



Inflammatory markers predict episodes of wheezing during the first year of life in Bangladesh



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ABSTRACT

Background: Environmental factors that influence wheezing in early childhood in the developing world are not well understood and may be useful in predicting respiratory outcomes. Therefore, our objective was to determine the factors that can predict wheezing.

Methods: Children from Dhaka, Bangladesh were recruited at birth and episodes of wheezing were measured alongside nutritional, immunological and socioeconomic factors over a one-year period. Poisson Regression with variable selection was utilized to determine what factors were associated with wheezing.

Results: Elevated serum IL-10 (rate ratio (RR) = 1.51, 95% confidence interval (CI): 1.22–1.87), IL-1 β (RR = 1.55, 95% CI: 1.26–1.93) C-reactive protein (CRP) (RR = 1.41, 95% CI: 1.03–1.93) in early life, and male gender (RR = 1.52, 95% CI: 1.27–1.82) predicted increased wheezing episodes. Conversely, increased fecal alpha-1-antitrypsin (RR = 0.87, 95% CI: 0.76–1.00) and family income (RR = 0.98, 95% CI: 0.97–0.99) were associated with a decreased number of episodes of wheezing.

Conclusions: Systemic inflammation early in life, poverty, and male sex placed infants at risk of more episodes of wheezing during their first year of life. These results support the hypothesis that there is a link between inflammation in infancy and the development of respiratory illness later in life and provide specific biomarkers that can predict wheezing in a low-income country.

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1. Introduction

Wheezing in early life in low income countries often occurs with acute lower respiratory infections, which are a leading cause of morbidity and mortality in children under five years of age [1,2]. Early childhood wheezing also increases the risk of later development of asthma, which in addition to increasing morbidity, places significant socioeconomic burden on already distressed populations [3,4]. Early life markers that predict the development of wheezing in infants in low-income populations are not well understood and could be useful in allowing early interventions and in understanding the pathogenesis of respiratory diseases. Systemic

inflammation might provide such a marker. In high income countries autoimmune and inflammatory diseases often predispose to or co-occur with wheezing and asthma, however most studies have focused on adult populations [5–7]. Recent studies and a more nuanced understanding of the hygiene hypothesis, the idea that early life infections might help prevent the development of allergies and asthma, and in turn wheezing, has suggested that infections with some pathogenic organisms are in fact detrimental to later respiratory health [8–11]. Clinical and subclinical infection with enteric and non-enteric organisms is very common in children in low income countries and likely represents an environmental factor that contributes to a persistent inflammatory response in those children [12,13].

Pathogens encountered by children in these communities can significantly elevate serum levels of pro-inflammatory cytokines such as IL-1 β and macrophage inflammatory protein (MIP1 β) along

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with regulatory cytokines such as IL-10 [12,14,15]. In high income countries these cytokines have also been shown to be associated with obstructive respiratory diseases and wheezing [16,17]. In addition to inflammation stimulated by respiratory pathogens and exposures, children in developing country settings may have additional exposures leading to inflammation, especially in settings of poor sanitation and repeated exposure to enteric pathogens. Indeed, environmental enteropathy, an inflammatory condition of the intestine that can occur in individuals without evidence of overt diarrhea and disease, is also very common in children in low income countries and is thought primarily to be the result of poor sanitation and repeated infection with enteropathogens [12,13,18–20]. Environmental enteropathy is defined pathologically by inflammatory cell infiltration and villous blunting in the mucosa of the small intestine and is associated with gut barrier dysfunction and intestinal and systemic inflammation, including elevated serum IL-1 β , and elevated C-reactive protein at multiple time points [13,19,21]. Markers of gut barrier dysfunction include, but are not limited to, α 1 antitrypsin (ATT). AAT in stool is commonly utilized as a marker of protein-losing enteropathy in children [22].

Thus, considering the potential impact of systemic inflammation on respiratory outcomes, we postulated that markers associated with environmental enteropathy, including serum inflammatory cytokines in the first weeks of life, might predict wheezing outcomes over the first year of life in children in Mirpur, Dhaka Bangladesh. To test this idea an exploratory analysis of the ability of early inflammation to predict wheezing was conducted in an independent cohort from the same community. 37.5% of children in this exploratory cohort had at least one instance of wheezing. Elevated serum IL-10 (top 25th percentile) at 6 months of life was significantly associated with increased episodes of wheezing by one year of age (rate ratio (RR) = 1.48, 95% confidence interval (CI) 1.19–1.77). This preliminary data suggested that systemically elevated serum cytokines early in life might predict wheezing.

2. Methods

2.1. Hypothesis generation cohort

A preliminary investigation of the association of serum cytokine levels with number of nebulizer treatments was performed in a small subset of children (147) from an earlier birth cohort study from the Mirpur area of Bangladesh. These 147 infants were enrolled after birth, beginning in January 2008, and followed until one year of age. The study period ended September 2009. Full details of the design of this birth cohort study have been described [23]. The results from this subset of 147 infants showing significant association of cytokine measures led us to the detailed investigation of biomarker effects on wheezing outcomes in the “Performance of Rotavirus and Oral Polio Vaccines in Developing Countries” (PROVIDE) study cohort of 700 infants.

2.2. Study design and subjects

The characteristics of the PROVIDE study population and study design have been previously described [20,24]. Briefly, a birth cohort of 700 children from the Mirpur urban slum in Dhaka, Bangladesh were recruited and followed for 2 years. The objectives of the study were to determine the effect of environmental enteropathy and inflammation on oral vaccine performance and infant health. Our objective was to evaluate respiratory outcomes in the first year of life in this cohort. In the first year of life, 626 children remained in the study by month 6 and 609 by month 12 of follow-up. There were 4 deaths during the entire PROVIDE study which occurred before one year of age and were due to respiratory

distress, acute diarrhea, neonatal sepsis, and cardio-respiratory failure. All studies were approved by the Ethical Review Committee of the ICDDR, B and the Institutional Review Boards of the Universities of Virginia and Vermont. Informed consent was obtained for all participating mothers and infants, including permission for repeated blood draws.

2.3. Measurement of wheezing

Episodes of wheezing requiring clinician-administered nebulizer treatment were counted over the first year of life for each child in the study. Wheezing was assessed by the clinic physician as a continuous whistling or coarse airway sound during inspiration and/or exhalation [25]. An episode of wheezing was formally defined for this study as at least one nebulizer treatment (salbutamol, 0.1 mg per kilogram body weight) within a 10 day period [26]. In this study, our clinic served as the primary care clinic for the enrolled children and access to other healthcare was extremely limited, including home use of nebulizers.

2.4. Baseline characteristics and biomarkers

Baseline characteristics in this study included monthly family income, expenditure and maternal education. Biomarkers utilized in this analysis and the number of children available for each marker in both univariate and multivariate analyses are indicated in Table S1, along with clinical reference values when available. Mean \pm Standard Error (S.E.) for continuous biomarkers and percentage for categorical measures is also provided in Table S1. Only biomarkers measured at 6, 12, and 18 or 24 weeks were included in the univariate and multivariate analyses, and those children with missing biomarker measurements were excluded from the individual analysis. Cytokine biomarkers of systemic inflammation were categorized into the bottom 50th percentile, 50th–75th, and 75th and above, with the reference the bottom 50th.

2.5. Measure of sustained inflammation

C-reactive protein (CRP) was measured at weeks 6, 18 and 40. A CRP value was considered to be elevated if it was above the median value of CRPs at each time. Children were classified into four groups: **Group 0** consisted of those in which none of their CRPs were elevated, **Group 1** if one CRP measure was elevated, **Group 2** if two CRPs were elevated and **Group 3** if all three CRPs were elevated. **Group 0** was considered as the reference in this analysis. Sustained inflammation with respect to CRPs was defined as if at least two CRP measures were elevated.

2.6. Statistical analysis

Univariate Poisson regression was performed to evaluate the association of biomarkers from the PROVIDE study with episodes of wheezing. Based on univariate p values, the false discovery rate (FDR) was calculated to correct for multiple comparisons and those biomarkers with a FDR < 20% were considered as informative or important. The objective of the univariate analysis with FDR correction was to identify significant biomarkers individually that predicted episodes of wheezing over a one year period. While univariate analysis indicates the marginal effect of individual biomarkers, multivariable analysis can show joint effects of biomarkers. However, since there are nearly 50 predictors (Table S1) in this analysis, a situation of high-dimensional data, traditional multivariable analysis was not an optimal approach. Thus, a modern variable selection method with smoothly clipped absolute deviation (SCAD) regularization was utilized to identify a subset of

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