Office of Evidence Based Practice (EBP) – Specific Care Question: MDI vs. NEB for a Mild to Moderate Asthma Exacerbation

Specific Care Question:

For the patient who presents to the ED/UCC with a mild to moderate asthma exacerbation, is treatment using metered-dose inhalers (MDI) comparable to treatment using nebulizer mask for the provision of albuterol?

Question Originator:

The Asthma in the Emergency Department/ Urgent Care Center Clinical Practice Guideline Team

Literature Summary

Background. In an asthma attack, the airways, or the small tubes in the lungs, get narrow and swell. Chest tightness, coughing, and wheezing are usually present as well. This makes the patient feel "short of breath" (DynaMed Plus,2018). Patients inhale or breathe in medications to stop asthma symptoms during an asthma attack. Metered-dose inhaler (MDI) is one method to deliver the medication, and using a nebulizer is the other way to give the medicine. Literature was reviewed to see which method was better was better in delivering medications when a patient came to the Emergency Department or Urgent Care Center for an asthma exacerbation.

Study Characteristics. The search for suitable studies was completed Sept 5, 2017. Drs. Walsh and Michael reviewed the 86 titles and abstracts found in the search. Seven studies were identified that compared the two methods. Overall the studies were of very low quality (see Table 1). It appears the methods are comparable when treating patients with mild to moderate asthma attacks when measuring how quickly the patient's breathing (respiratory rate) returns to normal and the asthma score shows improvement. The methods used to perform the included studies could have been stronger. For example, in 2/3rds of the studies, neither subjects nor researchers were blinded to the treatment delivered to the subject. Also, the asthma score used to determine the severity of the asthma attack were not the same.

Key results. Based on low to very low evidence published since the parent guideline (GINA, 2018) the Asthma ED CPG team makes a strong recommendation to use a MDI with spacer (add a mask in children < 4 years old) preferentially for mild to moderate asthma exacerbations in the ED/UCC. There was no difference in the number of patients admitted to the hospital when either method was used, which means that either therapy is appropriate. Using a MDI did not cause adverse effects.

Summary by Outcome

Hospitalization. Based on six randomized control trials (Dhuper et al., 2011; Jamalvi, Raza, Naz, Shamim, & Jamalvi, 2006; Mitselou, Hedlin, & Hederos, 2016; Rotta, Amantea, Froehlich, & Becker, 2010; Schuh et al., 1999; Vangveeravong, 2008) that compared albuterol given as 4-10 100 mcg/puff MDI with spacer to albuterol given 15 mg/hour continuously by nebulization there was no difference in number of subjects admitted to the hospital, *OR* = .80, 95% CI [0.44, 1.46] (see Table 1 and Figure 3). The included studies had a total of 478 subjects. The studies are graded as very low-quality evidence due to (a) lack of blinding in the RCTs, two of the studies are non-randomized studies, and one is a cross-sectional study (See Figure 2); (b) inconsistency in the equipment used to deliver the medication; and (c) there was a low number of admissions.

Respiratory Rate. Based on two randomized control trials (Deerojanawong et al., 2005; Jamalvi et al., 2006) that compared albuterol given as 4-10 100 mcg/puff MDI with spacer to albuterol given 15 mg/hour continuously by nebulization there was no difference in the respiratory rate of subjects one hour after treatment, Mean difference = 0.98, 95% CI [-4.01, 20.4] (see Table 1

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and Figure 4).The included studies had a total of 197 subjects. The studies are graded as low very low-quality evidence due to (a) lack of blinding, it is not clear how blinding was attained, and one study is a non-randomized cross-sectional study (see Figure 2); (b) inconsistency in the equipment used to deliver the medication; and (c) the confidence interval is wide, and the mean difference is less than one breath per minute.

Asthma Score. Based on three randomized control trials (Deerojanawong et al., 2005; Jamalvi et al., 2006; Vangveeravong, 2008) that compared albuterol given as 4-10 100 mcg/puff MDI with spacer to albuterol given 15 mg/hour continuously by nebulization there was no difference in the asthma score one hour after treatment. The mean asthma score after one hour of treatment was 3.9 points, and those treated with MDI and spacer had an asthma score that was 0.07 points lower, with a range of 0.4 points lower to 0.26 points higher, *Mean Difference* = -0.07, 95% CI [-0.40, 0.26] (see Table 1 and Figure 5). The included studies had a total of 233 subjects. The studies are graded as very low quality due to (a) lack of blinding, it is not clear how blinding was attained, and one study is a non-randomized cross-sectional study (see Figure 2); (b) various asthma scores were utilized in the studies; and (c) the mean difference in the asthma scores is less than one point.

Search Strategy and Results:

Search: (("status asthmaticus") OR (("Asthma"[Mesh] OR asthma[tw]) AND ("accident and emergency" OR "A and E" OR "Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[Mesh] OR "emergency department"[tw]))) AND (("administration and dosage" [Subheading] OR "Administration, Inhalation"[Mesh] OR "Nebulizers and Vaporizers"[Mesh] OR "Metered Dose Inhalers"[Mesh] OR dose[tw] OR dosing[tw]) AND ("Albuterol"[Mesh] OR albuterol[tw] OR levalbuterol[tw] OR SABAs[tw] OR "Adrenergic beta-2 Receptor Agonists"[Mesh] OR "Short-acting beta-agonists" OR "adrenergic β2 receptor agonists")) AND (infant OR child OR paediatr* OR pediatr* OR adolescence OR children OR childhood) AND ("2010/01/01"[PDAT]: "2017/12/31"[PDAT]) 86 results, ten were selected for inclusion by the team leaders. Five articles from the previous CAT are included (see Figure 1).

Studies included in this review:

Mitselou, Hedlin, & Hederos (2016)
Dhuper et al., (2011)
Deerojanawong et al., (2005)
Jamalvi, Raza, Naz, Shamim, & Jamalvi, (2006)
Rotta, Amantea, Froehlich, & Becker, (2010)
Schuh et al., (1999)
Vangveeravong, (2008)

Studies <u>not</u> included in this review with exclusion rationale:

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Authors	Reason for exclusion
Pardue Jones, Fleming, Otillio, Asokan, & Arnold, (2016)	Narrative review
Mecklin, Paassilta, & Korppi, (2012)	Does not answer the question
Fagbuyi et al., (2016)	Outcome: hourly diastolic blood pressure; does not answer the question
Wisecup, Eades, Hashmi, Samuels, & Mosquera, (2015)	Outcome: hourly diastolic blood pressure; does not answer the question
Phumeetham, Bahk, Abd-Allah, & Mathur, (2015)	Outcome: hourly diastolic blood pressure; does not answer the question
Kenyon et al., (2014)	Outcome: clinical deterioration; does not answer the question
Sarnaik et al., (2013)	Outcome: hourly diastolic blood pressure; does not answer the question
Wilkinson et al., (2017)	Does not compare MDI to nebulizer

EBP Scholar's responsible for analyzing the literature:
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Jena Servatius, BS, RDMS, CPST

EBP team member responsible for reviewing, synthesizing, and developing this document:
Nancy H. Allen, MS, MLS, RD, LD

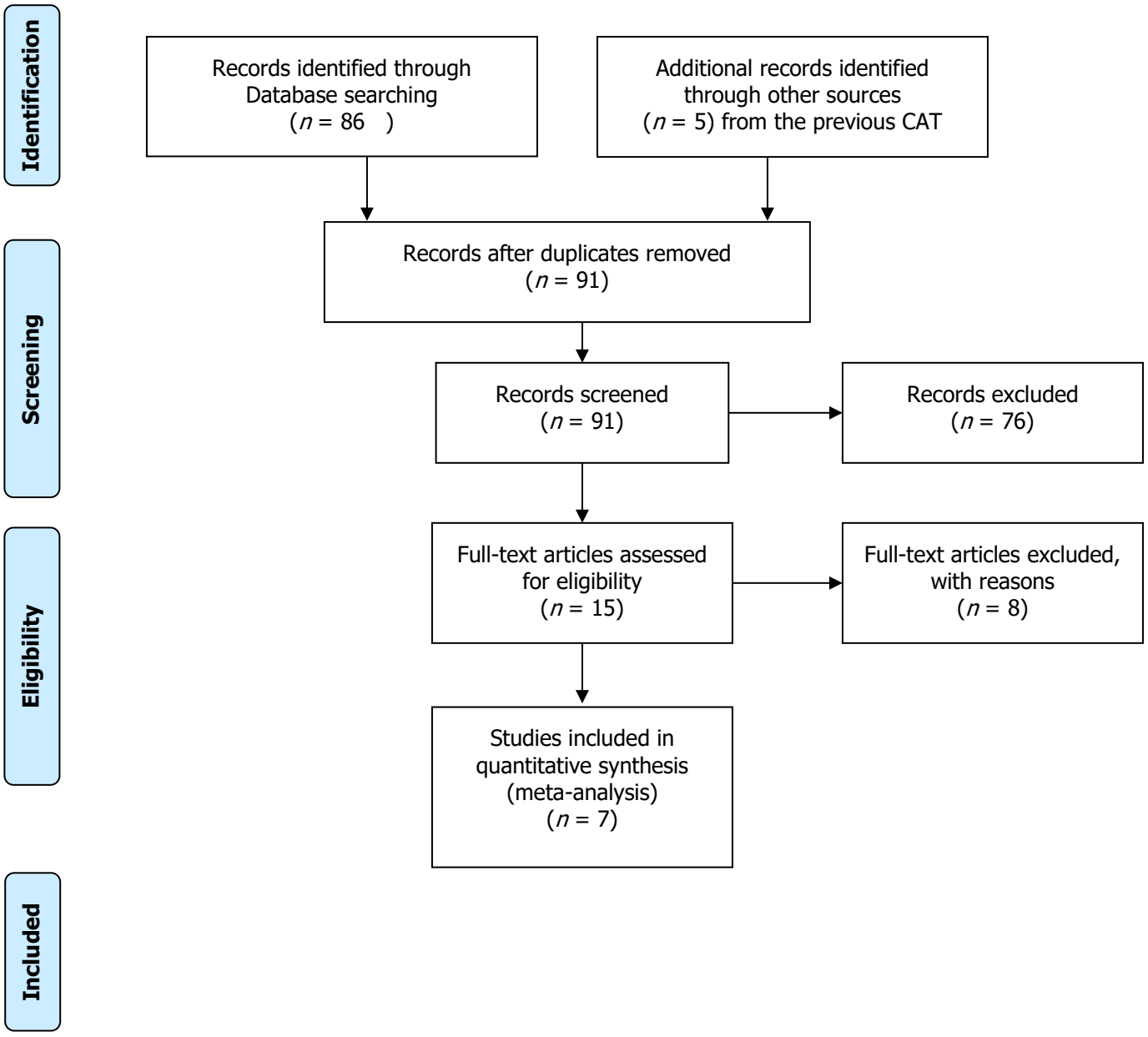
Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize the XXX included studies. GRADEpro GDT (Guideline Development Tool) is the tool used to create the Summary of Findings Tables for this analysis.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

Date Developed/Updated: December 2017

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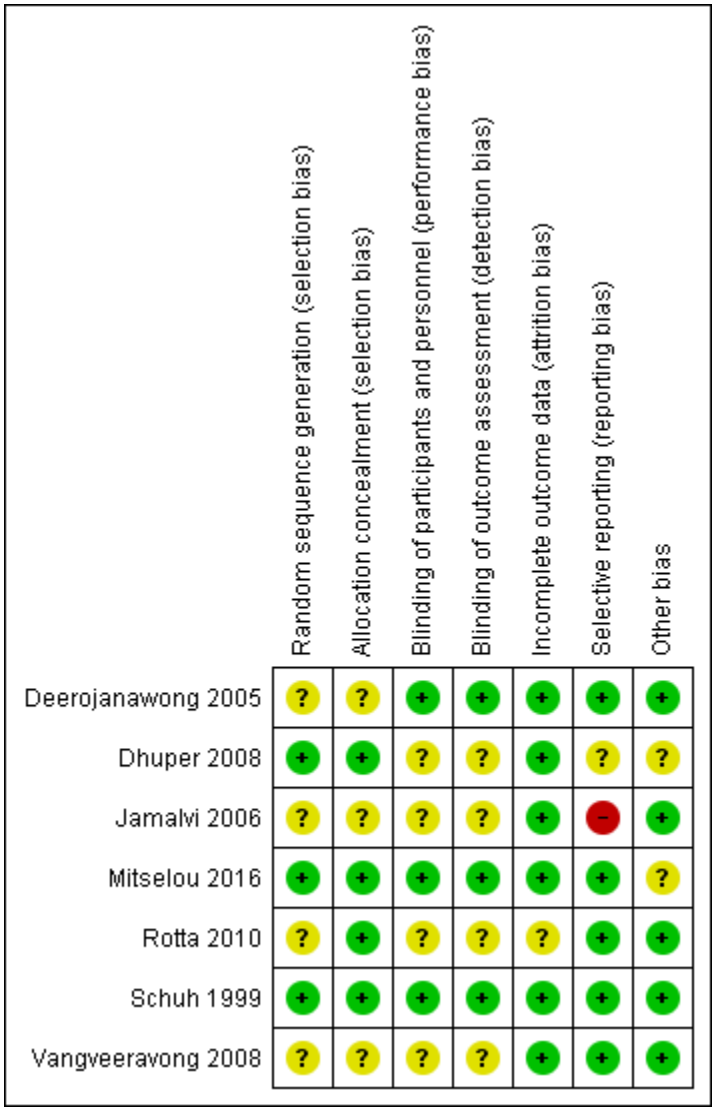
Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) [b]



[b]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

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Figure 2
Risk of Bias Summary



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Figure 3
MDI versus Nebulizer, Outcome: Hospitalization

	MDI		Nebulizer			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Dhuper 2008	1	29	2	29	8.1%	0.48 [0.04, 5.63]
Jamalvi 2006	4	84	7	66	31.5%	0.42 [0.12, 1.51]
Mitselou 2016	7	45	6	53	19.6%	1.44 [0.45, 4.66]
Rotta 2010	14	25	14	21	28.3%	0.64 [0.19, 2.12]
Schuh 1999	4	60	2	30	10.5%	1.00 [0.17, 5.79]
Vangveeravong 2008	1	18	0	18	1.9%	3.17 [0.12, 83.17]
Total (95% CI)		**261**		**217**	**100.0%**	**0.80 [0.44, 1.46]**
Total events	31		31			

Heterogeneity: Chi² = 2.99, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

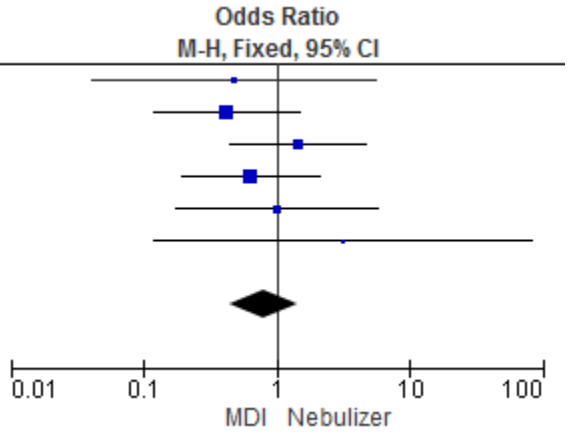
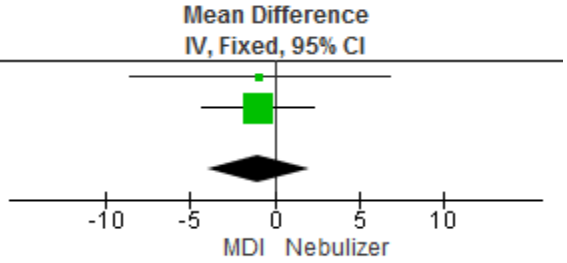


Figure 4
MDI versus Nebulizer, Outcome: Respiratory Rate

	MDI			Nebulizer				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Deerojanawong 2005	42.6	14.5	24	43.5	12.5	23	15.3%	-0.90 [-8.63, 6.83]
Jamalvi 2006	30	9.2	84	31	10.9	66	84.7%	-1.00 [-4.28, 2.28]
Total (95% CI)			**108**			**89**	**100.0%**	**-0.98 [-4.01, 2.04]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



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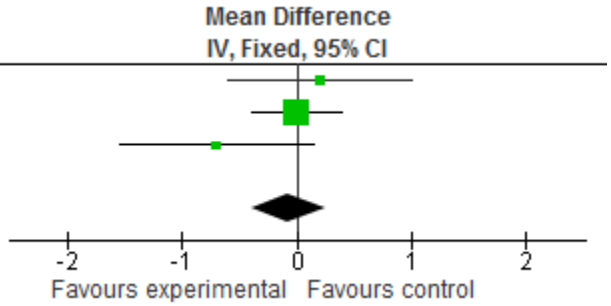
Figure 5

MDI versus Nebulizer, Outcome: Asthma Score

	MDI			Nebulizer				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Deerojanawong 2005	3.4	1.4	24	3.2	1.4	23	16.9%	0.20 [-0.60, 1.00]
Jamalvi 2006	7	1	84	7	1.4	66	67.9%	0.00 [-0.40, 0.40]
Vangveeravong 2008	1	1.23	18	1.7	1.35	18	15.2%	-0.70 [-1.54, 0.14]
Total (95% CI)			**126**			**107**	**100.0%**	**-0.07 [-0.40, 0.26]**

Heterogeneity: Chi² = 2.70, df = 2 (P = 0.26); I² = 26%

Test for overall effect: Z = 0.43 (P = 0.66)



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Table 1
Summary of Findings Table

Albuterol administered by MDI and spacer versus NEB for children 6 years and older with a severe asthma exacerbation in the ED											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With 4-10 puff 100 mcg/puff [MDI and spacer] repeat every 20 minutes of 1 hours	**With albuterol 15 mg/hour NEB**		**Risk with 4-10 puff 100 mcg/puff [MDI and spacer] repeat every 20 minutes of 1 hours**	**Risk difference with albuterol 15 mg/hour NEB**
Hospitalization											
478 (6 RCTs)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	31/261 (11.9%)	31/217 (14.3%)	**OR 0.80** (0.44 to 1.46)	119 per 1,000	**21 fewer per 1,000** (63 fewer to 46 more)
Respiratory Rate											
197 (2 RCTs)	serious [d]	not serious	not serious	serious [e]	none	⨁⨁◯◯ LOW	108	89	-	The mean respiratory Rate was **37.3** breaths per minute	MD **0.98 breaths per minute lower** (4.01 lower to 2.04 higher)

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Asthma Score											
233 (3 RCTs)	serious [d]	not serious	serious [f]	serious [g]	none	⊕◯◯◯ VERY LOW	126	107	-	The mean asthma Score was **3.9** points	MD **0.07 points lower** (0.4 lower to 0.26 higher)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Lack of blinding of patients, personnel, or outcome assessors occurred in 67% of the included studies. Two of the included studies are non-randomized studies, a prospective cohort study and a cross-sectional study.

b. The equipment used varied across studies. Some MDIs used spacers, and other used did not. Some of the spacers were specific products, "nebunnett", or 'Easyhaler', etc. Nebulized albuterol was administered by mouthpiece, or mask in the included studies.

c. There is a low number of events. The confidence intervals of the included studies are wide.

d. It is not clear how the included studies randomized study participant or if allocation to study groups was concealed. Jamalvi et al. (2006) is a non-randomized, cross sectional study.

e. Confidence interval is wide, and the mean difference is less than one breath per minute.

f. Various asthma scores were employed in the included studies.

g. Confidence intervals of the included studies are wide. The difference in the scores is less than one.

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Table 2
Study Characteristics
Deerojanawong 2005

Methods	Randomized Control Trial
Participants	Children up to 5 years of age. 47 children
Interventions	**Group 1:** two puffs placebo via MDI with spacer followed by .15 mg/kg salbutamol respiratory via jet nebulizer, *N* = 23 **Group 2:** 2 puffs (100 micrograms per puff) of salbutamol via MDI spacer followed by placebo via jet nebulizer, *N* = 24 Medication was actuated into the spacer 30 seconds apart. 5 tidal breaths were allowed after each actuation. All patients received 50 mg/kg of chloral hydrate 30 minutes prior to the study. 30 minutes after the assigned aerosol treatment, pulmonary function tests were completed.
Outcomes	• Clinical scores • Tidal breathing pulmonary function test • Vital signs
Notes	Thailand. Nebulizer takes longer and is more expensive

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Probably, but does not give details
Allocation concealment (selection bias)	Unclear risk	Probably, but does not give details
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	Power calculation performed on airway resistance as the outcome. The calculated sample size was 21 per group.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Dhuper 2008

Methods	Randomized Control Trial
Participants	**Setting:** Two emergency departments, New York, USA 2004-2005. Data was collected from August 2004-August 2005 **Randomized into study:** *N* = 60

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	• **Group 1** LiteAire**:** *n = 30* • **Group 2** Nebulizer: *n* = 30 **Completed Study:** *N= 58* • **Group 1** LiteAire**:** *n = 29* • **Group 2** Nebulizer: *n = 29* **Gender, males:** • **Group 1** LiteAire**:** *n = 5* (17%) • **Group 2** Nebulizer**:** *n = 12* (41%) **Age: ALL ADULTS** **Inclusion Criteria:** • Diagnosis of asthma • Age 18–70 years • Ability to perform peak flow maneuvers with good effort **Exclusion Criteria:** • Requiring intubation and mechanical ventilation, • Smoking history 20 pack years, • The presence of coexistent systemic diseases such as congestive heart failure, pulmonary disease other than asthma such as pneumonia, tuberculosis, bronchiectasis, interstitial lung disease, sarcoidosis, pleural diseases, kyphoscoliosis, chronic obstructive pulmonary disease, renal failure, or cancer. **Power Analysis:** • The authors did not disclose a specific power value, but discussed how the sample size was projected
Interventions	• **Group 1 (LiteAire):** The MDI/spacer group received 540 micrograms of chloroflourocarbon (CFC) albuterol by MDI (six actuations of 90 micrograms/actuation; Warwick Pharmaceutical Corporation, Reno, NV) with the spacer followed by 3 mL of normal saline solution (0.9%) by nebulizer every hour until disposition. • **Group 2 (Nebulizer):**The Nebulizer group received six actuations of placebo MDI with spacer followed by 2.5 mg (3 cc) albuterol (Dey, Napa, CA) by nebulizer (Cardinal Health Edison, NJ) on a similar schedule. Technique: • MDI was shaken before each actuation and medication was administered one actuation at a time into the spacer • Each actuation was delivered just before inhalation and the aerosol was inhaled from the spacer by six tidal breaths • All MDI/spacer treatments were self-administered by the patient after a one-time demonstration of its use by a respiratory therapist (RT) • All nebulizer treatments were administered by a RT in the asthma treatment room in the ED • The Respiratory Therapist documented in the electronic medical chart the vital signs, room air oxygen saturation, lung examination, and a pre- and post-treatment peak flow rate for every treatment administered
Outcomes	**Primary outcome(s):**

	• Changes in patients' symptoms • Peak flow rates, • Disposition (admission to hospital or discharge to home from the ED) **Secondary outcome(s)** • Length of stay in the ED • Cost of therapy • Number of rescue treatments required
Notes	• Median and interquartile range values were reported • Medians (IQR) for increase in peak flow from entry to disposition were similar for the two groups, with 120 (75–180) L/minute for the MDI/spacer group and 120 (80 – 155) L/minute for the Nebulizer group (p = .56) • The median length of ED stay was 2 h for both groups, with an IQR of 1.5–3.0 hour for the MDI/spacer group and an IQR of 1–2.5 hours for the Nebulizer group (p =.78)

Risk of Bias Table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization table
Allocation concealment (selection bias)	Low risk	Randomization codes were selected by a pharmacist who was not involved in the study
Blinding of participants and personnel (performance bias)	Low risk	Only the pharmacist knew the study codes. All personnel involved in patient recruitment and medication delivery were blinded to the randomization
Blinding of outcome assessment (detection bias)	Low risk	Placebo MDIs were prepared by a pharmacist who was not involved in the study or in the assignment of randomization codes
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	median and interquartile range values were reported.
Other bias	Unclear risk	The study was funded by a grant from the manufacturer of the LiteAire device

Jamalvi 2006

Methods	Cross-sectional study
Participants	150 children > 6 months
Interventions	**Group A:** standard dose of beta agonist (salbutamol) by MDI/accessory device (100 microgram/puff) 2 puffs three times per hour at 20 minute intervals with the help of a one way valve accessory device. Two types of spacers, a mouthpiece spacer for older children and a babyhaler with mask for younger children. (N= 84)

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	Group B: standard dose of beta agonist (salbutamol) by small volume nebulizer (0.3 mg/kg/ salbutamol solution) Salbutamol solution with 2 ml Normal Saline in one hour with 20 minutes interval with the help of New Nebulizer type 3 Nuova S.P.A. Bresia, Italy (*N*= 66)
Outcomes	• Clinical exam • Peak Expiratory Flow Rate (PEFR) • Assessment at 10, 20 minutes, and 2 hours, after completion of treatment
Notes	3 drop outs- no indication of which group they came from

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not describe
Allocation concealment (selection bias)	Unclear risk	Did not describe
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	High risk	No indication from which group the dropout came from
Other bias	Low risk	

Mitselou 2016

Methods	Prospective study
Participants	**Setting:** Pediatric emergency department at Central Hospital, Karlstad, Sweden **Randomized into study**: *N* = 98 • **Group 1:** Nebulizer:beta-2-agonist salbutamol (Ventoline 5 mg/ml) 4ml *n* = 53 • **Group 2:** Spacer: salbutamol MDI (Airomir 100ug/puff) with spacer (nebunette) n=45 **Completed Study:** *N* = 98 • **Group 1:** 53 • **Group 2:** 45 **Gender, males:** • **Group 1:** 34 (64.2%) • **Group 2:** 33 (73.3%) **Age, months: Mean +/- (SD)**

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	• **Group 1:** 23.36 (15.77) • **Group 2:** 22.71 (11.85) **Inclusion Criteria:** • 0-6 y/o • Presented with virus infection associated with wheezing or acute exacerbation of asthma to ED **Exclusion Criteria:** • Symptoms consistent with pseudocroup • Clinically suspected or lab confirmed RSV • Multi-handicapped pts • Life threatening asthma exacerbation • Signs of impending respiratory failure **Power Analysis:** Based on finding a 25% difference in hospitalization rate, the power estimation found that 80% power with 95% significance is 49 subjects were in each group.
Interventions	**Group 1:** Nebulizer:beta-2-agonist salbutamol (Ventoline 5 mg/ml) 4ml • <35kg: continuous nebulization for one minute • >35kg: continuous nebulization for two minutes **Group 2:** Spacer : salbutamol MDI (Airomir 100ug/puff) with spacer (nebunette) • <2y/o: 4 puffs (10 breathes/puff) • >2 y/o: 6 puffs (5 breathes/puff) Treatment could be repeated up to 3x during first hour (20-30min intervals) in both groups.
Outcomes	**Primary outcomes:** • Length of stay in PED-similar • Admission rate-similar • Parents experience-no significant difference
Notes	• Family history of asthma and atopic diagnosis was greater in nebulizer group. • Comparison of who had asthma medication versus who parents described as having asthma was not similar-parental report may lead to underestimation of asthma prevalence.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed in respective envelopes mixed in a box containing the same number of envelopes.
Allocation concealment (selection bias)	Low risk	Doctor picked new envelope from box in a blind manner.
Blinding of participants and personnel (performance bias)	Low risk	No blinding but not likely to be influenced

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Blinding of outcome assessment (detection bias)	Low risk	Assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Outcomes were reported upon, but difficult to locate them in the paper
Other bias	Unclear risk	Appears free of other bias

Rotta 2010

Methods	Randomized Control Trial
Participants	Children 1-5 years of age with the diagnosis of acute asthma in the ED
Interventions	**Experimental:** salbutamol MDI with spacer 50 microgram per kilo, 1 puff for every 2 kg of body weight. Each dose was administered 3 times in a one hour period. **Control:** salbutamol nebulizer 150 microgram per kilo. Each dose was administered 3 times in a one hour period. each patient received 1 mg/kg/ prednisone after the first treatment one blood sample drawn for plasma concentration of salbutamol drawn 10 minutes after third treatment
Outcomes	Plasma salbutamol concentration ≤ 2 years and > 2 years reported as median and interquartile range- cannot use. need for hospitalization
Notes	Brazil Exclusion criteria O2 sat < 90% on ambient air, fever > 38 degrees C., signs of cardiac instability, use of beta agonist in 12 prior to ED visit.

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer generated, blocks of five, children were "selected by the clinical staff" not certain what this means
Allocation concealment (selection bias)	Low risk	Medication prepared independent from the care team.
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Used a pilot study to determine sample size, 46 patients, and 23 in each group.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

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Schuh 1999

Methods	Randomized Control Trial
Participants	90 children between 5 and 17 years of age, % predicted FEV1 between 50-79%.
Interventions	**High MDI group** 4-8 puffs of albuterol via MDI number of puffs based on weight: < 25 kg 4 puffs, 25-34 kg 6 puffs and > 35 kg 8 puffs **Low MDI group** 2 puffs albuterol regardless of weight Nebulizer 0.15 mg/kg albuterol (maximum 5 mg) by jet nebulizer.
Outcomes	Primary outcome: % predicted FEV1. Secondary outcomes respiratory rate, heart rate, room air oxygen saturation, and accessory muscle score, wheezing score and dyspnea score.
Notes	Exclusion criteria- In the ED in the 2.5 year time frame, 6000 potential subjects were treated. Exclusion criteria- < 5 years of age, able to perform spirometry, FEV1 < 50% or greater than 80% predicted, first wheezing or bronchodilator treatment, use albuterol within the previous 4 hours, associated medical problem, language barriers, refusal to participate, arrived at the ED outside 0800-2200 when study nurses were available.

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized in the pharmacy using a block randomization schedule and random numbers.
Allocation concealment (selection bias)	Low risk	Randomization occurred in the pharmacy, and study drug came up with identical labels
Blinding of participants and personnel (performance bias)	Low risk	Only the pharmacy knew the treatments
Blinding of outcome assessment (detection bias)	Low risk	Only the pharmacy knew the treatments
Incomplete outcome data (attrition bias)	Low risk	Intent to treat analysis was used. There was a protocol violation. Sixteen subjects received albuterol within 4 hours of being enrolled. High Dose group- 6 subjects, low dose group- 2 subjects and nebulizer group-8 subjects.
Selective reporting (reporting bias)	Low risk	All outcomes reported upon
Other bias	Low risk	None identified

Vangveeravong 2008

Methods	Randomized Control Trial multicenter- 7 study sites
Participants	children 5-18 years of age mild to moderate asthma
Interventions	**Group 1:** Nebulizer 0.5% Ventolin respiratory solution 0.03 ml/kg/dose (maximum dose 1 ml) diluted with NSS to 3 ml, delivered via an oxygen-driven flow 6-8 liters per minute.

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	Group 2: MDI with volumatic spacer MDI spacer, using 6 puffs of Ventolin evohaler (100mg/puff) delivered via volumatic spacer 2 puffs at a time for 3 times. Group 3 DPI Easyhaler- DPI (Easyhaler) using 6 puffs of Buventol Easyhaler (100 mg/puff), 1 puff at a time for 6 times. 3 actuations in an hour
Outcomes	Asthma score, Oxygen saturation, vital signs, side effects (tremor, palpitations). Improvement defined at clinical score reduces < 50% form baseline, or clinical score < 3, or a total of 3 treatments. if If subjects failed 3 treatments they were admitted.
Notes	Thailand

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

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