Impact of HIV-1 status on the radiological presentation and clinical outcome of children with WHO defined community-acquired severe pneumonia

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Arch Dis Child 2007;92:976-979. doi: 10.1136/adc.2006.104406

Aims: We compared the radiological features and outcome of WHO defined severe pneumonia among HIV infected and exposed uninfected children randomised to receive penicillin or oral amoxicillin in Durban, South Africa.

Methods: Of 425 children aged between 3 and 59 months with WHO defined severe pneumonia, 366 had anonymous HIV testing performed. Outcome was assessed by failure to improve at 48 h after enrolment or deterioration within 14 days. Chest radiographs were evaluated according to WHO defined radiological criteria for pneumonia and internationally standardised radiological criteria. Findings were stratified for HIV status.

Results: 82 (22.4%) children were HIV infected, 40 (10.9%) were HIV exposed and 244 (66.7%) were HIV uninfected. The day 14 outcome in children <12 months of age was significantly worse in HIV-1 infected than HIV uninfected children (OR 2.8 (95% CI 1.35 to 3.5), $p=0.002$), while HIV-1 infected and uninfected children aged ≥ 12 months had equivalent outcomes. Parental penicillin and oral amoxicillin had equivalent response rates in all HIV groups. According to the WHO radiological classification, children who failed WHO standard antimicrobial treatment had significantly higher "other consolidates/infiltrates" than "endpoints for consolidation" in the HIV infected group (OR 5.45 (95% CI 1.58 to 21.38), $p<0.002$), while the reverse was true for HIV exposed uninfected children (OR 4.13 (95% CI 0.88 to 20.57), $p<0.036$).

Conclusions: The WHO standard treatment guideline for severe pneumonia is inadequate for HIV-1 infected infants. The increased prevalence of "other consolidates/infiltrates" among HIV-1 infected children who failed standard treatment supports the addition of co-trimoxazole to WHO standard treatment.

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Accepted 18 June 2007
Published Online First
26 June 2007

The global incidence of acute lower respiratory infections (ALRI) is 154 million new episodes per annum with 7-13% of patients requiring hospitalisation.¹ ALRI causes 1.9 million deaths among children annually, accounting for over a fifth of all deaths in Africa.² The World Health Organization (WHO) response to this burden of disease has been the introduction of standard case management guidelines. The benefit of this intervention in HIV non-endemic areas was recently shown in a meta-analysis where pneumonia related mortality among neonates, infants and children between 0 and 4 years of age was reduced by 27%, 27% and 20%, respectively.³ The HIV-1 epidemic has altered the prevalence, presentation and outcome of ALRI.

The role of chest radiographs in the management of children with ALRI has had mixed reviews. Some studies suggest that radiographs help confirm the diagnosis of pneumonia in only 36% of episodes, help change the diagnosis in approximately 20% of cases and result in a change in treatment plan in 34%.^{4,5} The chest radiographic features of HIV associated pneumonia in childhood have scarcely been reported. Sivit *et al* described the radiological features of *Pneumocystis jiroveci* (carinii) pneumonia in infancy (PCP) and found that a ground glass interstitial appearance with pulmonary air cysts and thoracic air leak syndromes were common.⁶ The WHO has defined radiological criteria to assist in the determination of bacterial pneumonia in their vaccine trials on streptococcal pneumonia.⁷ While several studies have described the aetiology of HIV related pneumonia in children, none have evaluated the differences in radiology and response rates to standard WHO therapy.

We therefore performed a prospective nested substudy of a larger international pneumonia study⁸ to define the radiological

features on admission and clinical response at day 14 of HIV-1 infected and exposed children with WHO defined severe pneumonia treated with either oral amoxicillin or injectable penicillin.

METHODS

Children between 3 and 59 months of age with WHO defined severe pneumonia, enrolled at one of the nine study sites, King Edward VIII Hospital, Durban, South Africa, were entered into this study. The criteria for WHO defined severe pneumonia included presence of cough, tachypnea and chest indrawing and standardised treatment includes parental penicillin for 48 h followed by oral amoxicillin or oral amoxicillin alone. Treatment failure was defined as failure to improve on prescribed therapy by 48 h or deterioration in respiratory status as evidenced by increasing respiratory rates and chest indrawing, increasing oxygen requirements and onset of danger signs at any point during the 14-day study period.

Children were included in the study if they had fast breathing, cough, fever and chest indrawing (WHO defined severe pneumonia), they did not respond to two doses of salbutamol if wheeze was present, and parents had provided written informed consent. Children with danger signs of very severe pneumonia, severe malnutrition (weight for age z scores less than -3), chronic cardiopulmonary conditions, asthma or measles, or penicillin allergies were excluded at screening. All children had a posterior/anterior chest radiograph performed on admission.

Abbreviations: ALRI, acute lower respiratory infections; DSMB, data and safety monitoring board; PCP, *Pneumocystis jiroveci* (carinii) pneumonia

Table 1 Baseline characteristics of the children

Characteristics	HIV infected, n = 82 (%)	HIV exposed uninfected, n = 40 (%)	HIV uninfected, n = 244 (%)	OR (95% CI) HIV infected vs uninfected
Male	48 (58.5)	24 (60)	133 (54.5)	1.07 (0.87 to 1.33)
<12 months of age	27 (32.9)	37 (92.5)	88 (36.1)	0.91 (0.64 to 1.3)
Malnourished	17 (20.7)	4 (10)	30 (12.3)	1.69 (0.98 to 2.89)
Respiratory rate >60 bpm	36 (43.9)	9 (22.5)*	84 (34.4)*	1.28 (0.94 to 1.72)
Saturation <90%	5 (6.1)	5 (12.5)†	17 (7)†	0.88 (0.33 to 2.3)
Amoxicillin treatment group	32 (39)	20 (50)	130 (53.3)	0.73 (0.55 to 0.98)

*OR 0.65 (95% CI 0.36 to 1.19); †OR 1.79 (95% CI 0.7 to 4.59).

Statistical analysis was not performed on the age of HIV exposed versus HIV infected or uninfected children because of skewed sample by definition.

The primary endpoint of the study was to determine the impact of HIV disease on the outcome of WHO defined severe pneumonia and the usefulness of chest radiography in determining the risk of treatment failure.

A second consent for anonymous linked HIV-1 testing was obtained with HIV pretest counselling and a clear explanation of the following protocol. Samples were taken, labelled with the study number and stored for later analysis. These samples were tested at the end of patient recruitment and just before data analysis. An HIV-1 ELISA antibody test (Determine, Abbott Laboratories, Johannesburg, South Africa) was performed. Samples from children less than 15 months old with a positive HIV-1 ELISA test were re-tested with an HIV-1 DNA PCR test (Amplicor, Roche Diagnostics, Basel, Switzerland), while children over 15 months old had a repeat HIV-1 ELISA test. Children with a positive HIV DNA PCR result or those with two positive HIV-1 ELISA tests (if >15 months old) were regarded as HIV-1 infected, while children under 15 months of age who were HIV-1 ELISA positive but PCR negative were regarded as HIV exposed. Children who were HIV ELISA negative were regarded as HIV uninfected. Patients who refused this test were still included in the study but were regarded as HIV untested.

The study was approved by the ethics committee of the University of KwaZulu-Natal and monitored by an independent data and safety monitoring board (DSMB). Initially all children with WHO defined severe pneumonia regardless of their HIV status were enrolled with consent. During the second interim analysis, the DSMB recommended expansion of the exclusion criteria to omit children with known or clinically suspected HIV disease based on the evidence that PCP had become increasingly recognised as an important pathogen in HIV seropositive children and was not covered by the study treatments. This change was accepted and implemented. Anonymous HIV-1 screening continued until the end of the study.

The radiographic findings were interpreted according to predefined criteria by independent radiologists. Radiological features and the site of involvement were evaluated according to the proposed WHO radiological classification for pneumonia.⁹⁻¹⁰

A WHO defined endpoint for consolidation was a dense opacity that may be fluffy consolidation (dense, often homogenous (confluent) opacity) of a portion or whole of a lobe, often containing air bronchograms and sometimes associated with a pleural effusion (dense opacification within the pleural space). Atelectasis, a dense opacity and a positive silhouette sign with the mediastinal border, was considered to be an endpoint for consolidation.

Other consolidation/infiltrates were defined as linear and patchy in-homogenous airspace densities in a lacy pattern involving both lung fields and featuring peribronchial thickening, perivascular cuffing, nodular or reticular nodular changes and multiple small areas of atelectasis and hyperinflation. These included interstitial infiltrates and bronchopneumonia with perihilar/paratracheal lymphadenopathy.

A chest radiograph was considered to be normal when no abnormal opacities were seen.

The admission radiographic findings of HIV infected exposed and uninfected children were compared. The radiological findings of children who failed to clinically respond were evaluated according to HIV status.

Statistical analysis

All data were analysed with SPSS 11.5 for Windows (SPSS, Chicago, IL). Analyses were performed using the Student t test for continuous variables and the χ^2 and Fisher exact tests for categorical variables. Any two-tailed p value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 425 children with WHO defined severe pneumonia were entered into the study. Of these, HIV-1 status was determined in 366 (86.1%). Fifty nine children (13.9%) did not have their status determined and were classified as HIV untested. The outcome and radiological features in these children did not bias the data and consequently these children were omitted from further analysis. Eighty two of the 366 children tested (22.4%) were HIV infected, 40 (10.9%) were HIV exposed uninfected and 244 (66.7%) were HIV uninfected. The

Table 2 Treatment outcome at 14 days by age and HIV status

Characteristics	HIV-1 infected, n = 82 (%)	HIV-1 exposed, n = 40 (%)	HIV uninfected, n = 244 (%)	OR (95% CI) and p values for the comparison of outcomes HIV infected vs HIV uninfected
Overall treatment failures (n = 65)	20 (24.4)	9 (22.5)	36 (14.8)	1.53 (0.92 to 2.55), $p = 0.02$
Treatment failures				
Age 2–11 months	11/27 (40.7)	9/37 (24.3)*	17/88 (19.3)	2.8 (1.35 to 3.5), $p = 0.002$
Age 12–59 months	9/55 (16.4)	0/3 (0)	19/156 (12.2)	1.4 (0.88 to 2.8), $p = 0.59$
Deaths* (n = 5)	3 (3.6)	1 (2.5)	1 (0.4)	–

*Deaths also reflect non-responders and no statistical analyses were performed because of small sample size.

Table 3 Description and comparison of radiological endpoints with HIV status among children with WHO defined severe pneumonia that responded or failed to respond to standard WHO recommended therapy

HIV status	WHO defined radiological features of pneumonia						Statistics Comparison of “endpoint for consolidation” with “other infiltrates” in non-responders, OR (95% CI) and p values
	Endpoint for consolidation		Other infiltrates		Normal chest radiograph		
	Overall prevalence, n (%)	Prevalence in non-responders, n (%)	Overall prevalence, n (%)	Prevalence in non-responders, n (%)	Overall prevalence, n (%)	Prevalence in non-responders, n (%)	
HIV infected (n=82)	45 (54.9)	5 (11.1)	37 (45.1)	15 (40.5)	0 (–)	0	5.45 (1.58 to 21.38), p=0.002
HIV exposed (n=40)	16 (40)	5 (31.3)	23 (57.5)	3 (13.0)	1 (2.5)	1 (100)	4.13 (0.88 to 20.57), p=0.036
HIV uninfected (n=244)	84 (34.6)*	20 (13.7)	158 (64.8)*	25 (15.8)	2 (0.8)	1 (66.7)	0.82 (0.52 to 12.1), p=0.72
Overall radiological features	145 (39.6)	20 (13.7)	218 (59.6)	43 (19.7)	3 (0.008)	2 (66.7)	0.65 (0.52 to 21.38), p=0.62

mean age of these subjects was 17 months (range 3–58 months) and the male to female ratio was 1.24:1 (table 1).

Treatment failure rates on day 14

The overall treatment failure rate for the 425 children enrolled on an intent-to-treat analysis was 16.7% (n = 72) and this was equally distributed in the oral amoxicillin and parental penicillin arms (16.7 vs 17.1%, respectively). Among the children where HIV status was determined (n = 366), the treatment failure rate was 17.7% (n = 65), being equally distributed in both treatment arms for all HIV groups. Treatment failure rates among the HIV infected, HIV exposed and HIV uninfected children were 24.4%, 22.5% and 14.8%, respectively (table 2). A similar trend was seen for deaths. Age less than 1 year was a predictor of worse outcome in the HIV infected and uninfected groups (p = 0.027 and p = 0.04, respectively). Higher treatment failure rates were recorded for the HIV-1 infected than the HIV uninfected infants. In children older than 12 months of age, similar rates of treatment failure were recorded for HIV-1 infected and uninfected children.

Radiographic characteristics on admission

Overall, 39.6% of children with severe pneumonia had a WHO defined radiographic endpoint equivalent of consolidation and 59.6% had other infiltrates. Three children had normal chest radiographs (table 3). "Endpoint for consolidation" was recognised in a significantly higher proportion of HIV infected than HIV uninfected children, while "other infiltrates" (patchy consolidation) was more common in HIV uninfected than HIV-1 infected children. Among the HIV infected and HIV exposed group, segmental parenchymal lung involvement was more commonly seen in the left lower lobe (51.1% and 50.0%, respectively), while HIV uninfected children frequently had bilateral and paracardiac/perihilar patchy changes (29.2% and 26.5%, respectively). Lobar changes were rarely seen in any of three groups. A higher proportion of HIV infected children with "other infiltrates" than "endpoint for consolidation" failed to respond to either oral amoxicillin or injectable penicillin, while a higher proportion of HIV exposed uninfected children with "endpoint for consolidation" failed therapy. Fifty eight (15.8%) children with WHO clinically defined severe pneumonia had chest radiographic features suggestive of bronchiolitis (hyperinflation with air trapping).

DISCUSSION

The main finding of this study was the three-fold poorer response of HIV infected infants with WHO defined severe pneumonia to recommended standard antibiotic therapy than HIV exposed and uninfected infants. Overall, infants with WHO defined severe pneumonia had a significantly poorer outcome

than children aged 12 months and over, regardless of HIV status. These findings have practical relevance in resource-poor countries and suggest the need to revise WHO standard acute respiratory infection (ARI) case management guidelines in HIV endemic areas. We did not investigate the aetiological agents in children with treatment failure, but recent ante-mortem and post-mortem studies of HIV infected infants have confirmed an increased burden of *P. jiroveci* and other Gram-negative bacterial pathogens at this age.¹¹ In HIV endemic areas, the routine administration of high dose co-trimoxazole and broad spectrum antibiotics for the treatment of severe pneumonia in infancy should be considered. Further studies to confirm the benefits of these interventions prior to revising WHO ARI case management guidelines are needed. On the other hand, children over the age of 12 months respond well to standard antimicrobial therapy regardless of their HIV status.

The main radiological finding of this study was the higher treatment failure rates in HIV infected children with "other consolidation/infiltrates" as compared to "endpoint for consolidation", even though the latter was more common in the HIV infected group. "Other consolidation/infiltrates" may represent viral pathogens or PCP, which are unlikely to respond to standard WHO recommended antimicrobials, supporting the need for co-trimoxazole. Although 60% of children had WHO defined "other consolidation/infiltrates" overall, HIV infected children had more "endpoints for consolidation" than "other consolidation/infiltrates". Children with "endpoints for consolidation" would be expected to respond to WHO standardised antimicrobial therapy as the WHO radiographic classification was based on an attempt to identify bacterial pneumonia as "endpoint consolidation" in the vaccine trials.⁷ The predictive value of radiological appearance in determining the aetiology of pneumonia in HIV infected children is further confounded by the frequent occurrence of mixed infections with bacteria and viruses. Studies have confirmed the role of purulent Gram-positive and Gram-negative bacteria, cytomegalovirus and tuberculosis in these children.^{11 12} Madhi *et al* in a recent publication on the role of influenza in lower respiratory tract infection showed a 78.1% bacterial co-infection rate in HIV-1 infected children as compared to a 35.1% bacterial co-infection rate in uninfected children.¹³ The distribution of lung disease in determining the likelihood for HIV disease was of limited value.

Some limitations of this study must be taken into consideration. The lack of lateral or follow-up chest radiographs and the omission of microbiology testing to determine the aetiology of treatment failures in this cohort prevent confirmation of the reasons for the poorer outcomes.

In conclusion, this study clearly demonstrates the negative effect of HIV-1 infection on the outcome of severe pneumonia in infancy. According to WHO defined radiological criteria, a

What is already known on this topic

- Children with WHO defined severe pneumonia are treated worldwide with the standardised antimicrobial therapy of either parental penicillin or oral amoxicillin.
- The radiological features of these children are non-specific and do not help in the choice of antimicrobial therapy.

What this study adds

- HIV-1 infected infants with WHO defined severe pneumonia had a three-fold increased rate of treatment failure following standardised antimicrobial therapy with either parental penicillin or oral amoxicillin.
- HIV-1 infected children with WHO defined "other consolidation/infiltrates" on chest radiography are more likely to fail on the standardised antimicrobial therapy of parental penicillin or oral amoxicillin than children with "endpoint for consolidation".

preponderance of "other infiltrates" was demonstrated in these children. The addition of co-trimoxazole to standard antibiotics should be urgently considered.

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Competing interests: None.

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