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Bronchiolitis: Recent Evidence on Diagnosis and Management

abstract

Viral bronchiolitis is a leading cause of acute illness and hospitalization of young children. Research into the variation in treatment and outcomes for bronchiolitis across different settings has led to evidence-based clinical practice guidelines. Ongoing investigation continues to expand this body of evidence. Authors of recent surveillance studies have defined the presence of coinfections with multiple viruses in some cases of bronchiolitis. Underlying comorbidities and young age remain the most important predictors for severe bronchiolitis. Pulse oximetry plays an important role in driving use of health care resources. Evidence-based reviews have suggested a limited role for diagnostic laboratory or radiographic tests in typical cases of bronchiolitis. Several large, recent trials have revealed a lack of efficacy for routine use of either bronchodilators or corticosteroids for treatment of bronchiolitis. Preliminary evidence suggests a potential future role for a combination of these therapies and other novel treatments such as nebulized hypertonic saline. *Pediatrics* 2010;125:342–349

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KEY WORDS

bronchiolitis, respiratory syncytial virus

ABBREVIATIONS

RSV—respiratory syncytial virus
AAP—American Academy of Pediatrics
HMPV—human metapneumovirus
ED—emergency department

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Bronchiolitis is a disorder of the lower respiratory tract that occurs most commonly in young children and is caused by infection with seasonal viruses such as respiratory syncytial virus (RSV). Bronchiolitis is the leading cause of infant hospitalization in the United States and has been associated with increasing morbidity rates and cost over recent decades.¹⁻³ Multiple studies have documented variation in diagnostic testing, treatment, hospitalization rates, and length of hospital stay for bronchiolitis, suggesting a lack of consensus and an opportunity to improve care for this common disorder.⁴⁻⁶ Recognition of this need led to a clinical practice guideline⁷ published by the American Academy of Pediatrics (AAP) and other organizations in 2006 based on a review of the scientific evidence funded by the Agency for Healthcare Research and Quality.⁸

Bronchiolitis is an active area of research, and many important studies have advanced the understanding of this disorder in the past few years. In this review we focus on new developments in the scientific evidence that relate to the pathophysiology, epidemiology, diagnosis, and management of bronchiolitis. Because the AAP guideline recently summarized the previous body of research, we highlight subsequently available information relevant to those recommendations. The prevention and potential long-term effects of bronchiolitis, although active research areas, will not be reviewed.

DEFINITION AND PATHOPHYSIOLOGY

Although the term “bronchiolitis” refers to inflammation of the bronchioles, these findings are rarely observed directly but inferred in a young child who presents with respiratory distress in association with signs of a viral infection. Definitions of bronchiolitis vary and may account for some of

the variability in the clinical evidence derived from published studies. In the United Kingdom, the term tends to be used more specifically. The authors of University of Nottingham study derived a consensus definition of “a seasonal viral illness characterized by fever, nasal discharge, and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high-pitched expiratory wheeze.”⁹ In North America, bronchiolitis commonly is applied more broadly but is linked to the specific finding of wheeze. The AAP guideline defined bronchiolitis as “a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age.”⁷ The distinction is important, because recurrent wheezing among older children is often triggered by viruses that are typically limited to the upper respiratory tract, such as rhinoviruses (see discussion below). Researchers have often attempted to focus the population of children with bronchiolitis by limiting inclusion to infants younger than 12 months with a first-time episode of wheezing, although even then heterogeneity in the population may persist. Recognizing the pathologic picture that occurs in the airways of children with bronchiolitis is important in understanding the clinical manifestations and developing rational management.¹⁰ The viral infection occurs through the upper respiratory tract and spreads lower within a few days, resulting in inflammation of the bronchiolar epithelium, with peribronchial infiltration of white blood cell types, mostly mononuclear cells, and edema of the submucosa and adventitia. Plugs of sloughed, necrotic epithelium and fibrin in the airways cause partial or total obstruction to airflow. The degree of obstruction may vary as these areas are cleared, resulting in rapidly

changing clinical signs that confound an accurate assessment of the severity of illness. A “ball-valve” mechanism can result in trapping of air distal to obstructed areas, with subsequent absorption, atelectasis, and a mismatch of pulmonary ventilation and perfusion that may lead to hypoxemia. Atelectasis may be accelerated by the lack of collateral channels in young children and potentially by the administration of high concentrations of supplemental oxygen, which is absorbed more rapidly than room air. Smooth-muscle constriction seems to have little role in the pathologic process, which may explain the limited benefit of bronchodilators observed in clinical studies.

The number of viruses recognized to cause bronchiolitis has markedly expanded with the availability of sensitive diagnostic tests that use molecular amplification techniques. RSV continues to account for 50% to 80% of cases.¹¹ Other causes include the parainfluenza viruses, primarily parainfluenza virus type 3, influenza, and human metapneumovirus (HMPV).¹²⁻¹⁴ HMPV has been estimated to account for 3% to 19% of bronchiolitis cases.^{15,16} The clinical courses of RSV and HMPV seem to be similar; most children are infected during annual widespread wintertime epidemics, with a subset developing bronchiolitis.^{12,17,18}

Molecular diagnostic techniques have also revealed that young children with bronchiolitis and other acute respiratory illnesses often are infected with more than 1 virus. Rates of coinfection have ranged from 10% to 30% in samples of hospitalized children, most commonly with RSV and either HMPV or rhinovirus.¹⁹ A recent large prospective study of children younger than 5 years of age hospitalized with RSV infection revealed a coinfection rate of 6%.³ Whether concomitant infection increases the severity of bronchiolitis is controversial. A 10-fold in-

crease in the risk of mechanical ventilation was associated with dual RSV and HMPV infection in 1 small study.²⁰ Other studies, however, have revealed no increased illness severity associated with the presence of more than 1 virus.^{19,21}

The role of rhinoviruses in bronchiolitis is unclear because of their well-documented role in triggering exacerbations of wheezing among older children with reactive airway disease or asthma.^{22–25} A multicenter emergency department (ED)-based study of children younger than 2 years diagnosed with bronchiolitis revealed that children infected with rhinovirus were more likely to be black, to have a previous history of wheezing, and to be treated with corticosteroids than infants with other viral infections.¹³

Genomics is an emerging area of research for bronchiolitis. Studies have identified single-nucleotide polymorphisms in a number of genes, including those involved in innate immunity, that are associated with risk for more severe bronchiolitis.^{26,27} Other genes, such as the vitamin D receptor gene, have been associated with bronchiolitis and may link to preliminary evidence associating neonatal vitamin D levels with wheezing in young children.^{28,29}

DISEASE COURSE AND PREDICTION

Epidemiologic study results of bronchiolitis have suggested a high degree of morbidity but low mortality. More than one third of children develop bronchiolitis during the first 2 years of life.^{7,30} Of these, approximately 1 in 10 (~3% of all infants in the United States) will be hospitalized, up from approximately 1% in the 1970s.¹ The rate of hospitalization retrospectively estimated during 1995–2003 from a Tennessee Medicaid population was 7.1%, which suggests that higher rates may occur among some groups

TABLE 1 Selected Risk Factors for Outcomes of Bronchiolitis in 3 Prospective Studies of Outpatients

	Shaw et al ³⁸ (1991)	Mansbach et al ⁴⁰ (2008)	Voets et al ³⁹ (2006)
Outcome	Severe disease ^a	Hospitalization	Hospitalization
Risk factors			
Age			
<2 mo		4.5/0.78	
<3 mo	2.2/0.75		
<6 mo			2.2/0.53
Prematurity			
<34 wk	5.4/0.77		
<35 wk		1.5/0.96	
Ill appearance	3.2/0.32		
Oxygen saturation			
<94%		5.4/0.77	
<95%	16/0.69		5.2/0.37
Respiratory rate			
>45 breaths per min			3.8/0.39
At or higher than normal for age (40–45 breaths per min according to age)		1.3/0.61	
≥70 breaths per min	5.8/0.75		
Work of breathing			
Accessory muscle use	2.2/0.42		
Moderate/severe retractions		3.2/0.76	
Chest radiograph result			
Atelectasis	10.5/0.81		
Abnormal		1.2/0.73	

Risk factors are presented as positive or negative likelihood ratios (+LR/–LR). The likelihood ratio can be multiplied by the pretest odds (ratio of the risk/1-risk) to obtain the posttest odds. For example, with a previous risk of hospitalization of 33% (odds of 0.33/0.66 = 0.5), a finding with a positive likelihood ratio of 4 increases the odds to 2 (4 × 0.5), corresponding to a posttest risk of 67% (2/2 + 1).

^a Severe disease was defined as unable to maintain alert, active, and well hydrated while taking oral fluids throughout the illness.

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of children.³¹ A recent prospective population-based study showed that the yearly rate from RSV alone for infants younger than 6 months of age was 17 hospitalizations, 55 ED visits, and 132 office visits per 1000 children.³ Although the number of hospitalizations seems to have increased, the mortality rate is low; fewer than 400 deaths related to RSV occur annually.^{3,32,33} Most deaths that result from bronchiolitis occur in infants during the first 6 months of life; infants with prematurity and underlying cardiopulmonary disease or immunodeficiency are at higher risk.^{7,34} Studies of preventive immune therapies, such as palivizumab, have documented a reduction in RSV hospitalization rates for specific high-risk groups, and AAP recommendations were updated recently.^{35–37}

The potential for disease progression has led to research to identify risk factors for severe bronchiolitis. Table 1 presents the clinical predictors of hospitalization evaluated in several outpatient populations.^{38–40} The likelihood ratios demonstrate the limited predictive value of individual clinical findings on the physical examination to predict outcomes, which may be related to the typical minute-to-minute variability of these findings among children with bronchiolitis. When evaluated independently, other predictors, including atelectasis on chest radiography, have been correlated with outcomes in some studies.³⁸ However, a recent study showed that chest radiographic abnormalities correlated with overall clinical severity on physical examination, which suggests that the pre-

sence of atelectasis adds little to the assessment.⁴¹

Pulse oximetry is among the measures most strongly correlated with outcomes of bronchiolitis. In a recent multicenter prospective study, a pulse oximetry level of <94% was associated with a more-than-fivefold increase in likelihood of hospitalization.⁴⁰ A cohort study conducted when oximetry was not in routine use revealed that mild hypoxemia was correlated with a more severe course, which likely reflects pulmonary ventilation-to-perfusion mismatch.³⁸ However, arbitrary thresholds for oxygen therapy may also influence outcomes. A survey of emergency physicians revealed that reducing the oximetry level from 94% to 92% in a clinical vignette significantly increased the likelihood of recommending hospitalization.⁴² Furthermore, a substantial proportion of infants remain in the hospital to receive oxygen when other abnormalities have improved.⁴³ A recent British study revealed that the mean lag time for oxygen saturation to normalize was 66 hours after all other problems had resolved.⁴⁴ Continuous oximetry may enhance this situation, because it will detect the characteristic transient dips in oxygenation associated with bronchiolitis. This evidence further supports the AAP recommendations that oxygen therapy be initiated judiciously when oxygen saturation levels fall below 90% and that the intensity of monitoring oxygen saturation levels be reduced as the infant improves.⁷ Novel approaches, such as the use of home oxygen therapy, have been studied in some populations, and further research on oxygen use in bronchiolitis is needed.^{45,46}

Apnea is a specific and important concern in the management of young infants with bronchiolitis, especially those with RSV. The incidence of this complication may be much lower than previous reports have suggested.^{47,48} A retrospective study of 691 infants

younger than 6 months of age who were hospitalized for bronchiolitis revealed that apnea occurred in 19 (2.7%).⁴⁹ All of these apneic infants were identified by risk criteria including either (1) history of an apneic episode having already occurred or (2) young age, defined as less than 1 month for term infants or a postconceptional age of <48 weeks for premature infants.⁴⁹

DIAGNOSTIC TESTING

The type and frequency of diagnostic tests used for bronchiolitis, such as viral detection and radiographs, vary markedly among clinicians.⁵ As stated in the AAP guideline, results of evidence-based reviews have not supported a role for any diagnostic tests in the management of routine cases of bronchiolitis.^{7,50} In addition, studies of efforts to standardize care have demonstrated substantial reductions in diagnostic testing rates with potential benefits on costs and outcomes.^{51,52} Recent evidence further supports a limited role for diagnostic testing in most cases of bronchiolitis.

Rapid viral antigen tests have variable sensitivity and specificity depending on the test and when they are used during the respiratory season.⁵³ Their predictive value is generally good during the peak viral season but decreases considerably at times of low prevalence. Because most viruses that cause bronchiolitis have similar clinical courses, the value of identifying the specific agent varies according to the setting. In typical outpatient cases, results would likely have little impact on management. In the hospital setting, however, specific viral testing has been used as part of successful interventions to reduce nosocomial infection.^{48,49}

For the specific clinical scenario of an infant presenting during the first few

months of life with bronchiolitis and fever, studies have evaluated prospectively the ability of a positive viral test to predict a low likelihood for a bacterial infection. Authors of 1 study documented a low but not insignificant rate of bacterial infection accompanying RSV infection, mostly in the urinary tract.⁵⁴ Low rates of coinfections also have been observed in recent studies only on the basis of the clinical diagnosis of bronchiolitis.⁵⁵ In a prospective pediatric office-based study of 218 febrile infants younger than 3 months of age with clinically diagnosed bronchiolitis, no serious bacterial infections were identified.⁵⁶ These findings further support the idea that, for most cases of bronchiolitis, the clinical diagnosis of bronchiolitis is sufficient, and viral testing adds little to routine management.

The use of chest radiography for diagnosis and management of bronchiolitis has also varied widely and is not recommended routinely by the AAP.⁷ A subsequent prospective study of children aged 2 to 23 months who presented to the ED with bronchiolitis further showed the low yield of routine radiography as well as a potential detrimental effect.⁵⁷ Of 265 children with "simple" bronchiolitis (defined as coryza, cough, and respiratory distress accompanying a first episode of wheeze in a child without underlying illness), routine radiography identified findings inconsistent with bronchiolitis in only 2 cases, and in neither case did the findings change acute management. After reviewing the radiographs, clinicians were more likely to treat with antibiotics, although the findings did not support treatment.

Although the diagnosis of most cases of bronchiolitis is clinically evident and does not require diagnostic testing, the differential diagnosis is broad and always warrants consideration (see

Table 2). This is essential for children with atypical presentations, such as the absence of viral symptoms, severe respiratory distress, and frequent recurrences. Children with this type of presentation may require diagnostic evaluation to rule out another cause.

THERAPY

The role of bronchodilators in the treatment of bronchiolitis has been the subject of many studies and systematic evidence-based reviews of the literature.⁵⁸ Summarizing the results of these studies is confounded by the variety of therapies and outcome measures, which range from short-term clinical scores obtained soon after treatment to broader clinical outcomes such as hospitalization or duration of illness. Even score-based studies are difficult to compare, because many of the measures used do not have established validity or proven correlation with clinically significant improvement. Pooling the results of clinical scores from a large number of studies may result in a statistically significant difference of questionable clinical importance.

In a recent Cochrane collaboration systematic review, studies that dichot-

TABLE 2 Differential Diagnosis for a Wheezing Infant

Viral bronchiolitis
Other pulmonary infections (eg, pneumonia, <i>Mycoplasma</i> , <i>Chlamydia</i> , tuberculosis)
Laryngotracheomalacia
Foreign body, esophageal or aspirated
Gastroesophageal reflux
Congestive heart failure
Vascular ring
Allergic reaction
Cystic fibrosis
Mediastinal mass
Bronchogenic cyst
Tracheoesophageal fistula

omized patients into those who did and did not respond to bronchodilators were compared (Fig 1).⁵⁸ Several overarching principles are demonstrated in Fig 1. First, the results are heterogeneous, with a minority of studies finding improvement. This likely mirrors the heterogeneity of the responses among individual patients. Second, a high rate of improvement among control subjects (43%) exists that may result from the characteristic clinical variability observed with bronchiolitis or from a response to other supportive measures that could be mistakenly attributed to a bronchodilator response in an uncontrolled setting. The modest difference in the treatment group

(57%) did not reach statistical significance in this analysis. The questionable clinical importance of this response is underscored by a meta-analysis of studies that found no effect of bronchodilator administration on hospitalization rates.⁵⁸ Furthermore, results of a multicenter clinical trial of epinephrine administration revealed that epinephrine had no effect on duration of hospitalization.⁵⁹

A 2006 Cochrane systematic review of studies that compared bronchodilators for the management of bronchiolitis in outpatients suggested a potential benefit with epinephrine administration.⁶⁰ However, several more recent studies did not support the routine use of epinephrine. A study of 703 children with bronchiolitis in 2 EDs compared 3 doses of albuterol with 1 dose of racemic epinephrine and revealed a small benefit that favored albuterol in successful discharge.⁶¹ A multicenter study from the Pediatric Emergency Research Canada network enrolled 800 healthy infants with a first episode of bronchiolitis and compared epinephrine to placebo as part of a factorial design trial with 4 groups that also evaluated dexamethasone (see discus-

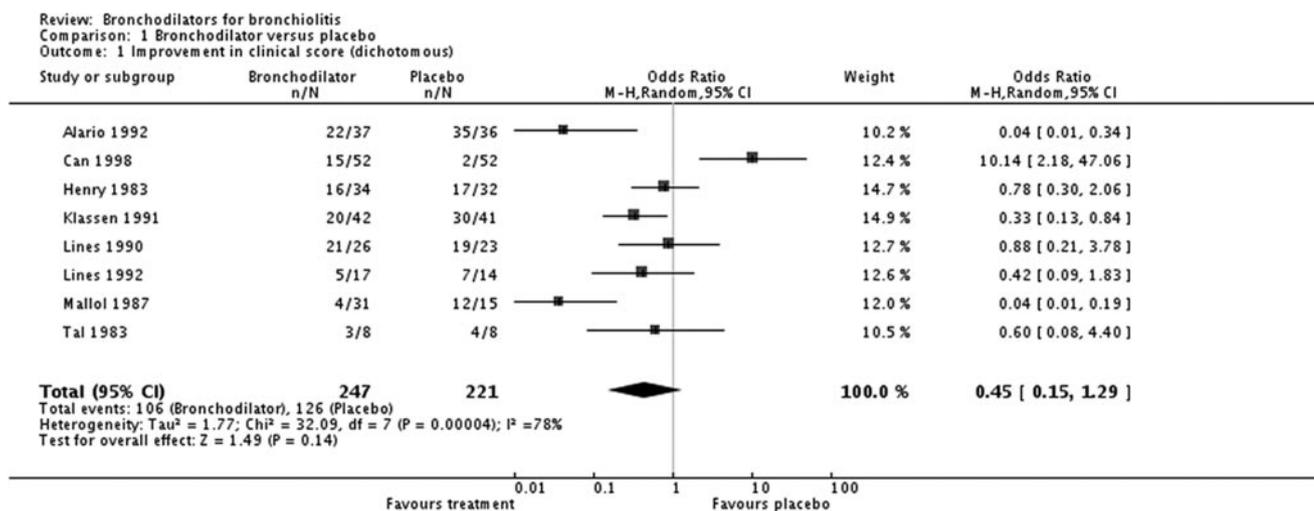


FIGURE 1

Cochrane collaboration systematic review of studies that assessed the difference in rate of improvement after β_2 -agonist bronchodilators or placebo among children with bronchiolitis. (Reproduced with permission from Gadomski AM, Bhasale AL. *Cochrane Database Syst Rev*. 2006;(3):CD001266.)

TABLE 3 Summary of Recent Evidence for Therapies Used for Bronchiolitis

Therapy	Summary	Recommendation
Bronchodilators	No improvement in duration of illness or hospitalization ^{58,59}	No routine use
	May improve short-term clinical scores in a subset of children ⁵⁸	Use only after proven benefit in a trial of therapy, if chosen as an option
Corticosteroids	No improvement in duration of illness or hospitalization ^{7,63}	No routine use
Leukotriene receptor antagonists	No improvement in duration of illness ^{67,75}	Not recommended
Nebulized hypertonic saline	May reduce length of inpatient hospitalization ⁷⁰	None

sion below).⁶² Two doses of nebulized epinephrine did not reduce the number of hospitalizations when compared with placebo. Overall, the available current evidence continues to support the AAP recommendation against the routine use of bronchodilators for bronchiolitis.⁷ A monitored trial of a bronchodilator can be considered as an option, but it should be continued only after a documented beneficial response (Table 3).

Corticosteroid administration for the treatment of bronchiolitis also has been controversial. The studies reviewed in the AAP guideline revealed that corticosteroid administration was not associated with significant reductions in clinical scores, hospitalization rates, or length of hospitalization.⁷ Several large studies subsequently expanded these data. A multicenter trial from the Pediatric Emergency Care Applied Research Network, which enrolled 600 previously healthy infants with a first episode of bronchiolitis, showed that a single oral dose of dexamethasone resulted in no significant improvement compared with placebo in the rates of hospitalization or clinical scores.⁶³

The Pediatric Emergency Research Canada study, mentioned above, con-

firmed this finding by using a regimen of 6 days of dexamethasone and also revealed no improvement in disease course.⁶² It is interesting to note that in this factorial design study, the group of those who received dexamethasone combined with 2 doses of nebulized epinephrine had a lower admission rate over 7 days compared with those who were on placebo (17.1% vs 26.4%). The study authors did not anticipate this potential interaction in the design, and after adjustment for multiple comparisons the difference did not reach statistical significance ($P = .07$). Interpretation of this result awaits further investigation before it can be implemented in routine practice. Synergy between adrenergic agents and corticosteroids has been well described in asthma and has been observed in other small studies of bronchiolitis.^{64–66} If confirmed, the moderate effect (11 infants needing to be treated for 1 not to be admitted) could, nevertheless, represent a potentially important relative reduction in the number of hospitalizations for this common disorder. Future studies may evaluate whether a larger effect may be present among a subgroup of infants and assess other dose combinations.

Among other therapies explored for potential use in bronchiolitis is the leukotriene receptor antagonist, montelukast, which did not seem beneficial in resolution of symptoms.^{67,68} Nebulized hypertonic saline has been associated in recent randomized trials and in a Cochrane meta-analysis with improvement in clinical score and duration of hospitalization.^{69,70} Other therapies such as helium/oxygen, nasal continuous positive airway pressure, and surfactant are being assessed for use in critically ill patients.^{71–73}

CONCLUSIONS

Bronchiolitis continues to be an active area of investigation across the spectrum from genetic mechanisms to population-based research. Surveillance studies continue to identify new causes of bronchiolitis and explore the role of viral coinfections. Research on prediction of the course of illness has revealed comorbidities as important risk factors and specific physical or diagnostic test findings as less predictive of outcomes for most bronchiolitis cases. The use of pulse oximetry has likely contributed to longer hospitalizations and greater use of health care resources, suggesting that the standard of care for oxygen therapy requires better definition. Recent multicenter research on therapy for bronchiolitis supports previous AAP recommendations against the routine use of bronchodilators or corticosteroids. Further investigation is needed to explore the combination of these therapies and other interventions, such as nebulized hypertonic saline.

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