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Bronchiolitis: Recent Evidence on Diagnosis and Management

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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 guideline[7] 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 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]

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.

Adapted with permission from Zorc JJ. *Recent Advances in Paediatrics*. London, United Kingdom: Royal Society of Medicine Press; 2009:19.

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 dichotomized 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]

TABLE 2 Differential Diagnosis for a Wheezing Infant

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

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-

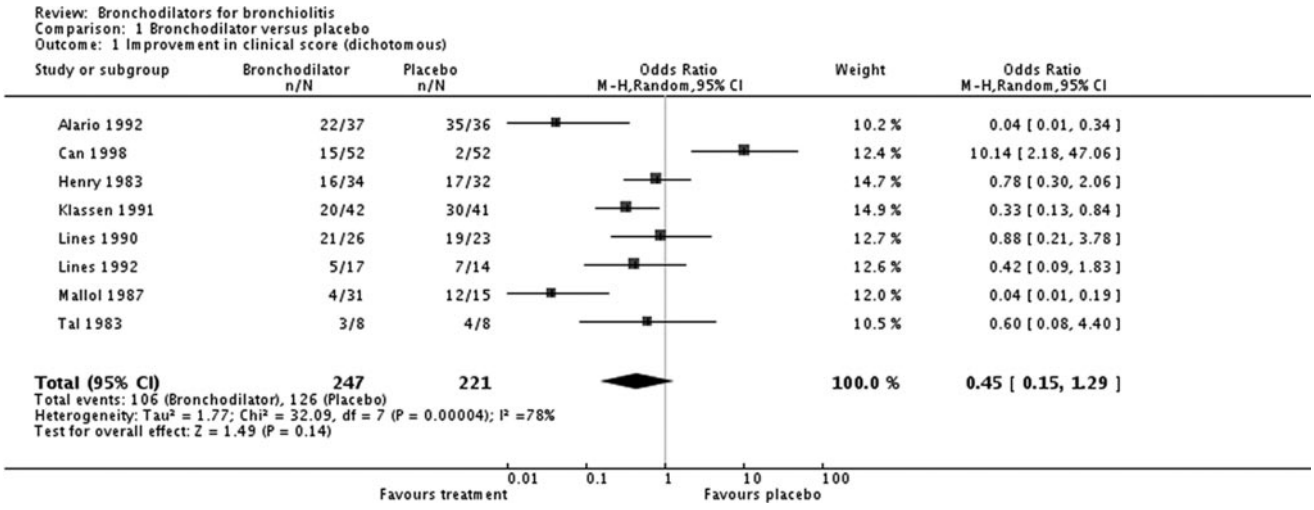

FIGURE 1
Cochrane collaboration systematic review of studies that assessed the difference in rate of improvement after β_2-agonist bronchodilators or placebo among children with bronchiolitis. (Reproduced with permission from Gadomski AM, Bhasale AL. *Cochrane Database Syst Rev.* 2006;(3):CD001266.)

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, confirmed 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.

REFERENCES

1. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*. 1999;282(15):1440–1446
2. Pelletier AJ, Mansbach JM, Camargo CA Jr. Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics*. 2006;118(6):2418–2423
3. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009; 360(6):588–598
4. Behrendt CE, Decker MD, Burch DJ, Watson PH. International variation in the management of infants hospitalized with respira-

tory syncytial virus. International RSV Study Group. *Eur J Pediatr*. 1998;157(3):215–220

5. Christakis DA, Cowan CA, Garrison MM, Molteni R, Marcuse E, Zerr DM. Variation in inpatient diagnostic testing and management of bronchiolitis. *Pediatrics*. 2005;115(4):878–884
6. Willson DF, Horn SD, Hendley JO, Smout R, Gassaway J. Effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. *Pediatrics*. 2001;108(4):851–855
7. American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. *Pediatrics*. 2006;118(4):1774–1793
8. Agency for Healthcare Research and Quality. *Management of Bronchiolitis in Infants and Children*. Rockville, MD: Agency for Healthcare Research and Quality; 2003. AHRQ publication No. 03-E014
9. Lakhanpaul M, Armon K, Eccleston P, et al. *An Evidence Based Guideline for the Management of Children Presenting With Acute Breathing Difficulty*. Nottingham, United Kingdom: University of Nottingham; 2002. Available at: www.nottingham.ac.uk/paediatric-guideline/breathingguideline.pdf. Accessed December 7, 2009
10. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med*. 2001;344(25):1917–1928
11. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol*. 1989;129(6):1232–1246
12. Wolf DG, Greenberg D, Kalkstein D, et al. Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. *Pediatr Infect Dis J*. 2006;25(4):320–324
13. Mansbach JM, McAdam AJ, Clark S, et al. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. *Acad Emerg Med*. 2008;15(2):111–118
14. Boivin G, De Serres G, Côté S, et al. Human metapneumovirus infections in hospitalized children. *Emerg Infect Dis*. 2003;9(6):634–640
15. Kahn JS. Epidemiology of human metapneumovirus. *Clin Microbiol Rev*. 2006;19(3):546–557
16. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med*. 2001;7(6):719–724
17. Williams JV, Tollefson SJ, Heymann PW, Carper HT, Patrie J, Crowe JE. Human metapneumovirus infection in children hospitalized for wheezing. *J Allergy Clin Immunol*. 2005;115(6):1311–1312
18. Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med*. 2004;350(5):443–450
19. Paranhos-Baccalà G, Komurian-Pradel F, Richard N, Vernet G, Lina B, Floret D. Mixed respiratory virus infections. *J Clin Virol*. 2008;43(4):407–410
20. Semple MG, Cowell A, Dove W, et al. Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. *J Infect Dis*. 2005;191(3):382–386
21. Caracciolo S, Minini C, Colombrita D, et al. Human metapneumovirus infection in young children hospitalized with acute respiratory tract disease: virologic and clinical features. *Pediatr Infect Dis J*. 2008;27(5):406–412
22. Rakes GP, Arruda E, Ingram JM, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care: IgE and eosinophil analyses. *Am J Respir Crit Care Med*. 1999;159(3):785–790
23. Miller EK, Lu X, Erdman DD, et al. Rhinovirus-associated hospitalizations in young children. *J Infect Dis*. 2007;195(6):773–781
24. Peltola V, Waris M, Osterback R, Susi P, Hyypia T, Ruuskanen O. Clinical effects of rhinovirus infections. *J Clin Virol*. 2008;43(4):411–414
25. Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpaa R, Reijonen TM. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J*. 2004;23(11):995–999
26. Janssen R, Bont L, Siezen CL, et al. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. *J Infect Dis*. 2007;196(6):826–834
27. Siezen CL, Bont L, Hodemaekers HM, et al. Genetic susceptibility to respiratory syncytial virus bronchiolitis in preterm children is associated with airway remodeling genes and innate immune genes. *Pediatr Infect Dis J*. 2009;28(4):333–335
28. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007;85(3):853–859
29. Mansbach JM, Camargo CA Jr. Bronchiolitis: lingering questions about its definition and the potential role of vitamin D. *Pediatrics*. 2008;122(1):177–179
30. Yorita KL, Holman RC, Sejvar JJ, Steiner CA, Schonberger LB. Infectious disease hospitalizations among infants in the United States. *Pediatrics*. 2008;121(2):244–252
31. Carroll KN, Gebretsadik T, Griffin MR, et al. Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan. *Pediatrics*. 2008;122(1):58–64
32. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143(5 suppl):S127–S132
33. Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979–1997. *J Infect Dis*. 2001;183(1):16–22
34. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Arch Dis Child*. 2009;94(2):99–103
35. Romero JR. Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: results from four years of palivizumab usage. *Pediatr Infect Dis J*. 2003;22(2 suppl):S46–S54
36. Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. *Health Technol Assess*. 2008;12(36):iii, ix–x, 1–86
37. American Academy of Pediatrics, Committee on Infectious Diseases. Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6). Available at: www.pediatrics.org/cgi/reprint/peds.2009–2345
38. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants with bronchiolitis. *Am J Dis Child*. 1991;145(2):151–155
39. Voets S, van Berlaer G, Hachimi-Idrissi S. Clinical predictors of the severity of bronchiolitis. *Eur J Emerg Med*. 2006;13(3):134–138
40. Mansbach JM, Clark S, Christopher NC, et al. Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department. *Pediatrics*. 2008;121(4):680–688
41. Schuh S, Canny G, Reisman JJ, et al. Nebulized albuterol in acute bronchiolitis. *J Pediatr*. 1990;117(4):633–637
42. Mallory MD, Shay DK, Garrett J, Bordley WC. Bronchiolitis management preferences and

the influence of pulse oximetry and respiratory rate on the decision to admit. *Pediatrics*. 2003;111(1). Available at: www.pediatrics.org/cgi/content/full/111/1/e45

43. Schroeder AR, Marmor AK, Pantell RH, Newman TB. Impact of pulse oximetry and oxygen therapy on length of stay in bronchiolitis hospitalizations. *Arch Pediatr Adolesc Med*. 2004;158(6):527–530
44. Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. *Pediatrics*. 2008;121(3):470–475
45. Bajaj L, Turner CG, Bothner J. A randomized trial of home oxygen therapy from the emergency department for acute bronchiolitis. *Pediatrics*. 2006;117(3):633–640
46. Tie SW, Hall GL, Peter S, et al. Home oxygen for children with acute bronchiolitis. *Arch Dis Child*. 2009;94(8):641–643
47. Church NR, Anas NG, Hall CB, Brooks JG. Respiratory syncytial virus-related apnea in infants: demographics and outcome. *Am J Dis Child*. 1984;138(3):247–250
48. Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. *J Pediatr*. 2009;155(5):728–733
49. Willwerth BM, Harper MB, Greenes DS. Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. *Ann Emerg Med*. 2006;48(4):441–447
50. Bordley WC, Viswanathan M, King VJ, et al. Diagnosis and testing in bronchiolitis: a systematic review. *Arch Pediatr Adolesc Med*. 2004;158(2):119–126
51. Perlstein PH, Kotagal UR, Bolling C, et al. Evaluation of an evidence-based guideline for bronchiolitis. *Pediatrics*. 1999;104(6):1334–1341
52. Todd J, Bertoch D, Dolan S. Use of a large national database for comparative evaluation of the effect of a bronchiolitis/viral pneumonia clinical care guideline on patient outcome and resource utilization. *Arch Pediatr Adolesc Med*. 2002;156(11):1086–1090
53. Henrickson KJ, Hall CB. Diagnostic assays for respiratory syncytial virus disease. *Pediatr Infect Dis J*. 2007;26(11 suppl):S36–S40
54. Levine DA, Platt SL, Dayan PS, et al; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*. 2004;113(6):1728–1734
55. Bilavsky E, Shouval DS, Yarden-Bilavsky H, Fisch N, Ashkenazi S, Amir J. A prospective study of the risk for serious bacterial infections in hospitalized febrile infants with or without bronchiolitis. *Pediatr Infect Dis J*. 2008;27(3):269–270
56. Luginbuhl LM, Newman TB, Pantell RH, Finch SA, Wasserman RC. Office-based treatment and outcomes for febrile infants with clinically diagnosed bronchiolitis. *Pediatrics*. 2008;122(5):947–954
57. Schuh S, Lalani A, Allen U, et al. Evaluation of the utility of radiography in acute bronchiolitis. *J Pediatr*. 2007;150(4):429–433
58. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*. 2006;(3):CD001266
59. Wainwright C, Altamirano L, Cheney M, et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med*. 2003;349(1):27–35
60. Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev*. 2004;(1):CD003123
61. Walsh P, Caldwell J, McQuillan KK, Friese S, Robbins D, Rothenberg SJ. Comparison of nebulized epinephrine to albuterol in bronchiolitis. *Acad Emerg Med*. 2008;15(4):305–313
62. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med*. 2009;360(20):2079–2089
63. Corneli HM, Zorc JJ, Majahan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med*. 2007;357(4):331–339
64. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J*. 2007;29(3):587–595
65. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics*. 1983;71(1):13–18
66. Kuyucu S, Unal S, Kuyucu N, Yilgor E. Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis. *Pediatr Int*. 2004;46(5):539–544
67. Amirav I, Luder AS, Kruger N, et al. A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. *Pediatrics*. 2008;122(6). Available at: www.pediatrics.org/cgi/content/full/122/6/e1249
68. Bisgaard H, Flores-Nunez A, Goh A, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med*. 2008;178(8):854–860
69. Kuzik BA, Al-Qadhi SA, Kent S, et al. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr*. 2007;151(3):266–270, 270e1
70. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*. 2008;(4):CD006458
71. Martinón-Torres F, Rodriguez-Nunez A, Martinon-Sanchez JM. Nasal continuous positive airway pressure with heliox in infants with acute bronchiolitis. *Respir Med*. 2006;100(8):1458–1462
72. Thia LP, McKenzie SA, Blyth TP, Minasian CC, Kozlowska WJ, Carr SB. Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. *Arch Dis Child*. 2008;93(1):45–47
73. Ventre K, Haroon M, Davison C. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev*. 2006;(3):CD005150
74. Zorc JJ. Diagnosis and management of bronchiolitis. In: David TJ, ed. *Recent Advances in Paediatrics*. London, United Kingdom: Royal Society of Medicine Press; 2009:15–27
75. Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med*. 2003;167(3):379–383