

## Bronchiolitis

*Case objectives are provided in order to assist in ensuring that minimum session objectives are achieved. Learners may address other objectives beyond the list provided.*

### Group Objectives :

1. Identify the important treatable disorders with similar presentations to acute viral bronchiolitis (Medical Expert)
2. Describe the clinical indicators of severe and/or worsening pulmonary status in an infant with bronchiolitis, with discussion on pathophysiology (Medical Expert)
3. Discuss the evidence for and against the investigations and treatment modalities commonly ordered for infants with bronchiolitis (Medical Expert)
4. Outline an evidence based management plan for an infant with viral bronchiolitis including criteria for discharge (Medical Expert)
5. Describe the mechanism of action of palivizumab, current guidelines for its use and the strength of evidence regarding it's efficacy (Medical Expert)
6. Describe how you would educate parents on the seasonal flu vaccine, the indications, & contraindications (Communicator)

### Relevant Literature :

1. Pediatrics in Review (2009). Bronchiolitis. PIR 2009;30;386
2. Plint AC et al. (2009). Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med 360(20); 2079-89.
3. CPS. (2011). Policy Statement— Preventing respiratory syncytial virus Infections.
4. JL Robinson; Canadian Paediatric Society, Infectious Diseases and Immunization Committee CPS. (2011). Influenza vaccine recommendations for children and youth for the 2011–2012 season.
5. CPS. Colds in children. <http://www.caringforkids.cps.ca/whensick/colds.htm>

It is a Thursday night on call in mid December. You have just finished watching “So You Think You Can Dance” and you are in a foul mood because your favorite dancer was voted off the show. To make matters worse, you are paged to the ER to see a 5-month-old infant with “pneumonia”. The ER physician indicates that the baby was saturating 85% in R/A when she arrived in ER. She was given a series of “back to back” ventolin nebulizations, with modest improvement. She had a chest X-ray that showed right middle lobe pneumonia so a dose of Azithromycin had been given. The baby is “stable” at this time but is requiring 3 lpm of oxygen by nasal prongs to maintain saturations and thus the ER physician is requesting admission. You scrape the ice and snow off your car and head into the hospital.

You arrive in ER to find the baby, Emily Thomas, in her father Paul’s arms. You introduce yourself and before taking the history, indicate to Paul that you should quickly assess Emily’s status.

She appears pink and settled. She has nasal prongs in place, running at 3 lpm. She is awake, alert and attentive to her surroundings. HR on the monitor is 188, RR 65, BP 78/34 and O2 Saturation is 95%. You note some slight nasal flaring and intercostal retractions with each inspiration but no expiratory grunting. You note profuse nasal discharge and crusting. She has good air entry through all lung zones but diffuse, soft crackles and wheezes. Cardiac exam is normal (other than the HR). Cap refill is 3 seconds.

You quickly write your initial orders and hand them to the ER nurse assigned to Emily.

You return to Paul to take the rest of the history. Three days ago, she developed a low-grade fever, some nasal congestion, a cough and some hoarseness to her cry. When she has a prolonged coughing episode, she vomits quite a bit of formula. They had taken her to a clinic that afternoon and she was given Amoxil for “pneumonia”. Her symptoms have been worsening today and she is having a hard time nursing because of her nasal congestion and the fact that she seems breathless with feeding. Her diapers have been distinctly less wet and less frequent than usual. She usually nurses every 3 hours all day but sleeps through the night. She has just started solids. You learn that she was a premature infant of 30 weeks. Paul tells you that she was on a ventilator for the first 2 days of life and then on another breathing machine for about a week. She was discharged from the NICU at 8 weeks of age having had no complications of her premature delivery. This is her first illness and she is fully immunized. She has been getting an “RSV shot” at her family doctor’s office each month. She has been growing well. Review of systems is otherwise unremarkable. She lives at home with her parents and 3-year-old brother (at home tonight with his mother Anna Marie) who just started daycare in September.

The family history is notable for allergies and asthma in her dad, but is otherwise unremarkable. Development is appropriate for her corrected age.

You complete the physical exam. Her weight (4.7kg) and length are each at the 25th percentile for corrected age. Head circumference is at the 50th percentile. Dad indicates that these are consistent with the percentile curves at her Family Doctor's office. Her fontanelle, sutures and tympanic membranes are normal. Oropharynx is moist and appears normal. Abdomen, skin, neuro and msk exams are unremarkable. Genitalia are normal.

Paul states that he and Anna Marie were nervous having Emily at home because they were concerned that she is not feeding well and that her breathing is getting worse. You indicate that you agree that hospital admission is probably a good idea but you will discuss it with your preceptor, Dr. Davidson, the pediatrician on call.

Dr. Davidson has been a pediatrician in this community for 34 years. He has many endearing qualities but has a reputation for being "strong willed". You tell him about Emily and when he asks what your management plan would be, you share your interpretation of the literature on the management of bronchiolitis, acknowledging that there is much variation from hospital to hospital and among different clinicians. You outline your plan and he agrees, but tells you to also give the baby a dose of dexamethasone, 0.6 mg/kg now and in 12 hours. You initiate a discussion regarding the evidence for using steroids in bronchiolitis. He listens attentively and then tells you to go ahead and order it because in his experience, babies with bronchiolitis get better faster when they get dexamethasone, and that it is unlikely to do any harm.

You start to write out the admission orders when you remember that the hospital has a "Clinical Pathway" for asthma admissions. You ask the nurse in charge if the hospital has such a thing for bronchiolitis but you are told that it does not. You hand write the orders quickly, including an entry for 2 doses of 2.5 mg of Dexamethasone 12 hours apart, and complete the rest of your paper work. You check in on Emily and note that her status is unchanged. You ask her nurse to call you if there are any changes in her status. You head home.

The next morning, on rounds with Dr. Davidson, Emily's nurse Karen indicates that she had a good night. Her respiratory rate is lower and she is beginning to feed better. Her urine output has been 2.4 cc/kg /hr. She is down to 1lpm of oxygen and could be ready to try room air.

"See, I told you the steroids would work." Dr. Davidson says, looking satisfied.

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# Bronchiolitis

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Dr Wagner has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Recognize the clinical presentation of bronchiolitis.
2. Be aware of the recommendations made in the current American Academy of Pediatrics clinical practice guideline for diagnosis and management of bronchiolitis.
3. Describe the role of laboratory testing in the diagnosis of bronchiolitis.
4. Delineate the efficacy of current therapeutic interventions in the treatment of bronchiolitis.
5. Discuss the evaluation for serious bacterial infections in patients who have bronchiolitis.
6. Outline the prognosis and risk of recurrent wheezing in patients diagnosed with bronchiolitis.

## Introduction

Bronchiolitis, defined as inflammation of the bronchioles, usually is caused by an acute viral infection. Viral bronchiolitis is the most common lower respiratory tract infection in infants and children who are 2 years of age and younger. The most commonly identified infectious agent is the respiratory syncytial virus (RSV). Other identified pathogens include adenovirus, human metapneumovirus, influenza virus, and parainfluenza virus.

The pathophysiology of bronchiolitis begins with an acute infection of the epithelial cells lining the small airways within the lungs. Such infection results in edema, increased mucus production, and eventual necrosis and regeneration of these cells. The clinical presentation of bronchiolitis includes rhinitis, cough, tachypnea, use of accessory respiratory muscles, hypoxia, and variable wheezing and crackles on auscultation.

The evaluation and management of bronchiolitis varies substantially. Although bronchiolitis is a well-recognized clinical syndrome, additional tests such as viral isolation, blood serology, and chest radiographs often are ordered, although they have little impact on diagnosis. Most clinical interventions have no significant impact on length of hospital stay, severity of clinical course, or subsequent outcomes such as episodes of recurrent wheezing or ultimate diagnosis of asthma. In 2006, the American Academy of Pediatrics (AAP) released a clinical practice guideline for the diagnosis, testing, and management of bronchiolitis (Table 1). (1) These recommendations are based on current available evidence and expert opinion where necessary (Table 2). Adherence to the AAP clinical practice guideline can decrease unnecessary diagnostic testing, focus practitioners on effective therapeutic interventions, and provide appropriate anticipatory guidance for families who are caring for a child who has bronchiolitis.

## Epidemiology

Infection with RSV, the most common cause of bronchiolitis, leads to more than 90,000 hospitalizations annually. (2) The cost of such hospitalizations for children younger than 1 year of age has been estimated to be more than \$700 million. Hospitalization for bronchiolitis in the United States has been increasing over the past decade. For most previously well patients, bronchiolitis is a self-limited disease that responds well to supportive care within the home. However, young patients and patients who have pre-existing medical conditions form a vulnerable population that may require inpatient admission.

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**Table 1. Summary of American Academy of Pediatrics Clinical Practice Guidelines for Diagnosis and Management of Bronchiolitis**

Recommendation	Summary	Statement	Evidence Level
Recommendation 1 a	Clinicians should diagnose bronchiolitis based on history and physical findings without routine laboratory and radiologic studies	Recommendation	Level B
Recommendation 1 b	Clinicians should assess risk factors for severe disease including age <12 wk, prematurity, cardiopulmonary disease, and immunodeficiency	Recommendation	Level B
Recommendation 2 a	Bronchodilators should not be used routinely in the management of bronchiolitis	Recommendation	Level B
Recommendation 2 b	A monitored trial of alpha-adrenergic or beta-adrenergic is an option, with continuation only if a response is documented	Option	Level B
Recommendation 3	Corticosteroid medications should not be used routinely in the management of bronchiolitis	Recommendation	Level B
Recommendation 4	Ribavirin should not be used routinely in children who have bronchiolitis	Recommendation	Level B
Recommendation 5	Antibacterial medications are indicated only for treatment of coexisting bacterial infection	Recommendation	Level B
Recommendation 6 a	Clinicians should assess hydration status and ability to take fluids orally	Strong Recommendation	Level X
Recommendation 6 b	Chest physiotherapy should not be used in the management of bronchiolitis	Recommendation	Level B
Recommendation 7 a	Supplemental oxygen is indicated if oxyhemoglobin saturation persistently falls below 90%	Option	Level D
Recommendation 7 b	As the child's clinical course improves, continuous monitoring of Sp <sub>o</sub> <sub>2</sub> is not needed routinely	Option	Level D
Recommendation 7 c	Infants who have a known history of prematurity, lung disease, or hemodynamically significant heart disease require close monitoring during oxygen weaning	Strong Recommendation	Level B
Recommendation 8 a	Clinicians may administer palivizumab to infants who have a history of prematurity, chronic lung disease, or congenital heart disease	Recommendation	Level A
Recommendation 8 b	Palivizumab should be given in five monthly doses beginning in November or December at a dose of 15 mg/kg per dose intramuscularly	Recommendation	Level C
Recommendation 9 a	Hand decontamination is the most important step in preventing nosocomial spread of respiratory syncytial virus	Strong Recommendation	Level B
Recommendation 9 b	Alcohol rubs are preferred for hand decontamination	Recommendation	Level B
Recommendation 10 a	Infants should not be exposed to passive smoking	Strong Recommendation	Level B
Recommendation 10 b	Breastfeeding is recommended to decrease a child's risk of having lower respiratory tract infection	Recommendation	Level C
Recommendation 11	Clinicians should inquire about use of complementary alternative medicine	Option	Level D

Level A=Well-designed randomized clinical trials or diagnostic studies on relevant populations  
Level B=Randomized clinical trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies  
Level C=Observational studies (case control and cohort design)  
Level D=Expert opinion, case reports reasoning from first principles  
Level X=Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit or harm  
Sp<sub>o</sub><sub>2</sub>=oxygen saturation by pulse oximetry  
From Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118:1774–1793.

Table 2. Guideline Definitions and Evidence Quality

Statement	Definition	Implication
Strong Recommendation	Anticipated benefits of recommended intervention exceed harms; quality of supporting evidence is excellent	Clinicians should follow unless compelling rationale for alternative approach is present
Recommendation	Anticipated benefits exceed potential harm; quality of supporting evidence is not as strong	Clinicians would be prudent to follow recommendation; should remain alert to new information and patient preference
Option	Evidence has not shown clear advantage of one approach over another	Clinicians should consider the option; patient preference may have substantial role
No Recommendation	Lack of evidence required to make recommendation	Clinicians should be alert to new published evidence

From Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118:1774–1793.

The most common risk factor for hospitalization is age. Most inpatient admissions are patients younger than 1 year of age. Infants younger than 3 months of age are at increased risk for apnea and severe respiratory distress. Prematurity is another important risk factor for severe bronchiolitis, especially if associated with a previous diagnosis of neonatal respiratory distress syndrome. Children who have unrepaired congenital heart disease, particularly if associated with pulmonary over-circulation, and children afflicted with chronic lung disease have diminished pulmonary reserve, thereby increasing the chance for hospitalization during an episode of acute bronchiolitis. Children born with airway abnormalities such as laryngomalacia, tracheomalacia, and cleft lip or palate may need supportive care to manage a bronchiolitis-associated increase in upper airway secretions. Patients who have neurologic abnormalities with associated dystonia also may need additional support for secretion management.

Improved recognition and advances in critical care support have decreased mortality over the past 20 years. RSV-associated deaths are rare, accounting for fewer than 500 deaths per year in the United States. Although children who have the pre-existing medical conditions listed previously are at increased risk for severe bronchiolitis, most RSV-associated deaths occur in children who have no pre-existing medical conditions.

## Diagnosis

Bronchiolitis should be diagnosed on the basis of history and physical examination. Routine laboratory or radiologic studies are not recommended to support the diagnosis. Patients commonly present with a history of recent upper respiratory tract symptoms. Lower respiratory tract findings, which include cough, tachypnea, and increased work of breathing, follow the upper respiratory

prodrome. Physical findings on visual inspection include nasal congestion, rhinorrhea, cough, tachypnea, and increased respiratory effort. Nasal flaring; grunting; and intercostal, supracostal, and subcostal retractions demonstrate increased respiratory effort.

Upper airway obstruction can contribute significantly to increased work of breathing. Nasal suctioning and repositioning may help decrease respiratory effort and allow a more accurate assessment of lower respiratory tract involvement. Auscultation reveals a variety of findings, including crackles, wheezes, and referred upper airway noise. In very young infants, especially those who have a history of prematurity, apnea alone may be the presenting sign as well as a complication of bronchiolitis.

The clinical presentation of bronchiolitis can range from mild tachypnea to impending respiratory failure. Physical findings reflect the dynamic nature of the disease. Significant variability between serial examinations is common. An elevated respiratory rate is the earliest and most sensitive vital sign change. In addition, patients may have tachycardia due to dehydration and variable degrees of hypoxemia. Currently, no robustly supported guidelines for vital sign parameters or physical findings that correlate with clinical outcomes exist, likely due to the high variability of physical findings in affected patients. Respiratory rate, work of breathing, and hypoxia are the most clinically significant parameters in determining illness severity and should be assessed routinely in all patients who have bronchiolitis.

The course of bronchiolitis follows a characteristic pattern. Patients can be expected to have worsening clinical symptoms, with peak symptomatology around day 3 to 4 of illness. “Day of illness” is an important variable in providing anticipatory guidance for outpatient management and in making decisions regarding admission and discharge of patients.



Figure. Chest radiograph of infant who has respiratory syncytial virus bronchiolitis, demonstrating hyperinflation and small areas of patchy, bilateral atelectasis.

Chest radiographs are not recommended routinely for diagnosis. Patients who have bronchiolitis often have abnormal-appearing radiographs. Common findings include hyperinflation, areas of atelectasis, and infiltrates (Figure). These findings do not correlate with disease severity and do not guide management. In addition, abnormal chest radiologic findings may prompt the use of unnecessary antibiotics for a perceived primary or concurrent bacterial pneumonia, which is rare in viral bronchiolitis.

Viral studies are not recommended for the diagnosis of bronchiolitis, and antiviral agents are not recommended in its treatment. Hence, the identification of the particular infectious agent does not affect clinical management. Because many infectious agents can cause the same clinical presentation, viral studies are useful if the information is needed for cohorting patients infected by the same viral pathogen. Isolation procedures should be based on clinical signs, regardless of viral testing.

Patients older than 60 days of age who have bronchiolitis and fever have a low risk of serious bacterial infection (SBI). This fact should reassure the practitioner that additional laboratory evaluation and use of antibiotics are not needed in routine cases.

Infants younger than 60 days of age who have clinical bronchiolitis and fever often are admitted to the hospital and receive a full sepsis evaluation for potential SBIs such as urinary tract infections, bacteremia, and meningitis. Evaluation and treatment for sepsis has been associated with parental dissatisfaction, increasing antibiotic resistance, and iatrogenic complications. There are no cur-

rent guidelines for the management of young febrile infants who have obvious viral infections, including bronchiolitis. Recent literature has demonstrated that infants who present with fever and are diagnosed as having bronchiolitis are at decreased risk for SBIs compared with infants who present with fever alone. (3)(4)(5)(6)(7) Most of these studies are retrospective and based on small numbers of febrile infants younger than 60 days of age.

Management of clinical bronchiolitis in young febrile infants remains controversial. The largest prospective study examining the occurrence of SBIs in febrile infants younger than 60 days of age who had bronchiolitis concluded that such infants have a low but potential risk for concurrent SBIs. (3) Urinary tract infections are the most commonly diagnosed concurrent SBI.

Based on the current literature, the risk of SBI among infants 30 days of age or younger remains substantial and is unchanged by the diagnosis of bronchiolitis. Such patients should continue to receive conservative management for fever, including full evaluation for SBI and administration of empiric antibiotics. Recognition that infants older than 30 days who have clinical bronchiolitis are at a lower risk for SBIs may allow for decreased invasive testing and observation without administering antibiotics to patients who have classic presentations. Viral testing may provide additional reassurance to practitioners electing to observe without administering antibiotics. Further studies that have large cohorts of young febrile infants are needed to examine the relationship between bronchiolitis and concurrent SBIs in the youngest febrile infants.

## Management

Possible therapeutic interventions for bronchiolitis are multiple: bronchodilators, corticosteroids, antiviral agents, antibacterial agents, chest physiotherapy, nasal suction, and decongestant drops have been used. Despite this extensive list, none of these therapies have demonstrated significant impact on duration of illness, severity of clinical course, or subsequent clinical outcomes, such as postbronchiolitis wheezing. (8) Newer management strategies for bronchiolitis clearly emphasize supportive care, with hydration and oxygenation as the primary therapeutic interventions.

All infants who have bronchiolitis require assessment of hydration status. Elevated respiratory rate, copious secretions, fever, and poor feeding all contribute to dehydration. Patients may require intravenous fluid rehydration and continued intravenous fluid or nasogastric feedings until feeding improves. Bronchiolitis has been

described as an independent stimulus for antidiuretic hormone release and may put patients at risk for iatrogenic hyponatremia if given hypotonic fluids. Use of isotonic fluids for such patients may be beneficial in decreasing the risk for iatrogenic hyponatremia. (9)(10) Patients who have severe bronchiolitis may benefit from nasogastric feeding for nutrition support until feeding improves.

Bronchiolitis is characterized by variable hypoxemia resulting from impaired diffusion across the blood-gas membrane as well as ventilation-perfusion mismatch caused by heterogeneous plugging of distal bronchioles. Oxygen administration is a key therapeutic intervention. The ultimate goal of maintaining normal blood oxygen saturation is to prevent hypoxia or insufficient delivery of oxygen to metabolically active tissue. Debate within the literature regarding the lower limit of tolerated saturations for patients who have a primary respiratory process is significant. Some authors have advocated a pulse oximetry saturation range of 92% or higher in a previously well patient. Others have stated that pulse oximetry saturations higher than 90% are acceptable, noting that this saturation still is associated with appropriate oxygen delivery on the oxyhemoglobin dissociation curve. The need and duration of supplemental oxygen should be based on a complete assessment of the patient.

The day of illness can guide practitioners in determining if the patient requires an increase or decrease in supportive care, including oxygen therapy. As expected on day 3 or 4, a clinically improving patient may experience intermittent decreases in pulse oximetry saturation, which should not prompt automatic continuation or reinitiation of oxygen supplementation. Reinitiation of oxygen therapy often is associated with prolonged hospitalization and may not offer significant benefit. Oxygen should be discontinued once pulse oximetry saturations rise to between 90% and 92% for most of the time and the patient is demonstrating overall clinical improvement, as evidenced by adequate feeding and improved work of breathing.

Variability in the use and interpretation of pulse oximetry in patients who have bronchiolitis is wide. The obvious advantage of pulse oximetry is rapid assessment of oxygenation without invasive testing. The disadvantages include variation in product accuracy, motion artifact, and decreased sensitivity in patients who have poor perfusion. Although pulse oximetry readings often are instrumental in determining the need for admission, use of continuous monitoring has been associated with unnecessary increased length of hospital stay for patients who have bronchiolitis. In addition, after many days of

continuous monitoring, many parents feel uncomfortable taking the child home and may request a home monitor. There are no guidelines for the use of pulse oximetry in patients who have bronchiolitis but have no prior history of chronic illness.

Two strategies that may minimize unwanted consequences of prolonged monitoring in the hospital setting are: 1) scheduled spot checks along with measurement of vital signs and unscheduled checks when clinically indicated or 2) scheduled spot checks after a fixed period of monitoring. Continuous pulse oximetry monitoring should be reserved for those who previously required continuous oxygen supplementation, those who have risk factors for apnea, and those who have underlying cardiopulmonary conditions. Similar to pulse oximetry, there are no guidelines for cardiac monitoring of patients who have bronchiolitis. Cardiopulmonary monitoring may be considered in select patients, such as infants who have had episodes of apnea that may be associated with bradycardia or patients who have underlying cardiac conditions.

The AAP does not recommend use of bronchodilators in the routine treatment of bronchiolitis. A monitored trial of a bronchodilator may be considered but should be continued only if a clinical response is documented. Epinephrine and albuterol are the bronchodilators used most commonly. Epinephrine has been associated with slightly better temporary clinical improvement than albuterol. This effect likely is due to the alpha-adrenergic-mediated vasoconstriction that may aid in decreasing nasal congestion. Epinephrine should be reserved for hospitalized patients or those being evaluated in the emergency department. Epinephrine is not recommended in the outpatient setting due to limited data regarding safety with unmonitored administration. Albuterol is the recommended bronchodilator for continued therapy in the outpatient setting. (11)

If an improvement in clinical status is documented, continued treatment with bronchodilator therapy might be considered. A good clinical response to bronchodilator therapy may manifest as diminished work of breathing, decrease in respiratory rate, and improvement in hypoxemia. Many institutions have bronchiolitis-specific assessment tools to assess these and other clinical variables in response to medical interventions. An important area of research is development of a robust bronchiolitis scoring tool predictive of clinical course and outcome.

Corticosteroid medications, inhaled or administered systemically, should not be used in the treatment of bronchiolitis. Ambiguity regarding their use has resulted from a heterogeneous and at times difficult-to-interpret

body of medical literature. Previously, studies of corticosteroid use in bronchiolitis have suffered from interstudy design variability and wide variation in study sample size. However, an inclusive Cochrane database review on the use of corticosteroids for acute bronchiolitis concluded that there is no significant difference in length of stay or severity of disease for patients receiving such therapy. (12) The review included randomized clinical trials and involved nearly 1,200 patients who had bronchiolitis. Further, steroids have a well-established undesirable adverse effect profile. Based on current available evidence, corticosteroids should not be used to treat bronchiolitis.

Ribavirin should not be used routinely in the treatment of bronchiolitis; trials have demonstrated variable outcomes. Although some of the studies have shown benefit, this finding has not been consistent. Also, many of the studies have suffered from small sample size and variable design quality. Ultimately, high cost, difficult administration, and lack of robust evidence of benefit have limited the role of this therapy. Additional research into more cost-effective agents that are administered more easily may result in a more significant role for antiviral agents in the treatment of RSV bronchiolitis. Ribavirin may be considered in select situations of severe bronchiolitis. Examples include patients whose medical conditions are pre-existing, such as organ transplantation, malignancy, or congenital immunodeficiencies, or patients who remain critically ill despite maximized support.

**Because** RSV causes most cases of bronchiolitis, influenza-associated bronchiolitis represents a unique, small subset of affected patients.

Because RSV causes most cases of bronchiolitis, influenza-associated bronchiolitis represents a unique, small subset of affected patients. Treatment of influenza infection with antiviral medications may decrease the severity of symptoms and associated complications, especially if initiated within the first 48 hours of presentation. The two classes of anti-influenza medications include the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). The adamantanes no longer are recommended as treatment for influenza due to their lack of activity against influenza B strains and increased resistance by influenza A strains.

The Centers for Disease Control and Prevention (CDC) now recommends oseltamivir, approved for use in children older than 1 year of age, and zanamivir, approved for children older than 5 years of age, for the treatment of influenza infection. Challenges in maintaining safe and effective anti-influenza medications underscore the importance of annual influenza vaccinations. Viral testing and initiation of influenza-directed therapy should be considered only when the clinical presentation, in addition to surveillance reports in the community, suggests a high positive predictive value for influenza infection.

Antibacterial agents have no impact on viral bronchiolitis and should be used only in patients diagnosed with a concurrent bacterial infection. Acute otitis media (AOM) is the concurrent bacterial infection diagnosed most commonly. Although otitis media with middle ear effusion (OME) may be caused by the viral infection itself, no reliable physical characteristics allow the clinician to distinguish between a viral and bacterial OME. Hence, treatment should follow current AAP guidelines, which emphasize the use of key physical findings, including tympanic membrane position and mobility, distortion of light reflex, and disappearance of translucency to differentiate between AOM and nonbacterial OME.

Initiation of antibiotic therapy for suspected AOM should be based on patient age, severity of illness, and diagnostic certainty. Patients younger than 6 months of age should receive amoxicillin 80 mg/kg per day divided into two doses for 7 to 10 days. Patients older than 6 months of age and younger than 2 years of age should receive treatment if diagnostic certainty is strong but may be considered for observation if the infection is not severe. Many physicians elect to provide such patients with a “safety scrip” for antibiotics, should symptoms worsen. Patients older than 2 years of age should receive antibiotic treatment only if the diagnostic certainty is strong and the infection severe.

Chest physiotherapy should not be used to treat bronchiolitis. As described previously, the pathophysiology of bronchiolitis involves infection of the epithelial cells lining the small airways. This process is diffuse, causing heterogeneous regions of perfusion-ventilation mismatch that are unaffected by regional chest physiotherapy.

Nasal suction often is used to relieve upper airway obstruction. Suctioning may increase comfort and improve feeding. However, excessive suction can be associ-

Table 3. Palivizumab Prophylaxis Guidelines

Prematurity <28 weeks gestational age 29 to 32 weeks gestational age 32 to 35 weeks gestational age	Prophylaxis recommended throughout first postnatal year Prophylaxis recommended throughout first 6 postnatal months Consider if infant is younger than 6 months of age and has two of the following risk factors: child care attendance, school-age siblings, exposure to environmental air pollutants, congenital abnormalities of the airway, or severe neuromuscular disease
Chronic lung disease	Prophylaxis recommended for patients <2 years who have chronic lung disease and have required medical therapy, including supplemental oxygen, diuretics, or bronchodilator or corticosteroid therapy, within 6 months of bronchiolitis season
Hemodynamically significant congenital heart disease	Prophylaxis recommended for patients <2 years of age who have cyanotic congenital heart disease or pulmonary hypertension or patients receiving medication to control congestive heart failure
From American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. <i>Red Book. 2009 Report of the Committee on Infectious Diseases</i> . 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:560–569.	

ated with nasal edema and lead to additional obstruction. Judicious nasal suction is most beneficial before feeding and in response to copious secretions. No evidence exists to support “deep” suctioning of the lower pharynx.

Nasal decongestant drops have been used to manage upper airway obstruction, but no evidence supports the use of such medications. Various components of the medications have been shown to be harmful in adult patients, and there is no significant information regarding their use in pediatric patients. Lack of efficacy and potentially harmful adverse effects prompted the United States Food and Drug Administration to issue a public health advisory in January 2008 strongly stating that over-the-counter cough and cold products, including nasal decongestants, should not be used for infants and children younger than 2 years of age. Many manufacturers have withdrawn pediatric cough and cold preparations voluntarily from the market. Nasal decongestants should not be used to treat bronchiolitis.

### Prevention

Administration of palivizumab, a monoclonal antibody (immunoglobulin G) directed against RSV, to select groups of infants might prevent hospitalization for bronchiolitis. These groups include infants who have a history of prematurity, infants who have chronic lung disease, and infants born with hemodynamically significant congenital heart disease (Table 3).

Because the risk of severe bronchiolitis increases with degree of prematurity, recommended guidelines are stratified into categories of prematurity. Infants born at 28 weeks’ gestation or less benefit from protection throughout their first bronchiolitis season and should

receive prophylaxis whenever bronchiolitis occurs in the community throughout their first postnatal year. Infants born at 29 through 32 weeks’ gestation receive the most benefit during the first 6 postnatal months. Should a patient qualify for initiation of prophylaxis at the start of the bronchiolitis season, he or she should continue to receive prophylaxis throughout the remainder of the season. Patients born at 32 through 35 weeks’ gestation should be considered for prophylaxis if they are younger than 6 months of age at the beginning of the bronchiolitis season and have at least two of the following risk factors: child care attendance, school-age siblings, exposure to environmental air pollutants, congenital abnormalities of the airway, or severe neuromuscular disease.

Palivizumab prophylaxis should be considered for patients younger than 2 years of age who have chronic lung disease and have required medical therapy, including supplemental oxygen, diuretic use, and bronchodilator or corticosteroid therapy, within 6 months before the bronchiolitis season. Select patients who have severe chronic lung disease may benefit from prophylaxis during subsequent seasons. However, the effectiveness of palivizumab beyond the second postnatal year is unknown. Consulting with a pulmonologist is suggested before initiating prophylaxis in this older age group.

All children younger than 2 years of age who have hemodynamically significant congenital heart disease of either cyanotic or acyanotic form may benefit from palivizumab prophylaxis. Among those who have congenital heart disease, children who receive the most benefit are those younger than 2 years of age who currently are receiving medication to control congestive heart failure,

those who have moderate-to-severe pulmonary hypertension, and those who have cyanotic heart disease.

Palivizumab prophylaxis should be administered in five monthly doses beginning in November or December at a dose of 15 mg/kg per dose. This recommended schedule accommodates the national variation in bronchiolitis seasons. The primary benefit of prophylaxis is a decrease in the rate of RSV-associated hospitalization. No studies have demonstrated a significant decrease in mortality among patients who received palivizumab prophylaxis. Additionally, palivizumab is not effective in the treatment of an acute RSV infection.

Despite decreased rates of hospitalization, economic analysis of palivizumab prophylaxis has not demonstrated overall cost-effectiveness, even among high-risk infants. The effect likely is due to the very high cost of the medication, the variability in cost of hospitalization, and the low mortality rates associated with RSV bronchiolitis. Future areas of research include development of less expensive prophylactic agents that have improved cost-effective benefits in the prevention of bronchiolitis.

Strict hand hygiene and isolation policies remain the cornerstone of preventing nosocomial RSV infections. The CDC has published a review of the hand hygiene literature and made recommendations regarding hand washing and the use of hand antiseptic products by patients who have bronchiolitis. Hands should be washed after direct contact with patients, after removal of gloves, and after contact with inanimate objects in the direct vicinity of the patient. If hands are not visibly soiled, an alcohol-based rub is preferred; the alternative is thorough hand washing. Additional methods for controlling nosocomial infection include changing gloves frequently, wearing gowns during direct contact with patients, and isolating or cohorting RSV-positive patients, with medical personnel specifically assigned to only their care. All physicians should model and enforce appropriate hand hygiene when caring for patients who have bronchiolitis. Physicians also should be aware of the current infection control policy at their institutions for patients who have bronchiolitis.

Additional preventive strategies include avoidance of tobacco smoke and encouragement of breastfeeding throughout the bronchiolitis season. Parents should be advised that tobacco smoke has been found to be an independent risk factor for contracting bronchiolitis. Human milk is a protective factor for decreasing the risk of RSV infection. Human milk contains immune factors that can prevent RSV infection, including immunoglobulin G, immunoglobulin A, and alpha-interferon. Human milk also has been shown to have neutralizing

activity against RSV independent of the immune factors described previously.

## Prognosis

Most infants who experience bronchiolitis recover without sequelae, although a portion develop recurrent wheezing episodes, especially with subsequent viral infections. Approximately 40% of infants diagnosed with bronchiolitis have subsequent wheezing episodes through 5 years of age; 10% have subsequent wheezing episodes after 5 years of age. (13) Currently, the relationship between the diagnosis of bronchiolitis in infants and subsequent wheezing is unclear. Previous theories proposed that acquiring bronchiolitis at an early age might contribute to recurrent wheezing and increased airway reactivity later in life. As the complex interaction of the developing immune system, atopic genetic predisposition, and infectious agents becomes more apparent, newer theories propose that patients who develop post-bronchiolitic wheezing may have an underlying predisposition to the original RSV infection and subsequent recurrent episodes of wheezing. Anticipatory guidance regarding episodes of recurrent wheezing should be based on the known incidence of postbronchiolitis wheezing and other independent risk factors such as familial atopic disposition.

## Summary

- Based on good evidence, the diagnosis of bronchiolitis should be based on clinical evaluation without supportive laboratory or radiologic studies.
- Based on good evidence, the mainstay of therapy is supportive care and involves oxygen, hydration, and nutrition support.
- Based on good evidence, many current therapeutic interventions have not demonstrated efficacious improvement in the clinical course or subsequent outcomes. A trial of bronchodilator therapy is optional but should be continued only if a clinical response is documented. Corticosteroids should not be used to treat bronchiolitis, and ribavirin therapy should be reserved for special situations.
- Based on good evidence, effective measures to prevent bronchiolitis include administration of palivizumab, encouragement of breastfeeding, avoidance of tobacco smoke, and strict handwashing as well as adherence to other institutional infection control policies.
- Future areas of research include defining the roles of pulse oximetry and oxygen therapy in bronchiolitis, developing a robust clinical scoring tool for assessing respiratory distress in patients who have bronchiolitis, delineating the relationship between early clinical bronchiolitis and recurrent wheezing episodes, and developing cost-effective immunoprophylaxis and ultimately vaccination against RSV.

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## PIR Quiz

Quiz also available online at [pedsinreview.aappublications.org](http://pedsinreview.aappublications.org).

5. The *most* important triad of findings for assessing severity of bronchiolitis are respiratory rate, work of breathing, and:
  - A. Degree of cough.
  - B. Level of oxygen saturation.
  - C. Pitch of wheezing.
  - D. Presence of crackles.
  - E. Rapidity of heart rate.
  
6. Among the following, the *best* reason to obtain viral studies in those suspected of having bronchiolitis is to:
  - A. Administer specific antiviral therapy.
  - B. Determine the need for hospitalization.
  - C. Guide the type of supportive care needed.
  - D. Identify febrile infants >30 days of age who are at low risk for serious bacterial infection and may not need empiric antibiotics.
  - E. Provide the most accurate diagnosis.
  
7. Among the following, the febrile patients *most* likely to have a serious bacterial infection associated with bronchiolitis:
  - A. Are younger than 30 days of age.
  - B. Are 31 to 60 days old.
  - C. Are neurologically impaired.
  - D. Have infiltrates on chest radiography.
  - E. Have survived neonatal respiratory distress syndrome.
  
8. The primary treatment of bronchiolitis includes hydration and:
  - A. Bronchodilators.
  - B. Chest physiotherapy.
  - C. Corticosteroids.
  - D. Decongestants.
  - E. Oxygenation.
  
9. The major benefit of palivizumab prophylaxis is:
  - A. Decreased hospitalization rate.
  - B. Improved treatment.
  - C. Increased cost-effectiveness.
  - D. Lower mortality rate.
  - E. Shorter duration of illness

**Bronchiolitis**  
Tamara Wagner  
*Pediatrics in Review* 2009;30;386  
DOI: 10.1542/pir.30-10-386

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# Preventing respiratory syncytial virus infections

JL Robinson; Canadian Paediatric Society, Infectious Diseases and Immunization Committee



Full text at [www.cps.ca](http://www.cps.ca)  
Français en page 489

## ABSTRACT

Respiratory syncytial virus infection is the leading cause of lower respiratory tract infections in young children. Palivizumab, a respiratory syncytial virus-specific monoclonal antibody, reduces the hospitalization rate of high-risk children but it is very costly. This statement replaces three previous position statements from the Canadian Paediatric Society about this topic, and was updated primarily to discuss recent changes in the American Academy of Pediatrics guidelines in the Canadian context. It reviews the published literature and provides recommendations regarding palivizumab use in high-risk children.

**Key Words:** *At-risk infants; Palivizumab; Prematurity; Prophylaxis; RSV*

## RECOMMENDATIONS

The levels of evidence are described using the evaluation of evidence criteria outlined by GRADE (Grades of Recommendation Assessment, Development and Evaluation). In this system, evidence is graded as high, moderate, low or very low. Then, values and preferences of patients and of society are taken into account, leading to a weak (conditional) or strong recommendation. Only the evidence from randomized controlled studies or from observational studies with a control group was considered for the present guidelines. Such evidence had to relate to respiratory syncytial virus (RSV) and not to respiratory tract infections in general.

### I. Do nonpharmacological measures prevent the spread of RSV to children at high risk for severe RSV infection?

**Recommendation.** Preventive measures, such as good hand hygiene in the home and limiting direct contact of high-risk children with other children and adults with respiratory tract infections, where practical, remain paramount for RSV prevention (strong recommendation/no evidence).

**Remarks.** Although there is no evidence supporting these simple, inexpensive interventions preventing RSV specifically, there is evidence of efficacy for preventing respiratory tract infections. Given that the prevention of RSV and its associated hospitalizations by palivizumab is only approximately 55%, and that even in the pre-palivizumab era, most hospitalizations occurred in healthy term infants, more attention should be paid to these measures.

### II. Should high-risk children receive palivizumab to prevent RSV hospitalization?

#### 1. For children with chronic lung disease of prematurity who require ongoing medical therapy, children with hemodynamically significant congenital heart disease who are younger than 24 months of age at the start of RSV season, and infants born before 32 weeks 0 days' gestational age (GA) who are younger than six months of age at the start of the RSV season:

**Recommendation.** These children should receive up to five doses of palivizumab (strong recommendation/high-quality evidence).

**Remarks.** Decisions regarding the use of palivizumab in this and all other high-risk groups need to take competing local priorities for funding into account, which may allow for use of palivizumab in only selected infants in this cohort.

**Values and preferences.** This recommendation places a high value on preventing hospitalizations in these vulnerable infants despite the high cost of palivizumab.

#### 2. For children born at 32 weeks 0 days to 35 weeks 6 days' GA:

**Recommendation #1.** A panel of experts should be convened in each province or territory (weak recommendation/no evidence) to establish a policy for these infants.

**Remarks.** The upper limit of GA may need to be determined by available funding.

**Recommendation #2.** The panel may want to use the American Academy of Pediatrics (AAP) criteria, or the Canadian risk-scoring tool, to select infants eligible for palivizumab prophylaxis (weak recommendation/no evidence).

**Remarks.** It seems likely that applying the AAP criteria would result in more infants being prophylaxed, but for a shorter time. It is impossible to predict the relative impact on hospitalizations.

**Recommendation #3.** Irrespective of the criteria chosen, giving the last dose at three months' chronological age should be considered in this GA cohort (weak recommendation/no evidence).

**Remarks.** This recommendation is an attempt to balance cost and benefit, and is designed to protect infants at greatest risk of hospitalization.

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### 3. For infants in remote communities who would require air transportation for hospitalization:

**Recommendation #1.** Consideration should be given to administering up to five doses of palivizumab for all infants born before 36 weeks' GA and younger than six months of age at the beginning of RSV season (strong recommendation/high-quality evidence).

*Remarks.* It is not clear whether this recommendation should apply only to Inuit infants, to all Aboriginal infants or to all infants in remote communities. The incidence of RSV hospitalization in a remote community in previous years should be taken into account when making this decision. A practical issue is that the onset and duration of RSV season is unpredictable in the Far North. Occasionally, more than a year goes by between RSV seasons. To save money, one would delay administering palivizumab until there is confirmed RSV activity in a remote community. The attendant risk is that significant spread may have already occurred.

*Values and preferences.* This recommendation places high value on preventing RSV hospitalizations because of the high cost of such admissions.

**Recommendation #2.** Consideration may be given to administering up to five doses of palivizumab to term Inuit infants younger than six months of age in communities with documented persistent high rates of RSV hospitalizations (weak recommendation/no evidence).

*Remarks.* There is no direct evidence of the efficacy of palivizumab in term Inuit infants, but observational studies in preterm Inuit infants and in term infants with other risk factors suggest that there would be efficacy. There are insufficient data regarding the morbidity from RSV to recommend use in term infants in other Northern populations.

### 4. For children with immunodeficiencies, Down syndrome, cystic fibrosis, upper airway obstruction or a chronic pulmonary disease other than chronic lung disease of prematurity:

**Recommendation.** Palivizumab is not routinely recommended. However, it may be considered for children younger than 24 months of age (because they may not yet have encountered their first RSV infection) who are likely to be exposed to RSV and are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease, or are severely immunocompromised (weak recommendation/no evidence).

*Remarks.* This recommendation should be expanded to include more children with pulmonary disease if evidence becomes available that avoidance or delay of the initial RSV hospitalization impacts long-term pulmonary function.

### III. How should palivizumab be administered?

**Recommendation.** Each jurisdiction should optimize processes to implement these recommendations in the most cost-effective manner. Well-organized palivizumab clinics decrease drug wastage (strong recommendation/no evidence).

### RESEARCH PRIORITIES INCLUDE BUT ARE NOT LIMITED TO THE FOLLOWING:

- Further validating the criteria used to identify highest-risk infants born between 32 and 35 weeks' GA and the study of such criteria at 29 to 31 weeks' GA. Validation of the AAP's criteria in previously assembled cohorts would be informative.
- Determining the efficacy of three versus five doses of palivizumab, and of lower doses of palivizumab.
- Determining the efficacy of palivizumab in term infants.
- Tracking the seasonality of RSV in Northern communities.
- Studying the impact of socioeconomic status, ethnicity and environmental factors on the severity of RSV, and the efficacy of palivizumab prophylaxis in children with immunodeficiencies, cystic fibrosis, other chronic pulmonary disorders and Down syndrome.
- Setting criteria for determining which week of the year to start and end palivizumab prophylaxis.
- Studying palivizumab resistance.

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**ACKNOWLEDGEMENTS:** This position statement has been reviewed by the Fetus and Newborn, and the First Nations, Inuit and Métis Health Committees of the Canadian Paediatric Society.

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# Influenza vaccine recommendations for children and youth for the 2011/2012 season



Marina I Salvadori; Canadian Paediatric Society, [Infectious Diseases and Immunization Committee](#)

Paediatr Child Health 2011;16(9):570-1

[Index of position statements from the Infectious Diseases and Immunization Committee](#)

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The National Advisory Committee on Immunization and the Canadian Paediatric Society encourage annual influenza vaccination for ALL children and youth six months of age and older. When this is not practical, priority should be given to individuals at high risk of influenza-related complications and to those capable of transmitting infection to individuals at high risk of complications. This group includes the following:

- Children six to 23 months of age;
- Members of households expecting a newborn during influenza season;
- Pregnant women, for their own protection and to protect their newborn infant;
- Children with cardiac or pulmonary disorders including risk of aspiration, cystic fibrosis or asthma, and children with other chronic conditions including diabetes mellitus, metabolic diseases, renal disease, anemia and hemoglobinopathies;
- Children with cancer or illness-associated immunodeficiency or immune suppression;
- Children treated for long periods with acetylsalicylic acid;
- Children with morbid obesity;
- Aboriginal children; and
- Residents of chronic care facilities.

Adults and children who are household contacts of individuals at high risk, or their caregivers, and all health care providers, should also be immunized.

The three antigenic components of the influenza vaccine are unchanged from last year's vaccine. Although some vaccinated individuals will retain immunity from one season to the next, not all individuals will. It is, therefore, recommended that everyone be revaccinated, even if they received vaccine or had documented influenza last year.

A major change is that the National Advisory Committee on Immunization is now recommending that all age groups, including children six to 35 months of age, receive 0.5 mL per dose of influenza vaccine (1). This recommendation replaces previous guidance suggesting that these children receive 0.25 mL per dose. The rationale for this change is the demonstration of a modest improvement in immunity with the 0.5 mL dose compared with the 0.25 mL dose, without any increase in adverse effects.

The first year that children younger than nine years of age receive influenza immunization, two doses are required to achieve protection. The doses are administered at least four weeks apart, and both doses should be 0.5 mL. If a child younger than nine years of age received one influenza immunization last season (2010/2011), only one immunization is required this season.

FluMist (Medimmune, USA) is an intranasal, live attenuated vaccine (2). Multiple studies demonstrate a statistically significant superior efficacy of FluMist over injectable, trivalent, inactivated influenza vaccine against culture-confirmed influenza in children. Important side effects include mild rhinitis in most recipients and exacerbations of wheezing in those with severe asthma. This year, the National Advisory Committee on Immunization is preferentially recommending FluMist for healthy children and youth two to 17 years of age. However, it is very unlikely that this vaccine will be easily available through publicly funded programs because of supply and contract issues. FluMist is contraindicated for people with immune-compromising conditions or severe asthma (defined as active wheezing or current use of inhaled or oral glucocorticosteroids), and those with medically attended wheezing in the seven days before vaccination.

For patients with an egg allergy, please see the recent Canadian Paediatric Society position statement on this subject at <<http://www.cps.ca/english/statements/ID/ID11-06.htm>> (3).

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**Posted: November 2011**

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ORIGINAL ARTICLE

# Epinephrine and Dexamethasone in Children with Bronchiolitis

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for Pediatric Emergency Research Canada (PERC)

## ABSTRACT

### BACKGROUND

Although numerous studies have explored the benefit of using nebulized epinephrine or corticosteroids alone to treat infants with bronchiolitis, the effectiveness of combining these medications is not well established.

### METHODS

We conducted a multicenter, double-blind, placebo-controlled trial in which 800 infants (6 weeks to 12 months of age) with bronchiolitis who were seen in the pediatric emergency department were randomly assigned to one of four study groups. One group received two treatments of nebulized epinephrine (3 ml of epinephrine in a 1:1000 solution per treatment) and a total of six oral doses of dexamethasone (1.0 mg per kilogram of body weight in the emergency department and 0.6 mg per kilogram for an additional 5 days) (the epinephrine–dexamethasone group), the second group received nebulized epinephrine and oral placebo (the epinephrine group), the third received nebulized placebo and oral dexamethasone (the dexamethasone group), and the fourth received nebulized placebo and oral placebo (the placebo group). The primary outcome was hospital admission within 7 days after the day of enrollment (the initial visit to the emergency department).

### RESULTS

Baseline clinical characteristics were similar among the four groups. By the seventh day, 34 infants (17.1%) in the epinephrine–dexamethasone group, 47 (23.7%) in the epinephrine group, 51 (25.6%) in the dexamethasone group, and 53 (26.4%) in the placebo group had been admitted to the hospital. In the unadjusted analysis, only the infants in the epinephrine–dexamethasone group were significantly less likely than those in the placebo group to be admitted by day 7 (relative risk, 0.65; 95% confidence interval, 0.45 to 0.95,  $P=0.02$ ). However, with adjustment for multiple comparisons, this result was rendered insignificant ( $P=0.07$ ). There were no serious adverse events.

### CONCLUSIONS

Among infants with bronchiolitis treated in the emergency department, combined therapy with dexamethasone and epinephrine may significantly reduce hospital admissions. (Current Controlled Trials number, ISRCTN56745572.)

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**I**N INFANCY, BRONCHIOLITIS IS THE MOST common acute infection of the lower respiratory tract, characterized by rhinorrhea, cough, wheezing, respiratory distress, and hypoxemia,<sup>1,2</sup> and is most often caused by the respiratory syncytial virus (RSV). Hospital admissions for bronchiolitis have almost doubled over the past 10 to 15 years in both Canada and the United States.<sup>3,4</sup> In the United States, annual hospital costs for RSV-associated bronchiolitis were estimated at \$365 million to \$691 million in 1998.<sup>5</sup>

The current treatment of bronchiolitis is controversial. Bronchodilators and corticosteroids are widely used but not routinely recommended.<sup>6</sup> A meta-analysis of the treatment effects of nebulized selective beta-agonists<sup>7</sup> failed to show any consistent benefits, whereas a meta-analysis of the treatment effects of nebulized epinephrine suggested a decrease in clinical symptoms as compared with either placebo or albuterol.<sup>8</sup> In one small, randomized, controlled trial, treatment with dexamethasone led to a 40% relative reduction in admission rates as compared with placebo.<sup>9</sup> However, a large, recently published study of dexamethasone failed to show any difference in hospital-admission rates or respiratory clinical scores as compared with placebo.<sup>10</sup>

The current study was undertaken in response to the continued controversy concerning the use of nebulized epinephrine and systemic corticosteroids in the treatment of bronchiolitis in infants and in recognition of the substantial burden that the care of infants with this disease adds to the health care system. We conducted a randomized, double-blind, placebo-controlled, clinical trial with a factorial design at multiple sites to determine whether treatment with nebulized epinephrine, a short course of oral dexamethasone, or both resulted in a clinically important decrease in hospital admissions among infants with bronchiolitis who were seen in the emergency department.

## METHODS

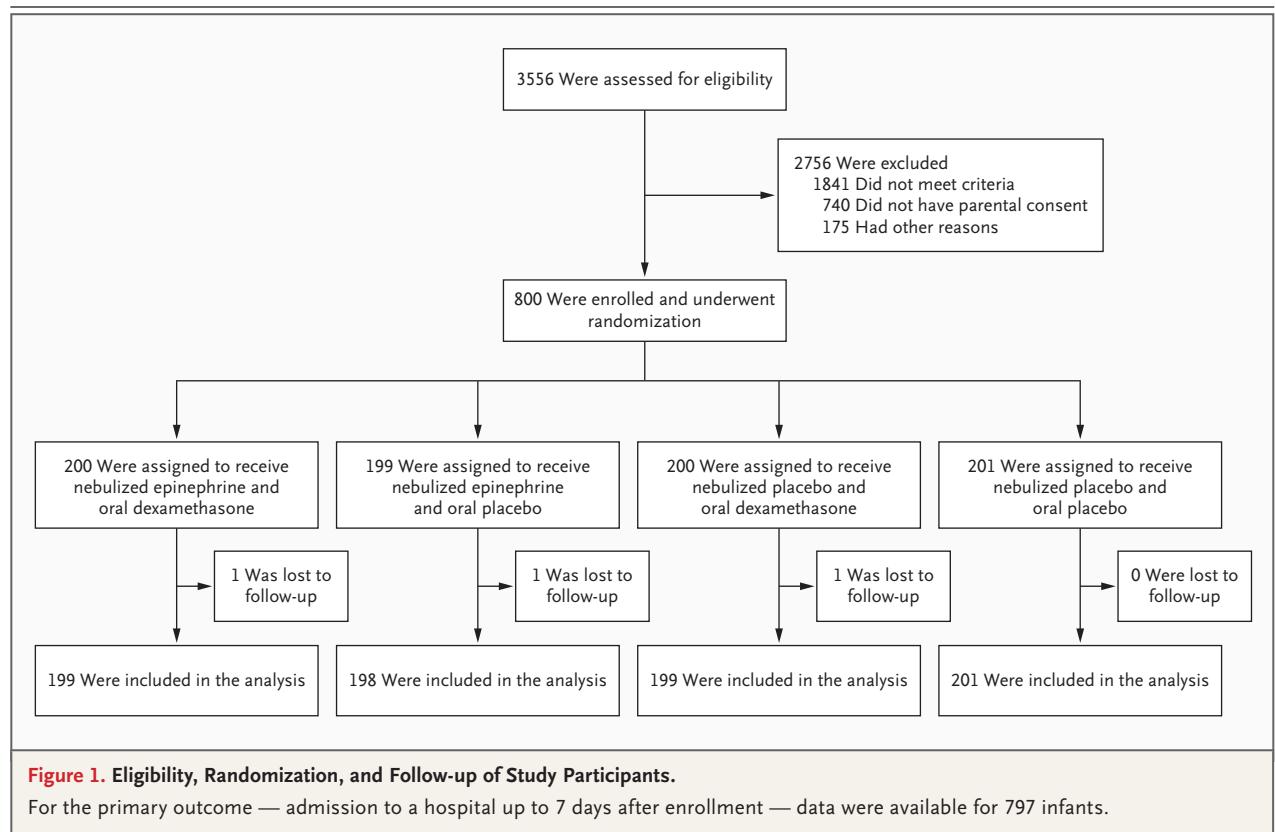
### PATIENTS

Patients were recruited during the bronchiolitis season (December through April) at eight Canadian pediatric emergency departments from 2004 through 2007. All hospitals are members of the research group Pediatric Emergency Research Canada (PERC). Written informed consent was obtained

from the parents or guardians of all infants included in the study, and the study was approved by the ethics committee at each site and by Health Canada. The study protocol and manuscript were written by the investigators; data were collected by research nurses and analyzed by PERC statisticians. The granting agencies covered all costs, including the cost of medications, required no confidentiality agreements, and played no role in study design, data analysis, or manuscript preparation.

Infants 6 weeks to 12 months of age with bronchiolitis who were seen at participating emergency departments were eligible for the study if they had a score of 4 to 15 on the respiratory distress assessment index (RDAI).<sup>11</sup> The RDAI, which has good interobserver reliability, rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. Bronchiolitis was defined as the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season. We excluded infants who received bronchodilator treatment in the emergency department before being assessed by a research nurse, infants who had received oral or inhaled corticosteroids during the preceding 2 weeks, infants with a previous episode of wheezing or a diagnosis of asthma, previous bronchodilator use, any chronic cardiopulmonary disease, or immunodeficiency, and infants in severe distress (defined as a pulse rate >200 beats per minute, a respiratory rate >80 breaths per minute, or an RDAI score >15) or with profound lethargy, and infants who had been exposed to varicella within the preceding 3 weeks. Also excluded were infants born at less than 37 weeks of gestation who had a corrected age of less than 6 weeks at presentation. Finally, infants were excluded if there were insurmountable barriers to communication with the family (a language barrier or lack of a telephone on the part of the parent or guardian).

A research nurse was present in the emergency department up to 16 hours daily to recruit participants. Once a physician had confirmed the diagnosis and parental consent had been obtained, the nurse documented demographic information, obtained a medical history, and obtained a nasal pharyngeal aspirate for RSV testing. Any child with an oxygen saturation of less than 92% while breathing ambient air received supplemental oxy-



gen, and any child with a fever (rectal temperature  $>38^{\circ}\text{C}$ ) received acetaminophen (15 mg per kilogram of body weight).

#### INTERVENTION

Using a computer-generated randomization sequence, the research nurse assigned participants to one of four study treatments: nebulized epinephrine plus oral dexamethasone (group 1), nebulized epinephrine plus oral placebo (group 2), nebulized placebo plus oral dexamethasone (group 3), or nebulized placebo plus oral placebo (group 4). The two nebulized treatments, administered 30 minutes apart with the use of the 1730 Updraft II nebulizer (Hudson RCI) and an oxygen flow rate of 8 liters per minute, consisted of 3 ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline.<sup>12-17</sup> The oral treatments, based on a study by Schuh et al.,<sup>9</sup> consisted of 1.0 mg of dexamethasone per kilogram of body weight (maximum dose, 10 mg) or placebo given after the first nebulized treatment in the emergency department, followed by five once-daily doses of dexamethasone (0.6 mg per kilogram; maximum

daily dose, 10 mg) or placebo. The dexamethasone suspension consisted of generic dexamethasone phosphate injection solution mixed with Ora-Plus and Ora-Sweet (Paddock Laboratories). The placebo consisted of Ora-Plus and Ora-Sweet. The research nurse administered all drugs in the emergency department and taught parents how to administer the oral drug at home. The treating physician in the emergency department was allowed to provide cointerventions after 90 minutes and independently determined whether to admit or discharge the infant.

#### RANDOMIZATION

The computer-generated randomization sequence, stratified by center, used randomized permuted blocks of 8 and 12. Codes were secured at each center's pharmacy until enrollment and data entry were complete. In order to conceal the allocation sequence, the pharmacy at each site prepared the study drugs in sequentially numbered, visually identical packets. The active drugs and placebo were identical in appearance, volume, weight, odor, and taste.

## ASSESSMENTS

The research nurse recorded the patient's RDAI score, respiratory rate, heart rate, and oxygen saturation in ambient air at baseline, between the two nebulizations, and at 60, 90, 120, 180, and 240 minutes; rectal temperature at 120 and 240 minutes (or at discharge); blood pressure at 240 minutes or at discharge; and any side effects

throughout the observation period in the emergency department. Using a standardized telephone follow-up procedure,<sup>18</sup> the research nurse obtained data regarding compliance with administration of study medication after discharge and health care visits, as well as details about the infant's feeding, sleep, breathing, and coughing. Follow-up by telephone was performed daily until day 7, then

Table 1. Baseline Characteristics of the Patients.\*

Characteristic	Epinephrine– Dexamethasone Group (N=200)	Epinephrine Group (N=199)	Dexamethasone Group (N=200)	Placebo Group (N=201)
Age — mo				
Median	5	5	5	5
Interquartile range	3–7	3–7	3–7	3–7
Male sex — no. (%)	124 (62.0)	122 (61.3)	127 (63.5)	120 (59.7)
Clinical characteristics				
RDAI score				
Median	8	8	8	8
Interquartile range	6–10	6–10	6–10	6–10
Respiratory rate — breaths/min				
Median	48	48	50	48
Interquartile range	41–57	44–56	44–60	40–58
Heart rate — beats/min				
Median	150	149	152	150
Interquartile range	138–160	138–160	141–161	137–160
Oxygen saturation — %				
Median	97	97	97	97
Interquartile range	95–98	95–98	95–98	95–98
Temperature — °C				
Median	37.6	37.7	37.6	37.7
Interquartile range	37.3–38.0	37.3–38.0	37.2–38.0	37.2–38.1
Duration of symptoms before enrollment — days				
Median	3	4	3	4
Interquartile range	2–5	3–6	2–5	2–6
RSV-positive — no. (%)	128 (64.0)	129 (64.8)	127 (63.5)	136 (67.7)
History — no. (%)				
Atopy				
Personal history†	28 (14.0)	20 (10.0)	19 (9.5)	22 (10.9)
Family history‡	124 (62.0)	112 (56.3)	113 (56.5)	114 (56.7)
Prematurity§	22 (11.0)	22 (11.1)	23 (11.5)	16 (8.0)
Clinically significant illness¶	7 (3.5)	10 (5.0)	14 (7.0)	11 (5.5)
Previous intubation	6 (3.0)	4 (2.0)	8 (4.0)	6 (3.0)
One or more smokers in home	84 (42.0)	72 (36.2)	67 (33.5)	82 (40.8)

Table 1. (Continued.)

Characteristic	Epinephrine– Dexamethasone Group (N = 200)	Epinephrine Group (N = 199)	Dexamethasone Group (N = 200)	Placebo Group (N = 201)
Previous treatment for current illness — no. (%)				
Bronchodilators	27 (13.5)	21 (10.6)	20 (10.0)	24 (11.9)
Antibiotics	24 (12.0)	20 (10.1)	21 (10.5)	17 (8.5)

\* The Respiratory Distress Assessment Index (RDAI) rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. RSV denotes respiratory syncytial virus.

† A personal history of atopy was defined as a history of eczema or allergies.

‡ A family history of atopy was defined as allergies, asthma, or eczema in a parent or any sibling.

§ Prematurity was defined as birth at less than 37 weeks of gestation.

¶ Clinically significant illness was defined as any illness requiring surgery, hospital admission, or ongoing medical care.

|| Fourteen of the infants who were previously intubated were premature.

every 2 days until day 14, and then every 3 days until day 22. A review of the patient's hospital chart was completed 22 days after enrollment.

#### OUTCOME MEASURES

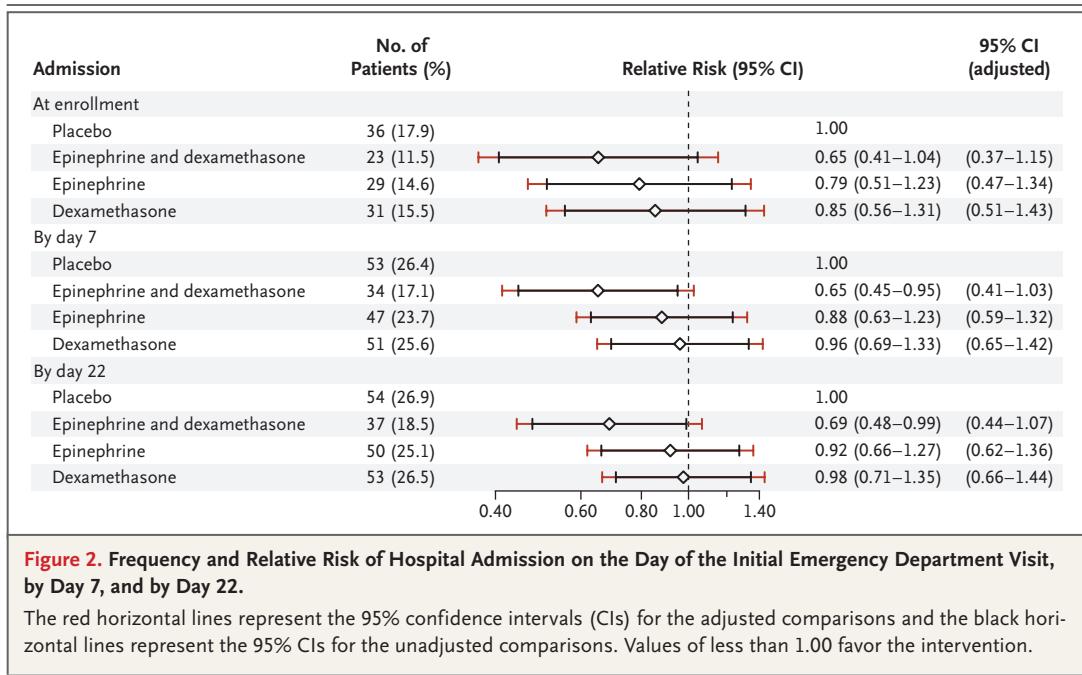
The primary outcome — hospital admission up to 7 days after enrollment, which occurred during the visit to the emergency department — was determined through telephone follow-up and confirmed by chart review, as were rates of admission at enrollment and by day 22. The secondary outcomes of change in heart and respiratory rate, RDAI score, and oxygen saturation from baseline to 30, 60, 120, and 240 minutes were determined by direct measurement by the research nurse. Secondary outcomes of length and severity of symptoms were determined by standardized telephone follow-up. Time to discharge, determined by chart review, was defined as the time between the triage time at the enrollment and the time of discharge from the last emergency department visit or from the last hospitalization for each patient within the next 7 days. Patient return to the health care provider for bronchiolitis symptoms within 22 days of enrollment was determined by telephone follow-up and confirmed by chart review.

#### STATISTICAL ANALYSIS

A sample size of 800 infants was chosen to provide 80% power (with a 5% type I error rate) to detect an absolute difference of 10 percentage points in admission rates resulting from administration of each drug and assumed no interaction between epinephrine and dexamethasone. Data analysis was performed with the use of Stata soft-

ware, version 10.0. Two interim analyses were planned and conducted with the use of the Haybittle–Peto approach (with a stopping rule that specified a P value of less than 0.001)<sup>19,20</sup>; both interim analyses had nonsignificant results. Subgroup analyses that were planned a priori included analyses according to the presence or absence of atopy, RSV status, and duration of illness at presentation.

All analyses followed the intention-to-treat principle.<sup>21</sup> Admission and return visits due to symptoms of bronchiolitis were analyzed with the use of relative-risk regression for binary outcomes. Our analysis plan, as specified by our protocol and based on published recommendations regarding analysis of data in studies with factorial designs,<sup>22</sup> was to first conduct a factorial analysis incorporating terms for epinephrine, dexamethasone, and study center, then examine associated interactions, and finally, if evidence of interaction was found, analyze and present our results as separate comparisons of each of the three treatment groups with the placebo group. Evidence of a clinically significant interaction between epinephrine and dexamethasone was found. To accommodate the uncertainty arising from this unanticipated interaction, we provide both unadjusted results and results adjusted for multiple comparisons with the use of the approach described by Westfall<sup>23</sup> and as implemented by Hothorn et al.<sup>24</sup> Time to discharge was analyzed with the use of a Cox proportional-hazards model. To allow for intervals between follow-up telephone calls and censoring before the end of the study, time to symptom relief was analyzed by means of para-



metric survival models with Weibull distributions assumed. We analyzed clinical characteristics (e.g., RDAI score) with the use of linear mixed-effects regression, incorporating baseline values. Assumptions such as proportional hazards and normality were examined graphically.

## RESULTS

### RECRUITMENT AND BASELINE CHARACTERISTICS

A total of 3556 infants were screened for eligibility, 1715 met the criteria for enrollment, and 800 were enrolled (Fig. 1). Of the 1841 ineligible infants, 867 (47.1%) had a previous episode of wheezing or diagnosis of asthma, 90 (4.9%) had an RDAI score above 15, and 343 (18.6%) had an RDAI score below 4. (For more details on patient exclusion, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) A total of 200 patients were randomly assigned to the epinephrine–dexamethasone group, 199 to the epinephrine group, 200 to the dexamethasone group, and 201 to the placebo group. No data were available on the primary outcome for three patients (one each in the first three groups); these patients were not included in the intention-to-treat analysis. Because of a pharmacy error, a total of 23 patients in group 1 and 23 patients in group 3 received dexamethasone at 80% of the planned dose (0.8 mg per kilogram of

body weight in the emergency department and 0.48 mg per kilogram of body weight at home); these patients were included in the analysis. Other deviations from the protocol were minor and equally distributed among the groups. Baseline clinical and demographic characteristics were similar among the groups (Table 1). The additional use of bronchodilators 90 minutes after enrollment was similar across groups, with 18.4% of patients receiving albuterol and 20.6% receiving epinephrine (median number of treatments, 1). At follow-up, the parents or guardians of 19 infants in the epinephrine–dexamethasone group, 13 in the epinephrine group, 20 in the dexamethasone group, and 12 in the placebo group reported that they had stopped administering the study syrup; for all 19 children in the epinephrine–dexamethasone group, all 20 in the dexamethasone group, and 3 of the 12 in the placebo group, the study syrup was withdrawn so that a physician could prescribe oral corticosteroids. The study groups did not differ significantly with respect to use of nonstudy medications at discharge from the initial emergency department visit through day 7.

### HOSPITAL ADMISSIONS

By the seventh day, 34 of the 199 infants in group 1 (17.1%) had been admitted to the hospital, as had 47 of the 198 infants in group 2 (23.7%), 51 of the 199 infants in group 3 (25.6%), and 53

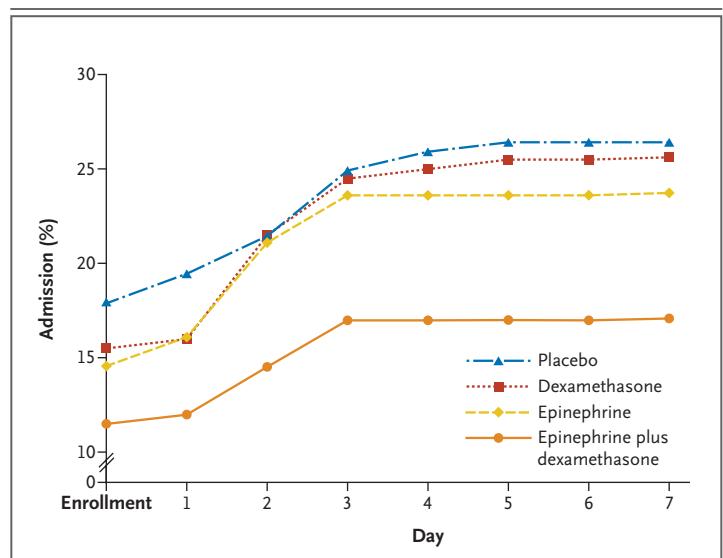
of the 201 infants in group 4 (26.4%). The relative risk of admission, unadjusted and adjusted for multiple comparisons, is shown in Figure 2. The relative risk of admission by day 7 in group 1 as compared with group 4 was 0.65 (95% confidence interval, 0.45 to 0.95;  $P=0.02$  and  $P=0.07$  for the unadjusted and adjusted analyses, respectively); 11 infants would need to be treated to prevent one hospital admission. In contrast, in both unadjusted and adjusted analyses, neither treatment with dexamethasone alone nor treatment with epinephrine alone reduced the rate of admission, as compared with placebo ( $P=0.87$  and  $P=0.52$ , respectively, for the unadjusted analysis). Positive RSV status, personal or family history of atopy, presentation early in the course of illness ( $\leq 2$  days after the onset of symptoms), severe illness (defined as an RDAI score  $\geq 6$ ), and the pharmacy error (lower dexamethasone dose) did not affect the primary results. The effects of combining epinephrine and dexamethasone were most apparent in the first 3 days after study enrollment (Fig. 3).

#### CLINICAL MEASURES

The RDAI score and the respiratory rate improved in all groups during the initial emergency department visit. Infants in the epinephrine group and those in the epinephrine–dexamethasone group had significantly lower RDAI scores during the first hour of the study than did infants in the placebo group; the RDAI scores for infants in the dexamethasone group did not show significant improvement as compared with the change in the scores for infants in the placebo group (Table 2). Infants in the epinephrine–dexamethasone group also had lower respiratory rates during the first hour than did those in the placebo group. As compared with infants in the placebo group, those in the epinephrine group and the epinephrine–dexamethasone group had elevated heart rates during the first hour, whereas infants in the dexamethasone group did not.

#### OTHER OUTCOMES

The median time until discharge from the emergency department or hospital for group 1 was slightly shorter than that for group 4 (4.6 and 5.3 hours, respectively; unadjusted  $P=0.02$ ), whereas neither group 3 (5.1 hours) nor group 2 (4.9 hours) differed from group 4 on this measure. In group 1, 95 patients (47.7%) returned to a health care provider for bronchiolitis-related symptoms, as did 93



**Figure 3. Cumulative Admissions during the First 7 Days after the Initial Emergency Department Visit, According to Study Group.**

Enrollment data represent all patients admitted at their initial visit to the emergency department, and data for day 1 represent patients admitted within 24 hours of this visit.

in group 2 (47.0%), 106 in group 3 (53.3%), and 86 in group 4 (42.8%); only the difference between group 3 and group 4 was significant, and only in the unadjusted analysis ( $P=0.04$ ).

Infants in group 1 appeared to return to quiet breathing and normal or almost normal feeding more quickly than those in group 4 (Fig. 4).

#### ADVERSE EVENTS

Adverse events were uncommon (see the Supplementary Appendix). Pallor was reported in 76 infants (9.5%), tremor in 15 (1.9%), and vomiting in 14 (1.8%), with no significant differences among the groups. One hospitalized infant in group 2 and one in group 3 had mild, transient hypertension, which resolved rapidly.

#### DISCUSSION

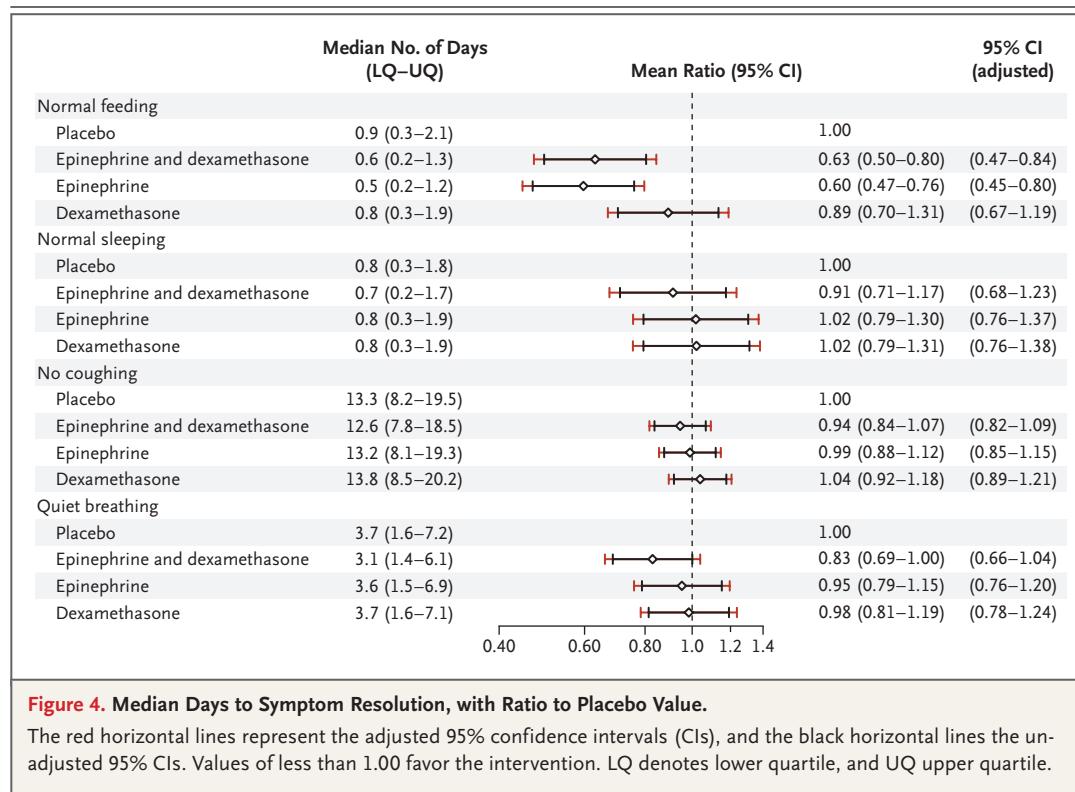
In this randomized, controlled trial of the treatment of acute bronchiolitis in infants, we found an unexpected synergism between epinephrine and dexamethasone. Combined therapy with epinephrine and dexamethasone, as compared with placebo, appeared to reduce the rate of hospital admission in the 7 days after study enrollment by 9 percentage points, with a relative risk reduction of 35%. These results were not modified by RSV status, presence or absence of a history of atopy,

**Table 2. Changes in Clinical Characteristics of Patients and Time to Discharge.\***

Variable	Epinephrine– Dexamethasone Group (N=199)	Epinephrine Group (N=198)	Dexamethasone Group (N=199)	Placebo Group (N=200)
<i>change</i>				
RDAI score				
30 min	-1.62±2.23	-1.44±1.94	-0.98±2.07	-1.06±2.16
60 min	-2.50±2.58	-2.45±2.32	-1.75±2.40	-1.65±2.42
P value				Reference
Unadjusted	<0.001	0.003	0.75	
Adjusted	<0.001	0.005	0.75	
Respiratory rate (breaths/min)				
30 min	-2.40±8.29	-1.35±8.53	-1.63±8.32	-0.59±8.34
60 min	-4.04±9.17	-3.68±8.89	-3.30±9.60	-2.88±10.20
P value				Reference
Unadjusted	0.04	0.44	0.83	
Adjusted	0.09	0.66	0.83	
Heart rate (beats/min)				
30 min	3.57±17.40	4.20±15.7	-0.17±17.80	1.65±18.80
60 min	5.20±17.80	4.80±17.60	-3.76±17.70	-3.24±18.80
P value				Reference
Unadjusted	<0.001	<0.001	0.41	
Adjusted	<0.001	<0.001	0.41	
Oxygen saturation (%)				
30 min	-0.35±2.61	0.17±2.09	-0.52±2.45	-0.24±2.77
60 min	-0.73±2.56	0.07±2.70	-1.02±2.57	-0.77±3.23
P values				Reference
Unadjusted	0.59	0.005	0.22	
Adjusted	0.59	0.013	0.36	
Temperature (°C)				
At discharge or at 240 min	-0.19±0.78	-0.17±0.66	-0.10±0.71	-0.29±0.76
P value				Reference
Unadjusted	0.76	0.26	0.18	
Adjusted	0.76	0.42	0.39	
Time to discharge (hr) †				
Median	4.6	4.9	5.1	5.3
Interquartile range	3.5–7.0	3.7–9.6	3.6–17.0	3.8–21
P value				Reference
Unadjusted	0.02	0.78	0.99	
Adjusted	0.94	0.94	1.00	

\* Plus–minus values are means SD. The Respiratory Distress Assessment Index (RDAI) rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. Since almost one third of the patients (283) had been discharged home by 120 minutes and the majority of patients (583) had been discharged by 240 minutes, we do not report clinical measures for times beyond 60 minutes after treatment. P values are for comparisons of treatment with placebo in the linear mixed-effects regression of repeated measures over time.

† The time to discharge was defined as the time between the triage time at the enrollment visit and the time of discharge from the last emergency department visit or the last hospitalization for each patient within the next 7 days.



or the severity or the duration of illness. The effects of combining epinephrine and dexamethasone were most apparent in the first 3 days after study enrollment. We also found an apparent benefit from combined therapy on our secondary outcomes: infants in this group were discharged earlier from medical care and resumed quiet breathing and normal feeding sooner than did those in the placebo group. In contrast, neither dexamethasone alone nor epinephrine alone had any effect on these outcomes.

Three small studies — two published since our trial began — have also reported a benefit from combining epinephrine and dexamethasone<sup>25,26</sup> or albuterol and dexamethasone<sup>25,27</sup> in similar populations and have reported no benefit from the administration of epinephrine or albuterol alone. Furthermore, although the mechanism of action is not known, synergism between corticosteroids and beta-agonists in the treatment of chronic asthma is well documented.<sup>28–30</sup>

Dexamethasone has been studied in a similar population, with conflicting results.<sup>9,10</sup> Schuh et al.<sup>9</sup> reported a 40% reduction in admissions in a small, single-site study, whereas Corneli et al.<sup>10</sup> reported no effect in a large, multisite study. The

patients in the study by Schuh et al. were consistently treated with bronchodilators, whereas the patients in the study by Corneli et al. were not.

A meta-analysis has suggested that when epinephrine is used in outpatients with a diagnosis of bronchiolitis, as compared with either placebo or salbutamol, there is short-term improvement in clinical measures.<sup>8</sup> Our study showed an improvement in the clinical score in the first hour after treatment with epinephrine, as compared with placebo, but with no significant difference in admission rates.

Although there were no serious short-term adverse events among the infants enrolled in our study, we do not have findings from long-term follow-up to establish whether our study treatments caused adrenal suppression, arrest of somatic growth, or neurodevelopmental delay. Adrenal suppression from exogenous corticosteroid use remains a risk; however, with short courses of corticosteroids, any suppression is likely to be transient.<sup>31–33</sup> Concern has been expressed about possible developmental delay after treatment with corticosteroids.<sup>34</sup> To date, this concern has been limited to preterm infants with very low birth weight (<1501 g) who are given corticosteroids in

the first few days of life.<sup>35-37</sup> The effect of a short course of corticosteroids on otherwise healthy infants is unknown.

Our study has several limitations. First, in order to exclude children with early asthma, we restricted enrollment to infants who had wheezing for the first time. Our results are thus not generalizable to older children or to those with recurrent wheezing, but they are directly pertinent to infants with typical viral bronchiolitis. Second, we enrolled infants at academic centers. Nonetheless, the eligibility criteria were chosen with the intention of enrolling otherwise healthy infants with a wide range in severity of symptoms who did not have complex coexisting conditions, so that our results could be broadly generalized. Third, we did not anticipate the synergism between epinephrine and dexamethasone in our study design, and fourth, our factorial study design raises the issue of multiple comparisons. To address these limitations, we present the results of both unadjusted analyses and analyses adjusted for multiple comparisons. The results of the unadjusted analyses show that combined treatment with epinephrine and dexamethasone led to a significant reduction in hospital admissions, but the results of the adjusted analyses are above the threshold for statistical significance.

In summary, our multicenter study of 800 in-

fants with bronchiolitis suggests that combined treatment with epinephrine and dexamethasone reduces hospital admissions as well as shortening both the time to discharge and the duration of some symptoms. Given the unexpected synergy we found between epinephrine and dexamethasone and the lack of any apparent benefit when either drug is used alone, our results should be considered exploratory. Although some clinicians consider a trial of a bronchodilator to be standard therapy,<sup>6</sup> published data show, at most, mild transient clinical benefits and no effect on the admission rate. Therefore, confirmation of our findings by a study powered specifically to compare combined epinephrine and dexamethasone therapy with placebo is needed.

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#### APPENDIX

From the Departments of Pediatrics and Emergency Medicine, University of Ottawa and Children's Hospital of Eastern Ontario, Ottawa (A.C.P.); the Departments of Pediatrics and Pharmacology and Therapeutics, University of Calgary, and Alberta Children's Hospital, Calgary (D.W.J.); the Department of Pediatrics, McGill University, and Montreal Children's Hospital, Montreal (H.P., M.B.); the Departments of Medicine (N.W.) and Pediatrics (T.T., T.P.K.), University of Alberta, Edmonton; the Clinical Research Unit, Children's Hospital of Eastern Ontario Research Institute, Ottawa (R.C.); the Departments of Statistics (R.B.) and Pediatrics (S.W.), University of British Columbia, Vancouver; the Child and Family Research Institute, BC Children's Hospital, Vancouver (R.B.); the Department of Health Studies, University of British Columbia Okanagan, Kelowna (C.M.); the Department of Pediatrics, University of Montreal, and Centre Hospitalier Universitaire Sainte-Justine, Montreal (S.G.); the Departments of Pediatrics and Medicine, University of Western Ontario, and the London Health Sciences Centre and Children's Hospital, London (G.J.); the Departments of Pediatrics and Emergency Medicine, Dalhousie University, and the IWK Health Centre, Halifax, NS (K.J.L.B.); Stollery Children's Hospital, Edmonton, AB (T.T., T.P.K.); and BC Children's Hospital, Vancouver (S.W.) — all in Canada.

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