impact the levels of pro-inflammatory and anti-inflammatory cytokines (all p>0.05).

Conclusion: Administration of HAART and adjunctive care, which includes airway clearance and treatment of exacerbations, in children with HIV-related bronchiectasis is associated with improvement in pulmonary function tests and IL-8, with no additional benefit from the use of erythromycin.

Keywords: Cytokine; Erythromycin; Chemokine; Exacerbations; Lung function

Introduction

Bronchiectasis is pathological bronchial dilatation occurring as a result of recurrent chest infections or destructive lung disease. Non-cystic fibrosis (CF)-related bronchiectasis is an "orphan" lung disease on which little research has been focused, especially in developing countries, where available data is mostly on the epidemiological and clinical features [1,2]. In South Africa, the epidemic co-infections of human immunodeficiency virus (HIV)-1 infection and TB, have become important drivers of recurrent pulmonary infections and increasing rates of bronchiectasis [3-5].

The natural history of bronchiectasis is characterized by periods of quiescence interspersed with intermittent exacerbations. Exacerbations result in airway inflammation, the end product of which is progressive lung tissue destruction, pulmonary function decline and poor quality of life [6]. In order for the infection-related inflammatory process to be halted, there is a need to correct underlying pathology, as well as prompt implementation of effective anti-inflammatory therapy [7].

Medical interventions to treat HIV-related bronchiectasis should incorporate immune system restoration with highly active antiretroviral therapy (HAART). In addition there is a strong evidence base for the use of macrolides as immunomodulatory agents in CF bronchiectasis subjects colonized with *Pseudomonas aeruginosa (Pa)* [8]. There is currently emerging evidence of the beneficial effects of macrolides in CF and non-CF bronchiectasis subjects without *Pa* [9,10]. The immunomodulatory effects of macrolides are thought to result in reduction in sputum volume, inhibition of virulence factor production by bacteria, diminished production of interleukin (IL)-8 and neutrophil influx and neutrophil elastase into the lung [11-13]. This in turn effects a reduction in pulmonary exacerbations, improved pulmonary function and improved quality of life. This therefore makes macrolides a natural choice for investigation as a candidate therapeutic intervention in bronchiectasis.

This study evaluated the efficacy of erythromycin compared to placebo, in reducing the number of pulmonary exacerbations in children with HIV-related bronchiectasis over a period of 52 weeks. The secondary end-points were to assess whether erythromycin could impact pulmonary function parameters, pro-inflammatory and anti-inflammatory chemokines and cytokines.

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Materials and Methods

Setting and study population

This study was conducted as a randomised, double-blind, placebo-controlled trial of erythromycin at the Paediatric Chest Clinic, Steve Biko Academic Hospital, Pretoria. The baseline characteristics of some of the participants have been previously described, as they form part of a larger study of children with HIV-related bronchiectasis [4].

Inclusion criteria: Children aged 6 to 18 years with confirmed HIV infection. The presence of bronchiectasis was confirmed on high resolution CT scanning, with exclusion of other causes of bronchiectasis including a sweat test to rule out CF. All children had to be able to perform reliable pulmonary function tests.

Exclusion criteria: Children were excluded if there was presence of the following: abnormal liver function tests (ALT/AST > 2.5 times normal) and abnormal urea/creatinine. Other exclusion criteria included the use of: carbamazepine, warfarin, cyclosporin or long-term midazolam.

All the participants were randomised to receiving either erythromycin (Adco erythromycin estolate) at a dose of 125 mg per os daily if ≤15 kg body weight or 250 mg per os daily if >15 kg body weight or a matching placebo daily. This erythromycin dose was chosen as a quarter of the expected daily dose in line with previous studies [14]. Enrolment occurred from January 2009 to June 2011, with monthly follow up for one year.

Randomisation and blinding

Participants were randomly assigned (1:1) to the erythromycin group (55%) or placebo group (45%). All study personnel performing the clinical evaluations were blinded to treatment assignment, with usual care treatment of exacerbations. An exacerbation was per protocol defined; as the presence of at least two of the following: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on the chest X-ray. Compliance was assessed with the use of a medication diary and verbal interviews.

Clinical investigations

Clinical information collected included: the age at HIV diagnosis, timing of initiation of HAART and growth parameters (according to World Health Organization (WHO) weight z-scores, height z-scores and BMI z-scores) [15]. Lung functions included % predicted values for (forced expiratory volume in one second {FEV_1}, forced vital capacity {FVC} and forced expiratory flow {$FEF_{25/75}$}) measured using the Viasys SpiroPro Jaeger Spirometer (Hoechberg, Germany).

Laboratory investigations

The pre-treatment cytokine data for this group of participants was described in an earlier study [4]. In the current study, the pre- and post-treatment serum and sputum cytokine specimens were analysed simultaneously using a modified, improved version of the original assay using the Bio-Plex Suspension Array System (Bio-Rad Laboratories, Inc. Hercules, Canada) and a Bio-Plex Pro™ assay kit (Bio-Rad Laboratories, Inc). The assay kit used included: interleukins (IL)-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α) and interferon gamma-induced protein-10 (IP-10).

Serum immunoglobulins: Circulating concentrations of immunoglobulin (Ig)-G) were assayed by nephelometry (Siemens Healthcare Diagnostics, BN Prospec Nephelometer, Newark, NJ, USA).

Blood samples: Were also collected for total white cell count, C reactive protein (CRP), $CD4^+$ T lymphocytes and HIV-1 viral load.

Sputum elastase: Concentrations of the sputum elastase were measured using a commercial, capture, sandwich ELISA procedure (Hycult Biotechnology, Uden, The Netherlands).

Sputum samples: Sputum samples were collected at monthly intervals for microbiological testing including *Mycobacterium tuberculosis* where indicated.

CT scanning: High resolution CT scanning was performed. Two blinded radiologist carried out the CT scan scoring without viewing any clinical data, morphological testing and special investigations. The Bhalla scoring system was utilised to score the CT scans [14].

Statistical analyses

The sample size calculation was based on the number of pulmonary exacerbations requiring antibiotic therapy estimated at 3 per year. A sample size of 20 patients per study arm was determined to have a 90% power to detect a clinically relevant reduction in exacerbations of 30%, where a mean of 2 and a standard deviation of 1 exacerbation were assumed; with a presumed dropout rate of 10%, when testing was one-sided at the 0.05 level of significance. Analysis of variance (ANOVA) was used to compare medication groups with respect the mean number of exacerbations, as there was no baseline value. For the study variables, treatment arms were compared with respect to change from baseline to end of study using ANCOVA, with baseline values as covariates. Wilcoxon test was used to assess the pooled data for IL-8, TNF-α and lung function tests. The Spearman correlation test was used to assess correlations between the cytokines and markers of HIV disease activity. Data analysis was performed using Stata Release 11 (Statacorp LP, College Station, TX, USA).

Ethical approval was granted by the Research Ethics Committee of the University of Pretoria.

Results

As demonstrated in figure 1, a total of fifty-six children were screened with forty-three meeting all inclusion criteria. One child died prior to randomisation and in one child parents declined to participate. Ten (23%) participants (four in placebo arm and six in erythromycin

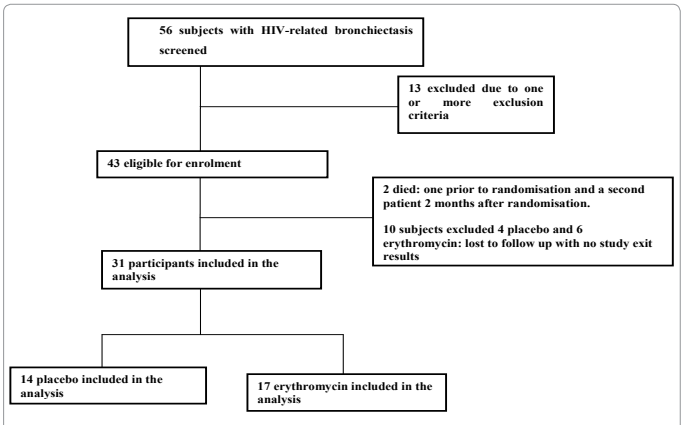

Figure 1: Enrolment and randomisation of participants included in the study.

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arm) were lost to follow up during the 52-week follow up period. A total of thirty-one participants of whom 58% were male, were included in the final analysis. The baseline characteristics of the two treatment arms are reflected in table 1. The characteristics of the two study arms were generally balanced, with the exception of gender distribution with more males (55%) in the erythromycin arm and more females in the placebo arm.

All children were on HAART prior to enrolment. HIV virological suppression was achieved in 56% of participants with a geometric mean of (0.0 ± 22514.3 copies/ml and 80 ± 9635.2 copies/ml, p=0.97) in the erythromycin and placebo arms, respectively. The total $CD4^+$ T cell counts and percentage counts in the erythromycin arm were lower than in the placebo arm (650.9×10^9 ± 446.7 *vs.* 881.6×10^9 ± 505.8; p<0.01 and 16.3% ± 6.7 *vs.* 22.6% ± 11.9; p=0.01), respectively and this was statistically significant. The lower $CD4^+$ T cell counts were reflective of a shorter period on HAART when comparing the two study arms with the number of months on HAART being (12.0 months ± 12.8 *vs.*17.0 months ± 22.0), in the erythromycin arm when compared to the placebo arm, although this was not statistically significant.

There was no statistically significant difference in the mean number of exacerbations in the treatment versus the placebo arm (2.14 ± 2.28) *vs.* (2.18 ± 1.59) per year (p=0.17). However, 18% (erythromycin) *vs.* 0% (placebo) of study participants had no exacerbations during the study duration.

At study entry the growth parameters of children in both study arms were within the normal range. The compliance in both study arms was excellent, with more than 90% patients taking study medication.

There was no statistically significant change when comparing the Bhalla scores at baseline and study end in both treatment arms, indicating stability in the degree of bronchiectasis.

Of the microbiological cultures over the year only 2% of organisms cultured were *Pa* and 2% mycobacteria other than tuberculosis- *M. fortuitum* and *M. avium intracellulare,* with *one M.TB*.

For the characteristics of the participants at the end of the study period (summarised in table 2), there was an improvement in weight, which was more pronounced in the placebo versus the erythromycin arm, which was not statistically significant (p=0.45). There was a marginally significant improvement in the BMI z-scores when comparing the two study arms; more so in the placebo arm than the erythromycin arm (-0.6 ± 0.9 to -0.2 ± 1.0 *vs.* -0.5 ± 1.3 to -0.4 ± 1.6; p=0.08). The immunological status of the subjects improved in both study arms with increases in the $CD4^+$ T cell counts and decrease in the HIV viral load, although these differences were not statistically significant (p=0.88 and p=0.43), respectively.

For the pulmonary functions, there was an improvement (although not statistically significant) in FEV_1 % predicted (56.0 ± 15.1 to 68.0 ± 21.0, and 53.5 ± 13.6 to 62.5 ± 13.6; p=0.31) and FVC % predicted (49.0 ± 14.4 to 63.0 ± 17.9; 45.0 ± 14.3 to 58.0 ± 12.1, p=0.46); pre-and post therapy for the erythromycin and placebo groups, respectively. After pooling the data for the pulmonary functions, increases in both the FEV_1 % predicted and FVC % predicted, from baseline to end of study, were statistically significant (52.7 to 61.5; p=0.005 and 46.0 to 59.9; p<0.001), respectively. There was no change in the pooled data for $FEF_{25/75}$ % predicted at study entry compared to study end (53.4 ± 28.1 *vs.* 52. ± 25.2).

After intervention in both erythromycin and placebo study groups, there was a decrease in IgG. The change in IgG from baseline to study

Characteristic	Placebo (mean ± SD)	Erythromycin (mean ± SD)	P value
Gender (M:F)	5:9	13:4	
Age (years)	9.1 ± 2.1	8.4 ± 2.4	0.15
Exacerbations	2.1 ± 2.3	2.2 ± 1.6	0.47
Months on HAART	17.0 ± 22.0	12.0 ± 12.8	0.57
Weight z-score (kg)	-1.8 ± 0.9	-1.6 ± 1.6	0.77
Height z-score (cm)	-1.7 ± 1.4	-1.7 ± 1.5	0.50
BMI z-score (kg/m^2)	-0.6 ± 0.9	-0.5 ± 1.3	0.91
CD4 count (%)	22.6 ± 11.9	16.3 ± 6.7	0.01
CD4 (total$\times10^6$)	881.6 ± 505.8	650.9 ± 446.7	<0.01
HIV viral-load (copies/ml)*	80.0 ± 22514.3	0.0 ± 9635,2	0.97
FEV1 (% predicted)	53.5 ± 13.6	56.0 ± 15.1	0.54
FVC (% predicted)	45.0 ± 14.3	49.0 ± 14.4	0.94
$FEF_{25/75}$ (% predicted)	55.1 ± 25.3	56.0 ± 25.7	0.89
IgG (g/ml)	24.8 ± 15.4	26.2 ± 8.4	0.54
CRP (mg/l)	3.6 ± 16.1	9.4 ± 18.8	0.08
Bhalla score¶	11.5 ± 4.3	15.0 ± 4.0	0.02
Compliance (% medication)	91.0 ± 9.9	92 ± 9.9	0.87

SD: Standard deviation; BMI: Body mass index; HAART: Highly active antiretroviral therapy; CD4: Cluster differentiation cell; HIV: Human immunodeficiency virus; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IgG: Immunoglobulin G; CRP: C reactive protein; WCC: White cell count; ¶Bhalla score: Appendix D. *Geometric means reported.

Table 1: Baseline characteristics of children with HIV-related bronchiectasis treated with erythromycin or placebo.

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end, was not attributed to the use of erythromycin (p=0.24). There was no correlation between IgG and FEV_1 at study entry and study end (p=0.75 and p=0.73) for the pooled data for the study population. CRP decreased from study entry when compared to the end of the study, although there was not statistically significant difference when comparing the treatment arms (p=0.98).

With respect to the pro-inflammatory cytokines, the chemokine IL-8 was most significantly elevated in the sputum, with a moderate non-statistically significant different decrease post-intervention in both the erythromycin and placebo arms (p=0.99) (Table 3). After pooling the data for sputum IL-8 for the whole study population, there was a statistically significant decrease of log values of sputum IL-8 from baseline to study end (geometric means 1234.5 to 434.5; p=0.04). Sputum IL-1β was elevated with a modest decline in the erythromycin arm and a moderate elevation in the placebo arm. The change of IL-1β from baseline to study end was not statistically significant in the treatment arms (p=0.99). Although TNF-α levels declined in both treatment arms, the decline could not be attributed to the use of erythromycin. The pre- and post treatment serum TNF-α levels were independent of $CD4^+$ T cell percentage counts (p=0.74 and p=0.62) and

Characteristic	Placebo (SD)		Erythromycin (SD)		P Value
	Entry	End	Entry	End	
Weight z -score (kg)	-1.8 ± 0.9	-0.9 ± 0.8	-1.6 ± 1.6	-1.7 ± 1.7	0.45
Height z-score (cm)	-1.7 ± 1.4	-1.6 ± 1.4	-1.7 ±1.5	-1.9 ± 1.4	0.97
BMI z-score (kg/m^2)	-0.6 ± 0.9	-0.2 ± 1.0	-0.5 ± 1.3	-0.4 ± 1.6	0.08
CD4 count (%)	22.6 ± 11.9	29.3 ± 11.4	16.3 ± 6.7	21.7± 7.8	0.88
CD4 (total×10^6)	881.6 ± 505.8	939.3 ± 530.6	650.9 ± 446.7	1036.7 ± 461.8	0.47
HIV viral load (copies/ml)	80.0 ± 22514.3	0.0 ± 26685.9	0.0 ± 9635.2	0.0 ±19231.2	0.34
FEV_1 (% predicted)	53.5 ± 13.6	62.5 ± 13.6	56.0 ± 15.1	68.0 ± 21.0	0.31
FVC (% predicted)	45.0 ± 14.3	58.0 ± 12.1	49.0 ±14.4	63.0 ±17.9	0.46
IgG (g/ml)	24.8 ± 15.4	22.7 ± 6.9	26.2 ± 8.4	19.0 ± 5.4	0.24
CRP (mg/l)	3.6 ± 16.1	2.4 ± 21.0	9.4 ± 18.8	4.0 ± 73.9	0.98
Bhalla score	11.5 ± 4.3	12.5 ± 4.1	15.0 ± 4.0	15.0 ± 3.3	0.62

Z-scores according to WHO growth charts [2,19]; CD4: cluster differentiation 4 cells; HIV: Human immunodeficiency virus; FEV_1: Forced expiratory flow in 1 second; FVC: Forced vital capacity; IgG: Immunoglobulin G; CRP: C-reactive protein.

Table 2: Characteristics of children with human immunodeficiency virus related bronchiectasis pre- and post- treatment with erythromycin and placebo.

Cytokine	Erythromycin N (95% CI)		Placebo N (95% CI)		P value
	Entry	End	Entry	End	
Serum					
IL-1β	3.3 (1.1-9.7)	4.0 (2.3-7.0)	4.1 (2.1-8.0)	5.3 (2.1-13.3)	0.31
IL-6	6.9 (3.0-15.9)	6.1 (3.0-12.5)	18.4 (4.9-69.2)	14.9 (4.6-47.8)	0.31
IL-8	18.9 (9.0-39.6)	18.1 (7.4-44.2)	24.2 (7.0-83.7)	39.4 (12.9-119.8)	0.26
IL-10	3.9 (3.0-5.2)	3.9 (2.5-6.1)	4.8 (3.3-6.9)	4.3 (3.0-6.0)	0.51
IP-10	4667.9 (2620.9-8613.5)	3636.9 (2420.0-5465.8)	2734.6 (2341.7-5956.0)	3235.4 (2311.7-4528.3)	0.24
TNF-α*	101.9 (-70.3-274.1)	78.2 (-63.5-219.8)	55.0 (-27.2-137.2)	51.7 (3.8-99.7)	0.74
TNF-R1	111.8 (94.7-132.0)	106.9 (92.5-123.6)	119.5 (103.8-137.5)	115.4 (100.8-132.1)	0.95
Sputum					
IL-1β	544.8 (198.0-1499.1)	575.3 (177.1-1869.1)	870.3 (366.8-2064.9)	823.2 (434.5-1559.6)	0.99
IL-6	5.6 (2.5-12.6)	2.9 (1.4-6.2)	5.6 (2.4-13.1)	4.6 (92.2-9.9)	0.39
IL-8	932.7 (341.1-2550.2)	268.4 (81.0-888.9)	1476.6 (537.5-4056.6)	808.3 (274.7-2378.3)	0.99
IL-10	0.6 (0.5-0.9)	0.6 (0.4-1.0)	0.8 (0.4-1.33)	0.7 (0.5-0.9)	0.93
IP-10	16.7 (4.1-68.5)	7.8 (5.9-10.5)	9.1 (6.9-11.9)	11.2 (6.3-19.7)	0.32
TNF-α*	15.0 (8.2-21.8)	10.5 (5.7-19.4)	17.0 (9.9-24.2)	10.9 (6.2-19.0)	0.97
Elastase	17.6 (13.2-23.4)	18.9 (13.0-66.6)	17.9 (13.1-24.6)	20.3 (16.5-25.0)	0.92

All mean reported as geometric means unless indicated; *Arithmetic means reported; sTREM: Soluble triggering receptor expressed on myeloid cells; IL- Interleukin: TNF-α: Tumour necrosis factor alpha, IP-10: Interferon gamma induced protein -10; Units of all the cytokines in picograms per millimetre except elastase in nanograms per litre. ANCOVA test used to obtain p-values for mean change from post treatment to mean change pre-treatment.

Table 3: Summary of serum and sputum cytokines in children with human immunodeficiency virus related bronchiectasis before and after treatment with erythromycin or placebo.

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HIV viral load (p=0.48 and p=0.90), respectively. Sputum elastase did not change at baseline or studies end in the two treatment arms.

For the anti-inflammatory cytokine IL-10, the values were not elevated in both serum and sputum, with no statistically significant change in the levels after intervention with erythromycin or placebo (p=0.51 and p=0.93), respectively.

The chemokine IP-10 was elevated in serum and less so in sputum at baseline. There was a modest decline in serum IP-10 in the erythromycin arm and an increase in the placebo arm, although the change from baseline was not statistically significant (p=0.24). There was no correlation between IP-10 and $CD4^+$ T cell percentage count (p=0.34) and HIV viral load (p=0.11). IP-10 was not correlated with FEV_1 % predicted (p=0.55) or FVC % predicted (p=0.15).

Discussion

The use of macrolides for their immunomodulatory properties in CF-bronchiectasis is currently regarded as standard of care in those with *Pa* colonisation. In paediatric non-CF bronchiectasis, there is need for more robust data on the role of macrolides in a form of bronchiectasis where *Pa* is rarely cultured. The current study showed no additional benefit of erythromycin relative to placebo on the reduction of exacerbations in a cohort of HAART treated children with HIV-related bronchiectasis, although there was a statistically significant difference in the CD4 T^+ cell counts with higher levels in the placebo arm may have influenced the outcome of the study, Erythromycin had no effect on local and systemic pro-inflammatory and anti-inflammatory cytokines. This is consistent with findings in a group of HIV-positive women on HAART [16]. Pulmonary functions and sputum IL-8 improved, although this cannot be attributed to the use of erythromycin.

Medical interventions to treat HIV-related bronchiectasis should incorporate immune system restoration with HAART, physiotherapy and adequate nutrition. There is currently no data on the effect of HAART on lung disease progression. One adult study suggested possible decline in pulmonary functions in patients on HAART, although this was confounded by more than half of the subjects being smokers [17]. The restoration of the immune system with the use of HAART is accompanied by a reduction of pro-inflammatory cytokines, with its effect on the $CD4^+$ T cell population continuing for the first three to five years [16,18]. Although physiotherapy forms a fundamental part of current guidelines for bronchiectasis treatment, its effect is mainly on reduction of cough frequency and improved quality of life [19,20].

The newer macrolides (clarithromycin and azithromycin) and erythromycin have been studied in non-CF bronchiectasis for their immunomodulatory effects, but erythromycin has the added benefit of being cheap and freely available. Previous studies of macrolides have shown a reduction in pulmonary exacerbations and modest improvements in lung functions, although this is limited by lack of long-term randomised controlled trials [21-23]. A small study by Serisier and Martin demonstrated a reduction in the number of exacerbations observed over 12 months (from four to two per year) [21]. A one-year retrospective review by Anwar et al, showed a reduction in exacerbations with the use of azithromycin, but in this study 32% of participants had a previous culture or were colonized with *Pa* [10]. The lack of efficacy in the current study may be attributed to the fact that there were no participants colonized with *Pa.* The data on the effect of macrolides on pulmonary functions is conflicting. Tsang et al. found a significant improvement in FEV_1 and FVC, over 8 weeks in 11 patients treated with erythromycin, whilst Yalcin et al. found no effect of clarithromycin on 17 children [22,24]. We found no effect of erythromycin on either FEV_1 or FVC in this study. However, on pooling the data a significant increase in both pulmonary function parameters was evident at the end of the study period. This finding we postulate could be attributable to either "continued" sub-clinical immune restoration from HAART or improved overall care of subjects, which includes physiotherapy and early treatment of exacerbations.

In vitro data has shown declines in cytokines with the use of macrolides in bronchiectasis [11]. One randomised study assessed cytokines as an end-point after three months of clarithromycin and found a decrease in IL-8, but not TNF-α [24]. This study did not replicate this finding, possibly due to the superior tissue penetration of clarithromycin when compared to erythromycin or the waning effect of the beneficial effect of the macrolides over time.

Serum IP-10- a cytokine, involved in the trafficking of monocytes and activated T helper cells was significantly elevated in the serum. Elevated levels of IP-10 were previously found to be associated with HAART failure or TB [25,26]. These associations were, however, excluded in our cohort of children who were screened for TB and found to be un-infected and there was actually improvement in HIV disease activity markers.

Elastase, a protease released by disrupted neutrophils, has been found in CF to be responsible for 90% of the protease activity resulting in damage to the extracellular components such as elastin, collagen and proteoglycans with subsequent pulmonary destruction [27-29]. Values in CF, greater than 500 ng/ml have been found in adults in stable state CF [28]. In the current study, the levels were significantly lower than those previously described in CF and did not change over time. One explanation for this may be the low prevalence of *Pa,* which can be an independent source of proteases. Downey et al. demonstrated no change in soluble and free elastase levels in a group of CF participants after a course of antibiotic therapy [30].

Prior studies in CF reveal a correlation between elevated IgG levels and respiratory morbidity [31,32]. In the current study there was a decrease in the IgG levels in both treatment arms, but this was not correlated to pulmonary function parameters.

The strengths of this study are that preliminary evidence of the effect of HAART and adjunctive care on pulmonary functions and sputum IL-8 in children with HIV-related bronchiectasis. The limitations of this study are that the number of patients was small. In addition, quality of life assessments were not conducted. The study was also confounded by the fact that the CD4 T^+ cell count levels were higher in the placebo group when compared to the active study arm. It is, however, very unlikely that even a larger study, would find benefit from erythromycin on exacerbations as no numerical difference in exacerbations was seen and patients would have to be followed up for many years to detect the slightest benefit.

Conclusion

Administration of HAART and adjunctive care, which includes airway clearance and treatment of exacerbations, in children with HIV-related bronchiectasis is associated with significant improvement

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in pulmonary function tests and IL-8, with no additional benefit from the use of erythromycin.

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Original Article

Phenotypic expression of the 3120+1G>A mutation in non-Caucasian children with cystic fibrosis in South Africa

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Abstract

Introduction: Cystic fibrosis (CF) is the most common genetic disorder in Caucasians. Presentation of CF in non-Caucasians is less well studied.
Objective: This audit was undertaken to determine the phenotypic expression of the 3120+1G>A mutation in black and mixed race children in South Africa.
Methods: A multi-centre retrospective chart review of clinical, laboratory and spirometry data of non-Caucasian CF patients in four CF centres in South Africa was collected. Data was collected at diagnosis and after a five-year follow-up period. Ethical approval was granted for the study.
Results: A total of 30 participants were enrolled of whom 14 (47%) were homozygous and 16 (53%) heterozygous for the 3120+1G>A mutation. The mean age of diagnosis was 13 months. Twenty-four (80%) patients had malnutrition (mean weight z-score −3.6) or failure to thrive (77%) at presentation. Twenty (67%) presented with non-specific abdominal symptoms, whilst fifteen (50%) had recurrent respiratory tract infections. *Pseudomonas aeruginosa* was detected at a mean age of 21 months. The mean FEV1 was 73% predicted (95% CI 54.0–91.1) at study entry and 68% predicted (95% CI 49.74–87.06) at follow-up.
Conclusion: Failure to thrive and a diagnosis of protein energy malnutrition (kwashiorkor) are the common presenting features of CF in children with the 3120+1G>A mutation. Meconium ileus is a rare presenting feature of CF in black and mixed race children with this deletion in South Africa.

Keywords: Growth; Meconium ileus; Lung function; Failure to thrive; *Pseudomonas aeruginosa*

1. Introduction

Cystic fibrosis (CF) is a one of the most common severe autosomal recessive disorders in Caucasians. CF occurs as a result of mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene found on the long arm of chromosome 7 [1–3]. Over 1900 mutations have been identified, with p.F508del being the most common mutation in Caucasians [4]. In the South African Caucasian population, p.F508del accounts for up to 81% of all CF alleles [5]. The p.F508del mutation is less frequent in the South African mixed-race (53%) and black African populations where it's rarely detected.

The 3120+1G>A *CFTR* mutation was first reported in three African-American CF patients by Macek et al., and has subsequently been shown to account for 9–14% of African-American CF mutations [6]. Analysis of the *CFTR* gene and its expression in African-American CF patients has shown a significantly different profile from that observed in Caucasian

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CF patients [6]. Previous studies comparing the phenotypic presentation of black and white patients with CF have shown some differences in clinical presentation and morbidity related to CF. Differences include a higher incidence of malnutrition, severe lung disease and a higher rate of meconium ileus in black patients [7–9], with one case series describing the phenotype associated with the 3120+1G>A mutation as presenting with mild to moderate sinopulmonary symptoms [10].

In South Africa, the most common CF disease causing mutation in black South Africans is the 3120+1G>A mutation, which is detected in 46% of all CF alleles, with a carrier rate of 1 in 90 [11]. With this carrier rate and the presence of other mutations, over 1000 black African babies with CF are estimated to be born each year in South Africa [9]. A study conducted in Cape Town, revealed that the 3120+1G>A mutation was the second most common mutation in the mixed race children, after the p.F508del mutation [12].

Until recently, the spectrum of disease in the mixed race and black African population has remained poorly understood. Recognition of CF in an African context is difficult due to the overwhelming burden and high prevalence of poverty-associated conditions with similar presentations namely protein energy malnutrition (PEM), human immunodeficiency virus infection (HIV) and tuberculosis. Therefore, diagnosis of CF and institution of therapy may be delayed, impacting negatively on the outcome.

We therefore undertook this study with the primary aim being to assess the phenotypic expression of the 3120+1G>A mutation in black and mixed race children with CF in South Africa. A secondary objective was to assess the age of diagnosis and the overall morbidity of children with the 3120+1G>A mutation.

2. Patients and methods

2.1. Study population

A retrospective chart review of black and mixed race CF patients at four CF centres was conducted, namely, the Paediatric Cystic Fibrosis Clinics at Steve Biko Academic Hospital (SBAH), Pretoria; the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg; the Tygerberg Hospital (TBH), Cape Town and the Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town. Subjects were included in the study if there was laboratory confirmation of CF with the presence of at least one copy of the 3120+G>A mutation by molecular testing.

2.2. Clinical investigations

The clinical data collected included: age at diagnosis, weight, height, and body mass index (BMI) {World Health Organization defined z-scores for weight, height and BMI} [13]. All data was collected at diagnosis and after a five year follow-up period.

2.3. Laboratory investigations

The data collected included: screening sweat chloride conductivity (Nanoduct™ Neonatal Sweat Analysis System, Wescor, Inc., South Logan, UT, USA) and faecal elastase (ELISA kit, ScheBo® Pancreatic Elastase 1 Stool Test). Results of sputum microbiology were collected. The colonisation status of the airway pathogens identified was also noted. Colonisation was defined as the persistence of a pathogen on two or more sputum samples over a period of six months as defined in the Leeds criteria for chronic infection [14].

Pulmonary function parameters for all subjects over the age of six years were collected for forced expiratory flow in 1 s (FEV_1) and forced vital capacity (FVC) [ViasysSpiroPro Jaeger Spirometer Cardinal Health, Hoechberg, Germany].

2.4. Ethical clearance

Ethic approval to access the patient records was obtained from the Research Ethics Committees of the University of Pretoria, Witwatersrand University and University of Cape Town.

3. Results

A total of 30 patients of whom 20 (67%) were black Africans were included in the study. There were 53% males. Of the total number of subjects the patient distribution per site was: 47% (RCWMCH), 27% (SBAH), 20% (CMJAH) and 6% (TBH). Fourteen (47%) of the participants were homozygous for the 3120+G>A mutation, whilst sixteen (53%) were heterozygous. The baseline characteristics of the participants are summarised in Table 1. The mean age at diagnosis was 13.0 months (95% CI 6.5; 19.4). At presentation the subjects were stunted and severely underweight with height and weight z-scores of −2.6 (95% CI −3.9; −1.3) and −3.6 (95% CI −4.6; −2.6), respectively (Table 2).

Table 1
Baseline data of black and mixed race children with cystic fibrosis with a 3120+1G>A mutation.

Variable	Frequency	Percentage (%)
Gender (M/F)	16:14	53:47
Age diagnosis (months)	13	
Ethnic group		
Mixed race	10	33
Black African	20	67
Mutation		
Homozygous 3120+1G>A	14	47
Heterozygous 3120+G>A	16	53
Clinical presentation		
Respiratory tract infection	15	50
Failure to thrive	24	80
PEM (kwashiorkor)	23	77
Abdominal symptoms	20	67
Other	9	30
Pancreatic insufficiency	29	97

PEM: protein energy malnutrition; abdominal symptoms: included meconium ileus, rectal prolapse and chronic diarrhoea.

Table 2
Baseline clinical parameters of children with a 3120+1G>A cystic fibrosis at diagnosis and follow-up.

Variable	Presentation (mean; 95% CI)	Follow-up (mean; 95% CI)
Age (months)	13.0 (6.6; 19.4)	69.2 (44.9; 93.5)
WAZ	−3.6 (−4.6; −2.6)	−1.2 (−2.5; 0.6)
HAZ	−2.6 (−3.9; −1.3)	−2.4 (−3.3; −1.6)
BMI	12.9 (11.9; 14.0)	14.7 (13.1; 16.3)
FEV_1	72.5 (54.0; 91.1)	68.4 (49.7; 87.1)

HAZ: height for age z-score; WAZ: weight for age z-score; BMI: body mass index; FEV_1: forced expiratory flow in 1 s.

The majority of the participants (97%) were pancreatic insufficient at diagnosis. In twenty-three (77%) participants the original diagnosis at presentation was protein energy malnutrition. Fifteen patients (50%) already had respiratory symptoms at diagnosis. Pulmonary function tests were available in thirteen subjects (43%) with a mean FEV_1 of 72.5% predicted (95% CI 53.9; 91.1) at baseline. *Staphylococcus aureus* (40%) and *Pseudomonas aeruginosa* (*Pa*) (60%) were the most common colonising the airway. The mean age of the first identification of *S. aureus* and *Pa* was 17.0 months and 21.0 months of age, respectively. Gastrointestinal complications were identified at presentation in 27% with liver cholestasis present in 10% of the participants.

On 5 year follow-up, six (20%) of the participants had died and there were twenty-three survivors (77%) (Table 3). Of the 6 patients who died, three demised from respiratory failure (two were colonised with *Pa* and one with *S. aureus*), one each from overwhelming sepsis, liver failure and hypovolemic shock from gastroenteritis. In one patient outcome was unknown as the patient was lost to follow-up.

On follow-up, there was improvement in all the growth parameters (Table 2). Lung function decline in those with Pa was more severe than in those without Pa; FEV_1 decline of 15% versus 4%, respectively, over the five year follow-up period. One patient developed CF-related diabetes, and this patient was a compound heterozygote with the 3120+1G>A/p.F508del mutation.

The most common complications at follow-up were respiratory in nature (46%) with recurrent chest infections defined as more than 4 exacerbations per year for the study period.

Table 3
The follow-up of black and mixed-race children with cystic fibrosis.

	Frequency	Percentage (%)
Respiratory cultures		
Pseudomonas aeruginosa	13	43
Staphylococcus aureus	13	43
Complications		
Respiratory	13	46
Abdominal	8	27
Liver dysfunction	3	10
Poor growth	3	10
Outcome		
Alive	23	77
Dead	6	20
Unknown	1	3

Abdominal complications were the second most common (27%), which included distal intestinal obstruction, meconium ileus equivalent and rectal prolapse. Only 10% of the subjects developed liver cholestasis and had poor growth on follow-up.

4. Discussion

There is a wide range of phenotypic presentations in CF with striking differences between black and white patients, mostly being noted in gastrointestinal manifestations and nutritional status [15]. Previous studies have suggested that the 3120+1G>A mutation is a milder mutation with more abdominal symptomatology, especially meconium ileus. This mutation has been more commonly observed among black patients, reflecting the lower prevalence of p.F508del in that group [15]. In the current study, we have shown that the mean age of diagnosis of the study population was over the age of one year. In the majority of patients failure to thrive and protein energy malnutrition were the most common presenting features. Abdominal symptoms were a presenting feature in only a third of the study population. Moreover, the acquisition of *Pa* colonisation was within the first two years of life. Almost all the participants had pancreatic insufficiency at presentation.

There is a delay in the diagnosis of children with CF in our population. This is in contra-diction to African-American children where the mean age of diagnosis is eight months [8]. This can be attributed to the lack of awareness of CF (which is believed to be rare in this population group), poor access to medical care and missed diagnosis as malnutrition secondary to conditions of poverty. The classic triad for a CF diagnosis is recurrent or persistent respiratory symptoms, pancreatic insufficiency and poor weight gain [16]. A previous study of 181 CF patients in South Africa showed that only 4.6% of patients presented with all 3 features thus limiting its value in this context [17]. This may account for the delay in diagnosis in the current cohort. Another diagnosis limiting factor is that in order for CF to be confirmed, identification of the *CFTR* gene mutations is necessary, and in the current mutational analysis panel used in South Africa, only 76% and 46% of mutations are detected in the mixed race and black African CF, respectively [17]. Full sequencing of the entire *CFTR* coding region is also unavailable to the majority of South African patients due to cost restraints. This implies that a significant number of patients are missed due to inability to identify 2 disease-causing *CFTR* mutations [18].

Pulmonary function parameters, particularly FEV_1 have been shown to be a reliable outcome measure in most studies and are used as a predictor of lung disease progression and mortality [19]. Vandenbranden et al. demonstrated that nutrition remained a strong predictor for accelerated decline in FEV_1 [20]. Morrow et al. in a longitudinal 8 year follow-up of children in Cape Town, demonstrated a 20% improvement in the median pulmonary function scores over the follow-up period [21]. They ascribed this to the improved multidisciplinary team approach in the management of CF patients. The current study revealed a decline of FEV_1 of between 3%/year in those with *Pa* compared to 0.8%/year in those not colonised with *Pa*. This decline is slightly higher than that reported by Morrow et al., where the rate of FEV_1

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decline was 0.43%/year [21]. These results indicate that 3120+1G>A mutation may confer a more severe lung disease when compared to a cohort of whom the majority largely had the p.F508del mutation.

The strength of this study is that all possible children with the 3120+1G>A mutation in South Africa were included and should serve as a study of the phenotypic presentation and longitudinal follow-up of non-Caucasian children with the 3120+1G>A mutation. The study has a number of limitations, one being the small number of participants and limits generalisability. There were also few participants who provided pulmonary function data.

In summary, failure to thrive and protein energy malnutrition are the commonest presenting features of CF in black and mixed race South African children with the 3120+1G>A mutation. Increased awareness of CF in non-Caucasian African children is therefore necessary. Clinicians should consider CF when investigating children who present with unexplained malnutrition, where nutritional and social factors have been optimised and growth still remains sub-optimal.

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Atopy in HIV-infected children in Pretoria

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Introduction. The development or aggravation of a pre-existing atopic state in patients with human immunodeficiency virus (HIV) has not been thoroughly investigated in South Africa. HIV-infected adults have been shown to have a higher prevalence of atopy in some international studies, but this has not been documented in children.

Methods. A prospective convenience sample of 50 children aged between 3 months and 12 years attending the Tshwane District Hospital Paediatric HIV Clinic in Pretoria was recruited. Their personal and family histories of atopy, World Health Organization (WHO) HIV clinical staging and Centers for Disease Control (CDC) immunological staging with CD4 counts were documented. An age- and sex-matched control group of 50 HIV-negative children was included. Skin prick tests (SPTs) to identify common aeroallergens were conducted on all patients.

Results. One hundred children were enrolled, with 50 in each group. Ten per cent of the HIV-infected patients compared with 16% of controls had positive SPTs to aeroallergens. A higher percentage of the HIV-infected patients had chronic rhinitis and eczema (60% and 68%, respectively). There was no relationship between CD4 count and positive SPTs (p=0.61), mean log CD4 count and presence of reported asthma (p=0.71), and CD4 count and presence of reported dermatitis (p=0.84). The CD4 count was not statistically different between children with and without a family history of atopy (p=0.68).

Conclusion. It appears that the stage of HIV disease does not influence the development or expression of allergy. There is a high prevalence of dermatitis and chronic rhinitis in HIV-infected children, probably not atopic in origin.

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Both atopic and HIV-related diseases are common in South Africa. Atopy is a genetic predisposition to form excessive immunoglobulin E (IgE), leading to a generalised and prolonged hypersensitivity to common environmental allergens – both inhaled and dietary. Atopic individuals manifest one or more of a group of diseases, including asthma, atopic eczema, allergic rhinitis, urticaria and gastrointestinal conditions, which tend to run in families.[1] These have been shown to be associated with Th2 cytokines. Regulatory T cells via interleukin-10 (IL-10), a cytokine known to play a pivotal role in the expression of specific immune pathways in a specific individual, are involved.[2]

The burden of human immunodeficiency virus (HIV) infection in sub-Saharan Africa is high, with 230 000 children born annually to HIV-infected mothers in this region.[1] The epidemic proportions of the disease make it essential for appropriate diagnosis and management of affected children. This disease has a significant impact on mortality, with HIV-infected infant death rates as high as 130 - 390 per 1 000 live births.[3] The availability of highly active antiretroviral treatment (HAART) in the last decade in the developed world has had a significant effect on the survival of patients infected with HIV.[4] Patients infected with HIV are therefore now demonstrating morbidity similar to other chronic conditions, including atopic conditions.

HIV is a retrovirus which, after gaining entry into the body, binds to a host of cells involved in innate and adaptive immunity.[5] Resulting abnormalities affect both the cellular and humoral immune system. T-cell abnormalities that result in depletion of CD4 cells, as well as polyclonal activation of B cells with hyperglobulinaemia, are well known.[6] This hyperglobulinaemia also affects IgE, with a marked elevation of this immunoglobulin. Adult studies have suggested an association between atopy and HIV;[6,7] the evidence in children is scanty.

The switch from a Th1 to a Th2 cytokine profile has previously been shown to be a critical step in the progression of HIV infection to acquired immunodeficiency syndrome (AIDS) in adults.[8,9] Even before depletion of CD4 cells, there is a qualitative defect in CD4 that results in loss of antigen and mitogen-induced interleukin-2 (IL-2) and interferon gamma (INF-γ) production. IL-2 and INF-γ are important cytokines in the Th1 pathway. A reduction in IL-2 results in a switch to interleukin-4 (IL-4) production, which is a critical step in the switch to a Th2-mediated response.[8] IL-4 drives the development and expansion of Th2 cells and mediates

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downstream effector functions, such as B-cell activation, in particular increased major histocompatibility complex class II expression and isotype switching to IgE production.[10] Although the exact mechanism is not well understood, a possible role of HIV antigen gp120 and HIV-1 trans-activating protein (Tat protein) is suspected. Gp120 is thought to act as a super-antigen, stimulating the immune system with a bias toward Th2 cytokine production via release of IL-4 and interleukin-13 (IL-13) from human F epsilon R-positive cells ($F_{ce}R1+$ cells).[11] Tat protein may also act as a chemo-attractant for $F_{ce}R1+$ cells and also upregulate chemokine receptor 3 (CCR3) expression.[12]

We aimed to study the association between atopy (sensitivity to environmental factors, i.e. allergy and clinical disease states) and HIV infection in children and the role of HIV infection on the development of allergy.

Methods

A prospective convenience sample of children aged 3 months - 12 years attending the Tshwane District Hospital Paediatric HIV Clinic was obtained. Informed consent to take part in the study was one of the inclusion criteria. All HIV-infected patients in the study were receiving antiretroviral therapy. Subjects for whom informed consent could not be obtained were excluded. Information regarding the children's personal and family histories of atopy was recorded from information provided by parents/guardians. An overview of the children's medical history and a general examination of their current state of well-being were conducted. The World Health Organization (WHO) HIV clinical staging, CD4 counts obtained by flow cytometric analysis, and evidence of atopy were also recorded.[13] An age- and sex-matched control group of 50 healthy HIV-negative children attending routine follow-up at the cardiology and neurology clinics of Pretoria Academic Hospital were included. Skin prick tests (SPTs) (Alk-Abello) for common aeroallergens were conducted on all patients with negative saline and on positive (histamine-dihydrochloride 10mg/ml) controls. An induration of 3 mm or greater than the negative control was regarded as a positive result. The allergen extracts used were: Bermuda grass, five-grass mix, tree mix, dog hair dander, cat hair dander, standard mite (*Dermatophagoides pteronyssinus*), and cockroach (*Blatana* sp).

Diagnoses of asthma, allergic rhinitis and eczema were offered to respondents in the questionnaire but were neither investigated nor proven.

Statistical analysis

A Welch two-sample *t*-test with unequal variances was employed in the analysis of the CD4 count with regard to family history of atopy, dermatitis and asthma. A *p*-value of <0.05 was considered statistically significant.

Approval for the study was obtained from the Research Ethics Committee of the University of Pretoria. Informed consent was obtained from all parents or guardians of the patients. Assent was also obtained from all subjects >7 years old.

Results

A total of 100 children were enrolled, with half in the study arm and half in the control group. Forty-five (90%) of the 50 HIV-infected children and 42 (84%) of the control group had a negative SPT to common aeroallergens (Tables I and II). There was no statistical difference between groups (p=0.95). The most common allergen identified was *D. pteronyssinus* in both groups, with 3 of the 5 HIV-infected patients being monosensitive to house dust mite (Fig. 1).

Twelve (24%) of the HIV-infected children tested had a positive family history of atopy, while only 2 of them had a reactive SPT. Eleven (22%) HIV-infected children had been diagnosed with asthma. The majority of these (9 patients) had

Table I. Summary of findings of HIV infection given as number of patients in each category (*N*=50 (%))

	N (%)	SPT positive	Family history of atopy	Asthma	Rhinitis	Eczema
WHO HIV clinical stage						
1	17 (34)	1 (2)	2 (4)	2 (4)	13 (26)	14 (28)
2	16 (32)	1 (2)	5 (10)	3 (6)	8 (16)	9 (18)
3	14 (28)	2 (4)	3 (6)	4 (16)	8 (16)	9 (18)
4	3 (6)	1 (2)	2 (4)	2 (4)	1 (2)	2 (4)
CDC immunological stage CD4 count*						
<15%	16 (32)	2 (4)	5 (10)	6 (12)	9 (18)	13 (26)
15 - 24%	21 (42)	2 (4)	5 (10)	3 (6)	15 (30)	15 (30)
>25%	13 (26)	1 (2)	2 (4)	2 (4)	6 (12)	6 (12)

*Centers for Disease control staging: <15% (stage 3), 15 - 24% (stage 2), >25% (stage 1).
SPT = skin prick test.

Table II. Summary of HIV-negative subjects (*N*=50 (%))

Number of positive SPTs	8 (16)
One aeroallergen	3 (6)
Two aeroallergens	2 (4)
Three or more aeroallergens	3 (6)

SPT = skin prick test.

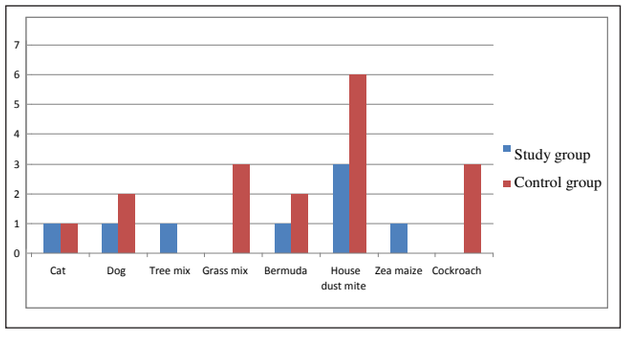

Fig. 1. Graphic presentation of specific positive skin prick tests in HIV-infected and non-infected children.

a negative SPT. Two of the asthmatic patients were WHO HIV stage 1, and only one of them had a positive SPT.

Of the 12 HIV-infected patients who had a family history of atopy, 8 (66.6%) gave a positive history of 'allergic' rhinitis. Thirty HIV-infected children (60%) gave a positive history of allergic rhinitis. All 5 patients who had a positive SPT had allergic rhinitis. Of the children with no family history of atopy, 3 had positive SPTs; this constituted the majority of the total group (60%) with a positive SPT.

Thirty-four (68%) of the HIV-infected group had dermatitis. Of these, 10 had a family history of atopy and 10 had asthma. There was no relationship between CD4 count and SPT positivity, Welch *t*-test (p=0.61), logarithmic transformed CD4, and reported presence of asthma (p=0.71) (95% confidence interval (CI): -0.472 - 0.674), and log CD4 and reported presence of dermatitis (p=0.84) (95% CI: -0.556 - 0.457). There was also no relationship between CD4 count and family history of atopy (p=0.63) (95% CI: -0.329 - 0.532) (Table I).

The comparison between family history of atopy and log CD4 count was subject to the Welch two-sample *t*-test with unequal variances, with no correlation demonstrated (p=0.68) (Fig. 2). Group A (positive family history) and group B (negative family history) did not differ significantly (p=0.63) with regard to log CD4 counts, with mean log transformed CD4 counts 6.385 (95% CI 6.017 - 6.0753) and 6.487 (95% CI 6.229 - 6.745), respectively. Twenty-eight (56%) of the total HIV-infected group had a CD4 <20%; 17 (35%) of these were WHO clinical stage 3 or 4. Seventeen (34%) were HIV stage 1; of these, only 2 had a family history of atopy. Only 1 of these children had a positive SPT.

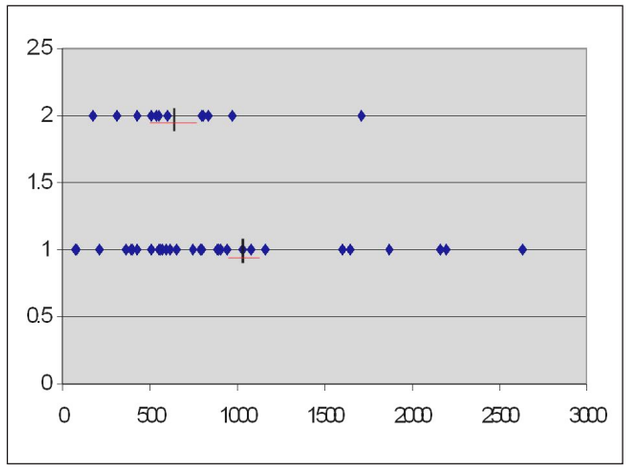

Fig. 2. Plot of CD4 count (absolute) v. family history of atopy (mean CD4 count in group A = 686, mean CD4 count in group B = 850).

Discussion

This pilot study suggests that there is no significant association between atopy and HIV-related disease, with no difference in allergy SPT positivity between HIV-infected children and a control group of healthy children. It also appears that the stage of HIV disease in HIV-infected children does not influence the development of allergy, which may be because the immune mechanisms are truly different. This is consistent with the findings by Bowser *et al*. in perinatally HIV-infected children.[14]

Ninety per cent of the HIV-infected children had negative SPTs to environmental allergens, demonstrating the absence of antigen-specific IgE to the measured allergens. Ten per cent of the HIV-infected children, who had evidence of atopy and a reactive SPT, probably have an inherent but independent genetic predisposition to atopy. In a study by Bacot *et al*., SPTs were positive in 28% of HIV-infected children, although adult studies report an incidence of around 10%.[6] Interestingly, the most common aeroallergen in this study was *D. pteronyssinus*, which has been found to be present in 45% of asthmatics in Johannesburg.[15]

The pathogenesis of eczema is thought to be related to allergen uptake by the Langerhans cells in the skin via specific IgE bound to the high-affinity IgE receptors on cell surfaces, resulting in an allergen-specific T-cell response in memory CD4 cells. It is well known that HIV-infected patients have a higher incidence of dermatitis;[16] this may present as inflammatory or eczematous eruptions. Patients with HIV have dry skins, and this barrier disruption has been postulated by Rudikoff to favour a Th2-mediated response to exogenous allergens.[16] Bacot *et al*. found no correlation between the presence of atopic dermatitis and the level of immunosuppression in CD4 levels.[6] Our study confirmed this finding.

Adult studies have, however, demonstrated chronic pruritic or eczema rashes occurring much more frequently with more

severe HIV disease with CD4 counts <200/dl.[17] HIV-infected patients may display inflammatory or erythematous rashes, including HIV eosinophilic folliculitis, papular urticaria, seborrhoeic dermatitis, psoriasis and pruritus nodularis, which resemble atopic dermatitis. This makes the distinction between atopic and non-atopic dermatitis difficult, particularly pruritus nodularis, which has a pruritic component.[16] The presence of dermatitis in our study population was quite striking. Whether or not all these patients had eczema is difficult to delineate. All patients with a reactive SPT also had dermatitis. It therefore seems reasonable to suppose that a fair number of them were truly atopic. Other causes of dermatitis should also be included in a differential diagnosis, especially drug-related eruptions.

Sinusitis and ear infections are more common and are associated with hay fever and chronic nasal symptoms. The incidence of allergic rhinitis has been reported to be 20.7% in South Africa.[17] There is a higher prevalence of rhinosinusitis related to a decrease in cellular immunity but unrelated to IgE-mediated hypersensitivity. Most patients in our group had house dust mite allergy. Evidence of causality of rhinitis in patients is complex, as most cases of rhinitis may be the result of an infection.[18]

The dermatitis and chronic rhinitis prevalent in these individuals is probably due to some other factor, such as infective processes or a dysfunctional immune system. Although there is a suggestion of differences in mean CD4 counts between HIV-infected individuals, with and without a family history of atopy, it is not statistically significant, with overlapping 95% CIs. This measure of atopy is not related to HIV infection.

In the International Study of Asthma and Allergy in Childhood (ISAAC), South Africa reported on asthma prevalence of 13.6% in 13 - 14-year-old children in Cape Town.[19] In the current study, 22% of patients were diagnosed with asthma, suggesting a higher prevalence in HIV-infected children. However, the possibility of chronic lung disease with airway reversibility may be contributing to the higher percentage. The absence of objective lung function testing is a weakness of the study. The reasonable correlation of CD4 count with HIV stage is an expected finding, as the CD4 count forms part of this assessment.

Many studies define atopy on the basis of elevation of IgE. In South African children, the burden of parasitic infection is high. One previous study demonstrated a 44% *Ascaris lumbricoides* positivity in the stool of children.[20] Therefore, a total IgE level in this context becomes unreliable. In a study by Koutsonikolis *et al*., HIV-infected children had a higher total but not specific IgE.[21]

Our study has several limitations. No attempt was made to assess whether reported rhinitis in patients was truly allergic via Hansel staining. No CAP RAST testing was conducted for inhaled or food allergens. Because of the limitations of using a total IgE in our context where parasitic infection accounts for elevated levels, this was not tested. This study should be regarded as a pilot study of the important association between two extremely common disease states in South Africa. Both conditions are currently experiencing a rising prevalence in the country, and it is logical to assume that they will co-exist in some individuals.

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