Are Chest X-ray Patterns Associated with Specific Clinical and Acute Phase Reactants in Children Hospitalized with WHO Defined Severe, Very Severe Pneumonia in a High HIV Prevalence Setting?

Mahomed N, Moore D P, Sewchuran T, Moodley H, Madhi S A and PERCH Team

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INTRODUCTION

- Pneumonia is the leading infectious cause of morbidity and mortality in children <5 years globally.
- *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib) are the most important causes of vaccine-preventable pneumonia deaths in children <5 years.
- The chest X-ray remains the most readily available imaging modality for the assessment of childhood pneumonia, especially in resource limited countries.

OBJECTIVES

To determine if chest X-ray patterns are associated with clinical and acute phase reactant parameters in HIV-unexposed, HIV-Exposed-Uninfected (HEU), and HIV-infected children hospitalized with WHO defined severe community acquired pneumonia.

METHODS

- This study was nested within PERCH project, South African site at Chris Hani Baragwanath Academic hospital, Soweto, Gauteng Province.
- Children hospitalized with WHO-defined severe or very severe pneumonia 28 days-59 months were prospective enrolled from 17 August 2011 to 31 August 2013 (2 years).
- Radiographic parameters and sub-parameters were developed using modified WHO standardized chest X-ray interpretation, with chest X-rays being classified as being primary end-point pneumonia ± other infiltrate (CXR-PEP), other infiltrate (OI) only, normal or uninterpretable.
- Chest X-rays were read independently by 3 South African radiologists blinded to all clinical, laboratory and immunological data. The majority consensus reading was used during data analysis.
- HEU was defined as a positive maternal HIV ELISA test with either a negative HIV PCR or HIV Viral load in a child < 18 months or negative HIV ELISA in a child ≥ 18 months
- Significant variables from univariate analyses (age, HIV status, malnutrition, hypoxia, tachypnea, wheeze) was incorporated into multivariate analyses, using stepwise logistic regression to determine the association between chest X-ray patterns, clinical parameters and acute phase reactants.

RESULTS

- 920 cases were enrolled
- 858 (96%) of 885 available CXRs were interpretable
- 108 (13%) HIV-infected, 284 (33%) HEU, N=108 and 428 (50%) HIV-unexposed
- Features predictive of CXR-PEP included presence of fever (71% vs 60%; aOR: 1.8; 95% CI:1.3-2.4), CRP >40mg/dl (40% vs 19%; aOR: 3.2; 95% CI:2.2-4.5), presence of serum antimicrobial activity (55% vs 47%; aOR:1.3; 95% CI:1.0-1.9) and mechanical ventilation (14% vs 5%; aOR 2.8; 95% CI 1.6-4.8).
- There was a non-significant association to death (9% vs 4%; aOR: 1.4; 95% CI: 0.7-0.3) hospital stay > 3 days (94% vs 91%; aOR 1.5; 95% CI 0.9-2.7).
- CXR-PEP was less likely to present with wheezing (21% vs 39%; aOR 0.5; 95% CI 0.3-0.7); Table 1.
- Conversely clinical diagnosed pneumonia cases in whom the CXR was evaluated as being normal were less likely to present with fever (49% vs 69%; aOR: 0.5; 95%CI: 0.3-0.6), tachypnea (72% vs 80%; aOR: 0.6; 95% CI: 0.4-0.9), require mechanical ventilation (4% vs 10%; aOR 0.4; 95% CI 0.2-0.8), have a CRP >40mg/dl (18% vs 30%; aOR 0.6; 95% CI:0.4-0.9) or have detectable serum antimicrobial activity (42% vs 53%; aOR: 0.6, 95% CI: 0.5-0.9).
- Also, presence of a normal CXR trended to be associated with lower likelihood of death (aOR: 0.5; 95% CI: 0.2-1.6).
- Aside from being less likely to have a CRP >40 mg/dl, (20% vs 29%; OR 0.6; 95% CI 0.4-0.8) there were no other clinical or laboratory associations observed in cases with an "other-infiltrate only"; Table 1.
- Exploring for associations of clinical and laboratory acute-phase reactant parameters to other CXR features indicated that those with bilateral air trapping were less likely to have a CRP >40 mg/dl; (18% vs 29%; OR 0.5; 95% CI 0.3-0.9), but 2-fold more likely to have wheezing (45% vs 30%; aOR 2.3; 1.5-3.5).
- In contrast, those with CXR features with chronic lung disease had a higher likelihood of having a CRP >40mg/dl (47% vs 26% aOR: 2.1; 95% CI: 1.1-4.1), as well as being more likely to having underlying malnutrition (64% vs 29%; aOR: 3.9; 95% CI:1.2-12.6); Table 1.

Table 1: Chest X-ray pattern association with clinical parameters and acute phase reactants all children using a multiple logistic regression model

All Children	CXR-PEP aOR (95% CI)	Other infiltrate only aOR (95% CI)	Intrathoracic Lymphadenopathy aOR (95% CI)	Chronic Lung disease aOR (95% CI)	Bilateral air trapping aOR (95% CI)	Normal chest X-ray aOR (95% CI)
Fever	**1.8 (1.3-1.4)**	1.1 (0.8-1.6)	1.4 (0.9-2.2)	0.8 (0.3-2.5)	1.0 (0.7-1.5)	**0.5 (0.3-0.6)**
Hypoxia	1.2 (0.8-1.7)	1.1 (0.7-1.6)	1.0 (0.6-1.6)	1.7 (0.4-6.4)	1.0 (0.6-1.5)	1.0 (0.7-1.5)
Tachypnea	1.0 (0.7-1.4)	1.1 (0.7-1.7)	1.3 (0.8-2.2)	0.6 (0.2-1.9)	1.5 (0.9-2.6)	**0.6 (0.4-0.9)**
Crackles	1.1 (0.8-1.6)	1.0 (0.7-1.4)	1.1 (0.7-1.6)	0.9 (0.3-3.2)	0.8 (0.6-1.3)	0.8 (0.6-1.2)
Malnutrition	**1.9 (1.4-2.7)**	0.8 (0.6-1.2)	1.0 (0.7-1.6)	**3.9 (1.2-12.6)**	1.0 (0.7-1.6)	**0.6 (0.4-0.9)**
Wheezing	**0.5 (0.3-0.7)**	1.1 (0.7-1.6)	1.4 (0.9-2.1)	1.1 (0.3-3.9)	**2.3 (1.5-3.5)**	1.3 (0.9-1.9)
Hospital stay ≥3 days	1.5 (0.9-2.7)	1.3 (0.7-2.4)	1.1 (0.5-2.1)	1	0.8 (0.4-1.5)	0.7 (0.4-1.1)
Mechanical Ventilation	**2.8 (1.6-4.8)**	0.9 (0.5-1.8)	**0.2 (0-0.8)**	0.9 (0.1-7.2)	0.6 (0.2-1.3)	**0.4 (0.2-0.8)**
Death within 30 days of hospitalization	1.4 (0.7-3.0)	1.5 (0.7-3.3)	0.2 (0.1-1.4)	1.0	0.5 (0.2-1.8)	0.5 (0.2-1.6)
Raised CRP	**3.2 (2.2-4.5)**	**0.6 (0.4-0.8)**	0.7 (0.4-1.1)	**2.1 (1.1-4.1)**	**0.5 (0.3-0.9)**	**0.6 (0.4-0.9)**
Leucocytosis	1.2 (0.9-1.6)	0.8 (0.5-1.1)	0.8 (0.6-1.2)	1.0 (0.4-3.1)	0.9 (0.6-1.3)	1.0 (0.7-1.4)
Positive Antibiotic serum activity	**1.3 (1.0-1.9)**	1.2 (0.9-1.7)	1.0 (0.6-1.4)	1.4 (0.5-4.2)	0.9 (0.6-1.3)	**0.6 (0.5-0.9)**
PCV partially vaccinated	1.2 (0.8-1.8)	0.8 (0.5-1.3)	1.4 (0.7-2.7)	1.2 (0.2-5.9)	1.8 (0.9-3.2)	0.9 (0.6-1.4)
PCV fully vaccinated	0.7 (0.5-1.1)	1.6 (0.9-2.6)	**2.1 (1.1-4.1)**	0.3 (0.1-1.5)	1.6 (0.8-3.0)	0.9 (0.6-1.5)
HIV-infected	**2.1 (1.3-3.3)**	1.5 (0.9-2.5)	1.0 (0.6-1.9)	2.3 (0.6-8.9)	1.6 (0.9-2.8)	**0.2 (0.1-0.4)**
HEU	0.8 (0.5-1.0)	**1.5 (1.0-2.1)**	0.9 (0.6-1.4)	1.1 (0.3-4.2)	1.1 (0.7-1.7)	1.0 (0.7-1.4)

aOR: Adjusted odds ratios were obtained using a multiple logistic regression model: adjusting for age, HIV status, malnutrition, hypoxia, tachypnea, wheeze
Fever: axillary temperature >38C on admission or history of fever in the past 48 hours
Hypoxia: O2 saturations < 90% on room air on admission or supplemental O2 requirement
Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute (bpm); Age 2-11 months RR >50 bpm; Age >12 months RR >40 bpm.
Malnutrition: Weight-for-age Z score ≤ -3 standard deviations (SD) below the mean using WHO growth standards
Death: Died < 30 days of discharge from hospital
Raised CRP: CRP >40 mg/dL
Leucocytosis: For age categories 1 and 2: white cell count >15 × 109/L, for age category 3: white cell count >13 × 109/L
Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter > 6mm
PCV partially vaccinated compared to PCV unvaccinated
PCV fully vaccinated compared to PCV unvaccinated
HIV-infected vs HIV-unexposed
HEU vs HIV-unexposed

CONCLUSIONS

- Features predictive of CXR-PEP included presence of fever, raised CRP >40mg/dl, presence of serum antimicrobial activity and mechanical ventilation.
- CXR-PEP was less likely to be present in children with wheezing.
- Conversely clinical diagnosed pneumonia cases in whom the CXR was evaluated as being normal were less likely to present with fever, tachypnea, require mechanical ventilation, have a CRP >40mg/dl or have detectable serum antimicrobial activity.
- Children with bilateral air trapping were less likely to have a CRP >40 mg/dl, but 2-fold more likely to have wheezing.
- Children with CXR features of chronic lung disease had a higher likelihood of having a CRP >40mg/dl (47% vs 26% aOR: 2.1; 95% CI: 1.1-4.1), as well as being more likely to having underlying malnutrition.

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Pneumonia Etiology Research for Child Health

University of the Witwatersrand

VPD
RMPRU
Respiratory & Meningeal Pathogens Research Unit