Pharmacologic Treatment of Bronchiolitis in Infants and Children

A Systematic Review

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Background: Bronchiolitis is the most common lower respiratory tract infection in infants. Up to 3% of all children in their first year of life are hospitalized with bronchiolitis. Bronchodilators and corticosteroids are commonly used treatments, but little consensus exists about optimal management strategies.

Objective: To conduct a systematic review of the effectiveness of commonly used treatments for bronchiolitis in infants and children.

Data Sources: We searched MEDLINE and the Cochrane Controlled Trials Register for references to randomized controlled trials of bronchiolitis treatment published since 1980.

Study Selection: Randomized controlled trials of interventions for bronchiolitis in infants and children were included if they were published in English between 1980 and November 2002 and had a minimum sample size of 10.

Data Extraction: We abstracted data on characteristics of the study population, interventions used, and results of studies meeting entry criteria into evidence tables and analyzed them by drug category.

Data Synthesis: Interventions were grouped by drug category and qualitatively synthesized.

Results: Of 797 abstracts identified in the literature search, we included 54 randomized controlled trials. This review includes 44 studies of the most common interventions: epinephrine (n=8), β2-agonist bronchodilators (n=13), corticosteroids (n=13), and ribavirin (n=10). Studies were, in general, underpowered to detect statistically significant outcome differences between study groups. Few studies collected data on outcomes that are of great importance to parents and clinicians, such as the need for and duration of hospitalization.

Conclusions: Overall, little evidence supports a routine role for any of these drugs in treating patients with bronchiolitis. A sufficiently large, well-designed pragmatic trial of the commonly used interventions for bronchiolitis is needed to determine the most effective treatment strategies for managing this condition.

chondilators and corticosteroids. Little consensus exists about the best management strategies for this common disease, and, thus, care varies substantially across settings and countries.4,6

Given the conflicting practices in diagnosing, treating, and preventing RSV, a systematic review of the evidence on the management of bronchiolitis was of particular concern to the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians, which nominated the topic for the Agency for Healthcare Research and Quality Evidence-based Practice Program. The Agency for Healthcare Research and Quality chose the Research Triangle Institute International—University of North Carolina Evidence-based Practice Center to develop an evidence report on this issue, including the diagnosis, treatment, and prophylaxis of bronchiolitis and the cost-effectiveness of prophylaxis in moderately premature infants (32-35 weeks' gestation) and in all premature infants with comorbidities.7 The AAP, the American Academy of Family Physicians, health plans, and other groups may use this evidence report as a basis for guidance on the optimal management of bronchiolitis. This article presents the systematic review of the effectiveness of commonly used pharmacologic treatments for bronchiolitis; a companion article presents the results concerning diagnosis.8

To design a detailed search of the scientific literature, we sought the advice of a technical expert advisory group and developed specific key clinical questions and a search strategy about the overall issue of the efficacy of various therapies for bronchiolitis in young children. Primary outcomes of interest were mortality, morbidities related to the acute episode (hypoxia) and to possible long-term sequelae (recurrent respiratory problems), and use of health services, such as the need for and length of hospitalization. Table 1 provides the inclusion and exclusion criteria used to select articles for review.

We searched MEDLINE and the Cochrane Collaboration’s Database of Controlled Clinical Trials. Table 2 details the search terms used for the MEDLINE searches; we included existing meta-analyses to examine their lists of included and excluded studies. We conducted hand searches of the reference lists of relevant included articles to ensure that we did not miss key studies. In addition, we consulted with the technical expert advisory group about any studies that were under way but not yet published. The search was last updated November 25, 2002, and it contains all abstracts entered into MEDLINE until that date. Two more recently published studies (both of nebulized epinephrine) identified during the review process for this article were also included.

Trained abstractors completed detailed data collection forms for each included study; 1 of us (M.V.) summarized these results in evidence tables. Senior study personnel (V.J.K. and C.B.) performed data integrity checks by reviewing the articles a second time against the evidence tables. They also rated the quality of each study on a 4-category scale (poor, fair, good, and excellent) based on randomized controlled trial (RCT) quality criteria that included factors such as adequacy of randomization, concealment of allocation, masking of study personnel and patients or parents, and statistical analysis.9 Disagreements in either abstraction or quality rating were adjudicated by senior authors (V.J.K., M.V., C.B., and A.M.J.) in consultation with subject area or method experts as required.

Our a priori analytic framework set priorities on outcomes based on their clinical relevance to key study questions. Specifically, we presented outcomes such as length of hospitalization or need for more intensive therapies as primary study outcomes in the full evidence report; in assessing effectiveness of therapies, we gave these outcomes priority over physiologic measures such as respiratory rate or composite clinical scores. The summary tables in this article similarly give priority to these key primary outcomes.

We identified 797 abstracts from the entire systematic review of the diagnosis, treatment, and prophylaxis of bronchiolitis in infants and children; 54 met the inclusion criteria for treatment of bronchiolitis. Including 2 additional studies published during the review process, this article focuses on 44 studies (and an additional 2 articles reporting on long-term follow-up of included studies) of commonly used interventions; major classes of pharmacologic agents include epinephrine, β2-agonist bronchodilators (albuterol and salbutamol), corticosteroids, and ribavirin. Most of these agents can be given by various routes of administration. For example, we found studies of corticosteroids used by inhalation, parenterally, and orally.

We also identified RCTs of several unusual therapies, including RSV immunoglobulin as a treatment rather than as a prophylactic agent,10,11 interferon,12 inhaled helium-oxygen gas,13 Chinese herbs,17 surfactant,19 nebulized furosemide,19 and nebulized recombinant human deoxyribonuclease.17 These interventions are either novel or not in common use in US settings, so we did not include them in this review. A complete review of all in-

### Table 1. Inclusion and Exclusion Criteria for Studies of the Treatment of Bronchiolitis in Infants and Children

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Human</td>
</tr>
<tr>
<td>Study settings</td>
<td>Infants and children</td>
</tr>
<tr>
<td>Publication language study design</td>
<td>English only</td>
</tr>
<tr>
<td>Minimum sample size</td>
<td>10</td>
</tr>
<tr>
<td>Publication period</td>
<td>January 1980 through November 2002</td>
</tr>
</tbody>
</table>

### Table 2. Medical Subject Heading Terms for the MEDLINE Literature Search on the Treatment of Bronchiolitis in Infants and Children

<table>
<thead>
<tr>
<th>Topic</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploded terms for treatment</td>
<td>Steroidal anti-inflammatory agents, steroids, bronchodilator agents, antiviral agents, antimicrobial cationic peptides, antibiotics, antimicrobials, anti-infective agents</td>
</tr>
<tr>
<td>Study design for treatment</td>
<td>Randomized controlled trial, single-blind method, double-blind method, random allocation</td>
</tr>
<tr>
<td>Outcomes for treatment</td>
<td>Morbidity, mortality, adverse effects or harms</td>
</tr>
<tr>
<td>Limiting terms</td>
<td>Human, year (1980 through 2002), newborn infant (birth to 1 mo) or infant (1-23 mo) or preschool child (2-5 y)</td>
</tr>
</tbody>
</table>

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Interventions studied can be found in the full evidence report that forms the basis for this article, available from the Agency for Healthcare Research and Quality (http://www.ahrq.gov/clinic/evrptfiles.htm#bronch).

Most studies in this field are relatively small; few reported a priori sample size calculations or post hoc power analyses. Study quality was generally adequate: 7 studies were rated as excellent, 20 as good, 15 as fair, and 2 as poor. We did not exclude studies on the basis of quality.

Few studies reported outcomes that were prespecified as being of the greatest salience and of primary interest to clinicians and parents, such as need for hospitalization, length of hospital stay, need for more intensive supportive therapies, and development of long-term symptoms. Most studies reported outcomes based on (1) short-term changes in a clinical scoring system; (2) individual measures of physiologic status, such as heart rate, respiratory rate, or oxygen saturation; or (3) physical examination findings, such as retractions and wheezing. The range of clinical scoring systems that we encountered among these studies can be found in the full report, but most are a composite of physiologic and physical examination variables.

Tables 3, 4, 5, and 6, specific to a category of drug, generally report on results (differences between groups) that were statistically significant at \( P < 0.05 \); we also noted findings of no difference if they were of clinical interest. Studies are ordered alphabetically by first author; outcomes listed first are duration of hospitalization or similar outcomes, followed by clinical scores or individual clinical measures.

**EPINEPHRINE**

Nebulized epinephrine has been compared with placebo and 2 nebulized β-2-agonist bronchodilators, sal-
Table 4. Bronchiolitis Treatment Trials: β2-Agonist Bronchodilators

<table>
<thead>
<tr>
<th>Source</th>
<th>Quality Category</th>
<th>Intervention and Comparison*</th>
<th>Patients, No. †</th>
<th>Primary Outcomes</th>
<th>Significant Outcome Differences</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can et al.26 1998</td>
<td>Fair</td>
<td>Salbutamol vs saline placebo vs mist in a tent</td>
<td>156</td>
<td>Clinical score at 0, 30, and 60 min</td>
<td>Better at 30 and 60 min for salbutamol group</td>
<td>Frequency of tachycardia and hypoxia did not reach a statistically significant difference between groups, but no details were provided</td>
</tr>
<tr>
<td>Cengizlier et al.27, 1997†</td>
<td>Fair</td>
<td>Inhaled salbutamol vs oral salbutamol vs control (no treatment)</td>
<td>31</td>
<td>Duration of hospitalization</td>
<td>Clinical score change from hospital admission to discharge</td>
<td>None</td>
</tr>
<tr>
<td>Chowdhury et al.28, 1995</td>
<td>Fair</td>
<td>Salbutamol vs ipratropium bromide vs salbutamol + ipratropium bromide vs saline placebo</td>
<td>89</td>
<td>Duration of hospitalization</td>
<td>Clinical score at 30 and 60 min, and at 6, 12, 23, and 36 h</td>
<td>None</td>
</tr>
<tr>
<td>Dobson et al.29, 1998</td>
<td>Good</td>
<td>Albuterol vs saline placebo</td>
<td>52</td>
<td>Percentage of patients discharged at 24, 48, and 72 h and total length of hospitalization</td>
<td>Oxygen saturation at 0-24 h</td>
<td>None</td>
</tr>
<tr>
<td>Gadomski et al.30, 1994</td>
<td>Excellent</td>
<td>Albuterol vs saline vs oral albuterol vs oral rehydration solution</td>
<td>169</td>
<td>Clinical score at 0, 30, and 60 min</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gadomski et al.31, 1994</td>
<td>Good</td>
<td>Nebulized albuterol vs nebulized saline placebo vs oral albuterol vs oral placebo</td>
<td>76</td>
<td>Need for hospitalization or additional treatment</td>
<td>None</td>
<td>Increased heart rate, facial flushing, hyperactivity, tremor in nebulized or oral albuterol groups</td>
</tr>
<tr>
<td>Goh et al.32, 1997</td>
<td>Fair</td>
<td>Salbutamol vs ipratropium bromide vs saline placebo vs humidified oxygen</td>
<td>89</td>
<td>Duration of hospitalization</td>
<td>Clinical score on days 1, 2, and 3</td>
<td>None</td>
</tr>
<tr>
<td>Ho et al.33, 1991</td>
<td>Fair</td>
<td>Salbutamol vs saline placebo</td>
<td>21</td>
<td>Oxygen saturation at 5-min intervals from 5 to 25 min after each of 2 treatments</td>
<td>None</td>
<td>Most patients had desaturation compared with baseline after receiving salbutamol</td>
</tr>
<tr>
<td>Klassen et al.34, 1991</td>
<td>Excellent</td>
<td>Salbutamol vs saline placebo</td>
<td>83</td>
<td>Clinical score at 0, 30, and 60 min</td>
<td>Heart rate, respiratory rate, and oxygen saturation at 0, 30, and 60 min</td>
<td>Improved in salbutamol group at 30 min only</td>
</tr>
<tr>
<td>Schuh et al.35, 1990</td>
<td>Good</td>
<td>Albuterol vs saline placebo</td>
<td>40</td>
<td>Hospitalization</td>
<td>4/21 In albuterol group vs 2/19 in saline placebo group (P value not reported)</td>
<td>Increased heart rate in albuterol group</td>
</tr>
<tr>
<td>Schuh et al.36, 1992</td>
<td>Good</td>
<td>Albuterol + ipratropium bromide vs albuterol + saline placebo</td>
<td>69</td>
<td>Change in respiratory rate after each dose</td>
<td>Significantly lower in placebo group</td>
<td>Declines in oxygen saturation seen in both groups</td>
</tr>
<tr>
<td>Totapally et al.37, 2002</td>
<td>Good</td>
<td>Albuterol vs saline placebo with crossover after 6 h</td>
<td>19</td>
<td>Wheeze score, oxygen saturation, respiratory rate, and heart rate</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wang et al.38, 1992</td>
<td>Good</td>
<td>Salbutamol + ipratropium bromide vs salbutamol vs ipratropium bromide vs saline placebo</td>
<td>62</td>
<td>Duration of hospitalization</td>
<td>Mean change in oxygen saturation</td>
<td>Improved for salbutamol + ipratropium bromide vs both agents alone but not vs placebo; worse for salbutamol vs placebo</td>
</tr>
</tbody>
</table>

* Nebulized unless otherwise indicated. † Number of patients completing the study. ‡ Mode of administration was metered dose inhaler.

butamol and albuterol, in 8 RCTs (Table 3).16-25 The total number of children studied in these trials was 660.

Few results favoring nebulized epinephrine emerged, and most outcomes reported were short term.

Of 5 trials that examined duration of hospitalization, 218,22 noted either shorter hospitalization or fewer admissions in the epinephrine (vs salbutamol) group. Five studies16-20,22,23 commented on changes in clinical
<table>
<thead>
<tr>
<th>Source</th>
<th>Quality Category</th>
<th>Intervention and Comparison</th>
<th>Patients, No.*</th>
<th>Primary Outcomes</th>
<th>Significant Outcome Differences</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger et al,39 1998</td>
<td>Good</td>
<td>Prednisone vs placebo</td>
<td>38</td>
<td>Hospitalization</td>
<td>25% in prednisone group vs 11% in placebo group; no P-value given</td>
<td>Not reported</td>
</tr>
<tr>
<td>Goebel et al,40 2000</td>
<td>Good</td>
<td>Prednisolone + albuterol vs placebo + albuterol</td>
<td>48 (32 with complete data)</td>
<td>Clinical score</td>
<td>Clinical score on days 0, 2, 3, and 6</td>
<td>None</td>
</tr>
<tr>
<td>Klassen et al41 1997</td>
<td>Excellent</td>
<td>Dexamethasone vs placebo</td>
<td>67</td>
<td>Duration of hospitalization, readmission, and need for outpatient treatment</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Schuh et al,42 2002</td>
<td>Excellent</td>
<td>Dexamethasone vs placebo</td>
<td>67</td>
<td>Rate of hospitalization</td>
<td>Lower in dexamethasone group (19% vs 44%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>van Woensel et al,43 1997</td>
<td>Fair</td>
<td>Prednisolone vs placebo</td>
<td>27 Completed 5-y study</td>
<td>Transient, persistent, or late-onset wheezing at age 5 y</td>
<td>None</td>
<td>None observed</td>
</tr>
<tr>
<td>van Woensel et al,44 2000</td>
<td>Good</td>
<td>Prednisolone vs placebo</td>
<td>53</td>
<td>Duration of hospitalization in ventilated patients</td>
<td>Fewer days in prednisolone group</td>
<td>1 Death unrelated to intervention</td>
</tr>
<tr>
<td>De Boeck et al,45 1997</td>
<td>Fair</td>
<td>Dexamethasone vs placebo</td>
<td>29</td>
<td>Duration of hospitalization</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Roosevelt et al,46 1996</td>
<td>Good</td>
<td>Dexamethasone vs placebo</td>
<td>118</td>
<td>Time to resolution</td>
<td>None</td>
<td>Occult blood in stool seen in both groups, 2/65 (treatment) vs 1/53 (placebo)</td>
</tr>
<tr>
<td>Cade et al,47 2000</td>
<td>Good</td>
<td>Nebulized budesonide vs vehicle placebo</td>
<td>161</td>
<td>Duration of hospitalization</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fox et al,48 1999</td>
<td>Fair</td>
<td>MDI budesonide vs placebo</td>
<td>49</td>
<td>Coughing/wheezing episodes at 12-mo follow-up</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kajosaari et al,49 2000</td>
<td>Poor</td>
<td>Inhaled budesonide \times 7 d vs inhaled budesonide \times 2 mo vs symptomatic usual treatment</td>
<td>109</td>
<td>Need for asthma inhalation therapy at 2 y</td>
<td>Budesonide groups had less need (37% in symptomatic treatment vs 18% in budesonide for 7 d vs 12% in budesonide for 2 mo groups)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Reijonen et al,50 1996</td>
<td>Fair</td>
<td>Inhaled budesonide vs inhaled cromolyn sodium vs no treatment control</td>
<td>92</td>
<td>Days of symptomatic wheezing at 1 to 4, 5 vs 8, 9 vs 16, and 13 vs 16 wk</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Richter and Seddon,51 1998</td>
<td>Good</td>
<td>Nebulized budesonide vs placebo</td>
<td>40</td>
<td>Days on oxygen</td>
<td>None</td>
<td>Median growth 0.43 cm/wk (budesonide) vs 0.47 cm/wk (placebo); P = .16</td>
</tr>
<tr>
<td>Wong et al,52 2000</td>
<td>Good</td>
<td>MDI fluticasone propionate vs placebo</td>
<td>41</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MDI, metered dose inhaler.

*Number of patients completing the study.
scores measured at various times. Three studies reported better clinical scores immediately after initial treatment compared with placebo\textsuperscript{19} and salbutamol,\textsuperscript{18,22} but the study\textsuperscript{18} that collected data at 24 and 36 hours did not see a persistent improvement. Four research groups\textsuperscript{19,20,22,24} commented on oxygen saturation; 3 found short-term differences of unclear clinical significance: 1 at 15 minutes of treatment (but not at 30, 45, or 60 minutes),\textsuperscript{19} 1 at 60 minutes (but not at 30 or 90 minutes),\textsuperscript{20} and 1 at 60 minutes.\textsuperscript{22} One trial\textsuperscript{24} reported that respiratory rates were lower in the epinephrine group.

Six studies reported adverse effects: short-term pallor in the epinephrine groups in 2 studies\textsuperscript{19,20} and increased heart rates with epinephrine use in 4 studies.\textsuperscript{18,21,22,23}

### β2-AGONIST BRONCHODILATORS

We included 13 studies\textsuperscript{26-38} of various bronchodilator agents for the treatment of bronchiolitis; most had multiple treatment arms (Table 4). Of these studies, 11 used salbutamol or albuterol in at least one treatment arm com-
pared with saline placebo, nebulized saline placebo, or unspecified placebo or control. Four studies\textsuperscript{28,32,36,38} did comparisons with nebulized ipratropium bromide, and 2\textsuperscript{10,31} with oral salbutamol or albuterol. One study\textsuperscript{27} was of salbutamol administered via a metered dose inhaler (MDI) compared with oral salbutamol.

These studies reported results for a total of 956 patients. Two studies\textsuperscript{34,37} mentioned sample size calculations; numbers of children assigned to any particular study arm were generally small. Outcomes studied were largely surrogate measures, such as change in clinical severity score, and were primarily short term in nature. Differences in agents, doses, delivery systems, settings, and outcomes limit overall comparisons.

Seven trials examined a primary outcome measure related to need for or length of hospitalization; none reported significance differences between groups. Of 12 studies with a saline placebo comparison, 3\textsuperscript{26,34,35} demonstrated improvements in various types of clinical measures in the short term (30 to 60 minutes after treatment) for patients receiving nebulized bronchodilator therapy and 1\textsuperscript{30} demonstrated worse scores.

Six studies did not report on adverse events associated with treatments. Symptoms such as increased heart rate and temporarily decreased oxygen saturation consistent with the known adverse effects of treatment with \cfrac{\beta_2}{\alpha}-agonist agents were reported in the remaining 7 studies.

Nebulized ipratropium bromide, an anticholinergic bronchodilator, in combination with salbutamol has been compared with either drug alone and placebo in two 4-arm studies.\textsuperscript{28,38} Another team\textsuperscript{32} compared nebulized ipratropium bromide to nebulized salbutamol in a nebulized saline controlled trial, and a fourth group\textsuperscript{36} compared nebulized ipratropium bromide plus albuterol with albuterol plus saline placebo. Duration of hospitalization and changes in clinical scores were studied in both trials involving salbutamol, but neither type of outcome measure demonstrated significant differences among the comparison groups.\textsuperscript{28,32,38} One trial\textsuperscript{38} showed improved mean oxygen saturation for the combination of ipratropium bromide plus salbutamol vs either ipratropium bromide or salbutamol used as single agents, but no significant differences emerged when the combination was compared with placebo. Respiratory rates did not differ significantly between the groups that received albuterol plus saline placebo vs ipratropium bromide plus albuterol.\textsuperscript{36}

CORTICOSTEROIDS

In all, we included 5 studies\textsuperscript{30-42,44} of oral corticosteroids (273 patients) (one additional article\textsuperscript{43} was a 5-year follow-up of a prednisolone vs placebo trial), 2 studies\textsuperscript{45,46} of parenteral corticosteroids (147 patients), and 6 studies\textsuperscript{47-51} of inhaled corticosteroids (492 patients). One study\textsuperscript{39} compared oral prednisone with placebo. Three studies\textsuperscript{40,43,44} compared oral prednisolone with placebo and allowed additional supportive treatments that could include bronchodilators. The use of oral dexamethasone vs placebo was the subject of 2 RCTs.\textsuperscript{51,62} Both studies\textsuperscript{45,46} of parenteral corticosteroids used dexamethasone vs placebo. Five of the 6 inhaled corticosteroid studies\textsuperscript{47-51} used budesonide, and the sixth study\textsuperscript{52} used a fluticasone propionate MDI (Table 5).

Many of the inhaled and oral corticosteroid studies evaluated longer-term outcomes, such as persistent cough or wheezing, weeks to years after the initial bronchiolitis episode. Most studies were small; none included a power analysis. As with the previous medications, comparisons among these studies are limited by the variety of drugs, dosages, durations of treatment, co-interventions, and populations studied.

Oral Corticosteroids

Four oral corticosteroid studies\textsuperscript{30,41,42,44} reported either rates or duration of hospitalization. Rates of hospitalization for patients in the emergency department were lower in 1 study\textsuperscript{42} using dexamethasone. A second study\textsuperscript{41} using prednisolone showed a decreased length of stay in ventilated patients only; no difference was seen in nonventilated patients. In contrast, no difference was seen in duration of hospitalization in a second study\textsuperscript{41} of oral dexamethasone. In addition, 1 study\textsuperscript{39} found higher rates of hospitalization among children who received oral prednisone. The study\textsuperscript{40} of prednisolone plus nebulized albuterol reported that clinical scores improved at 2 days for the treatment group vs the placebo plus albuterol group, but these differences were not demonstrated at 3 or 6 days. The 5-year follow-up study\textsuperscript{43} of prednisolone vs placebo did not demonstrate any long-term differences in transient, persistent, or late-onset wheezing.

Parenteral Corticosteroids

Neither intravenous dexamethasone\textsuperscript{45} nor intramuscular dexamethasone against placebo\textsuperscript{46} showed differences between the study groups for outcomes such as duration of hospitalization or time to resolution of clinical symptoms.

Inhaled Corticosteroids

We included 6 studies of inhaled corticosteroids: 5 using budesonide in either a nebulized or an MDI form\textsuperscript{47-51} and 1 using a fluticasone propionate MDI.\textsuperscript{52} These studies were, on average, of lower quality than the oral and parenteral corticosteroid studies. Treatments were continued for 2 weeks to 3 months, and outcome measurements were reported for correspondingly longer intervals than for most of the previous categories of agents.

One budesonide study\textsuperscript{49} demonstrated less need for asthma inhalational therapy 2 years after study entry for the group that used budesonide for 2 months compared with the group that used it for 7 days and the usual treatment control group. No other budesonide studies\textsuperscript{47,48,50,51} showed significant improvements for the treatment group.

Of concern, 2 of these studies found longer term clinical worsening of symptoms in the inhaled budesonide group, measured either as wheeze or cough at 1 year\textsuperscript{49} or hospital readmission in the 6 months after study entry for respiratory problems.\textsuperscript{51} The small study\textsuperscript{52} of a fluticasone propionate MDI used for 3 months vs placebo showed a decrease in episodes of night coughing at
36 weeks after study entry in the treatment group but did not demonstrate differences in overall cough or wheezing symptoms at 3, 6, 12, or 24 weeks.

**Adverse Events**

Four of the oral\(^{30,41,42}\) and parenteral\(^{45}\) corticosteroid studies did not report adverse events as an outcome. Jitteriness related to the dose of albuterol used with oral prednisolone was reported in 1 child.\(^{40}\) The study\(^{51}\) that measured growth rates among children who were receiving inhaled corticosteroids did not find any significant differences. Half of the inhaled corticosteroid studies did not include adverse events in their reported outcomes.\(^{37,49,50}\) Oral candidiasis was reported as an adverse effect in 2 children in the fluticasone propionate group.\(^{52}\)

**RIBAVIRIN**

We located 10 RCTs of ribavirin for more severe RSV bronchiolitis\(^{53-60,62,63}\) and a long-term follow-up from 1 of these 10 studies.\(^{61}\) The total number of patients in the primary studies was 320, and the overall quality was low, with half of the primary studies rated as fair or poor. Five studies\(^{53,56,59,60,62}\) reported on our primary outcomes of interest, such as days of hospitalization, length of time that a child required more intensive supportive interventions, and duration of illness. Four of these studies\(^{53,56,59,60}\) found no significant differences with ribavirin treatment compared with saline placebo. The study\(^{62}\) that did find differences in duration of mechanical ventilation and hospitalization favoring ribavirin used sterile water in the placebo arm. This study has been criticized for use of a sterile water placebo, which can induce bronchospasm, making the ribavirin treatment seem more effective.\(^{63}\) Six of 10 studies\(^{53,55,57,58,60,61}\) reported items that we classified as secondary outcomes, such as clinical symptoms and clinical scores. Differences favoring ribavirin were found for hours to improvement in cough and crepitations but not for wheezing or improved feeding in 1 study.\(^{57}\) Illness severity scores were better in the ribavirin group compared with the water placebo group on days 1 and 4 but not on days 2 and 3 of treatment in another study.\(^{57}\) Similarly, another study\(^{63}\) found better clinical scores in the ribavirin group compared with the saline placebo group on day 3 but not on days 1 and 2 of treatment. Three of the 6 studies\(^{55,58,60}\) reporting secondary outcomes did not find significant differences between the groups.

The long-term follow-up study\(^{61}\) found fewer children with greater than 2 episodes of wheezing during years 1 through 6 after ribavirin treatment but no significant differences in occurrence of overall respiratory illnesses or symptoms in those 6 years. Another study\(^{54}\) measured outcomes such as number of episodes of reactive airway disease and lower and upper respiratory disease in a 1-year follow-up period after use of ribavirin vs usual treatment and found fewer episodes of each in the ribavirin group. Aside from patient withdrawals in 2 studies\(^{56,57}\) for respiratory compromise, eyelid erythema was the only drug-specific adverse event reported in these studies.\(^{57}\) A total of 3 deaths (2 in the ribavirin treatment group and 1 in the water placebo group) were reported in 2 studies\(^{55,60}\); none of these events were believed to be caused by the intervention.

**COMMENT**

We did not find a substantial and convincing body of evidence to suggest that most treatments used for infants and children with bronchiolitis improve overall clinical outcomes compared with routine supportive therapy. Our results are consistent with previous systematic reviews and meta-analyses on the use of \(\beta_2\)-agonist bronchodilators,\(^{65,66}\) corticosteroids,\(^ {67}\) and ribavirin.\(^{68}\) We are unaware of any previous review of the use of epinephrine for the treatment of bronchiolitis. Aside from some transient improvements in clinical scores and related measures, we found little evidence to suggest that epinephrine is an effective treatment for bronchiolitis. Although 1 small study\(^ {60}\) demonstrated a reduction in the length of hospitalization with nebulized epinephrine use and another\(^ {62}\) found a decreased rate of hospital admissions, the weight of evidence does not support the use of nebulized epinephrine.

The widespread use of \(\beta_2\)-agonist bronchodilators for bronchiolitis is likely explained by the similarity of symptoms and signs between bronchiolitis and asthma. Two systematic reviews\(^{65,66}\) of bronchiolitis treatment with \(\beta_2\)-agonist bronchodilators have been published. Flores and Horwitz\(^ {57}\) found no evidence that \(\beta_2\)-agonist use either improved oxygenation by a clinically significant amount or reduced admission rates from outpatient and emergency department settings in a meta-analysis that included 8 RCTs. In a Cochrane review, Kellner et al\(^ {66}\) examined 20 RCTs and found a statistically significant increase in the proportion of bronchodilator-treated infants who demonstrated an improvement in their clinical scores (odds ratio, 0.29; 95% confidence interval [CI], 0.19-0.45). However, bronchodilator recipients did not show improvement in measures of oxygenation; the difference favored the control population (pooled difference, 0.7; 95% CI, 0.36-1.35). The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with controls (odds ratio, 0.7; 95% CI, 0.36-1.35).

The results of these 2 previous systematic reviews are consistent with our findings. Most studies demonstrated short-term improvements in various clinical scores, but 2 studies also showed worsening hypoxia in children who received a \(\beta_2\)-agonist compared with those who received saline placebo. However, we found no significant differences in outcome measures likely to be of greatest importance to clinicians and parents, such as whether a child must be hospitalized and the duration of hospitalization.

Infants with bronchiolitis have been treated with corticosteroids because they are well-known anti-inflammatory agents acting at a multitude of cellular levels.\(^ {67}\) Clinicians have considered them for use in infants with acute bronchiolitis partly because of the clear benefits of corticosteroid therapy in children with acute asthma and croup. However, as with inhaled \(\beta_2\)-agonists, data supporting the use of corticosteroids are not convincing. Garrison et al\(^ {67}\) published a meta-analysis of 6 RCTs of hospitalized infants. Infants who received corticosteroids had a mean...
length of stay or duration of symptoms that was 0.43 day less than those who received the placebo treatment (95% CI, −0.81 to −0.05 day). The effect size for improvement in mean clinical score was 1.60 (95% CI, −1.92 to −1.28), favoring treatment. They concluded that the combined published studies of the effects of systemic corticosteroids on the course of bronchiolitis suggest a statistically significant improvement in clinical symptoms and in duration of hospitalization and symptoms. Although the authors found a positive effect, they excluded several potentially relevant studies, and the clinical significance of an effect size of 1.6 is unclear.

We found inconclusive evidence that systemic corticosteroid therapy may offer a benefit in terms of rates and duration of hospitalization. Of 5 studies reporting this outcome, 2 saw a statistically significant benefit, although in 1 study the improvement was found only in children who required mechanical ventilation. Two studies actually found increased rates of hospitalization in the corticosteroid group. The preponderance of evidence does not favor the use of corticosteroids to decrease hospitalization. Reminiscent of the history of croup research, these studies all used different doses of corticosteroids, and the 1 that showed a convincing positive effect used the highest dose (1 mg/kg per day of dexamethasone). These authors did not report adverse effects, and their results have not been duplicated.

Five of 6 inhaled corticosteroid studies collected data on clinical symptoms as an outcome. The studies that used nebulized or MDI corticosteroids did not demonstrate a benefit for either hospitalizations or most symptom scores. With the exception of 1 poor-quality study that showed a decreased need for asthma treatment 2 years after the episode of bronchiolitis in infants given up to 8 weeks of budesonide, we did not find overall evidence that short-term treatment (1-12 weeks) with inhaled corticosteroids was effective. We also found some evidence to suggest that inhaled budesonide may pose harms; 2 small studies demonstrated longer term worsened clinical outcomes in children who received budesonide.

The 2003 Red Book states: “In hospitalized infants with RSV bronchiolitis, corticosteroids are not effective and are not indicated.” The findings of individual studies incorporated by this systematic review differ by the particular corticosteroid drug and dose used and by the populations and outcomes studied. Although an updated meta-analysis might be useful, technical difficulties are likely for such an analysis because of the heterogeneity among studies. Given current evidence, systemic corticosteroids do not seem to offer an overall benefit, even when examining surrogate outcomes, such as clinical scores.

Given the promising initial studies of the use of ribavirin in certain infants at high risk of serious RSV disease, the AAP initially endorsed this treatment approach in 1993. However, the AAP modified its recommendation in 1996 from “should be used” to “may be considered” after several subsequent trials showed no significant effect on clinical outcomes. The use of ribavirin is further constrained by its high cost and possible risk to health care personnel who administer it. A systematic review of 8 RCTs of ribavirin therapy published by Randolph and Wang in 1996 found that ribavirin use does not significantly affect mortality, lower the likelihood of respiratory compromise, or shorten hospitalization. However, statistical power is insufficient to rule out an effect. Our review excluded some studies that Randolph and Wang had included because they did not have an adequate control group or because of inability to assign outcomes to a relevant subset of randomized patients. We did not find evidence that ribavirin use led to consistent or more than transient improvements in clinical outcomes.

The results of this systematic review should be interpreted in light of several important limitations. First, we restricted included studies to those published in English. As a precaution against publication bias, we looked for abstracts in any language at the initial search stage and did not find evidence that limiting our selection to English-language publications missed any RCTs. Second, by limiting our search to the MEDLINE database and Cochrane Controlled Trials Register, we may have missed studies included only in other databases. Publication bias can affect all systematic reviews and meta-analyses. Unpublished and privately published literature is difficult to locate. We asked our technical expert advisory group and peer reviewers for the full evidence report whether they knew of literature we were missing, but we still could have inadvertently overlooked relevant studies. We are grateful to manuscript reviewers for directing our attention to 2 additional studies published after our original evidence report was completed. These 2 methodologically strong studies added substantial numbers to the epinephrine trials and altered our previous conclusions regarding this therapy. The importance of updating systematic reviews when new evidence emerges is underscored.

A third limitation is that this systematic review did not include a formal meta-analysis. Most of the studies found were small and were likely to be underpowered, although most did not include a sample size or power calculation. By statistically combining results of studies that used the same drugs and outcome measures, we might have found more conclusive evidence of whether a drug is an effective treatment for bronchiolitis. However, in most cases, the heterogeneity introduced by study differences (such as specific drug used in the class, dose and duration of therapy, other interventions used as part of routine care, outcomes measured, and population and setting of the study) would make formal meta-analysis inappropriate and misleading.

Further work to determine whether there are enough similar studies for some or all of the drug classes we examined would be useful. On initial inspection, for example, one might conclude that enough studies of nebulized salbutamol vs saline placebo exist to perform a meta-analysis. However, a closer look reveals that few of these studies used comparable outcome measures. Although most reported a composite clinical score, they did not necessarily use the same scoring method, and breaking the scores down into components such as respiratory rate or the presence of wheezing would require the original study data.

Investigators conducting future studies should choose clinically relevant outcomes. Most of the outcomes studied in this literature are short term. Often they
Despite the numerous clinical trials on treatments for bronchiolitis, such as bronchodilators, corticosteroids, and ribavirin, little evidence exists for the effectiveness of any of these interventions, particularly when measured in terms of significant patient-based outcomes. However, most of the studies in this area are not of sufficient size or quality to conclusively rule out the most commonly used treatments in the face of widespread and continued clinician use. This review justifies a large pragmatic clinical trial testing the more common interventions currently used for bronchiolitis.

were surrogate outcomes, such as oxygen saturation or respiratory rate immediately after treatment. Investigators should concentrate on measuring outcomes that matter to parents, clinicians, and health systems, such as rates of hospitalization or readmission, duration of hospitalization or emergency department care, the need for more intensive services during hospitalization, the costs of care, parental satisfaction with treatment, and development of chronic respiratory symptoms.

Few studies reported adverse events associated with treatments. Determining whether the risks of a particular treatment are sufficient to exclude its clinical use is difficult with current data. Clinicians commonly use interventions such as inhaled bronchodilators, corticosteroids, and epinephrine, for which current evidence of either benefit or harm is insufficient. These drugs are all available as relatively inexpensive generic products and are often used for other indications, such as asthma. Most clinicians consider them to be safe, although our review found evidence of adverse effects for all these classes of drugs. At the very least, the use of ineffective drugs diverts limited health care resources. Future investigations should carefully monitor and report adverse events.

The treatment studies we reviewed were also almost universally underpowered and as such were unable to give clinicians adequate guidance for management of bronchiolitis. However, we believe that all of these types of treatments will continue to be used unless a large pragmatic trial of the most commonly used interventions is mounted. Such a trial, using the most important outcome measures, would need to be large enough to examine each of the interventions not only in the overall population but also in subpopulations of interest, such as infants with more and less severe disease. Given that no optimal best treatment strategy for bronchiolitis currently exists, aside from supportive care, such as hydration and oxygenation, the use of new pharmacologic agents should be studied in well-designed, adequately sized studies. Using Placebos in the control groups of these studies, whenever feasible, is appropriate until such time as it is demonstrated that treatments other than supportive care are effective.

The AAP Committee on Infectious Diseases made recommendations about treatment for RSV bronchiolitis in the 2003 Red Book. The committee recommends supportive care as needed, including hydration, supple-

mental oxygen, and mechanical ventilation as the primary treatment modalities for bronchiolitis. On the basis of this systematic review, we find no evidence to disagree with these recommendations.

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The authors of this article are responsible for its content, including any clinical or treatment recommendations.

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REFERENCES

8. Bordley WC, Viswanathan M, King VJ, et al. Diagnosis and testing in bronchiol-


