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Predictors of Poor Outcomes among Infants with Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Botswana

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Abstract

Among children one to 23 months of age with respiratory syncytial virus-associated acute lower respiratory infection in Botswana, young age (<6 months), household use of wood as a cooking fuel, moderate or severe malnutrition, and oxygen saturation <90% on room air were independent predictors of clinical non-response at 48 hours. Among HIV-uninfected infants less than six months of age, HIV exposure was associated with a higher risk of in-hospital mortality.

Keywords

respiratory syncytial virus; outcomes; children; HIV-exposed; Botswana

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Introduction

Lower respiratory infection is the leading infectious cause of death among children, and more than half of these deaths occur in sub-Saharan Africa (SSA) (1). Respiratory syncytial virus (RSV) is the most common viral cause of lower respiratory infection in young children. Relative to lower respiratory illnesses caused by other viruses, RSV-associated acute lower respiratory infection (RSV-ALRI) results in a prolonged illness course and higher utilization of acute care resources, which can strain already overburdened health care systems in resource-poor settings (2). Previous studies identified predictors of poor outcomes from RSV-ALRI in developed countries. Few data exist from SSA where potential risk factors such as human immunodeficiency virus (HIV) infection or exposure, malnutrition, and exposure to household air pollution are common (3, 4). Within the context of a prospective cohort study of children with pneumonia, we sought to identify risk factors for poor outcomes among the subset of children with RSV-ALRI.

Methods

The study setting and population were previously described in detail (2, 5). Briefly, we recruited infants one to 23 months of age with pneumonia, defined by the World Health Organization (WHO) as “cough or difficulty breathing with lower chest wall indrawing,” at a tertiary hospital in Gaborone, Botswana between April 2012 and June 2016. Exclusion criteria included chronic medical conditions predisposing to pneumonia with the exception of HIV infection, hospitalization in the prior 14 days, asthma, or wheezing with resolution of 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 residents under the supervision of pediatricians. Antibiotic treatment decisions were at the discretion of these supervising pediatricians. Supplemental oxygen and continuous positive airway pressure (CPAP) were routinely available; mechanical ventilation was available on a limited basis. Respiratory virus testing was not performed by the hospital microbiology laboratory during the study period.

A nasopharyngeal swab was obtained from each subject at enrollment and later tested for RSV and other common respiratory viruses using real-time polymerase chain reaction (2). Only children from whom RSV was detected were included in the present analyses. Children of mothers with documented negative HIV testing during pregnancy, at delivery, or at enrollment were classified as HIV-unexposed, uninfected. Children whose mothers tested positive for HIV before or at delivery were classified as HIV-exposed, uninfected (HIV-EU) if they tested negative for HIV after six weeks of age if exclusively formula fed, at least 6 weeks after breastfeeding cessation, or at enrollment. The primary outcome, clinical non-response, was assessed at 48 (± 2) hours by a study physician or nurse blinded to enrollment data. Clinical non-response was defined as persistent lower chest wall indrawing, new WHO danger signs, oxygen saturation $< 80\%$ on room air, a continued requirement for CPAP or mechanical ventilation, or death. This definition was adapted from a prior WHO-funded study of childhood pneumonia (6). Secondary outcomes included days of respiratory support (supplemental oxygen, CPAP, or mechanical ventilation) and length of stay. We excluded

children with severe malnutrition from length of stay analyses because these children often remain hospitalized for nutritional rehabilitation after resolution of their respiratory illness.

We analyzed baseline characteristics of the study population using Chi-square or Fisher's exact tests for categorical variables and Mann-Whitney U tests for continuous variables. Multivariable analyses included variables that were associated with clinical non-response at 48 hours in univariable analyses ($P < 0.05$). For multivariable analyses, we used modified Poisson regression to estimate risk ratios (RRs) for clinical non-response. We used this approach, as opposed to logistic regression, since the odds ratio provides an upwardly biased estimate of the RR when the outcome is common ($>10\%$). For our secondary outcomes, days of respiratory support and length of stay, we estimated incidence rate ratios (IRRs) using negative binomial regression due to the rightward-skewed distribution of these outcomes. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

We enrolled 398 children with pneumonia during the study period, including 123 children with RSV infection who were included in the analyses presented herein. Characteristics of the study population are shown in Table 1. Clinical non-response at 48 hours occurred in 53 children (43%). The criteria met for clinical non-response were persistent lower chest wall indrawing ($n=32$), new WHO danger signs ($n=8$), oxygen saturation $<80\%$ ($n=4$), a continued requirement for CPAP or mechanical ventilation ($n=5$), and death ($n=4$). Median [interquartile range (IQR)] duration of respiratory support was 2 (0, 4) days and median (IQR) length of stay among children surviving to hospital discharge was 4 (2, 8) days. Eighty-five (69%) children required supplemental oxygen, thirteen (11%) children required CPAP, and four (3%) children required mechanical ventilation. Four (3%) children died including one HIV-infected infant and three HIV-EU infants. In univariable analyses, age less than 6 months, HIV exposure status, household use of wood as a cooking fuel, moderate or severe malnutrition, WHO severe disease, and oxygen saturation $<90\%$ on room air at enrollment were associated with clinical non-response at 48 hours.

In multivariable analyses, age less than 6 months (RR: 1.97; 95% CI: 1.19–3.25; $P=0.01$), household use of wood as a cooking fuel (RR: 1.66; 95% CI: 1.10–2.52; $P=0.02$), moderate or severe malnutrition (RR: 1.71; 95% CI: 1.09–2.69; $P=0.02$), and oxygen saturation $<90\%$ (RR: 1.56; 95% CI: 1.03–2.37; $P=0.04$) were independent predictors of clinical non-response. Oxygen saturation $<90\%$ (IRR: 2.01; 95% CI: 1.23–3.28; $P=0.01$) and HIV exposure or infection (IRR: 1.63; 95% CI: 1.02–2.61; $P=0.04$) predicted a longer duration of respiratory support. Age less than 6 months (IRR: 1.43; 95% CI: 1.04–1.95; $P=0.03$) and oxygen saturation $<90\%$ (RR: 1.46; 95% CI: 1.03–2.06; $P=0.03$) were independently associated with a longer length of stay.

To further investigate the effects of HIV exposure on outcomes of RSV-ALRI, we performed secondary analyses stratified by age. Among HIV-uninfected children less than 6 months of age, in-hospital mortality was higher in HIV-EU (3 of 23; 13%) than in HIV-unexposed, uninfected (0 of 47; 0%) children in univariable analyses ($P=0.03$). Clinical non-response

did not differ in HIV-EU (15 of 23; 65%) and HIV-unexposed, uninfected (21 of 47; 45%) children ($P=0.11$).

Discussion

Among children with RSV-ALRI in Botswana, young age, household use of wood as a cooking fuel, moderate or severe malnutrition, and oxygen saturation <90% at enrollment were independent predictors of clinical non-response at 48 hours. HIV exposure was associated with higher in-hospital mortality among HIV-uninfected children less than 6 months of age in univariable analyses.

Household air pollution is responsible for nearly 300,000 child deaths each year in SSA (7). We previously found an association between exposure to smoke from biomass fuels and outcomes in this cohort of children with clinical pneumonia (8). However, to our knowledge, this is the first description of such an association among children with RSV-ALRI. There are multiple factors that contribute to the relationship between household air pollution and respiratory infections in children. In animal models, exposure to particulate matter has been shown to lead to chronic airway inflammation and impairment of mucociliary clearance and other immune defenses (9). Young children may be exposed to particularly high levels of these pollutants because they are often in close proximity to their caregivers during meal preparation. Our findings provide further evidence of the detrimental health effects of exposure to smoke from biomass fuels and support interventions aiming to reduce household air pollution.

Moderate or severe malnutrition was an independent predictor of clinical non-response at 48 hours. This finding is consistent with a study conducted in the Philippines in which malnutrition was associated with a higher risk of RSV-ALRI hospitalization among infants (10). Malnutrition impairs immune function and can disrupt epithelial integrity in the respiratory tract, increasing susceptibility to lower respiratory infection and prolonging recovery from illnesses. Nutritional rehabilitation improves outcomes from respiratory infections among malnourished children and should be a cornerstone of therapy when these children are hospitalized for RSV-ALRI (11).

HIV exposure was associated with in-hospital mortality among HIV-uninfected children less than 6 months of age in univariable analyses. Although this result should be interpreted with caution given the small number of deaths from RSV-ALRI in our cohort, it is consistent with findings from a study of more than 800 South African infants with RSV-ALRI; in this study, the case fatality rates for HIV-EU and HIV-unexposed, uninfected infants less than 6 months of age were 3% and 1%, respectively (4). Possible explanations for the higher mortality observed in HIV-EU infants include impaired transfer of protective maternal antibodies and other immune abnormalities resulting from *in utero* exposure to HIV or antiretroviral medications (12). Taken together, these findings suggest that HIV-exposed children should be prioritized for future preventative and therapeutic interventions for RSV-ALRI.

Our study has several limitations. First, it was conducted at a single referral hospital in Botswana, and the results may not be generalizable to other settings. Additionally, limited

diagnostic capabilities precluded advanced testing for bacterial pathogens. While in high-income countries the rate of bacterial co-infection in RSV-ALRI is low, few data exist in settings with a high prevalence of HIV infection or exposure, severe malnutrition, and other established risk factors for bacterial pneumonia. Notably, 9-valent pneumococcal conjugate vaccine reduced the incidence of RSV-associated pneumonia in a study of South African children (13). Thus, we cannot exclude the possibility that bacterial co-infection contributed to the associations that we observed between potential risk factors and RSV-ALRI outcomes. In addition, the small sample size limits our ability to draw definitive conclusions about associations between certain factors and outcomes in RSV-ALRI. Finally, although we identified potential risk factors for poor outcomes of RSV-ALRI a priori based on a literature review, the potential for bias by unmeasured confounding exists.

In summary, we identified several risk factors for poor outcomes from RSV-ALRI among children in Botswana. These data could inform future use of RSV vaccines and therapeutics in these populations.

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Characteristics of children one to 23 months of age with respiratory syncytial virus-associated acute lower respiratory infection in Gaborone, Botswana, April 2012 to June 2016.

	Total (N = 123)		Clinical Non-Response (N = 53)		Clinical Response (N = 70)		<i>P</i> ^a	<i>P</i> ^b
	n	(%)	n	(%)	n	(%)		
Demographics								
Age							0.01	0.01
<6 months	74	(60)	39	(74)	35	(50)		
6 to 23 months	49	(40)	14	(26)	35	(50)		
Female sex	60	(49)	24	(45)	36	(51)	0.50	
Birth weight <2500 grams (n=122)	24	(20)	14	(26)	10	(14)	0.10	
HIV exposure status (n=121)							0.03	0.06
HIV-exposed, infected	4	(3)	4	(8)	0	(0)		
HIV-EU	36	(30)	18	(35)	18	(26)		
HIV-unexposed, uninfected	81	(67)	30	(58)	51	(74)		
Household use of wood as a cooking fuel	54	(44)	31	(58)	23	(33)	0.005	0.02
Number of household members, median (IQR)	5	(4,7)	6	(4,8)	5	(4,7)	0.43	
Nutrition and feeding practices								
Moderate or severe malnutrition ^c (n=116)	14	(12)	10	(20)	4	(6)	0.02	0.02
Current breastfeeding	64	(52)	23	(43)	41	(59)	0.10	
Current illness factors								
WHO severe disease ^d	48	(39)	27	(51)	21	(30)	0.02	0.71
Oxygen saturation <90%, room air	45	(37)	28	(53)	17	(24)	0.001	0.04
Days of cough, median (IQR)	3	(2, 5)	3	(2, 5)	3	(2, 5)	0.37	
Respiratory virus co-infection ^e	18	(15)	7	(13)	11	(16)	0.70	

HIV-EU, HIV-exposed, uninfected; WHO, World Health Organization; IQR, interquartile range

^aUnivariable *P*-values from Chi-square or Fisher's exact tests (for categorical variables) or Mann-Whitney U test (for continuous variables)

^bMultivariable *P*-values from modified Poisson regression

^c Defined as weight-for-length less than the -2 standard deviation on WHO growth curves, mid-upper arm circumference <125mm (for children 6 months), or bilateral edema of nutritional origin

^d Pneumonia accompanied by WHO danger signs (central cyanosis, convulsions, inability to drink, or abnormal sleepiness)

^e Respiratory virus co-infections included adenovirus (n=2), influenza B (n=1), rhinovirus A (n=6), rhinovirus B (n=2), and rhinovirus C (n=7)