Serum Soluble Receptor for Advanced Glycation End Products in Infants With Bronchiolitis: Associations With Acute Severity and Recurrent Wheeze

Jason T. Patreggani,^{1,2,3,4,a} Michimasa Fujiogi,^{5,a} Carlos A. Camargo Jr,⁵ Bonnie A. Brooks,¹ Claire E. Hoptay,² Jonathan M. Mansbach,⁶ Stephen J. Teach,⁷ Robert J. Freishtat,^{2,7} and Kohei Hasegawa⁵

¹Division of Cardiac Critical Care Medicine, Children's National Hospital, Washington, DC, USA, ²Department of Genomics and Precision Medicine, George Washington University, Washington, DC, USA, ³Division of Pediatric Critical Care Medicine, Maine Medical Center, Portland, Maine, USA, ⁴Tufts University, Medford, Massachusetts, USA, ⁵Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, ⁶Division of General Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA, and ⁷Division of Emergency Medicine, Children's National Hospital, Washington, DC, USA

Background. Although bronchiolitis contributes to substantial acute (eg, intensive care use) and chronic (eg, recurrent wheeze) morbidities in young children, the pathobiology remains uncertain. We examined the associations of serum soluble receptor for advanced glycation end products (sRAGE) with acute and chronic morbidities of bronchiolitis including recurrent wheeze.

Methods. A multicenter, multiyear, cohort study of infants hospitalized for bronchiolitis was analyzed. We measured the serum sRAGE level at hospitalization and its association with intensive care use (use of mechanical ventilation and/or admission to the intensive care unit) and development of recurrent wheeze by age 3 years. We performed causal mediation analysis to estimate indirect (mediation) and direct effects of sRAGE on recurrent wheeze.

Results. In 886 infants with bronchiolitis, the median age was 2.9 months. Overall, 15% underwent intensive care and 32% developed recurrent wheeze. In multivariable modeling adjusting for 11 confounders, a higher presenting sRAGE level was associated with lower risk of intensive care (odds ratio for each 1-log increment, 0.39; 95% confidence interval [CI], .16–.91; $P = .03$) and significantly lower rate of recurrent wheeze (hazard ratio [HR], 0.58; 95% CI, .36–.94; $P = .03$). In mediation analysis, the direct effect was significant (HR, 0.60; 95% CI, .37–.97; $P = .04$), while the indirect effect was not ($P = .30$).

Conclusions. Serum sRAGE levels were inversely associated with acute and chronic morbidities of bronchiolitis. The effect of sRAGE on development of recurrent wheeze is potentially driven through pathways other than acute severity of bronchiolitis.

Keywords. glycation end products; advanced; bronchiolitis; pediatrics; cohort; mediation; asthma.

Bronchiolitis is the leading cause of infant hospitalizations in the United States, with approximately 110 000 hospitalizations each year [1]. In addition to substantial acute morbidity, 30%–40% of infants hospitalized for bronchiolitis subsequently develop recurrent wheeze and acute respiratory infections in later childhood [2]. The underlying mechanisms that link these conditions remain unclear. This knowledge gap has hindered efforts to prevent and treat severe bronchiolitis and to prevent chronic morbidities in this high-risk population [3].

Among many components of the host immune system, recent research has suggested a potential role of the receptor

for advanced glycation end products, which is a multiligand, transmembrane, glycoprotein receptor [4] that is expressed on type I alveolar cells in the lungs [5, 6], in the pathobiology of bronchiolitis. Membrane-bound receptor for advanced glycation end products (mRAGE) is known to stimulate NF κ B signaling and its related inflammatory cascade [7]. In contrast, the cleaved form, soluble RAGE (sRAGE), acts as a decoy receptor by binding proinflammatory ligands destined for mRAGE, thereby offering antiinflammatory benefit [8, 9]. Research has shown the role of the RAGE inflammatory axis in multiple pulmonary pathophysiologic processes, including acute respiratory distress syndrome and asthma [10]. While a few case-control studies (both $N < 100$) have measured the levels of sRAGE in bronchiolitis [11, 12], it remains unclear whether sRAGE is related to acute severity and chronic outcomes among infants with bronchiolitis.

To address this knowledge gap, we analyzed multicenter, prospective cohort data of infants hospitalized for bronchiolitis to investigate the associations of serum sRAGE levels with acute and chronic morbidities of bronchiolitis.

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^aJ. T. P. and M. F. contributed equally to this work.

Correspondence: J. Patreggani, Pediatric Critical Care Medicine, Maine Medical Center, 22 Bramhall Street, Portland, ME, 04102 (Jpatreggani@gmail.com).

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Additionally, we also applied a causal mediation approach to determine whether the effect of sRAGE on the subsequent development of recurrent wheeze is mediated through acute severity of illness.

METHODS

Study Design, Setting, and Participants

We analyzed data from the 35th Multicenter Airway Research Collaboration (MARC-35) [13], which is a multicenter, prospective cohort study of infants hospitalized with bronchiolitis that is coordinated by the Emergency Medicine Network (EMNet; www.emnet-usa.org). Site investigators enrolled infants (aged <1 year) hospitalized with bronchiolitis at 17 sites across 14 states (Supplementary Table 1) during 3 consecutive bronchiolitis seasons (from November through April) in 2011–2014. Bronchiolitis was defined by the American Academy of Pediatrics guidelines [14] as an acute respiratory illness with some combination of rhinitis, cough, tachypnea, wheezing, crackles, and retractions and was diagnosed by an attending physician. We excluded infants with known heart–lung disease, immunodeficiency, immunosuppression, or gestational age of <32 weeks and those who were transferred to a participating hospital >24 hours after the original hospitalization. All infants were treated at the discretion of the attending physicians. Of 1016 infants initially enrolled into the MARC-35 study, 921 (91%) completed the run-in procedures, that is, contact at both 1 week after hospital discharge and 3 weeks after hospitalization, and comprised the longitudinal cohort. All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of the World Medical Association. The institutional review board at each participating hospital approved the study. Written informed consent was obtained from the parent or guardian.

Data Collection

Clinical data (infants' demographic characteristics, family and medical history, and details of the acute illness) were collected via structured interview and chart reviews using a standardized protocol [13]. After the index hospitalization for bronchiolitis and the run-in procedures, interviewers contacted parents/legal guardians by telephone at 6-month intervals. Using standard protocols [13, 15], nasopharyngeal and serum specimens were collected by trained site investigators within 24 hours of hospitalization. Nasopharyngeal specimens were tested for 17 respiratory viruses using real-time polymerase chain reaction assays at the Baylor College of Medicine (Houston, TX) [13]. Serum specimens were tested for sRAGE using an enzyme-linked immunosorbent assay provided by MesoScale Discovery System (Rockville, MD) at Children's National Hospital (Washington, DC).

Outcome Measures

The outcomes of interest were acute severity of bronchiolitis (as measured by intensive care use and hospital length of stay during the index hospitalization for bronchiolitis), as well as chronic morbidity (as measured by the development of recurrent wheezing by age 3 years). Intensive care use was defined as the use of invasive and/or noninvasive mechanical ventilation (eg, continuous positive airway pressure ventilation) and/or intensive care unit admission [16, 17]. According to the 2007 National Institutes of Health asthma guidelines [18], recurrent wheezing was defined as having at least 2 corticosteroid-requiring exacerbations in 6 months or at least 4 wheezing episodes in 1 year that last at least 1 day and affect sleep [13].

Statistical Analyses

First, we described the baseline infants' characteristics, clinical presentation, virology, laboratory data at the index hospitalization, and outcomes. Second, to visualize the relationship of the exposure (serum sRAGE level) at the hospitalization with each outcome, we used a locally estimated scatterplot smoothed (loess) curve. Third, to investigate the association between the serum sRAGE level (which is $\log_{10}$ -transformed given its skewed distribution) with the outcome of interest, we constructed unadjusted and adjusted mixed effects logistic regression models (for intensive care use outcome), Poisson regression models (for hospital length-of-stay outcome), and Cox proportional hazards model (for development of recurrent wheeze). In the multivariable model, we adjusted for the following 11 potential confounders based on clinical plausibility [13, 19]: age, sex, race/ethnicity, parental history of asthma, history of prematurity, history of previous breathing problems before the index hospitalization, history of eczema, daycare use, body weight at presentation, infecting viruses (respiratory syncytial virus [RSV] and rhinovirus), and allergic (specific immunoglobulin E) sensitization, and we accounted for patient clustering at the hospital level. The proportionality of hazards assumption was verified through evaluation of the Schoenfeld residuals.

Causal Mediation Analysis

We constructed a directed acyclic graph to represent our proposed causal hypothesis linking the exposure (serum sRAGE) to potential mediator (acute severity represented by intensive care use) and chronic outcome (development of recurrent wheeze) with the potential confounders listed above. To examine the direct and indirect (causal mediation) effects in a counterfactual framework, we performed causal mediation analysis using the R *regmedint* package [20–22]. This method enabled us to examine the total effect and extent to which the effect of exposure on the outcome is direct (natural direct effect) and to what extent it is mediated by the mediator (natural indirect effect). More specifically, the natural direct effect represents how much the rate of developing recurrent wheeze would change if

the patient were set to be exposed vs unexposed; however, for each patient, the individual intensive treatment use was kept at the level it would have taken in the absence of exposure. The natural indirect effect represents how much the rate of developing recurrent wheeze would change if the patient were set to be exposed but the intensive treatment use was changed from the level it would take if unexposed to the level it would take if exposed.

Sensitivity Analyses

We performed sensitivity analyses to determine the robustness of our inferences. First, we conducted subgroup analyses in the solo RSV and RSV coinfection groups to examine the potential heterogeneity by infecting virus. Second, to address potential heterogeneity of recurrent wheeze [23, 24], we further stratified the recurrent wheeze outcome by subsequent asthma status at age 5 years [13]. Asthma was defined using the following commonly used epidemiologic definition [25]: physician diagnosis of asthma, with either asthma medication use (such as albuterol inhaler or inhaled corticosteroids) or asthma symptoms (eg, wheezing or nocturnal cough) in the preceding year. Last, we computed E-values to examine the robustness of causal inference to potential unmeasured confounding by using the R Evalue package [26]. The E-value, a method to gauge the evidence for causality [26], indicates the minimum magnitude of association that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away the association of interest, conditional on the measured covariates [26]. For example, an E-value of 2.0 means that the hazard ratio for the association of an unmeasured confounder with both the exposure and outcome would have to be >2.0 to explain away the observed exposure-outcome association. All analyses were performed at a 2-sided significance level of 0.05. We performed the analysis using R version 3.6.1.

RESULTS

Of 921 infants in the longitudinal cohort, 886 (96%) underwent serum sRAGE measurements, passed quality control measures, and comprised the analytic cohort. The analytic and nonanalytic cohorts had no significant differences in all patient characteristics (all $P > .05$; [Supplementary Table 2](#)). In the analytic cohort, the median age was 3.2 months (interquartile range, 1.7–5.9), 40% were female, and 19% had a history of prematurity ([Table 1](#)). Additionally, 15% underwent intensive care and 39% had a hospital length of stay ≥ 3 days (median length of stay, 2 days) during the index hospitalization for bronchiolitis. Overall, 32% of infants subsequently developed recurrent wheeze by age 3 years.

Associations of Serum sRAGE Level With Acute Severity of Bronchiolitis

[Figure 1](#) shows the relationship of serum sRAGE level at the index hospitalization with the risk of acute and chronic

Table 1. Characteristics of the 886 Infants Hospitalized for Bronchiolitis

Characteristic	Overall (N = 886)	
Baseline		
Age, median (IQR), month	3.2 (1.7–5.9)	
Female sex	352	(40)
Race/ethnicity		
Non-Hispanic White	384	(43)
Non-Hispanic Black	201	(23)
Hispanic	267	(30)
Other	34	(4)
Parental history of asthma	293	(33)
Maternal smoking during pregnancy	121	(14)
C-section delivery	299	(34)
Prematurity (32–36.9 weeks of gestation)	166	(19)
Previous breathing problems before the index hospitalization, episodes		
1	141	(16)
≥2	40	(5)
History of eczema	134	(15)
Mostly breastfed for the first 3 month of life	399	(45)
Daycare use	204	(23)
Corticosteroid use before the index hospitalization	82	(9)
Lifetime history of systemic antibiotic use	282	(32)
Clinical presentation		
Body weight at presentation, median (IQR), kg	6.1 (4.8–7.7)	
Respiratory rate at presentation, median (IQR), per minute	48 (40–60)	
Oxygen saturation at presentation, %		
<90	81	(9)
90–93	126	(14)
≥94	659	(74)
Detected pathogen		
Respiratory syncytial virus	726	(82)
Rhinovirus	179	(20)
Other pathogens ^a	200	(23)
Laboratory data		
Serum soluble receptor for advanced glycation end products, median (IQR), pg/mL	756 (510–1126)	
Allergic (specific immunoglobulin E) sensitization	175	(20)
Acute clinical outcomes		
Intensive care use ^b	132	(15)
Hospital length of stay, median (IQR), days	2 (1–3)	
Length of hospital stay ≥3days	349	(39)
Chronic clinical outcomes		
Recurrent wheezing by age 3 years ^c	284	(32)
Asthma at age 5 years ^d	226	(26)

Data are n (%) of infants unless otherwise indicated. Percentages may not equal 100, because of missing data.

Abbreviation: IQR, interquartile range.

^aAdenovirus; bocavirus; *Bordetella pertussis*; enterovirus; human coronavirus NL63, OC43, 229E, or HKU1; human metapneumovirus; influenza A or B virus; *Mycoplasma pneumoniae*; and parainfluenza virus 1–3.

^bDefined as use of positive pressure ventilation (invasive and/or noninvasive mechanical ventilation [eg, continuous positive airway pressure ventilation]) and/or intensive care unit admission.

^cDefined by parental report of at least 2 corticosteroid-requiring breathing problems in 6 months or at least 4 wheezing episodes in 1 year that last at least 1 day and affect sleep.

^dDefined by physician diagnosis of asthma at age 5 years, plus either asthma medication use (eg, albuterol inhaler, inhaled corticosteroids, Montelukast) or asthma-related symptoms in the preceding year.

bronchiolitis morbidities. In the multivariable model adjusting for 11 confounders, the sRAGE level was significantly associated with a lower risk of intensive care use (adjusted odds ratio [aOR] for

Figure 1. Relationships of serum sRAGE level with acute severity and chronic outcomes in infants hospitalized for bronchiolitis. The fitted lines represent locally estimated scatterplot smoothed (loess) curves for infants hospitalized for bronchiolitis. The gray bars at the bottom represent the range in which 95% of corresponding data are present. *A*, Intensive care use during the index hospitalization for bronchiolitis. *B*, Hospital length of stay ≥ 3 days during the index hospitalization for bronchiolitis. *C*, Development of recurrent wheeze by age 3 years. Abbreviations: LOS, length of stay; sRAGE, soluble receptor for advanced glycation end products.

each 1-log increment, 0.39; 95% confidence interval [CI], .16–.91; $P = .03$; E-value = 4.62; Table 2). Likewise, the sRAGE level was significantly associated with a shorter length of stay (aOR for each 1-log increment, 0.81; 95% CI, .68–.97; $P = .02$; E-value = 1.76). In

the sensitivity analysis that examines potential heterogeneity by infecting virus (Supplementary Table 3), the negative associations of serum sRAGE with acute severity were consistent in the solo RSV and RSV coinfection groups (Supplementary Tables 4 and 5).

Table 2. Associations of Serum Soluble Receptor for Advanced Glycation End Products Level With Clinical Outcomes in Infants Hospitalized for Bronchiolitis

Outcome	Point Estimate ^a	95% Confidence Interval	P Value	E-Value ^b
Intensive care use^c				
Unadjusted model	Odds ratio			
	0.80	(.36–1.79)	.59	...
Adjusted model ^d	0.39	(.16–.91)	.03	4.62 (1.44)
Hospital length of stay^e				
Unadjusted model	Rate ratio			
	1.09	(.92–1.29)	.34	...
Adjusted model ^d	0.81	(.68–.97)	.02	1.76 (1.23)
Recurrent wheeze^f				
Unadjusted model	Hazard ratio			
	0.57	(.35–.91)	.02	2.92 (1.43)
Adjusted model ^d	0.58	(.36–.94)	.03	2.82 (1.31)

^aValues are estimated per each incremental increase in $\log_{10}$ scaled soluble receptor for advanced glycation end products level.

^bThe E-value (with its lower 95% confidence interval bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.

^cMixed effects logistic regression models accounting for patient clustering by site.

^dAdjusted for age (<2 vs ≥ 2 months), sex, race/ethnicity, parental history of asthma, prematurity (32–36.9 weeks), history of previous breathing problems before the index hospitalization, history of eczema, daycare use, body weight at presentation, infecting viruses (respiratory syncytial virus and rhinovirus), and allergic sensitization.

^eMixed effects Poisson regression models accounting for patient clustering by site.

^fCox proportional hazards models accounting for patient clustering by site.

Associations of Serum sRAGE Level With the Rate of Developing Recurrent Wheeze

Similar to the acute severity of bronchiolitis, infants with a higher sRAGE level had a lower rate of developing recurrent wheeze (unadjusted hazard ratio [HR] for each 1-log increment, 0.57; 95% CI, .35–.91; $P = .02$; Table 2 and Figure 1C). The negative association remained significant in the multivariable model (adjusted HR for each 1-log increment, 0.58; 95% CI, .36–.94; $P = .03$; E-value = 2.82). In the sensitivity analysis, while the statistical power was limited, the negative associations between serum sRAGE and risk of recurrent wheeze were consistent in the solo RSV and RSV coinfection groups (Supplementary Tables 4 and 5).

To address potential heterogeneity of recurrent wheeze, we stratified the outcome by subsequent asthma status at age 5 years. Despite the limited statistical power, a higher sRAGE level was associated with a nonsignificantly lower rate of recurrent wheeze that resulted in asthma (adjusted HR for each 1-log increment, 0.50; 95% CI, .25–1.01; $P = .054$; Supplementary Table 6) and with a significantly lower rate of recurrent wheeze that did not result in asthma (adjusted HR for each 1-log increment, 0.47; 95% CI, .23–.96; $P = .04$; E-value = 3.64). In contrast, there was no significant association between sRAGE and overall asthma status at age 5 years (adjusted HR for each 1-log increment, 0.75; 95% CI, .41–1.37; $P = .35$).

Causal Mediation Analysis

In the mediation analysis (Figure 2), a higher level of serum sRAGE was associated with a lower rate of developing recurrent wheeze (total effect; adjusted HR for each 1-log increment, 0.59; 95% CI, .36–.95; $P = .03$; Table 3). While the estimated natural indirect (mediation) effect was not statistically significant

Table 3. Effect of Serum Soluble Receptor for Advanced Glycation End Products Level on Rates of Developing Recurrent Wheeze by Age 3 Years Mediated by Intensive Care Use

Effect	Point Estimate	95% Confidence Interval	P Value
Hazard ratio ^a			
Total effect	0.59	(.36–.95)	.03
Natural direct effect	0.60	(.37–.97)	.04
Natural indirect effect	0.98	(.93–1.02)	.30
Proportion			
Proportion mediated	3.5%	-	.50

^aMultivariable Cox proportional hazards model was used for the outcome model and multivariable logistic regression model was used for the mediator model, followed by a 2-way decomposition of the total effect into the natural direct and indirect effects. Both models adjusted for 11 potential confounders (ie, age [<2 vs ≥ 2 months], sex, race/ethnicity, parental history of asthma, prematurity [32–36.9 weeks], history of previous breathing problems before the index hospitalization, history of eczema, daycare use, body weight at presentation, infecting viruses [respiratory syncytial virus and rhinovirus], and allergic sensitization).

($P = .30$), the estimated natural direct effect was significant (adjusted HR for each 1-log increment, 0.60; 95% CI, .37–.97; $P = .04$), indicating that the effect of serum sRAGE on the development of recurrent wheeze was potentially driven through pathways other than acute severity of bronchiolitis.

DISCUSSION

In this 17-center prospective cohort study of infants hospitalized with bronchiolitis, we found that infants with a higher level of serum sRAGE at presentation had a significantly lower acute risk of intensive care use and shorter hospital length of stay during their index hospitalization. Additionally, those infants with a higher sRAGE level had a lower rate of developing recurrent wheeze by age 3 years. In the causal mediation analysis using a counterfactual framework, the data also demonstrate that the effect of sRAGE on the development of recurrent

Figure 2. Directed acyclic graph of the proposed causal structure. The graph was constructed to represent our proposed causal hypothesis linking the exposure (serum sRAGE level) and potential mediator (acute severity represented by intensive care use) to chronic outcome (the development of recurrent wheeze by age 3 years) with the potential confounders. Abbreviations: RSV, respiratory syncytial virus; sRAGE, soluble receptor for advanced glycation end products.

wheeze is likely driven through pathways other than acute severity of bronchiolitis (ie, direct effects).

As those infants with higher levels of sRAGE had a less-severe clinical presentation of bronchiolitis, our findings are consistent with the hypothesis that circulating sRAGE acts as a decoy receptor and binds proinflammatory ligands that were destined for mRAGE. sRAGE is produced secondary to proteolytic cleavage of mRAGE or through alternative splicing [27, 28]. These soluble subtypes contain the same binding domain as mRAGE but without the transmembrane or cytosolic domain that activates downstream inflammatory pathways [27, 28]. Based on 2 single-center analyses (both $n < 100$), previous data of sRAGE in bronchiolitis have been inconsistent. First, in agreement with our data, a case-control study of 93 infants hospitalized with bronchiolitis reported that those infants had significantly lower sRAGE levels compared with controls, without correlation to disease severity [11]. By contrast, another case-control study of 37 children (aged <24 months) hospitalized in an intensive care unit with bronchiolitis and 43 controls reported a higher level of serum sRAGE in the cases. This study also showed an inverse correlation between sRAGE levels and Wood-Dowes score, which is a clinical severity score [12]. These apparently conflicting results may be attributable to the difference in study design, setting, population, outcome definition, analytical methods, or any combination of these factors. Additionally, in these studies, the median sRAGE value at presentation was higher than in our sample. This is illustrative of the need for normative values across ages to better understand the role of sRAGE in pathologic processes.

In the acute phase of bronchiolitis, the role of sRAGE in the disease pathobiology requires further clarification. While sRAGE is found in serum and alveolar fluid of all humans, it remains unclear why its levels vary at baseline and if this leads to differing presentations of acute infections. It is possible that there is a causal relationship, that is, children with constitutively lower sRAGE levels are predisposed (through a relative deficiency of its antiinflammatory effect) to more-severe disease. Specifically, as an infection occurs, a series of proteins (eg, HMGB1, S100A) are released and act as ligands for mRAGE, which is a damage-associated molecular pattern (DAMP) receptor, thereby activating the host immune response [29]. With low sRAGE levels, this process is not counteracted, resulting in more-severe disease. Indeed, in animal models of acute lung injury, administration of exogenous sRAGE consistently showed improvement in pathologic and clinical measures of lung function, presumably due to its antiinflammatory effect, further suggesting that having a higher sRAGE level may be beneficial [30, 31]. Alternatively, if a particularly virulent pathogen causes excessive cellular damage, sRAGE levels may become depleted secondary to increased consumption as they bind the large quantity of DAMP-type proteins [11]. All of these potential mechanisms are likely not mutually exclusive, and the role

of sRAGE in bronchiolitis specifically is likely multifactorial. Clarification of this role may allow for better understanding of ways to modify the clinical course of bronchiolitis.

In addition to the acute disease severity, we also found that sRAGE levels were inversely related to the subsequent risk of developing recurrent wheeze and that its effect was mediated through pathways other than acute severity of bronchiolitis. While the components of direct effect merit further clarification, it is plausible that depleted sRAGE in early infancy may result in more frequent respiratory infections and altered airway structure in early childhood, thereby leading to a higher risk of developing recurrent wheeze. The RAGE axis is known to be associated with several chronic lung conditions, including cystic fibrosis and chronic obstructive pulmonary disease [32–34], disease states where acute respiratory infection is the major cause of their exacerbations and progression [35, 36]. A similar pattern is noted in children with recurrent wheeze and asthma, in which viral respiratory infections lead to recurrent exacerbations [34]. In experimental asthma models, RAGE knockout mice were protected against eosinophilic inflammation, goblet cell hyperplasia, airway remodeling, and airway hyperresponsiveness [37]. Additionally, administration of sRAGE to wild-type mice reduced airway inflammation in those with induced asthma [37]. Notwithstanding the complexity, the identification of sRAGE as a primary culprit in the relationships between the host response, viral bronchiolitis, and its chronic morbidity is an important finding. Our findings should facilitate further investigations to disentangle this complex pathobiology.

Our study has several potential limitations. First, some patients in the longitudinal cohort were excluded from the analysis due to lack of serum specimen or suboptimal quality. However, the analytical and nonanalytical cohorts did not materially differ, arguing against substantial selection bias. Second, the serum sRAGE level was measured within 24 hours of the index hospitalization at a single time point, and the levels may have differed from participants' baseline levels. The pathobiology of bronchiolitis initially involves injury of the small airways, which can progress to alveolar damage. Our study design precluded us from examining the progression of circulating levels (or the levels in the lungs) and how they relate to the acute and chronic morbidities of bronchiolitis. Third, as with any observational study, causal inferences could be confounded by unmeasured factors (eg, host genetics, detailed nutritional information) despite rigorous adjustment. Yet, the large E-values indicated that the evidence for causality was "reasonably strong" [26]. Furthermore, while there are possible between-hospital differences in intensive care resources, we statistically accounted for patient clustering at the hospital level to mitigate this effect. Finally, even with our racially/ethnically and geographically diverse US sample, we must generalize the inferences cautiously beyond infants hospitalized with bronchiolitis (eg, infants with

mild to moderate illness who do not require hospitalization). Regardless, our data are highly relevant to more than 110 000 hospitalized US children every year [1].

CONCLUSIONS

Based on the prospective, multiyear, multicenter cohort data of 886 infants hospitalized for bronchiolitis, we found that higher serum sRAGE levels were significantly associated with both lower acute severity (intensive care use and longer hospital length of stay) and chronic morbidity (development of recurrent wheeze by age 3 years). The data also demonstrate that the effect of sRAGE on the development of recurrent wheeze is potentially driven through pathways other than acute severity (ie, direct effects). Our observations should facilitate further investigations into the role of the RAGE axis in the pathobiology of bronchiolitis as well as its long-term sequelae. Furthermore, the RAGE axis is an attractive target for modulation to offer new avenues for prevention and treatment of bronchiolitis and its chronic morbidities.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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