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Pediatr Crit Care Med. Author manuscript; available in PMC 2013 December 19.

Published in final edited form as:
Pediatr Crit Care Med. 2004 September ; 5(5): 482–489.

Efficacy of interventions for bronchiolitis in critically ill infants: A systematic review and meta-analysis

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Abstract

Background—Viral bronchiolitis is the leading cause of respiratory failure among infants in the United States. Currently, the mainstay of treatment is supportive care. The effectiveness of treatments used for mechanically ventilated infants with bronchiolitis is unclear.

Objective—To evaluate the strength of the evidence supporting the use of currently available treatments for critically ill infants with bronchiolitis.

Data Source—We searched PubMed, citations of relevant articles, personal files, and conference proceedings, and we contacted experts in the field.

Study Selection—Randomized, controlled trials evaluating any therapy for bronchiolitis that included children in an intensive care unit.

Data Extraction—Two reviewers independently extracted data and assessed methodologic quality.

Data Synthesis—A total of 2,319 citations were screened, and 16 randomized, controlled trials were included. There were three trials of surfactant, three of ribavirin, three of immune globulin, three of systemic corticosteroids, and one each of vitamin A, interferon, erythropoietin, and heliox. A meta-analysis of the three surfactant studies showed a strong trend toward a decrease in duration of mechanical ventilation of 2.58 days (95% confidence interval, −5.34 to 0.18 days; $p = .07$) and a significant decrease of 3.3 intensive care unit days (95% confidence interval, −6.38 to −0.23 days; $p = .04$). A meta-analysis of the three systemic corticosteroid studies showed no overall effect on duration of mechanical ventilation when all three trials were combined (−0.62 day; 95% confidence interval, −2.78 to 1.53 days; $p = .57$). We identified one published meta-analysis of three ribavirin studies showing a significant decrease in ventilator days with ribavirin (−1.2 days; 95% confidence interval, −0.2 to −3.4 days; $p = .2$).

Conclusions—Currently, there are no clearly effective interventions available to improve the outcome of critically ill infants with bronchiolitis. Surfactant seems to be a promising intervention, and corticosteroids or ribavirin may also be beneficial.

Keywords

bronchiolitis; critical care; mechanical ventilation; therapy; systematic review; surfactant; immune globulin; steroids; pediatrics; child

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In the United States and other developed nations, viral bronchiolitis is the most common cause of respiratory disease in children <2 yrs of age requiring hospitalization (1). The most important cause of bronchiolitis is respiratory syncytial virus (RSV), which is responsible

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for up to 80% of cases, although parainfluenza viruses, rhinoviruses, adenoviruses, influenza viruses, and enteroviruses can also produce the clinical syndrome. Annual epidemics of RSV bronchiolitis occur during the winter and spring months, which dependably produce a sizable disease burden on the pediatric population (2).

The past 20 yrs have seen a greater than 2-fold increase in the number of infants hospitalized with bronchiolitis. The cause for this increase is likely to be multifactorial, and it may be related in large part to an increased survival among both premature infants and infants with complex chronic conditions, who are at high risk for severe RSV disease (3). An increase in the use of daycare facilities may also promote exposure to the disease among a larger population of susceptible infants and children (3). According to a recent descriptive analysis, the annual rate of hospitalization in the United States for infants <1 yr of age with a diagnosis of bronchiolitis is increasing, and it may be as high as 31.2 per 1,000 (3). Between 62,500 and 100,000 children <5 yrs of age with bronchiolitis are reportedly admitted to U.S. hospitals each year (3).

Among previously healthy infants and children who are hospitalized with bronchiolitis, 10–15% require intensive care, and half of those admitted to the intensive care unit (ICU) will develop respiratory failure requiring mechanical ventilatory support (4). Infants and children with congenital heart disease, chronic lung disease, or immunocompromise are at high risk for severe disease, and the rate of ICU admission in this population may be as high as 31–36%, and 11–19% can be expected to require mechanical ventilation (4). The mortality attributable to RSV bronchiolitis is <1% in all hospitalized infants, but it may be as high as 3.5% in high-risk infants (4). Many of these patients have been identified as candidates to receive the presently available monoclonal antibody against RSV (Palivizumab) as prophylaxis each month during RSV season. However, it is not clear that the use of prophylactic monoclonal antibody as currently recommended by the American Academy of Pediatrics will diminish the burden of RSV disease that is presently handled by pediatric ICUs (5, 6).

Treatment of bronchiolitis is primarily supportive. Numerous medical therapies have been used in the management of the clinical syndrome, but few have demonstrated an important influence on outcome. Data supporting the use of any specific medical therapy in the management of bronchiolitis in the critically ill child are especially scant. The objective of this study was to systematically review all presently available randomized trials on medical therapies for the management of the critically ill child with RSV bronchiolitis to determine whether therapies exist that are of proven benefit in the intensive care setting.

METHODS

Study Identification

Trials included in the analysis were identified by searching PubMed from 1966 to October 2003 using the terms *bronchiolitis* AND *therapy* for all publications in all languages. Searching was performed by two reviewers, independently. We examined the full manuscript of each retrieved article, and we searched the reference list of each. Finally, we contacted experts in the field and searched the personal files of the authors for potential randomized, controlled trial (RCT) citations.

Study Selection

The following criteria were used to identify studies for inclusion in this review:

Study Design: RCT

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Population: pediatric patients in an ICU

Intervention: any intervention for the treatment of bronchiolitis

Outcomes: mortality, ventilator days, length of ICU stay, length of hospital stay

All studies not meeting the above inclusion criteria were excluded.

Data Abstraction

Data abstraction was conducted by two independent investigators. Disagreements were resolved by a third investigator. We asked authors to supply further information when data needed for appraisal or analysis were missing or unclear.

Assessment of Methodologic Quality

Two investigators independently assessed the quality of allocation concealment. Disagreement was resolved by consensus. Allocation concealment was scored A ("adequate," e.g., opaque, sealed envelopes issued from a central pharmacy or other centralized randomization and allocation schemes that cannot be influenced by study investigators), B (unclear), and C (inadequate) as described in the Cochrane Reviewers' Handbook (7). Characteristics of each study included in the review are presented in Tables 1 and 2 and include data pertinent only to study subjects who were in an ICU. For studies in which only a portion of all subjects were in an ICU, some of the descriptive data are designated in the tables as pertaining to the entire study population.

Data Analysis

Meta-analyses were performed when applicable using Rev-Man Meta-View 4.1 with the random effects model. A chi-square test for homogeneity was also performed using this software. A significant test ($p < .05$) means that the observed variation is greater than one can attribute to chance alone.

RESULTS

After reviewing all 2,319 citations retrieved with PubMed, both investigators independently identified 18 published RCTs that included children in an ICU. Two trials were excluded. One trial of nebulized corticosteroids in RSV bronchiolitis included only three patients who were transferred to the ICU, and outcome data were not available for the ICU population (8). In another trial of nebulized immune globulin in infants with bronchiolitis, a total of eight mechanically ventilated patients were included without specific outcome data (9).

We included 16 published RCTs that met our criteria. These included three trials of surfactant, three of ribavirin, three of immune globulin, three of systemic corticosteroids, and one each of vitamin A, interferon, erythropoietin, and heliox. The characteristics of these studies are listed in Table 1. When possible, we also listed the number of patients with specific underlying conditions. There were a sufficient number of trials for surfactant, corticosteroids, and ribavirin to perform meta-analyses. The results of these three categories will be reported first.

Surfactant

Three RCTs were identified involving a total of 79 patients (10–12). Luchetti et al. (10, 12) used porcine surfactant and no placebo in both studies. Tibby et al. (11) used bovine surfactant and an air placebo. As shown in Figure 1, a meta-analysis of the three studies demonstrated a nonsignificant decrease in duration of mechanical ventilation by 2.6 days (95% confidence interval [CI], −5.34 to 0.18 days; $p = .07$). The test for heterogeneity was

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strongly significant (chi-square = 63.22, *df* = 2, $p < .00001$). This was because the 1998 Luchetti et al. (10) trial demonstrated a 4.5-day decrease in duration of mechanical ventilation, whereas the decrease in duration of mechanical ventilation in the other two studies was <1.73 days. Figure 2 shows the significant decrease in duration of ICU stay. Overall, surfactant decreased the ICU stay by 3.3 days (95% CI, −6.38 to −0.23 days; $p = .04$). As shown in Figure 2, the test for heterogeneity was again significant with the 1998 Luchetti et al. (10) study, showing a much larger decrease in duration of ICU stay.

Corticosteroids

We identified three studies investigating the role of corticosteroids in the management of critically ill children with bronchiolitis (13–15). The three studies used different corticosteroid dosing and treatment durations. van Woensel et al. (15), in 1997, initially reported the results of a subgroup of 14 mechanically ventilated children from a larger RCT comparing the effects of 1 mg/kg oral prednisolone for 7 days vs. placebo on duration of hospital stay. Buckingham et al. (14) used 0.5 mg/kg of dexamethasone intravenously every 12 hrs for 4 days vs. saline placebo in 41 mechanically ventilated infants. In 2003, van Woensel et al. (13) performed the largest study of 0.15 mg/kg dexamethasone every 6 hrs for 48 hrs vs. 0.15 mg/kg placebo every 6 hrs for 48 hrs in 85 mechanically ventilated infants. All three trials restricted the population to RSV-positive infants.

Although the treatments were of different duration and potency, we combined the three studies in a meta-analysis. As shown in Figure 3, corticosteroids had no overall effect on duration of mechanical ventilation (−0.62 day; 95% CI, −2.78 to 1.53 days; $p = .57$). As shown in Figure 4, corticosteroids also had no effect on duration of hospitalization (−1.73 days; 95% CI, 8.42 to 4.96 days; $p = .61$). The tests for homogeneity were nonsignificant for both analyses.

Ribavirin

We found one published systematic review (16) that included three trials of a total of 104 ventilated patients (17–19). According to a published meta-analysis of the three studies, the use of ribavirin was associated with a significant decrease in ventilator days of 1.2 days (95% CI, −0.2 to −3.4; $p = .03$). Also evident was a trend toward a decrease in hospital stay of 1.9 days (95% CI, +0.9 to −4.6; $p = .2$). Including only the two studies that used a saline placebo (17, 19), the use of ribavirin was associated with a strong trend toward reduction in days of hospitalization by 1.87 days (95% CI, 1.08 to −4.81; $p = .2$) and in a reduction in ventilator days by 1.08 days (95% CI, 0.67 to −2.83; $p = .2$). A trend toward decreased mortality was also seen in the ribavirin group (relative risk, 0.36; 95% CI, 0.07 to 1.77; $p = .21$). The test for heterogeneity was nonsignificant for all of the above comparisons.

Immune Globulin

We found three RCTs on the use of immune globulin in ICU patients (20–22). Because the interventions used were so different, we did not combine the data from the studies in a meta-analysis.

One trial of 35 ventilated infants showed no change in ventilator days associated with the administration of monoclonal antibody in the Palivizumab group vs. the control group (8.8 days vs. 6.2 days, respectively; $p = .45$). There was also no change in length of hospital stay attributable to the administration of monoclonal antibody in the Palivizumab group vs. the control group (14.5 days vs. 11.5 days, respectively; $p = .25$). In this study, there was one death in the placebo group (20).

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Polyclonal antibody against RSV (RespiGam) was administered to a subgroup of ICU patients in a larger study of previously healthy hospitalized patients who were RSV positive. A total of 52 ICU patients, of whom 33 were ventilated, were randomized to receive 1500 mg/kg respiratory syncytial virus immunoglobulin (RSVIG) intravenously or albumin placebo. ICU patients treated with RSVIG showed a nonsignificant decrease in ventilator days (4.31 days [SD 2.4] vs. 5.54 days [SD 6.5], $p = .45$) and a nonsignificant decrease in ICU stay (3.92 [SD 2.9] days vs. 6.6 days [SD 7.5]; $p = .06$) (21).

The same group conducted a randomized, double-blind, placebo-controlled trial of 1500 mg/kg RSVIG with albumin placebo in high-risk infants with RSV. They randomized 107 patients, of whom 38 were in an ICU at enrollment, and 25 of these were mechanically ventilated. The authors note a higher proportion of ICU patients in the treatment group compared with the placebo group. When adjusted for entry scores, there was no difference between the groups in number of ICU days (9.77days [SD 9.2] for RSVIG vs. 10.27 days [SD 7.7] for placebo; $p = .90$) or days of mechanical ventilation (9.71 [SD 7.8] vs. 9.91 [SD 6.7]; $p = .94$). Adverse reactions were comparable in both groups, and two deaths in the RSVIG group were not attributed to the medication infusion (22).

Helium

We found one RCT of the use of helium/oxygen in children in an ICU (23). The authors entered 18 patients admitted to an ICU with RSV bronchiolitis into a double-blind, randomized, crossover study in which each would receive 20 mins of exposure to a mixture of either air/oxygen or helium/oxygen (heliox) via a face mask. Ultimately, only 13 patients were randomized because the physicians chose to use heliox in the sickest patients. The authors report an improvement in clinical asthma scores during heliox delivery. However, continuous positive airway pressure was used in six children, and one child was mechanically ventilated, so 39% of the study patients required another form of respiratory support. The authors do not provide data on the effect of heliox administration on length of stay in the ICU (23).

Vitamin A

Vitamin A is believed to be important to the maintenance of humoral and cellular immunity and for epithelial integrity (24). Vitamin A deficiency has been associated with measles infection, and supplementation in this disease has been associated with a reduction in morbidity and mortality (25–27). More recently, vitamin A deficiency has also been identified in RSV infections (28). In a single study, 32 RSV-positive children (of whom nine were in an ICU) were randomized to receive vitamin A supplementation or placebo. The authors report a nonsignificant trend (Table 2) toward increased ICU days in the children who received vitamin A (29).

Interferon

One study of intramuscular alpha 2A interferon in 22 patients included six ventilated children but excluded high-risk patients. There were no significant differences (Table 2) in ventilator requirements between the alpha 2A interferon and placebo groups (30).

Erythropoietin

Low serum levels of erythropoietin have been associated with anemia that develops in the context of critical illness (31). We identified one RCT on the use of erythropoietin in 44 ventilated children with RSV bronchiolitis. As shown in Table 2, there was no significant difference between the treatment and control groups in ventilator days or ICU days (32).

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DISCUSSION

Despite the fact that bronchiolitis remains a major cause of ICU admission for pediatric patients, we were unable to clearly identify any intervention showing solid evidence of benefit. Based on data from small, underpowered studies, the two interventions that may be effective for RSV bronchiolitis in our analysis were surfactant and ribavirin. The most promising intervention seems to be surfactant; however, the strongest effect was from the 1998 Luchetti et al. (10) study, in which patients received an unusually long course of mechanical ventilation, and no ventilator management protocol was used. The duration of mechanical ventilation for bronchiolitis has decreased in the interim. More recent surfactant studies showed a more modest effect. The 1998 Luchetti et al. (10) study also contains several important differences when compared with other similar trials. For example, a minority of the study population in Luchetti et al. (10) was found to have RSV disease. Although these infants demonstrated a similar degree of oxygenation impairment compared with those included in the other studies, they were enrolled after receiving mechanical ventilation for 24 hrs. Many of the patients in the study by Luchetti et al. (10) had consolidative changes on chest radiographs, whereas the population of Tibby et al. (11) included only RSV-positive patients who had been ventilated for <24 hrs and who primarily demonstrated hyperinflation without alveolar consolidation. Whereas the study by Tibby et al. (11) used a strategy of permissive hypercapnia, Luchetti et al. (10) used an aggressive ventilator strategy that targeted a tidal volume of 10 mL/kg body weight, and weaning from mechanical ventilation did not begin until normal blood gas tensions were achieved. These differences may explain the much longer mean duration of mechanical ventilation in the population of Luchetti et al (10). Also important is that the surfactant-treated infants in the 1998 Luchetti et al. (10) study received a period of manual ventilation before drug instillation. This maneuver alone may have resulted in marked clinical improvement among those infants because it would have recruited underinflated lung regions. In the 2002 study, Luchetti et al. (12) eliminated many of these potential sources of bias by exposing both treatment and control groups to a period of manual ventilation and by establishing guidelines for ventilator management for all study centers, and the duration of mechanical ventilation was shorter among all patients in this study compared with the original study. Both studies by Luchetti et al. (10, 12) are notable for having small standard deviations of the mean values for each outcome measure, which contribute to their overall statistical power (Table 2).

Among the ribavirin studies, the trial by Smith et al. (18) had the strongest effect, but use of a water placebo led to speculation that this could have caused bronchospasm in the placebo group (17). Although larger RCTs may be able to establish statistically significant differences in relevant outcome measures, use of ribavirin, if even for additional clinical trials, is likely to be limited because of ongoing concerns over its safety, occupational hazards, cost, and mechanism of delivery (17, 33–35). Although both ribavirin and surfactant are expensive therapies, the cost may be offset by a possible decrease in ICU stay.

Other commonly used treatments in mechanically ventilated children with bronchiolitis such as bronchodilators, antibiotics, and corticosteroids are of unclear benefit. There were no trials evaluating the use of bronchodilators or antibiotics. The three trials of corticosteroids used different treatment regimens, but none individually showed a significant benefit. All other interventions tested (heliox, vitamin A, immune globulin, interferon, and erythropoietin) failed to show strong evidence of benefit in individual trials.

Use of corticosteroids has been reported in up to 60% of hospitalized patients with RSV bronchiolitis (36). A systematic review of the effect of corticosteroids on nonintubated infants with bronchiolitis showed a 0.5-day decrease in duration of hospitalization (37). A

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recent trial conducted among children in an emergency department showed that a single high dose of dexamethasone could prevent hospital admission in bronchiolitis (38). The most recent steroid study by van Woensel et al. (13) showed a trend toward a 1.6-day decrease in duration of mechanical ventilation but was underpowered to detect such a small effect. The study by Buckingham et al. (14) used a higher dose of dexamethasone and a longer duration of therapy and found no effect, but the mean in the dexamethasone group was skewed due to the presence of an outlier who was ventilated for >30 days. The median durations of mechanical ventilation were more similar. Given that the cumulative data on steroids includes only 66 infants total who were randomized to steroids, one cannot determine with certainty whether steroids are beneficial.

Our study has some limitations. Studies with positive results are more likely to be published in journals, and given the broad range of interventions included in this review, we were not able to construct funnel plots or other means to evaluate publication bias.

There are many important issues to consider in the design of future trials to determine the efficacy of therapies for bronchiolitis. Most of the studies included in our analysis were small. Because recent studies report that the mean duration of mechanical ventilation in patients with bronchiolitis across centers is approximately 8.3 days ($_{SD}$ 6.8 days) (39), a study would require 264 patients per study arm to detect a 20% decrease (−1.66 days) in ventilator days at an alpha of .05 and a power of 80%, and 169 patients per study arm would be required to detect a 25% decrease (−2.08 days). None of the trials included in this review included even 50 ICU patients per arm.

The use of adjuvant therapies for bronchiolitis remains widespread, despite a lack of evidence to support their effectiveness. The use of unproven therapies is needlessly expensive and exposes many children to the potential for adverse treatment effects. Because future prospects for providing lasting immunity to RSV remain doubtful (2), there is an ongoing need for studies that are adequately powered to identify therapies that may benefit critically ill children with this disease. Because the mortality associated with bronchiolitis is low, large multicenter trials that focus on continuous outcome measures such as duration of mechanical ventilation and ICU or hospital length of stay will provide the best opportunity to demonstrate a clinical benefit with adequate statistical power. Given the high frequency of recurrent wheezing in this population (40, 41), longer-term outcomes such as need for readmission or for pulmonary medications should also be evaluated.

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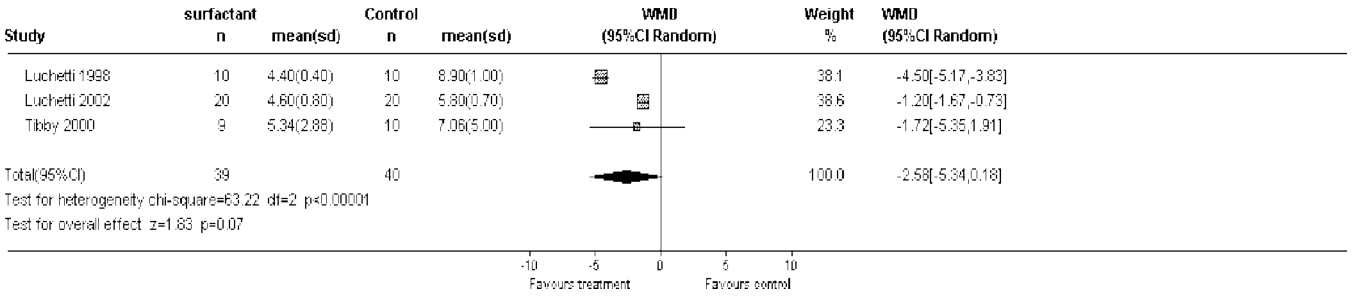

Figure 1.

Meta-analysis of surfactant trials in bronchiolitis: effect on duration of mechanical ventilation. *WMD*, weighted mean difference; *CI*, confidence interval.

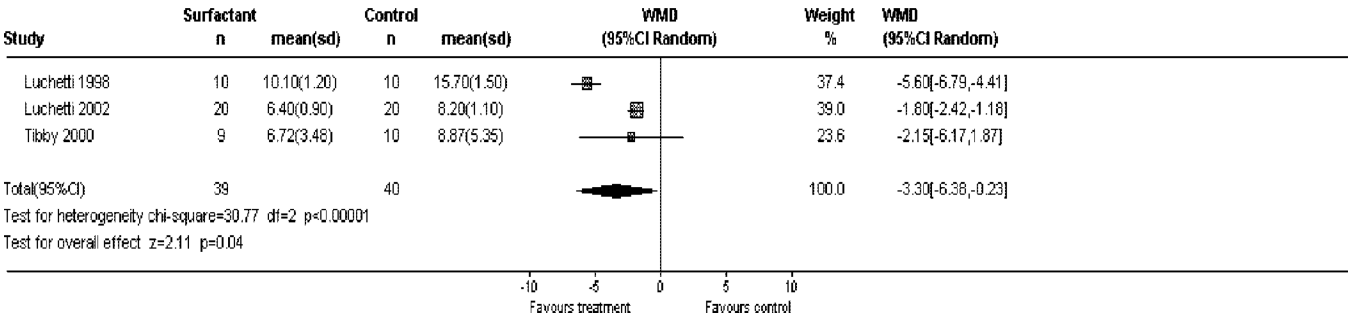

Figure 2.

Meta-analysis of surfactant trials in bronchiolitis: effect on intensive care unit (ICU) length of stay. *WMD*, weighted mean difference; *CI*, confidence interval.

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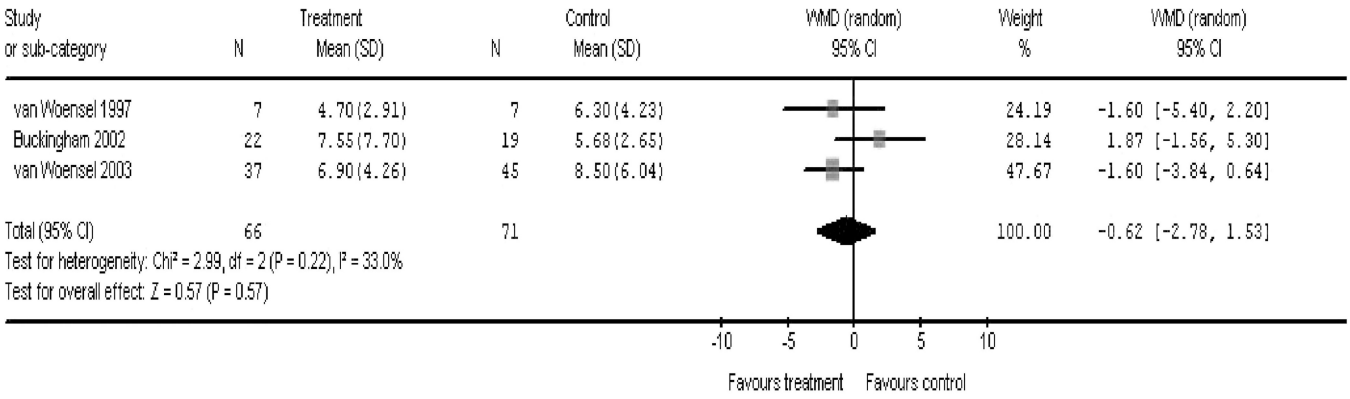

Figure 3.

Meta-analysis of systemic corticosteroid trials in bronchiolitis: Effect on duration of mechanical ventilation. *WMD*, weighted mean difference; *CI*, confidence interval.

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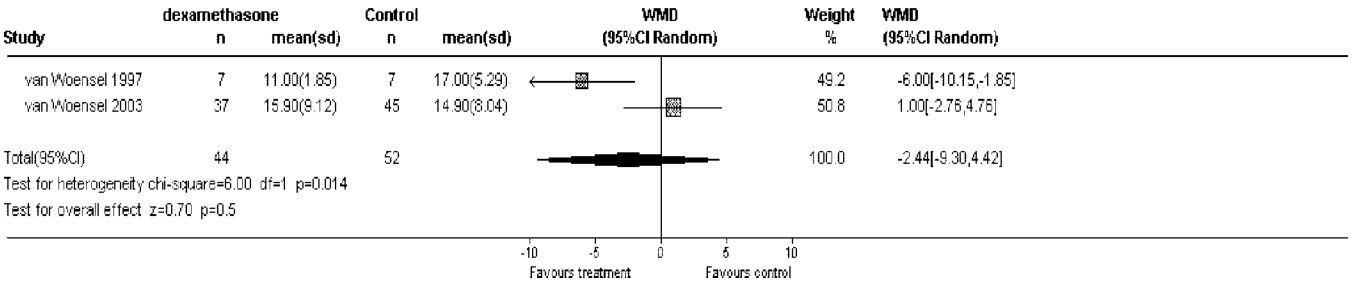

Figure 4.

Meta-analysis of systemic corticosteroid trials in bronchiolitis: Effect on hospital length of stay. *WMD*, weighted mean difference; *CI*, confidence interval.

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Table 1

Study characteristics of therapy trials in bronchiolitis in critically ill children

Study	Characteristics of ICU Subjects Enrolled (Unless Otherwise Specified)	Design/Quality[a]	Interventions
Luchetti et al., 1998 (10)	10 surfactant, 10 control RSV+ and RSV− Mean age: 10.4 mos surfactant, 11.2 mos control No chronic disease exclusions	Unblinded, randomized trial/A	Porcine surfactant, 50 mg/kg IT No placebo
Luchetti et al., 2002 (12)	20 surfactant, 20 control RSV+ Mean age: 8.7 mos surfactant, 7.4 mos control Excluded chronic lung disease, congenital heart disease	Unblinded, randomized trial/A	Porcine surfactant, 50 mg/kg IT No placebo
Tibby et al., 2000 (11)	9 surfactant, 10 control RSV+ Median age: 9 wks surfactant, 6.5 wks control Excluded uncorrected congenital heart disease	Randomized, controlled trial/B	Bovine surfactant, 100 mg/kg IT × 2 Air placebo
Guerguerian et al., 1999 (17)	20 ribavirin, 21 control RSV+ Mean age: 62.5 days ribavirin, 62.7 days control Excluded congenital heart disease associated with cyanosis or pulmonary hypertension, chronic lung disease, immune deficiency	Double-blind, randomized, controlled trial/A	Ribavirin, 6 g each day over 18 hrs while intubated × maximum of 7 days Normal saline placebo
Smith et al., 1991 (18)	14 ribavirin, 14 control RSV+ Mean age: 1.1 mos ribavirin, 1.6 mos control No chronic disease exclusions	Double-blind, randomized, controlled trial/A	Ribavirin administered continuously while intubated × maximum of 7 days Sterile water placebo
Meert et al., 1994 (19)	22 ribavirin, 19 control RSV+ Mean age: 5.2 mos ribavirin, 4.9 mos control Included 4 with congenital heart disease, 16 with chronic lung disease, 2 with immunodeficiency	Double-blind, randomized, controlled trial/A	Ribavirin × 18 hrs each day while intubated × maximum of 5 days Normal saline placebo
Hollman et al., 1998 (23)	13 patients RSV+ Median age: 2.5 mos Included 5 with congenital heart disease, 1 with acquired heart disease	Double-blind, randomized, controlled crossover trial and nonrandomized prospective trial/A	Air/oxygen mixture or He/oxygen mixture × 20 mins, followed by crossover therapy × 20 mins
Quinlan et al., 1996 (29)	7 vitamin A, 2 control RSV+ Mean age[b]: 11.8 mos vitamin A, 10.9 mos control Included 7 with congenital heart disease, 5 with chronic lung disease	Double-blind, randomized, controlled trial/B	Oral vitamin A, 100,000 IU × 1 Unspecified placebo
Jacobs et al., 2003 (32)	22 erythropoietin, 22 control RSV+ and RSV− Mean age: 3.5 mos erythropoietin, 2.7 mos control Excluded chronic lung disease	Blinded, randomized, controlled trial/A	Erythropoietin, 200 units·kg^{-1}·day^{-1} intravenously, plus enteral iron, 3 mg·kg^{-1}·day^{-1} Albumin/iron placebo
Chipps et al., 1993 (30)	4 interferon, 2 control RSV+ Patients <24 mos of age Excluded cyanotic congenital heart disease and any underlying chronic disease	Double-blind, randomized, controlled trial/A	Alpha-2A interferon 70,000 units·kg^{-1}·day^{-1} intramuscularly × 5 days Normal saline placebo

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Study	Characteristics of ICU Subjects Enrolled (Unless Otherwise Specified)	Design/Quality[a]	Interventions
Malley et al., 1998 (20)	17 Palivizumab, 18 control RSV+ Median age: 3.2 mos Palivizumab, 1.7 mos control Excluded significant heart disease, chronic lung disease, immunodeficiency	Double-blind, randomized, controlled trial/A	Palivizumab, 15 mg/kg intravenously Saline placebo
Rodriguez et al., 1997 (21)	22 RSVIG, 30 control RSV+, previously healthy infants Mean ageb: 0.20 yrs RSVIG, 0.19 yrs control Excluded cardiopulmonary disease, immunodeficiency	Double-blind, randomized, controlled trial/A	RSVIG[f], 1500 mg/kg intravenously Albumin placebo
Rodriguez et al., 1997 (22)	24 RSVIG, 14 control RSV+, high-risk infants Mean age[b]: 0.55 yrs RSVIG, 0.58 yrs control Excluded chronic lung disease other than bronchopulmonary dysplasia, chronic ventilator dependency, immunodeficiency	Double-blind, randomized, controlled trial/A	RSVIG[f], 1500 mg/kg intravenously Albumin placebo
van Woensel et al., 1997 (15)	7 prednisolone, 7 control RSV+ Median age[b]: 3.3 mos prednisolone, 3.9 mos placebo Total study population included 15 with either congenital heart disease or chronic lung disease	Double-blind, randomized, controlled trial/A	Prednisolone, 1 $mg \cdot kg^{-1} \cdot day^{-1}$ orally in 2 divided doses × 7 days Unspecified placebo
Buckingham et al., 2002 (14)	22 dexamethasone, 19 control RSV+ Mean age: 60 days dexamethasone, 44 days control Excluded immunodeficiency	Double-blind, randomized, controlled trial/B	Dexamethasone, 0.5 mg/kg intravenously every 12 hrs × 4 days Saline placebo
van Woensel et al., 2003 (13)	37 dexamethasone, 45 control RSV+ Mean age: 5.9 wks dexamethasone, 9.8 wks control Included 2 with congenital heart disease, 3 with chronic lung disease	Double-blind, randomized, controlled trial/A	Dexamethasone, 0.15 mg/kg intravenously every 6 hrs × 48 hrs Unspecified placebo

ICU, intensive care unit; RSV, respiratory syncytial virus; IT, intratracheal; RSVIG, respiratory syncytial virus immune globulin.

[a]Quality of allocation concealment: A = adequate, B = unclear, C = inadequate (7);

[b]includes ICU and non-ICU study subjects.

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Table 2

Study outcomes

Study (Intervention)	Outcomes Among Critically Ill Subjects (Unless Otherwise Noted)			
	Mean Ventilator Days Control (SD):Treatment (SD)	Mean ICU days Control (SD):Treatment (SD)	Mean Hospital Days Control (SD):Treatment (SD)	No. of Deaths Control: Treatment
Luchetti et al., 1998 (10) (surfactant)	8.9 (1.0):4.4 (0.4) days ($p < .05$)	15.7 (1.5):10.1 (1.2) days ($p < .05$)	N/A	0:0
Luchetti et al., 2002 (12) (surfactant)	5.8 (0.7):4.6 (0.8) days ($p < .0001$)	8.2 (1.1):6.4 (0.9) days ($p < .0001$)	N/A	0:0
Tibby et al., 2000 (11) (surfactant)	170:126 hrs ($p = .4$)	213:161 hrs ($p = .3$)	17:13 days ($p = .3$)	0:0
Guerguerian et al., 1999 (17) (ribavirin)	126.28 (78.72):102.16 (65.26) hrs ($p = .29$)	161.45 (86.06):140.20 (80.87) hrs ($p = .42$)	294.95 (124.40):255.85 (124.93) hrs ($p = .32$)	0:0
Smith et al., 1991 (18) (ribavirin)	9.9 (5.6):4.9 (3.7) days ($p = .01$)	N/A	15 (5.4):13.3 (13.3) days ($p = .04$)	1:0
Meert et al., 1994 (19) (ribavirin)	8.2 (10.1):6.4 (6.9) days ($p = .5$)	10.3 (11.0):7.9 (7.0) days ($p = .7$)	16.2 (14.0):12.9 (9.7) days ($p = .6$)	4:2
Hollman et al., 1998 (23) (heliox)	N/A	N/A	N/A	0:0
Quinlan et al., 1996 (29) (vitamin A)	N/A	3:10.3 days ($p = .36$)	3.5:6.6 days ($p = .08$)	0:0
Jacobs et al., 2003 (32) (erythropoietin)	8.6 (4.7):8.1 (2.8) days (p = NS)	10.1 (5.2):9.5 (2.8) days (p = NS)	13.6 (6.6):12.4 (3.3) days (p = NS)	0:0
Chipps et al., 1993 (30) (interferon)	N/A	N/A	N/A	0:0
Malley et al., 1998 (20) (monoclonal antibody)	6.2 (6.4):8.8 (9.5) days ($p = .45$)	N/A	11.5 (6.4):14.5 (8.7) days ($p = .25$)	1:0
Rodriguez et al., 1997 (21) (immune globulin)	5.54 (6.5):4.31 (2.4) days ($p = .45$)	6.6 (7.5):3.92 (2.9) days ($p = .06$)	5.52 (5.0):4.58 (2.7) days ($p = .24$)[a]	0:0
Rodriguez et al., 1997 (22) (immune globulin)	9.91 (6.7):9.71 (7.8) days ($p = .94$)	10.27 (7.7):9.77 (9.2) days ($p = .90$)	8.89 (7.0):8.41 (6.9) days ($p = .73$)[a,b]	0:2
van Woensel et al., 1997 (15) (corticosteroids)	6.3 (4.2):4.7 (2.9) days ($p = .56$)	N/A	17 (5.3):11 (1.9) days ($p < .01$)	1:0
Buckingham et al., 2002 (14) (corticosteroids)	Median, 6 (IQR 4.5):5.5 (IQR 4.0) days ($p = .86$)	Median, 8 (IQR 4.0):7 (IQR 7.0) days ($p = .76$)	Median, 10 (IQR 5.5):11 (IQR 6.0) days ($p = .40$)	0:1
van Woensel et al., 2003 (13) (corticosteroids)	8.5 (6.0):6.9 (4.3) days ($p = .19$)	9.9 (6.0):9.1 (5.5) days ($p = .53$)	14.9 (8.0):15.9 (9.1) days ($p = .52$)	0:1

ICU, intensive care unit; N/A, not available; NS, not significant.

[a] ICU and non-ICU study subjects;

[b] adjusted for entry respiratory score.