

TABLE 1 Characteristics of included studies

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
Al-Ansari, 2010, Qatar ²⁰	Outpatient (ED)	< 18 mo Moderate/Severe Bronchiolitis (Wang classification)	- 0.9% saline+Ep1.5mg - HS3%+Ep1.5mg - HS5%Ep1.5mg	Nebulization given on enrollment and every 4 hours thereafter until discharge	- Primary: Wang CSS at 48 hours - Secondary: LOS, Wang CSS at 24 hours and 72 hours, rate of admission to ICU, rate of ER readmissions after 1 week, AEs.	Consistent trend (but no statistical difference) favoring HS5% Intermediate results for HS3% No difference in LOS between groups No patient was withdrawn because of apnea, cyanosis or decreased SaO ₂ , no evidence of toxicity among groups
Anil, 2010, Turkey ²⁴	Outpatient (ED)	6 – 24 mo Mild/Moderate Bronchiolitis (Wang classification)	- 0.9% saline+Ep1.5mg - HS3%+Ep1.5mg - 0,9% saline+Salbutamol - HS3%+Salbutamol - 0.9% saline	Nebulization given at 0 and 30 min	- Primary: Wang CSS - Secondary: SaO ₂ , heart rate, AEs Outcomes were assessed at 0, 30, 60 and 120 minutes	No clinically significant difference in CSS score, SaO ₂ and heart rate among groups No adverse events occurred in treatment groups, no children were withdrawn due to side-effects or clinical deterioration
Campaña, 2014, Spain ²⁵	Inpatient	< 6 mo Moderate Bronchiolitis (McConnochie classification)	- HS3%+Ep0.5mL/Kg (max 3mL) - 0,9% saline+Ep0.5mL/Kg (max 3mL) via high flow therapy	Nebulization given every 4 hours until discharge	- Primary: difference in mean RACS at 30min before nebulization and 60-90 minutes after - Secondary: difference in mean comfort score over the monitoring period (Comfort1– Comfort6), LOS and rate of admission to ICU	No difference in RACS, comfort evaluation, LOS or rate of admission to ICU between groups No adverse events were observed
Del Giudice, 2012, Italy ³⁸	Inpatient	< 24 mo Children with significant respiratory	- HS3%+Ep1.5mg - 0,9% saline	Nebulization given every 6 hours until discharge	- Primary: LOS - Secondary: Wang CSS Outcomes were assessed before and 30	Significant difference favoring HS3% in LOS and CSS, seen already after the first 24 hours of therapy and was sustained

		distress and SatO ₂ < 94%			minutes after nebulization	through the third day of treatment
Faten, 2015, Tunisia ²¹	Inpatient	1 mo – 12 mo Moderate Bronchiolitis (Wang classification)	- HS5%+Ep2mg - HS5% - 0.9% saline	Nebulization given every 4 hours until discharge	- Primary: Wang CSS - Secondary: respiratory rate, heart rate, SaO ₂ , AEs Outcomes were assessed at 0, 30, 60, 120 minutes	No benefit of HS5% plus epinephrine on CSS, respiratory rate or SaO ₂ at any time point or duration of hospital stay No significant adverse side effects (tachycardia, flushing, tremor or bronchospasm)
Flores- Gonzales, 2015, Spain ²⁶	Inpatient	< 24 mo Mild/Moderate Bronchiolitis (WDF classification)	- HS3%+Ep3mg - HS3%	Nebulization given every 4 hours until discharge	- Primary: LOS - Secondary: respiratory rate, heart rate, oxygen saturation, inhaled FIO ₂ , WDF score, AEs Outcomes were assessed daily until discharge.	The addition of epinephrine significantly shortens LOS WDF score improved more rapidly in HS3% plus epinephrine group observed already at day 3 and sustained by day 5 No adverse events (i.e. tachycardia, sweating, pallor, trembling, or hypertension) during hospitalization
Grewal, 2009, Canada ³⁵	Outpatient (ED)	6 wk – 12 mo Mild/Moderate Bronchiolitis (RDAI classification) and SaO ₂ between 85 e 96%	- 0.9% saline+Ep1.125mg - HS3%+Ep1.125mg	Nebulization given once on enrollment. A second dose could be administered within 120 minutes if needed	- Primary: RACS 0-120 minutes, change in SaO ₂ 0-120 minutes - Secondary: rate of admission to hospital, rate of readmission to ED Outcomes were assessed at 0, 30, 60,90 e 120 minutes	No significant difference between groups in RACS, admission rates and readmission to ED Adverse effects were noted in 4 infants (vomiting:3; diarrhea:1); all were enrolled in the HS group.
Jacobs, 2014, USA ²⁸	Outpatient (ED)	6 wk – 18 mo Moderate/Severe Bronchiolitis (Wang classification) and SaO ₂ > 85%	- HS7%+Ep1.125mg - 0.9% saline+Ep1.125mg	Nebulization given once on ED and every 4 hours thereafter until discharge	- Primary: change in modified Wang BSS, assessed before, immediately after, and 4 hours after nebulization, or at	HS7% plus epinephrine was no better than normal saline with epinephrine in improvement of CSS, or decreasing admission rate, discharge rate or LOS Neither group had any adverse

					disposition - Secondary: hospitalization rate, discharge rate at 23 hours, LOS, AEs	effects.
Khanal, 2015, Nepal ³⁹	Outpatient (ED)	6 wk – 24 mo Mild/Moderate Bronchiolitis (Wang classification)	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given at 0 and 30 min	- Primary: mean change in Wang CSS - Secondary: SaO ₂ , respiratory rate, heart rate, discharge readiness at 2h, readmission rates 24h after discharge Outcomes were assessed at 30, 60 and 120 minutes after the first nebulization	Significant difference in the mean change in CSS, heart rate, respiratory rate and SaO ₂ between the two groups, favoring the combination therapy More infants were eligible for early discharge and less likely to need hospital re-visit within the next 24 hours in the combination therapy group No adverse events occurred in either treatment groups, no children were withdrawn from the trial due to side effects
Mandelberg, 2003, Israel ³⁰	Inpatient	< 12 mo SaO ₂ > 85%	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given every 8 hours until discharge	- Primary: LOS, change in Wang CSS each day - Secondary: heart rate, SaO ₂ , radiograph assessment score, number of add-on treatments, AEs Outcomes were assessed before and 30 minutes after nebulization	Significant statistical reduction of LOS in the experimental group, compared to control No difference when compared post nebulization CSS between the two groups No adverse effects were observed.
Pandit, 2013, India ³⁶	Outpatient (ED)	2 – 12 mo Severity not specified	- HS3%+Ep1mg - 0.9% saline+Ep1mg	Nebulization given three times with an interval of one hour between two nebulizations	- Primary: LOS - Secondary: improvement in RDAI score, respiratory rate, SaO ₂ , heart rate,	No significant improvement in LOS or clinical parameters (RDAI, respiratory rate and SaO ₂) pre to post nebulization between groups recorded on

					number of add-on treatment, AEs Outcomes were assessed before and 30 minutes after the third nebulization	days 1 and 2 4 infants had side effects (4%) (vomiting:3; diarrhea:1), all were enrolled in 0.9% saline + epinephrine group No adverse effects as tremors or paleness reported
Reisi, 2018, Iran ²²	Inpatient	Age and severity not specified	- HS7%+Ep1mg - HS5%+Ep1mg - HS3%+Ep1mg - 0.9% saline+Ep1mg	Nebulization given on enrollment and every 4 hours until discharge	- Primary: Wang CSS - Secondary: LOS, SaO ₂ and oxygen therapy duration Outcomes were assessed at 0, 1 hour, 5 hours, 12 hours and 24 hours after enrollment	Nebulization with HS (3%, 5%, 7%) had not significant superiority to 0.9% saline to reduce LOS, duration of oxygen supplementation use or BSS
Sharma, 2020, India ²⁹	Outpatient (ED)	6 – 12 mo Moderate/Severe Bronchiolitis (Wang classification)	- HS3%+Ep 2mg - 0.9% saline+Ep 2mg	Nebulization given on enrollment twice with 30 min intervals and thereafter every 6 hours until discharge	- Primary: LOS - Secondary: Wang CSS, respiratory rate, SaO ₂ , AEs Outcomes were assessed at 0, 15 minutes after each nebulization and then every 1-4 hours	Improvement of CSS was significantly more pronounced in HS3% group at 24 hours than in control group, but this improvement didn't translate into early discharge or decrease in length of hospital stay No significant adverse events occurred in either of the treatment groups, no children were withdrawn from the trial due to side effects
Sharmin, 2014, India ³⁷	Outpatient (ED)	2 – 24 mo Moderate/Severe Bronchiolitis (Wang classification)	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Single dose on enrollment	Respiratory rate, Wang CSS, SaO ₂ , heart rate, AEs Outcomes were assessed at 0 and 30 minutes after nebulization	Nebulized adrenaline plus HS3% is more effective than nebulized epinephrine diluted with 0.9% saline in improving CSS, but no difference on respiratory rate or SaO ₂ No adverse effects were noticed, no significant change in heart rate after nebulization

Sreenivasa, 2015, India ³²	Inpatient	1 – 24 mo Severity not specified	- HS3%+Ep1mg - 0.9% saline+Ep1mg	Nebulization given every 4 hours until discharge	- Primary: LOS - Secondary: Wang CSS, SaO ₂ , heart rate, number of add-on treatment, AEs Outcomes were assessed at 12-hour intervals until discharge	Significantly shorter LOS and better improvement in CSS after combination therapy as compared to 0.9% saline plus epinephrine No adverse effects were observed in patients in either of the groups and no significant difference was seen in pulse rate at any time between two groups.
Tal, 2006, Israel ⁴⁰	Inpatient	< 12 mo SaO ₂ > 85%	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given every 8 hours until discharge	- Primary: LOS, Wang CSS - Secondary: radiographic score, AEs Outcomes were assessed at admission and daily, before and 30 minutes after nebulization	Significant reduction in LOS following treatment with combination therapy. Fall in values of CSS and radiographic score differed significantly between the two groups during the first 2 days after treatment, favoring the experimental group No adverse effects were observed in either of the groups.
Uysalol, 2017, Turkey ²³	Outpatient (ED)	2 – 24 mo Moderate Bronchiolitis (Wang classification)	- HS3% - Ep0.1mg/Kg - Salbutamol - HS3%+Ep0.1mg/Kg - 0.9% saline	Nebulization given at 0, 30, and 60 minutes, and every 4 hours thereafter if needed to a maximum of 24 hours	- Primary: LOS, discharge rates at 4 / 24 hours, readmission rate within 15 days - Secondary: AEs, number of add-on treatment	The mean LOS was significantly shorter for children in the group receiving HS3% plus epinephrine than in other groups and had the highest dismissal rate at 4 th hour of all five groups Within the treatment options, there was no statistically significant difference in terms of dismissal rates at 24th hour The total frequency of adverse events was 5.5%; frequencies were not different when

Zayed, 2018, Egypt ³⁴	Outpatient (ED)	< 24 mo Mild/ Moderate Bronchiolitis SaO ₂ < 95%	- HS3%+Ep1mg - HS3% - 0.9% saline+Ep 1mg	Nebulization given every 30 minutes to a maximum of 4 doses	- Primary: Heart rate on admission and before discharge - Secondary: SaO ₂ on admission and before discharge, Wang CSS after each dose until discharge upon improvement or inpatient admission.	compared between groups No significant difference between change of heart rate before and after treatment in the three study groups. No significant differences in the change of clinical score after treatment between the first group (HS3%) and the second group (HS3% plus epinephrine), but there were significant differences between both those groups and the third group (normal saline 0.9% plus epinephrine)
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AEs: Adverse events; BSS: Bronchiolitis severity score; CSS: Clinical severity Score; ED: Emergency Department; Ep: Epinephrine; RACS: Respiratory Assessment Change Score; SaO₂: Saturation of oxygen in room air; WDF Score: Wood-Downes Clinical Scoring System Modified by Ferres

