Acute Viral Bronchiolitis: To Treat or Not to Treat—That Is the Question

Acute viral bronchiolitis is one of the most common conditions caused by respiratory viruses in infants and young children. For decades, controversy has surrounded both the treatment of bronchiolitis in early life and its sequelae. Part of the confusion in the literature comes from there being no common definition of acute viral bronchiolitis that is used internationally. In the United Kingdom, Australia, and New Zealand, acute viral bronchiolitis is a term used for a condition characterized by the presence of tachypnea, inflhyperinflation of the chest, and widespread fine end-inspiratory crackles (also called crepitations) heard on auscultation. Wheeze on expiration may or may not be present. This typical clinical pattern is generally seen in the first year of life, with most children requiring admission to hospital in the first 6 months of life. It is largely caused by obstruction of respiratory and terminal bronchioles by mucosal edema and mucus production caused by the viral infection with formation of fluid menisci in the bronchioles. The fine crackles are caused by the "popping open" of these small airways in late inspiration.[1] The developmental stage of the lung in the first year of life, with poorly developed collateral ventilation between adjacent lung units, facilitates the development of widespread airway obstruction. In North America and parts of Europe, however, the term bronchiolitis is commonly used to describe any lower respiratory viral infection occurring in the first 2 years of life.[2] In these older children, wheeze and bronchospasm may play a greater role in the disease pathogenesis.

Traditionally, most studies of infants with acute viral bronchiolitis have involved infants requiring hospitalization, and the virus responsible for most cases has been the respiratory syncytial virus (RSV).[3-5] Studies following populations of such infants have shown a substantial rate of respiratory problems up to the age of 5 to 6 years,[6,7] but longer term follow-up suggests that these children do not have an increased rate of atopy or of persistent asthma in later life.[7-9]

The situation appears to be somewhat different when community-based cohorts are studied. Two recent studies[10,11] have shown the major contribution of rhinoviruses (RV) to lower respiratory infection associated with wheeze (wLRI) in the first year of life. In both of these studies, RV was responsible for approximately 3-times as many wLRI as was RSV in the first year of life. The children in both of these studies have been observed to the age of 5 years, and wLRI associated with RV in the first year of life was a major risk factor for asthma at the age of 5 years. These recent reports raise significant doubts about RSV having a "special" role in inducing asthma and favor the "susceptible host" theory.

Despite decades of study, the mechanisms underlying viral-induced airway obstruction are not clear. Some authors have suggested that RSV picks out susceptible hosts. Two cohort studies that measured lung function in early life before any significant viral infections had occurred reported that low pre-morbid lung function was a major risk factor for wheezing during a lower respiratory tract infection in early life.[12,13] A genetic predisposition or environmental exposures, such as maternal smoking during pregnancy, that result in sluggish maturation of the fetal and neonatal immune systems[14] may increase the risk of contracting infection with RSV and other viruses in early life.[15] Although there is no doubt that admission to hospital with acute viral bronchiolitis is associated with recurrent respiratory problems during early childhood and is a major risk factor for asthma at 5 to 6 years of age, the association with long-term persistent asthma is much less clear.

Acute viral bronchiolitis is associated with considerable acute morbidity and mortality, with associated economic and social imposts on the community. The cost of hospitalization for acute viral bronchiolitis in children <1 year of age was estimated to exceed $700 million per year in the United States in 2001.[16] Although mortality has been falling in the past decades,[17,18] young children still die from acute viral bronchiolitis. The aim of treatment should therefore be to reduce mortality, to reduce the economic and social burden (decrease the length of stay in hospital and associated costs), and to reduce the long-term sequelae (recurrent respiratory problems and maybe persistent asthma).

Part of the problem in designing and implementing effective treatments is a lack of understanding of the underlying disease pathogenesis. Treatment with β-adrenergic agents, including albuterol and epinephrine, anti-cholinergic agents, corticosteroids, and, more recently, leukotriene receptor antagonists during the acute or recovery phase have been tried with varying success. Acute viral bronchiolitis is characterized by acute inflammation of the respiratory and terminal bronchioles; the process includes edema, necrosis of epithelial cells, production of mucus,

AAP	American Academy of Pediatrics
RSV	Respiratory syncytial virus
RV	Rhinoviruses
wLRI	Lower respiratory infection associated with wheeze

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and possibly some degree of bronchospasm. A variety of treatments designed to overcome the acute airway obstruction have been championed throughout the years. In the 1980s, bronchodilators, in particular β_2-agonists, were championed. Numerous articles debated their benefits and adverse effects. Studies measuring lung function during the acute disease phase claimed improvements[19] or deterioration in lung function, referred to as a "paradoxical effect."[20-22] Other studies showed no effect on lung function either way.[23] The potential for a decrease in arterial oxygen saturation relating to a worsening of the already disturbed ventilation-perfusion balance in the lungs was recognized.[24] Despite these physiological disturbances, bronchodilators were reported to result in an acute improvement in clinical score.[25] The use of nebulized epinephrine has also been controversial. A multicenter randomized double-blind controlled trial conducted in Australia that included 194 children reported that the length of stay in the hospital was not reduced in the group treated with epinephrine.[26] A recent meta-analysis published by the Cochrane Collaboration[27] concluded that bronchodilators improved clinical scores in the short term, but at a penalty of increased costs and increased adverse effects. This analysis included studies using albuterol, ipratropium bromide, and epinephrine. The rate and duration of hospitalization was not significantly reduced in the group treated with bronchodilators versus the control group.[27] The American Academy of Pediatrics (AAP) recommends that "bronchodilators should not be used routinely in the management of bronchiolitis."[28]

Corticosteroids have also been favored as an acute treatment for infants hospitalized with acute viral bronchiolitis. This practice is more common in some parts of the world than others; it is uncommon in Australia,[29] but common in many parts of the world.[30] Despite an earlier review of 6 trials of steroid therapy supporting a small reduction (mean, 0.43 days) in hospital length of stay compared with placebo,[31] a more recent and larger review has disputed this conclusion. A meta-analysis that included data from 1198 children between the ages of 0 and 30 months concluded that there was no decrease in length of stay or clinical score in infants and young children treated with systemic glucocorticoids when compared with children treated with placebo,[30] thus questioning the efficacy of this mode of treatment. In addition, the use of inhaled steroids during the acute phase of bronchiolitis to reduce post-bronchiolitis wheeze has been questioned, with a systematic review not able to demonstrate a significant benefit.[32] The AAP recommends that "corticosteroid medication should not be used routinely in the management of bronchiolitis."[28]

In this issue of *The Journal*, Kuzik et al[33] report a clinically relevant 26% reduction in the length of hospitalization in children with acute viral bronchiolitis treated with nebulized 3% hypertonic saline (2.6 $\pm$ 1.9 days compared with 3.5 $\pm$ 2.9 days with normal saline; $P = .05$). Although this study has some methodological deficiencies, it does provide some hope of a way forward. The use of nebulized hypertonic saline is not new. This treatment is commonly used in children with cystic fibrosis as an aid to physiotherapy by improving muco-ciliary clearance.[34] It has also been previously shown to reduce the length of hospitalization for infants with acute viral bronchiolitis when combined with epinephrine[35] and to reduce symptom scores more rapidly in ambulatory patients with bronchiolitis when added to inhaled terbutaline.[36] Kuzik et al[33] randomized 47 infants to receive nebulized 3% hypertoninc saline and 49 infants to receive nebulized normal saline in addition to "regular therapy" prescribed by the infant's attending physician. A major strength of this study was that although the age range included children as old as 12 months, most children (38/47 and 35/49) were aged 0 to 6 months. This makes the data presented by Kuzik et al[33] directly relevant to those treating acute viral bronchiolitis in other parts of the world. Unfortunately, the study did not have sufficient power to demonstrate conclusively a treatment effect in this younger age group alone. The major weakness of this study was that most infants also received other, discredited treatments, including albuterol (37%), racemic epinephrine (23%), or inhaled steroids (3%). Despite the clear recommendations from the AAP on the basis of solid evidence from Cochrane reviews that these treatments should not be used routinely in the management of acute viral bronchiolitis, they clearly are still being used.

The authors do discuss the potential for adverse effects from treatment with nebulized 3% hypertonic saline and correctly state that this is not likely to be a major problem in infants with acute viral bronchiolitis. The other issue they raise—whether there is additional benefit to combining a bronchodilator with 3% hypertonic saline—cannot be addressed by their study. The authors have, correctly, not reported the length of hospitalization separately in those children who received the study solution alone or in combination with other treatments; they would not have had sufficient power to make any valid comparisons. The authors highlight the need for further definitive studies. The results of this study, with the background literature, provide sufficient rationale for a study of nebulized 3% saline versus normal (0.9%) saline, excluding other treatments. However, the question of a synergistic interaction between 3% hypertonic saline and albuterol is worth considering. To this end, a study design with a double randomization (3% versus 0.9% saline and albuterol versus placebo-0.9% saline) would be feasible. We urge that such a study be restricted to children aged $\leq$6 months and that steroids, epinephrine, and antibiotics be "banned' during the study period. The question is worth pursuing because, if treatment with nebulized 3% saline does reduce the length of hospitalization in infants with acute viral bronchiolitis, the economic and social benefits gained from an inexpensive therapy would be worthwhile.

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"And Things that Go Bump in the Night": Nothing to Fear?

Ever since the first crib bumper pads were sold, they have held a seemingly irresistible appeal to new parents. All parents, after all, are protective of their children and do their best to keep them from harm. This includes lumps, bumps, and other injuries. Childhood rhymes, such as "he went to bed and bumped his head, and couldn't get up in the morning," and traditional prayers equating "things that go bump in the night" with "ghoulies and ghosties" provide reinforcement that bumps are dangerous and to be avoided at all cost. Protection from these injuries is often provided in the form of a soft surface that can cushion a fall or bump. Thus, it is no surprise that parents are often unable to resist providing a soft envi-

AAP	American Academy of Pediatrics
CPSC	Consumer Product Safety Commission
SIDS	Sudden Infant Death Syndrome

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