ORIGINAL ARTICLE

Allergists *versus* pediatricians: primary choice of metered-dose inhaler with spacer or nebulizer

Primary choice of metered-dose inhaler with spacer or nebulizer

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ABSTRACT

Background. Many physicians believe delivering medications for asthma exacerbation via nebulizers is more efficacious than using a metered dose inhaler (MDI) with spacer. This study aimed to evaluate pediatricians and allergists' chosen method in children under 5 years: MDI with spacer or nebulizer.

Methods. A brief survey was sent via electronic mail to a randomly selected group of pediatricians and allergists. There was a 15.8% (430/2718) total response rate. We divided respondents into 2 groups. Group A comprised 289 primary care pediatricians, and Group B included 141 practicing allergists.

Results. In Group A, 68.5% (196/286) respondents indicated an MDI with spacer as their method of choice to deliver bronchodilator therapy during an asthma exacerbation; 64.7% (187/289) reported an MDI with spacer is an effective method; and 48% (135/281) believe delivering medication through a nebulizer will produce increased adverse effects than MDIs with spacers. In Group B, 55% (77/140) of respondents indicated MDI with spacer as their method of choice; 48.9% (69/141) reported a nebulizer is an effective method; and 65.7%

(90/137) believe delivering medication through a nebulizer will produce increased adverse effects.

Conclusions. Contrary to evidence-based recommendations, most allergists, compared to pediatricians, are not only prescribing nebulizers as their first choice for delivering bronchodilator therapy, but also half of these asthma specialists consider nebulizers to be an effective mode of delivery. As far as safety is concerned, ironically, almost two-thirds of allergists believe more side effects are associated with delivering bronchodilator therapy through a nebulizer.

Key words

Asthma; spacer; inhalation devices; metered dose inhaler; nebulizer.

Impact Statement: Despite evidence-based guidelines favouring MDI with spacer, this study reveals how many allergists and pediatricians still prefer nebulizers for asthma treatment in young children, highlighting a significant practice gap.

INTRODUCTION

Asthma is a chronic respiratory disease increasing in prevalence worldwide, especially in the younger age group. The Center for Disease Control and Prevention's most recent national asthma data reported an estimated 1.6 million emergency department (ED) visits and 183,000 hospitalizations in the United States due to asthma (1). Data show about 1 in 6 children with asthma visit the ED and about 1 in 20 are hospitalized each year for acute exacerbations (2). Short acting beta-agonists (SABA) are the mainstay in providing treatment during these acute episodes. The 2 main methods of delivering bronchodilators are via a nebulizer or a metered-dose inhaler (MDI) with a spacer.

For over a decade multiple studies have investigated the advantages of each delivery method and found considerable evidence supporting the use of MDIs with spacers over nebulizers. In comparison to MDIs with spacers, nebulizers are less convenient to use (especially in children because of the increased time needed for medication delivery and the need for an external power source), more expensive, and are associated with higher systemic side effects and hospital admission rates. In addition, the most recent Global Initiatives for Asthma (GINA) guidelines recommend avoiding nebulizers, when possible, in the case of confirmed or suspected SARS-CoV2 to decrease the viral transmission to other patients, family members and healthcare providers (3).

Regardless of these findings, many physicians strongly believe medication delivery for asthma exacerbation via a nebulizer is more effective than an MDI with spacer.

This study aimed to evaluate physicians' chosen method (MDI with spacer or nebulizer) for delivering bronchodilator therapy for children aged 5 and under. Another objective of this study was to review the results of studies that compared the effectiveness of inhalers and nebulizers in pediatric patients with asthma and examine their implications on clinical practice. To the best of our knowledge, there have been no studies comparing current

practices by asthma specialists to pediatricians with regards to the preferred type of SABA delivery mechanism.

METHODS

We received an exemption from our local institutional review board for this study.

A brief survey questionnaire was sent via e-mail to a randomly selected group of pediatricians and allergists. Survey results were recorded anonymously and collected over a 24-month period from 2019 to 2021. The questionnaire consisted of 5 items to help determine the preferred device choice to deliver SABA at the time of acute asthma exacerbation, and which device they considered more effective with less adverse effects (Table I). All surveyed physicians also were asked if they were interested in receiving both the findings of the survey and the resulting expert opinion on this topic. Once the data were analyzed and documented, all the related e-mails and surveys were deleted. Additionally, we reviewed the results of studies that compared the effectiveness of inhalers and nebulizers in pediatric patients with asthma and examined their implications on clinical practice. A comprehensive search was conducted of MEDLINE/PubMed for randomized trials involving children (including infants) with asthma and comparing delivery of SABA via MDIs with spacers versus nebulizers. The search terms included “children,” “asthma,” “metered dose inhaler,” “spacer,” and “nebulizer”. A total of 61 studies were identified, of which 33 were excluded for mixed populations of asthma and chronic obstructive pulmonary disease, adult population studies, and non-randomized trials; this left 28 studies for inclusion.

RESULTS

Physician survey

Of 2718 surveys sent, a total of 430 physicians completed the survey (response rate of 15.8%). We divided the respondents into 2 groups: Group A (n = 289) comprised of

pediatricians and Group B (n = 141) comprised of practicing allergists. Some respondents did not answer all the survey questions. For unanswered questions, those responses were excluded from the analysis for that question. Each participant's answers were used to calculate segment totals. Almost all the respondents (98.6%) in both groups were involved in treating children with asthma. In Group A, 40.3% (116 out of 288) of physicians had less than 5 years of clinical practice, while 36.8% (106 out of 288) had more than 10 years of practice. Most of the respondents in Group B (n = 78) had been in practice for more than 10 years (Figure 1).

Categorical Data Analysis and Study Results

The analysis and results of the study are summarized in Table 2. A chi-square testing methodology was employed to compare proportions between Group A and Group B across various categories. This analysis evaluated the significance of differences in preferences (MDIs with spacers versus nebulizers), perceived effectiveness, and adverse effects between the two groups.

Key Findings

1. Group B had a significantly higher proportion of respondents with more than 10 years of experience compared to Group A.
2. There were significant differences in preference between groups for both MDIs with spacers and nebulizers; Group A showed a stronger preference for MDIs with spacers, while Group B slightly favoured nebulizers.
3. Both MDIs with spacers and nebulizers were considered significantly differently effective between the two groups. Group A leaned towards MDIs with spacers and Group B showed more balanced perceptions.
4. Group B perceived significantly more adverse effects associated with nebulizers compared to Group A.

Review of Medical Literature

We reviewed 28 studies which compared the use of MDIs with spacers to nebulizers in the pediatric population (3137 children) (Supplementary Table I). These studies have been included in two systematic reviews, a meta-analysis (4, 33), and a Cochrane meta-analysis (34).

Pediatric Studies

Hospital Admission Rates

A systematic review with meta-analysis by Castro-Rodriguez and Rodrigo (4) in 2004 reviewed six studies and found significantly lower admission rate in the group who received β-agonists by MDIs with spacers compared to nebulizers (5, 6, 16, 22, 28). In the Cochrane meta-analysis by Cates et al. (34), data from 9 studies of children were reviewed and found no difference between the hospital admission rates in terms of the two delivery methods of SABA (6, 7, 16, 17, 24, 30, 32, 35, 36). Similar results were found in the updated Payares-Salamanca et al. (33) meta-analysis which analyzed eight studies (6, 13, 18, 20, 23, 25, 27, 28).

Duration in the Emergency Department

Cates et al. (34) examined the time spent in the ED by collecting data from three studies (14, 24, 35). The results showed the amount of time in the ED was significantly shorter for the group who used MDIs with spacers (33 minutes) compared to nebulizers (103 minutes). In two other studies, the length of the stay in the ED was similar for both groups (18, 20).

Length of Stay in the Hospital

There are three inpatient trials that studied length of hospital stay in children admitted with asthma in the two groups (MDIs with spacers or nebulizers). Parkin et al. conducted a study on hospitalized children with moderate acute asthma between ages 1 and 5 years and

found no significant difference between the two groups in the time to discharge from the hospital (10). Parent-reported symptoms at 7 and 14 days after discharge also were not significantly different in both groups. Similarly, in the study by Leelathipkul et al., SABA delivery via an MDI with a DIY-spacer was compared to nebulization, and length of hospital stay was comparable (19). In a study by Dewar et al., there was no significant difference in the median hospital stay for either group (29).

Clinical Asthma Scores

Various studies have found no significant differences in clinical asthma severity scores when using either MDIs with spacers or nebulizers. There was wide variability in the types or methods of clinical asthma scores used in the different studies (Pulmonary Index, Modified Wood's clinical score, Siriraj Clinical Asthma Score, respiratory distress assessment scale, modified Silverman score) thus making it difficult to examine the data. In general, the various studies looked at respiratory rate (RR), heart rate (HR), wheezing, cyanosis, oxygen saturation (SaO_2) and accessory respiratory muscle utilization (ARMU). No significant differences were demonstrated between the two delivery methods with regards to the clinical scores (5, 6, 10-13, 15-17, 19, 21-24, 27).

In a study by Robertson et al., 155 children between the ages of 4 and 12 years were studied and randomized to receive salbutamol 2.5 mg via the jet nebulizer (JN) or 600 µg (6 puffs) from the pressurized MDI (PMDI) (9). The study concluded that improvement in the clinical score from baseline at 30 minutes was 1.87 for the JN and 1.43 for the PMDI ($P = 0.09$) and, at 60 minutes, was 2.15 for the JN and 1.12 for the PMDI ($P = 0.0001$), thus favouring the JN over the PMDI for clinical efficacy. This difference may represent a dose response effect which will be further explained in the Drug Potency section of this paper.

Pulmonary Function Test

There has been no significant difference noted in the mean peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) in either group of patients receiving an MDI with spacer or a nebulizer.

Side Effects

Studies found extrapulmonary sympathetic adverse effects including tachycardia, tremor, and anxiety were more prevalent in patients who received beta-agonists via nebulizer compared to an MDI with spacer. This is likely due to larger systemic absorption of medication via nebulizer. Spacers, on the other hand, decrease particle velocity and reduce the number of large particles. This reduces oropharyngeal and large airway deposition with a consequent reduction in systemic absorption (9).

Type of Spacer

Many of the studies included commercially available spacers, but some studies used homemade, non-valved spacers (HM NVS).

A randomized control study by Yasmin et al., looked at efficacy of a JN and an MDI with HM NVS in acute exacerbation of asthma in children (8). Fifty children between 2 and 12 years of age with acute asthma exacerbation received salbutamol via an MDI with HM NVS or nebulized salbutamol solution. The change in SaO2, RR, HR and wheezing were measured. There was no significant difference in these parameters between either group ($P > 0.05$).

A prospective, randomized study which evaluated the efficacy of non-valved spacers was conducted by Duarte and Camargos, who studied 196 children aged 4 to15 years (14). No difference was noted in the clinical findings, PEFR, SaO2, HR or RR in either group. The nebulizer group needed prolonged observation in the ED and had more side effects, such as increased HR compared to patients who received SABA via an MDI with a non-valved spacer.

Chong Neto et al. compared 40 children between the ages of 6 and 18 years who received salbutamol in four groups (30): a nebulizer group, an MDI group with a commercially available spacer (CAS), an MDI group with a HM NVS, and a dry powder inhaler group (DPI). Outcome measures included FEV1, hospital admission, change in asthma symptom score, and side effects such as tachycardia, tremor, nausea, vomiting or hypokalemia. The study found MDI with a CAS was safer and more efficient compared to a nebulizer, homemade spacer, or dry powder inhaler when treating acute attacks of mild to moderate asthma in school-aged children and adolescents. Increased tachycardia and tremors were noted in patients who used an MDI with a HM NVS, but it is an efficient and inexpensive alternative if used with caution.

Drug Potency Ratio

There has been a wide variation reported for the beta-agonist dose needed to produce a comparable therapeutic response for each delivery system. A review of literature shows variations ranging from 1:1 to 1:12.5. Overall, we have seen the comparative drug potency ratio for bronchodilator response is 6:1 to 7:1 (nebulizers versus MDIs with spacers), which means that 2.5 mg of albuterol via nebulizer is equal to 4 puffs of an MDI with spacer. Schuh et al. (25), demonstrated that treatment with 2 puffs of albuterol (200 μg) via an MDI with spacer was as clinically effective (similar improvement in percent predicted FEV1) as treatment with 3 to 5 times higher doses delivered via an MDI with spacer or nebulizer in children with mild acute asthma.

One of the other disadvantages to using a nebulizer is that a majority of the aerosol delivered does not reach the respiratory tract. Most of the medication remains in the nebulizer tubing or gets impacted in the oropharynx and is swallowed. Robertson et al. found salbutamol administration via an MDI and large volume spacer device provided effective relief in management of acute asthma in children aged 4 to 12, but to a lesser extent

compared to a JN (9). The study concluded the difference may be due to a dose response effect. The study identified three factors in the design of their study that could have led to reduced efficiency:

1. New, plastic spacers have higher electrostatic charge, which attracts aerosol particles to adhere to the inner surface thereby reducing the drug output to 64%. Repeated use of the spacer provides a "coating" of the drug particles and rinsing with domestic ionic detergents reduces the electrostatic charge thereby greatly improving the drug delivery (37).
2. It is a common pediatric practice to place multiple actuations into the spacer for convenience, but this can decrease the efficiency by an increase in impaction of particles on the wall of the device (38). Loading the spacer device with 2 actuations reduces the output by 22%, and with 5 actuations, the output is reduced by 62% for particles less than 5 μg compared with single actuations (39). In this study, the spacer device was loaded with 3 actuations which may have resulted in reduced MDI treatment efficiency (39).

Infant Studies

Younger children often are unable to coordinate inspiration with MDI activation thereby limiting the amount of drug inhaled, but the introduction of spacers has solved the problem. By holding medication in chambers, the spacer allows the patient to receive inhaled medication while taking normal breaths through a face mask or mouthpiece.

Rubilar et al. studied the clinical score of 123 children aged 1 to 24 months comparing treatment with an MDI with a spacer to nebulization (5). After the first hour of treatment with salbutamol, the clinical score dropped to ≤ 5 in 90% (56/62) of the children in the MDI with spacer group, versus 71% (43/61) of the children in the nebulizer group (odds ratio 3.9, 95% CI 1.5-10.4, $P = 0.01$). After the second hour, the response was 100% in the

MDI with spacer group and 94% in the nebulizer group ($P > 0.05$). The study concluded that children less than 2 years of age with moderate to severe exacerbation of wheezing responded faster to salbutamol delivered via an MDI with spacer compared to a nebulizer. Only one patient in the nebulizer group was hospitalized following treatment failure.

Delgado et al. evaluated 168 wheezing infants aged 2 to 24 months who received albuterol via nebulizer or MDIs with spacers (28). No significant differences were noted between the groups in percentage improvement in pulmonary index score, SaO_2, or percentage of patients with vomiting. Patients in the spacer group were significantly less likely to be admitted, received fewer treatments, were less likely to receive steroids, and had a lower mean increase in HR.

A study by Closa et al. compared responses of 34 infants (1 to 24 months of age) with acute wheezing to treatments of inhaled terbutaline administered via nebulizer or MDI with spacer (21). There was no difference in the rate of improvement in the clinical score between infants who received terbutaline via nebulizer or those who received it via MDI with spacer.

DISCUSSION

The findings of our survey highlight notable differences in the preferences and practices between pediatricians (Group A) and allergists (Group B) regarding the use of MDIs with spacers and nebulizers for asthma management in children. These differences provide valuable insights into clinical decision-making and align with existing evidence in the medical literature, but they also underscore areas for potential improvement in aligning practice with evidence-based guidelines.

When comparing the results of the two groups, we found a greater number of pediatricians are following evidence-based recommendations and prescribing MDIs with spacers for delivering SABA. They also consider MDIs with spacers as an effective mode of SABA delivery compared to allergists. As far as safety is concerned, significantly more

allergists believe increased side effects are associated with delivering bronchodilator therapy through a nebulizer.

Multiple studies have compared the use of MDIs with spacers to nebulizers in infants and young children younger than 5 years old during an asthma exacerbation (4-6). These show that MDIs with spacers have lower admission rates, and clinical scores compared to patients receiving medication via nebulizers.

Changing old habits can be challenging; therefore, a review of previous literature is of paramount importance to educate physicians and encourage the adoption of evidence-based medicine.

The literature reviewed strongly supports the use of MDIs with spacers over nebulizers, particularly in pediatric populations. Studies have consistently demonstrated lower hospital admission rates, shorter emergency department stays and reduced adverse effects with MDIs and spacers. These findings reinforce the importance of disseminating evidence-based guidelines to clinicians across specialties.

CONCLUSION

Our study reveals that, contrary to evidence-based guidelines, many allergists treating children prioritize nebulizers over MDIs with spacers for delivering short-acting beta-agonists (SABA). This contrasts with robust evidence from randomized controlled trials and meta-analyses, which demonstrate that MDIs with spacers are equally effective as nebulizers for managing acute asthma exacerbations in children. Pediatric studies show MDIs with spacers significantly shorten emergency department visits, reduce systemic side effects, and improve clinical scores compared to nebulizers.

Additionally, nebulizers are less economical, requiring more equipment, time, and effort, and carry a risk of cross-contamination if not properly cleaned. Despite these

advantages, our study highlights the persistent underutilization of MDIs with spacers by allergists, suggesting awareness of their benefits alone is insufficient to drive change.

This study underscores the need for broader investigations into barriers preventing the routine adoption of MDIs with spacers. A lack of consensus among healthcare providers compounds caregiver resistance, as caregivers often rely on guidance from physicians.

While our survey and literature review provide valuable insights, the scarcity of recent studies on this topic limits the available data, necessitating reliance on older but significant research. The findings emphasize the urgency of bridging the gap between evidence-based recommendations and clinical practice, promoting the widespread adoption of MDIs with spacers for pediatric asthma management.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings: None.

Contributions: SM, EY: Conceptualization. SM, EY: Data curation. SM, EY: Investigation. SM, EY: Methodology. SM, EY: Project administration. SM, EY: Supervision. SM, EY: Writing – original draft. SM, EY: Writing – review & editing.

Conflict of Interests: The authors declare they have no conflicts of interest.

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Table 1. Survey questionnaire.

Do you take care of children with asthma?

- *Yes*
- *No*

How long have you been in practice?

- *Less than 5 years*
- *5-10 years*
- *More than 10 years*

Which is your preferred choice of device to deliver Albuterol/Levalbuterol during asthma exacerbation?

- *Metered dose inhaler with spacer*
- *Metered dose inhaler without spacer*
- *Nebulizer*

Which of the devices do you consider effective to use in the event of an asthma exacerbation?

- *Metered dose inhaler with spacer*
- *Metered dose inhaler without spacer*
- *Nebulizer*

Which of the following devices is associated with more adverse effects while delivering bronchodilator therapy?

- *Metered dose inhaler with spacer*
- *Metered dose inhaler without spacer*
- *Nebulizer*

Please let us know if you are interested in receiving both the findings of the survey and the expert opinion on this topic by checking one the following:

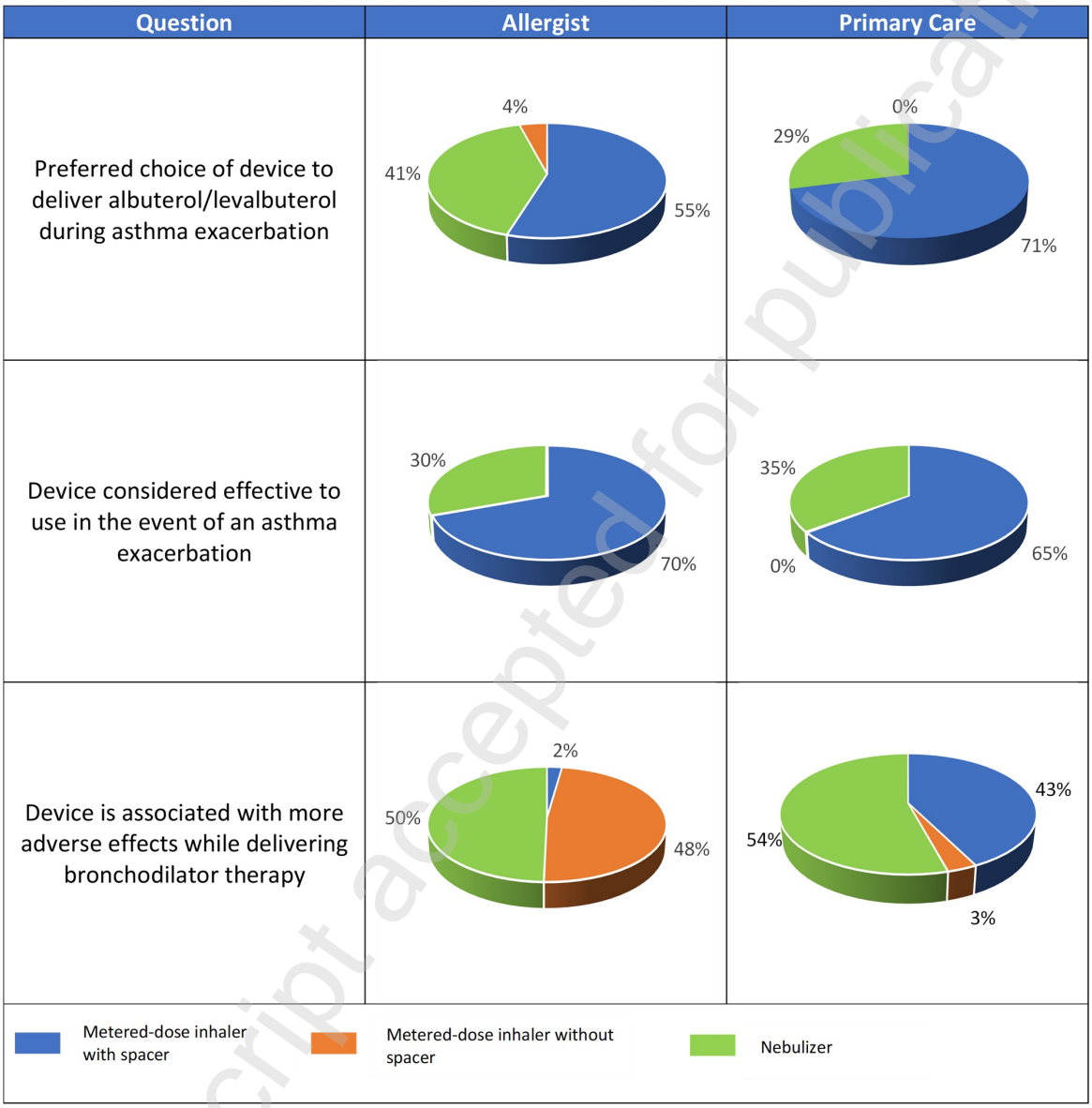
- *Interested in receiving the findings of this survey and expert opinion on this topic*
- *Not interested in receiving the findings of this survey and expert opinion on this topic*

Table 2: Summary of Categorical Data Analysis

Category	Group A	Group B	p-value
Years of Clinical Practice (<5 yrs)	40.4% (116/288)	44.7% (63/141)	0.389
Years of Clinical Practice (>10 yrs)	36.9% (106/288)	55.3% (78/141)	**<0.001**
Preferred Delivery Method: MDIs with spacer	68.5% (196/286)	55.0% (77/140)	**0.007**
Preferred Delivery Method: Nebulizers	30.8% (88/286)	41.4% (58/140)	**0.011**
Effectiveness of MDIs with spacer	64.7% (187/289)	48.2% (68/141)	**0.001**
Effectiveness of Nebulizers	34.9% (101/289)	48.9% (69/141)	**0.004**
Adverse Effects: MDIs without spacer	49.1% (138/281)	58.1% (82/141)	0.098
Adverse Effects: Nebulizers	48.0% (135/281)	65.7% (90/137)	**<0.001**

Bolded values indicate statistically significant differences between groups

Figure 1. Physician perspective and preference in the choice of metered-dose inhaler with spacer versus nebulizer.



Supplementary Table 1. Studies comparing the use of metered-dose inhalers with spacers compared to nebulizers in the pediatric asthmatic population.

Study Name	**Williams et al. (7)**
Study Design	Randomized control
Population Patient Demographics	ED[a] of Children's Hospital, Denver CO, USA 60 patients (6-18 years)
Dose/Route of Delivery and Duration of Therapy	All patients received 3 albuterol treatments given at 30-minute intervals: 1)Nebulizer (PARI-JET II) group 2.5 mg of albuterol given every 30 minutes in 3 mL saline driven by pressurized air at 6 L per minute. 2) MDI[b] with spacer (Aero chamber v. ACE spacers) group, 4 x 90 mcg actuations of salbutamol given separately every 30 minutes, inhaled using tidal breathing for 1 minute each
Outcome Measures	Pre- and posttreatment percent predicted RR[c] and percent predicted PEFR[d]
Key Outcomes	No significant difference was found in improvement of RR or PEFR
Study Name	**Yasmin et al. (8)**
Study Design	Randomized control
Population Patient Demographics	Department of Pediatrics, Dhaka Medical College, Bangladesh 50 patients (2-12 years)

Dose/Route of Delivery and Duration of Therapy	3 treatments given at 20-minute intervals: 1)Salbutamol via MDI and home-made spacer (25 participants) 6 puffs of salbutamol. 2) Nebulized salbutamol solution (25 participants) 0.15 mg/kg and minimum 2.5 mg in 2.5 mL normal saline.
Outcome Measures	Change in oxygen saturation, RR, HR[e], and wheezing were measured.
Key Outcomes	No significant difference in both groups for oxygen saturation, RR, HR and wheezing ($p>0.005$).
Study Name	**Robertson et al. (9)**
Study Design	Randomized, double blind, parallel design
Population Patient Demographics	ED, Multicenter, Australia 155 children (4-12 years)
Dose/Route of Delivery and Duration of Therapy	1)MDI with spacer: Volumatic dosage:600 mcg (<25 kg) and 1200 mcg (>25 kg) given in bursts of 3 puffs with 15 seconds of tidal breathing. 2)Nebulizer (AVA-NEB Hudson). Dosage: 2.5 mg (< 25 kg) or 5 mg (> 25 kg) in 2.5 mL saline driven by oxygen at 8 to 10 L/min. Dose ratio spacer: nebulizer = 1:4.2. Single-dose study.
Outcome Measures	Clinical asthma scores, PEFR, incidence of side-effects, tremor, HR, and BP[f]
Key Outcomes	Clinical asthma scores, PEFR, incidence of side-effects, tremor, HR, and BP as well as withdrawals from the

	study were acceptable and similar in both treatment groups.
Study Name	**Parkin et al. (10)**
Study Design	Randomized control
Population Patient Demographics	Hospital inpatients (after stabilization in ED), Canada 60 children (1-5 years, mean age 35 months)
Dose/Route of Delivery and Duration of Therapy	1)MDI with spacer (Aerochamber): Salbutamol 4 puffs (400µg) if <12 kg, 5 puffs (500µg) if 12 to 16 kg, and 6 puffs (600 µg) if ≥16 kg, with ipratropium bromide 2 puffs (40 µg). 2)Nebulizer: Salbutamol 0-15 m/lkg and ipratropium bromide 125 µg, in 3 ml of normal saline solution over 15 minutes via facemask driven by compressed air.
Outcome Measures	Primary outcome: a 10-point clinical asthma score measuring 5 parameters (RR, wheezing, indrawing, observed dyspnea, and inspiratory to expiratory ratio) measured at baseline and every 12 hours for the first 60 hours of hospitalization. Secondary outcome: time to discharge, time to 4-hourly dosing interval, and total number of inhaled doses required.
Key Outcomes	No significant differences noted in primary as well as secondary outcomes.
Study Name	**Freelander et al. (11)**
Study Design	Randomized

Population Patient Demographics	ED, Australia 28 children (3-13 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (Nebuhaler): 5 puffs (1.25 mg) <20 kg, 10 puffs (2.5 mg) > 20kg. Nebulizer group (Hudson): driven by air at 6 L/minute. Dosage: 2.5 mg in 2 mL saline <20 kg, 5 mg in 2 mL saline >20 kg. Single treatment for both groups.
Outcome Measures	Patients evaluated clinically at 0, 15 and 30 minutes, clinical variables assessed were dyspnea, wheezing, muscle contraction, supraclavicular excavations, thoracoabdominal paradox, HR, RR, and pulsus paradoxus, assessed on a scale of 0-4. PEFR (in children old enough to perform test)
Key Outcomes	No significant differences between the groups at any time but both groups showed improvements at 15 and 30 minutes.
Study Name	**Pendergast et al. (12)**
Study Design	Randomized, open, parallel group
Population Patient Demographics	Children's hospital Camperdown or Westmead Hospital, Australia 27 children (3-6 years)
Dose/Route of Delivery and Duration of Therapy	Group 1: MDI with spacer (Nebuhaler): low dose, 1 puff (0.25mg) per 5 kg.

	Group 2: MDI with spacer (Nebuhaler): high dose, 2 puff (0.5mg) per 5 kg. Each dose (bursts of 3 or 4 puffs) inhaled with 2 breaths and then a minute of tidal breathing. Group 3: Nebulizer group (Unicorn): driven by air at 6 L/minute. Dosage: 0.2 mg per kg weight in 2 mL saline (max 5 mg).
Outcome Measures	Clinical variables assessed were dyspnea, wheezing, muscle contraction, supraclavicular excavations, thoracoabdominal paradox, HR, RR, and pulsus paradoxus, assessed on a scale of 1-4.
Key Outcomes	No significant difference was found in the mean baseline clinical score among the 3 groups and a significant decline was seen in all 3 groups at 15 minutes which was maintained to 60 minutes.
Study Name	**Kerem et al. (13)**
Study Design	Randomized, double-blinded
Population Patient Demographics	ED Hospital for Sick Children, Toronto, Ontario, Canada 33 children (6-14 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (VentAHaler): 100 µg/puff. 6 puffs <25 kg, 8 puffs for 25-35 kg, 10 puffs for >35 kg Total dose discharged into the spacer device in rapid sequence followed by tidal breathing for 1minute. Nebulizer group (Whisper Jet Nebulizer): 0.15 mg/kg to a maximum of 5 mg, mixed with 3 ml 0.9% saline solution

	and delivered continuously by a face mask using 100% oxygen at a flow rate of 6 to 10 L/min until nebulization was complete. Single treatment for both groups.
Outcome Measures	Clinical score, oxygen saturation, forced expiratory volume in 1 second, RR, HR before and 10, 20 and 40 minutes after treatment and hospital admission.
Key Outcomes	No difference in the rate of improvement of clinical score, RR, oxygen saturation, or forced expiratory volume in 1 second was noted between children who received albuterol by nebulizer and those who received it by MDI with spacer. HR increased in the nebulizer group and decreased in the MDI-spacer group ($p < 0.05$).
Study Name	**Duarte et al. (14)**
Study Design	Prospective, randomized
Population Patient Demographics	ED Child and Adolescent Institute, Juiz de Fora, Brazil 196 children (4-15 years)
Dose/Route of Delivery and Duration of Therapy	MDIs (with homemade non-valved spacer made from 500 ml plastic mineral water bottle coated with detergent to avoid electrostatic charge): 5x100 µg/puff. after each actuation tidal breathing for 20 seconds. Oxygen-driven nebulizer group (Nevoni): 0.15 mg/kg to a maximum of 5 mg, mixed with 4 ml 0.9% saline solution and delivered continuously by a face mask using 100% oxygen at a flow rate of 6

	L/min. Each group had repeated treatment up to 3 doses assessed every 15 mins until PEFR ≥80% predicted value.
Outcome Measures	PEFR, oxygen saturation, HR, RR, clinical score, ED length of stay
Key Outcomes	No difference in the clinical findings, PEFR, oxygen saturation, HR, RR means in both groups. Side effects of salbutamol included increased HR observed in 17.2% of patients in oxygen-driven nebulizer group, and 4.1% homemade non-valved spacer group, so higher in oxygen-driven nebulizer group. Also, during asthma attacks oxygen-driven nebulizer group needed a prolonged observation in the emergency department.
Study Name	**Lin et al. (15)**
Study Design	Randomized
Population Patient Demographics	ED and pediatric allergy clinic of the Taipei Municipal Chung Hsiao Hospital 111 children (5-16 years)
Dose/Route of Delivery and Duration of Therapy	The MDI with spacer group (Aero chamber): 60 patients, Dose: 3 x 0.25 mg puffs, each inhaled by 3 deep breaths. Nebulizer group (Pulmo-Aide): 57 patients, Dose: 2.5 mg in 2 mL saline, driven by air at 8 L/min. Single treatment for both groups.
Outcome Measures	Measured at 15 minutes after the start of treatment: clinical severity score (RR, wheezing, cyanosis, and

	accessory respiratory), spirometry (forced expiratory volume in 1 second, forced vital capacity, PEFR, forced expiratory force 25-75), oxygen saturation, and HR.
Key Outcomes	No statistically significant difference between the 2 groups in spirometry, clinical severity score, or HR. The mean absolute increase of PEFR and oxygen saturation for the MDI with spacer group, and the mean percent increase of forced expiratory volume in 1 second, peak expiratory force, and oxygen saturation were significantly higher than those for the nebulizer group.
Study Name	**Leversha et al. (16)**
Study Design	Randomized, double-blind, placebo-controlled trial
Population Patient Demographics	ED Starship Children's Hospital in Auckland, New Zealand 60 children (1-4 years)
Dose/Route of Delivery and Duration of Therapy	The MDI with spacer group (Aerochamber): 6x 100µg puffs ventolin inhaled separately followed by 5 tidal breaths followed by nebulization of normal saline. Nebulizer group (Marquest bowl with Hudson face mask): 2.5 mg in normal saline, driven by wall oxygen at 8 L/min, they also received 6 actuations of placebo MDI with spacer. Treatments repeated at 20-minute intervals until the patient was judged by the attending clinician to need no

	further doses of bronchodilator, up to a maximum of 6 treatments.
Outcome Measures	Clinical score, HR, RR, wheezing, and oxygen saturation were recorded at baseline, 20 mins after each treatment, and 60 minutes after the last treatment.
Key Outcomes	The spacer was as effective as the nebulizer for clinical score, RR, and oxygen saturation but produced a greater reduction in wheezing (P = .03). HR increased to a greater degree in the nebulizer group (11.0/min vs 0.17/min for spacer, P < .01). Fewer children in the spacer group required admission (33% vs 60% in the nebulizer group, P = .04, adjusted for sex). No differences were seen in rates of tremor or hyperactivity. The mean cost of each ED presentation was less for the spacer group than for the nebulizer group (P = .03); 86% of children and 85% of parents preferred the spacer.
Study Name	**Ploin et al. (6)**
Study Design	Randomized, double-blind, parallel group equivalence trial
Population Patient Demographics	Pediatric ED of 2 teaching hospitals in Lyon, France 64 children (1-5 years)

Dose/Route of Delivery and Duration of Therapy	The MDI with spacer group (Babyhaler): 50 mcg/kg (maximum of 10 puffs) each puff followed by 8 breaths over 1 - 2 minutes. Nebulizer group (Ultrasonic (ARP 70) used in room air): Dosage: 150 mcg/kg diluted in 4 mL saline, nebulizer air flow at 8L/min, given over 8-9 minutes. Treatment given 3 times at 20-minute intervals for 60 mins.
Outcome Measures	Pulmonary index, hospitalization, ease of use, acceptability, and oxygen saturation.
Key Outcomes	The median absolute changes in pulmonary index values were equivalent between the 2 groups. Less than 10% of the children (3 in each group) required hospitalization (2 in each group attributable to treatment failure). Parents considered administration of albuterol using the spacer device easier (94%) and better accepted by their children (62%).
Study Name	**Jamalvi et al. (17)**
Study Design	Randomized (no details)
Population Patient Demographics	ED National Institute of Child Health in Karachi, Pakistan 150 children (6 months-15 years)

Dose/Route of Delivery and Duration of Therapy	Group A, MDI with spacer (Babyhaler for younger children and spacer with mouthpiece for older children): 2 x 100 mcg repeated 3 times at 20-minute intervals. Group B, nebulizer (Type 2 Fleam Nuova S.P.A., Bresia, Italy): 0.3 mg/kg with 2 mL normal saline repeated 3 times at 20-minute intervals.
Outcome Measures	RR, HR, BP, cyanosis, pulsus paradoxus, dyspnea, wheezing, PEFR, clinical score, hospital admission
Key Outcomes	No significant differences in all outcome measures between the 2 groups except for PEFR. PEFR significantly improved after completion of treatment between the 2 groups, although no significant difference was seen in PEFR values independently for the 2 groups.
Study Name	**Mitselou et al. (18)**
Study Design	Randomized, double blind, placebo-controlled trial
Population Patient Demographics	ED Central Hospital, Karlstad, Sweden 98 children (0-6 years)
Dose/Route of Delivery and Duration of Therapy	Group A, nebulizer group (type not specified): Ventolin 5 mg/ml, 4 ml delivered by an oxygen-driven nebulizer. Continuous nebulization for 1 minute for those weighed < 35 kg, and for 2 minutes for those weighed > 35 kg. Group B, MDI with spacer (Nebulette): Children aged < 2 years: 4 x 100 mcg (10 breathes/puff), children aged >2 years received: 6x 100 mcg (5 breathes/puff). Treatment

	repeated up to 3 times during the first hour (with 20–30-minute intervals).
Outcome Measures	Primary outcome: Hospital admission, ED length of stay, parent experience of child's acute asthma treatment in ED. Secondary outcome: oxygen saturation, RR, HR
Key Outcomes	No significant differences in all outcome measures between the 2 groups.
Study Name	**Leelathipkul et al. (19)**
Study Design	Prospective, randomized control
Population Patient Demographics	Thammasat University Hospital, Thailand 40 children (1-15 years)
Dose/Route of Delivery and Duration of Therapy	Salbutamol administered every 2-6 hours depending on symptoms of both groups. No other details.
Outcome Measures	Vital signs, oxygen saturation, asthma scores, hospital stay, and side effects were recorded at admission, 24 hours, 48 hours, and before discharge.
Key Outcomes	No significant difference between 2 groups when comparing vital signs, oxygen saturation, asthma scores and hospital stay. Homemade non-valved spacer group had significantly less tachycardia and agitation. Satisfaction of parents and healthcare workers were higher in the homemade non-valved spacer group.
Study Name	**Snider et al. (20)**

Study Design	Randomized, non-blinded, non-inferiority
Population Patient Demographics	ED Memphis, Tennessee 890 children (2-17 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (Type not specified): For mild and moderate ≤20 kg (6 puffs), >20 Kg (12 puffs) Nebulizer group: For mild 2.5 mg/0.5 mL with 0.5 mL normal saline, for moderate-≤20 kg (2.5 mg/0.5 mL), >20 Kg (5 mg/1 mL)
Outcome Measures	Primary outcome: patient disposition (hospital admission or discharge from the ED) Secondary outcome: ED length of stay, frequency of possible albuterol dose-related adverse events measured by age adjusted tachycardia at the time of disposition, and ondansetron administration for nausea or vomiting
Key Outcomes	No significant differences in all outcome measures except tachycardia between the 2 groups. Admission rates and ED length of stay for the MDI with spacer cohort was noninferior to the nebulizer cohort. Tachycardia was more common in the nebulizer group (141 [32%] of nebulizer vs. 101 [23%] of MDI with spacer, p = 0.002)
Study Name	**Closa et al. (21)**
Study Design	Randomized, double blind
Population Patient Demographics	ED Hospital in Spain 34 infants (1-24 months)

Dose/Route of Delivery and Duration of Therapy	The MDI with spacer group (Aerochamber): 2 x 250 mcg/dose given twice at 20-min intervals Nebulizer group (Oxinova): 2 doses of 0.2 ml of 10 mg/ml terbutaline sulfate solution in 2.8 mL saline driven by oxygen at 5-6 L/min at 20-min intervals
Outcome Measures	Clinical score (respiratory distress assessment scale): RR, wheezing, retractions, degree of cyanosis, oxygen saturation
Key Outcomes	No difference in the rate of improvement in the clinical score between infants who received terbutaline by nebulizer and those who received it by MDI with spacer.
Study Name	**Mandelberg et al. (22)**
Study Design	Randomized, double blind, placebo-controlled trial
Population Patient Demographics	ED Tel Aviv, Israel 42 children (10 months-4 years)
Dose/Route of Delivery and Duration of Therapy	Group 1, nebulizer group (Aeromist): 2.5 mg in 1.5 mL saline driven by oxygen at 5 L/min at 20-min intervals, and 4 puffs of placebo MDI with facemask Group 2, MDI with spacer (Nebuchamber): wet aerosol inhalation of 2 mL saline solution and 4 puffs of salbutamol MDI with facemask (400 mcg) Both groups received 3 treatments, repeated at 20-min intervals.

Outcome Measures	Clinical score: (1) objective measures, RR, HR, and oxygen saturation; and (2) subjective measures, (wheezing, reduced intensity of breath sounds, and retractions).
Key Outcomes	No significant difference between RR, clinical scores, hospitalization rate and side effects between 2 groups.
Study Name	**Rubilar et al. (5)**
Study Design	Randomized, prospective
Population Patient Demographics	ED, Exequiel Gonzalez Cortes Children's Hospital, Santiago, Chile 123 children (1-24 months)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (Aerocell, vol of 500 ml): 2 x 100 mcg/dose given every 10 mins for 5 doses Nebulizer group (Hudson): 3 doses of 0.5% Salbutamol (0.25 mg/kg weight) in 3.5 ml of normal saline given every 13 mins
Outcome Measures	Clinical score (RR, wheezing, cyanosis, accessory respiratory muscle utilization), hospital admission rate
Key Outcomes	After the first hour of treatment with salbutamol clinical score dropped to ≤5 in 90% (56/62) MDI with spacer group vs 71% (43/61) in the nebulizer group (Odds ratio 3.9, 95% CI 1.5-10.4, p=0.01). The response was 100% in the MDI with spacer group and 94% in the nebulizer group (p>0.05) after the second hour.

	They concluded that children < 2 years of age with moderate to severe exacerbation of wheezing responded faster to salbutamol delivered by MDI with spacer compared to nebulizer.
Study Name	**Batra et al. (23)**
Study Design	Randomized, prospective
Population Patient Demographics	Pediatric ER, India 60 children (1-12 years)
Dose/Route of Delivery and Duration of Therapy	Group 1 nebulizer group: 3 doses of Salbutamol 0.15 mg/kg in 2.5 ml saline at an interval of 20 minutes. Group 2 MDI with spacer (M/S Cipla volume 750 ml) with or without attached facemask: 2 x 100 mcg salbutamol per puff) every 5-10 minutes till the end of 60 minutes from the start of therapy. Both groups examined at 20, 40 and 60 mins.
Outcome Measures	Dyspnea (subjective assessment), HR, RR, pulsus paradoxus, auscultatory findings, accessory muscle usage, arterial blood gas analysis and PEFR. 16 subjects could perform the PEFR at the baseline.
Key Outcomes	Subjective parameters like dyspnea and intercostal muscle retraction were more severe at presentation in Group 2. All the outcome measures showed significant (p<O.05) improvement with time in both the groups and all the

	recovery parameters including arterial blood gas were comparable.
Study Name	**Chou et al. (24)**
Study Design	Randomized trial, non-blinded
Population Patient Demographics	Bronx Municipal Hospital Center pediatric ED, USA 152 children (>2 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer (AeroChamber, Monaghan medical Corporation): Standard dose of 3 puffs per dose (90 mcg/puff) Nebulizer: Standard dose of 0.15 mg/kg of albuterol in 3 mL saline driven by oxygen at 6 L/min
Outcome Measures	Primary outcome: percent change in asthma severity score (pulmonary index), percent predicted PEFR for children older than 5 years and oxygen saturation Secondary outcome: Number of treatments given, which steroids were used, admission rate, treatment time in the ED
Key Outcomes	No significant differences between the groups in changes in asthma severity score or percent predicted PEFR from baseline to the time of final disposition. No significant differences in final oxygen saturation, mean number of treatments given, administration of steroids, or admission rate. The mean ED treatment time for children in the nebulizer group was 103 minutes compared with 66 minutes for

	children in the spacer and group ($p<0.001$). Significantly fewer patients in the spacer group experienced episodes of vomiting during treatment. The nebulizer group had a significantly greater mean percent increase in HR at final disposition compared with the spacer group.
Study Name	**Schuh et al. (25)**
Study Design	Randomized, double-blind trial
Population Patient Demographics	ED of Hospital for Sick Children ED, Toronto 90 children (5-17 years)
Dose/Route of Delivery and Duration of Therapy	1. High-dose MDI with spacer group: 6 to 10 puffs (100 µg/puff) of albuterol by an MDI with a clear plastic 140 mL spacer device with a mouthpiece (Aerochamber). Children weighing < 25 kg received 6 puffs, those 25- 34 kg received 8 puffs, and those weighing >34 kg received 10 puffs. 2. Low-dose MDI with spacer group: 2 puffs of albuterol with MDI with spacer. 3. Nebulizer group: received 0.15 mg/kg albuterol (maximum 5 mg) by a jet nebulizer in 3 mL saline driven by oxygen at 6-8 L/min.
Outcome Measures	Primary outcome: percent predicted forced expiratory volume in 1 second. Secondary outcome: RR, HR, oxygen saturation, and accessory muscle, wheezing, and dyspnea scores.

	Outcomes were measured before treatment and 30, 60, and 90 minutes after experimental therapy.
Key Outcomes	No significant differences between treatment groups in the degree of improvement in percent predicted forced expiratory volume in 1 second (P = .12), clinical score, RR or oxygen saturation. Nebulizer group had a significantly greater change in HR (P = .0001).
Study Name	**Ba et al. (26)**
Study Design	Randomized, double-blind trial
Population Patient Demographics	Inpatient, Sainte-Justine Hospital, Canada 27 children (7-18 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (Nebuhaler): 2 mL 0.9% saline (placebo) via nebulizer, immediately followed by continuous tidal breathing of 2 puffs salbutamol every 10 seconds (total 12 puffs = 1.2 mg) with MDIs. Nebulizer group: 1 mL (5 mg) salbutamol added to 1 mL of 0.9% saline via Hudson nebulizer, immediately followed by tidal breathing with a placebo via MDI with spacer.
Outcome Measures	Pulmonary function, HR, BP, RR, tremor was assessed before (-11 mins) and at 10, 30, 60, 90, 120 and 180 mins after inhalation from MDI with spacer.
Key Outcomes	MDIs with spacers perform at least as efficaciously as the standard nebulizer in moderate to severe acute asthma.

	Also, Nebuhaler was found to be most efficient compared to other spacers.
Study Name	**Vangveeravong (27)**
Study Design	Prospective, Randomized control
Population Patient Demographics	ED Queen Sirikit National Institute of Child Health, Bangkok 54 children (5-18 years)
Dose/Route of Delivery and Duration of Therapy	Group 1 nebulizer: using 0.5% ventolin respiratory solution 0.03 ml/kg/dose (maximum dose 1 ml) diluted with normal saline to 3 ml, delivered via an oxygen-driven flow 6-8 L/min Group 2 MDI with spacer: using 6 puffs of ventolin (Evohaler) (1OOmg/puff) delivered via Volumatic spacer, 2 puffs at a time for 3 times Group 3 Dry Powder Inhaler (Easyhaler): using 6 puffs of buventol (Easyhaler) (100/mg/puff), 1 puff at a time for 6 times
Outcome Measures	Clinical scores, number of treatments, oxygen saturation, RR and HR, side effects, admission
Key Outcomes	No significant difference among the 3 groups in terms of clinical scores, number of treatments, oxygen saturation, HR, RR
Study Name	**Delgado et al. (28)**
Study Design	Randomized, double-blind, placebo-controlled
Population	ED, Jacobi medical center, Bronx, New York, USA

Patient Demographics	168 patients (2-24 months)
Dose/Route of Delivery and Duration of Therapy	Nebulizer group: 3 puffs of a placebo MDI with a spacer, followed immediately by 0.15 mg/kg of albuterol in 3 ml of isotonic sodium chloride solution delivered by an oxygen-driven nebulizer (Acorn 11) at a flow rate of 6 U/min.
Outcome Measures	Primary outcome: admission rate Secondary outcomes: percentage improvement in perfusion index score, final oxygen saturation, mean number of treatments, whether steroids were given in the ED, percent increase in HR, and percent of subjects with vomiting in the ED
Key Outcomes	No significant differences between the groups in percent improvement in perfusion index score, final oxygen saturation, or percent of patients with vomiting. Patients in the MDI with spacer group were significantly less likely to be admitted, received fewer treatments, were less likely to receive steroids, and had a lower mean increase in HR.
Study Name	**Dewar et al. (29)**
Study Design	Randomized, control
Population Patient Demographics	Inpatient Southampton University Hospital and Poole District General Hospital, UK 62 children (≥3 years)

Dose/Route of Delivery and Duration of Therapy	Nebulizer group: Salbutamol 5 mg up to 1 hourly by jet nebulizer driven by oxygen at 6-8 L/min. MDI with spacer group: Salbutamol 100 µg by large volume spacer (Volumatic), up to 10 puffs per 1 hour
Outcome Measures	Hospital length of stay, cost, asthma morbidity 2 weeks after discharge, frequency of re-admissions during the study period and following 12 months.
Key Outcomes	Median hospital stay was 40 hours in the nebulizer group and 36.5 hours in the MDI with spacer group. Asthma disability scores at 2 weeks after discharge were significantly improved in the MDI with spacer group. Drug costs were £14.62 less for each patient in the MDI with spacer group.
Study Name	**Chong Neto et al. (30)**
Study Design	Randomized, double-blind, placebo-controlled
Population Patient Demographics	24-hour ER, Curitiba, Brazil. 40 children (6-18 years)
Dose/Route of Delivery and Duration of Therapy	Nebulizer group (NEB Pari Jet): Salbutamol 0.15 mg/kg in saline 0.9% complemented with 3 ml of solution followed by 4 jets of placebo via an MDI with commercially available spacer. MDI group with commercially-available spacer (Aerochamber): 4 x 100 µg separate actuations of salbutamol given at 30-second intervals, followed by 2 aspirations with Pulvinal™ placebo.

	MDI group with homemade non-valved spacer: 4 x 100 µg separate actuations of salbutamol given at 30-second intervals, followed by 2 aspirations with Pulvinal™ placebo. Dry Powder Inhaler: 2 x 100 µg of salbutamol with slow and deep inspiration, followed by 4 jets of MDI placebo.
Outcome Measures	Forced expiratory volume in 1 second, admission to hospital, change in symptom score, increase in HR, tremor, nausea, vomiting, hypokalemia.
Key Outcomes	MDI with a commercially available spacer is as efficient as the nebulizer, homemade spacer, and dry powder inhaler in treating acute attacks of mild to moderate asthma in school-aged children and adolescents, and produces fewer adverse events, but has a high cost. Nebulizers should be considered as a second-line device for the management of acute asthma attacks. MDI with a homemade spacer is an efficient and inexpensive alternative, but it should be used with caution, because it causes more tachycardia and tremors than commercially available spacers.
Study Name	**Deerojanawong et al. (31)**
Study Design	Randomized, double-blind, placebo-controlled
Population Patient Demographics	Department of Pediatrics, King Chulalongkorn Memorial Hospital 47 children (up to 5 years)

Dose/Route of Delivery and Duration of Therapy	MDI with spacer group (Babyhaler): 200 µg of salbutamol (100 mg/actuation Ventolin1, Glaxo) delivered via an MDI with spacer and followed by 0.03 ml/kg of placebo in 2.5 ml of normal saline solution delivered via an oxygen-driven (flow rate, 6 l/min), small-volume nebulizer. Nebulizer group: received 2 actuations of placebo via an MDI with spacer, followed by 0.03 ml/kg of salbutamol respiratory solution (0.5% Ventolin Respiratory Solution1, Glaxo) in 2.5 ml of normal saline solution, delivered via an oxygen-driven, small-volume nebulizer.
Outcome Measures	HR, RR, clinical scores, oxygen saturation, and pulmonary function tests
Key Outcomes	Clinical scores were significantly improved in both groups without a statistical difference between groups. Respiratory rate and oxygen saturation were slightly improved (no statistical significance) in both groups after treatment. Nebulizer group had a significantly higher HR after treatment when compared to the MDI with spacer group ($P = 0.004$). No significant difference in changes of all pulmonary function parameters after treatments between both groups.
Study Name	**Direkwatanachai et al. (32)**

Study Design	Multicenter, randomized, controlled study
Population Patient Demographics	7 centers in Thailand (ED and out-patient department) 216 (5-18 years)
Dose/Route of Delivery and Duration of Therapy	MDI with spacer (Volumatic): 2 puffs x 100 µg of ventolin repeated 3 times. Dry Powder Inhaler (Easyhaler): 1 puff x 100 µg repeated 6 times. Nebulizer group: 0.15 mg/kg of salbutamol maximum to 5 mg, added to normal saline solution to 3 mL, nebulized via oxygen flow 6-8 LPM or compressed air. All groups received treatments at 20 min intervals.
Outcome Measures	Primary outcome: clinical response assessed using the modified Wood's asthma score. Secondary outcomes: hospitalization, asthma revisit within 3 days, systemic corticosteroid use and adverse events.
Key Outcomes	There were no significant differences between the 3 groups in the clinical responses noted at 1st, 2nd, or 3rd dose of salbutamol, also no difference noted between the groups for oxygen saturation and RR. Children had significantly less tachycardia when salbutamol administered via the Easyhaler®. The incidence of adverse effects (including tremor, palpitation) was acceptable and not different among the 3 groups.

[a]ED, Emergency department; [b]MDI, Metered-dose inhaler; [c]RR, Respiratory rate; [d]PEFR, Peak expiratory flow rate; [e]HR, Heart rate; [f]BP, blood pressure.