Do Bacteria in the Gut Set the Stage for Who Gets Viral Bronchiolitis and Its Severity?

Patrick C. Seed, MD, PhD

Until recently, much of the respiratory tract was assumed to be sterile in the absence of an overt infection such as pneumonia or bronchiolitis. However, contemporary molecular genetic tools have revealed rich communities of microbes, the microbiota, throughout the respiratory tract, even during states of health.[1,2] This paradigm shift has led to new ideas about how endogenous lung microbes may prime the local lung immune system and subsequently alter the responses to infectious and noninfectious respiratory diseases such as pneumonia and asthma.[3] However, the story about microbes and lung physiology is even more complex and interesting. Emerging data have also demonstrated potent physiologic and immune crosstalk between distant organs in contact with the microbiota. One new area of interest is the gut–lung axis, in which the microbiota of the enteric tract conditions immunologic responses in the lungs to environmental challenges such as allergens and infectious agents or even endogenous exposures such as cancer and autoantigens.[4]

In this issue of *Pediatrics,* Hasegawa et al[5] report an association between different bacterial compositions of the gut microbiota in infants hospitalized for viral bronchiolitis compared with healthy controls. In a cohort of 40 infants with viral bronchiolitis and 115 healthy, age-matched controls, the authors identified 4 primary profiles of bacteria in the fecal microbiota. Infants hospitalized with viral bronchiolitis were more likely to have a fecal microbiota dominated by the bacterial genus *Bacteroides* compared with healthy infants, with an odds ratio of 4.59. A profile dominated by the genera *Enterobacter* and *Veilonella* was proportionately lowest among infants hospitalized for bronchiolitis. Furthermore, the *Bacteroides*-dominant microbiota was paradoxically more rich and diverse than the other microbiota profiles found more often in the healthy control infants.

This cross-sectional, case–control study raises multiple hypotheses about the relationship between different gut microbiota compositions and the presence of bronchiolitis while also exposing limitations in the study. For instance, polysaccharide A of *Bacteroides* suppresses T-cell responses to inflammatory stimuli.[6,7] Inappropriate suppression of "cellular learning" in infancy may alter subsequent mucosal immunity upon infection, resulting in exacerbated inflammatory responses to environmental challenges. Thus an increased abundance of enteric *Bacteroides* before a viral challenge may be hypothesized to increase the likelihood of reduced viral immunity and an inappropriate response to an infection. However, in the study by Hasegawa et al, the gut microbiota was sampled only at the time of hospitalization for infection and once in age-matched controls. Any of the observed microbiota profiles may not reflect earlier states of the microbiota

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and critical windows of early immune priming. Therefore, prospective longitudinal studies will be essential to determine whether the observed microbiota profiles at the time of bronchiolitis preceded symptoms, were concurrent with the disease onset, or occurred after the disease was well under way. Only through these types of studies, coupled with preclinical mechanistic models of bronchiolitis, can causality be established.

Both randomized and retrospective studies of antibiotic treatment in bronchiolitis have failed to show that it improves key outcomes such as supplemental oxygen requirements and hospital length of stay.[8] Notably, the antibiotics commonly used in the past for bronchiolitis, chosen to target potential respiratory tract bacterial superinfections, would not be expected to target *Bacteroides*. Conversely, *Veilonella,* found by Hasegawa et al to be proportionately lowest among infants with bronchiolitis, may be suppressed by the administration of some antiinfectives such as ampicillin that were been previously trialed for the treatment of bronchiolitis. The associations identified by Hasegawa et al, if upheld by the necessary prospective and causal studies, may yield new insights into the failures of antibiotic therapy and suggest alternative approaches to therapeutically modify the microbiota and thus reduce the risk and severity of viral bronchiolitis in infants.

Respiratory tract research has entered a new era. Through a combination of clinical and preclinical models, genomics, immunology, and metabolomics, investigations into the gut–lung axis are expected to drive a paradigm shift in which pulmonary health is viewed through a wider lens of multisystem interactions that includes the microbiota, and through which new preventive strategies, diagnostics, and therapeutics may be envisioned for common respiratory diseases. Observational studies such as that by Hasegawa et al are essential first steps to move this new area of research forward.

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