Biomarkers for Predicting Illness Severity in Children With Acute Lower Respiratory Tract Infections

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Acute lower respiratory tract infections (LRTIs), such as bronchiolitis and pneumonia, account for a substantial proportion of pediatric hospitalizations and health resource utilization [1]. Despite the availability of national guidelines, there remains substantial variation in emergency department and inpatient management for children with these conditions, particularly with regards to ancillary testing and hospitalization decisions [2–4]. Such practice variation highlights the uncertainty among pediatricians in assessing the severity of illness of children with common acute LRTIs. Biological markers, or biomarkers, have been proposed as objective measures of disease onset or progression to inform clinical decision making.

In this issue of the *Journal of the Pediatric Infectious Diseases Society*, Beigelman et al [5] used a prospective cohort study design to evaluate the association of vitamin D and illness severity among children with bronchiolitis caused by respiratory syncytial virus (RSV). Vitamin D deficiency in cord blood (serum vitamin D levels below 20 ng/mL) has been associated with development of RSV bronchiolitis

in the first year of life in a small birth cohort of infants [6]. Furthermore, serum vitamin D levels are of interest as biomarkers in patients with LRTIs, in part, because of the role of vitamin D in modulating the innate immune response. The active form of vitamin D, 1,25(OH)₂D, induces the production of antimicrobial peptides including cathelicidin and β -defensin 2. These peptides disrupt bacterial cell membranes, attract other inflammatory cells, and contribute to wound repair [7]. Relevant to viral LRTIs, vitamin D has also been implicated in modifying the signaling pathways that bind respiratory viruses. For example, 1,25-dihydroxyvitamin D decreases the expression of intercellular adhesion molecule-1, the major cellular receptor for human rhinovirus [8].

Beigelman et al [5] enrolled infants 12 months and younger with RSV bronchiolitis. Unlike most previous studies, which measured vitamin D levels in cord blood, vitamin D levels were measured at hospital admission in 145 infants, thereby indicating vitamin D status at the time of the bronchiolitis episode. Clinical outcomes such as length of hospitalization, lowest

oxygen saturation during hospitalization, and the Bronchiolitis Severity Score at admission were not significantly associated with vitamin D levels or with vitamin D deficiency (using categorical cutoffs of either <20 ng/mL or <30 ng/mL) when adjusting for either age or formula consumption. Although this study suggests that vitamin D may not be an optimal biomarker to predict RSV disease severity, the study had several limitations and raises additional questions.

The prevalence of vitamin D deficiency, although consistent with that expected in the United States, was relatively low (~10%), making it possible that the study was underpowered to detect important differences in outcomes; a power calculation was not provided to inform interpretation of the results. In addition, although duration of hospitalization is commonly used as a proxy for illness severity, discharge decisions are often subjective and may be influenced by nonclinical factors, limiting the utility of this measure as a proxy for illness severity. Standardized discharge criteria or time to clinical stability, both of

which have been described for respiratory illness [9, 10], may serve as more objective measures.

Accurate assessment and prediction of disease severity is critical to the effective management of children with LRTIs, including decisions to initiate antibiotics and admit children to the hospital. Biomarkers offer the potential to improve risk stratification and clinical decision making, thus improving clinical outcomes. In adults with pneumonia, several well established severity scores using clinical findings and conventional biomarkers facilitate treatment and disposition decisions [11]. Additional biomarkers, such as procalcitonin and proadrenomedullin, further improve the prediction of pneumonia severity in adults [12]. Unfortunately, the evidence for biomarkers predicting disease severity in children with LRTIs is less developed. Several biomarkers have been proposed as markers of severity in bronchiolitis and influenza, including nasal lactate dehydrogenase [13], serum surfactant protein-D [14], Krebs von den Lungen 6 antigen [15], and interleukin-6 (IL-6) [16] and other cytokines [17]. Likewise, in pediatric pneumonia, small studies have examined the role of conventional and novel biomarkers, including procalcitonin [18] and IL-6 [19], in severity prediction without convincing conclusions. Although these studies offer promise for severity assessment in pediatric LRTIs, their limited and focused scope do not offer definitive conclusions regarding the use of biomarkers in severity classification for pediatric LRTIs.

Innovative technologies, including microarray-based whole-genome expression arrays, proteomics, and metabolomics, offer some of the most powerful platforms for biomarker discovery known to date. Gene expression profiling allows classification of infections based on host gene expression,

revealing pathogen-specific signatures of disease. For example, gene expression profiling of blood leukocytes in children with acute respiratory infections correctly distinguished bacterial from viral respiratory infections with 93% accuracy [20]. Furthermore, several investigators have used these techniques to apply a genomic severity score ("molecular distance to health") that correlates clinical markers of disease severity with changes in host gene expression [21, 22]. In 1 cohort of 91 children with RSV bronchiolitis, genomic severity scores significantly correlated with clinical severity scores, length of hospitalization, and duration of supplemental oxygen [23].

Given the limitations of vitamin D and other biomarkers in predicting severity in pediatric LRTIs, the search for accurate biomarkers of disease severity in these infections continues. New technologies offer promise for the discovery and development of novel biomarkers of bronchiolitis and pneumonia severity that will help to improve clinical outcomes through more accurate risk stratification.

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