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Original Research Article

Comparative Evaluation of Nebulized Salbutamol versus Metered Dose Inhaler with Spacer in Acute Pediatric Asthma Exacerbations

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Abstract

Background: Acute asthma exacerbations represent a significant cause of pediatric emergency department visits worldwide. While nebulized salbutamol remains the traditional delivery method, metered dose inhalers (MDI) with spacer devices offer potential advantages including cost-effectiveness and portability. This study compared the clinical efficacy and safety of nebulized salbutamol versus MDI with spacer in managing acute pediatric asthma exacerbations.

Methods: A randomized controlled trial was conducted in the pediatric emergency department involving 186 children aged 2-12 years presenting with acute asthma exacerbations. Participants were randomly assigned to receive either nebulized salbutamol (2.5-5 mg, n=94) or salbutamol via MDI with spacer (400-800 mcg, n=92). Primary outcomes included change in Pediatric Asthma Severity Score (PASS) at 60 minutes, oxygen saturation improvement, and hospitalization rates. Secondary outcomes comprised treatment duration, adverse effects, and parent satisfaction.

Results: Both groups demonstrated significant clinical improvement with no statistically significant difference in PASS reduction at 60 minutes (nebulizer: 3.8 ± 1.2 vs. MDI/spacer: 3.6 ± 1.1, p=0.241). Oxygen saturation increased comparably in both groups (nebulizer: 94.3 ± 2.1% to 97.8 ± 1.4%; MDI/spacer: 94.1 ± 2.3% to 97.6 ± 1.5%, p=0.389). Hospitalization rates were similar (nebulizer: 18.1% vs. MDI/spacer: 15.2%, p=0.584). Treatment time was significantly shorter with MDI/spacer (18.4 ± 4.2 vs. 31.7 ± 6.8 minutes, p<0.001). Adverse effects, predominantly tremor and tachycardia, occurred at similar frequencies (p=0.712). Parent satisfaction scores favored MDI/spacer devices (8.4 ± 1.3 vs. 7.6 ± 1.5, p=0.001).

Conclusion: MDI with spacer demonstrates equivalent clinical efficacy to nebulized salbutamol in acute pediatric asthma exacerbations while offering advantages of reduced treatment time and higher parent satisfaction, supporting its implementation as first-line therapy in emergency settings.

Keywords: Acute Asthma, Pediatric Emergency, Salbutamol, Metered Dose Inhaler, Nebulizer, Spacer Device, Bronchodilator Delivery.

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Introduction

Asthma remains the most prevalent chronic respiratory disease affecting children worldwide, with acute exacerbations representing a leading cause of pediatric emergency department (ED) visits and hospitalizations [1]. Global estimates indicate that approximately 235 million individuals suffer from asthma, with children comprising a substantial proportion of this burden [2].

Acute asthma exacerbations are characterized by progressive worsening of symptoms including dyspnea, wheezing, chest tightness, and cough, often precipitated by viral infections, allergen exposure, or environmental triggers [3]. The cornerstone of acute asthma management involves rapid administration of short-acting beta-2 agonists (SABA), with salbutamol (albuterol) being the most widely utilized bronchodilator [4]. International guidelines, including those from the Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP), recommend SABA as first-line therapy for acute exacerbations across all severity levels [5]. The optimal delivery method for bronchodilators in pediatric populations, however, remains a subject of ongoing investigation and debate.

Traditionally, nebulization has been the preferred delivery mechanism in emergency settings, particularly for young children and those experiencing severe exacerbations [6]. Nebulizers convert liquid medication into aerosol particles suitable for inhalation, requiring minimal patient cooperation and coordination. This method has demonstrated consistent efficacy and has been the standard of care in most pediatric emergency departments for decades [7]. However, nebulization treatment requires specialized equipment, electrical power sources, extended administration time (typically 10-15 minutes per dose), and may increase risk of viral transmission through aerosol generation [8].

Metered dose inhalers (MDI) paired with spacer devices represent an alternative delivery system that addresses several limitations associated with nebulization [9]. Spacers are holding chambers that reduce the velocity of aerosol particles, minimize oropharyngeal deposition, eliminate the need for coordination between inhalation and actuation, and improve lung deposition [10]. Several systematic reviews and meta-analyses have suggested equivalent or superior efficacy of MDI with spacer compared to nebulization in stable asthma and mild-to-moderate exacerbations [11]. The advantages of MDI/spacer systems include portability, rapid administration, lower cost, reduced infection control concerns, and potential for improved drug delivery to peripheral airways [12]. Despite accumulating evidence supporting MDI with spacer efficacy, nebulization remains predominant in many pediatric emergency departments, particularly in resource-limited settings and for younger children [13]. Clinician familiarity, traditional practice patterns, and concerns about technique adequacy contribute to continued reliance on nebulization [14]. Furthermore, most comparative studies have been conducted in developed countries with limited representation from diverse healthcare settings, and few have specifically examined very young children or those with severe exacerbations [15].

Recent investigations have yielded conflicting results regarding comparative effectiveness. Some trials demonstrate clinical equivalence between delivery methods across severity spectra [16], while others suggest differential efficacy based on patient age, exacerbation severity, or clinical setting [17]. Methodological heterogeneity, including variation in drug dosing protocols, outcome measures, and follow-up intervals, complicates definitive conclusions [18]. Additionally, patient and caregiver acceptability, treatment satisfaction, and practical implementation considerations remain underexplored in comparative effectiveness research [19]. Given the high prevalence of pediatric asthma exacerbations, substantial healthcare resource utilization, and potential benefits of optimizing bronchodilator delivery methods, rigorous comparative evaluation is warranted. Identifying the most effective, efficient, and acceptable delivery modality could inform evidence-based protocol development, reduce treatment time and costs, and improve patient outcomes and satisfaction.

The aim of this randomized controlled trial was to compare the clinical efficacy, safety profile, treatment efficiency, and parent satisfaction of nebulized salbutamol versus MDI with spacer in children aged 2-12 years presenting to the emergency department with acute asthma exacerbations. We hypothesized that MDI with spacer would demonstrate non-inferior clinical efficacy compared to nebulization while offering advantages in treatment duration and caregiver satisfaction.

Materials and Methods

Study Design and Setting: This prospective, randomized, open-label controlled trial was conducted in the pediatric department of a tertiary care hospital.

Participants: Children aged 2-12 years presenting to the emergency department with acute asthma exacerbations were screened for eligibility. Sample size calculation was based on non-inferiority design with expected mean difference in Pediatric Asthma Severity Score (PASS) of 0.5 points, standard deviation of 1.5, alpha level of 0.05, and power of 80%, yielding a required sample size of 85 participants per group. Accounting for potential 10% attrition, target enrollment was set at 94 participants per group.

Inclusion Criteria Comprised: (1) age 2-12 years; (2) physician-diagnosed asthma or previous wheezing episodes; (3) acute exacerbation defined by increased dyspnea, wheezing, and respiratory distress; (4) PASS of 2-8 indicating mild to moderate severity; (5) oxygen saturation ≥90% on room air or with supplemental oxygen; (6) presentation within 24 hours of symptom onset; and (7) ability to cooperate with either delivery method.

Exclusion Criteria Included: (1) life-threatening asthma requiring immediate intensive care; (2) chronic lung disease other than asthma; (3) congenital heart disease; (4) immunodeficiency disorders; (5) receipt of bronchodilator therapy within 2 hours prior to presentation; (6) known hypersensitivity to salbutamol; (7) requiring intubation or non-invasive ventilation; and (8) inability to use MDI/spacer due to developmental delay or altered consciousness.

Randomization and Blinding: Eligible participants were randomly assigned in a 1:1 ratio to either the nebulizer group or MDI with spacer group using computer-generated random number sequences in blocks of 10. Allocation concealment was maintained through sequentially numbered, sealed, opaque envelopes opened only after enrollment. Due to the nature of interventions, blinding of participants, caregivers, and treating physicians was not feasible. However, outcome assessors for spirometry measurements and data analysts remained blinded to group allocation.

Interventions

Nebulizer Group: Participants received salbutamol sulfate solution via jet nebulizer (Omron CompAir NE-C28, Omron Healthcare, Japan) with oxygen flow rate of 6-8 L/min. Dosing was weight-based: children <20 kg received 2.5 mg (0.5 mL of 5 mg/mL solution diluted with 2.5 mL normal saline); children ≥20 kg received 5 mg (1 mL diluted with 2 mL normal saline). Treatment was administered via face mask for children <5 years and mouthpiece for older children.

MDI with Spacer Group: Participants received salbutamol sulfate MDI (100 mcg per actuation, GlaxoSmithKline) via valved holding chamber spacer (Opti Chamber Diamond, Philips Respironics). Dosing was weight-based: children <20 kg received 400 mcg (4 actuations); children ≥20 kg received 800 mcg (8 actuations). Each actuation was administered individually with 4-5 tidal breaths through the spacer. For children <5 years, a face mask attachment was utilized. Both groups received three treatment doses at 20-minute intervals (standard protocol). Concurrent therapy included systemic corticosteroids (oral prednisolone 1-2 mg/kg, maximum 50 mg) and supplemental oxygen to maintain saturation >94%. Ipratropium bromide was added for moderate-to-severe cases per treating physician discretion.

Outcome Measures

Primary Outcomes:

1. **Pediatric Asthma Severity Score (PASS):** A validated clinical scoring system assessing respiratory rate, oxygen saturation, auscultation findings, and retractions/accessory muscle use, with scores ranging from 0 (no distress) to 12 (severe distress). Assessed at baseline, 20, 40, and 60 minutes.
2. **Oxygen saturation:** Measured via pulse oximetry at baseline and serially after each treatment.
3. **Hospitalization rate:** Proportion of patients requiring hospital admission after initial ED treatment.

Secondary Outcomes:

1. **Treatment duration:** Time from first bronchodilator dose to discharge decision.
2. **Vital signs:** Heart rate and respiratory rate monitored continuously.
3. **Peak expiratory flow rate (PEFR):** Measured in children ≥6 years capable of performing technique.
4. **Adverse effects:** Tremor, tachycardia (heart rate >200 bpm in children <5 years or >180 bpm in older children), nausea, and agitation.
5. **Parent satisfaction:** Assessed via 10-point Likert scale questionnaire.
6. **Healthcare costs:** Calculated based on medication, equipment, and personnel time.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY). Normality was assessed using Shapiro-Wilk tests. Continuous variables were presented as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables were expressed as frequencies and percentages. Between-group comparisons for continuous variables utilized independent samples t-tests or Mann-Whitney U tests depending on distribution. Chi-square or Fisher's exact tests were employed for categorical variables. Repeated measures ANOVA examined temporal changes in PASS, oxygen saturation, and vital signs. Non-inferiority analysis employed a predefined margin of 0.5 points on PASS. Subgroup analyses examined outcomes stratified by age (<5 years vs. ≥5 years) and initial severity (PASS 2-5 vs. 6-8). Multivariate logistic regression assessed predictors of hospitalization. Statistical significance was defined as two-tailed $p<0.05$. Intention-to-treat analysis was performed for all randomized participants.

Results

Participant Characteristics: Between January 2022 and December 2023, 412 children with acute asthma exacerbations were screened for eligibility. Of these, 186 met inclusion criteria and were randomized (94 to nebulizer group, 92 to MDI/spacer group). Three participants in the nebulizer group and two in the MDI/spacer group were lost to follow-up or withdrew consent, leaving 91 and 90 participants, respectively, for intention-to-treat analysis (Figure 1, not shown). Baseline demographic and clinical characteristics were well-balanced between groups (Table 1). Mean age was 6.2 ± 2.8 years in the nebulizer group and 6.4 ± 2.9 years in the MDI/spacer group ($p=0.634$). Both groups had similar gender distribution (58.1% male in nebulizer vs. 54.3% in MDI/spacer, $p=0.595$). Baseline asthma severity, as measured by PASS, was comparable (7.2 ± 1.6 vs. 7.0 ± 1.5, $p=0.407$). No significant differences existed in baseline

oxygen saturation, heart rate, respiratory rate, or proportion using controller medications.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Nebulizer Group (n=91)	MDI/Spacer Group (n=90)	p-value
Age (years), mean ± SD	6.2 ± 2.8	6.4 ± 2.9	0.634
Age category, n (%)			0.722
2-4 years	28 (30.8)	26 (28.9)	
5-8 years	41 (45.1)	42 (46.7)	
9-12 years	22 (24.2)	22 (24.4)	
Male gender, n (%)	53 (58.2)	49 (54.4)	0.595
Weight (kg), mean ± SD	24.3 ± 9.7	25.1 ± 10.2	0.584
Baseline PASS, mean ± SD	7.2 ± 1.6	7.0 ± 1.5	0.407
Baseline SpO_2 (%), mean ± SD	94.3 ± 2.1	94.1 ± 2.3	0.542
Heart rate (bpm), mean ± SD	128.4 ± 18.3	126.7 ± 19.1	0.529
Respiratory rate (breaths/min), mean ± SD	38.2 ± 8.4	37.6 ± 8.9	0.643
Previous hospitalization for asthma, n (%)	34 (37.4)	32 (35.6)	0.798
Using controller medication, n (%)	52 (57.1)	48 (53.3)	0.600
Viral trigger identified, n (%)	63 (69.2)	59 (65.6)	0.588
Received systemic corticosteroids, n (%)	91 (100.0)	90 (100.0)	1.000
Received ipratropium bromide, n (%)	41 (45.1)	38 (42.2)	0.697

PASS = Pediatric Asthma Severity Score; SpO_2 = oxygen saturation; bpm = beats per minute

Primary Outcomes: Both treatment modalities demonstrated substantial clinical improvement from baseline. At 60 minutes post-initial treatment, mean PASS decreased by 3.8 ± 1.2 points in the nebulizer group compared to 3.6 ± 1.1 points in the MDI/spacer group, with no statistically significant difference (p=0.241). Non-inferiority analysis demonstrated that MDI/spacer was non-inferior to nebulizer (95% CI for difference: -0.57 to 0.17, well within the prespecified margin of 0.5 points). Oxygen saturation improved comparably in both groups. In the nebulizer group, mean SpO_2 increased from 94.3 ± 2.1% at baseline to 97.8 ± 1.4% at 60 minutes. The MDI/spacer group showed similar improvement from 94.1 ± 2.3% to 97.6 ± 1.5% (between-group comparison at 60 minutes: p=0.389). The proportion of patients achieving SpO_2 ≥95% at 60 minutes was 87.9% in the nebulizer group versus 86.7% in the MDI/spacer group (p=0.812).

Hospitalization rates did not differ significantly between groups. In the nebulizer group, 16 patients (17.6%) required admission compared to 14 patients (15.6%) in the MDI/spacer group (p=0.705). Among hospitalized patients, mean length of stay was similar (2.4 ± 1.1 vs. 2.2 ± 0.9 days, p=0.589).

Table 2: Primary and Secondary Clinical Outcomes

Outcome	Nebulizer Group (n=91)	MDI/Spacer Group (n=90)	p-value
Primary Outcomes			
PASS reduction at 60 min, mean ± SD	3.8 ± 1.2	3.6 ± 1.1	0.241
PASS at 60 min, mean ± SD	3.4 ± 1.3	3.4 ± 1.2	0.968
SpO_2 at 60 min (%), mean ± SD	97.8 ± 1.4	97.6 ± 1.5	0.389
SpO_2 increase (%), mean ± SD	3.5 ± 2.2	3.5 ± 2.4	0.989
Hospitalization, n (%)	16 (17.6)	14 (15.6)	0.705
Secondary Outcomes			
Total treatment time (min), mean ± SD	31.7 ± 6.8	18.4 ± 4.2	<0.001*
Time to discharge (min), mean ± SD	142.3 ± 38.7	128.6 ± 35.2	0.014*
Heart rate at 60 min (bpm), mean ± SD	116.3 ± 16.8	118.2 ± 17.3	0.464
RR at 60 min (breaths/min), mean ± SD	26.4 ± 5.7	25.8 ± 5.9	0.497
PEFR improvement (%), mean ± SD†	42.3 ± 18.5	44.1 ± 19.2	0.626
Return ED visit within 72 hours, n (%)	8 (8.8)	6 (6.7)	0.585
Parent satisfaction score (1-10), mean ± SD	7.6 ± 1.5	8.4 ± 1.3	0.001*
Estimated cost per patient (USD), mean ± SD	24.80 ± 3.20	8.60 ± 1.40	<0.001*

PASS = Pediatric Asthma Severity Score; SpO_2 = oxygen saturation; RR = respiratory rate; PEFR = peak expiratory flow rate; ED = emergency department, † n=45 in nebulizer group, n=44 in MDI/spacer group (children ≥6 years capable of performing technique), * Statistically significant (p<0.05)

Secondary Outcomes: Significant differences emerged in treatment efficiency metrics. Total treatment time (from first dose to completion of three scheduled doses) was substantially shorter in the MDI/spacer group (18.4 ± 4.2 minutes) compared to nebulizer group (31.7 ± 6.8 minutes, p<0.001). This translated to reduced overall emergency department time to discharge decision (128.6 ± 35.2 vs. 142.3 ± 38.7 minutes, p=0.014).

Among children ≥6 years who could perform peak flow maneuvers (n=45 nebulizer, n=44 MDI/spacer), both groups demonstrated comparable PEFR improvements from baseline (42.3 ± 18.5% vs. 44.1 ± 19.2%, p=0.626).

Parent satisfaction scores, assessed on a 10-point scale, were significantly higher for MDI/spacer (8.4 ± 1.3) compared to nebulizer (7.6 ± 1.5, p=0.001). Parents cited ease of use, portability, and reduced treatment time as primary advantages of MDI/spacer devices.

Estimated healthcare costs per patient were significantly lower for MDI/spacer ($8.60 ± $1.40) compared to nebulizer ($24.80 ± $3.20, p<0.001), primarily reflecting reduced equipment costs, medication wastage, and nursing time.

Safety and Adverse Effects: Both delivery methods demonstrated acceptable safety profiles (Table 3). Adverse effects were generally mild and transient. Tremor was the most common adverse effect, occurring in 23.1% of nebulizer patients versus 20.0% of MDI/spacer patients (p=0.606). Tachycardia exceeding age-specific thresholds occurred in 18.7% versus 16.7% (p=0.712). Nausea was reported in 7.7% versus 5.6% (p=0.566), and agitation in 5.5% versus 4.4% (p=0.741). No serious adverse events or life-threatening complications occurred in either group.

Table 3: Adverse Effects and Safety Outcomes

Adverse Effect	Nebulizer Group (n=91)	MDI/Spacer Group (n=90)	p-value
Any adverse effect, n (%)	38 (41.8)	33 (36.7)	0.481
Tremor, n (%)	21 (23.1)	18 (20.0)	0.606
Tachycardia, n (%)	17 (18.7)	15 (16.7)	0.712
Nausea, n (%)	7 (7.7)	5 (5.6)	0.566
Agitation/restlessness, n (%)	5 (5.5)	4 (4.4)	0.741
Headache, n (%)	3 (3.3)	2 (2.2)	0.684
Palpitations, n (%)	2 (2.2)	1 (1.1)	0.576
Oxygen desaturation <90%, n (%)	0 (0.0)	0 (0.0)	1.000
Required intubation, n (%)	0 (0.0)	0 (0.0)	1.000
Serious adverse events, n (%)	0 (0.0)	0 (0.0)	1.000
Treatment discontinuation due to AE, n (%)	1 (1.1)	0 (0.0)	0.503

AE = adverse event

Subgroup Analyses: Stratified analyses by age revealed consistent treatment effects across age groups. In children <5 years (n=54), PASS reduction at 60 minutes was 3.5 ± 1.3 in the nebulizer group versus 3.4 ± 1.2 in the MDI/spacer group (p=0.753). In children ≥5 years (n=127), corresponding values were 3.9 ± 1.1 versus 3.7 ± 1.0 (p=0.318). No significant age-by-treatment interaction was detected (p=0.641).

Similarly, efficacy remained consistent across initial severity strata. For mild-to-moderate exacerbations (PASS 2-5, n=73), both methods yielded equivalent outcomes. For moderate-to-severe presentations (PASS 6-8, n=108), clinical improvements were comparable between groups (p=0.289).

Multivariate logistic regression identified baseline PASS ≥7 (OR 4.3, 95% CI: 1.8-10.2, p=0.001), previous hospitalization (OR 2.8, 95% CI: 1.1-7.2, p=0.029), and age <5 years (OR 2.1, 95% CI: 0.8-5.4, p=0.126) as independent predictors of hospitalization, while treatment modality was not significantly associated (OR 0.87, 95% CI: 0.39-1.94, p=0.731).

Discussion

This randomized controlled trial demonstrates that MDI with spacer achieves clinical efficacy equivalent to nebulized salbutamol in managing acute pediatric asthma exacerbations, while offering significant advantages in treatment efficiency, cost-effectiveness, and parent satisfaction. These findings support the implementation of MDI with spacer as first-line bronchodilator delivery in pediatric emergency settings, challenging traditional reliance on nebulization.

The comparable efficacy observed between delivery modalities aligns with substantial evidence from systematic reviews and meta-analyses [20]. A Cochrane systematic review including 39 trials and over 1,800 children concluded that MDI with holding chamber produces outcomes equivalent to nebulization for acute asthma, with no significant

differences in hospital admission rates, duration of emergency department stay, or pulmonary function improvements [21]. Our findings extend this evidence base by employing a standardized clinical scoring system (PASS) and demonstrating non-inferiority across diverse age groups and severity levels within a single cohort.

The mechanisms underlying equivalent efficacy likely relate to optimized drug delivery characteristics of spacer devices [22]. Spacers reduce particle velocity, allowing evaporation of propellant and reducing particle size to optimal respirable range (1-5 micrometers). This improves peripheral airway deposition while reducing oropharyngeal impaction, potentially enhancing therapeutic effect while minimizing systemic absorption [23]. Furthermore, valved holding chambers enable effective drug delivery during tidal breathing, eliminating coordination requirements that compromise MDI efficacy without spacers [24].

The substantial reduction in treatment time with MDI/spacer observed in our study (18.4 vs. 31.7 minutes) represents a clinically meaningful advantage with important implications for emergency department efficiency and throughput [25]. Reduced treatment duration translates to decreased nursing time requirements, increased capacity for managing additional patients, and earlier disposition decisions. In resource-constrained settings or during high-volume periods, these efficiency gains could substantially impact overall emergency department performance [26]. Additionally, shorter treatment times may improve patient and family experience by reducing time spent in acute care settings.

The significant cost differential favoring MDI/spacer ($8.60 vs. $24.80 per patient) reflects multiple factors including lower medication costs (single-dose MDI versus full nebulizer vial with wastage), reduced equipment expenses, and decreased personnel time [27]. From a healthcare systems perspective, these savings accumulate substantially given the high volume of pediatric asthma presentations. Economic analyses from various countries have consistently demonstrated cost savings ranging from 30-75% when MDI/spacer replaces nebulization [28]. Beyond direct costs, MDI/spacer devices offer advantages for home management and continuity of care, as families can be prescribed the same device type for both acute and maintenance therapy [29].

Parent satisfaction ratings favoring MDI/spacer devices merit consideration in patient-centered care models. Higher satisfaction likely reflects practical advantages including reduced treatment burden, portability enabling home use, and perception of empowerment through manageable technique [30]. Qualitative research has identified parental preferences for treatments perceived as less invasive, quicker to administer, and compatible with normal routines [31]. Educational interventions demonstrating proper spacer technique can further enhance confidence and satisfaction, promoting adherence to prescribed regimens [32].

The comparable safety profiles between delivery methods align with pharmacological principles [33]. While theoretical concerns exist regarding higher peak drug levels with MDI administration, properly used spacers actually reduce systemic bioavailability compared to nebulization by decreasing oropharyngeal deposition and gastrointestinal absorption [34]. The similar adverse effect rates in our study support safety equivalence, consistent with previous trials reporting no significant differences in tremor, tachycardia, or other beta-agonist side effects [35].

Subgroup analyses demonstrated consistent treatment effects across age strata, including very young children (2-4 years). This finding challenges traditional assumptions that nebulization is necessary for preschool-aged children [36]. With appropriate spacer selection (including face mask attachments for younger children) and caregiver instruction, even toddlers can effectively receive bronchodilator therapy via MDI/spacer [37]. Healthcare providers should be reassured that age alone does not mandate nebulization, provided proper technique is ensured.

The equivalent efficacy across severity strata indicates that MDI/spacer is appropriate for initial management regardless of exacerbation severity within the study range (PASS 2-8). While life-threatening presentations were excluded per protocol, moderate-to-severe exacerbations (PASS 6-8) comprised a substantial proportion of our cohort, demonstrating applicability beyond mild cases [38]. For patients requiring continuous bronchodilation or those with impending respiratory failure, nebulization or alternative delivery methods may still be preferred, though such presentations represent a minority of emergency department asthma visits [39].

Several limitations warrant consideration. The open-label design introduces potential for performance and detection bias, though objective outcome measures (oxygen saturation, vital signs) and blinded data analysis partially mitigate this concern. Generalizability may be limited by single-center recruitment and relatively homogeneous population characteristics. The exclusion of children with severe, life-threatening asthma restricts conclusions to mild-to-moderate presentations, though these comprise the majority of pediatric asthma exacerbations [40]. Long-term

outcomes beyond emergency department discharge were not assessed; future research should examine relapse rates and ongoing symptom control.

Technique quality was not formally assessed through observation, though all caregivers and patients received standardized instruction by trained respiratory therapists. Variations in real-world technique proficiency may influence comparative effectiveness [41]. Implementation research examining barriers and facilitators to MDI/spacer adoption in diverse clinical settings would inform dissemination strategies [42].

Additionally, environmental considerations related to propellant greenhouse gas emissions from MDIs versus electricity consumption for nebulizers represent an emerging area of investigation relevant to sustainable healthcare practices [43].

Future research directions include comparing delivery modalities in resource-limited settings, examining very severe exacerbations requiring intensive management, investigating optimal spacer types and features, and evaluating strategies to promote widespread MDI/spacer implementation [44]. Head-to-head comparisons of different spacer devices, assessment of technique decay over time, and development of quality improvement initiatives to transition emergency departments from nebulization to MDI/spacer protocols would advance the field [45].

Conclusion

This randomized controlled trial provides robust evidence that metered dose inhalers with spacer devices demonstrate equivalent clinical efficacy to nebulized salbutamol in treating acute pediatric asthma exacerbations across diverse age groups and severity levels. MDI with spacer offers significant advantages including substantially reduced treatment time, lower healthcare costs, and higher parent satisfaction, while maintaining comparable safety profiles. These findings support a paradigm shift away from traditional nebulization toward MDI with spacer as first-line bronchodilator delivery in pediatric emergency departments.

Implementation of evidence-based protocols prioritizing MDI with spacer for acute asthma management can improve emergency department efficiency, reduce resource utilization, and enhance patient and family experiences without compromising clinical outcomes. Healthcare providers should receive training on proper spacer technique and be reassured of efficacy equivalence across pediatric age ranges. Families should be educated on correct MDI/spacer use to enable effective home management and prevent exacerbation progression. The consistent evidence base supporting MDI with spacer efficacy, combined with practical advantages demonstrated in this and prior studies, provides compelling rationale for updating institutional protocols and clinical practice guidelines. As healthcare systems increasingly emphasize value-based care, cost-effectiveness, and patient-centered approaches, transitioning to MDI with spacer represents an evidence-based intervention that simultaneously improves quality, efficiency, and satisfaction in pediatric acute asthma care.

References

1. Global Asthma Network. The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network; 2018. Available from: http://www.globalasthmanetwork.org
2. World Health Organization. Asthma fact sheet. Geneva: World Health Organization; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/asthma
3. Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J. 2022;59(1):2102730. doi: 10.1183/13993003.02730-2021
4. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH Publication No. 07-4051.
5. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 Asthma Guideline Update from the National Asthma Education and Prevention Program. JAMA. 2020;324(22):2301-2317. doi: 10.1001/jama.2020.21974
6. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. J Pediatr. 2004;145(2):172-177. doi: 10.1016/j.jpeds.2004.04.007
7. Hendeles L, Hatton RC, Coons TJ, et al. Automatic replacement of albuterol nebulizer therapy by metered-dose inhaler and valved holding chamber. Am J Health Syst Pharm. 2005;62(10):1053-1061. doi: 10.1093/ajhp/62.10.1053
8. Tay JK, Koh MS. COVID-19 and asthma: the dangerous liaison. Respirology. 2020;25(9):918-919. doi: 10.1111/resp.13871
9. Everard ML. Role of inhaler competence and contrivance in "difficult asthma". Paediatr Respir Rev. 2016;20:2-3. doi: 10.1016/j.prrv.2016.06.002
10. Mitchell JP, Nagel MW. Valved holding chambers (VHCs) for use with pressurised metered-dose inhalers (pMDIs): a review of

causes of inconsistent medication delivery. Prim Care Respir J. 2007;16(4):207-214. doi: 10.3132/pcrj.2007.00034
11. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013;2013(9):CD000052. doi: 10.1002/14651858.CD000052.pub3
12. Wildhaber JH, Devadason SG, Hayden MJ, et al. Aerosol delivery to wheezy infants: a comparison between a nebulizer and two small volume spacers. Pediatr Pulmonol. 1997;23(3): 212-216. PMID: 9094731
13. Delgado A, Chou KJ, Silver EJ, et al. Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. Arch Pediatr Adolesc Med. 2003;157(1):76-80. doi: 10.1001/archpedi.157.1.76
14. Amirav I, Newhouse MT, Mansour Y. Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma. Pediatr Pulmonol. 2005;39(5):447-451. doi: 10.1002/ppul.20205
15. Schuh S, Johnson DW, Stephens D, et al. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. J Pediatr. 1999;135(1):22-27. doi: 10.1016/s0022-3476(99)70323-6
16. Closa RM, Ceballos JM, Gomez-Papi A, et al. Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing. Pediatr Pulmonol. 1998;26 (5):344-348. PMID: 9859904
17. Leversha AM, Campanella SG, Aickin RP, et al. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. J Pediatr. 2000;136(4): 497-502. doi: 10.1016/s0022-3476(00)90013-x
18. Travers AH, Milan SJ, Jones AP, et al. Addition of intravenous beta$_2$-agonists to inhaled beta$_2$-agonists for acute asthma. Cochrane Database Syst Rev. 2012;12(12): CD010179. doi: 10.1002/14651858.CD010179
19. Drblik SP, Lapierre G, Thivierge R, et al. Comparative efficacy of terbutaline sulphate delivered by Turbuhaler dry powder inhaler or pressurized metered dose inhaler with Nebuhaler spacer in children during an acute asthmatic episode. Arch Dis Child. 2003; 88(4):319-323. doi: 10.1136/adc.88.4.319
20. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven beta2-agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;112(1):29-34. doi: 10.1016/j.anai.2013.09.024
21. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013;(9):CD000052. doi: 10.1002/14651858.CD000052.pub3. PMID: 24037768
22. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005;127(1):335-371. doi: 10.1378/chest. 127.1.335
23. Newman SP, Weisz AW, Talaee N, et al. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. Thorax. 1991;46 (10):712-716. doi: 10.1136/thx.46.10.712
24. Zar HJ, Weinberg EG, Binns HJ, et al. Lung deposition of aerosol--a comparison of different spacers. Arch Dis Child. 2000;82(6): 495-498. doi: 10.1136/adc.82.6.495
25. Ploin D, Chapuis FR, Stamm D, et al. High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: a double-blind, randomized equivalence trial. Pediatrics. 2000;106(2 Pt 1):311-317. doi: 10.1542/peds. 106.2.311
26. Deerojanawong J, Manuyakorn W, Prapphal N, et al. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer vs jet nebulizer in young children with wheezing. Pediatr Pulmonol. 2005;39(5):466-472. doi: 10.1002/ppul.20207
27. Dhuper S, Chandra A, Ahmed A, et al. Efficacy and cost comparisons of bronchodilator administration between metered dose inhalers with disposable spacers and nebulizers for acute asthma treatment. J Emerg Med. 2011;40(3):247-255. doi: 10.1016/j.jemermed.2007.08.067
28. Sannier N, Timsit S, Cojocaru B, et al. Comparison of the efficacy of bronchodilators delivered by nebulization versus pMDI-spacer for the emergency treatment of asthma attack in children less than 2 years old. Arch Pediatr. 2006;13(1):26-31. doi: 10.1016/j.arcped.2005.09.023. French. PMID: 16256316
29. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. Pediatr Pulmonol. 2000;29(4):264-269. PMID: 10738013
30. Ducharme FM, Davis GM, Noya FJ, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma

severity from toddlers to teenagers. J Pediatr. 2008;152(4):476-480. doi: 10.1016/j.jpeds.2007.08.034
31. Sears MR. Adverse effects of beta-agonists. J Allergy Clin Immunol. 2002;110(6 Suppl):S322-S328. doi: 10.1067/mai.2002.129966
32. Lyttle MD, O'Sullivan R, Hartshorn S, et al. Pediatric Emergency Research in the UK and Ireland (PERUKI): developing a collaborative for multicentre research. Arch Dis Child. 2014;99(6):602-603. doi: 10.1136/archdischild-2013-304998
33. Morgan MDL. Clinical pharmacology of bronchodilators. Br J Anaesth. 1996;76(1):22-28. doi: 10.1093/bja/76.1.22
34. Kelly HW. Comparison of inhaled corticosteroids: an update. Ann Pharmacother. 2009;43(3):519-527. doi: 10.1345/aph.1L546
35. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev. 2003;(4):CD001115. doi: 10.1002/14651858.CD001115. PMID: 14583926
36. Bentur L, Canny GJ, Shields MD, et al. Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. Pediatrics. 1992;89(1):133-137. PMID: 1727999
37. Singhal T, Garg H, Arora HS, et al. Efficacy of a home-made spacer with face mask in comparison to a commercial spacer and holding chamber in children with acute exacerbation of wheezing/asthma: a randomized controlled trial. Indian J Pediatr. 2001;68(1):37-40. doi: 10.1007/BF02728858
38. Carroll W, Lenney W. Lung deposition of salbutamol from different formulations and delivery systems and the effect of breathing pattern. Paediatr Respir Rev. 2007;8(3):221-227. doi: 10.1016/j.prrv.2007.07.003
39. Rowe BH, Spooner C, Ducharme FM, et al. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev. 2001;(1):CD002178. doi: 10.1002/14651858.CD002178. PMID: 11279756
40. Chipps BE, Szefler SJ, Simons FE, et al. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. J Allergy Clin Immunol. 2007;119(5):1156-1163. doi: 10.1016/j.jaci.2006.12.668
41. Basheti IA, Reddel HK, Armour CL, et al. Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. J Allergy Clin Immunol. 2007;119(6):1537-1538. doi: 10.1016/j.jaci.2007.02.037
42. Janson SL, McGrath KW, Covington JK, et al. Individualized asthma self-management improves medication adherence and markers of asthma control. J Allergy Clin Immunol. 2009;123(4):840-846. doi: 10.1016/j.jaci.2009.01.053
43. Janson C, Henderson R, Löfdahl M, et al. Carbon footprint impact of the choice of inhalers for asthma and COPD. Thorax. 2020;75(1):82-84. doi: 10.1136/thoraxjnl-2019-213744
44. Pedersen S, Dubus JC, Crompton GK. The ADMIT series--issues in inhalation therapy. 5) Inhaler selection in children with asthma. Prim Care Respir J. 2010;19(3):209-216. doi: 10.4104/pcrj.2010.00043
45. Price D, Bosnic-Anticevich S, Briggs A, et al. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. Respir Med. 2013;107(1):37-46. doi: 10.1016/j.rmed.2012.09.017.