aspen | LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Journal of Parenteral and Enteral Nutrition
Volume 42 Number 1
January 2018 186–195

DOI: 10.1002/jpen.1030
wileyonlinelibrary.com
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Network Meta-Analysis Comparing the Efficacy of Therapeutic Treatments for Bronchiolitis in Children

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Abstract

Background: This study aims to compare placebo (PBO) and 7 therapeutic regimens—namely, bronchodilator agents (BAs), hypertonic saline (HS), BA ± HS, corticosteroids (CS), epinephrine (EP), EP ± CS, and EP ± HS—to determine the optimal bronchiolitis treatment. *Methods:* We plotted networks using the curative outcome of several studies and specified the relations among the experiments by using mean difference, standardized mean difference, and corresponding 95% credible interval. The surface under the cumulative ranking curve (SUCRA) was used to separately rank each therapy on clinical severity score (CSS) and length of hospital stay (LHS). *Results:* This network meta-analysis included 40 articles from 1995 to 2016 concerning the treatment of bronchiolitis in children. All 7 therapeutic regimens displayed no significant difference to PBO with regard to CSS in our study. Among the 7 therapies, BA performed better than CS. As for LHS, EP and EP ± HS had an advantage over PBO. Moreover, EP and EP ± HS were also more efficient than BA. The SUCRA results showed that EP ± CS is most effective, and EP ± HS is second most effective with regard to CSS. With regard to LHS, EP ± HS ranked first, EP ± CS ranked second, and EP ranked third. *Conclusions:* We recommend EP ± CS and EP ± HS as the first choice for bronchiolitis treatment in children because of their outstanding performance with regard to CSS and LHS. (*JPEN J Parenter Enteral Nutr.* 2018;42:186–195)

Keywords

children; bronchiolitis; treatment efficacy; network meta-analysis

Clinical Relevancy Statement

This study compared placebo and 7 therapeutic regimens, and we recommend epinephrine ± corticosteroids and epinephrine ± hypertonic saline as the first choice for bronchiolitis treatment in children because of their outstanding performance with regard to clinical severity score and length of hospital stay.

Introduction

Infants and children are most susceptible to bronchiolitis.[1] Almost 3 million people are infected with this disease every year,[2] and most cases occur in spring and autumn. Low to moderate fever, coughing, running nose, wheezing, and sneezing are the usual symptoms. Respiratory syncytial virus (RSV) causes 50%–80% of bronchiolitis cases and is believed to be its primary cause.[3] In recent years, scientists found out that other viruses such as human rhinoviruses (HRV), coronaviruses, and bocavirus may also cause bronchiolitis.[4] Therefore, it is of great importance to determine the optimal therapeutic regimen.

Based on our investigation, most bronchiolitis regiments are controversial, and it is hard to draw a conclusive optimal treatment. Dexamethasone is considered efficacious because of significantly reduced hospitalization days and other clinical benefits.[5] However, there is also contradictory evidence.[6] One study proposed that 3% hypertonic saline (HS) ± epinephrine (EP) is more efficient than 0.9% normal saline ± EP in decreasing the length of hospitalization and other symptoms.[7] However, in another article, there was no significant discrepancy between the 2 treatments.[8] Through a 7-day observation, 1 study said EP ± dexamethasone lacked efficacy.[9] However, another article said this combination was effective and even performed better than bronchodilator agents (BAs) in reducing bronchiolitis

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Financial disclosure: None declared.

Conflicts of interest: None declared.

Received for publication June 8, 2017; accepted for publication June 30, 2017.

This article originally appeared online on November 3, 2017.

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attacks.[10] In reference to BA, salbutamol is also considered an effective BA for infants with mild bronchiolitis. However, not all agreed with this suggestion.[11] Moreover, the combination of HS and BA was more effective than normal saline ± BA in decreasing symptoms,[12] but no difference was found in the clinical bronchiolitis severity score (CBSS).[13] Researchers have proved that EP is more efficient and safer than salbutamol.[14] Another study supported EP's efficacy but could not reach a conclusion on which agent was safer.[15] It seems that EP is more reliable than salbutamol. Some scientists found that HS is better at reducing admission days than 0.9% normal saline.[16] However, another article suggested that the application of EP, HS, salbutamol, and normal saline showed no significant discrepancy in their efficacy in treating infants with mild bronchiolitis.[17] In summary, there is no consensus in current research; therefore, more trials and analysis are required.

Several meta-analyses (MAs) have been conducted to assess the efficacy and toxicity of different therapeutic regimens. These analyzed most mainstream treatments, including BA,[18-20] HS,[21] corticosteroids (CS),[22] EP,[23] antibiotics,[24] and montelukast.[25] However, MAs are pairwise comparisons and cannot display a network of multiple therapies. Therefore, due to a lack of direct evidence, we have not been able to evaluate the superiority and inferiority of other therapies. A new research method should be introduced to solve this problem. Network meta-analysis (NMA) based on a Bayesian framework could compensate for the disadvantages of a traditional MA. NMA can make the best use of both direct and indirect evidence. In fact, this statistical approach has been applied for pharmaceutical selection and assessments more and more frequently.[24]

This NMA aimed to compare the efficacy of 7 therapeutic regimens—BA, HS, CS, EP, BA ± HS, EP ± CS, and EP ± HS—and the placebo (PBO). We used the clinical severity score (CSS) and length of hospital stay (LHS) as the assessment criteria. In summary, this article synthesizes and ranks 8 interventions in terms of efficacy and finally proposes the optimal drug selection for the treatment of bronchiolitis in children.

Methods and Materials

Literature Search

The Embase, PubMed, and China National Knowledge Internet (CNKI) databases were searched for related publications. The cutoff date was August 26, 2016, and there were not any language restrictions. Our searching strategy included the use of keywords and correlated expressions such as *bronchiolitis*, *bronchodilator agents*, *hypertonic saline*, *epinephrine*, *corticosteroids*, *leukotriene inhibitors*, *antibacterial agents*, and *randomized controlled trial*. To avoid missing any relative studies, we checked the cited reference list of each selected articles. Two reviewers did this parallel literature screening independently.

Selection Criteria

There were 4 inclusion criteria: (1) patients were children who had a history of bronchiolitis or were diagnosed with bronchiolitis for at least 3 consecutive months, (2) study was a randomized controlled trial (RCT), (3) the study outcomes included CSS or LHS, and (4) there were enough relevant data concerning the outcomes.

Data Extraction

Two authors assessed the reports using the above selection criteria. If a study seemed to record a repeated patient sample, the report with the follow-up period most similar to the other included studies was selected. A third author resolved any disagreements that arose. Extracted characteristics of each report are displayed in Table 1. This includes but is not limited to the name of conductor(s), publication year, country, CSS and the standard they used, sample size, age, treatments, route, RSV positive, and duration of symptoms. Furthermore, we listed the Jadad scale of included studies. All records had a score of 4 or higher. This indicates that the studies retrieved were normative and reliable.

Statistical Analysis

This study built a random-effects network based on a Bayesian framework using the Markov chain Monte Carlo methods. We plotted networks of the curative outcomes of several studies and specified the relation by mean difference (MD), standardized MD (SMD), and 95% credible interval (CI) across experiments to compare different bronchiolitis treatments. The surface under the cumulative ranking curve (SUCRA) was used to calculate the probability of the curative effect. It separately ranked each therapy on CSS and LHS. Scores ranged from 0 to 1, and a higher score indicated a greater efficacy. Statistical heterogeneity across the studies was assessed using heat plots and node-splitting plots. All computations were performed using the STATA 13.1 (StataCorp LP, College Station, TX) and R 3.3.1 (Lucent Technologies, Jasmine Hill, NJ) software.

Results

Process of Eligible Study Selection

We screened out 2312 records using the search strategies previously described. A total of 1914 records remained after duplicates were removed, and 1874 articles were discarded due to unrelated treatment, comparison, or lack of quantitative outcomes. Forty articles were believed to have a high quality and valuable data.[5,6,8-11,13-17,26-54]

Table 1. Baseline Characteristics of the Included Studies.[a]

				Treatment A						Treatment B					
Author, Year, Country	Blinding	Inpatient/ Outpatient	CSS Standard	Intervention A	Route	Size A	Age, mo	Boys/ Girls	RSV ± (n/N)	Intervention B	Route	Size B	Age, mo	Boys/ Girls	RSV ± (n/N)
Wu et al,[16] 2014, United States	Double	ED	RDAI	HS	inh	231	6.57 (5.17)	136/95	42/64	PBO	inh	216	6.40 (5.33)	118/98	42/71
Ojha et al,[29] 2014, Nepal	Double	Inpatient	NR	HS	inh	28	8.61 (5.74)	7/21	NR	PBO	inh	31	8.51 (4.24)	8/23	NR
Jacobs et al,[8] 2014, United States	Double	ED	BSS	EP ± HS	inh	52	6.0 (3.9)	36/52	26/38	EP	inh	49	5.6 (3.3)	28/49	15/30
Florin et al,[30] 2014, United States	Double	Outpatient	RDAI	HS	inh	31	7.2 (5.1)	15/16	NR	PBO	inh	31	6.1 (3.6)	13/18	NR
Luo et al,[36] 2010, China	Double	Inpatient	Wang	BA ± HS	inh	50	6.0 (4.3)	30/20	35/50	BA	inh	43	5.6 (4.5)	26/17	30/43
Miraglia Del Giudice et al,[34] 2012, Italy	Double	Inpatient	RDAI	EP ± HS	inh	52	4.8 (2.3)	34/18	42/52	EP	inh	54	4.2 (1.6)	35/19	45/54
Bertrand et al,[15] 2001, Chile	Double	Inpatient	Tal	EP	inh	16	3.9 (1.6)	9/7	13/16	BA	inh	14	3.7 (2.25)	7/7	13/14
Al-Ansari et al,[37] 2010, Qatar	Double	ED	Wang	EP ± HS	inh	58	3.84 (2.84)	39/19	34/58	EP	inh	56	3.30 (2.43)	30/26	31/56
Luo et al,[35] 2011, China	Double	Inpatient	Wang	HS	inh	57	5.9 (4.1)	32/25	42/57	PBO	inh	55	5.8 (4.3)	31/24	40/55
Tal et al,[43] 2006, Israel	Double	Inpatient	Wang	EP ± HS	inh	21	2.8 (1.2)	10/11	18/21	EP	inh	20	2.3 (0.7)	13/7	15/20
Anil et al,[17] 2010, Turkey	Double	Outpatient	RDAI	EP ± HS	inh	39	9.4 (5.0)	29/10	NR	EP	inh	38	10.4 (5.7)	26/12	NR
				BA ± HS	inh	36	9.7 (6.2)	23/13	NR	BA	inh	36	9.0 (6.2)	20/16	NR
										PBO	inh	37	9.1 (4.4)	22/15	NR
Beck et al,[42] 2007, Israel	Double	Inpatient	Wang	EP	inh	12	4.9 (0.8)	8/4	NR	BA	inh	15	4.0 (1.35)	11/4	NR
John et al,[14] 2006, India	Double	Inpatient	RDAI	EP	inh	15	6.67 (3.01)	10/5	NR	BA	inh	15	6.73 (2.95)	9/6	NR
Kabir et al,[39] 2009, Bangladesh	Double	Inpatient	RDAI	BA	inh	25	—	15/10	NR	EP	inh	27	—	17/10	NR
Khashabi et al,[44] 2005, Iran	Double	Outpatient	RDAI	EP	inh	24	8.9	5/19	NR	PBO	inh	24	7.9	9/15	NR
				BA	inh	24	10.5	6/18	NR						
Kuyucu et al,[10] 2004, Turkey	Double	Outpatient	RDAI	EP ± CS	inh ± im	23	7.2 (0.8)	NR	NR	EP	inh ± im	11	9.6 (1.3)	NR	NR
				BA ± CS	inh ± im	23	7.9 (1.0)	NR	NR	BA	inh ± im	12	9.9 (1.7)	NR	NR
Menon et al,[53] 1995, Canada	Double	Outpatient	RDAI	BA	inh	21	—	—	NR	EP	inh	21	—	—	NR
Plint et al,[9] 2009, Canada	Double	Outpatient	RDAI	EP ± CS	inh	200	5	124/76	128/200	CS	inh	200	5	127/73	127/200
				EP	inh ± po	199	5	122/77	129/199	PBO	inh ± po	201	5	120/81	136/201
Can et al,[49] 1998, Turkey	Double	Outpatient	RDAI	BA	inh	100	7.2 (4.2)	48/52	NR	PBO	inh	100	6.8 (2.1)	76/24	NR
Chevallier et al,[54] 1995, France	Double	Inpatient	NR	BA	inh	16	—	11/5	13/16	PBO	inh	17	—	11/6	13/17
Goh et al,[11] 1997, Singapore	Double	Inpatient	Wang	BA	inh	30	5.7 (0.77)	24/6	15/30	PBO	inh	29	7.4 (0.89)	20/9	12/29
				BA	inh	30	5.2 (0.67)	20/10	10/30						
Ipek et al,[13] 2011, Turkey	Double	Outpatient	Wang	BA	inh	30	8.13 (4.75)	17/13	NR	HS	inh	30	8.4 (4.19)	17/13	NR
				BA ± HS	inh	30	7.9 (3.57)	18/12	NR	PBO	inh	30	7.4 (3.08)	19/11	NR
Scarlett et al,[33] 2012, United States	Double	Inpatient	RDAI	BA	inh	10	2.2 (1.07)	5/5	NR	PBO	inh	10	5.0 (3.96)	5/5	NR
Tinsa et al,[38] 2009, Tunisia	Double	Outpatient	RDAI	BA	inh	10	6.6 (2.02)	10/6	NR	PBO	inh	19	5.9 (2.3)	9/10	NR
Totapally et al,[46] 2002, United States	Double	Inpatient	NR	BA	inh	10	5.1	7/3	NR	PBO	inh	9	5.8	2/9	NR

(*continued*)

Table 1. (continued)

Author, Year, Country	Blinding	Inpatient/ Outpatient	CSS Standard	Treatment A						Treatment B					
				Intervention A	Route	Size A	Age, mo	Boys/ Girls	RSV ± (n/N)	Intervention B	Route	Size B	Age, mo	Boys/ Girls	RSV ± (n/N)
Bentur et al,[45] 2005, Israel	Double	Inpatient	Wang	EP ± CS	inh	29	3.3 (2.5)	14/15	29/29	EP	inh	32	3.8 (2.0)	14/18	32/32
Berger et al,[50] 1998, Israel	Double	Outpatient	Tal	CS	po	20	5.2 (0.7)	NR	10/20	PBO	po	18	4.8 (0.9)	NR	9/18
Corneli et al,[41] 2007, United States	Double	Outpatient	RDAI	CS	po	304	5.1 (2.6)	190/114	85/127	PBO	po	294	5.1 (2.8)	178/116	81/142
Klassen et al,[51] 1997, Canada	Double	Inpatient	RDAI	CS	po	35	4.68	22/13	30/35	PBO	po	32	4.68	15/17	28/32
Mesquita et al,[6] 2009, Paraguay	Double	Outpatient	RDAI	CS	po	33	7.3 (4)	19/14	17/29	PBO	po	32	5.9 (3)	15/17	19/23
Richter and Seddon,[48] 1998, United Kingdom	Double	Inpatient	NR	CS	inh	21	4.08	12/9	16/21	PBO	inh	19	2.7	10/9	17/19
Schuh et al,[5] 2002, Canada	Double	Outpatient	RDAI	CS	po	36	6.1 (3.5)	20/16	15/28	PBO	po	34	6.9 (3.9)	23/11	15/30
Sarrell et al,[47] 2002, Israel	Double	Inpatient	Wang	BA ± HS	inh	33	12.7 (5.17)	18/15	27/33	BA	inh	32	12.3 (6.2)	18/14	25/32
Grewal et al,[40] 2009, Canada	Double	Outpatient	RDAI	EP ± HS	inh	23	5.6 (4.0)	14/9	19/23	EP	inh	23	4.4 (3.4)	14/9	18/22
Reijonenet al,[52] 1995, Finland	Double	Inpatient	RDAI	EP	inh	24	10.6 (5.6)	14/10	NR	EP	inh	24	10.1 (5.7)	19/5	NR
				BA	inh	27	9.9 (5.5)	16/11	NR	BA	inh	25	10.3 (7.5)	22/5	NR
Bawazeer et al,[31] 2014, Saudi Arabia	Double	ED	RDAI	EP ± CS	inh	45	4.74 (2.84)	28/17	3/45	EP	inh	39	4.23 (2.46)	20/19	2/39
				BA ± CS	inh	40	4.55 (2.21)	21/19	3/40	BA	inh	38	4.85 (2.35)	17/20	3/38
Flores et al,[26] 2016, Portugal	Double	ED	Wang	HS	inh	33	3.3 (2.4)	18/15	29/33	PBO	inh	35	3.8 (2.5)	18/17	29/35
Khanal et al,[28] 2015, Nepal	Double	Outpatient	Wang	EP ± HS	inh	50	9.82 (5.06)	27/23	NR	EP	inh	50	9.51 (4.28)	21/29	NR
Skjerven et al,[32] 2013, Norway	Double	Inpatient	RDAI	EP	inh	203	4.2 (2.9)	123/80	NR	PBO	inh	201	4.2 (2.8)	117/84	NR
Zamani et al, [27] 2015, Iran	Double	Inpatient	RDAI	BA	inh	35	14.1 (5.6)	NR	NR	HS	inh	35	12.6 (5.6)	NR	NR

BA, bronchodilator agent; BSS, bronchiolitis severity score; CS, corticosteroids; CSS, clinical severity score; ED, emergency department; EP, epinephrine; HS, hypertonic saline; im, intramuscular; inh, inhalation; NR, no report; PBO, placebo; po, per os; RDAI, Respiratory Distress Assessment Instrument; RSV, respiratory syncytial virus; —, no data.

[a] Clinical score standards are from: Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis*. 1992;145:106-109. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics*. 1983;71:13-18.

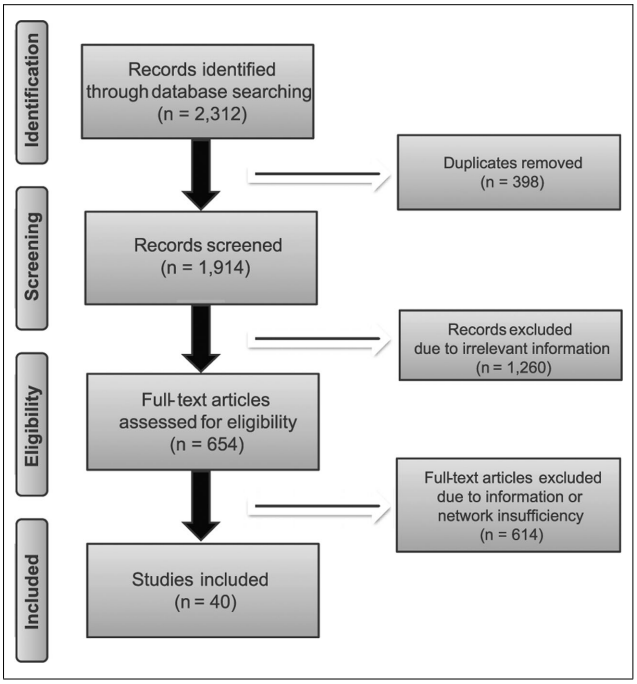

Figure 1. Flowchart.

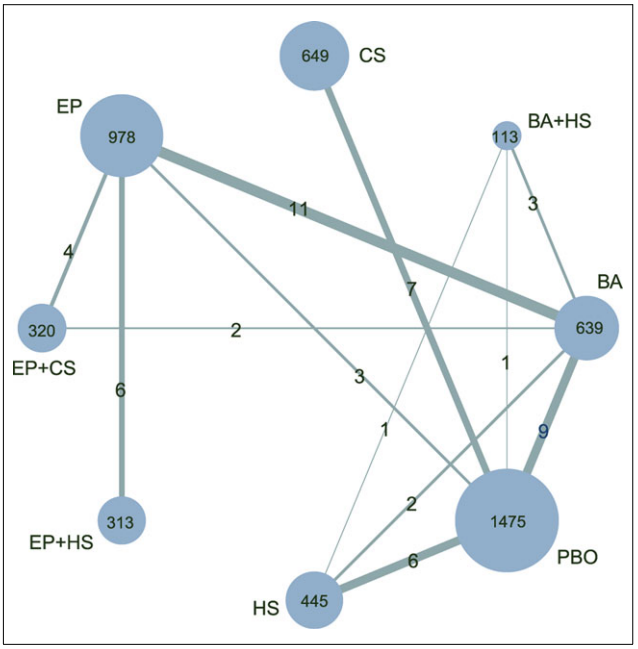

Figure 2. Network diagram of all included studies. Each node represents a treatment type; the number in circles represents the number of people involved in all included studies and the widths of lines with numbers between 2 nodes represent the number of study involved in the head-to-head comparison. BA, bronchodilator agent; CS, corticosteroids; EP, epinephrine; HS, hypertonic saline; PBO, placebo.

Figure 1 shows the entire literature screening process. Table 1 displays all included studies. The results of the Jadad scale on included studies are shown in Supplementary Table S1. Eight therapies, including the PBO, are synthesized into 1 network in Figure 2.

NMA on the Efficacy of 7 Therapeutic Regimens and PBO

This NMA synthesized and made comparison among the PBO and 7 therapeutic regimens, including BA, HS, BA ± HS, CS, EP, EP ± CS, and EP ± HS (Table 2). We found that all 7 therapeutic regimens showed no statistical difference from PBO with regard to CSS. Among the 7 therapies, BA performed better than CS (SMD, –0.36; 95% CI, –0.64 to –0.09), the other 5 displayed no significant statistical difference. With regard to LHS, EP and EP ± HS had an advantage over PBO (EP: MD, –2.23; 95% CI, –4.04 to –0.52; EP ± HS: MD, –2.70; 95% CI, –4.81 to –0.75). Moreover, EP and EP ± HS were also more efficient than BA (EP: MD, –1.89; 95% CI, –3.65 to –0.17; EP ± HS: MD, –2.37; 95% CI, –4.42 to –0.38). When it comes to LHS, these 2 therapies had a better efficacy than the others. The same conclusion can also be drawn from the forest plots (Figure 3).

Consistency Assessments

This NMA used both direct and indirect information; therefore, it was of great importance to assess the consistency of evidence collected. Node splitting (Table 3) and heat plots (Supplementary Figure S1) were applied to check the consistency between direct and indirect evidence. According to Table 3, there is a discrepancy between BA and HS ($P = .025$, less than the significance level of .05). The heat plots (Supplementary Figure S1) show no obvious inconsistency.

Ranking 8 Therapies With SUCRA

In this study, 2 SUCRA plots (Figure 4) on the related outcomes were constructed. In relation to CSS, EP ± CS ranked first and EP ± HS ranked second. EP or BA ± HS also demonstrated a strong performance. Of the 7 therapies, HS performed the worst. With regard to LHS, all treatments were more efficient than PBO. Among them, EP ± HS was suggested to be the best therapeutic regimen. EP ± CS and EP ± HS showed a great curative effect both in CSS and LHS. EP ranked third after the 2 outcomes, and while BA ± HS was the strongest performer in terms of CSS, it scored poorly in LHS.

In all, EP ± CS and EP ± HS proved to be the optimal treatments for bronchiolitis. EP also had a good curative effect.

Table 2. Comparisons of Bronchiolitis Treatments With Regard to Clinical Outcomes.[a]

Clinical Severity Score (CSS)							
BA	–0.07 (–0.34 to 0.20)	**–0.36 (–0.64 to–0.09)**	–0.13 (–0.33 to 0.06)	–0.13 (–0.37 to 0.11)	–0.02 (–0.39 to 0.34)	–0.18 (–0.40 to 0.04)	–0.21 (–0.41 to–0.02)
0.07 (–0.20 to 0.34)	**BA ± HS**	–0.29 (–0.62 to 0.04)	–0.06 (–0.39 to 0.27)	–0.06 (–0.42 to 0.30)	0.05 (–0.40 to 0.50)	–0.11 (–0.36 to 0.13)	–0.14 (–0.41 to 0.13)
0.36 (0.09–0.64)	0.29 (–0.04 to 0.62)	**CS**	0.23 (–0.11 to 0.56)	0.23 (–0.13 to 0.60)	0.34 (–0.12 to 0.79)	0.18 (–0.08 to 0.44)	0.15 (–0.05 to 0.35)
0.13 (–0.06 to 0.33)	0.06 (–0.27 to 0.39)	–0.23 (–0.56 to 0.11)	**EP**	0.01 (–0.18 to 0.19)	0.11 (–0.20 to 0.41)	–0.05 (–0.34 to 0.24)	–0.08 (–0.35 to 0.19)
0.13 (–0.11 to 0.37)	0.06 (–0.30 to 0.42)	–0.23 (–0.60 to 0.13)	–0.01 (–0.19 to 0.18)	**EP ± CS**	0.11 (–0.25 to 0.46)	–0.05 (–0.38 to 0.27)	–0.08 (–0.39 to 0.23)
0.02 (–0.34 to 0.39)	–0.05 (–0.50 to 0.40)	–0.34 (–0.79 to 0.12)	–0.11 (–0.41 to 0.20)	–0.11 (–0.46 to 0.25)	**EP ± HS**	–0.16 (–0.58 to 0.27)	–0.19 (–0.60 to 0.22)
0.18 (–0.04 to 0.40)	0.11 (–0.13 to 0.36)	–0.18 (–0.44 to 0.08)	0.05 (–0.24 to 0.34)	0.05 (–0.27 to 0.38)	0.16 (–0.27 to 0.58)	**HS**	–0.03 (–0.20 to 0.14)
0.21 (–0.02 to 0.41)	0.14 (–0.13 to 0.41)	–0.15 (–0.35 to 0.05)	0.08 (–0.19 to 0.35)	0.08 (–0.23 to 0.39)	0.19 (–0.22 to 0.60)	0.03 (–0.14 to 0.20)	**PBO**
Length of Hospital Stay (LHS)							
BA	–0.10 (–2.15 to 1.95)	0.66 (–2.31 to 3.55)	**1.89 (0.17–3.65)**	2.20 (–0.58 to 4.98)	**2.37 (0.38–4.42)**	0.44 (–1.32 to 2.08)	–0.34 (–2.19 to 1.43)
0.10 (–1.95 to 2.15)	**BA ± HS**	0.75 (–2.88 to 4.30)	1.99 (–0.72 to 4.69)	2.30 (–1.19 to 5.75)	2.46 (–0.42 to 5.38)	0.53 (–2.24 to 3.12)	–0.24 (–3.04 to 2.45)
–0.66 (–3.55 to 2.31)	–0.75 (–4.30 to 2.88)	**CS**	1.24 (–1.59 to 4.17)	1.54 (–2.01 to 5.22)	1.71 (–1.30 to 4.85)	–0.22 (–2.73 to 2.29)	–0.99 (–3.30 to 1.34)
–1.89 (–3.65 to–0.17)	–1.99 (–4.69 to 0.72)	–1.24 (–4.17 to 1.59)	**EP**	0.30 (–1.87 to 2.48)	0.47 (–0.55 to 1.52)	–1.46 (–3.36 to 0.32)	**–2.23 (–4.04 to–0.52)**
–2.20 (–4.98 to 0.58)	–2.30 (–5.75 to 1.19)	–1.54 (–5.22 to 2.01)	–0.30 (–2.48 to 1.87)	**EP ± CS**	0.17 (–2.21 to 2.59)	–1.76 (–4.67 to 1.00)	–2.53 (–5.35 to 0.21)
–2.37 (–4.42 to–0.38)	–2.46 (–5.38 to 0.42)	–1.71 (–4.85 to 1.30)	–0.47 (–1.52 to 0.55)	–0.17 (–2.59 to 2.21)	**EP ± HS**	–1.93 (–4.12 to 0.09)	**–2.70 (–4.81 to–0.75)**
–0.44 (–2.08 to 1.32)	–0.53 (–3.12 to 2.24)	0.22 (–2.29 to 2.73)	1.46 (–0.32 to 3.36)	1.76 (–1.00 to 4.67)	1.93 (–0.09 to 4.12)	**HS**	–0.77 (–1.75 to 0.25)
0.34 (–1.43 to 2.19)	0.24 (–2.45 to 3.04)	0.99 (–1.34 to 3.30)	**2.23 (0.52–4.04)**	2.53 (–0.21 to 5.35)	**2.70 (0.75–4.81)**	0.77 (–0.25 to 1.75)	**PBO**

BA– bronchodilator agent; CS, corticosteroids; EP, epinephrine; HS, hypertonic saline; PBO, placebo.

[a] Standardized mean difference and 95% credible interval (CI) for CSS. Mean difference and 95% CI for LHS. Bold values represent significant results.

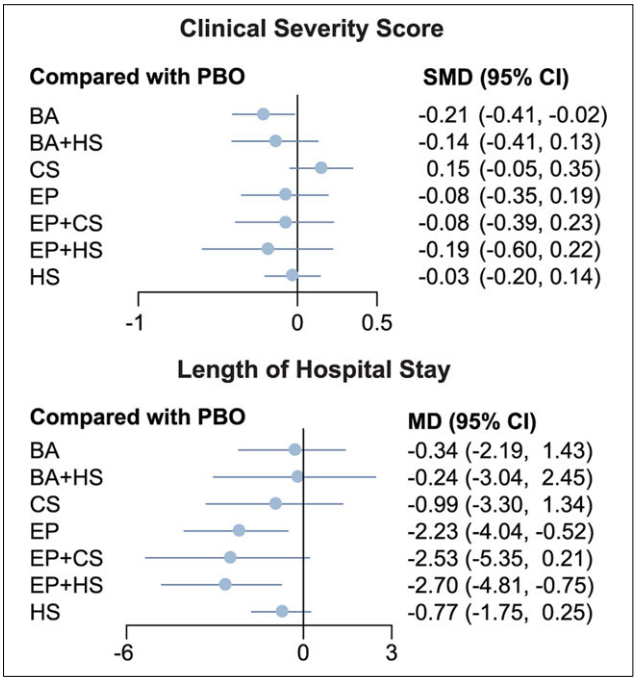

Figure 3. Forest plots for clinical severity score change and length of hospital stay of different treatment effects. BA, bronchodilator agent; CI, credible interval; CS, corticosteroids; EP, epinephrine; HS, hypertonic saline; MD, mean difference; MS, mean difference; PBO, placebo; SMD, standardized mean difference.

Publication Bias

According to the symmetrical characteristics of the funnel plots, no obvious publication bias is observed (Supplementary Figure S2).

Discussion

According to SUCRA, EP ± CS ranks first in CSS and second in LHS, while EP ± CS take first place in LHS and second in CSS. This result exhibits that EP ± CS and EP ± HS have an outstanding performance with respect to efficacy. EP is a hormone and neurotransmitter, and it is also used as medication.[55] It originates from some neurons and paranephros.[55] EP can control blood glucose, pupil dilation, cardiac output, and blood flow by affecting α and β receptors. CS is a type of steroid hormone that is extracted from vertebrates' adrenal cortex or some synthetic analogues of hormones. CS is usually applied to physiologic processes such as protein catabolism, immune response, and so on.[56] It is a widely used intervention, and there are several kinds of HS concentrations, the most common being 3%. Three percent HS plays an important role in treating severe hyponatremia, acutely increased intracranial pressure, and critical care settings.[57] Inhalational HS is believed to have a curative effect on respiratory problems such as bronchiolitis.[58] Based on our research, a combination of these medicines showed a better efficacy than therapy with the use of 1 treatment alone.

EP ± HS exhibited an outstanding curable effect in previous individual research and MAs. This research reveals that EP ± HS can successfully reduce LHS and CSS. This conclusion was confirmed by Miraglia Del Giudice et al,[7] who also demonstrated that 3% HS ± EP was able to decrease symptoms and LHS. A report that claimed that 3% HS ± EP could improve CSS in infants with mild to moderate viral bronchiolitis[28] also supports our conclusions. Some research also took into consideration the concentration of HS as this may have a significant effect on efficacy. For example, it was demonstrated that 5% HS ± EP and 3% HS ± EP had a better performance in

Table 3. Node-Splitting Results of Clinical Severity Score (CSS) and Heterogeneity Analysis.[a]

	Direct		Indirect		Difference		
Treatment	SMD	SD	SMD	SD	SMD	SD	*P* Value
BA vs PBO	–0.41	0.32	–0.36	0.54	–0.05	0.63	.940
BA ± HS vs PBO	–0.54	0.83	–1.32	0.61	0.78	1.03	.451
EP vs PBO	–1.29	0.47	–0.82	0.47	–0.47	0.66	.482
HS vs PBO	0.07	0.34	–0.21	0.81	0.27	0.88	.755
BA ± HS vs BA	–0.84	0.47	0.79	1.31	–1.63	1.40	.243
EP vs BA	–0.42	0.27	–2.00	0.65	1.58	0.70	**.025**
EP ± CS vs BA	–2.36	0.64	–0.89	0.61	–1.47	0.88	.095
HS vs BA	0.27	0.59	0.52	0.47	–0.25	0.76	.743
HS vs BA ± HS	–0.05	0.79	1.86	0.66	–1.91	1.03	.062
EP ± CS vs EP	–0.85	0.43	–2.02	1.25	1.17	1.31	.370
EP ± HS vs EP	–0.34	0.33	3.20	25.93	–3.54	25.93	.891

BA, bronchodilator agent; CS, corticosteroids; EP, epinephrine; HS, hypertonic saline; PBO, placebo.
[a]Standardized mean difference (SMD) and standard deviation (SD) for CSS. Bold values represent significant results.

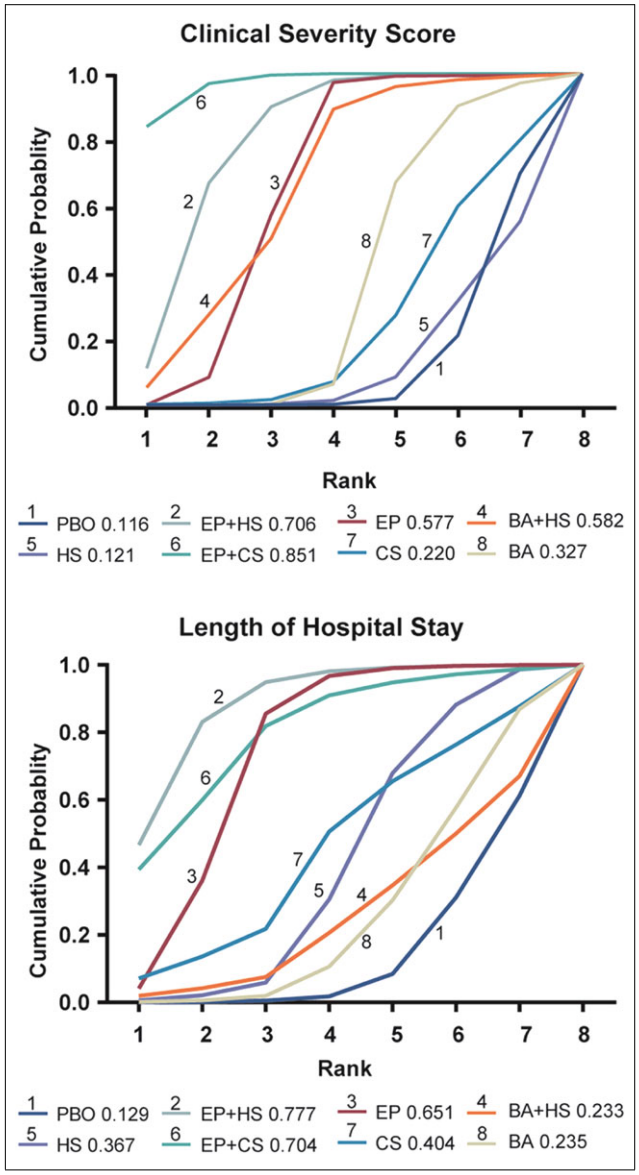

Figure 4. Ranking grams for clinical severity score change and length of hospital stay of different treatment effects. The surface under the cumulative ranking curve (SUCRA) values are listed in the legend. BA, bronchodilator agent; CS, corticosteroids; EP, epinephrine; HS, hypertonic saline; PBO, placebo.

improving CSS than 0.9% normal saline. However, 5% HS ± EP had a stronger potential to reduce clinical severity than 3% HS ± EP.[37] This reminded us of the importance of concentration and why we should pay more attention to it in clinical practice. EP ± CS also had a brilliant performance with respect to CSS and LHS. Through the investigation and study of infants with bronchiolitis treated in the emergency department, it was found that dexamethasone (a kind of CS) with EP may effectively reduce LHS.[9] In addition, another study of infants with acute bronchiolitis implied that EP ± CS (dexamethasone) was significantly different from BA.[10] This is consistent with our conclusions.

However, some researches and MAs had contradicting evidence to our results. A study that focused on the inhalation of 7% HS ± EP for patients with moderate to severe acute bronchiolitis[8] implied that 7% HS ± EP did not appear to show any significant clinical decrease in CSS compared with 0.9% normal saline ± EP. Grewal et al[40] conducted a randomized trial of severe bronchiolitis in the emergency department and concluded that 3% HS ± EP does not significantly reduce CSS compared with normal saline. Similarly, another experiment also could not find any difference in infants with mild bronchiolitis.[17] The above studies did not accord with most published results, but we could not simply omit them. Furthermore, some controversy also exists in the effect of EP ± CS. An RCT showed that EP ± CS did not play a role in bronchiolitis management for first-time wheezing infants due to a lack of positive effect on CSS and LHS.[31] This result was not reflected in our SUCRA results, and the inconsistency may be caused by several reasons. First, this NMA synthesized experimental data of HS without the consideration of HS concentration. The curative effect may be sensitive to concentration. Second, there may be some inconsistency between direct and indirect evidence. Last but not least, this study built a random-effects network based on a Bayesian framework using the Markov chain Monte Carlo methods, but it did not have an unbiased estimator.[59] This may consequently affect the SUCRA values.

In summary, this NMA synthesized 7 therapeutic regimens as well as the PBO and ranked them on curative effect on CSS and LHS. This NMA adopted >1 outcome to thoroughly assess the treatments and to make sure we had better understanding of these 7 interventions. Furthermore, this study takes into consideration a greater volume of data. This is the main advantage of an NMA over a traditional MA and individual trials. All research involved in this study included high-quality RCTs.

Some limitations affect our NMA results. First, there is a large discrepancy in sample size among the 7 treatments. This may have a significant impact on the corresponding 95% CI. The group partition was also very broad and did not consider intervention dose, patient age, patient health status, and so on. These factors should be further addressed. To some extent, a subgroup NMA could make up for these issues. This study could also have possibly missed some key data due to the omission of unpublished research. This study did not take into consideration any adverse effects, and as safety is an important aspect in assessing treatment, future studies should consider toxicity files.

Conclusion

EP ± CS and EP ± HS had outstanding efficacy performance in terms of CSS and LHS and should be the first choice of bronchiolitis treatment in children. However, this NMA did not analyze the adverse effects of these 2 combined therapies; therefore, further research is still required.

Statement of Authorship

C. Guo contributed to the conception/design of the research; and C. Guo and D. Chen drafted the manuscript. All authors contributed to the acquisition, analysis, or interpretation of the data; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the supporting information tab for this article.

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