In this review, we present and summarize data from recently conducted research regarding controversial aspects of the management of children with bronchiolitis. These data suggest that chronic medical history, gestational age at birth, postnatal age, and physiological variables can identify those children at higher risk for a more severe course of bronchiolitis. Large prospective studies also suggest that the likelihood of significant bacterial illness in febrile infants with bronchiolitis may be lower than in children without bronchiolitis. Nevertheless, urinary tract infections remain relatively common in young febrile children with bronchiolitis. Lastly and unfortunately, the data note a relative lack of effective therapies for children with bronchiolitis, although certain therapies such as systemic corticosteroids show potential efficacy and are in need of further study. The remaining uncertainty surrounding many issues pertaining to bronchiolitis highlight the need for more research aimed to: (1) develop prognostic models to identify patients at risk for a more severe clinical course, (2) develop generalizable diagnostic models to identify febrile infants with bronchiolitis at high and very low risk of significant bacterial illness, and (3) evaluate the effectiveness of promising therapies.

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Controversies in the Management of Children with Bronchiolitis

By Peter S. Dayan, MD, Cindy G. Roskind, MD, Deborah A. Levine, MD, and Nathan Kuppermann, MD, MPH

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BRONCHIOLITIS IS A COMMON VIRAL respiratory illness in children and accounts for a substantial portion of the pediatric burden of illness in the United States and overseas. Children younger than 5 years old with bronchiolitis accounted for an estimated 1.65 million US acute-care, non-federal hospital admissions between 1980 and 1996. Eighty-one percent of these admissions were among children younger than 1 year of age.1 Among children younger than 1 year old, the rate of admission for bronchiolitis in the United States has increased from 12.9/1000 children in 1980 to 31.2/1000 children in 1996, likely a result of changes in hospitalization criteria, an increasing population of premature infants, and those with significant chronic illnesses who are at risk for more severe respiratory syncytial virus (RSV)-associated illness.1 Fortunately, only an estimated 95 bronchiolitis-associated deaths occurred annually in the United States between 1979 and 1997, with 79% of these deaths afflicting children younger than 1 year of age.2

Many aspects of the management of bronchiolitis remain controversial as reflected in the variation in admission rates and use of specific therapies among clinicians, both at different institutions and in disparate geographical regions.3-6 In this review, we focus on 3 related aspects that impact upon the emergency department (ED) management of children with bronchiolitis: (1) the risk of and risk factors for progression in the severity of illness, (2) the risk of and risk factors for significant bacterial infection in febrile infants younger than 60 days with bronchi-
olitis, and (3) the relative utility of specific interventions. For each section, we present a clinical question followed by the details of studies that provide the highest quality of evidence available and/or data particularly relevant to ED management. For each topic, we reviewed bibliographies and conducted literature searches using PubMed, The Cochrane Library, and Clinical Evidence (when appropriate) to identify studies of bronchiolitis in general and studies that specifically assess RSV-associated lower respiratory tract illness. For purposes of clarity and comprehensiveness, we accompany our textual information with the pertinent data in tabular form whenever possible.

**Prognosis Question**

In the ED, we would like to accurately predict which children with bronchiolitis are likely to have a more severe course in order to more precisely determine which children need admission to the general inpatient service or intensive care unit. It is difficult, however, to identify unbiased, clinically-relevant outcomes that clearly define a severe course. We focus on the following outcomes: death, mechanical ventilation, admission to the general inpatient service, and admission or transfer to an intensive care unit.

**Question:** In children younger than 1 year with bronchiolitis, what are the risks of, and risk factors associated with death, mechanical ventilation, admission to the general inpatient service, and admission or transfer to an intensive care unit?

Data with which to answer this question and base recommendations come from studies involving different patient populations with bronchiolitis: hospitalized patients, all patients who present to the ED, and patients who re-presents to the ED. Most research in this area has been performed on inpatient populations.7-13

**All Hospitalized Patients**

In a prospective, observational study completed by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) network, 689 hospitalized children younger than 2 years with RSV-associated lower respiratory tract infections across seven pediatric tertiary care centers were assessed at the time of admission for risk factors potentially associated with a complicated hospitalization. Only 6 of 689 patients died (0.9%); 4 of these 6 had underlying disease (including congenital heart disease, chronic lung disease, and immunocompromise) and 2 were either premature or younger than 6 weeks old. None of 372 patients died if older than 6 weeks and without other known risk factors for severe disease (95% CI 0-0.8%).7

Considering that Canadian referrals to the ED may represent a sicker population than that in the United States, the low risk of death caused by bronchiolitis is reassuring.

Table 1 details risk factors associated with the outcomes of interest from this PICNIC study. Patients often had more than one underlying risk factor. In a regression model, it was also noted that hypoxia on admission (<90%) and atelectasis on chest radiograph were independently associated with an increased need for mechanical ventilation and admission to the intensive care unit (ICU).7 Except for admission oxygen saturation, the researchers did not assess the utility of physical examination findings in the ED to predict outcome. Most retrospective reviews corroborate the findings of the PICNIC study; age younger than 2 to 3 months, premature birth at < 34 to 37 weeks, congenital heart disease, chronic lung

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**TABLE 1. Measures of Morbidity in Different Subgroups of Children With Bronchiolitis**

<table>
<thead>
<tr>
<th>Cardiac Disease</th>
<th>Chronic Lung Disease</th>
<th>Immuno-compromised</th>
<th>Other Disease</th>
<th>Gestation &lt; 37 wk</th>
<th>Age &lt; 6 wk</th>
<th>No Known Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (No.)</td>
<td>57</td>
<td>79</td>
<td>21</td>
<td>52</td>
<td>148</td>
<td>101</td>
</tr>
<tr>
<td>Intensive care unit (%)</td>
<td>31.6</td>
<td>36.7</td>
<td>19.1</td>
<td>34.6</td>
<td>25.0</td>
<td>28.7</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>19.3</td>
<td>25.3</td>
<td>14.3</td>
<td>21.2</td>
<td>18.2</td>
<td>16.8</td>
</tr>
<tr>
<td>Death (No.)</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

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Other factors for more severe disease include patients with congenital heart disease and chronic lung disease. Although definitions differ between studies, chronic lung disease generally includes cystic fibrosis, recurrent aspiration pneumonia, bronchopulmonary dysplasia, congenital malformations, neurogenic disorders interfering with pulmonary toilet, tracheoesophageal fistula, and other substantial pulmonary conditions. Patients with congenital heart disease in these studies typically were patients with any anatomic defect, although patients with a patent ductus arteriosus were variably excluded. Immunosuppression was typically defined as patients with congenital immunodeficiency, those receiving chemotherapy or chronic corticosteroid therapy, and those who received a solid or bone marrow transplant.

Navas et al performed a 12-center retrospective review of RSV-positive hospitalized Canadian patients with a diagnosis of pneumonia or bronchiolitis who met at least one previously hypothesized high-risk criterion for severe illness. Death within 2 weeks occurred only in children in the congenital heart disease and chronic lung disease groups (3.4% and 3.5%, respectively). The need for mechanical ventilation and intensive care unit admission was similar among patients with congenital heart disease (33.4% and 18.8%), chronic lung disease (32.0% and 17.0%), and immunosuppression (31.4% and 14.2%). The high rates of mechanical ventilation and ICU admission were likely caused by patients often possessing more than one high-risk factor and inclusion of nosocomial cases of RSV.

Children with all types of substantial chronic lung disease appear to be at high risk for more severe RSV-associated lower respiratory tract illness. Of 159 patients with chronic lung disease in the PICNIC RSV database, mechanical ventilation was needed for 23.1%, 23.5%, 30.0%, 33.3%, and 22.2% of patients with bronchopulmonary dysplasia (BPD), recurrent aspiration pneumonia, congenital malformation, neurogenic disease, and tracheoesophageal fistula during an episode of RSV lower respiratory tract infection. It is notable that patients in this study were often older: the mean ages ranged from 61.2 weeks in patients with BPD to 161.6 weeks in patients with neurogenic disease.

Patients who were currently receiving home oxygen were statistically more likely to require mechanical ventilation (42.9%) than those never (18.2%) or not currently (9.5%) using home oxygen. In 2 small prospective, observational series of young children with cystic fibrosis who had viral lower respiratory infections, mechanical ventilation was required in 3/7 (43%) and 0/12 patients.

Although the association between severe course of bronchiolitis and substantial chronic illness is quite clear, more controversy surrounds the influence of young age and premature birth. Brooks et al assessed the risk of and risk factors for serious clinical deterioration in previously healthy children hospitalized with RSV-associated lower respiratory tract infection. The first part of the study was a secondary analysis of prospectively collected data from a single tertiary care center. Of 721 admitted infants younger than 1 year of age, 34/119 (28.6%) born at < 35 weeks gestation and 60/602 (10.0%) born at ≥ 35 weeks gestation were directly admitted to the ICU. Of the 542 patients ≥ 35 weeks gestation admitted to the general pediatric unit, only 9/353 (2.5%) and 1/189 (0.5%) patients ≤ 3 months and > 3 months were transferred to the ICU. All transfers resulted from respiratory distress or apnea. In the second part of the study, the analysis of data from 2 tertiary care centers revealed that no physical examination findings consistently differentiated patients who were transferred to the ICU after initial admission to the general ward from those who were not. Patients with extremes in respiratory rate (>80/min) and oxygen saturation (<86%) were at higher risk of ICU transfer but comprised the minority of patients.

In a prospective study that stratified patients < 6 months into subgroups, McIntosh et al assessed the clinical course of previously healthy RSV-positive children with bronchiolitis hospitalized at a single tertiary-care children's hospital. They noted that 20/95 (21.1%), 15/143 (10.5%), and 1/78 (1.3%) patients younger than 2 months, 2 to 4 months, and 5 to 6 months required mechanical ventilation. The data are unclear, however, as to the proportion in each group who were premature.

In the previously described, large retrospective study conducted by Navas et al, 0/761 patients died if they were > 36 weeks gestation or > 6 weeks of age without other risk factors from history. However, pa-

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disease, immunodeficiency, pulmonary consolidation on radiograph, and hypoxia on admission are risk factors for more severe disease.

**Subgroup of Hospitalized Patients With Congenital Heart Disease, Chronic Lung Disease, or Immunosuppression**

The risk of severe bronchiolitis is greater among children with substantial underlying chronic disease, particularly chronic lung disease. Although definitions differ between studies, chronic lung disease generally includes cystic fibrosis, recurrent aspiration pneumonia, bronchopulmonary dysplasia, congenital malformations, neurogenic disorders interfering with pulmonary toilet, tracheoesophageal fistula, and other substantial pulmonary conditions. Patients with congenital heart disease in these studies typically were patients with any anatomic defect, although patients with a patent ductus arteriosus were variably excluded. Immunosuppression was typically defined as patients with congenital immunodeficiency, those receiving chemotherapy or chronic corticosteroid therapy, and those who received a solid or bone marrow transplant.

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In the previously described, large retrospective study conducted by Navas et al, 0/761 patients died if they were > 36 weeks gestation or > 6 weeks of age without other risk factors from history. However, pa-
tients born at < 36 weeks gestation and those < 6 weeks had a 33.6% and 35.9% risk of ICU admission and 15.6% and 12.8% risk of mechanical ventilation. Again, patients with nosocomial RSV disease appear to have been included.12

Subgroup of Hospitalized Infants who Present With Apnea

Patients with bronchiolitis and apnea have been reported along with other patients with RSV-associated apnea in several single-center retrospective case series.18-21 Approximately 18% to 21% of hospitalized children younger than 12 months of age with RSV infections present with apnea.20,21 Apnea may be the first manifestation of RSV infection in infants, but it is most often associated with a upper respiratory infection (URI) or bronchiolitis. Consistently across studies, the major risk factors for RSV-associated apnea are a gestational age at birth of < 37 to 38 weeks and a postnatal age of < 2 to 3 months.18-21 Bruhn et al20 noted that 38%, 27%, and 16% of patients with RSV-associated apnea were younger than 1, 1 to 2, and 2 to 3 months, respectively. Of those patients who have been hospitalized with RSV-associated apnea, less than 2% have died because of the apnea itself, 80% have been admitted to the ICU, 18% to 60% have required mechanical ventilation, and 50% have experienced repeat episodes of apnea.18-24

All ED Patients

Shaw et al22 performed a prospective, observational study of all ED patients with bronchiolitis with two goals in mind: to assess the utility of clinical risk factors at the time of initial outpatient visit and to develop models to predict a more severe course. The study was completed at a single pediatric tertiary-care center. All patients younger than 13 months presenting to the ED with signs of bronchiolitis and symptoms of preceding URI were included. Forty-two percent had RSV infections. One investigator assessed the severity of illness until the patient was clinically well. Severity of disease course was defined as either (1) “mild” if the patient “remained alert and active” and was “well-hydrated while they were taking fluids orally throughout their illness,” or (2) “severe” for anyone not meeting the mild definition. One difficulty with the determination of severity of disease was that the clinical assessment of the patient was also an outcome; patients who were ill or toxic-ap- pearing on initial examination were likely considered to have a severe course.

Follow-up was achieved on 213/228 patients (93.4%). Seventy-four (34%) patients were hospital-ized during their illness, 31.5% on the initial ED visit. Eight of the 74 hospitalized patients (11%) received mechanical ventilation. Risk factors independently associated with a severe course and a predictive model are presented in Table 2. As can be seen, individual predictors and the overall model were helpful but imperfect in predicting the presence or absence of a more severe course. The model does give guidance as to patients who might benefit from admission or close follow-up. A relatively small sample of patients with significant chronic disease (congenital heart disease, chronic lung disease, or immunodeficiency) makes the model less useful for these patients. In addition, the model does not allow the clinician to predict the clinical course if multiple risk factors are present.22

Patients who Re-present (Return) to the ED

Roback et al23 completed a matched case-control study from a single tertiary care center to compare those patients younger than 1 year who were evaluated in the ED for bronchiolitis, discharged, and never admitted to those who were discharged but subsequently returned and were admitted within 96 hours. Patients with cardiac or underlying pulmonary disease were excluded. Overall, only 57/1226 (4.6%) patients diagnosed with bronchiolitis during the 18-month study period returned to the ED and required admission. No patient who re-presented and was admitted required mechanical ventilation or ICU admission. The patients admitted on re-presentation had lower mean oxygen saturations and were more likely to have chest retractions than on their initial presentations. The researchers evaluated multiple risk factors for admission but found no clinically relevant or statistically-significant difference between the initial ED visit findings in cases and controls in mean chronological age (20.4 vs. 22.9 weeks), mean gestational age (39.3 vs. 38.8 weeks), mean respiratory rate (49.9 vs. 48.0 per minute), proportion with retractions (54.8 vs. 54.4), and mean oxygen saturation (97.6 vs. 98.0). Although the study is inherently limited by the retrospective design (incomplete chart documentation, non-standardized assessments, etc), the data suggest that it is difficult to determine which patients are going to re-present and need admission. However, these patients are likely to do well.23

Recommendations

1. The data from hospitalized patients demonstrate that patients with chronic lung disease, congenital heart disease, and immunodeficiency are at higher risk of a more severe course of bronchiolitis and
deserve serious consideration for admission. Fortunately death is uncommon, even in high-risk patients.

2. Data from all hospitalized and ED patients with bronchiolitis suggest that patients younger than 2 to 3 months of age or those born at 34 to 37 weeks gestation also represent high-risk groups for severe disease. Admission for these patients should be strongly considered, especially in the presence of other clinical signs of more severe disease (oxygen saturation <95%, RR > 60/min, respiratory distress, or ill appearance).

3. For patients older than 3 months with bronchiolitis and no significant medical history, the data suggest that those with oxygen saturation <92% to 95%, RR > 70/min, atelectasis on chest radiograph, or ill appearance may have a more severe course and deserve consideration for admission or close follow-up.

4. All patients with bronchiolitis and apnea (or apnea associated with RSV) should be admitted to the hospital. ICU admission is appropriate, as repeat episodes of apnea during hospitalization are common.

5. Even though high-risk populations for a severe course of bronchiolitis have been identified, only one clinical model from one tertiary care center exists to predict clinical course. More models need to be derived which include large sample sizes from diverse patient populations, including all patients with bronchiolitis.

Risk of Significant Bacterial Infection

Clinicians and researchers debate whether a specific viral infection or recognizable viral syndrome such as bronchiolitis alters the risk of serious bacterial infection (SBI) in febrile infants in a clinically meaningful way. The fundamental question in the debate is whether a clinician might forego performing specific diagnostic tests such as blood cultures and cerebrospinal fluid analysis if the risk of concurrent SBI were sufficiently low in a well-appearing febrile infant with bronchiolitis. Because clinicians may not have access to rapid detection tests for specific viruses, we present data that address the effect of a clinical diagnosis of bronchiolitis on the risk of SBI in febrile infants.

**Question:** Does the risk of significant bacterial illness, specifically UTI, bacteremia, and bacterial meningitis, differ between febrile infants younger than 60 days old with and without bronchiolitis?

In a multi-site, large-sample prospective study, ED researchers in eight centers evaluated febrile (>38°C) infants ≤ 60 days old during three consecutive October-March periods. All enrolled patients had a standardized evaluation for fever that included rapid RSV antigen detection testing. Clinical bronchiolitis and all outcomes were strictly defined a priori. SBI was defined as the presence of bacterial meningitis, bacteremia, UTI, or bacterial enteritis.

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**TABLE 2. Model of Six Independent Factors Associated With Severity of Illness in Children With Bronchiolitis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance “ill” or “toxic”</td>
<td>76</td>
<td>76</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>Pulse oximetry while quiet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;97%</td>
<td>54</td>
<td>89</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td>&lt;95%</td>
<td>32</td>
<td>98</td>
<td>87</td>
<td>73</td>
</tr>
<tr>
<td>Gestation age &lt;34 weeks</td>
<td>27</td>
<td>95</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Respiratory rate ≥70/min</td>
<td>29</td>
<td>95</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Chest radiograph with atelectasis</td>
<td>21</td>
<td>98</td>
<td>82</td>
<td>70</td>
</tr>
<tr>
<td>Age &lt;3 months</td>
<td>38</td>
<td>83</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>Six-variable model</td>
<td>76</td>
<td>91</td>
<td>81</td>
<td>88</td>
</tr>
</tbody>
</table>

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One hundred fifty-six patients with and 1035 patients without bronchiolitis were studied. Ninety-four of the 156 (60.3%) patients with bronchiolitis were RSV-positive. The risks of concurrent bacterial illness are detailed in Table 3. Although the infants with bronchiolitis had fewer SBI's than those without bronchiolitis, there was a substantial rate of UTIs in both groups, and the differences between groups in SBI rates were not statistically significant. The sample size, however, was insufficient to detect small differences between groups that, in the case of bacteremia and meningitis, might be clinically relevant.25

Data from two other prospective and several retrospective studies have corroborated the potentially lower but non-zero risk of bacterial illness in febrile infants with bronchiolitis (Table 4).26-30 Most patients with bacteremia or bacterial meningitis in the retrospective series and in case reports have been clinically ill-appearing on presentation.29,31,32 The retrospective studies were also methodologically limited by the lack of standardized clinical evaluations, a significant proportion of patients not having laboratory studies performed, study populations including both febrile and afebrile patients, and the possibility that outcomes were known when patients were divided into bronchiolitis and non-bronchiolitis groups.27,29,30

**Recommendations**

1. Febrile infants with clinical bronchiolitis may be at lower risk of SBI than those without clinical bronchiolitis. However, the potentially reduced risk of bacteremia and meningitis is not zero and has not been shown to be statistically different from the rate of these infections in febrile infants without bronchiolitis. Most importantly, the rate of UTI, the predominant bacterial infection, remains significant.

2. Clinicians should perform an evaluation for UTI in febrile infants with bronchiolitis.

3. A less firm recommendation can be made regarding blood cultures and spinal fluid analysis in well-appearing febrile infants with bronchiolitis. Although there appears to be a trend towards lower rates of bacteremia and meningitis in these patients, larger studies are needed to assess for statistically-significant differences. In addition, these larger studies may determine if clinical bronchiolitis, perhaps in the presence of other low risk variables, decreases the risk of bacteremia and meningitis below a clinically reasonable threshold for performing laboratory tests to detect these infections.

**Acute Therapy Questions**

One of the biggest dilemmas and controversies in the management of children with bronchiolitis pertains to the effectiveness of individual therapies aimed at relieving airway inflammation, airway edema, and bronchoconstriction. Although several therapies have been studied, we present data only for those therapies that are commonly used in the ED or show particular promise.

**Question:** In children presenting to the ED with signs and symptoms of bronchiolitis, does bronchodilator therapy and, more specifically, beta-agonist
therapy, improve clinical outcome compared to placebo?

Clinicians frequently use bronchodilators in the ED to treat infants with bronchiolitis, likely because of the similarity in symptoms between bronchiolitis and asthma. Despite the widespread use of bronchodilators for bronchiolitis, the data lend little support to this practice for all patients. In a Cochrane collaboration meta-analysis, data were pooled from randomized clinical trials that compared the efficacy of bronchodilators to placebo in children younger than 36 months old with mild to moderately severe bronchiolitis. Studies of both hospitalized patients and outpatients were included. Table 5 displays the pooled results assessing the efficacy of nebulized bronchodilators for different outcomes. Although a statistically significant greater proportion of children treated with bronchodilators had improved clinical scores, the authors suggest that the data may have been biased to show such a difference as many studies included patients with recurrent wheezing.33

Recently, in a double-blinded, randomized clinical trial conducted since the completion of the Cochrane meta-analysis, Patel et al34 assessed the efficacy of nebulized albuterol (every 1-6 hrs) compared to saline placebo in 99 previously well, hospitalized children younger than 12 months old with bronchiolitis (with their first episode of wheezing). Mean length of stay (61.4 hrs albuterol, 63.3 hrs placebo), mean time to oxygen saturation ≥ 95% (33.0 hrs albuterol, 36.6 hrs placebo), and mean time to respiratory distress assessment instrument score ≤ 4 (45.7 hrs albuterol, 36.8 hrs placebo) were not statistically different between groups.34

In a separate systematic review, Flores et al35 assessed the efficacy of short-term use of nebulized beta agonists (mainly 2 doses at 30-minute intervals) in outpatients with bronchiolitis. The patients receiving bronchodilator treatment had a statistically non-significant 2% higher hospitalization rate (95% CI-9.3, 13.3). Clinical score data were not pooled because of excessive heterogeneity, and no statistically significant difference was found between groups in respiratory rate change (0.5 breaths per minute lower in treated group, 95% CI-1.3, 0.3).

In a recent randomized clinical trial of ED patients, Patel et al36 compared the efficacy of a 7-day, 3 times per day oral course of albuterol compared to placebo in 129 previously well patients younger than 12 months old with mild-moderate acute bronchiolitis who were discharged from the ED. Median time to resolution of illness (9 days albuterol, 8 days placebo) and median number of health care visits within 14 days of study enrollment (1.0 albuterol, 0.0 placebo) were not statistically different or clinically meaningful. No differences between groups were noted in the time to normal feeding and time to resolution of cough.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>RSV (+)</th>
<th>UTI N (%)</th>
<th>Bacteremia N (%)</th>
<th>Bacterial Meningitis N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuppermann et al³</td>
<td>ED patients, &lt; 2 months</td>
<td>46%§</td>
<td>0/33</td>
<td>0/36</td>
<td>0/36</td>
</tr>
<tr>
<td>Davies et al³</td>
<td>Hospitalized, &lt; 6 months, mean 12.9 wks</td>
<td>85%§</td>
<td>Unknown</td>
<td>0/52</td>
<td>Unknown</td>
</tr>
<tr>
<td>Titus et al†</td>
<td>Hospitalized, ≤ 56 days</td>
<td>100%</td>
<td>2/147‖</td>
<td>0/170‖</td>
<td>0/111‖</td>
</tr>
<tr>
<td>Antonow et al†</td>
<td>Hospitalized, ≤ 60 days</td>
<td>83%§</td>
<td>3/140‖    (2.1%)#</td>
<td>1/140‖ (0.7%)</td>
<td>1/140‖ (0.7%)</td>
</tr>
<tr>
<td>Liebelt et al†</td>
<td>ED patients, &lt; 90 days</td>
<td>81%</td>
<td>0/55</td>
<td>0/68</td>
<td>0/43</td>
</tr>
</tbody>
</table>

³Prospective trials.
†Retrospective trials.
§For total sample (unknown for febrile infant subgroup).
‖Includes febrile infants with RSV infections, unknown number of patients with bronchiolitis.
¶Unknown true denominator of febrile patients (ie, some were afebrile).
#One patient with UTI with hypothermia, the other was afebrile.
Recommendations

1. The data from randomized clinical trials, especially those high-quality recent trials, do not demonstrate a clear utility for bronchodilators for all patients with bronchiolitis (combined inpatient and outpatient settings).

2. Although there are fewer ED than inpatient clinical trials (with inpatients potentially representing a selective group of non-responders to ED therapy), the data suggest that clinicians who use nebulized beta agonist therapy should do so on a case-by-case basis, critically evaluating its effectiveness in the individual patient.

Question: In children presenting to the ED with signs and symptoms of bronchiolitis, does nebulized epinephrine improve clinical outcomes compared to placebo? Does nebulized epinephrine offer any benefit over that of beta-agonists?

Nebulized epinephrine is hypothesized to improve respiratory symptoms in patients with bronchiolitis in two ways: (1) via alpha-adrenergic effects that cause vasoconstriction and thus reduce airway edema, and (2) via beta-adrenergic effects that produce smooth muscle relaxation. We detail five English-language randomized controlled clinical trials that compare nebulized epinephrine to placebo in Table 6.\(^{34,37-40}\) The two largest clinical trials that included only patients with a first episode of wheezing showed little clinical improvement with the use of epinephrine in hospitalized patients.\(^{34,37}\) The single outpatient, placebo-controlled trial noted a statistically insignificant but potentially clinically meaningful 12% decrease in hospitalization rate in the epinephrine group. No differences in clinical symptoms were noted between groups.\(^{40}\)

Although neither is of consistent benefit compared to placebo, several studies have compared the efficacy of nebulized epinephrine to beta agonists. In two small-sample randomized clinical trials of outpatient children predominantly younger than 1 year with bronchiolitis, patients treated with nebulized epinephrine had lower admission rates and either more improved clinical scores or oxygen saturations compared to nebulized albuterol.\(^{41,42}\) In a randomized cross-over trial, Sanchez et al.\(^{43}\) noted statistically greater improvement in clinical scores and pulmonary resistance at 30 minutes post nebulized epinephrine administration compared to nebulized albuterol in 24 hospitalized infants younger than 1 year with a first episode of bronchiolitis. In the largest randomized trial of hospitalized patients, Patel et al.\(^{34}\) noted no statistical differ-

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**TABLE 5. Results From Cochrane Collaboration Meta-analysis Comparing Bronchodilators to Placebo for Children With Bronchiolitis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies Pooled (No.)</th>
<th>Characteristics of Included Trials</th>
<th>N in Treatment Group/Total</th>
<th>Results</th>
<th>Trials (No.) Including Patients With Recurrent Wheeze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in clinical score</td>
<td>8</td>
<td>4 nebulized beta agonist trials, 2 nebulized ipratropium trials, 1 epinephrine injection trial, 1 combination bronchodilator trial</td>
<td>211/394</td>
<td>0.29 OR (95%CI, 0.19, 0.45), favoring treatment</td>
<td>7/8</td>
</tr>
<tr>
<td>Rate of hospitalization</td>
<td>4</td>
<td>4 nebulized beta agonist trials</td>
<td>97/187</td>
<td>(\beta) agon 19.6% placebo 24.4% OR 0.76 (0.38, 1.53)</td>
<td>1/4</td>
</tr>
<tr>
<td>Length of stay if hospitalized</td>
<td>3</td>
<td>1 nebulized or oral beta agonist trial, 2 beta agonist +/- ipratropium trials</td>
<td>130/177</td>
<td>0.118 hours weighted mean difference, favoring placebo (95% CI, (-0.311, 0.547))</td>
<td>0/3</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
ences between 101 children younger than 12 months with a first episode of bronchiolitis on mean length of stay (59.8 hrs epinephrine, 61.4 hrs albuterol), mean time to normal oxygen saturation (25.0 hrs epinephrine, 33.0 hrs albuterol), mean time to respiratory distress assessment instrument score ≤ 4 (34.6 hrs epinephrine, 45.7 hrs albuterol), and mean time to infrequent nebulizations
(16.3 hrs epinephrine, 31.1 hrs albuterol). However, the sample size was insufficient to detect potentially meaningful differences for outcomes other than length of stay.

Recommendations

1. The data to date lend little support to the use of nebulized epinephrine in all children with moderate or severe bronchiolitis. The improvement in respiratory symptoms across studies has been inconsistent and potentially short-lived when compared to the effects of placebo. Pooled data from a forthcoming Cochrane collaboration meta-analysis may further clarify the efficacy of nebulized epinephrine for bronchiolitis.

2. Limited data from inpatient and outpatient populations suggest that clinicians who choose to use nebulized therapy might reasonably choose epinephrine rather than albuterol for children with first episodes of moderate to severe bronchiolitis. Clinicians must recognize, however, that no standardized outpatient regimen exists for the use of nebulized epinephrine. It may be appropriate, therefore, for clinicians to use nebulized epinephrine as a potential rescue medication for patients who are to be admitted.

**Question:** In children presenting to the ED with signs and symptoms of bronchiolitis, do systemic corticosteroids improve clinical outcomes compared to placebo?

Systemic corticosteroids have been suggested as an acute therapy for bronchiolitis because of their anti-inflammatory effects. There have been several studies assessing corticosteroid effectiveness in bronchiolitis, most conducted in hospitalized patients. Garrison et al44 performed a meta-analysis of randomized controlled trials comparing systemic corticosteroids to placebo for the treatment of hospitalized, non-ventilated children between the ages of 1 and 24 months with bronchiolitis. The pooled data revealed a mean length of stay 0.43 days shorter with corticosteroids therapy (95% CI, -0.81 to -0.05 days). The standardized mean clinical score at 24 hours was also 1.60 points lower (improved) in the treatment group (95% CI, 1.92 to 1.28 points lower). The meta-analysis was well designed; however, rigorous quality criteria for study inclusion were not described. Since the publication of this meta-analysis, one other randomized controlled trial conducted on 147 hospitalized children with RSV-associated bronchiolitis noted a statistically non-significant difference in median length of stay of 3.6 days in the prednisolone group compared to 4.0 days in the placebo group.45

The first clinical trial performed on ED patients has recently received substantial attention. Schuh et al46 performed a randomized, double-blind clinical trial on 70 ED patients 8 weeks to 23 months old with a first episode of wheezing who were in moderate to severe distress. Oral dexamethasone (1 mg/kg on day one followed by 0.6 mg/kg/day for 4 days) was compared to placebo. Forty-three percent of patients were RSV-positive. Ninety-six percent of patients received in-person follow-up at 7 days. The results during the ED phase of the study were relatively dramatic: mean respiratory assessment change score at 4 hours was significantly more improved in the treatment group (mean score change -5.0 corticosteroid vs. -3.2 placebo), fewer children in the treatment group had a poor response defined by clinical score (17% corticosteroid vs. 41% placebo), and hospitalization rate was lower in the treatment group (19% corticosteroid vs. 44% placebo [95% CI, 4%, 46%]). No differences in clinical scores between groups were noted at 7-day follow-up. One noteworthy issue was the relatively high dose of corticosteroid, although no adverse events were reported. We would suggest that a much larger (multicenter) study needs to be performed to validate these findings and to assess the safety of potentially widespread use of corticosteroids for this common condition.

**Recommendation**

The evidence for systemic corticosteroids use in both the ED and inpatient setting for bronchiolitis is limited in volume, but the available data suggest moderate potential efficacy. While a large randomized controlled trial of children treated for bronchiolitis as outpatients is necessary to validate and further clarify the role of corticosteroids, limited evidence suggests that systemic corticosteroids may be somewhat beneficial in hospitalized patients and, in higher doses, may decrease hospitalization rates and improve clinical symptoms at 4 hours in ED patients with moderate to severe bronchiolitis.

**Question:** In infants who present to the ED with moderate to severe bronchiolitis, does the use of continuous positive airway pressure (CPAP) via nasal prongs improve clinical outcomes?

CPAP is a commonly used therapy to maintain positive transpulmonary pressure in neonates with respiratory distress syndrome. CPAP may potentially benefit infants with bronchiolitis by stenting...
open the smaller airways during all phases of respiration, preventing air trapping and obstructive disease, and by serving as a constant stimulus in infants with a propensity to experience apnea. The evidence to support the utility of nasal CPAP comes from three observational case series with a composite sample size of 32 patients, each series performed in pediatric ICU settings on infants younger than one year with moderate to severe bronchiolitis.\textsuperscript{47-49} Two of these 32 patients eventually required mechanical ventilation. In two series, improvements were noted in mean respiratory rate and PaCO\textsubscript{2} at 2 hours and 3 hours after initiation of nasal CPAP.\textsuperscript{48,49} These limited data are promising, although without controlled trials, are inconclusive.

**Question**: In children who present to the ED with moderate-severe bronchiolitis, does a mixture of helium and oxygen (heliox) improve clinical outcomes?

Because infant bronchiolitis is a disease of high airway resistance, it has been hypothesized that heliox might improve work of breathing by reducing turbulent flow in constricted airways. Data to date come from studies performed in ICU settings. In the only published randomized trial, Hollman et al\textsuperscript{50} demonstrated significantly lower clinical asthma scores and a trend toward lower respiratory rate twenty minutes after initiation of heliox in moderately ill infants aged 3 to 34 weeks with RSV-positive bronchiolitis. Patients with the most severe respiratory distress had the greatest improvement in clinical asthma score. Limitations of the study included a lack of standardization of treatments other than heliox and only short-term use of heliox. In the only other interventional study identified, Martinon et al\textsuperscript{51} noted shorter ICU length of stay and improved clinical scores in 38 patients with RSV-positive bronchiolitis treated with heliox for a mean of 53 hours. The study, however, was neither randomized nor blinded. No harm was demonstrated but larger trials are required in which other outcomes such as need for mechanical ventilation are assessed.

**Summary**

Recently-conducted research has started to help answer clinical questions that frequently arise in the management of children with bronchiolitis. We have presented data to help clarify which risk factors place a patient at higher risk for a more severe clinical course, the likelihood of significant bacterial illness in febrile infants with bronchiolitis, and the efficacy of individual therapies for bronchiolitis. More research is needed, however, to develop clinically useful and generalizable models that allow the clinician to accurately determine which patients need specific laboratory evaluation, admission to a general service, and admission to an intensive care unit. Finally, we must continue to search for more effective acute therapies and further assess the utility of therapies that show early promise, such as corticosteroids and heliox.

**References**

12. Navas L, Wang E, de Carvalho V, et al: Improved outcome of respiratory syncytial virus infection in a high-
45. Bulow SM, Nir M, Levin E, et al: Prednisolone treatment of respiratory syncytial virus infection: A ran-


