Chest X-ray Findings in Children Hospitalized with WHO Defined Severe, Very Severe Pneumonia in a High HIV Prevalence Setting in the Era of Bacterial Conjugate Vaccines

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INTRODUCTION

- Pneumonia is the leading infectious cause of morbidity and mortality in children under 5 years globally, accounting for 18% of deaths in this age group.
- *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib) are the most important causes of vaccine-preventable pneumonia deaths in the absence of vaccination against these pathogens.
- HIV has affected the epidemiology of childhood pneumonia, changing the profile of pathogens causing pneumonia, antimicrobial susceptibility and prognostic outcome.
- In the African setting, HIV-Exposed-Uninfected (HEU) infants have two to four times higher mortality compared to HIV-unexposed infants, and pneumonia is an important cause.
- The chest X-ray remains the most readily available and commonest imaging modality for the assessment of childhood pneumonia, especially in resource limited countries.

OBJECTIVES

- To describe chest X-ray patterns in HIV-infected, HEU and HIV-unexposed children under 5 years hospitalized with WHO-defined severe, very severe pneumonia.
- To compare chest X-ray findings of HIV-infected with HIV-unexposed children, and HEU with HIV-unexposed children.

METHODS

- This study was nested within the prospective PERCH study, South African site.
- Children hospitalized with WHO-defined severe, very severe pneumonia in Soweto, Johannesburg, were enrolled over two years (August 2011 to August 2013).
- Chest X-rays were interpreted by 3 radiologists in South Africa independently, blinded to all clinical data, using modified WHO standardized chest X-ray interpretation criteria on customized report formatting. WHO end-point pneumonia (CXR-PEP) was defined as either airspace disease and /or pleural disease; which may include other infiltrate. Other infiltrate (OI) only excluded WHO end-point pneumonia. The majority consensus reading was used for analyses.

RESULTS

- 920 cases with WHO-defined severe or very severe pneumonia were enrolled, of whom CXRs wee available in 885 (96%) cases.
- **858 (93%) children had interpretable chest X-rays.**
- Median age 6 months (interquartile range, 2 to 12 months) , mean age 9.04 months
- 108 (13%) cases were HIV- infected, 284 (33%) HEU and 428 (50%) HIV-unexposed. Thirty-eight (4%) cases HIV-Exposure status was unknown.
- The commonest chest X-ray finding in all children was **WHO CXR-PEP**, prevalent among **60% of HIV-infected, 33% HEU and 38% HIV-unexposed children.** WHO CXR-PEP was primarily due to airspace disease; prevalent in 60% of HIV-infected, 32% HEU and 38% HIV-unexposed children.

- **WHO CXR-PEP** was twice as common in HIV-infected compared with HIV-unexposed children (OR 2.5; 95% CI 1.6-3.8).
- **Air space disease**: lobar consolidation was the commonest finding in all 3 groups, and was more common in HIV-infected (31%) compared with HIV-unexposed children (22%) (OR 1.6; 95% CI 1.0-2.5).
- Multi-lobar consolidation was more common in HIV-infected (17%) compared with HIV-unexposed children (8%) (OR 2.2; 95% CI 1.2-4.0).
- Similarly segmental/ sub-segmental consolidation was more common in HIV-infected (14%) compared with HIV-unexposed children (7%) (OR 2.0; 95% CI 1.1-3.8).
- Volume loss/lung collapse was similar across the 3 groups (9-11%). Lung expansion/ bulging fissure was found in 1%, while lung abscess was not found. Refer Table 1.

- **Pleural disease** was uncommon in the 3 groups (2-7%) and was due to pleural effusions. Pleural disease was four times as common in HIV-infected children (7%; OR 3.7; 95% CI 1 .4-9.9) compared to HIV-unexposed children (2%). Refer Table.

- **Other infiltrate**: reticular pattern was the commonest finding (18-28%), and was more common in HIV-infected (28%) compared with HIV-unexposed children (18%) (OR 1.7; 95% CI 1.1-2.9).
- Similarly, miliary infiltrate was more common in HIV-infected (13%) compared with HIV-unexposed children (6%) (OR 2.4; 95% CI 1.2-4.8).
- Ground glass infiltrate (3-6%), peri-bronchial thickening (6-10%), reticular-nodular infiltrate (3-6%), large nodular infiltrate (1-3%) and peri-hilar streakiness (5-7%) were uncommon in all 3 age categories, with no significant difference between HIV-infected compared to HIV-unexposed children, and HEU compared to HIV-unexposed children.
- **Other infiltrate only** (other infiltrate without WHO end-point pneumonia) was more common in HEU (27%) compared with HIV-unexposed children (21%) (OR 1.4; 95% CI 1.0-2.0). Refer Table.

- **Chronic lung disease** was uncommon (1-5%) in all 3 groups. Bronchiectasis was more prevalent in HIV-infected (4%) compared to HIV-unexposed children (1%) (OR 5.4; 95% CI 1.2-24.7). Refer Table.

- **Intrathoracic lymphadenopathy** was prevalent in 14-17% of children, with no significant difference between HIV-infected compared to HIV-unexposed children and HEU compared to HIV-unexposed children.
- The commonest pattern under intrathoracic lymphadenopathy was the doughnut sign (13-14%), followed by hilar mediastinal masses (5-8%), which occurred with similar prevalence across the 3 groups.

- **Bilateral air trapping** and **cardiomegaly** were prevalent in 14-19% and 4-5% children, respectively, with no significant difference between HIV-infected compared to HIV-unexposed children and HEU compared to HIV-unexposed children. Refer Table 1

Table 1: Chest X-ray findings in Children Stratified by HIV Status

Chest X ray Pattern	HIV infected N=108 n (%)	HEU* N=284 n (%)	HIV unexposed N=428 n (%)	HIV infected vs. HIV unexposed OR (95% CI)	HEU vs. HIV unexposed OR (95% CI)
Airspace disease	**65 (60)**	**91 (32)**	**163 (38)**	**2.5 (1.6-3.8)**	**0.8 (0.6-1.1)**
Sub segmental/sub segmental	15 (14)	16 (6)	32 (7)	**2.0 (1.1-3.8)**	0.7 (0.4-1.4)
Lobar	34 (31)	46 (16)	96 (22)	**1.6 (1.0-2.5)**	0.7 (0.5-1.1)
Multi-lobar	18 (17)	31 (11)	36 (8)	**2.2 (1.2-4.0)**	1.3 (0.8-2.2)
Volume loss/lung collapse	12 (11)	26 (9)	48 (11)	1.0 (0.5-1.9)	0.8 (0.5-1.3)
Expansion/bulging fissure	0 (0)	0 (0)	1 (1)	1.0	1.0
Lung abscess	0 (0)	0 (0)	0 (0)	-	-
Pleural disease	**8 (7)**	**9 (3)**	**9 (2)**	**3.7 (1.4-9.9)**	**1.5 (0.6-3.9)**
Pneumothorax	1 (1)	2 (1)	2 (1)	2.0 (0.2-22.2)	1.5 (0.2-10.8)
Pleural effusion	7 (7)	7 (3)	7 (2)	**4.2 (1.4-12.2)**	1.5 (0.5-4.4)
Pleural plaques/calcification	0 (0)	0 (0)	0 (0)	-	-
WHO end-point pneumonia	**65 (60)**	**94 (33)**	**163 (38)**	**2.5 (1.6-3.8)**	**0.8 (0.6-1.1)**
Other infiltrate	**55 (51)**	**103 (36)**	**131 (31)**	**2.4 (1.5-3.6)**	**1.3 (0.9-1.7)**
Peribronchial thickening	11 (10)	17 (6)	29 (7)	1.6 (0.8-3.2)	0.9 (0.5-1.6)
Reticulo-nodular infiltrate	6 (6)	10 (4)	12 (3)	2.0 (0.7-5.6)	1.2 (0.5-3.0)
Reticular infiltrate	30 (28)	60 (21)	77 (18)	**1.7 (1.1-2.9)**	1.2 (0.8-1.8)
Millary infiltrate (nodules < 2mm)	14 (13)	17 (6)	25 (6)	**2.4 (1.2-4.8)**	1.0 (0.5-1.9)
Large nodular infiltrate (nodules > 2mm)	3 (3)	1 (1)	4 (1)	3.0 (0.7-13.7)	0.4 (0-3.4)
Perihilar streakiness	8 (7)	21 (7)	21 (5)	1.6 (0.7-3.6)	1.5 (0.8-2.9)
Ground glass infiltrate	6 (6)	15 (5)	13 (3)	1.9 (0.7-5.1)	1.8 (0.8-3.8)
Other infiltrate only	**29 (27)**	**77 (27)**	**88 (21)**	**1.4 (0.9-2.3)**	**1.4 (1.0-2.0)**
Chronic lung disease	**5 (5)**	**4 (1)**	**5 (1)**	**4.1 (1.2-14.5)**	**1.2 (0.3-4.5)**
Fibroses	0 (0)	0 (0)	0 (0)	-	-
Bronchiectasis	4 (4)	3 (1)	3 (1)	**5.4 (1.2-24.7)**	1.5 (0.3-7.5)
Cavities	1 (1)	1 (1)	2 (1)	2.0 (0.2-22.2)	0.8 (0.1-8.3)
Intrathoracic lymphadenopathy	**18 (17)**	**41 (14)**	**68 (16)**	**1.1 (0.6-1.9)**	**0.9 (0.6-1.4)**
Hilar or mediastinal masses	5 (5)	18 (6)	34 (8)	0.6 (0.2-1.5)	0.8 (0.4-1.4)
Hilar elevation	0 (0)	0 (0)	0 (0)	-	-
Mediastinal shift	0 (0)	0 (0)	0 (0)	-	-
Tracheal or bronchial compression	3 (3)	8 (3)	12 (3)	1.0 (0.3-3.6)	1.0 (0.4-2.5)
Unilateral air-trapping	1 (1)	2 (1)	3 (1)	1.3 (0.1-12.9)	1.0 (0.2-6.1)
Lobar collapses	1 (1)	0 (0)	2 (1)	2.0 (0.2-22.1)	1.0
Doughnut sign	15 (14)	36 (13)	60 (14)	1.0 (0.5-1.8)	0.9 (0.6-1.4)
Bilateral air trapping	**21 (19)**	**42 (15)**	**60 (14)**	**1.5 (0.9-2.7)**	**1.1 (0.7-1.6)**
Cardiomegaly	**6 (6)**	**15 (5)**	**18 (4)**	**1.3 (0.5-3.5)**	**1.3 (0.6-2.6)**
Normal	**7 (6)**	**81 (29)**	**123 (29)**	**5.8 (2.6-12.9)**	**1.0 (0.7-1.4)**

CONCLUSION

- WHO end-point pneumonia (predominantly due to air space disease) remains the commonest chest X-ray abnormality in HIV-infected, HEU and HIV-unexposed children under 5 years hospitalized for WHO-defined severe, very-severe pneumonia, even in the era of routine Hib and pneumococcal immunization.

- HIV-infected children were more likely to have WHO end-point pneumonia and less likely to have normal chest X-rays compared with HIV-unexposed children.

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PERCH Pneumonia Etiology Research for Child Health

University of the Witwatersrand

VPD Vaccine Preventable Diseases RMPRU Respiratory & Meningeal Pathogens Research Unit