ARTICLE

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.

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BRONCHIOLITIS IS THE MOST common lower respiratory tract infection in infants. Each year, 21% of North American infants develop lower respiratory tract disease, although most infants and young children experience only a mild form of bronchiolitis. However, up to 3% of all children in their first year of life are hospitalized with bronchiolitis. Respiratory syncytial virus (RSV) is responsible for 70% of all bronchiolitis cases and for 80% to 100% of cases in winter months. Parainfluenza, adenovirus, and influenza account for most of the remaining cases.[1]

Bronchiolitis-associated hospitalizations have increased considerably since 1980.[2] Among children 1 year or younger, annual bronchiolitis hospitalization rates increased from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996. Although infant hospitalization rates for bronchiolitis increased substantially between 1988 and 1996, hospitalization rates for other lower respiratory tract diseases did not vary extensively. The percentage of hospitalizations for lower respiratory tract illnesses associated with bronchiolitis among children younger than 1 year increased from 22.2% in 1980 to 47.4% in 1996.[3]

See also pages 111 and 119

Treatments for bronchiolitis can be categorized as specific or symptomatic. The only known specific treatment is aerosolized ribavirin, an antiviral agent for bronchiolitis caused by RSV. Among the popular symptomatic treatments are bron-

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

Category	Criteria
Study population	Human Infants and children
Study settings	Inpatient, outpatient, home (all geographic areas accepted subject to publication language and study design criteria)
Publication language	English only
study design	Single- and double-masked randomized controlled trial
Minimum sample size	10
Publication period	January 1980 through November 2002

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

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

chodilators 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]

METHODS

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.

RESULTS

We identified 797 abstracts from the entire systematic review of the diagnosis, treatment, and prophylaxis of bronchiolitis in infants and children[7]; 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,[14] surfactant,[15] nebulized furosemide,[16] 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 3. Bronchiolitis Treatment Trials: Epinephrine

Source	Quality Category	Intervention and Comparison	Patients, No.*	Primary Outcomes	Significant Outcome Differences	Adverse Effects Reported
Bertrand et al,[18] 2001	Good	Epinephrine vs salbutamol	30	Duration of hospitalization	None	Increased heart rate in epinephrine group
				Clinical score change	Significant improvement in epinephrine group immediately after treatment but not at 24 and 36 h	
Kristjansson et al,[19] 1993	Fair	Racemic epinephrine vs placebo	29	Clinical score at 0, 15, 30, 45, and 60 min	Improved in the epinephrine group	Circumoral pallor
				Oxygen saturation at 0, 15, 30, 45, and 60 min	Improved in epinephrine group only at first time period	
Menon et al,[20] 1995	Good	Epinephrine vs salbutamol	41	Duration of hospitalization	Shorter hospitalization in epinephrine group	More pallor in epinephrine group at 30 and 60 min
				Clinical score	None	
				Oxygen saturation at 30, 60, and 90 min	Better in epinephrine group at 60 min only	
Patel et al,[21] 2002	Excellent	Racemic epinephrine vs albuterol vs saline placebo	149	Duration of hospitalization	None	Transient tachycardia, mild hypertension, and slight tremor reported in all groups, without significant differences among groups
Ray and Singh,[22] 2002	Fair	Epinephrine vs salbutamol	91	Admission to hospital	Lower admission rate in epinephrine group	Heart rates increased in both groups but significantly increased in epinephrine group
				Respiratory rate, heart rate, oxygen saturation, and clinical scores after 3 doses given over 1 h	Improvements for all variables except heart rate in epinephrine group after 1 h	
				Respiratory rate	Lower in epinephrine group	
				Oxygen saturation	None	
Reijonen et al,[23] 1995	Good	Racemic epinephrine followed by saline placebo vs albuterol followed by saline placebo vs each treatment preceded by saline placebo	100	Clinical score	None	None observed
Sanchez et al,[24] 1993	Fair	Racemic epinephrine vs salbutamol	24	Oxygen saturation	None	None observed
				Respiratory rate	Lower in epinephrine group	
Wainwright et al,[25] 2003	Excellent	Epinephrine vs vehicle placebo	196	Duration of hospitalization	None	Increased heart rate in epinephrine group
				Time to readiness for discharge	None	

*Number of patients completing the study.

terventions studied can be found in the full evidence report[7] 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,[7] 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 $P<.05$; 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

Source	Quality Category	Intervention and Comparison*	Patients, No.†	Primary Outcomes	Significant Outcome Differences	Adverse Effects Reported
Can et al,[26] 1998	Fair	Salbutamol vs saline placebo vs mist in a tent	156	Clinical score at 0, 30, and 60 min	Better at 30 and 60 min for salbutamol group	Frequency of tachycardia and hypoxia did not reach a statistically significant difference between groups, but no details were provided
Cengizlier et al,[27] 1997‡	Fair	Inhaled salbutamol vs oral salbutamol vs control (no treatment)	31	Duration of hospitalization Clinical score change from hospital admission to discharge	None None	Not reported
Chowdhury et al,[28] 1995	Fair	Salbutamol vs ipratropium bromide vs salbutamol + ipratropium bromide vs saline placebo	89	Duration of hospitalization Clinical score at 30 and 60 min, and at 6, 12, 23, and 36 h	None None	Not reported
Dobson et al,[29] 1998	Good	Albuterol vs saline placebo	52	Percentage of patients discharged at 24, 48, and 72 h and total length of hospitalization Oxygen saturation at 0-24 h	None None	No details provided
Gadomski et al,[30] 1994	Excellent	Albuterol vs saline vs oral albuterol vs oral rehydration solution	169	Clinical score at 0, 30, and 60 min Respiratory rate, heart rate, oxygen saturation at 0, 30, and 60 min	None None	Not reported
Gadomski et al,[31] 1994	Good	Nebulized albuterol vs nebulized saline placebo vs oral albuterol vs oral placebo	76	Need for hospitalization or additional treatment Respiratory rate, oxygen saturation at 0, 30, and 60 min Heart rate at 0, 30, and 60 min	None None Heart rate higher for oral albuterol group at 60 min	Increased heart rate, facial flushing, hyperactivity, tremor in nebulized or oral albuterol groups
Goh et al,[32] 1997	Fair	Salbutamol vs ipratropium bromide vs saline placebo vs humidified oxygen	89	Duration of hospitalization Clinical score on days 1, 2, and 3	None None	Not reported
Ho et al,[33] 1991	Fair	Salbutamol vs saline placebo	21	Oxygen saturation at 5-min intervals from 5 to 25 min after each of 2 treatments	None	Most patients had desaturation compared with baseline after receiving salbutamol
Klassen et al,[34] 1991	Excellent	Salbutamol vs saline placebo	83	Clinical score at 0, 30, and 60 min Heart rate, respiratory rate, and oxygen saturation at 0, 30, and 60 min	Improved in salbutamol group at 30 min only None	Higher heart rate in salbutamol group
Schuh et al,[35] 1990	Good	Albuterol vs saline placebo	40	Hospitalization Mean % decrease in respiratory rate after each dose	4/21 In albuterol group vs 2/19 in saline placebo group (*P* value not reported) Significantly lower in placebo group	Increased heart rate in albuterol group
Schuh et al,[36] 1992	Good	Albuterol + ipratropium bromide vs albuterol + saline placebo	69	Change in respiratory rate, heart rate, and clinical scores from 0 to 120 min	None	Declines in oxygen saturation seen in both groups
Totapally et al,[37] 2002	Good	Albuterol vs saline placebo with crossover after 6 h	19	Wheeze score, oxygen saturation, respiratory rate, and heart rate	None	Not reported
Wang et al,[38] 1992	Good	Salbutamol + ipratropium bromide vs salbutamol vs ipratropium bromide vs saline placebo	62	Duration of hospitalization Mean change in oxygen saturation	None Improved for salbutamol + ipratropium bromide vs both agents alone but not vs placebo; worse for salbutamol vs placebo	Tremulouness in 1 child in salbutamol group leading to withdrawal from the study

*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).[18-25] 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, 2[20,22] noted either shorter hospitalization or fewer admissions in the epinephrine (vs salbutamol) group. Five studies[18-20,22,23] commented on changes in clinical

Table 5. Bronchiolitis Treatment Trials: Corticosteroids

Source	Quality Category	Intervention and Comparison	Patients, No.*	Primary Outcomes	Significant Outcome Differences	Adverse Effects Reported
				Oral Corticosteroids		
Berger et al,[39] 1998	Good	Prednisone vs placebo	38	Hospitalization	25% In prednisone group vs 11% in placebo group; no *P* value given	Not reported
				Clinical score	None	
Goebel et al,[40] 2000	Good	Prednisolone + albuterol vs placebo + albuterol	48 (32 with complete data)	Clinical score on days 0, 2, 3, and 6	Both groups improved on day 2 compared with day 0 only	1 Child jittery in prednisolone + albuterol group; resolved after reduction in albuteral dose
Klassen et al[41] 1997	Excellent	Dexamethasone vs placebo	67	Duration of hospitalization, readmission, and need for outpatient treatment	None	Not reported
				Clinical score change from baseline at 12, 24, 36, 48, and 60 h	None	
Schuh et al,[42] 2002	Excellent	Dexamethasone vs placebo	67	Rate of hospitalization	Lower in dexamethasone group (19% vs 44%)	Not reported
				Clinical score from baseline to day 7	None	
van Woensel et al,[43] 1997	Fair	Prednisolone vs placebo	27 Completed 5-y study	Transient, persistent, or late-onset wheezing at age 5 y	None	None observed
van Woensel et al,[44] 2000	Good	Prednisolone vs placebo	53	Duration of hospitalization in Ventilated patients	Fewer days in prednisolone group	1 Death unrelated to intervention
				Nonventilated patients	None	
				Clinical score in nonventilated patients	Improved in prednisolone group	
				Parenteral Corticosteroids		
De Boeck et al,[45] 1997	Fair	Dexamethasone vs placebo	29	Duration of hospitalization	None	Not reported
				Clinical score	None	
Roosevelt et al,[46] 1996	Good	Dexamethasone vs placebo	118	Time to resolution	None	Occult blood in stool seen in both groups, 2/65 (treatment) vs 1/53 (placebo)
				Duration of oxygen therapy	None	
				Inhaled Corticosteroids		
Cade et al,[47] 2000	Good	Nebulized budesonide vs vehicle placebo	161	Duration of hospitalization	None	Not reported
				Readmission for respiratory illness within 12 mo	None	
				Coughing/wheezing episodes at 12-mo follow-up	None	
Fox et al,[48] 1999	Fair	MDI budesonide vs placebo	49	Wheezing/coughing symptoms at 1, 2, 6, and 12 mo	Worsened for budesonide group at 12 mo	Mild cough and wheeze in 1 child in budesonide group; 1 admission for viral gastroenteriits in placebo group
				Hospitalizations in 12 mo	None	
Kajosaari et al,[49] 2000	Poor	Inhaled budesonide × 7 d vs inhaled budesonide × 2 mo vs symptomatic usual treatment	109	Need for asthma inhalation therapy at 2 y	Budesonide groups had less need (37% in symptomatic treatment vs 18% in budesonide for 7 d vs 12% in budesonide for 2 mo groups)	Not reported
Reijonen et al,[50] 1996	Fair	Inhaled budesonide vs inhaled cromolyn sodium vs no treatment control	92	Days of symptomatic wheezing at 1 vs 4, 5 vs 8, 9 vs 16, and 13 vs 16 wk	None	Not reported
Richter and Seddon,[51] 1998	Good	Nebulized budesonide vs placebo	40	Days on oxygen	None	Median growth 0.43 cm/wk (budesonide) vs 0.47 cm/wk (placebo); *P* = .16
				Prevalence of wheezing and use of bronchodilatros during 6-mo follow-up	None	
				Duration of hospitalization	None	
				Hospital readmission for respiratory problems	More readmissions in budesonide group	
Wong et al,[52] 2000	Good	MDI fluticasone propionate vs placebo	41	Overnight oxygen saturation	None	Oral candidiasis in 2 fluticasone group patients
				Night cough episodes at 3, 6, 12, 24, and 36 wk	Better for fluticasone group at 36 wk only	
				Parent-reported symptom frequency	None	

Abbreviation: MDI, metered dose inhaler.
*Number of patients completing the study.

Table 6. Bronchiolitis Treatment Trials: Ribavirin

Source	Quality Category	Intervention and Comparison	Patients, No.*	Primary Outcomes	Significant Outcome Differences	Adverse Effects Reported
Barry et al,[53] 1986	Fair	Ribavirin vs saline placebo	26	Median hours to sustained improvement	Faster improvement for cough and crepitations but not for retractions, nasal flaring, wheezing, and feeding	Eyelid erythema in 1 rebavirin group patient
Edell et al,[54] 2002	Poor	Ribavirin vs conservative treatment (eg, albuterol, methylprednisolone, ranitidine, oxygen, hydration)	45	Reactive airway disease, lower and upper respiratory tract infections, repeated RSV bronchiolitis, and otitis media in 1-year follow-up	Fewer episodes of each in ribavirin group	Not reported
Everard et al,[55] 2001	Fair	Ribavirin vs saline placebo	35	Days to discharge	None	1 Death in ribavirin group, unrelated to intervention
				Clinical score	None	
				Days receiving oxygen	None	
Guerguerian et al,[56] 1999	Excellent	Ribavirin vs saline placebo	41	Duration of hospitalization	None	Acute respiratory distress syndrome leading to withdrawal from study for 1 ribavirin group patient
				Duration of ventilation	None	
Hall et al,[57] 1983	Good	Ribavirin vs water placebo	33	Illness severity score from hospital admission through day 4	Better in ribavirin group on days 1 and 4	None observed
Janai et al,[58] 1993	Fair	Ribavirin vs saline placebo	19	Respiratory rate	None	None observed
				Pulmonary function test results at 1, 2, and 7 d	Only improved lung compliance on day 7 compared with day 1 in ribavirin group	
Meert et al,[59] 1994	Good	Ribavirin vs saline placebo	37	Duration of mechanical ventilation	None	6 Patients discontinued study (ribavirin, 4; placebo, 2) secondary to severe hypoxemia or pneumothorax
				Intensive care hospitalization	None	
				Supplemental oxygen requirement	None	
Rodriguez et al,[60] 1987	Good	Ribavirin vs water placebo	30	Severity of symptoms at 0, 1, 2, 3, and 4 d	None	1 Death in each group, unrelated to treatment
				Rate of change of symptom severity, days 0 to 2, days 0 to 3	Faster improvement in ribavirin group	
Rodriguez et al,[61] 1999	Good	Ribavirin vs water placebo	35	Clinical score 1 to 3 y and 1 to 6 y after RSV	None	Not reported
Smith et al,[62] 1991	Good	Ribavirin vs water placebo	28	Duration of hospitalization	Shorter in ribavirin group	Not reported
				Mean duration of mechanical ventilation	Shorter in ribavirin group	
				Average cost per day of hospitalization	No difference	
Taber et al,[63] 1983	Fair	Ribavirin vs saline placebo	26	Clinical score at 0, 1, 2, and 3 d	Better in ribavirin group on day 3 only	None observed
				Duration of illness	None	

Abbreviation: RSV, respiratory syncytial virus.
*Number of patients completing the study.

scores measured at various times. Three studies reported better clinical scores immediately after initial treatment compared with placebo[19] and salbutamol,[18,22] but the study[18] that collected data at 24 and 36 hours did not see a persistent improvement. Four research groups[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),[19] 1 at 60 minutes (but not at 30 or 90 minutes),[20] and 1 at 60 minutes.[22] One trial[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[19,20] and increased heart rates with epinephrine use in 4 studies.[18,21,22,25]

β2-AGONIST BRONCHODILATORS

We included 13 studies[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[28,32,36,38] did comparisons with nebulized ipratropium bromide, and 2[30,31] with oral salbutamol or albuterol. One study[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[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[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[38] 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 β2-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.[28,38] Another team[32] compared nebulized ipratropium bromide to nebulized salbutamol in a nebulized saline controlled trial, and a fourth group[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.[28,32,38] One trial[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.[36]

CORTICOSTEROIDS

In all, we included 5 studies[39-42,44] of oral corticosteroids (273 patients) (one additional article[43] was a 5-year follow-up of a prednisolone vs placebo trial), 2 studies[45,46] of parenteral corticosteroids (147 patients), and 6 studies[47-52] of inhaled corticosteroids (492 patients). One study[39] compared oral prednisone with placebo. Three studies[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.[41,42] Both studies[45,46] of parenteral corticosteroids used dexamethasone vs placebo. Five of the 6 inhaled corticosteroid studies[47-51] used budesonide, and the sixth study[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[39,41,42,44] reported either rates or duration of hospitalization. Rates of hospitalization for patients in the emergency department were lower in 1 study[42] using dexamethasone. A second study[44] 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[41] of oral dexamethasone. In addition, 1 study[39] found higher rates of hospitalization among children who received oral prednisone. The study[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[43] of prednisolone vs placebo did not demonstrate any long-term differences in transient, persistent, or late-onset wheezing.

Parenteral Corticosteroids

Neither intravenous dexamethasone[45] nor intramuscular dexamethasone against placebo[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[47-51] and 1 using a fluticasone proprionate MDI.[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[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[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[48] or hospital readmission in the 6 months after study entry for respiratory problems.[51] The small study[52] of a fluticasone proprionate 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[39,41,42] 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.[47,49,50] Oral candidiasis was reported as an adverse effect in 2 children in the fluticasone proprionate 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[55,56,59,62,63] 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[55,56,59,63] 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.[64] Six of 10 studies[53,55,57,58,60,63] 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.[53] 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[56,59] for respiratory compromise, eyelid erythema was the only drug-specific adverse event reported in these studies.[53] 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 β2-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[20] demonstrated a reduction in the length of hospitalization with nebulized epinephrine use and another[22] found a decreased rate of hospital admissions, the weight of evidence does not support the use of nebulized epinephrine.

The widespread use of β2-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 β2-agonist bronchodilators have been published. Flores and Horwitz[65] found no evidence that β2-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 β2-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 β2-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).[42] 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[48,51] demonstrated longer term worsened clinical outcomes in children who received budesonide.

The *2003 Red Book*[69] 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.[70] A systematic review of 8 RCTs of ribavirin therapy published by Randolph and Wang[68] 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

What This Study Adds

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*.[69] The committee recommends supportive care as needed, including hydration, supplemental 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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