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Review

Principal findings of systematic reviews for the management of acute bronchiolitis in children

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EDUCATIONAL AIMS

- Several SRCTs on management of acute bronchiolitis in children have been published, making reading all of them a time-consuming process for busy physicians.
- After review of 20 SRCTs, we conclude that epinephrine (outpatients) and nebulized 3% saline (inpatients); and exogenous surfactant in ventilated children showed some small benefit only in short-term outcomes.
- Therefore it is still difficult to prepare a well-established and accepted guideline for the treatment of acute bronchiolitis due to few apparent clinically important improvements.

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SUMMARY

Bronchiolitis is the most common cause of hospitalization among infants during the first 12 months of life, with high direct and indirect cost for health system and families. Different treatment approaches co-exist worldwide resulting in many drugs prescribed, without any proven benefit. Twenty systematic reviews of randomized clinical trials (SRCTs) on management of acute bronchiolitis in children were retrieved through 5 databases and their methodological quality was determined using an AMSTAR tool. Epinephrine showed impact only in short-term outcomes among outpatients (reduced admission at day 1 and improved the clinical score in the first 2 hours, compared to placebo) and inpatients (decreased length of stay (LOS) and improved saturation only in the first 2 hours, compared to nebulized salbutamol, but with high heterogeneity). Nebulized 3% saline among inpatients (but not in the emergency department setting) decreased hospital LOS. In small trials, exogenous surfactant among children may decrease the duration of mechanical ventilation and intensive care unit LOS and had favorable effects on oxygenation and CO2 elimination at 24 hrs. Although several SRCTs are currently available, only few treatments show clinically important improvements. Therefore, it is still difficult to prepare a well-established and accepted guideline for the treatment of acute bronchiolitis.

INTRODUCTION

Bronchiolitis is one of the most common and serious lower respiratory tract illnesses in infants, causing breathlessness, coughing and wheezing [1]. It is a major cause of morbidity and mortality in this age group and a leading cause of infant hospitalization (annual hospitalization rates of 17 per 1000 children under six months of age and 3 per 1000 children under five years of age), mostly in children without coexisting illnesses [2]. It has been associated with increasing morbidity and health costs during recent

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Abbreviations: AEs, adverse effects; AMSTAR, Assess Systematic Reviews; CPT, chest physiotherapy; ICU, intensive care unit; LOS, length of stay; MD, mean difference; OCS, oral corticosteroids; OR, odds ratio; RCT, randomized clinical trials; RR, risk ratio; SAE, severe adverse effects; SRCTs, systematic reviews of randomized clinical trials; SMD, standardized mean differences; WMD, weighted mean differences.

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decades [1–4]. Most cases have a viral etiology, with respiratory syncytial virus (RSV) being the commonest virus isolated [5].

Supportive therapy, in the form of supplemental oxygen, fluid therapy, and respiratory support, remains the mainstay of treatment, proposed in several guidelines [6–10]. However; other therapies (e.g. bronchodilators, hypertonic saline, corticosteroids, antiviral, immunotherapy, chest physiotherapy, heliox, antibacterial agents, etc.) have been tested in randomized clinical trials (RCTs) and are still somewhat controversial. Several systematic reviews of those randomized clinical trials (SRCTs) have been published, making reading all of them a time-consuming process for busy physicians dealing with children with bronchiolitis. Therefore, it would be useful for most readers to have a summary of all this evidence in one manuscript.

The aim of this article was to summarize the principal findings of these published SRCTs on management of acute bronchiolitis in children.

METHODS

We identified published studies from MEDLINE, EMBASE, CINAHL, SCOPUS, and the Cochrane Database of Systematic Reviews (CDSR) databases up to June 2014, using the terms: (“Bronchiolitis” [Mesh] OR “Bronchiolitis, Viral” [Mesh]) OR “Bronchiolitis, Viral/therapy” [Mesh], filtered by “Meta-Analysis”. Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet the following criteria: systematic review of randomized clinical trials (SRCTs) (with or without meta-analysis) without language restriction (only the latest version was considered). Studies of safety/security, or prevention management, or cost-efficacy, or non-pharmacological treatment were excluded.

Data extraction and Assessment of Risk of Bias:

Titles, abstracts, and citations were independently analyzed by the two authors (JCR and CRM). From the full text, they independently evaluated all the studies for inclusion. After obtaining full reports about potentially relevant trials, they assessed eligibility. The methodological quality of the systematic reviews selected was assessed using the AMSTAR (Assess Systematic Reviews) tool [11]. Disagreements were discussed and resolved by consensus.

RESULTS

Fifty studies were retrieved from databases. Among those 30 were excluded (21 were abstract, only reviews, letters or expert opinions; 5 were non RCTs or post-hoc analysis; and 4 were duplicated SRCTs) and 20 were included: 4 were related to bronchodilators (one to epinephrine, and three to others mainly nebulized albuterol or salbutamol), 3 to corticosteroids, 2 to oxygen administration, 2 to antibiotics, and one to each of the following therapies: combined (bronchodilators and corticosteroids), hypertonic saline, surfactant, chest therapy, heliox, ribavirin, DNAase, immunoglobulin, and intensive care unit (ICU) management (Figure 1).

Their methodological qualification, using the AMSTAR tool (total score 11 points) showed that 3 SRCTs scored 11 points, 6 scored 10, 6 scored 9, 2 scored 8, 2 scored 7, and 1 scored 6 (Table 1).

Table 1
Quality evaluation of the 20 systematic reviews includes by AMSTAR tool [11].

Ref./AMSTARs Questions	1	2	3	4	5	6	7	8	9	10	11
Hartling L 2011	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Gadomski AM 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Flores G 1997	Y	N	N	Y	N	Y	Y	Y	Y	N	N
Kellner JD 1996	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N
Hartling L 2011b	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N
Zhang L 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Fernandes RM 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Garrison MM 2000	Y	Y	Y	N	Y	Y	N	N	Y	Y	N
Blom DJM 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Jat KR 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Roqué i Figuls M 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	CA
Umoren R 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Beggs S 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	CA
Liet JM 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ventre K 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Fuller HL 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	CA
Enriquez A 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
McCallum GB 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Spurling GKP 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	CA
Davison C 2004	Y	Y	N	Y	Y	Y	Y	N	Y	N	N

AMSTAR: Asses Systematic Reviews; Ref. = reference; Y = yes; N = no; CA = cannot answer; NA = not applicable.
AMSTARs Questions: 1. Was an “a priori” design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest included?

Bronchodilators

Epinephrine

Hartling et al. [12] examined the efficacy and safety of epinephrine in patients < 2 years of age (RCT = 19, n = 2256, up to 2010). Epinephrine vs. a placebo among outpatients showed a significant reduction in admission at day 1 (RR = 0.67, 95%CI [0.50 to 0.89], p = 0.0065, I^2 = 0%) but not at a day 7 post-emergency department (ED) visit; and there was no difference in the length of stay (LOS) for inpatients. Epinephrine significantly improved the clinical score at 1 and 2 hours (SMD = -0.40, 95%CI [-0.058 to -0.23], p < 0.0001, I^2 = 28%; and SMD = -0.73, 95%CI [-1.13 to -0.33], p < 0.0001, I^2 = 0%) compared to a placebo for outpatients. Epinephrine vs. nebulized salbutamol showed no differences among outpatients for admissions at day 1 or 7. However, inpatients receiving epinephrine had a significantly shorter LOS compared to nebulized salbutamol (MD = -0.28, 95% CI [-0.46 to -0.09], p = 0.0031, I^2 = 0%), improved clinical score at 60 and 120 min (SMD = 0.79, 95%CI [-1.45 to -0.13, p = 0.018, I^2 = 79%; and SMD = 0.52, 95%CI [0.86 to 0.18], p = 0.0025, respectively), and improved oxygen saturation (SpO_2) at 60 min (MD = 1.32, 95%CI [0.51 to 2.12], p = 0.0013, I^2 = 0%). One large RCT (n = 399) showed a significantly shorter admission rate at day 7 (RR = 0.65, 95%CI [0.44 to 0.95], p = 0.027, NNT = 11, 95% CI [7 to 76]) and improved clinical score (SMD = -0.34, 95%CI [-0.54 to -0.14, p = 0.0008) for epinephrine and steroid combined vs. placebo in outpatients. No important adverse effects (AEs) were described using epinephrine.

Albuterol and Others

Gadomski & Scribani [13] assessed the effects of bronchodilators (mainly nebulized albuterol) vs. placebo in infants; 30 RCTs (n = 1992, up to 2014) were included. In 11 inpatient RCTs and in 10 outpatient RCTs, the SpO_2 (primary outcome) did not improve with bronchodilators. The use of bronchodilators did not reduce the rate of hospitalization for outpatients, nor reduce the duration of hospitalization for inpatients. Among 8 inpatient RCTs there were no changes in clinical scores with bronchodilators. In 9 outpatient RCTs, the average clinical score decreased slightly with bronchodilators (SMD = -0.42, 95%CI [-0.79 to -0.06],

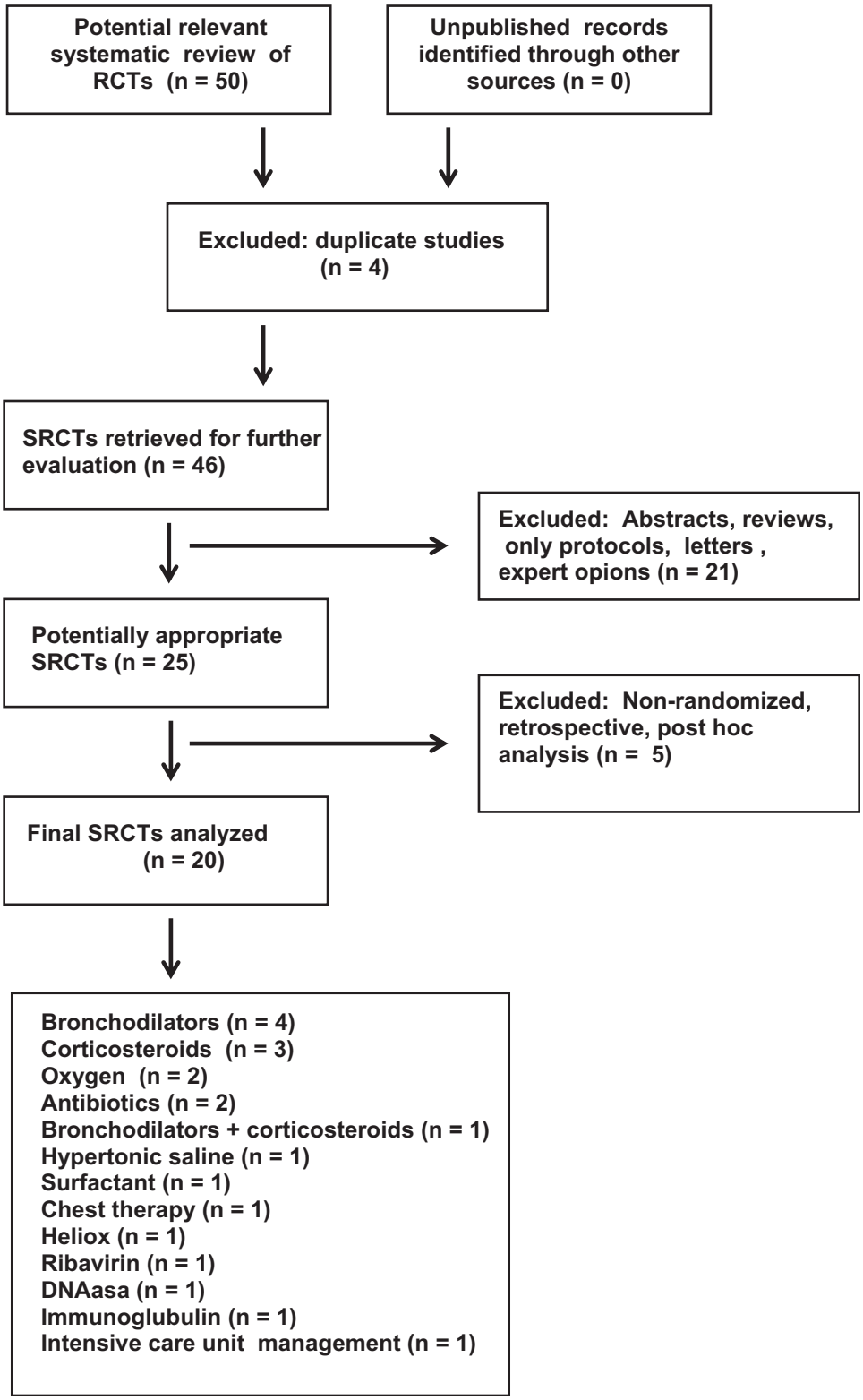

Figure 1. Flowchart for identification of usable systematic reviews of randomized clinical trials (SRCTs).

p = 0.00001, I^2 = 81%), a statistically significant finding of questionable clinical importance. Including only studies at low risk of bias showed little impact on the overall effect size of average clinical score (SMD = -0.22, 95%CI [-0.41 to -0.03], p = 0.025, I^2 = 37%). Sub-analysis limited to nebulized albuterol or salbutamol among outpatients (n = 9) showed no effect on oxygen saturation, average clinical score or hospital admission after treatment. AEs using bronchodilators included tachycardia, oxygen saturation and tremors.

Flores & Horwitz [14] (8 RCTs, n = 333 infants, up to 1995) evaluated the efficacy of Beta-2 agonists. Among inpatients, results of the three RCTs (2 with nebulized albuterol and 1 with nebulized fenoterol) that met the inclusion criteria were contradictory and meta-analysis was not possible due to the great variability in

outcomes, timing of outcome, and drug regimens. Among outpatients (5RCTs compared nebulized albuterol with placebo); albuterol had no impact on the hospitalization rate. Likewise, albuterol had a statistically significant but clinically insignificant impact on SpO_2 and heart rate.

Kellner et al. [15] (8 RCTs for primary analysis, up to 1995) determined the efficacy of bronchodilators (mainly nebulized albuterol) versus placebo in infants. Bronchodilators significantly improved the average clinical score and the clinical score measured as dichotomous variables (4 RCTs, SMD = -0.32, 95% CI [-0.54 to -0.11], $p < 0.01$, Breslow-day test of homogenicity p = 0.53; and 3 RCTs, RR = 0.76, 95% CI [0.60 to 0.95], p = 0.02, Breslow-day test of homogenicity p = 0.96, respectively). However, bronchodilators did not significantly reduce the hospitalization rate.

Bronchodilator with Corticosteroids

Hartling et al. [16] (48 RCTs, 4897 infants, up to 2009) compared a nebulized bronchodilator or steroid, alone or combined, with a placebo or another intervention (another bronchodilator, another steroid, standard care). Among outpatients, a significant reduction in admission rates to the ED (day 1) for adrenaline compared with a placebo was reported (4 RCTs, RR = 0.67, 95% CI [0.50 to 0.89], NNT = 15, 95% CI [10 to 45], $I^2 = 0\%$). Among inpatients, a shorter LOS for adrenaline compared with nebulized salbutamol (4 RCTs, MD = -0.28 days, 95% CI [-0.46 to -0.09], $I^2 = 0\%$) was reported.

Hypertonic Saline

Zhang et al. [17] assessed the effects of nebulized hypertonic ($\geq$ 3%) saline solution alone or in conjunction with bronchodilators vs. nebulized 0.9% saline in children up to 24 months of age with mild to moderate bronchiolitis. Eleven RCTs up to 2013 were analyzed (500 inpatients in 6 RCTs; 65 outpatients in 1 RCT; and 525 ED-patients in 4 RCTs). All but one of the RCTs included were of high quality with a low risk of bias. A total of 560 patients received hypertonic saline (3% saline in 503, and 5% saline in 57patients). Inpatients and outpatients (but not those patients in the ED setting) treated with nebulized 3% saline, compared to those treated with nebulized 0.9% saline, had a significantly shorter mean hospital LOS-primary outcome- (MD:-1.15 days, 95%CI [-1.49 to -0.82], $p < 0.00001$, $I^2 = 30\%$) and lower post-inhalation clinical score during the first 3 days of treatment (day 1: MD = -0.88, 95%CI [-1.36 to -0.39], p = 0.0004, $I^2 = 78\%$; day 2: MD = -1.32, 95%CI [-2.00 to -0.64], p = 0.001, $I^2 = 89\%$; day 3: MD = -1.51, 95%CI [-1.18 to -1.14], $p < 0.0001$, $I^2 = 58\%$). Four ED-based RCTs did not show any significant short-term effects (30 to 120 minutes) of up three doses of nebulized 3% saline for a decreased rate of hospitalization (primary outcome), improved clinical score, and SpO_2. Further large RCTs with multiple doses of hypertonic saline over a longer period of time are still needed for evaluating the effect of nebulized hypertonic saline in improving clinical score and avoid hospitalization among patients seen in ED. No significant AEs related to hypertonic saline were reported.

Corticosteroids

Recently, Fernandez et al. [18] (17 RCTs, n = 2596 infants, up to 2013) compared the efficacy and safety of systemic and inhaled glucocorticoids (ICS) versus a placebo or another intervention. Among outpatients, glucocorticoids did not significantly reduce outpatient admissions at days 1 and 7 when compared to a placebo. Likewise, there were no significant differences between groups at any point in time for clinical scores. Among inpatients, there was no benefit for the LOS for inpatients; however, there were significant differences between groups, favoring glucocorticoids for clinical scores at earlier points in time: three to six hours (1 RCT, SMD = -1.03, 95% CI [-1.87 to -0.19, p = 0.02), and 6 to 12 hours after admission (3 RCTs, SMD = -0.62, 95% CI [-1.00 to -0.23], p = 0.002, $I^2 = 0\%$).

Previously, Garrison et al. [19] (6 RCTs, 347 infants hospitalized with bronchiolitis, up to 1999) compared the efficacy of systemic corticosteroids vs. a placebo. Compared to infants who received a placebo, those who received corticosteroids had a significantly lower pooled mean LOS and duration of symptoms combined (6 RCTs, MD = -0.43 days, 95% CI [-0.81 to -0.05], p = 0.03). Likewise, the pooled estimate of the differences in clinical scores at 24 hours after the initial treatment was significantly lower among those who received steroids compared with those who received the placebo (3 RCTs, SMD = -1.60, 95% CI [-1.92 to -1.28]). However, analyzing only studies for which randomization methods were clearly identified, studies which measured only LOS, and only studies which clearly excluded patients with previous wheezing, LOS, and duration of symptoms combined did not show significant differences between corticosteroids and a placebo.

Blom et al. [20] evaluated the effect of ICS, started during the acute phase of bronchiolitis, for the prevention of post-bronchiolitis wheezing. Five RCTs (n = 374 inpatients) up to 2006 were included. No effect of ICS for the prevention of wheezing through daily records or general practitioner diagnosed (primary outcome), hospital re-admission or use of corticosteroids or bronchodilators could be demonstrated. The duration of therapy, length of follow up, or causative agent (RSV or not) did not influence the pooled effect. No AEs were reported.

Surfactant

Recently, Jat & Chawla [21] (3 small RCTs, n = 79, up to 2012) evaluated the efficacy of exogenous surfactant administration compared to a placebo, no intervention, or standard care for reducing mortality and the duration of ventilation in infants and children with bronchiolitis requiring mechanical ventilation. The duration of the mechanical ventilation (primary outcome) was not different between the groups, but the duration of the ICU stay was shorter for the surfactant group compared to the control group (MD = -3.31, 95%CI [-6.38 to -0.25 days], p = 0.03, $I^2 = 93\%$). After excluding one trial which produced significant heterogenicity, the duration of mechanical ventilation and duration of ICU stay were significantly lower in the surfactant group compared to the control group (MD = -28.99, 95%CI [-40.10 to -17.8 hrs.]; and MD = -1.81, 95%CI [-2.42 to -1.19 days], respectively). The use of a surfactant had favorable effects on oxygenation (PO_2/FiO_2 at 24 hrs: MD = 109.64, 95%CI [63.29 to 155.99], $p < 0.00001$, $I^2 = 96\%$) and CO_2 elimination at 24 hrs. (MD = -7.90, 95%CI [-9.42 to -6.38 mmHg], $p < 0.00001$, $I^2 = 0\%$). No AEs or complications were observed with the use of surfactant.

Chest Physiotherapy

Recently, Roqué i Figuls et al. [22] determined the efficacy of chest physiotherapy (CPT) in infants (<24 months of age) as a main objective, and the efficacy of different techniques of CPT (i.e. vibration & percussion and passive forced exhalation) as secondary objective. Nine RCTs, (n = 891 inpatients) were included, comparing CPT vs. no intervention; five trials (n = 246) evaluated vibration & percussion techniques and four trials (n = 645) evaluated passive expiratory techniques. No pooling of data was possible for primary (respiratory parameters and improvement in severity of diseases) and secondary outcomes (hospital LOS, duration of oxygen supplementation and use of bronchodilators and steroids). No significant differences in the severity of diseases were observed (2 RCTs, n = 867), and results were negative for both types of CPT. No differences between groups for respiratory parameters, oxygen

requirements, LOS, or SAEs were observed. In a large trial (n = 496) significantly higher transient AEs were observed (vomiting: RR = 5.4, 95% CI [1.6 to 18.4], p = 0.002; and respiratory instability: RR = 10.2, 95% CI [1.3 to 78.8], p = 0.005) with the use of CPT (increased exhalation technique).

Oxygen Administration

Umoren et al. [23] (1 RCT, 156 participants, up to 2010) evaluated the effect of steam inhalation or humidified oxygen for relieving respiratory distress and evaluated adverse events in children up to three years old. The results showed that compared to mist in a tent, the group of children on nebulized salbutamol was associated with a significant reduction in respiratory distress symptom score at 30 and 60 minutes (1 RCT, MD = 3.80, 95% CI [2.51 to 5.09], $p < 0.001$; and MD = 4.40, 95% CI [3.35 to 5.45], $p < 0.001$, respectively). When comparing children on mist in a tent vs. nebulized saline, the mean differences in respiratory distress symptom scores at 30 and at 60 minutes were not statistically significant.

Recently, Beggs et al. [24] assessed the effects of heated, humidified, high-flow nasal cannula (HFNC) therapy compared with conventional respiratory support in the treatment of infants. Only one RCT (n = 19 inpatients, up to 2013) compared HFNC with oxygen delivery via a head box. Therefore, no meta-analysis can be performed. The SpO_2 was higher for the HFNC group at 8 hrs. (100 vs. 96%, p = 0.04) and at 12 hrs. (99 vs. 95%, p = 0.04), but similar at 24 hrs. There was no clear evidence of a difference in total duration of oxygen therapy, time to discharge or total LOS between groups. No AEs were reported.

Heliox

Liet et al. [25] assessed heliox in addition to standard medical care for acute bronchiolitis in infants with respiratory distress caused by RSV and requiring ICU admission (4 RCTs, n = 84, up to 2009). Infants treated with heliox inhalation had a lower clinical respiratory score in the first hour after starting treatment compared to those treated with air or oxygen inhalation (MD = -1.15, 95%CI [-1.98 to -.033], p = 0.006; $I^2 = 92\%$). However, there were no clinically significant reductions in the rate of intubation, the need for mechanical ventilation (primary outcome), oxygen index, or the LOS in the ICU. No AEs related to heliox inhalation were reported.

Ribavirin

Ventre & Randolph [26] assessed the efficacy of aerosolized ribavirin for infants with LRTI due to RSV. Twelve RCTs (n = 227) up to 2006 were included, but due to lack sufficient power to provide reliable estimates of the effects, no meta-analysis was performed. In four RCTs (n = 158), mortality with ribavirin was lower than with a placebo, although significance was not reached. In three RCTs (n = 116), the probability of respiratory deterioration with ribavirin was lower than with a placebo, but significance was not reached. In three RCTS (n = 104 ventilated infants), the group of children on ribavirin showed a reduction in the days of mechanical ventilation (MD = -1.8, 95%CI [-3.4 to -0.2]) and a tendency for less hospitalization than those on a placebo. No differences in long-term pulmonary function or in incidence of recurrent wheezing following RSV infection were associated with the use of ribavirin.

Immunoglobulin

Fuller & Del Mar [27] assessed the efficacy of adding human or humanized immunoglobulin therapy vs. placebo to supportive therapy in infants hospitalized with RSV (bronchiolitis, pneumonia, or lower respiratory tract infection). The primary outcomes were mortality, LOS, length of ventilation, and oxygen dependence. Four RCTs (n = 311) up to 2006 were selected, but due to wide heterogeneity of the outcomes assessed across the studies, it was not possible to undertake a meta-analysis. In 2 RCTs (n = 163), children on RSV-Ig showed less LOS in hospitalized days than on a placebo (MD = -0.93, 95%CI [-1.15 to -0.70], $p < 0.0001$, $I^2 = 11\%$).

DNAse

Enriquez et al. [28] (3 RCTs, 333 children, up to 2012) evaluated the efficacy of nebulized rhDNase vs. placebo for the severity and duration of bronchiolitis in inpatient < 24 months of age. There were significant differences between groups, favoring the control group for LOS (3 RCTs, MD = 0.50 days, 95% CI [0.10 to 0.90], p = 0.01, $I^2 = 0\%$) and almost significant differences, also favoring the control group, in clinical score improvement (2 RCTs, SMD = -0.24, 95% CI [-0.50 to 0.01], p = 0.06, $I^2 = 51\%$).

Antibiotics

McCallum et al. [29] (1 RCT, 30 infants, up to 2012) determined the efficacy of oral clarithromycin compared to a control (no treatment or placebo) for 3 weeks for persistent respiratory symptoms following acute RSV bronchiolitis. No significant difference between groups was shown for the proportion of children who had persistent symptoms or re-hospitalization within six months.

Spurling et al. [30] evaluated the effectiveness of antibiotics for bronchiolitis in children < 2 years of age, up to 2010. Five RCTs (n = 543) were included. The primary outcomes included time to resolution of signs or symptoms. One RCT (n = 52) found no significant differences between the ampicillin and placebo for length of illness. Two RCTs (n = 267) providing adequate data for hospital LOS showed no difference between macrolides and control. Two RCTs (n = 399) randomized children for IV ampicillin, oral erythromycin, and control, and found no differences for most symptom measurements (eg. wheeze, shortness of breath, oxygen saturation, not smiling socially, fever, cough).

Treatment in Pediatric ICU

Davison et al. [31] (16 RCTs, 523 infants, up to 2003) evaluated the strength of the evidence supporting the use of any therapy for bronchiolitis that included children in the ICU. A meta-analysis of the three surfactant studies showed a strong trend toward a decrease in duration of mechanical ventilation (3 RCTs, WMD = -2.58, 95% CI [-5.34 to 0.18], p = 0.07), and a significant effect on ICU-LOS, favoring surfactant therapy (3 RCTs, WMD = -3.30, 95% CI [-6.38 to -0.23], p = 0.04). A meta-analysis of the studies that compared systemic corticosteroid vs. placebo showed no significant effect, either in the duration of mechanical ventilation or in the hospital LOS.

DISCUSSION

As a consequence of this extensive review of 20 SRCTs for acute bronchiolitis treatment (Table 2), it is still difficult to prepare a well-established and accepted guideline for the treatment of acute bronchiolitis. Epinephrine showed impact only in short-term outcomes among outpatients (reduced admission at day 1 and improved the clinical score only in the first 2 hours, compared to placebo) and inpatients (decreased LOS and improved saturation only in the first 2 hours, compared to nebulized salbutamol, but with high heterogeneity among studies). Nebulized 3% saline among inpatients (but not in the ED setting) decreased hospital LOS. In small trials, administration of exogenous surfactant among children may decrease the duration of mechanical ventilation

Table 2
Principal findings of the 20 SRCTs included according to setting.

	Inpatients	Outpatients
Flores G 1997		
Beta-2 agonist vs. placebo		
- Oxygen saturation (%)		1.2; 95% CI (0.8 to 1.6)[1]
- Heart rate (beats per minute)		1.4; 95% CI (0.8 to 2.0)[1]
Garrison MM 2000		
Systemic corticosteroids vs. placebo		
- Length of stay	-0.43 days, 95% CI (-0.81 to -0.05), p = 0.03[1]	
- Duration of symptoms	-0.43 days, 95% CI (-0.81 to -0.05), p = 0.03[1]	
- Clinical scores	-1.60, 95% CI (-1.92 to -1.28)[2]	
Hartling L 2003		
Epinephrine vs. placebo		
- Clinical score at 60 min	-0.52; 95% CI, (-1.00 to -0.03)[2]	-0.81; 95% CI, (-1.56 to -0.07)[2]
- Oxygen saturation at 30 min		2.79; 95% CI, (1.50 to 4.08)[3]
- Respiratory rate at 30 min		-4.54; 95% CI, (-8.89 to -0.19)[3]
- Improvement		25.06; 95% CI, (4.95 to 126.91)[4]
Epinephrine vs. albuterol sulfate		
- Oxygen saturation at 60 min		1.91; 95% CI, (0.38 to 3.44)[3]
- Heart rate at 90 min		-14.00; 95% CI (-22.95 to -5.05)[3]
- Respiratory rate at 60 min		-7.76; 95% CI (-11.35 to -4.17)[3]
- Improvement		4.51; 95%CI (1.93 to 10.53)[4]
- Respiratory rate at 30 min	-5.12; 95%. CI (-6.83 to -3.41)[3]	
Davison C 2004		
Surfactant vs. placebo		
- Duration of mechanical ventilation	-2.58 days; 95% CI (-5.34 to 0.18), p = 0.07[3]	
- Intensive care units days	-3.3 days; 95% CI (-6.38 to -0.23), p = 0.04[3]	
Systemic corticosteroids vs. placebo		
- Duration of mechanical ventilation	-0.62 days; 95% CI (-2.78 to 1.53), p = 0.57[3]	
Ribavirin vs. placebo		
- Ventilator days	-1.2 days; 95% CI (-0.2 to -3.4), p = 0.03[3]	
Hartling L 2011		
Epinephrine vs. placebo		
- Admissions on day 1		0.67; 95% CI (0.50 to 0.89), p = 0.006[5]
- Clinical score at 60 min		-0.40; 95% CI (-0.058 to -0.23), p < 0.0001[2]
- Clinical score at 120 min		-0.73, 95% CI (-1.13 to -0.33), p < 0.0001[2]
Epinephrine + dexamethasone vs. placebo		
- Admissions on day 7		0.65; 95% CI (0.44 to 0.95), p = 0.027[5]
- Clinical score		-0.34, 95% CI (-0.54 to -0.14), p = 0.0008[2]
Epinephrine vs. salbutamol		
- Length of stay	-0.28 days; 95% CI (-0.46 to -0.09), p = 0.003[1]	
- Clinical score at 60 min	0.79, 95% CI (-1.45 to -0.13), p = 0.018[2]	
- Clinical score at 120 min	0.52, 95% CI (0.86 to 0.18), p = 0.0025[2]	
- Oxygen saturation at 60 min	1.32, 95% CI (0.51 to 2.12), p = 0.0013[1]	
Umoren R 2011		
Steam inhalation vs. nebulised salbutamol		
- Reduction respiratory distress score 30 m	3.80; 95% CI (2.51 to 5.09), p < 0.001[1]	
- Reduction respiratory distress score 60 m	4.40; 95% CI (3.35 to 5.45), p < 0.001[1]	
Enriquez A 2012		
Nebulised rhDNase vs. placebo		
- Length of stay	0.50 days; 95% CI (0.10 to 0.90), p = 0.01[1]	
- Clinical score improvement	-0.24; 95% CI (-0.50 to 0.01), p = 0.06[2]	
McCallum GB, 2012		
Antibiotics vs. placebo		
- Persistence of symptoms	0.20; 95% CI (0.02 to 2.02)[4]	
- Re-hospitalization within six months	0.11; 95% CI (0.01 to 1.29), p = 0.08[4]	
Fernandes RM 2013		
Glucocorticoids vs. placebo		
- Admissions by day 1		0.92; 95% CI (0.78 to 1.08), p = 0.30[5]
- Admissions by day 7		0.86; 95% CI (0.7 to 1.06), p = 0.17[5]
- Length of stay	-0.18 days; 95% CI (-0.39 to 0.04), p = 0.12[1]	
- Clinical scores 3 to 6 h after admission	-1.03; 95% CI (-1.87 to -0.19), p = 0.02[2]	
- Clinical scores 6 to 12 h after admission	-0.62; 95% CI (-1.00 to -0.23), p = 0.002[2]	
Epinephrine + dexamethasone vs. placebo		
- Admissions on day 7		0.65; 95% CI (0.44 to 0.95), p = 0.027[5]
Spurling GKP 2011		
Antibiotics vs. placebo		
- Length of hospital stay	0.34; 95% CI (-0.71 to 1.38), p = 0.53[1]	

Table 2 (*Continued*)

	Inpatients	Outpatients
Gadomski AM 2014		
Bronchodilators (no epinephrine) vs. placebo		
- Oxygen saturation	-0.62; 95%CI (-1.40 to 0.16), p = 0.12[1]	-0.25; 95% CI (-0.61 to 0.11), p = 0.17[1]
- Rate of hospitalization		0.75; 95% CI (0.46 to 1.21), p = 0.24[4]
- Duration of hospitalization	0.06 days; 95% CI (0.27 to 0.39), p = 0.70[1]	
- Clinical score	-0.14; 95% CI (-0.41, 0.12),p = 0.29[1]	-0.42; 95% CI(-0.79 to -0.06),p = 0.024[1]
Zhang L 2013		
Nebulized hypertonic (≥ 3%) saline solution vs. nebulized 0.9% saline		
- Length of hospital stay	-1.15 days; 95% CI (-1.49 to -0.82), p < 0.001[1]	
- Rate of hospitalization		0.63; 95% CI (0.37 to 1.08), p = 0.08[5]
- Clinical severity score at day 1	-0.99; 95% CI (-1.48 to -0.50), p < 0.001[1]	-1.28; 95% CI (-1.92 to -0.64), p < 0.001[1]
- Clinical severity score at day 2	-1.45; 95% CI (-2.06 to -0.85), p < 0.001[1]	-2.00; 95% CI (-2.93 to -1.07), p < 0.001[1]
- Clinical severity score at day 3	-1.44; 95% CI (-1.78 to -1.10), p < 0.001[1]	-2.64; 95% CI (-3.85 to -1.43), p < 0.001[1]
Liet JM 2010		
Heliox inhalation vs. air or oxygen inhalation		
- Clinical respiratory score in the first hour	-1.15; 95% CI (-1.98 to -0.33), p = 0.006[1]	
- Rate of intubation	1.38; 95% CI (0.41 to 4.56), p = 0.60[5]	
- Need for mechanical ventilation	1.11; 95% CI (0.36 to 3.38), p = 0.86[5]	
- Length of stay in an Intensive Care Unit	-0.15 days, 95% CI (-0.92 to 0.61), p = 0.69[1]	
Fuller HL 2006		
Immunoglobulin therapy vs. placebo		
- Length of stay in hospital in days	-0.93; 95% CI (-1.15 to -0.71), p < 0.001[1]	
Ventre K 2007		
Aerosolized ribavirin vs. placebo		
- Mortality	0.58; 95% CI (0.18 to 1.85)[4]	
- Probability of respiratory deterioration	0.37; 9% CI (0.12 to 1.18)[4]	
- Days of mechanical ventilation	1.8 days; 95% CI (-3.4 to -0.2)[1]	
Jat KR 2012		
Exogenous surfactant vs. placebo, no intervention or standard care		
- Duration of mechanical ventilation	-63.04 hours; 95% CI (-130.43 to 4.35), p = 0.067[1]	
- Duration of Intensive Care Unit stay	-3.31 days; 95% CI (-6.38 to -0.25), p = 0.03[1]	
- PO_2/FIO_2 ratio at 24 hours	109.64; 95% CI (63.29 to 155.99), p < 0.001[1]	
- pCO_2 at 24 hours (mmHg)	-7.90; 95% CI (-9.42 to -6.38), p < 0.001[1]	
Kellner JD 1996		
Bronchodilators vs. placebo		
- Clinical score	-0.32; 95% CI (-0.54 to -0.11), p < 0.01[2]	
- Improvement in clinical score	0.76; 95% CI (0.60 to 0.95), p = 0.02[5]	
- Hospitalization rate	0.76; 95% CI (0.45 to 1.27), p = 0.29[5]	
Roqué I 2012		
Chest physiotherapy vs. no intervention or another type of physiotherapy	No differences between groups in the severity of the disease, respiratory parameters, length of hospital stay, or oxygen requirements were observed. However, no pooling of data was possible for these outcomes	
Beggs S 2014		
Heated, humidified, high-flow nasal cannula (HFNC) vs. conventional respiratory support	In the only study that compared HFNC to conventional respiratory support, the oxygen saturation was higher in the HFNC group at 8 and 12, but no at 24 hours. No metha analysis could be performed.	
Bloom DJM 2007		
Inhaled corticosteroids vs. placebo		
- Prevention of post-bronchiolitic wheezing	1.15; 95% CI (0.80 to 1.65), p = 0.46[5]	
- Hospital re-admissions	1.14; 95% CI (0.76 to 1.72), p = 0.53[5]	
- Use of corticosteroids	0.85; 96% CI (0.64 to 1.12), p = 0.25[5]	
- Use of bronchodilators	0.95; 95% CI (0.76 to 1.17), p = 0.61[5]	

1. Mean difference; 2. Standardized mean difference; 3. Weighted mean difference; 4. Odds ratio; 5. Relative risk.

and duration of ICU stay and had favorable effects on oxygenation and CO2 elimination at 24 hrs.

Even though the vast majority (85%) of the 20 SRCTs included in the present review had a high methodological qualification (AMSTAR: ≥8/11 points), it is important to consider that these SRCTs were constructed from RCTs. As we know, RCTs of acute bronchiolitis lack adequate outcomes standardization. As a result, our ability to examine and compare outcomes across RCTs and interpret evaluations of new and available therapeutic modalities for this disease on a scale larger than a single trial may be impaired. Also, it is relevant for future RCTs (that comparing any drug vs. placebo) to distinguish for a determinate outcome if the difference is clinically important or only statistically significant (i.e. the effect of albuterol on clinical score in outpatients) [13]. In that sense, it is better to use the minimal clinically important difference (MCID). However, MCD for clinical or laboratory parameters for the management of acute bronchiolitis has not been determined as yet; in contrast to those described for asthma management in

children [32]. Adequate outcome measures for the management of need to be discussed. Questions to consider include: Which clinical scores should be used? How validated are they? Which SaO_2 measurement is better to use: sporadic or continuous? When considering length of stay, is it better to use hours or days? Which parameters are appropriate for stopping treatment and discharging the patient? etc.

In 2006, the American Academy of Pediatrics (AAP) [1] published an evidence-based practice management guideline for bronchiolitis and recommended (B grade): to use inhaled bronchodilators only if there is a documented positive clinical response using an objective means of evaluation, not to use corticosteroid routinely and to use antibiotics only for children who have specific indications of the coexistence of a bacterial infection. Recently, two studies designed to determine the impact of this AAP guideline were published. The first study analyzed data on 130,262 inpatients from 41 pediatric hospitals demonstrated differences in rates of change before and after the guidelines with significant decrease in the use of corticosteroids and bronchodilators; the antibiotic use also decreased but did not reach significance [10]. McCulloh et al. [33] assessed changes in physician behavior before and after the guidelines, evaluating therapeutic interventions prior to and during hospitalization of 1,233 children with acute bronchiolitis. In the post-guidelines period, fewer children received a trial of racemic epinephrine or albuterol, physicians more often discontinued albuterol when it was documented as ineffective, and the use of corticosteroid in children without a history of reactive airway disease or asthma dropped. However, due to this modest change in physician behavior, the authors recommended additional training and education to reduce unnecessary interventions and healthcare resources use.

One way to implement recommendations is to use the high level of evidence available (e.g. SRCTs) for each modality of treatment. The review of these 20 SRCTs, (up to June 2014) showed that only epinephrine (for outpatients), nebulized 3% saline (for inpatients) and exogenous surfactant (small trials in ventilated children) had some small benefit mainly in short-term outcomes as was described previously. A 2014 AAP guideline [34] recommended: do not administer salbutamol nor epinephrine (evidence quality B, strong recommendation), nor systemic corticosteroids (evidence quality A, strong recommendation) for infants and children with a diagnosis of bronchiolitis. Consider administering nebulized hypertonic saline only for inpatients (evidence quality B, weak recommendation). However, a new large multicenter RCT [35] (n = 317 infants admitted to hospital with acute bronchiolitis requering oxygen therapy) reported no difference in time to being declared fit for discharge (primary outcome) nor to actual discharge (secondary outcome) comparing usual care alone therapy vs. nebulised 3% hypertonic saline administered 6-hourly.

Clinicians should carefully analyze various aspects of the SRCTs (inclusion and exclusion criteria, severity of the disease, dose and duration of interventions, subgroup and sensitivity analyses, and overall quality of the meta-analyses) before applying this knowledge to local practice and implementing these therapies on a regular basis for treating children with acute viral bronchiolitis. Another consideration for SRCTs is the assessment of heterogeneity among the RCTs included in the analysis. For tested homogeneity of outcome effect measurements between studies being meta-analyzed, most SRCTs used both the Chi^2 test for heterogeneity (Cochrane Q test) and the I^2 statistic ($P < 0.10$ for the former or an $I^2 > 40\%$ was deemed indicative of significant heterogeneity). If significant heterogeneity was present, a random-effects model was used to aggregate the outcome effect measurements; otherwise, a fixed-effect model was reported [36]. All of the 20 SRCTs included reported correctly the heterogeneity of the studies. However, as was many of the primary or secondary outcomes reported had high heterogeneity, precluding substantial recommendations for that particular treatment. Also, it is important to note that 6 out of 20 SRCTs were published more than 6 years ago.

CONCLUSION

A review of 20 SRCTs of acute bronchiolitis management found that among outpatients epinephrine, compared to placebo, reduced admission at day 1 and improved the clinical score only in the first 2 hours; and among inpatients, compared to nebulized salbutamol, epinephrine decreased LOS and improved saturation only in the first 2 hours; but no benefits in longer-term outcomes were observed. Nebulized 3% saline among inpatients (but not in the ED setting) decreased hospital LOS. In small trials, administration of exogenous surfactant among children may decrease the duration of mechanical ventilation and of ICU LOS and had favorable effects on oxygenation and CO2 elimination at 24 hrs. Although several SRCTs are currently available, only few treatments show clinically important improvements. Therefore, it is still difficult to prepare a well-established and accepted guideline for the treatment of acute bronchiolitis.

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FUTURE DIRECTIONS

More well designed RCTs on the management of bronchiolitis need to be done (mainly with adequate sample size and pre-established outcomes measurements).

CONFLICT OF INTERESTS

Dr. Castro-Rodriguez has participated as a lecturer, advisor, and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis. Dr. Rodriguez-Martinez has participated as a lecturer, advisor and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Merck Sharp & Dome, Novamed, and Takeda. Dr. Sossa-Briceño has no conflicts of interest to declare.

CONTRIBUTOR'S STATEMENTS

Jose A. Castro-Rodriguez: Dr. Castro-Rodriguez conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Carlos E. Rodriguez-Martinez: Dr. Rodriguez-Martinez carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Monica P. Sossa-Briceño: Dra. Sossa-Briceño critically reviewed and revised the manuscript, and approved the final manuscript as submitted approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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