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Editorial
Practicing Paediatric Pulmonology in South Africa – An Honour and a Privilege

Extracts from an Inaugural Address: Robin J Green

Professor and Head: Department of Paediatrics and Child Health University of Pretoria

In South Africa we live with the unenviable distinction of having the most individuals living with HIV infection and one of the highest rates of TB in the world. Whilst this is clearly undesirable it has provided us, in medicine, with a unique opportunity to treat children with both acute and chronic lung disease and to conduct research to improve their lot in life. In addition we have an asthma and allergic rhinitis prevalence today of 20%. That means that 1 in 5 children will have one of these conditions. We live then in a part of the world where we have an opportunity to treat children with the common infectious diseases associated with poverty (HIV and TB) as well as the diseases previously linked to affluence (asthma and allergic rhinitis). Having said this about these two atopic diseases it is no longer true that they occur in wealthy children. In 1979 Christo van Niekerk documented that the urban – rural gradient for asthma was 22. Meaning that asthma was uncommon in rural black children but becoming increasingly common in their urban counterparts. In two subsequent studies in later years this gradient has come down to 1.7 and 2. Asthma is now as common in rural African children as those living in cities. In fact more children in South Africa have asthma than are HIV infected. However this trend in prevalence is completely reversed in mortality. Very few South African children now die of asthma whilst HIV infection is the leading cause of death in South Africa (figure 1).

At the University of Pretoria we have been actively involved with research into HIV-related lung diseases and atopic conditions. Our research has uncovered diagnostic and management issues in the many conditions.

Bronchiolitis is a disease of infancy and presents as the first episode of wheeze in HIV-infected and HIV-uninfected children alike. 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. HIV-infected bronchiolitics isolate the same viral organisms as the HIV-uninfected children, mainly RSV. RSV occurs from February to August annually although actual numbers and disease severity vary from year to year (Figure 2). Bacterial co-infection is a rare event and predicting bacterial infection is not aided by the measurement of C-reactive protein.

Figure 1
Leading specific causes of death in South Africa 2000

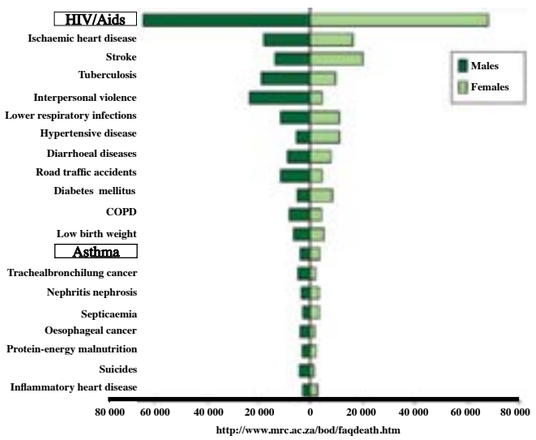
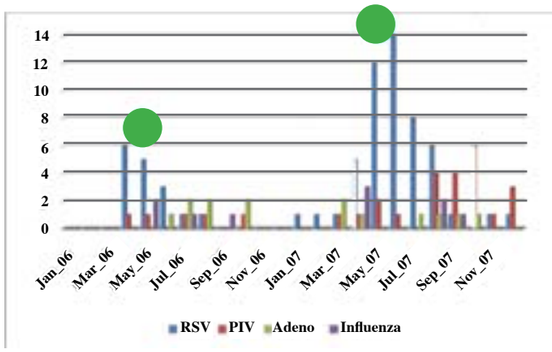


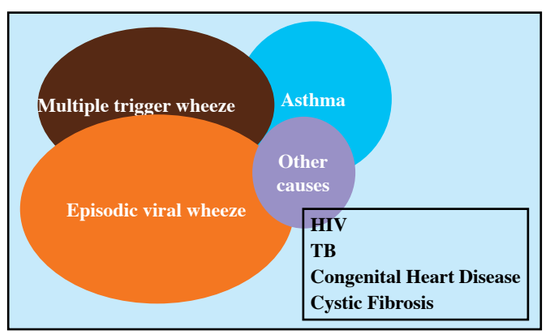
Figure 2
Viral Isolates Bronchiolitis - SBAH



Moodley T et al. *S Afr J Epidemiol Infect* 2010; 25(2): 5-8

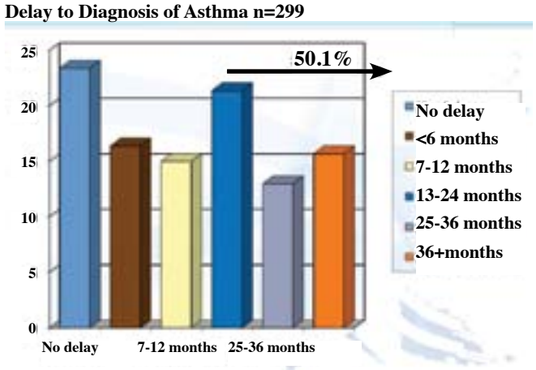
Many infants who have bronchiolitis go on to wheeze repeatedly with each new viral lower respiratory tract infection. They don't have asthma. However our research work has demonstrated that in Africa the differential diagnosis of recurrent wheeze in infancy is much longer than in the Northern Hemisphere. We must add HIV infection and TB to this list (Figure 3).

Figure 3
Causes of Recurrent Wheezing in Infancy
Differences between USA/RSA



My early research began with asthma. Together with David Luyt we demonstrated that many asthmatics had their asthma diagnosis delayed. 50.1% of 299 asthmatic children had asthma symptoms for at least a year before asthma diagnosis was made (Figure 4). This delay led to significant impairment

Figure 4
Delay to Diagnosis of Asthma n=299

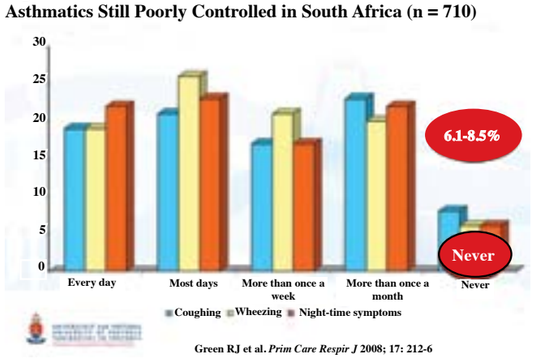


Green RJ, Luyt DK. S Afr Med J 1997; 87: 878-882

in quality of life as well as incurred costs for unnecessary antibiotics, home nebulisers and hospitalisations.

This impairment in quality of life is what makes asthma such an important disease to pulmonologists. In a study conducted with Gloria Davis and David Price of Aberdeen in Scotland, we documented significant quality of life impairment for South African asthmatics. All asthma guidelines tell us that the aim of asthma management is to return an asthmatic to normal life, free of symptoms and asthma exacerbations. We questioned over 3 500 patients who thought they had asthma. Interestingly only 20% were being treated with anti-inflammatory therapy, today regarded as the only important asthma therapy for all asthmatics. In

Figure 5
Asthmatics Still Poorly Controlled in South Africa (n = 710)

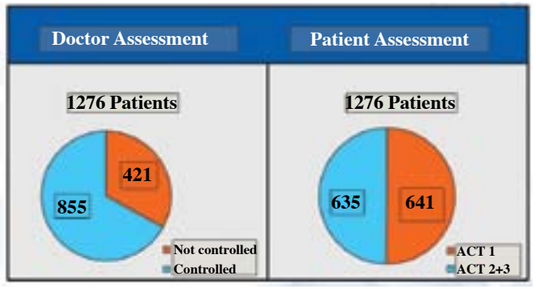


Green RJ et al. *Prim Care Respir J* 2008; 17: 212-6

the remaining 710 individuals, disappointingly only 6-8% were well controlled (Figure 5). At least 20% had symptoms every day of life. This is completely unacceptable for asthma control.

Dr Mike Greenblatt, Charles Feldman and I performed a similar study a few years later. In this study we attempted to define differences in asthma control as perceived by patients and their doctors. Whilst 50% of patients thought they were well controlled, and this was encouraging because of the dismal figures of the earlier study, a full 17% were assessed to be well controlled by their doctor (Figure

Figure 6
Doctors Overestimate Asthma Control



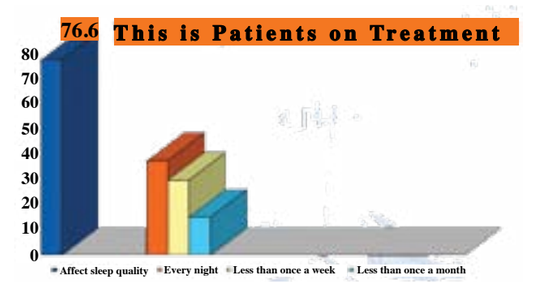
Greenblatt, M et al. *Respir Med* 2010; 104: 356-361

6). 17% of asthmatics are therefore left to suffer without appropriate modification of their management. This study revealed two other interesting results. Firstly it suggested that only asthmatics treated by a specialist pulmonologist could expect good asthma control. Secondly it suggested that only asthmatics treated with a combination inhaled corticosteroid and long acting beta-agonist medication were well controlled. Both these findings suggest, not that all asthmatics need this form of therapy or treatment by specialists, but that we must find what these therapies offer and utilise their benefits.

In order to uncover why asthma is so badly controlled, despite the availability of very useful therapies, we conducted a study of the value of the measurement tools we are told to use in asthma guidelines. We measured asthma control by doctor assessments, patient questionnaires, spirometry and exhaled nitric oxide. The study revealed that no one measurement correlates with any other. It may not be surprising then that asthma is difficult to control because we don't really no what 'control' means.

Allergic rhinitis is the other airway disease which has fascinated me. Since allergic rhinitis does not carry mortality risk the reason to treat this condition is to improve quality of life. As with asthma, we found that allergic rhinitis was causing significant impaired life. 76% of sufferers had

Figure 7
Do Allergic Rhinitis Symptoms Affect the Quality of Your Sleep (n=1181) (%)



Green RJ et al. *Prim Care Respir J* 2007; 16: 299-303

impaired sleep and 33% of those every night of their lives (Figure 7). This study also revealed that allergic rhinitis in South Africa is a perennial condition. Hayfever is extremely uncommon.

A final comment on asthma in South Africa is that whilst this condition is said to be allergy related in most children in the northern hemisphere, this appears not to be the case in

South Africa. In Pretoria, for example, only 45% of asthmatics are allergic.

Admission to hospital is a frequent event for children with pneumonia. We have been auditing the costs of admission of children with pneumonia and document that the case fatality rate for HIV-associated acute pneumonia is 14% in a general ward and 46% in a 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 (Table 1).

Table 1
Severe/Very Severe Pneumonia in Pretoria
(67% HIV-infected)

	Ward	PICU
Age - Under 1 Year	79%	83%
Length of Stay (days)	8.7	9.4
Cost - Our Hospital	R2 798.98 / R2 035.44	R4 939.40 / R2 364.10
Cost - Private	R13 830.20	R41 091.90

Kitchin O, et al. Pharmacoeconomics 2010, submitted

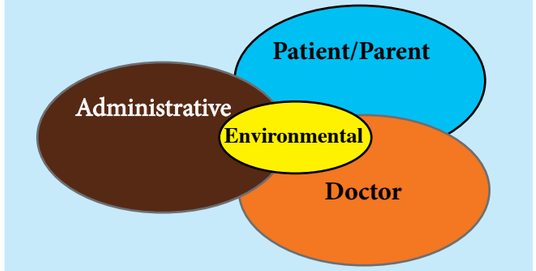
With regard to severe pneumonia in HIV-infected children we have been experimenting with strategies to reduce mortality in PCP. Through the use of lung protective ventilation and addition of oral steroids and ganciclovir we have reduced mortality from 90% to 22%. We also wish to describe PCP as a new pulmonary syndrome with multiple overlapping aetiologies (Table 2).

Table 2
PCP is a Disease of Co-morbidities

- **CMV**
- **Other respiratory viruses**
- **Bacteria**
- **?Other**

Bronchiectasis in Africa is increasingly commonly linked to HIV-related lung disease. However this epidemic has limited the differential diagnosis in many children who may have another cause for their disease. Cystic fibrosis (even in black children), congenital immune deficiency and primary ciliary dyskinesia remain important conditions. We report the successful use of routine daily macrolides in HIV-related bronchiectasis. There was a significantly elevated IgE in our study population. Previous studies in adults and children infected with HIV have shown a relationship between IgE and the staging of HIV. There does not appear to be any correlation between IgE level and the stage of HIV infection in our 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 we also found no increase in skin prick test positivity in HIV-infected, confirming that atopy is not responsible for IgE. The only other potential explanation for elevated IgE is the presence of allergic bronchopulmonary aspergillosis. This condition should also be ruled out. With regard to passive smoke exposure we also found no relationship between this exposure and disease severity in HIV-infected children.

Figure 8:
Future challenges to Paediatric Pulmonology



Finally we must recognise that the future of paediatric pulmonology rests on 3 pillars. The care of our patients is in the hands of patients themselves, their doctors and our health administrators who hold the purse strings (Figure 8). I am optimistic that as anti-retroviral roll-out continues many of the conditions we have been investigating should begin to disappear. This is most desirable.

It has been a true honour …

The Inaugural address of Robin Green, centre (also Prof James Ker - Acting Dean – Faculty of Health Sciences, Prof Robin Crewe – Deputy Vice Chancellor Research, University of Pretoria)

Cipla Medpro Travelling Lectureship 2011

The Cipla Medpro Travelling Lectureship is an annual award (made at the SATS Congress) to a senior member of the SA Thoracic Society to enable the recipient to deliver lectures in centres in SA other than their home town. They are requested to deliver one lecture in another academic centre and a second in a city/town that has no Health Sciences Faculty. The topics of the lecture/s should be negotiated between the recipient and the host centre/s.

The value of the award is R10 000.

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Dr Michelle Wong (2003)
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Previous recipients of the award were:
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Email : Gillian.Ainslie@uct.ac.za

Closing date for nominations:
1st November 2011

Pulmonary hypertension leading to heart failure secondary to respiratory diseases in children in developing countries; more awareness to avoid delayed diagnosis

Marian Kwofie-Mensah
Fellow Paediatric Pulmonology, Division Paediatric Pulmonology, University of Pretoria

Introduction

Pulmonary hypertension (PH) although commonly associated with cardiac conditions, is found to be associated with a wide variety of other conditions in children. The HIV epidemic and its association with respiratory diseases is a big contributor. The aetiology and management of PH has therefore become relevant in Paediatrics.

Definition

Pulmonary hypertension (PH) defined as mean pulmonary arterial pressure (Ppa) of greater than 25mmHg at rest or greater than 30mmHg with exercise, is applicable to both paediatrics and adults. This definition was confirmed at the WHO guideline meeting in Venice 2003.[1] However, the definition was debated and challenged at the Fourth World Symposium on Pulmonary Hypertension in 2008 in Dana Point, California, USA and the new haemodynamic definition of PH is a Ppa at rest of greater than 25mmHg.[2]

Cor pulmonale, by definition, is pulmonary hypertension associated with disorders of the respiratory system and or hypoxia and must be distinguished from idiopathic pulmonary arterial hypertension and other causes such as pulmonary venous hypertension and thromboembolic pulmonary hypertension.[3]

Many of the studies conducted on PH are adult based, however many of the findings can be applied to children. Recent studies have shown that disruption of lung vascular growth impairs distal airspace structure during development and this usually contributes to the pathobiology of diverse lung diseases.[4]

These are some common chronic lung diseases which are known to cause PH outside the neonatal period and infancy (**Table 1**).

The common initiating factor leading to PH in these respiratory conditions is hypoxia and the mechanism needs to be understood and emphasised as it is associated with a poor prognosis and this can indeed help in the awareness and prevention of disease progression.

Mechanism of pulmonary hypertension due to hypoxia

It is well known that respiratory disease is one of the main contributors to the development of hypoxia.

Pulmonary vasoconstriction is a basic reflex in response to hypoxia. When the lung is faced with high altitude or chronic hypoxic lung disease the reflex is operational and causes PH as a usual complication. PH is independently associated with increased morbidity and reduced survival in patients suffering from hypoxic lung disease and is both accompanied and caused by pulmonary vascular remodelling.[5]

Our understanding of the pathophysiology is that the pulmonary vascular wall remodels. Normally this consists of three layers: adventitia, media, and intima, whose cellular components are fibroblasts, smooth muscle and endothelial cells, respectively. The remodelling of the pulmonary arteries (which is the structural change of the vascular bed) leads to an increase in pulmonary pressure due to increase resistance.[5]

Proliferation of adventitial fibroblasts increases within hours of hypoxic exposure and within a few days thickening of the media layer begins to develop.[2] Hypoxia increases cell proliferation by inhibition (production and/or release) of antimitogenic factors (e.g. Nitric oxide (NO) and prostacyclin (PGI_2) and by increasing mitogenic stimuli (e.g. 5-hydroxytryptamine, endothelin-1(ET-1), platelet–derived growth factor (PDGF), vascular endothelial-derived growth factor (VEGF) and inflammatory mediators (e.g. interleukins (IL)-6, IL-8 and monocyte chemo attractant factor-1) from smooth muscle cells, fibroblasts, endothelial cells and platelets.[4]

Endothelial cells produce vasoconstrictive proliferative factors (ET-1, angiotensin II, thromboxane A_2) and reduce production of vasodilatory, anti-proliferative mediators (NO) and prostaglandins-I_2). Increased vasoconstriction is likely related to an imbalance between the impaired production of endogenous vasodilators including NO, PGI_2 and others, and excessive production of vasoconstrictors, such as ET-1 and serotonin (5HT). These changes reflect endothelial cell dysfunction, which results from injury due to several mechanisms including hypoxia, haemodynamic stress, inflammation, oxidative stress and altered growth factor production.[4]

Table 1
Common respiratory illness/hypoxia causing pulmonary hypertension

Chronic obstructive airway disorders
Upper airway obstruction e.g. adenoids, webs
Laryngo-tracheo malacia
Vascular rings
Obstructive lung disorders
Asthma
Cystic fibrosis
Bronchiectasis
Bronchiolitis obliterans
Restrictive lung diseases
Neuromuscular diseases
Scoliosis/kyphoscoliosis
Progression of pulmonary TB
Interstitial lung diseases
Ciliary dyskinesia
Bronchopulmonary dysplasia
Others
Sleep disorders (obstructive sleep apnoea)

Hypoxia also dramatically increases the level of Ca^{2+} in the cytoplasm of the smooth muscle cell (SMC) and has shown to modulate proliferation and growth as well as contraction of the SMC.

Disease progression

PH, if untreated results in right ventricular enlargement commonly known as cor pulmonale, which, with progression, leads to right heart failure.

This progression is mostly due to the response of the right ventricle (RV) to the increased afterload. It is the ability of the RV to adapt to the increase in afterload that determines both the degree and nature of symptoms. Adaptation depends on the rapidity at which the increase in afterload occurs i.e. the degree of RV increase in mass. RV hypertrophy begins within several hours following the acute increase in afterload and therefore if the rate and magnitude of the increase in RV afterload outpaces the development of ventricular hypertrophy, RV failure ensues (**Figure 1**).[7]

In an adult study conducted in Italy, it was found that chronic PH determines various adaptive changes one of which invokes the right atrium (RA), but its exact role has never been investigated. It is hypothesised that the RA increases in volume and function to assist the RV during the chronic pressure overload due to the PH. The RA initiates the increased volume and systolic function prior to development of RV dilatation and systolic dysfunction. In the Italian study, the RA size was assessed in relation to clinical, echocardiographic and haemodynamic parameters in patients with PH and its enlargement is one of the independent predictors of adverse outcome in the setting of primary PH.[6]

Table 2. Symptoms of PH

Breathlessness/dyspnoea
Palpitations
Chest pain (central)
Haemoptysis
Oedema
History of exercise induced syncope
Occasionally cyanosis
Failure to thrive

Diagnosis

Clinical presentation

Though of great importance, diagnosis can be difficult as the symptoms of PH are interconnected and may overlap with that of the chronic respiratory illness.

Symptoms commonly observed are reflected in Table 2.

Dyspnoea on exertion and fatigability is generally present in advanced chronic respiratory disease and that may prompt the clinician to investigate for the presence of PH. Some of the symptoms occur as a late sign e.g. peripheral oedema from right ventricular failure. The progression of PH is slow and patients may remain stable over many years.

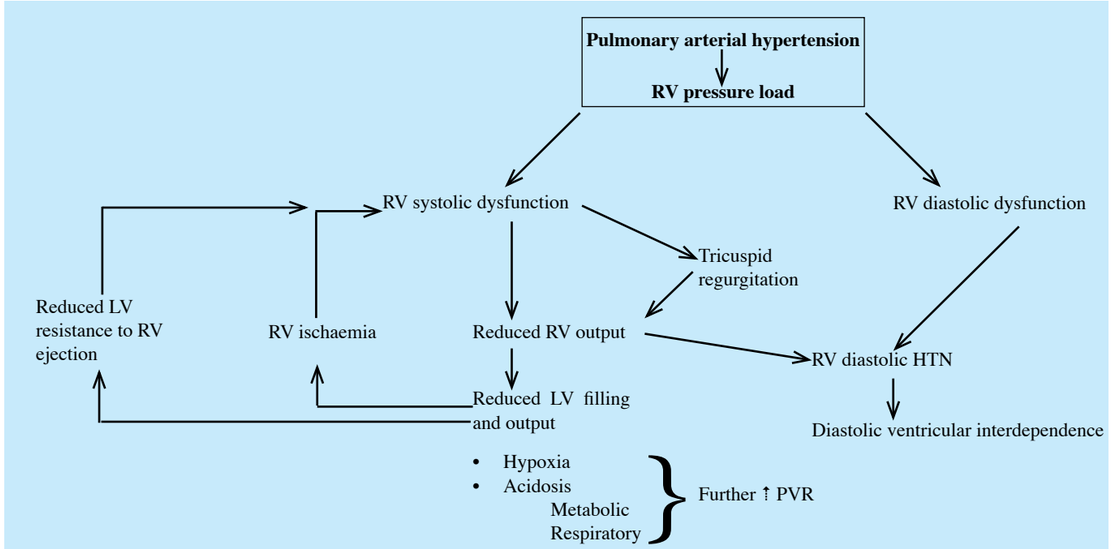
Special investigations

Most patients with chronic lung disease should have a regular electrocardiogram (ECG) although the sensitivity is only 20-40% but specificity is higher. Doppler echocardiography is by far the best method.[3]

A summary of investigations recommended in the British Cardiac Society (BCS) Guidelines is shown in **Table 3.**[8]

Most of these special investigations are only available in special centres and this contributes greatly to the delay in the diagnosis of these patients, especially in developing countries. Most of these patients are firstly managed in the primary or secondary health sectors for their chronic illnesses and emphasis on complications is seldom appropriate.

Figure 1. Pathophysiology of right ventricular failure due to pulmonary arterial hypertension.[7]



RV, right ventricle; HTN, hypertension; LV, left ventricle; PVR, pulmonary vascular resistance.

Table 3
Imaging investigations recommended for the assessment of PH[8]

Investigation	Comments
Chest radiography	May show increase in cardiac chamber or PA size, hypoperfused areas of lung and parenchymal lung disease.
ECG	May demonstrate RVH
Echocardiography	Screening tool of choice for PAH. Detects cardiac disease (congenital, myocardial, valvular, intra-cavity clot etc)
Cardiac catheterisation	Gold standard to define the extent of disease. PA pressures, PVR, cardiac output and oxygen saturations can be calculated accurately.
6 minute walk test (6MWT)	Provides a functional assessment of exercise capacity and degree of limitation of activity.
Arterial blood gases, lung function tests	May be useful, although in patients with IPAH the results of lung function tests may be normal. A decline in PaO_2 is typically seen.
Blood investigations	Essential to exclude connective tissue diseases or pulmonary hypertension secondary to systemic disease
CT pulmonary angiography (CTPA)	Used to look for enlargement of pulmonary arteries, filling defects and webs in the arteries.
Ventilation perfusion scanning	More sensitive for chronic pulmonary thromboembolism than CTPA but not helpful when there is underlying parenchymal disease.
High resolution lung CT	May show parenchymal lung disease, mosaic perfusion and features of pulmonary venous hypertension.
Cardiac MRI	Good investigation for imaging the right ventricle. Helpful in delineating congenital heart defects.
Abdominal ultrasound	Used for investigation of liver disease and suspected portal hypertension.
PA - pulmonary artery; RVH - right ventricular hypertrophy; PAH - pulmonary arterial hypertension; PVR - pulmonary vascular resistance; IPAH - idiopathic pulmonary arterial hypertension	

In developing countries most of our focus is on the preventative management and very little focus is given to possible complications and their management. It is essential that a campaign of awareness is conducted in order to prevention disease progression and improve the quality of life of patient.

There are also other setbacks which are due to barriers and challenges that are experienced in our health system. Some of these barriers to consider are;

- Limited infrastructure and resources
- Lack of trained staff to assess and identify condition
- Unavailable multidisciplinary approach
- Understanding of the complexity and pathophysiology of the condition
- Poor organisation and communication across paediatric care centres and late referrals
- The vague presentation of the disease itself
- Cultural beliefs that always interfere with early diagnosis and management
- Poor education (poor adherence and compliance to treatment)

Management

The management of PH has been in constant evolution and changes in the treatment still target the steps involved in the pathophysiology such as ET-1 receptor inhibitors.

With our understanding that hypoxia is the greatest initiating factor, our main focus should still be on its prevention. This is certainly possible, even in developing countries, as the timing of pulmonary vascular injury is a critical determinant of the subsequent response of the developing lung to adverse stimuli e.g. hypoxia, inflammation. This highlights the importance of saturation monitoring on a regular basis to identify deterioration and alert the clinician to the risk of PH and should be emphasised in all primary and secondary sectors of health care. Home oxygen support may be needed and should be started as early as possible. This will help decrease the need for additional medicines for children who are already burdened by multiple drug therapies such as those for HIV.

Conclusion

Pulmonary hypertension in children contributes significantly to morbidity and mortality. Severe exacerbations of chronic respiratory disease, worsens hypoxia and this simultaneously compounds the increase in pulmonary pressures. If not managed appropriately and acutely this favours the development of right ventricular failure with poor outcome. Therefore continued effort is necessary to optimise strategies that improve the impact of respiratory disease on the heart.

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Asthma exacerbations – allergens or viruses?

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Introduction

For many asthmatic patients (both adults and children), the disease is characterised by periods of good control of symptoms, interrupted by a series of exacerbations. The cause of such exacerbations is hotly debated. Sensitisation to allergens is a risk factor for asthma but there is now a significant body of evidence that allergens are in fact, not responsible for asthma exacerbations and that advances in respiratory tract virus detection have allowed clear demonstration of the important link between viral infections and asthma exacerbations. There is no universally accepted definition of an exacerbation of asthma although the Global Strategy for Asthma Management and Prevention 2009 defines it as 'acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing and chest tightness – or some combination of these symptoms'. The underlying problem is inflammation, with concomitant bronchoconstriction.[1]

Asthma Pathophysiology

Allergy was thought to play a central role in asthma pathogenesis, and even though it still does, it seems as though less than 40% of all asthmatics in South Africa are atopic and other phenomena are sought to explain asthma onset e.g. bacterial super antigens, pollutants (indoor, tobacco smoke, vehicle emissions), dietary factors (allergens, lack of immunomodulatory factors, genetically modified foods, toxins, dietary salt and magnesium), lack of physical activity, obesity and drugs (including paracetamol).[2]

Allergen exposure leads to a process of sensitisation followed by subsequent inflammation. The process of sensitisation involves antigen-presenting cells (APCs), TH_2 cells (which interact with allergens on APCs in conjunction with MHC II epitopes), B cells (which respond to TH_2 cytokines and become specific IgE producing plasma cells), IgE (specific to that initial stimulating antigen) and mast cells (to which IgE binds). Eosinophils and other inflammatory cells are subsequently recruited. The process is largely orchestrated by the cytokines (intracellular messengers) IL-3, IL-4, IL-5, IL-13 and GM-CSF. On allergen re-exposure, antigens cross-react with mast cell-bound IgE and degranulation of mast cells occurs. This process, and the release of the inflammatory mediators, facilitates the atopic inflammatory disease process seen in many organs.[2] (**Figure 1**).

In an asthmatic individual the process of inflammation results in airway hyper-responsiveness followed by variable airway obstruction and finally symptoms i.e cough, wheeze, tight chest and shortness of breath.[2]

Allergens and asthma exacerbations

Sensitisation to allergens is a risk factor for asthma. At a biennial congress of the World Allergy Organisation, Beunos Aires 6-10th December 2009, a proclamation of the Asthmatic Children's Charter was made that states "allergy is clearly not only a trigger for asthma exacerbation,

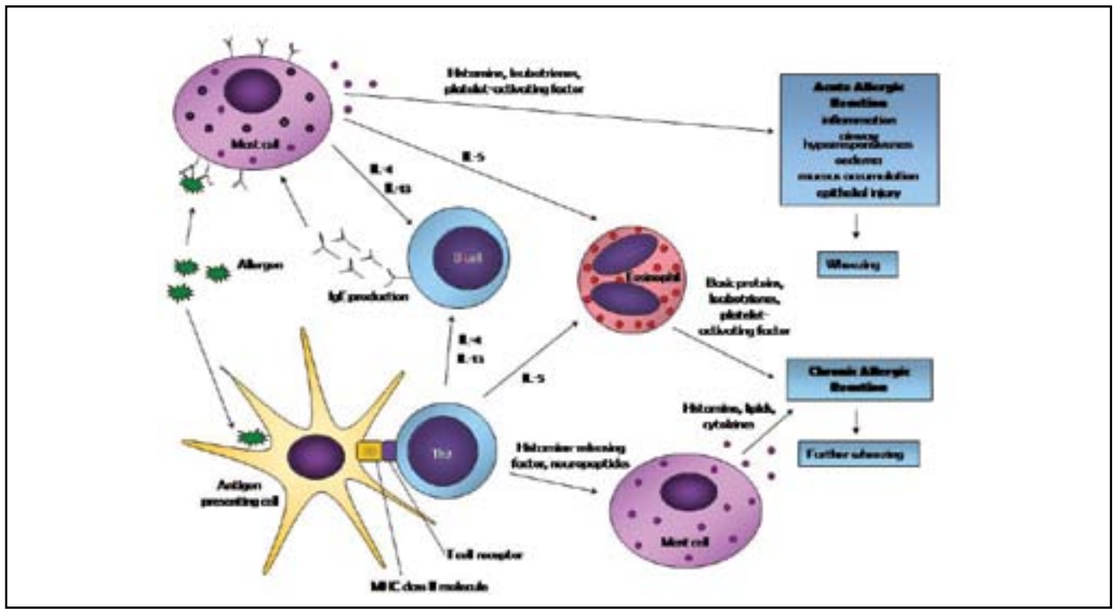

Figure 1.
Pathophysiology of Asthma

particularly interacting with viral infection, but also the more severe the asthma the higher the probability of allergy being a significant contributor. The majority of patients with asthma experience rhinitis symptoms, and allergic rhinitis commonly precedes asthma exacerbation, increasing the risk of asthma attacks, emergency visits and hospital admissions for asthma. Sensitisation to inhalant allergens is a risk factor for wheezing. Early onset allergy is a strong predictor of ongoing more severe and persistent disease".[3] Peter D Sly *et al*,[4] report that the risk of asthma after a viral lower respiratory tract infection (RTI) is increased in the presence of allergic sensitisation in early life, and if the infection is more severe. Atopy-associated mechanisms also appear to be involved in viral-induced acute exacerbations of asthma, especially in prolonging symptomatology after the virus has been cleared from the lungs.[4]

200 000 of the 450 000 emergency department adult asthma admissions per year in the United States have been attributed to the risk associated with sensitisation to mite, cat or cockroach allergen.[5] In an American study of inner city children with asthma, those who were sensitised and highly exposed to cockroach allergen were more likely to be hospitalised with their asthma. They also had more unscheduled medical visits, and had more time off school compared with either the nonexposed or the nonsensitized.[6] Among children admitted to hospital with an acute attack of asthma in the United Kingdom, those who were sensitised and exposed to dust mite were at increased risk of readmission during the following month.[7]

Some sources report that after 3 years of age, viral RTIs and allergy synergistically increase the risk of acute wheezing and exacerbations of childhood asthma.[8-10]

Viruses and asthma exacerbations

Viral RTIs are one of the most common illnesses in human subjects, with 500 million cases and an economic burden estimated at $40 billion annually, in the United States alone.[11] Since the early 1970's, viral RTIs have been reported as triggers for exacerbations of asthma in both adults and children.[11] Virus- induced wheezing in infancy is associated with an increased risk for recurrent wheezing as children grow older.[12] It is important to note that the fundamental question of whether these viral respiratory tract infections are causal factors or instead serve as indicators of a predisposition to asthma is still unresolved.[12]

Advances in respiratory tract virus detection have led to critical new insights into the development and exacerbation of asthma. Previously, respiratory tract viruses were difficult to detect by using conventional methods because some do not grow well in culture.[12] In clinical studies of acute viral illnesses, detection rates of 30-50% were the norm with techniques such as viral culture, antigen detection (with labelled antibodies) or serologic detection. More recently, molecular techniques have greatly improved overall rates of viral detection e.g. polymerase chain reaction (PCR), multiplex PCR, sequencing and microarrays, and some studies of acute respiratory tract illnesses have reported viral detection rates of as high as 90%, especially in infants.[12]

Of the respiratory tract viruses identified in these circumstances, human rhinoviruses (RV) are the most commonly found and are detected approximately 65% of the time[11] especially in children over the age of 2 years.[10] In addition to RV, other respiratory tract viruses such as respiratory syncytial virus (RSV), influenza viruses, coronaviruses, human metapneumoviruses, parainfluenza viruses, adenoviruses, and bocaviruses, have all been detected in subjects with asthma exacerbations.[11]

A caveat with regard to these dramatically improved PCR-based methods of viral detection is that with increased sensitivity in detecting viral genetic material in the host, the presence of a pathogen in respiratory secretions is not necessarily associated with clinical illness.[12] This is particularly true for RV, which can be found in a considerable proportion of healthy subjects. Studies using sequential sampling in children indicate that detection of RV in well children represents asymptomatic infection. Therefore it has been important to link symptomatic illnesses, particularly wheezing illnesses, with RV detection when estimating its role in determining asthma risk. Chronic infection with RV does not occur except in association with marked immunosuppression.[12]

A study by Kling et al[13] detected RV in >40% of asthmatic children 6 weeks after an acute exacerbation and asthma exacerbations were more severe in patients with persistence of RV, suggesting that the severity of acute asthma may be linked to prolonged and possibly more severe RV infections. Johnston and co-workers[14] performed a study in 9 to 11 year old children and viruses were detected in 80% of reported episodes of a decrease in PEFR of 50 ml/minute or more, 80% of reported episodes of wheeze, and 85% of all reported episodes of upper respiratory symptoms, cough, wheeze, and fall in PEFR. Again, the most commonly identified virus was RV.

Several mechanisms by which RV induces asthma exacerbations have been postulated, including direct infection of the lower respiratory tract, induction of inflammatory responses to RV, reduction in lung function, exacerbation of bronchial reactivity, and upregulation of surface intercellular adhesion molecule 1 (ICAM-1) expression in bronchial epithelium.[15] This is presently an exciting field of research.

Preventative and therapeutic interventions

Understanding the mechanisms provoking virus-induced airway inflammation in asthmatic subjects might offer significant opportunities for improved disease management. The reality at present is that current drugs for the treatment of virus-induced exacerbations of asthma are poorly effective, and alternate therapies to modulate viral pathogenesis are desperately needed.[11] The most obvious therapeutic intervention would be to prevent viral infection in infants. Currently, there are no safe and effective human vaccines for RSV or RV. The antigenic diversity of the more than 100 serotypes of RV means that creating a truly successful vaccine is an extremely difficult task. Palivizumab, a monoclonal antibody (mAb) against the RSV fusion protein, is the only US Food and Drug Administration-approved mAb for RSV.[11] The results of two nonrandomised studies of passive immunisation to RSV in early life suggest that preventing severe RSV infection in infancy with mAb might reduce subsequent asthma.[16,17]

Safe antiviral agents might eventually become as important as antibiotics in the management of lower respiratory tract infections and a variety of novel therapeutics are at various stages of development.

Treatment with anti-inflammatory drugs, such as inhaled corticosteroids and leukotriene receptor antagonists can reduce the risk of exacerbations by 40-50%, and this suggests that moderating inflammation might reduce the chance that a cold will precipitate bronchospasm.[12] The 'PREVIA' study[18] was designed to investigate the role of montelukast in the prevention of asthma exacerbations in children aged 2-5 years with a history of episodic symptoms. 549 children were enrolled in a randomised, double-blind, placebo-controlled study. Montelukast reduced the rate of asthma exacerbations by 32% ($p<0.001$), the rate of inhaled corticosteroid courses ($p=0.027$), the rate of oral corticosteroid courses ($p=0.024$), eosinophil counts and time to first exacerbation episode compared to placebo.[18] Notably, recent placebo-controlled trials suggest that neither high-dose inhaled nor oral corticosteroids are suitable for virus-induced wheezing in infancy.[12] Additional research is needed to determine the effects of current asthma controllers on virus-induced exacerbations.

Because viral RTIs and allergen exposure in allergen-sensitised subjects can combine to increase the risk of asthma exacerbations, therapies targeting allergic airway inflammation such as anti-IgE treatment, might be promising for allergic subjects prone to virus-induced exacerbations.[12] In addition, macrolides deserve more attention as possible anti-inflammatory agents targeting exacerbations and may offer some promise to asthmatics not responding to conventional therapy. In infants with RSV-induced bronchiolitis, clarithromycin reduced systemic inflammation acutely and led to fewer wheezing episodes in the following 6 months.[19]

Strategies aiming at reduction of respiratory tract virus exposure, achievable by simple means, such as hand washing, can have a significant effect on morbidity.[12]

Conclusion

Can the nexus among viral RTIs, atopy, and asthma be broken? Viral RTIs play a key role in the pathogenesis of asthma exacerbations. Despite this, no specific treatments exist that are able to significantly alter the clinical outcome of infection.[11] Strategies to reduce the impact of asthma exacerbations should include interventions directed at both viruses and reducing allergen exposure. However, factors other than allergens and viruses (such as air pollution, cigarette smoking, compliance with and availability of treatment, and psychological factors) are undoubtedly relevant in some exacerbations of asthma and make the elucidation of possible interactions more complex.[15]

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Not all respiratory infections need antibiotics

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Introduction

In the current era of antibiotic stewardship a difficult and important management decision for most practitioners is whether to treat a respiratory tract infection with an antibiotic or not and if so, which one to use. Frequent and inappropriate antibiotic use for respiratory tract infections has contributed to the emergence of resistant bacterial species.[1] Not only does inappropriate antibiotic use lead to increased colonisation by resistant organisms, recent antibiotic use increases the risk of contracting invasive disease caused by these resistant organisms.[2]

The challenge for all practitioners is to try and determine the microbiology of an infective episode and to answer the question; 'Is the infection viral or bacterial or a mixture of both'. This answer will determine whether or not the patient needs an antibiotic, since most respiratory infections are self limiting and will resolve without antibiotics. Besides the factors discussed above, which determine a practitioners choice in antibiotic, patients' expectations and other non clinical factors (**Table 1**) may influence the decision to prescribe an antibiotic.[3]

Making these difficult choices requires clear definitions and guidelines. Defining whether an infection is of the upper or lower respiratory tract, using signs and symptoms to predict the microbiology and using current literature (both local and international) to develop new or use existing guidelines, is critical in managing these infections appropriately.

Defining upper versus lower respiratory tract infection (RTI)

Figure 1 provides a schema for differentiating an upper from lower RTI

Clinical features of upper respiratory infections:

1. ***Common cold:***
   Nasal stuffiness, sneezing, coryza, throat irritation, with or without fever. Mucopurulent rhinitis usually occurs with a common cold. Common colds can occur 3-8 times per year, even in health children, and sometimes more if the child attends school or day care.

Table 1
Non-clinical factors influencing the decision to prescribe antibiotics[3,4]

1. **Time pressures**
2. **Wanting to do something active and signal sympathy**
3. **Medico-legal concerns**
4. **Fear of losing patients to other doctors**
5. **Satisfying parents**
6. **Protocol of day care requiring antibiotics for return of an ill child**

2. ***Otitis media:***
   Acute otitis media (AOM) must have an acute onset of symptoms and signs consistent with inflammation of the middle ear. These include erythema and or a bulging yellow tympanic membrane, distinct otalgia, otorrhoea and effusion of the middle ear. However, these symptoms and signs, associated with AOM, have poor sensitivity and specificity. It is extremely important to distinguish between AOM and otitis media with an effusion(OME).[5] OME is a middle ear effusion not accompanied with other clinical signs or symptoms. OME usually follows on a viral upper respiratory infection or AOM and may persist for weeks or months.[6,7]
3. ***Sinusitis:***
   Acute sinusitis is a clinical diagnosis. Prolonged, non specific upper respiratory tract signs and symptoms occur. Nasal congestion, nasal discharge and a cough with no improvement for more than 10-14 days or fever >39° Celsius, facial swelling and facial pain define acute sinusitis.[8] Radiological sinus changes does not correlate well with clinical signs. This prolonged period of non specific upper respiratory signs are based on the principle that a viral infection, like a common cold, will usually last for about 9 days.[9]
4. ***Pharyngitis:***
   Sore throat due to erythema, exudates or ulceration involving the nasopharynx, uvula, soft palate, or tonsils, swollen anterior cervical lymphadenopathy, scarlitinform rash with less cough, rhinorrhoea and conjunctivitis.

The positive predictive value for a Group A streptococcal infection with these features is less than 50%.[10,11]

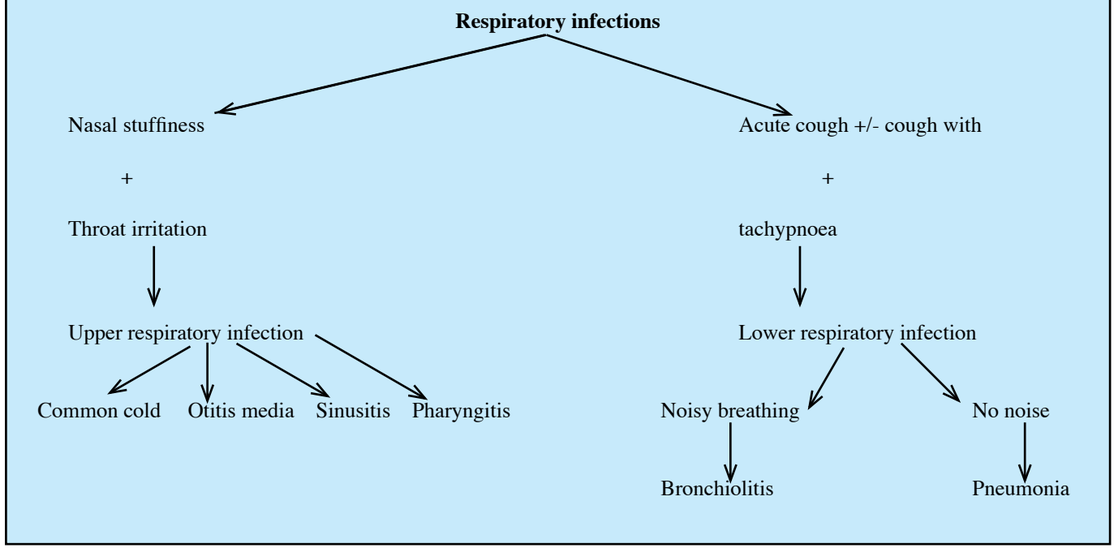
How to manage these infections - using guidelines and the current literature:

Upper respiratory tract infections

Common cold:
Rosenstein et al,[12] in controlled trials of antimicrobial treatment for the common cold, demonstrated that antibiotic treatment did not change the clinical course or outcome. Mucopurulent rhinitis is not an indication for antibiotics unless it persists for more than 10-14 days. A Cochrane review did however, reveal a benefit if antibiotics are used in chronic purulent rhinitis.[13]

AOM:
The rate of resolution AOM without antibiotics has been demonstrated to be 81% and given the common viral aetiology it could be argued that antibiotics should not routinely be given or given after an initial wait and see period.[14] This may be advocated if factors provide for adequate patient follow up and should be reserved for children older than 2 years of age.[15] OME does not require initial antibiotics but if the effusion persists for more than 3 months antibiotics might be considered. Prophylaxis is reserved for recurrent AOM; more

Figure 1.
Differentiating upper from lower respiratory tract infection



than 3 episodes in 6 months or 4 episodes in 12 months.[6]

Sinusitis:
Nasal congestion, nasal discharge and a cough with no improvement for more than 10-14 days or fever of greater than 39 degrees Celsius, facial swelling and facial pain are indications for antibiotics. In radiological confirmed acute maxillary sinusitis antibiotics may be used.[16]

Pharyngitis:
A Cochrane review found small differences between delayed or immediate antibiotic use for a sore throat.[17] The UK observational study revealed that reduced prescribing of antibiotics was not associated with an increase in hospital admissions for peri-tonsillar abscess or rheumatic fever (Sharland 2005).[17] If Group A streptococcal (GAS) infection is confirmed using an antigen test or throat swab, antibiotics are indicated. The timing of antibiotics in GAS is quite complex. A delay in treatment for up to 9 days can be tolerated without any compromise in the prevention of acute rheumatic fever.[18] In patients with recurrent pharyngotonsillitis an intentional delay of 2-3 days is advocated as this leads to a reduction in recurrences of GAS infection.[19]

Lower respiratory tract infections

Pneumonia:
Antibiotics are indicated for all children with pneumonia. Amoxicillin (90mg/kg/day tds po 5 days) or intravenous ampicillin is the drug of choice. For children less than 2 months of age, the addition of an aminoglycoside or cephalosporin is indicated and for children over 5 years of age the addition of a macrolide should be considered. In HIV-infected children, an aminoglycoside must be added due to the likelihood of a gram negative infection. In addition cotrimoxazole should be considered where pneumocystis pneumonia is suspected. This is likely in infants less than 6 months of age and who are HIV-exposed.[20]

Bronchiolitis:
According to the South African bronchiolitis guidelines a physician should treat the symptoms, the underlying cause of the infection and prevent complications, in managing bronchiolitis. No antibiotics are indicated in uncomplicated bronchiolitis and immunocompetent children, since it is a self limiting disease where secondary bacterial infection is uncommon.

Prevention is usually better than cure and in the high risk patient the use of Palivizumab to prevent bronchiolitis caused by Respiratory Syncytial Virus is indicated and highly recommended.[21] (**Table 2**)

Table 2: Indications for Palivizumab

1. Premature infants of gestational age <32 weeks at birth.
   Prophylaxis should be continued until the earlier of:
   - 6 months of chronological age, or
   - the end of the RSV season (last dose in July)

2. Premature infants of gestational age 32 - 36 weeks at birth.
   Prophylaxis should be continued until the earlier of:
   - 3 months of chronological age, or
   - the end of the RSV season (last dose in July)

3. Children of any gestation who are <24 months of age at the start of the RSV season with any of the following:
   Chronic lung disease of prematurity, chronic lung disease, primary immunodeficiency, cyanotic congenital heart disease.
   Prophylaxis should be used for 5 months beginning in February in most areas of South Africa except for KwaZulu-Natal, where it should be started in December.

4. High-risk premature infants should commence their prophylaxis while still in hospital.

Conclusion

The decision to use antibiotics in respiratory infections is extremely complex. By using the above principles and guidelines the correct and appropriate choice of antibiotics should be possible, helping to prevent emergence of antibiotic resistant organisms. There is an urgent need to reduce the use of antibiotics amongst practitioners especially in the primary care setting. To apply these principles and guidelines effectively adequate follow up of patients and access of patients to health care facilities is important. In addition the value of preventative measures for respiratory pathogens cannot be over-emphasised. Immunisation is critical and cannot be avoided.

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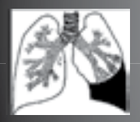

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Chylothorax

Aetiology of Chylothorax

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Chylothorax represents an uncommon type of pleural effusion with distinctive features.[1] It is defined by the presence of chyle in the pleural cavity, which is a type of lymphatic fluid enriched in lymphocytes (particularly T-lymphocytes), immunoglobulins, and lipids that are absorbed by the digestive tract. The thoracic duct transports the chyle from the cisterna chyli into the circulatory system, usually via the right jugular or subclavian veins.[2] Between the cisterna chyli and the central venous system, the thoracic duct runs in close proximity to various anatomical structures including the oesophagus, lungs, aorta, vertebrae and lymph nodes. Disease processes or mechanical injuries involving these structures may result in disruption and/or obstruction of the thoracic duct and/or its tributaries, resulting in leakage and accumulation of chylous fluid in the pleural cavity.

A recent retrospective observational study from the Mayo Clinic (203 patients over a 21-year period) suggests a change in the spectrum of causes for chylothorax compared to previous studies.[3]

Traumatic injuries to the thoracic duct represented 50% of all causes of chylothorax compared to 25% in older studies.[2-4] Thoracic surgical procedures, particularly oesophagectomy, represent the vast majority of these traumatic cases, although neck surgeries and complications associated with percutaneous procedures, such as placement of central venous indwelling catheters or other devices (e.g. pacemaker), have also been described. By contrast, lymphomas, previously the most common cause, only account for 10% to 12% of all chylothoraces in recent studies.[3,4] This may be due, in part, to earlier diagnosis of lymphoma and the availability of effective chemotherapy regimens that decrease the rate of complicating features, such as chylothorax. There are many unusual causes of chylothorax including cirrhosis, fungal infections, tuberculosis, sarcoidosis, congenital or acquired lymphatic malformations (lymphangiomatosis, lymphangiectasias, lymphangioleiomyomatosis, Noonan syndrome, yellow nail syndrome and Down syndrome), central venous thrombosis, chest radiotherapy, goitres, heart failure and constrictive pericarditis. Anecdotal cases of chylothorax have been described after seat-belt injuries from motor vehicle crashes, movements of neck hyperextension or even forceful sneezing and childbirth delivery. In approximately 5% of cases, a specific cause cannot be determined and the chylothorax is then labelled as idiopathic.

It should be emphasized that the diagnosis of chylothorax may not always be straightforward. The classical milky appearance of chylous effusions is only present in less than one-half of cases and is typically not seen when the patient is fasting or malnourished. In a recent study, the pleural fluid triglyceride level was <110 mg/dL in 15% of patients with chylothorax, and even <50 mg/dL in some cases.[4] Likewise, chylothorax can be transudative, as in cases associated with portal hypertension.[4,5]

Lipoprotein electrophoresis should be pursued when chylothorax is still suspected in the presence of atypical features. An accurate diagnosis will lead to more effective management strategies.[6]

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Pleural Fluid Analysis in Chylothorax

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A chylothorax develops when the thoracic duct or one of its large tributaries ruptures allowing chyle to flow into the surrounding tissues. The thoracic duct travels from its origin in the *cisterna chyli* through the aortic hiatus of the diaphragm, at the level of the tenth thoracic vertebrae, to the right of the aorta. At the level of the fifth or sixth thoracic vertebrae, the duct enters the left posterior mediastinum and eventually joins the venous circulation at the juncture of the left subclavian and internal jugular veins. Therefore, rupture of the thoracic duct below T5 to T6 results in a right-sided chylothorax, whereas injury to the duct above this level results in a left chylothorax.

Chylothorax is an uncommon (~2% incidence) cause of pleural effusion. On pleural fluid analysis, the fluid is white and opaque if fat is present; however, the fluid can be clear yellow in the neonate who has not yet ingested milk, serous in the adult who has not eaten for 12 hours, or haemorrhagic if trauma is involved. The supernatant of a chylothorax fails to clear following centrifugation. T lymphocytes are the primary cells in chyle, typically representing >80% of the cellular population.[1] The total nucleated cell count ranges from 400 to 6,800 cells/μL. Chyle is typically a protein discordant exudate (i.e. an effusion with a pleural fluid to serum protein ratio >0.5 and pleural LDH concentration less than two thirds of the upper limit of the normal serum LDH value) with pleural fluid protein ranging from 2.2 to 5.9 g/dL.[1,2] Since chyle is non-inflammatory, the LDH is in the normal range, virtually always <268 IU/L. The electrolytes in chyle are similar to plasma. Chylous fluid has been reported to have a pH ranging from 7.40 to 7.80 and a glucose concentration of 78-200 mg/dL.[1,2] Measurement of the pleural fluid to serum glucose ratio assists in differentiating a chylous effusion (ratio <1.0) from pleural fluid attributable to the extra-vascular migration of a central venous catheter in patients receiving total parenteral nutrition, which contains lipids and glucose (ratio >1.0).[3]

The diagnosis of a chylothorax is suspected when the fluid is milky. However, this appearance can also be observed with a cholesterol effusion. Cholesterol effusions have a different pathogenesis, clinical presentation, and pleural fluid characteristics. They represent a form of lung entrapment with an active pleural process, and are neutrophilic, concordant exudates with a cholesterol level of >250 mg/dL (range 300-1500 mg/dL) and a cholesterol/triglyceride ratio >1.02. In addition to chylothorax the two other protein discordant exudates are sarcoidosis and yellow-nail syndrome.

The diagnosis of chylothorax is highly likely if the triglyceride level in the pleural fluid is >110 mg/dL and highly unlikely if the pleural fluid triglyceride level is <50 mg/dL.[1] The presence of chylomicrons confirms the diagnosis. However, the patient who is fasting may have low triglyceride levels and chylomicrons may not be detected.

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Imaging of Chylothorax

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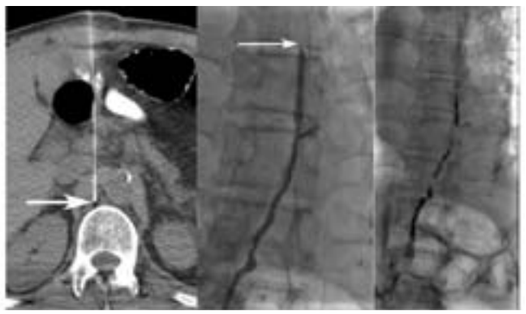
Traditionally, two imaging techniques for visualisation of the lymphatic vessels have been applied: conventional lymphangiography and lymphangioscintigraphy. Injection of an oil-based contrast iodine agent directly into a lymphatic vessel at a distal extremity enables visualisation of the lymph ducts after 24 hours using radiography (conventional lymphangiography). Injection of 99mTc labelled sulfur colloid or albumin intradermally at a distal extremity leads to clearance of the tracer into the lymphatic vessels and enables visualisation of the lymph ducts using a Gamma camera with serial images taken at 5 minute intervals post-injection for 45–60 min (lymphangioscintigraphy). The disadvantages of conventional lymphangiography and lymphoscintigraphy, namely invasiveness and patient discomfort, combined with advances in imaging technology and contrast media development, has prompted a search for better lymphatic imaging using CT, PET, US, and MRI. However, these newer techniques are focused on lymph node detection and evaluation rather than on anatomical imaging of the thoracic duct. In analogy to indirect lymphoscintigraphy, indirect MR lymphangiography can be performed by injecting gadolinium

based contrast agents intradermally or subcutaneously at a distal extremity, but experience is limited to animal studies and this technique has not yet been used routinely. Fluid-sensitive sequences such as half-Fourier single-shot turbo spin-echo (HASTE) sequences may also be used for visualisation of the *cisterna chyli* and the thoracic duct without need for gadolinium based contrast agents. However, spatial resolution of these techniques is limited compared to conventional lymphangiography.

Treatment of chylothorax due to thoracic duct injuries can be performed with chest tube drainage and maintenance of a low-fat diet. However, high output chylothorax may not respond to conservative management and may require intervention. Traditionally, surgical thoracic duct ligation has been performed. More recently, percutaneous imaging guided access to the thoracic duct allows for less invasive treatment modalities. Thus, access to the *cisterna chyli* may be obtained under fluoroscopy after bilateral pedal conventional lymphangiography to opacify the thoracic duct or under CT guidance without need for conventional lymphangiography.[1-4]

CT guided percutaneous transabdominal puncture, catheterisation of the *cisterna chyli* and injection of water-soluble iodine contrast allows for diagnosis and treatment of thoracic duct injuries. If catheterisation and embolization fails, needle disruption of the *cisterna chyli* can be performed to create a controlled leak which may divert lymph flow from the damaged thoracic duct to collaterals. However, disruption may be less successful than embolisation.[5,6]

An illustrative case is that of a 68-year-old male patient with persistent chylothorax after an oesophagectomy due to oesophageal cancer. A percutaneous CT guided access to the *cisterna chyli* with a 21-gauge needle was performed (*left, arrow*).



Fluoroscopy, after injection of water-soluble iodine contrast agent into the *cisterna chyli*, showed the thoracic duct abruptly ending at the T8-T9 level (*middle, arrow*). Utilizing the Seldinger technique, a microcatheter was advanced over a hydrophilic guidewire into the thoracic duct, which was embolised with multiple radiopaque micro coils (*right*).

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Surgical Management of Chylothorax

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Regardless of its aetiology, chylothorax represents a difficult problem that is potentially life-threatening if not dealt with promptly. A persistent high output drainage of chyle is associated with malnutrition and immunosuppression and consequent poor long-term outcomes.

The management of chylothorax is dependent upon both the aetiology as well as its duration and degree. Conservative management with dietary restriction of fat and intravenous hyperalimentation may be appropriate for low output chylothoraces (<1L/day). The administration of octreotide may also be of some benefit. On the other hand, persistent high output chylothoraces typically cannot be managed with conservative measures and may require some form of intervention, each being tailored to the particular clinical situation at hand. Interventions may include surgical pleurodesis/pleurectomy, operative thoracic duct ligation and/or percutaneous access to the thoracic duct to either fenestrate or embolise it.[1]

Primary thoracic duct ligation, with or without pleurodesis, is the ideal intervention for postoperative patients who have iatrogenic thoracic duct injury. Operative intervention for chylothorax should be contemplated when persistent chest tube output is greater than 1L/day.[2] Further delay will only worsen the metabolic and immunologic derangements from persistent chyle leak and may delay recovery. In centres where percutaneous embolization of the thoracic duct is routinely performed, radiological techniques may supplant initial operative intervention.

Surgical ligation of the thoracic duct requires knowledge of its anatomy. The duct originates at the *cisterna chyli* in the abdomen and enters the chest at the aortic hiatus anterior to the vertebral bodies and posterior to the aorta. It then ascends in the right chest along the anterior surface of the vertebral bodies between the aorta and azygous vein. It finally crosses over to the left side at the carina and drains into the junction of the left jugular and subclavian veins. However, numerous variants exist. Injury of the thoracic duct at any location along its course can lead to chylothorax. Since successful surgical ligation requires identification of the proximal thoracic duct in the right chest, orally administering cream 24 hours prior to surgical exploration often aids in this procedure.[2] If identification is not possible, then mass ligation of all tissues anterior to the oesophagus and between the aorta and azygous vein should be performed. Thoracic duct or mass ligation, using sutures or clips, can be performed through a low right thoracotomy (7th interspace), as well as by videoassisted techniques (VATS). Additionally, chemical pleurodesis with talc or pleurectomy can be performed to facilitate pleural symphysis. Our practice has been to use these measures as adjuncts to thoracic duct ligation for high output chylothoraces in the post-surgical setting.[2]

Primary chemical pleurodesis, performed either at the bedside through a chest tube or via VATS, can be effective in sealing persistently low output chylothoraces, such as those caused by lymphoma or other malignancies, in combination with conservative measures as previously outlined.

In summary, chylothorax arises from a variety of aetiologies. Prompt diagnosis and treatment is required to prevent life threatening malnutrition and immunosuppression. Low output chylothorax can often be managed with conservative measures, whereas high output chylothorax requires either surgical intervention or radiological techniques.

1. Boffa D, et al. *Eur J Cardiothorac Surg* 2008; **33**:435-439.
2. Paul S. *Thorac Cardiovasc Surg* 2009; **57**:226-8.

PLEURAL IMAGES

Chylothorax due to Retrosternal Goitre

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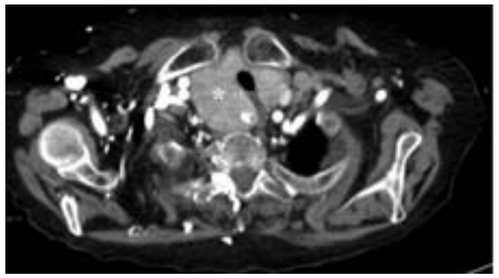
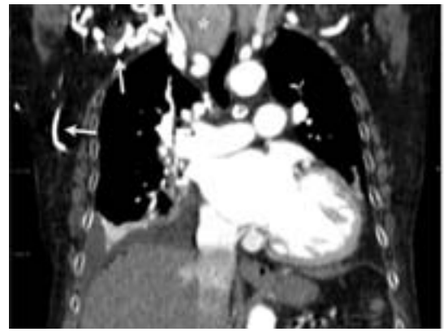
An 86-year-old woman was evaluated for progressive dyspnoea. Upon examination she was found to have decreased breath sounds at the right lung base and mild pedal oedema. A chest radiograph disclosed an enlarged cardiac silhouette and a right-sided pleural effusion. An echocardiogram demonstrated an ejection fraction of 35%.

Since the pleural effusion did not disappear with diuretics within a few days, a diagnostic thoracentesis was performed. The pleural fluid was milky and its analysis showed: erythrocytes 2,000/µL, leukocytes 250/µL with 92% lymphocytes, total protein 2.5 g/dL (serum 6.3 g/dL), lactate dehydrogenase 106 IU/L (serum 325 U/L), pH 7.53, adenosine deaminase 13.8 IU/L, triglycerides 340 mg/dL, cholesterol 20 mg/dL, negative cultures and no malignant cells on the cytological smear. The thyroid-stimulating hormone level was lower than 0.01 µU/mL and the free thyroxine (T4) level was 57 ng/dL.





The chest CT showed a large retrosternal multinodular goitre (Figures, asterisk) with mass effect on large vessels (e.g.. brachiocephalic veins) and thoracic lymphatics as noted by the presence of right-sided venous distension on the chest wall (Figure above, arrows) and pleural effusion.

The symptoms were partially relieved by a therapeutic thoracentesis of 500 mL. Due to the patient's age and comorbidities, goitre surgery was not a consideration. The patient passed away two weeks after hospital discharge.

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Foxair 25/125 Inhaler	R168
Foxair 25/250 Inhaler	R226

Reference: 1. IMS Data, December 2010

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AstraZeneca's Turbuhaler® recognised at international Good Design Award

AstraZeneca Pharmaceutical's Turbuhaler®, an inhaler used in the daily management of asthma, has been awarded a Good Design Award from the Japan Industrial Design Promotion Organisation (JIDPO).

Founded in 1957, the Good Design Awards is an annual international design competition which has earned the reputation for being a prestigious trademark for outstanding design. Turbuhaler® was selected based on the contribution it has made to asthma patients throughout the world. Judges comments included: "This product prioritises the asthma patient's care, focusing on the patient's actual use on a daily basis. The product is simple, user-friendly and suited for all age groups."

"This is a wonderful acknowledgment of AstraZeneca's contribution to both asthma management as well as patient care. It reaffirms the company's ongoing commitment to the improvement of patients' lives," says Dr Jasvanti Bhana, Senior Manager: Medical, Regulatory and Quality Assurance for AstraZeneca. "Ultimately, the Turbuhaler® is true to the ultimate purpose of innovation, which is to improve quality of life."

Turbuhaler® was originally created by Swedish designer Kjell Wetterlin in 1987 at the then Astra Draco, after his daughter complained about the taste of additives from her asthma medication. As the first powder inhaler on the market, it was welcomed as a revolutionary inhaler design. Unlike other inhalers available at that time, it was the first to be operated by the patients breathing and thus replacing the need for propellants such as CFCs.

This is not the first design prize that the Turbuhaler® has won; its unique design has been commended by several awards, including the Stratospheric Ozone Protection Award from the US Environmental Protection Agency in 1991. "Like most good designs, the Turbuhaler® design is timeless and still very relevant to today's asthma patients," concludes Dr Bhana.

For more information about the Good Design Awards visit:
www.g-mark.org/english/index.html

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AstraZeneca is a leading global pharmaceutical company which employs over 65,000 people in more than 100 countries across the Americas, Europe, Asia, Africa and Australasia. Its 2008 sales totalled over USD 32 billion, with R&D budgets of over USD 5 billion.

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Avelon® monotherapy shows strong performance in treating hospitalised pneumonia patients

Berlin, Germany, 15 May, 2008 – A recently published study in Clinical Infectious Diseases shows that Avelon® (moxifloxacin HCl) monotherapy is as powerful as a high dose combination regimen of ceftriaxone plus levofloxacin in the treatment of hospitalised patients with community-acquired pneumonia (CAP). A total of 569 patients at 69 centres in 17 countries, including South Africa, were treated in the MOTIV[1] trial (MOxifloxacin Treatment IV). The prospective, multicentre, randomised, double-blind, non-inferiority study, was sponsored by Bayer Schering Pharma and assessed by three independent committees of international experts.

"The results of MOTIV reinforce that moxifloxacin is an effective and well tolerated therapy for CAP patients in the hospital setting" said Dr. Antoni Torres, Professor of Pulmonology at the University of Barcelona (Spain) and one of the lead investigators of MOTIV.

CAP is one of the major causes of morbidity and mortality in developed countries. In fact mortality rates ranging from 4% to 14% have been reported for patients requiring hospitalisation.[2,3,4] In up to 50% of all hospitalised CAP patients, the causative pathogen is *Streptococcus pneumoniae*.[5] Moxifloxacin, has excellent activity against *S. pneumoniae*, along with the additional advantage of a once daily dosing.[6,7]

Vice President, Global Medical Affairs, Bayer Schering Pharma.

About MOTIV
The per protocol (PP) population of MOTIV consisted of 569 patients, 291 in the moxifloxacin and 278 in the comparator arm. Patients in the moxifloxacin arm received sequential intravenous (IV)/oral moxifloxacin 400mg once daily. Patients in the comparator arm received IV ceftriaxone 2g twice daily plus IV levofloxacin 500mg twice per day and later be switched to oral levofloxacin 500mg twice daily. Both groups were treated for a total of 7-14 days. At the test-ofcure assessment, there was no significant difference in the clinical cure rates obtained with the two treatments (86.9% moxifloxacin group vs. 89.9% comparator group; 95% CI: -8.1-2.2%) – irrespective of the severity of pneumonia. Both regimens were well tolerated and there were no significant differences in the incidence of adverse effects or mortality between both treatment arms.

Contact: Jill Hagley Tel.: 011 921 5040 Anti-infective Marketing Manager
Forward-Looking Statements: This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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The hectic pace of modern living and a lack of adequate support have forced many mothers to abandon breast feeding early on, preventing infants from getting the best possible start in life.

This is according to Sharlene Swart, National Operations Manager, Netcare Stork's Nest. "Not only does breast milk contain nutrients that are important for a baby's development, it also contains antibodies that help to protect against common childhood illnesses such as diarrhoea and pneumonia – the two leading causes of infant mortality worldwide."

"However, mothers have to learn how to breastfeed as it can be very difficult. It is therefore of the utmost importance that health facilities offer breastfeeding training and counselling," she says.

Only a very small percentage of women are physically incapable of breastfeeding. Most of the time the problem does not lie in production of milk but rather its delivery due to a poor latching technique.

Once correct latching and regular feeding has been established the mother will keep up an adequate supply of milk naturally. According to Swart many mothers today find it almost impossible to maintain supply in the weeks following birth, as they have to return to work. In such instances breast milk is commonly replaced with formula.

"Formula contains some vital nutrients but not the anti-bodies that protect your baby from dangerous illnesses. In addition, mothers with a lack of consistent access to clean water are advised against the use of formula because of the risk of waterborne diseases," she says.

There are also often cases of babies suffering from malnutrition due to an over-dilution of formula in order to make it last longer. By frequently breastfeeding a mother can maintain an adequate supply of the high quality food that her baby truly needs.

"With the proper support and care breastfeeding can be one of the most beneficial gifts a mother can give to her child. Netcare Maternity and Stork's Nest facilities such as those available at Netcare Christiaan Barnard Memorial Hospital are here to help new moms learn how to manage breastfeeding and modern living at the same time," concludes Swart.