Prolonged after-effects of pneumonia in children

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Summary

Sixty-two black children were prospectively followed up for 1 - 7 years after pneumonia contracted at a median age of 17 months. In 55% of cases the pneumonia was measles-associated and 27% had serological evidence of infection with other respiratory viruses. Recurrence of cough or wheeze for more than 6 months occurred in 85% with just over 50% having recovered during the follow-up period. While the highest incidence of persistent symptoms occurred in children after measles superinfected with another virus, this was not significant. Abnormal radiographic features persisted in 53% of children and consisted of peribronchial and/or parenchymal lesions. Abnormal large and small airway calibre and/or bronchial hyperreactivity were found in one-third of children, and were significantly more common in those children whose main symptom was recurrent wheezing. Clinical and lung function abnormalities years after lower respiratory tract infection in this group of disadvantaged children compare with reports from more privileged groups. Recognition that long-term sequelae occur may prevent inappropriate subsequent management of symptomatic children.

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Recurrent chest symptoms may follow acute lower respiratory tract infection (ALRTI) in children. The most frequently reported are the sequelae of bronchiolitis, usually caused by respiratory syncytial virus (RSV) contracted in the first year of life.[1-3] Other forms of ALRTI, for example pneumonia, may also be followed by abnormally frequent respiratory symptoms.[4-7]

Lung function abnormalities and increased bronchial hyperreactivity have been known to persist for years after ALRTI, and are detected by tests of varying sophistication from peak expiratory flow rate (PEFR) to body plethysmography.[1-3,6-9]

Host factors that predispose a child to developing recurrent symptoms, especially wheezing, after ALRTI are a young age (< 2 years), poverty, crowded home circumstances, attendance at a day-care centre and air pollution.[10-12] Whether atopy either in the child or his close family increases the likelihood of prolonged sequelae after pulmonary infection is controversial.[3,6,13-15]

The series quoted have been from communities in developed countries. After malnutrition and diarrhoeal diseases, the most prevalent condition in Third-World children is acute respiratory infections.

A prospective follow-up of children from a high-risk population was carried out in order to examine the burden incurred after pneumonia.

Patients and methods

Black children aged between 6 months and 12 years admitted to hospital with radiographically proven pneumonia were studied if they had a fixed abode in townships near Durban, which would facilitate follow-up, and if the parents consented to their child taking part in the study.

A history of wheezing before the present illness and a family history of asthma was particularly noted. Nutritional assessment consisted of height, weight and serum albumin levels on admission to the study.

Paired sera were tested for complement-fixing antibodies for respiratory viruses (influenza A, B; para-influenza 1, 2, 3; RSV; and adenovirus) and *Mycoplasma pneumoniae*. Children with measles-associated pneumonia were included.

After discharge from hospital, the children were seen at least twice a year, and had chest radiography at least once a year. The following data were specifically noted: (*i*) symptoms — cough more than once a month and any episode of wheezing; (*ii*) abnormal physical signs on auscultation; and (*iii*) radiographic abnormalities defined as coalescent pulmonary shadowing, and/or patchy airspace disease (3 - 6 mm opacities with ill-defined edges) and/or bronchial and peribronchial disease (bronchial wall thickness > 1 mm with ⩾ 3 bronchi seen near the hilum and any > 1,5 cm from the hilum).[16,17]

Lung function was tested at every follow-up visit, as the child's age permitted. Initially PEFR was examined. Later dynamic lung volumes were obtained using a water filled spirometer. Those children over 8 years of age could co-operate to perform flow-volume loops. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and forced expiratory flow for 25 - 75% FVC (FEF_{25-75}) were derived before and after nebulisation with 5 mg salbutamol respirator solution. Normal values used were those of American black children.[18,19] Increase in FEV_1 of > 15% or FEF_{25-75} of > 49% induced by salbutamol was taken as abnormal bronchial hyperreacticity.[20,21] A 6-minute free running exercise test was performed and significant bronchoconstriction was diagnosed if there was a fall in PEFR or FEV_1 of > 15%.

Results

Sixty-two black children (36 boys) were followed for a period of up to 7 years: 5 children were lost to follow-up after 1 - 2 years, 35 were studied for 2 - 5 years and 22 for more than 5 years. Their ages at the episode of acute pneumonia ranged from 6 months to 9 years 11 months with a median age of 17 months.

The nutritional status of the children is shown in Table I; of these 51% were marginally or moderately stunted and 29% were mildly underweight. In only 9% was weight for height above 90% of the standard. In 29% of the children the serum albumin level was < 34 g/l but there were none < 30 g/l.

TABLE I. NUTRITIONAL STATUS — PERCENTAGE OF NATIONAL CENTER FOR HEALTH STATISTICS (NCHS) STANDARDS

Height/age		Weight/age		Weight/height	
% of NCHS	% of group	% of NCHS	% of group	% of NCHS	% of group
> 95	49	> 90	71	> 90	91
90 - 95	38	78 - 89	29	85 - 90	9
85 - 89	13				

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Table II shows the results of the aetiological studies. The prevalence of measles in the community is evident: 35 children (57%) had measles-associated pneumonia, 11 of whom also had a four-fold rise in complement-fixing antibody titre for another virus. Seventeen children (27%) had evidence of specific virus infection and in the remaining 10 no viral aetiology was detected.

TABLE II. VIRAL AETIOLOGY OF PNEUMONIA

Viruses	No. of cases	%
Measles	**24**	**39**
Measles +		**18**
Adenovirus	**4**	
Influenza A or B	**3**	
Para-influenza 3	**2**	
RSV	**1**	
M. pneumoniae	**1**	
Specific		**27**
Adenovirus	**8**	
M. pneumoniae	**3**	
RSV	**3**	
Influenza A	**2**	
Para-influenza 3	**1**	
Serology negative	**10**	**16**

Table III shows the overall incidence of sequelae noted at the last assessment: 15% never experienced abnormal clinical features after the acute episode, 45% had recovered from these but wheeze or cough persisted in 40%. Two children were eventually assessed as being asthmatic and 1 developed bronchiectasis. Residual radiographic abnormalities were present in a total of 53% of the children: patchy airspace shadows with or without thickened bronchi in 35% and in 18% peribronchial disease only (Fig. 1). Abnormal lung function was detected in 21 children (34%).

Fig. 2 shows the incidence of sequelae related to the length of follow-up. Children with clinical abnormalities tended to recover; 60% were affected in the 1st year and 30% by 5 - 6 years after LRTI. The resolution of radiographic changes was less marked, residuae still persisting in 41% of children after 6 years. Abnormalities of lung function were consistently present in one-third of the children over the study period.

Table IV relates the aetiological agent to sequelae at the most recent assessment. Persistence of increased respiratory symptoms and abnormal pulmonary function were most common in children with measles plus other viral superinfection, but not significantly so.

Those children with recurrent wheezing for more than 6 months after pneumonia were compared with those with recurrent cough plus those who had no post-ALRTI symptoms (Table V). Eight of the 34 children (23%) in the wheezing group had a history of wheezing before the pneumonia, but none of the other group had this problem. Significantly more of the children in the wheezing group had abnormal lung function tests ($P = 0{,}002$), but 3 children with no symptoms had abnormal lung function.

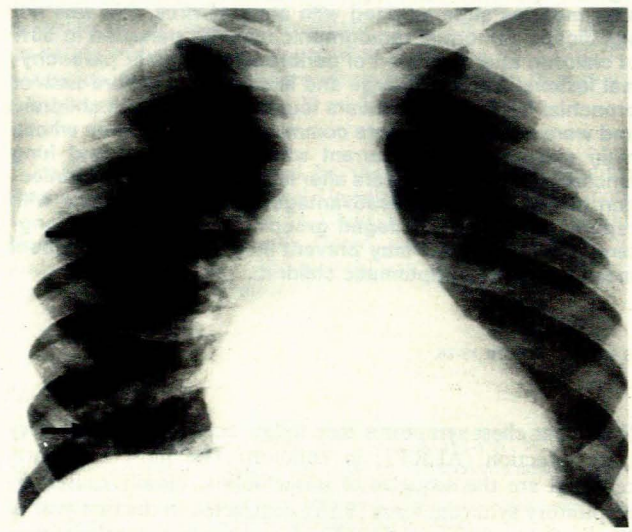

Fig. 1. Five years after acute pneumonia thickened bronchi persist.

Pulmonary function was classified into two categories: reduction in absolute values of dynamic lung volumes (12 children) and bronchial hyperreactivity (9 children) (Table VI). The first group consisted of 7 children with reduced FEF_{25-75} (2 of whom also had reduced FEV_1 and 4 had bronchial hyperreactivity) and 5 children with reduced FEV_1 or PEFR.

TABLE III. ABNORMALITIES AT LAST ASSESSMENT

Symptoms, signs	No.	%	Chest radiograph	No.	%	Lung function	No.	%
Never	**9**	**15**	**Normal**	**29**	**47**	**Normal**	**41**	**66**
Recovered	**28**	**45**	**T bronch.**	**11**	**18**	**EIB**	**5**	**8**
Persisting	**25**	**40**	**PP**	**22**	**35**	**Other**	**16**	**26**

T bronch. = thickened bronchi; PP = parenchymal pathology; EIB = exercise-induced bronchoconstriction.

TABLE IV. AETIOLOGICAL AGENT AND SEQUELAE AT LAST ASSESSMENT (% CASES)

	Clinical features			Chest radiograph			Abnormal
Aetiology	Never	Better	Persistent	Normal	T bronch.	PP	lung function
Specific virus and no virus ($N = 27$)	**15**	**48**	**37**	**41**	**22**	**37**	**26**
Measles and other virus ($N = 11$)	**10**	**18**	**72**	**54**	**18**	**27**	**36**
Measles ($N = 24$)	**17**	**46**	**37**	**46**	**12**	**42**	**25**

T bronch. = thickened bronchi; PP = parenchymal pathology.

TABLE V. COMPARISON OF WHEEZING CHILDREN AND THOSE WITH COUGH OR NO SYMPTOMS

	Wheezing children	Cough or no symptoms
No. of cases	**34**	**28**
Median age at onset of pneumonia (mo.)	**15**	**18**
Family history of asthma	**21 (62%)**	**12 (43%)**
Previous wheeze	**8 (23%)**	**—**
Abnormal PFT	**34 (62%)***	**5 (18%)***

*Four-fold test ($P = 0,002$).
PFT = pulmonary function tests.

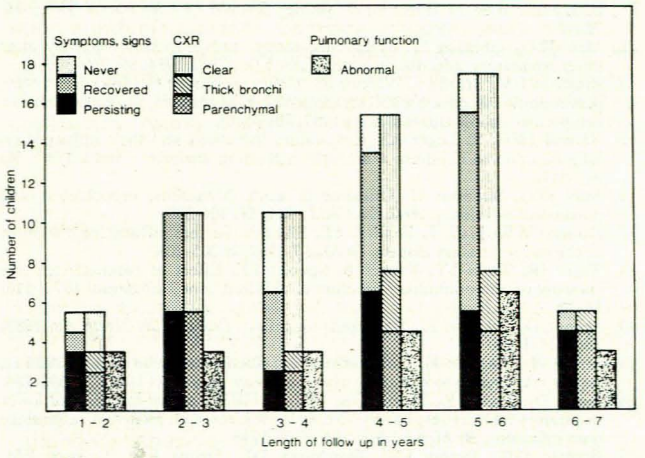

Fig. 2. Abnormalities compared with length of follow-up.

TABLE VI. ABNORMAL PULMONARY FUNCTION TESTS

Reduced absolute values ($N = 12$)		Hyperreactive airways ($N = 9$)		
			Post-nebulisation increase	
			FEV_1	FEF_{25-75}
$PEFR/FEV_1$	FEF_{25-75}	EIB	> 15%	> 50%
5		**5**	**—**	**—**
2	**7***	**1**	**3†**	**2**
		—	**—**	**1**

*4 children also had hyperreactive airways.
†1 of the 3 also had EIB and 2 also had $FEF_{25-75} > 50\%$.
EIB = exercise-induced bronchoconstriction.

Discussion

Prolonged recurrent respiratory symptoms can follow ALRTI whether this is bronchiolitis, bronchitis or pneumonia.[9] It has been found that several years after the acute episode the prevalence of recurrent symptoms, usually wheezing, is increased compared with controls and has been as high as 75%.[2,3,6,7]

Measles virus was the most common cause of pneumonia in this study (57% of cases), one-third of cases being superinfected with other respiratory viruses. Viruses that occurred most frequently in both measles and non-measles cases were adenovirus (19%) and influenzae or para-influenzae (19%). RSV was relatively uncommon (6%), which was partially due to the age of the study children (median 17 months) being older than the usual age of RSV ALRTI.

The persistence of recurrent cough or wheeze during follow-up when related to the aetiology of the pneumonia was highest in children after measles plus a superinfection but this did not reach significant levels. Measles virus, adenovirus and the two in combination are well-known causes of severe acute structural and often permanent pulmonary damage, resulting sometimes in bronchiectasis.[4,5,22,23]

Only 15% of the children in this study did not have prolonged troublesome respiratory symptoms; 45% have recovered from them but recurrent cough and/or wheeze still persists in 40%. In this last group 2 children were diagnosed after some years as asthmatic and 1 has developed bilateral bronchiectasis.

In children with wheezing as the prominent symptom there was a close family history in 62%, 23% had wheezed before the episode of pneumonia, and over 50% had some form of abnormal lung function. In comparison, among those who complained only of recurrent cough or who were symptom-free the proportion from an atopic family was less, and significantly fewer (18%) had abnormalities of lung function. Mok and Simpson[6] found that on follow-up after ALRTI the outcome of atopic subjects did not differ from that in children who were non-atopic, as did Henry *et al.*[2] However, in the series reported by Fernald *et al.*[15] most children with chronic pulmonary symptoms after ALRTI were atopic. The importance of the effect of wheezing compared with non-wheezing ALTRI on lung function after 5 - 15 years' follow-up was noted by Voter *et al.*[24]

Other factors which increase the likelihood of chronic clinical and functional sequelae after ALRTI are crowded urban settings, large families, poverty, day-centre care, and infection before 2 years of age.[10,12] The children in this study lived in over-crowded peri-urban housing, and 50% of them showed chronic nutritional deprivation (stunting) and 30% more acute malnutrition (decreased weight for age) and most were very young when they contracted pneumonia.

One-third of the children in the present series had abnormal lung function detected by the simple testing methods employed and this incidence did not decrease with the passage of time. Twelve children had obstructive features: 5 of large airways only (FEV_1 and PEFR) and 7 had reduced FEF_{25-75}, suggesting small airway disease. In 4 of the children with reduced airway calibre bronchial hyperreactivity was also present. In a further 9 children the abnormality was restricted to airway hyperreactivity: half had exercise-induced bronchospasm and the others showed excessive bronchodilation after a nebulised β-agonist.

These lung function abnormalities conform with previous follow-up studies of ALRTI in infancy. Reduced absolute values of FEV_1 or FEV/FVC have been demonstrated with an incidence of up to 60%.[8,9,15] Thoracic gas volume and airway resistance measured by plethysmography were found to be

increased in 50% and 25% of children, respectively, by Henry *et al.*[2] Reduced flow in the middle and latter portion of vital capacity reflecting mainly peripheral airway obstruction also occurs.[1,3,9] Bronchial hyperreactivity can occur in genetically susceptible individuals as well as after upper and lower respiratory tract insults.[1,6,12,25]

The present group of underprivileged children did not show noticeably worse morbidity after ALRTI than their more fortunate counterparts reported in medical publications. This is surprising, since mortality from ALRTI is highest in developing communities.

There is debate whether ALRTI in early childhood with its sequelae of increased respiratory symptoms, impaired peripheral airway calibre and bronchial hyperreactivity is a risk factor for the development of chronic obstructive airflow disease in later life. Retrospective studies depend on recall of childhood illness and prospective studies from infancy are needed to prove an association, but none are of sufficient duration as yet. At present the question remains unanswered.[26,27]

The prolonged persistence of chest radiographic abnormalities was most striking. Indeed some radiographs never returned to normal during the period of observation, although there was a tendency for the proportion of children with complete clearing to increase from 40% at 2 - 3 years follow-up to 60% at 5 - 6 years. Both increased bronchial wall thickness and persistent airspace disease were common in the present series, but hyper-inflation was unusual. The specific viral aetiology of the index illness, where it was known, did not influence the incidence of radiographic sequelae.

Housten *et al.*[17] reported an increase in radiographic bronchial-wall thickness persisting after pneumonia in North American Indian children, comparable to the abnormality seen in children with cystic fibrosis or bronchiectasis. They noted the absence of persisting changes in radiographs of white and, by inference, more privileged children. Prolonged radiographic abnormalities after adenovirus infection in infancy occur in 38 - 53% of cases for up to 5 years of follow-up and include consolidation, increased interstitial markings, bronchial-wall disease and hyper-inflation.[28,29]

In this series of underprivileged children 50% of whom were undernourished, clinical and lung function sequelae after pneumonia are in frequency and specific character comparable to studies from developed communities. The damaging infection was less commonly RSV and more commonly measles, influenzae, para-influenzae and adenovirus. The relationship between post-pneumonic recurrent wheezing and abnormal lung function was again noted.

The frequency of persistent, often subtle changes, in chest radiographs is clinically important. Implications in the acute illness are that, despite continued radiographic abnormalities, prolonged antibiotic therapy is usually not warranted after temperature dehiscence. In the chronic phase recurrent pulmonary symptoms with abnormal chest radiographs may be mismanaged with repeated courses of antibiotics. Appropriate therapy is as for other conditions of chronic lower respiratory damage: i.e. chest physiotherapy and bronchodilators for the bronchial hyperreactivity that so commonly occurs.

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