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Chest Radiographic Findings and Outcomes of Pneumonia Among Children in Botswana

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Abstract

Background—Chest radiography is increasingly used to diagnose pneumonia in low- and middle-income countries. Few studies examined whether chest radiographic findings predict outcomes of children with clinically suspected pneumonia in these settings.

Methods—Hospital-based, prospective cohort study of children 1-23 months of age meeting clinical criteria for pneumonia in Botswana. Chest radiographs were reviewed by two pediatric radiologists to generate a consensus interpretation using standardized World Health Organization criteria. We assessed whether final chest radiograph classification was associated with our primary outcome, treatment failure at 48 hours, and secondary outcomes.

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Results—From April 2012 to November 2014, we enrolled 249 children with evaluable chest radiographs. Median age was 6.1 months and 58% were male. Chest radiograph classifications were primary end-point pneumonia (35%), other infiltrate/abnormality (42%), or no significant pathology (22%). The prevalence of end-point consolidation was higher in children with HIV infection (P=0.0005), while end-point pleural effusions were more frequent among children with moderate or severe malnutrition (P=0.0003). Ninety-one (37%) children failed treatment and 12 (4.8%) children died. Primary end-point pneumonia was associated with an increased risk of treatment failure at 48 hours (P=0.002), a requirement for more days of respiratory support (P=0.002), and a longer length of stay (P=0.0003) compared with no significant pathology. Primary end-point pneumonia also predicted a higher risk of treatment failure than other infiltrate/abnormality (P=0.004).

Conclusions—Chest radiograph provides useful prognostic information for children meeting clinical criteria for pneumonia in Botswana. These findings highlight the potential benefit of expanded global access to diagnostic radiology services.

Keywords

childhood pneumonia; chest radiograph; outcomes

Introduction

Pneumonia is the leading killer of children worldwide, accounting for an estimated 900,000 deaths in 2013.[1] More than 99% of pneumonia-related deaths among children occur in low- and middle-income countries (LMICs).[1] Although chest radiograph is the preferred diagnostic modality for pneumonia, less than half of the world's population has access to basic radiology services.[2, 3] Historically, there have been several barriers to use of chest radiography in LMICs. Health care facilities may lack reliable access to the electricity needed to power radiography equipment or the water required for film development.[2] Moreover, the cost of radiography machines may be prohibitive for many hospitals in LMICs, while frequent equipment maintenance may be infeasible because of the poor accessibility of some facilities by road. Finally, despite the higher burden of lower respiratory infections, many LMICs have few or no radiologists available for interpretation of chest radiographs.[2]

However, several technological advances are likely to improve global accessibility to diagnostic radiography services. The most significant of these advances was the development of digital radiography, which uses digital x-ray sensors instead of the photographic film used in conventional radiography.[4] Digital radiography has largely supplanted conventional radiography in developed countries, and it is being used with increasing frequency in LMICs.[4] The main advantage of digital radiography systems is that they generate an electronic image that can be digitally enhanced using computer software or transferred over the internet for remote review.[5] Digital radiography and teleradiology services have already enabled many facilities in LMICs to overcome a current lack of trained radiologists, while computer-aided detection systems are likely to facilitate local interpretation of digital radiographs by non-radiologists.[6-8] Finally, the World Health Imaging System for Radiography (WHIS-RAD) is a radiography unit that was designed

specifically for use in LMICs, and can be operated on batteries or solar cells, requires minimal maintenance, and is less expensive than other conventional radiography machines.[9] As diagnostic radiology services become increasingly available in LMICs, an improved understanding of the utility of chest radiography in children with suspected pneumonia in these settings is needed. Within the context of a hospital-based, prospective cohort study, we examined whether findings on chest radiograph were associated with outcomes of children meeting clinical criteria for pneumonia. As a secondary objective, we explored differences in chest radiographic findings in the setting of HIV infection and moderate or severe malnutrition.

Materials and Methods

Setting

This study was conducted from April 2012 to November 2014 at a 550-bed tertiary hospital in Gaborone, Botswana. The country's HIV prevalence among adults aged 15-49 years is 21.9%.[10] *Haemophilus influenzae* type B conjugate vaccine was included in the country's immunization schedule in 2010, while pneumococcal conjugate vaccine (PCV-13) was introduced in July 2012.

Study population

Eligible children were 1 to 23 months of age with pneumonia, defined as "cough or difficulty in breathing with lower chest wall indrawing" by the World Health Organization (WHO).[11] The presence of one or more danger signs (central cyanosis, convulsions, inability to drink, or abnormal sleepiness) further classified children as having severe pneumonia.[11] We excluded children with a chronic medical condition predisposing to pneumonia (other than HIV), hospitalization in the prior 14 days, a diagnosis of asthma, or wheezing with resolution of lower chest wall indrawing after two or fewer bronchodilator treatments. All children were recruited within six hours of the triage time in the Emergency Department.

Clinical care was provided by medical officers and pediatric residents on a ward supervised by pediatric specialists. Supplemental oxygen and continuous positive airway pressure (CPAP) were routinely available, and there was limited access to mechanical ventilation in an intensive care unit. For patient care, chest radiographs were interpreted by non-radiologists on the pediatric medical team. Departmental guidelines for management of children with pneumonia were based on WHO guidelines, but antibiotic decisions were ultimately at the discretion of the treating pediatrician.

Data collection

Sociodemographic and clinical data were collected at enrollment from physical examination, review of infant and maternal medical records, and a detailed face-to-face interview with the child's caregiver(s). Research staff assessed children and reviewed hospital charts daily until discharge (or death), recording additional clinical information including antibiotic doses and level of respiratory support. Chest radiographs were downloaded as Digital Imaging and Communications in Medicine (DICOM) images from the hospital's Picture Archiving and

Communication System (PACS). After de-identification, two board-certified pediatric radiologists (EJC, MSR) reviewed the images independently and completed a standardized chest radiograph interpretation form. Any films for which there were discrepancies in the interpretations were reviewed together until a consensus was reached. Although the radiologists were aware that the images were from children meeting clinical criteria for pneumonia, they were otherwise blinded to enrollment and outcome data. Image quality and radiographic findings were classified using standardized WHO criteria.[12, 13] End-point consolidation was defined as "a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms and sometimes associated with pleural effusion." Other (non-end-point) infiltrates were "linear and patchy densities in a lacy pattern involving both lungs, featuring peribronchial thickening and multiple areas of atelectasis." End-point pleural effusion was fluid that is "in the lateral pleural space (and not just in the minor or oblique fissure) and is spatially associated with a pulmonary parenchymal infiltrate (including other infiltrate), or if the effusion obliterates enough of the hemithorax to obscure an opacity." Primary end-point pneumonia was identified by the presence of either end-point consolidation or endpoint pleural effusion. Final chest radiograph classification was: 1) primary end-point pneumonia, 2) other infiltrate/abnormality, or 3) no significant pathology.

HIV testing of HIV-exposed infants <18 months of age was performed using the Roche Amplicor 1.5 HIV DNA PCR (Roche, Alameda, CA). HIV-exposed infants ≥18 months were tested for HIV using dual parallel rapid testing with the Determine HIV 1/2 (Abbott Laboratories, North Chicago, IL) and Uni-Gold Recombigen HIV (Trinity Biotech, Inc., Wicklow, Ireland) tests. Moderate or severe malnutrition was defined as weight-for-length < −2 standard deviations on WHO growth curves, mid-upper arm circumference <125mm (for children ≥6 months), or bilateral edema of nutritional origin.[14]

Outcomes assessment

The primary outcome, treatment failure, was assessed at 48 hours by a study physician or nurse who was blinded to enrollment data. Treatment failure was defined as persistent lower chest wall indrawing, the development of new WHO danger signs, oxygen saturation <80% on room air, a requirement for CPAP or mechanical ventilation, or death. This definition was adapted for our setting from criteria used in a previous study of childhood pneumonia, and training sessions were held every three months during the study period to standardize the assessment process.[15] Children discharged before 48 hours were considered treatment responders but caregivers were contacted by telephone to confirm treatment response.

Secondary outcomes included days of respiratory support (supplemental oxygen, CPAP or mechanical ventilation), length of stay, and in-hospital mortality. For a given day, only the highest level of respiratory support required by a child was recorded. Length of stay was calculated from the Emergency Department triage time to the time of discharge from the ward.

Statistical analysis

For the purposes of these analyses, we included only children with an anterior/posterior image of the chest that was performed within one day of presentation to the hospital and was deemed by study radiologists to be of "adequate" quality using standardized WHO criteria.[12] Baseline characteristics of the population were described using frequencies and percentages for categorical variables and median and interquartile ranges (IQR) for continuous variables. We used Cox proportional hazards to directly estimate risk ratios (RR) for treatment failure at 48 hours according to final chest radiograph classification. Given the rightward-skewed distribution of days of respiratory support and length of stay, we used negative binomial regression to estimate incidence rate ratios (IRR) by final chest radiograph classification. All analyses adjusted for the following confounders identified a priori based on a literature review: young age (<6 months), HIV infection, moderate or severe malnutrition, and WHO pneumonia severity.[16-18] In addition, in constructing these models, we used a change-in-estimate approach to empirically test for confounding by the following variables: sex, low birth weight (<2500g), current breastfeeding, household use of wood as a cooking fuel, antibiotic treatment in the prior 7 days, caregiver-reported fever, and enrollment oxygen saturation <90% breathing room air. We included variables that were significant confounders of one or more exposure-outcome relationships in all final models. As antibiotic treatment may be an important determinant of outcomes and was likely informed in part by radiographic findings, we repeated primary analyses while restricting the cohort to children who received antibiotic therapy consistent with current WHO recommendations, as previously described.[11, 19] Briefly, these guidelines classify children as having non-severe or severe pneumonia, and recommend specific treatment for children with known or suspected HIV infection. For HIV-uninfected children, ampicillin or benzylpenicillin with gentamicin is recommended for severe pneumonia, while high-dose oral amoxicillin can be given for non-severe disease. For HIV-infected or HIV-exposed children, ampicillin or benzylpenicillin with gentamicin is recommended regardless of disease severity, and high-dose trimethoprim-sulfamethoxazole should be considered for treatment of *Pneumocystis jirovecii* pneumonia in infants. Cloxacillin and gentamicin are recommended regardless of HIV status if there is suspicion for staphylococcal pneumonia. Treatment with a third-generation cephalosporin is reserved for failure of first-line antimicrobial therapy. Written informed consent was obtained from a legal guardian after a detailed explanation of the study procedures. Study data were managed using Research Electronic Data Capture (REDCap) tools hosted at The Children's Hospital of Philadelphia (Philadelphia, PA).[20] All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). This study was approved by the Health Research and Development Committee (Ministry of Health, Botswana) and institutional review boards at Princess Marina Hospital, the University of Pennsylvania, and Duke University.

Results

We enrolled 329 children during the study period. Chest radiograph was performed in 318 of 329 (97%), and we were able to download radiographs as DICOM images for 266 children. We excluded two children for whom only a lateral chest radiograph was available, nine children with anterior-posterior images that were classified as "sub-optimal," and six

children with radiographs that were performed more than one day after the date of hospital presentation. Of children in the final study population (n=249), 142 (57%) had anterior-posterior and lateral radiographs and 107 (43%) had an anterior-posterior radiograph only. Table 1 presents radiographic findings by final chest radiograph classification. One hundred eighty-nine (76%) children had either primary endpoint pneumonia or other (non-end-point) infiltrates. Twenty-eight (11%) children had end-point pleural effusion, although the vast majority (96%) of pleural effusions were trace or small. Final chest radiograph classification was primary end-point pneumonia in 88 (35%) children, other infiltrate/abnormality in 105 (42%) children, and no significant pathology in 56 (22%) children.

Patient Characteristics

Characteristics of the study population by final chest radiograph classification are shown in Table 2. Nearly half (49%) of children were less than six months of age, and 58% were male. HIV infection was present in 9% and moderate or severe malnutrition was identified in 16% of children, while 34% had severe pneumonia. Significant differences in radiographic findings were observed by HIV infection and nutritional status. Compared with HIV-negative infants, HIV-infected infants were more likely to have primary end-point pneumonia (64% vs. 32%, P=0.004), end-point consolidation (64% vs. 28%, P=0.0005), and air bronchograms (64% vs. 30%, P=0.001). Primary end-point pneumonia was also more frequent among children with moderate or severe malnutrition than among children with no malnutrition (54% vs. 32%, P=0.01), although this was primarily accounted for by an increased prevalence of end-point pleural effusions (28% vs. 8%, P=0.0003). The effect of moderate or severe malnutrition on the prevalence of primary end-point pneumonia remained significant in analyses stratified by HIV infection status (P=0.01). The proportion of children with caregiver-reported fever and severe pneumonia also differed by final chest radiograph classification.

Outcomes

One-hundred fifty-nine (64%) children received respiratory support on one or more days during the hospitalization, including 27 (11%) children who required CPAP and five (2%) children who were mechanically ventilated. Ninety-one (37%) children failed treatment at 48 hours. Fifty-one children were discharged before the 48-hour treatment failure assessment; the caregivers of 49 (96%) of these children were contacted by phone and no child was reported to have required additional medical care. Twelve (4.8%) children died, including seven (8.0%) children with primary end-point pneumonia, four (3.8%) children with other infiltrate/abnormality, and one (1.8%) child with no significant pathology on chest radiograph.

Table 3 presents multivariable analyses by final radiograph classification. Compared with no significant pathology, primary end-point pneumonia predicted an increased risk of treatment failure at 48 hours (RR: 3.01, 95% confidence interval (CI): 1.52, 5.94, P=0.002), a requirement for more days of respiratory support (IRR: 2.14, 95% CI: 1.33, 3.45, P=0.002), and a longer length of stay (IRR: 1.65, 95% CI: 1.26, 2.17, P=0.0003). Outcomes of other infiltrate/abnormality were intermediate between those observed with primary end-point pneumonia and no significant pathology. In analyses limited to children with significant

pathology on chest radiograph (n=193), primary end-point pneumonia was associated with an increased risk of treatment failure (RR: 1.65, 95% CI: 1.18, 2.31, *P*=0.004) compared with other infiltrate/abnormality.

Two hundred one (81%) children received antibiotics during the hospitalization, including 80 (91%) children with primary end-point pneumonia, 81 (77%) children with other infiltrate/abnormality, and 40 (71%) children with no significant pathology on chest radiograph. One hundred fifty-nine of these children received antibiotic therapy during the first 48 hours that was in accordance with WHO guidelines.[11,19] In sensitivity analyses among children receiving WHO guideline-driven antibiotic treatment, the effect of chest radiographic classification on the risk of treatment failure at 48 hours was substantively unchanged (primary end-point pneumonia vs. no significant pathology, RR: 2.55, 95% CI: 1.10, 5.89, *P*=0.03; other infiltrate/abnormality vs. no significant pathology, RR: 1.40, 95% CI: 0.59, 3.36, *P*=0.45).

Discussion

Most children meeting clinical criteria for pneumonia in Botswana had radiographic evidence of pneumonia, and the presence of primary end-point pneumonia was an independent predictor of poor treatment outcomes. HIV infection and moderate or severe malnutrition were associated with a higher prevalence of primary end-point pneumonia.

Chest radiographic findings predict pneumonia outcomes in adults and are thus incorporated into a number of scoring systems for assessing disease severity.[21] However, few prior studies examined whether findings on chest radiograph predict outcomes of childhood pneumonia. In a study of 406 children and adolescents with radiographic pneumonia in the United States, bilateral multilobar infiltrates were associated with need for mechanical ventilation, while pleural effusion predicted an increased requirement for supplemental oxygen and a longer length of stay.[22] Similarly, among 167 children hospitalized in Greece, the presence of pleural effusion and the size of pulmonary consolidation on chest radiograph were associated with duration of hospitalization.[23] End-point consolidation also was an independent predictor of treatment failure and a longer time until recovery in Nepalese children.[24] Finally, WHO-defined significant pathology was associated with an increased risk of treatment failure in a study of more than 1,100 children enrolled in nine LMICs.[25] Although children with primary end-point pneumonia and other infiltrate/abnormality were analyzed separately in this study, the rate of treatment failure did not substantially differ in these two groups.[25] In our cohort, primary end-point pneumonia predicted a higher treatment failure rate than either other infiltrate/abnormality or no significant pathology on chest radiograph. Moreover, despite being identified in only 35% of the study population, primary end-point pneumonia was identified in more than half (58%) of fatal cases. These findings have important implications for the use of chest radiography in children with suspected pneumonia in LMICs. Notably, while the inter-observer reliability of other (non-end-point) infiltrates is poor, primary end-point pneumonia can be reliably identified by clinicians without specialized radiology training.[15,29,30] Assessing for primary end-point pneumonia on chest radiograph may help health care providers in LMICs identify children with suspected pneumonia who are likely to have a protracted illness. This information,

taken together with other clinical predictors of pneumonia outcomes, could be used to guide patient management and inform families about the anticipated hospital course.

We found that both HIV infection and moderate or severe malnutrition were associated with primary end-point pneumonia among children with clinical suspicion for pneumonia. In HIV-infected children, this primarily reflected an increased prevalence of alveolar consolidation, while most of the effect in malnourished children was related to end-point pleural effusions. These findings are consistent with prior studies in sub-Saharan Africa and may reflect previously described differences in pneumonia etiology in these groups.[16, 17] HIV-infected children are at increased risk of pneumonia caused by *S. pneumoniae*, Gram-negative bacteria, tuberculosis, and *P. jirovecii*.[26-28] Many of these pneumonia etiologies are also more frequent in the setting of severe malnutrition. The original description of *P. jirovecii* pneumonia was in severely-malnourished children living in orphanages following the Second World War.[29] Moreover, tuberculosis is diagnosed in up to 21% of severely-malnourished children with pneumonia in areas of high endemicity.[30,31]

In 1990, the WHO developed a clinical case definition of pneumonia to provide guidance to health care workers in settings with limited diagnostic capabilities.[32, 33] Over the ensuing 25 years, this definition has served as the primary means of identifying pneumonia among children in LMICs.[33] However, studies examining the specificity of this definition for radiographic pneumonia reported conflicting results. Puumalainen et al. found that only 38% of Filipino children identified using the WHO clinical case definition had radiographic evidence of pneumonia.[34] Similarly, only 44% of more than 7,800 children meeting these criteria in The Gambia had radiographic findings.[17] In contrast, the WHO case definition had a specificity of 78% in more than 1,300 children in Malawi, while the specificity was 74% among children presenting to an emergency department in the United States.[35, 36] Consistent with these latter studies, we observed primary endpoint pneumonia or other (non-end-point) infiltrates on chest radiograph in 76% of children identified using WHO clinical criteria. The conflicting results across studies may reflect differences in the study populations, variable application of the WHO case definition, or variation in the interpretation of chest radiographs.

Our study has several limitations. First, it was conducted at a single tertiary hospital in Botswana, and the findings may not be generalizable to hospitals in other LMICs or primary or secondary health care facilities. Second, we did not standardize antibiotic treatment. However, our results were similar when analyses were limited to children receiving guideline-driven antibiotic therapy. Third, although chest radiographs were performed in the vast majority (97%) of the cohort, images were unavailable (n=52), of sub-optimal quality (n=9) or lateral view only (n=2), or performed more than one day after presentation (n=6) for 69 (22%) children. Notably, however, images were unavailable due to technical issues in downloading images in the hospital's radiology department, and these data are likely to be missing completely at random. Finally, in-hospital mortality was relatively low (4.8%) in our cohort. Although the case fatality rate was highest in children with primary end-point pneumonia, we did not have sufficient power to evaluate for an association between final chest radiograph classification and mortality in multivariable analyses.

In conclusion, primary end-point pneumonia was an independent predictor of poor outcomes among children meeting clinical criteria for pneumonia in Botswana. These results highlight the potential benefit of expanding global access to diagnostic radiology services and to incorporating radiographic findings in the risk-stratification of children with suspected pneumonia.

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Table 1

Chest radiographic findings by final classification (n=249)

			n	%
Primary end-point pneumonia			**88**	**35%**
	End-point consolidation		77	88%
		Lobar opacification	49	64%
		Bronchopneumonia	28	36%
	End-point pleural effusion		28	32%
		Trace or small	27	96%
		Moderate or large	1	4%
	Air bronchograms		56	64%
	Hilar lymphadenopathy		12	14%
Other infiltrate/abnormality			**105**	**42%**
	Other (non-end-point) infiltrates		101	96%
		Interstitial infiltrates	72	71%
		Atelectasis	29	29%
	Non-end-point pleural effusion		4	4%
	Air bronchograms		25	24%
	Hilar lymphadenopathy		2	2%
No significant pathology			**56**	**22%**
	Normal chest radiograph		55	98%
	Hilar lymphadenopathy		1	2%

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Table 2

Baseline characteristics of the study population by classification of chest radiographic findings

	Chest Radiograph Classification								
	Overall (n=249)		**Primary End-point Pneumonia (n=88)**		**Other Infiltrate/ Abnormality (n=105)**		**No Significant Pathology (n=56)**		***P*** [a]
Demographics									
Age <6 months (n=249)	123	49%	42	48%	57	54%	24	43%	0.36
Male sex (n=249)	144	58%	51	58%	63	60%	30	54%	0.73
Birth weight <2500 grams (n=245)	50	20%	23	27%	17	16%	10	18%	0.14
HIV infection (n=247)	22	9%	14	16%	5	5%	3	5%	0.01
Moderate or severe malnutrition[b] (n=240)	39	16%	21	25%	12	12%	6	11%	0.03
Current breastfeeding (n=249)	96	39%	31	35%	46	44%	19	34%	0.34
Household use of wood as a cooking fuel (n=249)	94	38%	37	42%	40	38%	17	30%	0.37
Current illness factors									
Caregiver-reported fever (n=249)	187	76%	74	85%	73	70%	40	71%	0.04
Receipt of an antibiotic in the prior 7 days (n=248)	97	39%	28	32%	50	48%	19	34%	0.06
WHO severe pneumonia[c] (n=249)	85	34%	38	43%	34	32%	13	23%	0.04
Oxygen saturation <90%, room air (n=248)	95	38%	40	45%	38	37%	17	30%	0.17

WHO, World Health Organization

[a] Wald χ^2 *P*-values.

[b] Defined as weight-for-length <−2 standard deviation on WHO growth curves, mid-upper arm circumference >125mm (for children ≥6 months), or bilateral edema of nutritional origin.

[c] Pneumonia accompanied by central cyanosis, convulsions, inability to drink, or abnormal sleepiness.

Table 3

Treatment outcomes by chest radiograph classification

	n (%) or Median [IQR]		RR or IRR (95% CI)[a]		*P*
Primary Outcome					
Failed treatment at 48 hours					
Primary end-point pneumonia	49	56%	RR 3.01	(1.52, 5.94)	0.002
Other infiltrate/abnormality	33	31%	RR 1.83	(0.91, 3.68)	0.09
No significant pathology	9	16%	1	Ref	-
Secondary Outcomes					
Days of respiratory support					
Primary end-point pneumonia	2	[0, 6]	IRR 2.14	(1.33, 3.45)	0.002
Other infiltrate/abnormality	1	[0, 3]	IRR 1.49	(0.92, 2.39)	0.10
No significant pathology	1	[0, 2]	1	Ref	-
Length of stay, days					
Primary end-point pneumonia	6.2	[3.0, 11.1]	IRR 1.65	(1.26, 2.17)	0.0003
Other infiltrate/abnormality	4.1	[2.0, 8.0]	IRR 1.48	(1.14, 1.93)	0.003
No significant pathology	2.2	[1.2, 4.7]	1	Ref	-

IQR, interquartile range; RR, risk ratio; IRR, incidence rate ratio; CI, confidence interval; WHO, World Health Organization

[a]Risk ratios (or incidence rate ratios) estimated from Cox proportional hazards models (or negative binomial regression models) adjusted for age <6 months, HIV infection, moderate or severe malnutrition, WHO pneumonia severity, and receipt of an antibiotic in the prior 7 days.