

Early-Life Viral Bronchiolitis in the Causal Pathway of Childhood Asthma Is the Evidence There Yet?

Bronchiolitis is a leading cause of hospitalizations among infants worldwide, affecting around 30 per 1,000 in developed countries (1). Approximately 20% of children have at least one episode of lower respiratory illness with wheezing in the first year of life, with most being positive for respiratory viruses.

The question of whether acute viral bronchiolitis occurring in the first months of life is in the causal pathway of asthma or if it is only an early marker of asthma predisposition has been discussed for decades (2). Complex and multifactorial issues are involved. Episodes of respiratory infections with wheezing in the first years of life have been associated with recurrent wheeze in studies of high-risk and community-based cohorts. These early-life events are caused by viruses such as rhinovirus (RV), respiratory syncytial virus (RSV), and parainfluenza virus, and less frequently by adenovirus, human metapneumovirus, or influenza.

The concept that RSV is the main agent responsible for lower respiratory tract infections in infancy has been challenged recently by studies showing RV to be the most prevalent infection at this age in some locales (3, 4). RSV is especially associated with severe cases of bronchiolitis affecting young infants in winter months and has a typical seasonal pattern. The Children's Respiratory Study from Arizona is one of the best prospective studies evaluating the impact of early RSV disease on persistent/recurrent wheeze. This prospective study was conducted in a community-based population not at risk for disease. Among its main findings, RSV infections in the first 3 years of life were significantly and independently associated with persistent wheeze during the first decade of life, identifying a possible unique role for RSV that set it apart from other viruses (5). However, the role of RV was not evaluated in this study. Sigurs and coworkers conducted a hospital-based, prospective case-control study and showed that children with severe RSV bronchiolitis had greater risk for wheezing at the age of 13 when compared with community-based control subjects (6). Data from both of these studies have been interpreted as evidence that severe RSV bronchiolitis is associated with a 30–40% likelihood of subsequent asthma.

Recent data show that RV-caused bronchiolitis is at least as prevalent as RSV and that, in children at increased risk for developing asthma, it is associated with moderate to severe respiratory tract infections (4, 8). Children with bronchiolitis who are infected with RV alone are more likely to be older and to have evidence of atopic disease than are those infected with RSV. The Childhood Origins of Asthma (COAST) study, a cohort of children at high risk of developing asthma or allergies, has provided evidence of a close association between RV and subsequent wheezing (4, 7). A similar high-risk birth cohort study from Perth, Australia, reported findings similar to COAST, offering a slightly different perspective—that is, that atopic children with early-life respiratory infections (especially RV) are more likely to develop asthma at a later age when compared with nonatopic children or those sensitized when older (9).

Wu and colleagues, in this issue of the *Journal* (pp. 1123–1129), proposed to evaluate the causal role of winter viral respiratory epidemics in the development of asthma, retrospectively reviewing data from five seasons in a large registry of the Tennessee Medicaid program (10). The criteria for defining asthma variables and classification at early ages may be debatable because they were not defined *a priori* and were based on adult data. Nevertheless, the authors used elegant methodology to ensure that the main outcome variables had been defined in the best way the data allowed. Infants who were 4 months old at the beginning of the winter virus season were more likely to develop clinical bronchiolitis. Timing of birth in relation to the winter virus season appears to be the main predictor of asthma up to age 5 years, although children with documented bronchiolitis presented the greatest risk. Furthermore, this risk increases significantly among children with maternal history of asthma. Probably the single most fascinating finding of the study is that variation in incidence of bronchiolitis during the five evaluated seasons was paralleled by the variation of current high-risk asthma at age 5. As the authors suggest, “if this association were totally due to genetic factors, there would be a seasonal effect on infection, but not on asthma” (10).

An issue not explored in this dataset is that of atopic sensitization in early childhood. The combination of these two events—that is, atopic sensitization and early-life viral infections—has been associated with much higher odds ratios of asthma than when these two events occur separately (11). These observations led Holt and Sly to propose the “multiple hit hypothesis,” in which immune maturation status, atopic sensitization, and environmental factors, such as viral respiratory infections, play key roles leading to asthma (12).

A recent study from a nonaffluent community shows that nonatopic asthma is the most prevalent phenotype at age 10 (13). Children who had bronchiolitis before age 2 were almost 13 times more likely to have asthma at age 10 than children who did not have bronchiolitis (13). This risk increased almost five times for children presenting a combination of helminth infections (a variable that may represent a series of important environmental aggressors) and early-life bronchiolitis, thus suggesting that the “multiple hit hypothesis” may be valid in different environments. Common genetic pathways are behind these multiple risk factors leading to asthma, and new research in this area will likely advance the field (14).

The current findings are exciting and will likely heat up the debate of whether interventions for avoiding viral infections in early life are a worthy target. This is a controversial issue because children who attend daycare centers, and thus who are more exposed to recurrent respiratory infections, have been shown to have less asthma later in life (15). Infants who are young at the beginning of the virus season, and especially some subgroups at greater risk of developing asthma, such as those presenting an atopic background, may be the groups that experience the most benefit from preventive and therapeutic measures.

A case-control study of antiviral medication given in the first year of life to preterm infants, a population at risk for RSV

bronchiolitis and recurrent wheeze and asthma, has shown a 50% reduction in the occurrence of recurrent wheeze even after controlling for potential confounding variables (16). One can also speculate that RVs were likely to be responsible for many wheezing events in infants in that study who were not protected by the use of the RSV monoclonal antibody. Prospective trials with antiviral strategies, including potential new vaccines targeting RSV and RV in selected populations at risk, should give us better understanding of the role of viral infections in early life in the causation of childhood asthma.

Conflict of Interest Statement: R.T.S. has served as a consultant for Abbott in the past 3 years and received a total of \$3,600 in fees; he has also given lectures for Abbott in the past 3 years for which he received a total of \$7,700.

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Antibiotic Prophylaxis for Chronic Obstructive Pulmonary Disease

Resurrecting an Old Idea

On May 27, 1959, Dr. C. M. Fletcher of the Medical School of London delivered a lecture to the annual meeting of the American Trudeau Society (soon to be renamed the American Thoracic Society) (1). He elaborated an idea regarding the pathogenesis of chronic bronchitis, a condition that likely now would be diagnosed in most such patients as chronic obstructive pulmonary disease (COPD). In what became known as the “British Hypothesis,” Fletcher suggested that “atmospheric irritants (chiefly cigarette smoke) produce bronchial hypersecretion in susceptible subjects” and that “recurrent or persistent infection develops and leads to disability from bronchial obstruction.” (1). He also stated his belief that antibacterial drugs were capable of prolonging life in severe forms of this condition, and he ended his lecture with a call for more and better research on this subject.

The belief that recurrent respiratory infections played a central role in the pathogenesis of chronic bronchitis led to a number of randomized trials designed to study whether prophylactic antibiotics might prevent exacerbations and disability. These trials, mostly conducted in the 1950s and 1960s, were reviewed in a Cochrane Collaboration metaanalysis (2). Most studies included in the metaanalysis were relatively small, and there was much variation in quality, duration of treatment, and type of antibiotic administered. A summary estimate indicated that antibiotics statistically significantly decreased the likelihood of having an

exacerbation, but the relative reduction was only 9%. In addition, patients in two trials received daily antibiotics during the colder seasons of five consecutive years (3, 4). Compared with placebo, antibiotics had no discernible effect on loss of lung function during that period. As a consequence of these generally disappointing results, the practice of prescribing prophylactic antibiotics for COPD has been largely abandoned during the past 40 years.

In the 1980s, reports first emerged about the beneficial effects of erythromycin, a macrolide antibiotic, in diffuse panbronchiolitis (5, 6). Evidence suggested that the beneficial effects of erythromycin in this disease were not mediated by conventional antibacterial effects, but rather by a variety of antiinflammatory and immunomodulatory actions, which are now better understood (7, 8). Due to observed similarities between diffuse panbronchiolitis and cystic fibrosis, trials of macrolide antibiotics were undertaken in patients with cystic fibrosis (9). As reviewed in another Cochrane Collaboration metaanalysis, these trials (all of which used azithromycin) showed consistent, albeit modest, improvements in lung function and reductions in exacerbation frequency (10). A subsequent trial not included in the metaanalysis also showed a statistically significant reduction in exacerbation risk (11).

In this issue of the *Journal* (pp. 1139–1147), Seemungal and colleagues extend the investigation of macrolides in obstructive