There is a lack of effective treatment options for bronchiolitis, the most common viral respiratory tract infection in children and infants. Emerging evidence suggests that nebulized hypertonic saline may have some value.

Bronchiolitis is arguably the most common significant medical illness of childhood. At least 1 in 7 normal infants will develop symptomatic bronchiolitis in his or her first year of life. Hospitalization of infants for bronchiolitis is responsible for an annual expenditure of more than a half billion dollars. Despite the extraordinary prevalence of this condition, the disease confers very little mortality. There are about 100 deaths resulting from bronchiolitis each year, and the bulk of these deaths are in children with other underlying conditions such as chronic lung disease, congenital heart disease, or other chronic diseases.

Pathophysiology
Respiratory syncytial virus (RSV) infection remains the most common cause of bronchiolitis, but recently, multiple other viruses, including adenovirus, parainfluenza virus, influenza, coronavirus, rhinovirus, and human metapneumovirus, have been recognized as etiologic agents of the condition. The growing list of causative pathogens for bronchiolitis is not so much a reflection of rapid viral evolution as it is a result of our better understanding of the viral pool. Human metapneumovirus first gained recognition as a major pathogen in bronchiolitis in 2004. Previously considered the least pathogenic of viruses, rhinovirus has been implicated as an organism in particularly severe disease. There doubtlessly will be more viruses discovered in the near future.

Severity of illness in infants is related not only to the identity of the virus but also to the viral burden in the respiratory tract and perhaps also coinfection with multiple viruses. Coinfection is much more common than initially suspected, especially in ill patients. In 1 study, children infected with RSV and coinfection with another virus were more likely to have fever and leukocytosis and more likely to receive antibiotics than if they had RSV infection alone, although this was not necessarily true for other viruses.

Other studies have reported higher rates of pneumonia or gastrointestinal symptoms, increased hospital stay, and/or increased need for oxygen associated with coinfection.

All the studies, however, have some design limitations, so whether increased severity or other detrimental outcomes result from coinfection still requires further confirmation. In both inpatient and community settings, contact and droplet precautions should be the mainstay of prevention of viral transmission.
Making the diagnosis
Many practitioners rely on various tests to distinguish between viral and bacterial disease in infants with symptoms of bronchiolitis. However, questions have emerged regarding the usefulness of routine testing in this illness.

It usually is not necessary for clinicians to identify the exact pathogen(s) responsible for an individual case of bronchiolitis. The American Academy of Pediatrics (AAP) has recommended against routine viral testing because it rarely changes the management of the disease (which usually is symptomatic) and can be quite expensive. Similarly, the AAP has recommended against any other routine laboratory or radiographic testing in bronchiolitis. This recommendation allows for greater convenience in managing this condition in the primary care office.

Chest radiography, considered by many to be a staple in the diagnosis of bronchiolitis, may influence management yet probably has no effect on outcome. In 1 well-known, randomized study, half of more than 500 young children who met World Health Organization criteria for pneumonia underwent chest x-rays, and the other half did not. The children who had chest radiography performed were more likely to receive antibiotics, but there was no actual difference in outcomes between the 2 groups.

Other studies also demonstrated limited use of chest x-rays in mild to moderately ill children with bronchiolitis. Another study determined that more than 130 chest x-rays would have to be performed to identify a single abnormality suggestive of an alternate diagnosis in children with symptoms of bronchiolitis, and those abnormalities were not always agreed on by the physicians reading the films. Thus, chest x-rays can be avoided in most cases but still have a role in the patient who has severe illness or is not following a typical disease course, such as when a pneumothorax is suspected.

Changes in recommendations for management of bronchiolitis
The recent history of developments in the management of bronchiolitis is a story of recurrent buildup and disappointment. After initial reports of success, inhaled therapy with albuterol and racemic epinephrine have been shown to provide only a brief benefit to a small percentage of infants with bronchiolitis. The AAP agrees that clinicians may initiate a trial of bronchodilators but should continue their use only if it results in objective improvement of the patient's condition. Various studies of corticosteroids have shown no benefit in treating bronchiolitis. However, recent trial results showed that a combination of epinephrine and dexamethasone reduced the likelihood of hospitalization for infants with bronchiolitis who were seen in the emergency department (ED; relative risk reduction, 35%). When controlling for multiple variables, however, the data lost their statistical significance. Furthermore, the benefit from the epinephrine arose days after administration, which is not consistent with our understanding of the pharmacology of the drug.

In the hospital setting, there are interventions that have been found to shorten length of stay (LOS). These largely pertain to changes in how patients are monitored and to institutional changes, not to novel pharmacopoeia. One study argued that the measuring of pulse oximetry in a continuous fashion prolongs hospitalization unnecessarily. In addition, hospital adoption of pathways of care and consequential standardization of care has been shown to be effective for reducing unnecessary therapy and for reducing LOS of infants in several studies. The latter finding is noteworthy given that there still is considerable variation in how bronchiolitis is treated. This variation of care has been shown to be ineffective and costly. In 1 study, more than half of patients received antibiotics, which obviously are of no benefit in a viral syndrome and may have unwanted side effects.
Few evidence-based therapies are available for treatment of bronchiolitis. Management recommendations from the AAP largely are treatments to avoid, including antibiotics, corticosteroids, ribavirin, and routine chest physiotherapy (Table 1). The only treatments recommended include oxygen (if pulse oximetry is <90%) and bronchodilators (with continuation only if the patient shows response). In the absence of available therapies with proven efficacy, desperation among parents and providers alike often leads to use of therapies that have been shown to be less than helpful. Thus, there is a great need for new treatments for bronchiolitis, and many practitioners now are looking toward hypertonic saline inhalational therapy with cautious optimism.

**Nebulized hypertonic saline**

Nebulized hypertonic saline for bronchiolitis was first brought to public attention in 2002. It previously had been shown to be effective in patients with cystic fibrosis and nasal sinus diseases. The first study in bronchiolitis showed promise in a small outpatient-based trial. Further studies followed (Table 2). Five studies evaluated regimens consisting of 3% saline either alone or in combination with epinephrine or albuterol in inpatients. In these studies, the nebulized hypertonic saline regimens consistently decreased LOS by 0.9 to 1.6 days. Given the conflicting nature of the literature on albuterol and epinephrine in bronchiolitis, the consistency of the recent inpatient studies has generated an understandable excitement among clinicians caring for children admitted with this most common of diagnoses.

Some caution is needed, however, in interpreting these results. Limitations of the inpatient studies include small sample sizes (from 41 to 126 patients) and a variety of issues related to study design. For example, in their rather small, randomized, controlled trial, Kuzik and colleagues allowed patients to receive albuterol, racemic epinephrine, and steroids at the decision of the provider. This effectively resulted in several very small groups of patients receiving different therapeutic regimens, thus limiting the power of the study to detect additive differences of therapies. Also, in some of the studies, the overall LOS was far above the average for a typical patient with bronchiolitis in the United States. For example, the Chinese studies demonstrated an improvement in LOS by more than 1 day; however, the mean LOS was far higher than what typically is found in the other studies.

In contrast to the inpatient studies, the outpatient and ED studies have emerged with mixed results. A lack of utility was observed in 3 studies in which 3% saline plus either epinephrine or albuterol was given in the ED. A study of 65 outpatients treated with 3% saline plus terbutaline reported reductions in clinical severity scores on days 2 to 5. One explanation for the dichotomy between

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inpatient and outpatient studies of hypertonic saline may be that the medication needs to be delivered consistently over a long time period or at a higher total dosage before a treatment effect is seen. The 1 positive outpatient study followed patients over 5 days and delivered the drug every 8 hours throughout the study period.61

In contrast, the 3 negative ED studies delivered the drug for between 1 and 3 doses and followed patients for 2 hours or less.37-39 One study, during which 3% or 5% saline plus epinephrine was given to 187 patients in a short-stay observation unit, followed patients for between 24 and 48 hours and delivered the medication every 4 hours.40 In this study, which represents an intermediate between the outpatient and ED studies in terms of treatment administration and follow-up, the investigators found significant reductions in clinical severity scores for the 5% saline group after 48 hours, but there was no difference in the average LOS in the unit.

Currently, there are multiple studies under way further evaluating the efficacy of hypertonic saline. One large study, based in California, will recruit 700 patients and address key issues about whether the therapy is effective, even in the setting of the ED or short LOS.42 Another study is being performed in the ED,43 and a study from Chile is assessing hypertonic saline as a diluent for albuterol in the outpatient setting.44 No outpatient studies currently are planned in the United States, although they clearly are needed.

Mechanism of action

Although the mechanism of action of hypertonic saline in viral bronchiolitis remains to be fully explained, recent advances in our understanding of the physiology of the airway surface have led to a more complete theory of why it may work. Cilia from airway epithelial cells extend into a periciliary liquid that is coated with an outer mucus layer.45 The periciliary liquid and mucus layer are known together as the airway surface liquid. The airway surface liquid also contains antibacterial agents, migratory immune system cells, and signaling molecules that help protect against pulmonary infections. Recent evidence suggests that epithelial cell ion transporters keep the periciliary liquid layer at the optimal height for ciliary beating. In normal airways, cilia beat at a height just at the interface between the periciliary liquid and the mucus layer, and mucus transport is facilitated when mucus heights are maximized. In laboratory models of the airway surface epithelium, hypertonic saline solutions increase the height of the airway surface liquid and improve mucus transport.46,47 In healthy volunteers, mucociliary transport is improved by nebulized hypertonic saline as well, even producing supranormal rates of mucociliary clearance.48

Current understanding of the pathophysiology of viral bronchiolitis comes from autopsy studies and animal models. Viral infection of the bronchiolar epithelium usually is accompanied by a mononuclear infiltrate and submucosal edema. This is followed by epithelial cell
Proposed mechanism for hypertonic saline efficacy in bronchiolitis. (A) A normal bronchiole. Cilia effectively sweep through airway surface liquid, allowing effective clearance of debris in airway. (B) An infected bronchiole. Dehydration of airway surface liquid causes ineffective ciliary motility. This results in accumulation of debris such as deceased cells and mucous in airway, which causes plugging, atelectasis, and the need for increased work of breathing. (C) A bronchiole treated with hypertonic saline. Osmotic force from 3% normal saline causes influx of water, replenishing the airway surface liquid and allowing for effective clearance of the airway.

necrosis, cellular sloughing, and small-airway plugging. Mucociliary clearance is presumed to be decreased. Recently, it has been proposed that dehydration of the airway surface liquid is part of the pathophysiology of viral bronchiolitis. In light of new knowledge about the physiology of the airway surface liquid, this hypothesis would account for the apparent clinical utility of hypertonic saline. In other words, hypertonic saline may rehydrate the airway surface liquid and restore normal ciliary function (Figure).

There are other proposed mechanisms of action for hypertonic saline in viral bronchiolitis, most of which rely on extrapolation from its highly successful use in cystic fibrosis. For example, in cystic fibrosis, hypertonic saline has been shown to stimulate cough as well as reduce mucus viscosity and improve elasticity in vitro. Other investigators have proposed a conformational change in the mucus molecule induced by hypertonic saline. Ciliary beat frequency also may be increased by cytokines induced by hypertonic saline. Hypertonic saline is clinically established as promoting productive cough, and it already is used effectively for sputum induction in both normal persons and in asthmatic and cystic fibrosis patients.

Safety
Theoretical concerns about the safety of hypertonic saline have been raised because it has been used in asthma studies to induce bronchospasm (reversible airway obstruction). Initial studies of hypertonic saline in bronchiolitis paired the medication with bronchodilators in order to prevent bronchospasm. However, it is important to note that asthma studies typically use concentrations of 4.5% saline and deliver much higher nebulized volumes of solution.

Despite the high concentration and large volume, not all patients with asthma demonstrate bronchospasm. Most of the available studies in bronchiolitis evaluated 3% saline at doses of 2 cc to 4 cc per nebulization, a dose that is much lower in concentration and volume than that used to induce bronchospasm in patients with asthma. Also, given that albuterol is not indicated in the majority of bronchiolitis cases, infants with bronchiolitis should not be considered to have the same respiratory physiology as persons with asthma.

Safety of hypertonic saline without associated administration of bronchodilators has been assessed in 3 studies. Kuzik and colleagues were the first to investigate the use of 3% saline without directly specifying that it be used concomitantly with a bronchodilator (although bronchodilators were allowed to be prescribed to study participants). Participants received an average of more than 3 treatments of hypertonic saline alone each day, and there were no reported negative effects on respiratory status. A 0.3% rate of bronchospasm was observed in a retrospective study of 377 doses of 3% saline.
delivered without concomitant bronchodilators. This study addressed only the safety and not the efficacy of the medication. In the most recent randomized trial from China, bronchodilators were not administered to any of the study participants. The investigators delivered doses of hypertonic saline as frequently as every 2 hours to more than 100 study participants without reporting any episodes of bronchospasm or significant adverse events.

**How we might use this therapy**

Many children's hospitals already have incorporated use of nebulized hypertonic saline into their standard treatment protocols. During the 2010 annual Pediatric Hospital Medicine meeting, an informal poll revealed that about a third of pediatric hospitalists have moved forward and are routinely using hypertonic saline for bronchiolitis patients. If it proves effective, outpatient applications clearly are next up for study.

It may be best, however, for hospitals to refrain from introducing this therapy to await the results of future trials before we further muddy the waters of bronchiolitis management with another potentially ineffective therapy. Once something has been introduced, it can be difficult to curtail its use. In hospital-based pediatrics, there is a history of clinging to ineffective therapy far beyond the point at which it has been demonstrated ineffective.

Furthermore, the optimal dosing scheme for nebulized hypertonic saline has yet to be established. Early evidence suggests that routine and relatively frequent use for a prolonged period is likely to be most effective. In the outpatient realm, 3 times per day for 5 days seemed to reduce severity of symptoms. No other outpatient regimens have been reported in the literature. As of yet, no company has marketed convenient outpatient systems for administration of hypertonic saline in home nebulizer machines.

In the inpatient setting, administration schedules have not been consistent. Three studies administered nebulized hypertonic saline every 8 hours until discharge. In 2 others, hypertonic saline was dosed every 2 hours for 3 doses, every 4 hours for 5 doses, and then every 6 hours until discharge.

**Hope for the future**

It has been frustrating that the diagnostic modalities and therapies commonly employed for bronchiolitis have not been demonstrated to be effective. Lab testing and radiography add benefit only in unusual or severe cases. Corticosteroids and inhalational albuterol and epinephrine are ineffective in most cases. The common use and toxicity of over-the-counter preparations for infants with upper respiratory infections is well described. Hypertonic saline may be beneficial and likely is less toxic than many of the over-the-counter preparations designed for children with viral respiratory illness. Hypertonic saline is already being employed in many health centers around the country. Time will tell whether this promising new therapy deserves a solid foothold in the treatment of bronchiolitis and also how to optimize its delivery. If its efficacy is confirmed, it will be the first routine therapy that shows benefit for these patients.

**REFERENCES**

14. American Academy of Pediatrics Subcommittee on Diagnosis *CONTINUED ON PAGE 38*


