of VCT in averting further HIV infections4. Cotrimoxazole prophylaxis, recommended by UNAIDS as part of a minimum package of care for people living with AIDS in Africa5, should be considered for HIV-seropositive patients, and this may provide individual benefit. Antiretroviral therapy may become accessible to the population in the future. Health workers must take a lead in this difficult area, and can begin by "breaking the silence".

Acknowledgements

We thank the Department for International Development (DFID), UK, the Norwegian Agency for Development Cooperation (NORAD) and the Royal Dutch Tuberculosis Association (KNCV) for financial support as part of their aid contribution to Operational Research of the Malawi National Tuberculosis Control Programme. The study received the approval of the National Health Science Research Committee.

This article has previously been published in Tropical Doctor in 2002.

Authors:

Menco M Weismuller1, Sander Meijnen1, Niels JM Claessens1, Felix M Salaniponi MSc PhD2, Anthony D Harries MD FRCP2

1 Academic Medical Centre, University of Amsterdam, Amsterdam,The Netherlands

2 National Tuberculosis Control Programme, Ministry of Health, PO Box 30377, Capital City, Lilongwe 3, Malawi

Address for Correspondence:

Professor AD Harries, c/o British High Commission, PO Box 30042, Lilongwe 3, Malawi

Fax: (265) 772 657; Email: adharries@malawi.net

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The impact of HIV infection on childhood pneumonia: comparison between developed and developing regions

Stephen M Graham

Summary

Respiratory disease is the commonest cause of morbidity and mortality in HIV-infected children. While the pattern of HIV-related pneumonia in African adults is well documented and is recognised as quite different from that which occurs among HIV-infected adults in high-income regions, less is known of the situation in children. Most children are infected by mother-to-child transmission and presentation of HIV-related pneumonia is often in infancy or early childhood, an age group in which confirmation of the cause of pneumonia is difficult. However, aetiological data are important. Poor response of the infant with severe pneumonia to standard antibiotic (such as chloramphenicol) or of the older child with chronic pneumonia to anti-tuberculosis treatment are two very common clinical dilemmas that many Malawian health workers would recognise. This review aims to present the available data relevant to Malawi, contrast with experience from the developed world and to describe common HIV-related pneumonias such as PCP and LIP. Unlike for adults, the pattern of HIV-related pneumonia in Malawian children may not be so different in cause from that described for children in developed countries prior to the use of PCP prophylaxis and anti-retroviral therapies. The most important contrast is the higher prevalence and poorer outcome.

Introduction

Respiratory disease is a major cause of morbidity and mortality in HIV-infected children in developed and developing countries.[1-3] Prior to the HIV epidemic, there were already important differences between the regions that still exist. In developing countries, acute childhood pneumonia is more often due to bacteria, most commonly *Streptococcus pneumoniae* and *Haemophilus influenzae*, and more likely to be fatal.[4] The prevalence is much higher of important risk factors for pneumonia morbidity and mortality such as fetal and early childhood malnutrition. In addition, the community prevalence of smear-positive pulmonary tuberculosis (PTB) has increased dramatically in HIV endemic regions and maternal illness and death is common. It is therefore a difficult environment for an HIV-infected child to negotiate and perhaps not surprising that the majority of HIV-infected infants from a resource-poor region such as tropical Africa have died by 3 years of age.[5,6] Only about 25% survive up to 5 years compared to over 80% in USA or western Europe.1 Thus the majority of cases of HIV-related respiratory disease present in infancy and early childhood. However, because childhood HIV infection is so common in some countries, the presentation of HIV-infected school-aged children often with chronic respiratory disease is not unusual.

Causes of pneumonia in HIV-infected children living in high-income countries such as USA or UK are well documented.[3,7,8] It may not be correct to assume that the pattern of disease is similar in HIV-infected children in resource-poor Africa where it is estimated that over 90% of childhood HIV infection now

occurs.[9] Major differences between the regions have been recognized in HIV-infected adults such as the relative incidence of pulmonary tuberculosis (PTB) and Pneumocystis carinii pneumonia (PCP). Etiology of childhood respiratory disease is difficult to confirm in developing countries because diagnostic options are very limited yet such data are critical for effective prevention and management strategies. Children with pneumonia are mainly managed according to standard guidelines[4], HIV status is rarely known and therapeutic options such are limited to a few cheap antibiotics and oxygen delivered via nasopharyngeal catheter.

The pattern of respiratory disease in HIV-infected children in developed countries

It is more relevant to compare the pattern of respiratory disease as it was in developed countries prior to the availability of highly active anti-retroviral therapy and the routine use of cotrimoxazole prophylaxis in HIV-exposed infants[7,8], as this is still the scenario for most HIV-infected African infants. The incidence of bacterial pneumonia was far higher than in HIV-uninfected children and recurrent bacterial disease is an AIDS-indicator disease.[7] The common bacterial pathogens are S.pneumoniae and H.influenzae. The commonest opportunistic infections were PCP and lymphoid interstitial pneumonitis (LIP).[8,10] Most cases of PCP were in infants, although it did occur among older children, and PCP was associated with a poor survival.10 PCP is now uncommon due to the routine use of cotrimoxazole prophylaxis in HIV-exposed infants.[2] It may still present as first evidence of HIV infection in infants born to immigrant mothers from HIV-endemic regions who have not received proper antenatal care.[3] Cytomegalovirus (CMV) is also a cause of HIV-related pneumonia in infants, often in association with PCP. LIP occurs in an older age group and is associated with a "favorable" prognosis.[10] LIP is often complicated by bacterial pneumonia and bronchiectasis.[11,12] Tuberculosis is HIV-related but uncommon.[7,8]

The pattern of respiratory disease in HIV-infected African children

Cohort studies indicate that acute and chronic pneumonia are common causes of morbidity in HIV-infected African children.[5,6] However, these studies did not investigate for specific etiology. Autopsy studies have consistently shown that respiratory disease is a very common cause of death[13-15] but tend to over-represent causes of pneumonia that do not respond to standard available treatments or that present with end-stage HIV disease. Clinical studies of infants and children hospitalized with severe pneumonia in Malawi and South Africa found rates of HIV infection of 45-65%.[16-18] Case-fatality rate was increased three to six-fold in these children and this was mainly due to the poor outcome of PCP. It is from South Africa that most etiologic data are emerging. Childhood HIV infection is now very common there and diagnostic facilities more sophisticated than in other sub-Saharan countries. However, similar studies still need to be undertaken in tropical Africa where the pattern of disease does differ, such as the importance of *Salmonella* as an invasive pathogen of children in malaria endemic regions.[19]

BACTERIAL PNEUMONIA

Streptococcus pneumoniae is consistently the commonest cause of bacterial pneumonia and, similar to experience in the USA, the incidence is far higher than in HIV-uninfected children.[16-18] The clinical presentation and treatment response for most cases are similar to that in HIV-uninfected children but infection with antibiotic-resistant organisms is more common.[20] Children with advanced HIV disease are at greater risk of recurrent infection and death. *H.influenzae* is also common and the studies of South African children have found that *Staphylococcus aureus* is particularly common in HIV-infected children with chronic lung disease.[17,18] *Salmonella typhimurium* was the second commonest blood isolate after pneumococcus from Malawian children with acute severe pneumonia.*16* Other bacteria identified in HIV-infected African children with pneumonia include *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*.[14,17,18] These Gram-negative bacteria are associated with malnutrition, as they were prior to the HIV epidemic. Clinical management algorithms guide diagnosis and choice of antibiotic for most children with pneumonia.[4,21] Although the range of available antibiotics is limited, it would seem that these recommendations are still appropriate for HIV-infected children.

PNEUMOCYSTIS CARINII PNEUMONIA

Autopsy[13-15] and clinical1[6,22] studies have shown that PCP is common in HIV-infected African infants between 2 and 6 months of age and accounts for one-third or more of the deaths in this age group. Mixed infection with bacterial pneumonia or cytomegalovirus (CMV) is common. PCP is usually the first presentation of HIV-related disease and is often clinically recognizable. PCP presents with very severe pneumonia, hypoxia is common and there is no response to standard parenteral antibiotics. Intravenous cotrimoxazole is usually not available so treatment is high-dose oral cotrimoxazole, steroids and continuing parenteral antibiotic and oxygen. Demand for oxygen therapy is very high and yet outcome is very poor.[16,22] This can create a dilemma when oxygen supply is limited as more curable cases such as very severe bacterial pneumonia may be denied oxygen.

VIRAL PNEUMONIA

The proportion of pneumonia in hospitalized HIV-infected South African children due to viruses was significantly lower than in HIV-uninfected children because pneumonia due to other causes such as bacteria and PCP was more common.[23] However, the estimated burden of disease of viral pneumonia in HIV-infected children was increased for RSV, influenza virus, parainfluenza and adenovirus, and mortality was significantly higher. As for developed countries, respiratory syncytial virus (RSV) is the commonest cause of viral pneumonia in developing countries. In tropical regions it does not have a similar strong seasonal variation and this may be even less evident in HIV-infected children. The RSV pneumonia in HIV-infected African children is associated with less wheeze or typical features of bronchiolitis, is more commonly complicated by secondary bacterial pneumonia and mortality is higher.[23] Autopsy and clinical studies have commonly identified CMV in HIV-infected infants with pneumonia, often in association with PCP.[15,18] CMV pneumonia is difficult to recognize or confirm and therapy such as ganciclovir is not available. Measles is also more common in HIV-infected children and more likely to be fatal[24] but immunisation is usually protective.

LYMPHOID INTERSTITIAL PNEUMONITIS

LIP is a common cause of chronic respiratory disease in HIV-infected African children.[5,14,25] Diagnosis is rarely confirmed as this requires lung biopsy but when this was done in HIV-infected South African children with chronic respiratory symptoms, LIP was the commonest diagnosis.[25] As LIP was not a clinical problem prior to the HIV epidemic, many health workers have little knowledge of the condition and LIP is often misdiagnosed

as miliary or PTB.[1] Children with LIP usually present after 2 years of age and associated clinical features include generalised lymphadenopathy, bilateral non-tender parotid enlargement, digital clubbing and marked hepatomegaly. Secondary bacterial disease due to pneumococcus or *Salmonella* is common. Corticosteroids are useful in alleviating symptoms but prophylaxis or even treatment for PTB also needs to be considered.

PULMONARY TUBERCULOSIS

The association of TB and HIV in African children is still not entirely clear and is certainly not as strong as it is in adults.[1] The difficulty in defining the epidemiology in the context of HIV infection relates to difficulties in diagnosis in young children and to the overlap in clinical and epidemiological presentation. As mentioned, children with other forms of HIV-related lung disease such as LIP are often registered and treated as smear-negative PTB.[26] Notwithstanding, there is now good evidence that the incidence of PTB is increased in HIV-infected African children, partly because of immune suppression increasing susceptibility to TB disease but also because HIV-infected children are at greater risk of TB infection due to high rates of PTB among their parents.[17,18,26,27] The presentation of PTB is similar to that in HIV-uninfected children but the tuberculin test is less useful and treatment response is poorer especially in those with advanced HIV disease.[26,27] Aside from LIP, other diagnoses to consider in the HIV-infected child with chronic respiratory disease who is not responding to anti-tuberculous therapy are bronchiectasis and pulmonary Kaposi's sarcoma.

Summary

More etiological data are needed from resource-poor regions. However, unlike for adults, available evidence does suggest that the pattern of HIV-related pneumonia in children from sub-Saharan Africa is not markedly different from that described in HIV-infected children from developed countries in the earlier stages of the epidemic. Important differences are the far greater size of the problem, the increased frequency of disease, the lack of diagnostic and therapeutic options and the high early mortality. These differences largely reflect the same risk factors and the same problems of pneumonia management that existed prior to the HIV epidemic. In communities that are highly HIV endemic, the burden of HIV-related childhood pneumonia is enormous and affects the ability of already under-resourced and over-burdened health services to care for all sick children, HIV-infected or not. There is great potential to reduce this burden by reducing rates of vertical HIV transmission and by interventions such as PCP prophylaxis and conjugate vaccines against common bacteria. In practice, such measures are still a long way off.

Dr SM Graham, Research Fellow, Wellcome Trust Research Laboratories, PO Box 30096, Blantyre.
Fax: 265-675774
Email: sgraham@mlw.medcol.mw

Table 1: Causes of HIV-related lung disease in children

AGE GROUP	MOST COMMOM	LESS COMMON
INFANTS	Bacterial Pneumonia	ViralPneumonia(eg;CMV)
	PCP	Tuberculosis
CHILDREN	Bacterial Pneumonia	Viral pneumonia (eg; measles)
	LIP	Pulmonary Kaposi's Sarcoma
	Tuberculosis	Nocardiosis
		Candidiasis

Table 2: HIV-related clinical issues that affect incidence, aetiology and outcome of acute pneumonia

Opportunistic pathogens e.g., Pneumocystis carinii pneumonia
Uncommon pathogens e.g., Klebsiella pneumoniae, Salmonella
Mixed infections
Nosocomial infection
Antibiotic resistance
Underlying chronic lung disease
Advanced immunosuppression
Malnutrition
Maternal illness or death

Table 3: Common clinical features of PCP in Malawian children

Age: 2-6 months
Afebrile or low-grade fever
Marked respiratory distress
Auscultation: Clear chest or diffuse rather than focal signs
CXR: Hyperinflation or diffuse interstitial pattern
Poor response to standard antibiotic treatment for severe pneumonia
Severe and persistent hypoxia
First presentation of HIV-related disease
HIV seropositive

Table 4: Clinical features of LIP

Usually older than 2 years of age
Not severely wasted
Associated features:
Marked generalised lymphadenopathy
Hepatosplenomegaly
Parotid enlargement
Finger clubbing
CXR: diffuse reticular pattern and bilateral adenopathy
+/- local opacities or consolidation
Differential diagnosis: miliary TB, pulmonary TB, bronchiectasis

Table 5: Impact of HIV infection on the usefulness of features used to diagnose PTB in children

Diagnostic feature	Impact of HIV
Chronic symptoms	less specific
Smear-positive contact (if parent)	less specific
Malnutrition or failure to thrive	less specific
Positive tuberculin test	less sensitive
"Characteristic" CXR abnormalities	less specific
Satisfactory response to TB treatment	less sensitive

Table 6: Clinical differentiation of miliary TB from LIP in children

	Miliary TB	*LIP*
Clinical Features:-		
Respiratory symptoms	-/+	+++
Persistent fever	++	++
Wasting	+++	-/+
Generalised lymphadenopathy	-/+	+++
Parotid enlargement	-	++
Clubbing	-	+
Hepatomegaly	++	++
CXR Features:-		
Diffuse micronodular	++	+
Diffuse reticular	-	++
Lymphadenopathy	-/+	++

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