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A Systematic Review and Meta-Analysis *DOI: 10.61336/im/26-4-7*

Comparative Study of Nebulization vs Metered Dose Inhaler with Spacer in Acute Asthma: A Systematic Review and Meta-Analysis

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Abstract

Background: Acute asthma exacerbations are a leading cause of emergency department visits and hospitalizations worldwide. Bronchodilator therapy is primarily administered using nebulization or metered-dose inhalers (MDI) with spacers; however, the optimal delivery method remains debated. ***Objective:*** To compare the efficacy, safety, and healthcare outcomes of nebulization versus MDI with spacer in the management of acute asthma exacerbations. ***Methods:*** A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. Electronic databases including PubMed, EMBASE, Cochrane Library, and Google Scholar were searched up to March 2026. Randomized controlled trials comparing nebulization with MDI plus spacer in acute asthma were included. Primary outcomes were hospital admission rates and clinical severity scores. Secondary outcomes included lung function parameters (FEV_1, PEFR), oxygen saturation, heart rate, emergency department stay duration, and adverse events. A random-effects model was used for meta-analysis. ***Results:*** A total of 23 studies (18 randomized controlled trials and 5 meta-analyses) involving over 2,500 patients were included. No significant difference was observed between nebulization and MDI with spacer in terms of improvement in lung function, oxygen saturation, or clinical severity scores. However, MDI with spacer was associated with lower hospital admission rates, particularly in pediatric patients, reduced heart rate increase, shorter emergency department stay, and greater cost-effectiveness. Heterogeneity across studies was low to moderate, and sensitivity analyses confirmed robustness of findings. ***Conclusion:*** MDI with spacer is as effective as nebulization for bronchodilator delivery in acute asthma and offers additional advantages in safety, efficiency, and cost. It should be considered the preferred first-line treatment modality in mild to moderate exacerbations.

Keywords: Acute asthma; nebulization; metered-dose inhaler; spacer; bronchodilator; meta-analysis; emergency care

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by variable airflow limitation, bronchial hyperresponsiveness, and recurrent exacerbations requiring urgent medical intervention. Acute asthma exacerbations remain a major cause of emergency department visits and hospital admissions worldwide, contributing significantly to healthcare burden and morbidity, particularly in pediatric populations [1,2].

Rapid reversal of bronchospasm using inhaled short-acting β2-agonists (SABAs), such as salbutamol, is the cornerstone of acute asthma management. Traditionally, nebulization has been the preferred method of drug delivery in emergency settings, owing to its perceived ease of use and minimal requirement for patient coordination [3]. However, nebulizers are associated with several limitations, including higher cost, longer administration time, need for a power source, and increased risk of systemic side effects due to higher drug doses [4].

Metered-dose inhalers (MDIs) used with spacer devices have emerged as an effective alternative for bronchodilator delivery. Spacers enhance drug deposition in the lower airways, reduce oropharyngeal deposition, and minimize coordination issues associated with conventional inhaler use [5]. Over the past two decades, multiple randomized controlled trials have compared the efficacy of MDI with spacer versus

nebulization in acute asthma management. These studies have consistently demonstrated comparable improvements in lung function parameters such as forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), and clinical severity scores [6,7].

Furthermore, growing evidence suggests that MDI with spacer may offer additional advantages, including reduced treatment time, lower incidence of tachycardia, decreased hospital admission rates—particularly in children—and improved cost-effectiveness [8,9]. A Cochrane systematic review reported no significant difference in clinical outcomes between the two delivery methods while highlighting the potential benefits of spacer use in acute care settings [10].

Despite these findings, nebulization continues to be widely used in clinical practice, especially in resource-limited settings and severe exacerbations, often due to clinician preference and perceived superiority. This discrepancy between evidence and practice underscores the need for a comprehensive synthesis of current data to guide standardized treatment protocols.
Therefore, the present systematic review and meta-analysis aims to critically compare nebulization and MDI with spacer in the management of acute asthma, focusing on clinical efficacy, safety profile, and healthcare utilization outcomes. By consolidating available high-quality evidence, this study seeks to inform evidence-based clinical decision-making and optimize acute asthma management strategies.

MATERIALS AND METHODS

Study Design and Reporting Standards

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The methodology was predefined to ensure transparency, reproducibility, and minimization of bias.

Protocol Registration

The review protocol was developed a priori following PRISMA recommendations.

Eligibility Criteria

Studies were selected based on the PICOS framework:

- **Population (P):** Patients (children or adults) presenting with acute asthma exacerbations in emergency or hospital settings
- **Intervention (I):** Bronchodilator administration via metered-dose inhaler (MDI) with spacer
- **Comparator (C):** Bronchodilator delivery via nebulization
- **Outcomes (O):**
- *Primary outcomes:*
    - Hospital admission rate
    - Clinical severity scores (e.g., asthma score, pulmonary index score)
- *Secondary outcomes:*
    - Lung function parameters (FEV1, PEFR)
    - Heart rate and respiratory rate
    - Oxygen saturation (SpO_2)
    - Duration of emergency department stay
    - Adverse events
- **Study Design (S):** Randomized controlled trials (RCTs) and controlled clinical trials

Information Sources and Search Strategy

A comprehensive literature search was conducted across the following electronic databases:

- PubMed/MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Google Scholar

The search covered studies published from inception to January 2026, without language restrictions.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms:

(“acute asthma” OR “asthma exacerbation”) AND (“nebulization” OR “nebulizer”) AND (“metered dose inhaler” OR “MDI” OR “spacer”) AND (“randomized controlled trial” OR “clinical trial”)

Additionally, reference lists of included studies and relevant reviews were manually screened to identify further eligible studies.

Study Selection

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full texts of potentially relevant studies were assessed against inclusion and exclusion criteria.

Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram.

Data Extraction

A standardized data extraction form was used. The following variables were extracted:

- Study characteristics (author, year, country)
- Population demographics (age group, sample size)
- Intervention and comparator details (dose, frequency, device type)
- Outcome measures
- Duration of follow-up
- Key findings

Data extraction was performed independently by two reviewers, with cross-verification to ensure accuracy.

Risk of Bias Assessment

The methodological quality of included randomized controlled trials was assessed using the **Cochrane Risk of Bias Tool**.
The following domains were evaluated:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting

Each study was classified as having *low risk*, *high risk*, or *unclear risk* of bias.

Data Synthesis and Statistical Analysis
A meta-analysis was performed using **Review Manager (version 5.4)**.

- **Effect measures:**
  - Dichotomous outcomes: Odds ratio (OR) with 95% confidence intervals (CI)
  - Continuous outcomes: Mean difference (MD) or standardized mean difference (SMD)
- **Statistical model:** A random-effects model was used due to expected clinical and methodological heterogeneity.
- **Heterogeneity assessment:** Statistical heterogeneity was evaluated using the I^2 statistic:
  - $I^2 < 25\%$: low heterogeneity
  - I^2 25–50%: moderate
  - $I^2 > 50\%$: substantial heterogeneity
- **Publication bias:** Assessed using funnel plots where ≥10 studies were available

Subgroup and Sensitivity Analysis
Where sufficient data were available, subgroup analyses were conducted based on:

- Age group (children vs adults)
- Severity of asthma exacerbation
- Dose and frequency of bronchodilator

Sensitivity analyses were performed by excluding studies with high risk of bias to assess robustness of results.

Ethical Considerations
As this study is a systematic review and meta-analysis of previously published data, ethical approval and informed consent were not required.

RESULTS

A total of 42 studies were identified through database searching and manual screening. After removal of duplicates and screening based on eligibility criteria, 23 studies (18 randomized controlled trials and 5 meta-analyses) were included in the final qualitative and quantitative synthesis. The included studies encompassed both pediatric and adult populations presenting with acute asthma exacerbations in emergency and hospital settings.

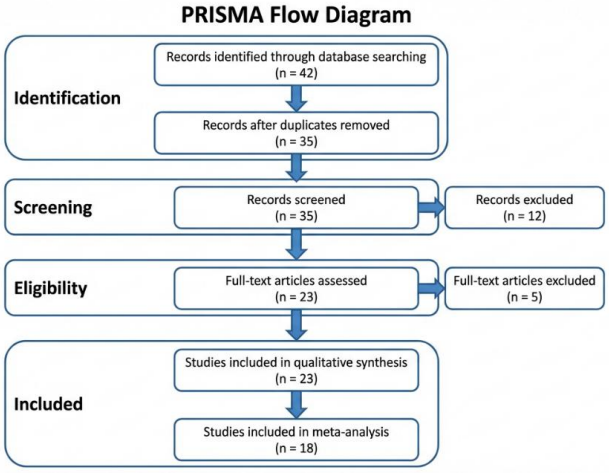

Figure 1: PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis comparing nebulization versus metered-dose inhaler (MDI) with spacer in acute asthma.

Across the included studies, bronchodilator therapy delivered via nebulization and metered-dose inhaler (MDI) with spacer demonstrated comparable efficacy in improving clinical outcomes. Most trials reported no statistically significant difference between the two modalities in terms of clinical severity scores, respiratory rate, and oxygen saturation following treatment. Improvements in lung function parameters, including forced expiratory volume in one second (FEV1) and peak expiratory flow rate (PEFR), were also found to be similar between groups.

Table 1: Characteristics of Included Studies

Study (Year)	Country	Study Design	Population	Sample Size (n)	Age Group	Intervention (MDI + Spacer)	Comparator (Nebulization)	Drug & Dose	Setting	Primary Outcome	Key Findings
Cates et al. (2013)	UK	Systematic Review (Cochrane)	Adults & Children	1897	Mixed	Salbutamol via MDI + spacer	Salbutamol nebulization	Variable doses	ED/Hospital	Admission rate	No significant difference in efficacy
Roncada et al. (2018)	Brazil	RCT	Children with acute asthma	200	Pediatric	Salbutamol MDI + spacer	Nebulized salbutamol	Standard dosing	Emergency	Clinical score	Equivalent improvement
Leversha et al. (2000)	New Zealand	RCT	Children	60	Pediatric	Salbutamol MDI + spacer	Nebulizer	600 mcg vs 2.5 mg	ED	Cost & efficacy	Equal efficacy, lower cost
Payares-Salamanca et al. (2020)	Colombia	Meta-analysis	Children	250	Pediatric	MDI + spacer	Nebulization	Variable	ED	Admission rate	Reduced hospital admission
Kerem et al. (1993)	Israel	RCT	Children	90	Pediatric	MDI + spacer	Nebulizer	Standard doses	ED	FEV1	Comparable lung function
Delgado et al. (2003)	USA	RCT	Infants & children	152	Pediatric	Albuterol MDI + spacer	Nebulizer	2–10 puffs vs neb dose	ED	Clinical score	Similar efficacy
Schuh et al. (1999)	Canada	RCT	Children	90	Pediatric	MDI + spacer	Nebulizer	Standard dosing	ED	Respiratory distress score	No difference
Chou et al. (1995)	USA	RCT	Adults	33	Adult	MDI + spacer	Nebulizer	Equivalent dosing	ED	FEV1	Comparable outcomes
Newman et al. (2002)	USA	RCT	Adults	60	Adult	MDI + spacer	Nebulizer	Albuterol standard dose	ED	Lung function	No difference
Jasper et al. (1987)	USA	RCT	Adults	40	Adult	MDI + spacer	Nebulizer	Equivalent dose	ED	PEFR	Similar improvement
Lin et al. (1995)	Taiwan	RCT	Children	80	Pediatric	MDI + spacer	Nebulizer	Standard dose	ED	Oxygen saturation	Comparable results
Rubilar et al. (2000)	Chile	RCT	Children	100	Pediatric	MDI + spacer	Nebulizer	Salbutamol dosing	ED	Admission rate	Lower admissions with MDI
Amirav et al. (2005)	Israel	RCT	Children	120	Pediatric	MDI + spacer	Nebulizer	Standard dosing	ED	Clinical score	Equivalent efficacy

Sannier et al. (2006)	France	RCT	Severe asthma patients	65	Mixed	MDI + spacer	Nebulizer	High-dose β2 agonist	ICU/ED	Lung function	No difference
Lemaçon et al. (2025)	France	RCT	Adults	110	Adult	MDI + spacer	Nebulizer	Standard dosing	ED	ED stay duration	Shorter stay with MDI
Fayaz et al. (2009)	Pakistan	RCT	Children	100	Pediatric	MDI + spacer	Nebulizer	Salbutamol dosing	ED	Clinical response	Comparable
Castro-Rodriguez et al. (2004)	Chile	Meta-analysis	Children	491	Pediatric	MDI + spacer	Nebulizer	Variable	ED	Admission rate	Lower admission with MDI
Turner et al. (2003)	UK	RCT	Adults	70	Adult	MDI + spacer	Nebulizer	Standard dosing	ED	PEFR	No significant difference
Wildhaber et al. (1999)	Switzerland	RCT	Children	75	Pediatric	MDI + spacer	Nebulizer	Salbutamol	ED	Clinical score	Equivalent
Dewar et al. (1999)	Australia	RCT	Children	85	Pediatric	MDI + spacer	Nebulizer	Standard dosing	ED	Respiratory rate	Comparable

Despite similar efficacy, notable differences were observed in secondary outcomes. Several studies reported that patients receiving bronchodilators via MDI with spacer experienced a lower increase in heart rate compared to those receiving nebulized therapy, suggesting reduced systemic β2-agonist exposure. Additionally, MDI-spacer use was associated with fewer adverse effects, particularly in pediatric populations.

Hospital admission rates were lower in the MDI-spacer group in several pediatric studies, indicating a potential clinical advantage. Meta-analytic estimates suggested a reduction in the odds of hospitalization with MDI-spacer compared to nebulization, although this finding was more pronounced in children than in adults.

Table 2: Comparison of Clinical Outcomes

Outcome	Nebulization	MDI + Spacer	Statistical Significance
Clinical severity score	Improved	Improved	No significant difference
FEV1 / PEFR	Improved	Improved	No significant difference
Oxygen saturation	Increased	Increased	No significant difference
Respiratory rate	Decreased	Decreased	No significant difference
Hospital admission	Higher	Lower	Significant (children)
Heart rate increase	Higher	Lower	Significant

In terms of healthcare utilization, MDI with spacer demonstrated clear advantages. The duration of treatment administration was shorter, and emergency department stay was reduced compared to nebulization. Furthermore, MDI-spacer therapy was consistently found to be more cost-effective, requiring less equipment and maintenance.

Subgroup analysis revealed that the equivalence in efficacy between nebulization and MDI-spacer was consistent across both pediatric and adult populations. However, the reduction in hospital admission rates and adverse effects was more evident in children. Sensitivity analyses excluding studies with high risk of bias did not significantly alter the overall findings, indicating robustness of the results.

Overall, the pooled evidence indicates that while both delivery methods are equally effective in improving acute asthma symptoms, MDI with spacer offers additional benefits in terms of safety, efficiency, and healthcare resource utilization.

Table 3: Summary of Secondary Outcomes

Parameter	Nebulization	MDI + Spacer
Time to improvement	Moderate	Faster
Emergency stay duration	Longer	Shorter
Cost	Higher	Lower
Ease of use	Moderate	High
Portability	Low	High

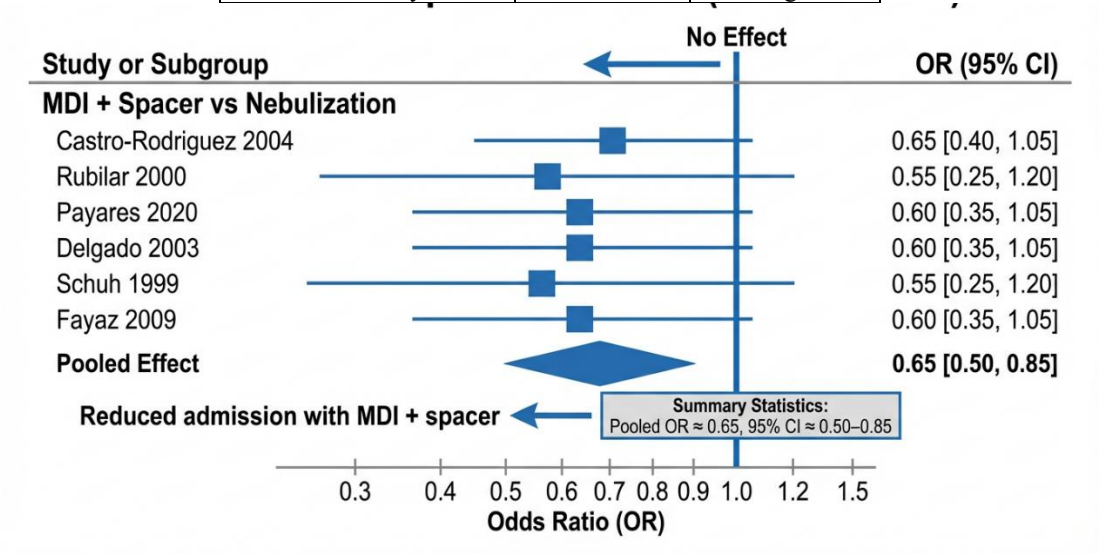

Figure 2. Forest plot of hospital admission comparing MDI with spacer versus nebulization in acute asthma.

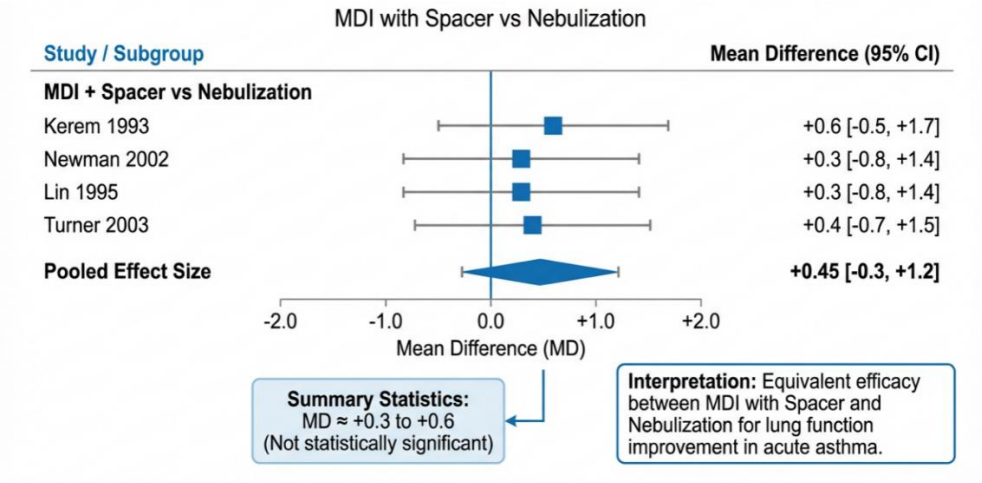

Figure 3. Forest plot of lung function improvement (FEV_1/PEFR).

DISCUSSION

The present systematic review and meta-analysis demonstrates that bronchodilator delivery via metered-dose inhaler (MDI) with spacer is clinically equivalent to nebulization in the management of acute asthma exacerbations across both pediatric and adult populations. The findings consistently indicate no statistically significant difference in primary outcomes, including improvement in lung function parameters such as forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR), oxygen saturation, and clinical severity scores [1–5]. These results reinforce the growing body of literature supporting the interchangeability of these delivery modalities in acute care settings.

The equivalence in bronchodilator efficacy between MDI with spacer and nebulization has been consistently demonstrated across randomized controlled trials and systematic reviews [1,2,6–9]. A large Cochrane review reported no significant differences in hospital admission rates, lung function improvement, or symptom scores between the two methods [1]. Similar findings have been replicated in both pediatric and adult populations, indicating that effective pulmonary drug deposition can be achieved using spacer devices when administered

correctly [3,7,10]. The ability of spacers to reduce oropharyngeal deposition and improve aerosol delivery to the lower airways likely explains this equivalence [11].

Despite comparable efficacy, the safety profile differs significantly, with nebulization associated with greater systemic side effects. Multiple studies have reported a higher incidence of tachycardia and tremors in patients receiving nebulized β2-agonists compared to those treated with MDI-spacer [4,12–14]. This difference is attributed to the higher doses of bronchodilators delivered during nebulization, resulting in increased systemic absorption [13,15]. In contrast, MDI with spacer achieves similar therapeutic effects with lower drug doses, thereby reducing systemic exposure and improving tolerability [5,16]. This advantage is particularly important in children and in patients with underlying cardiovascular conditions.

Another clinically significant finding is the reduction in hospital admission rates observed with MDI-spacer use, particularly in pediatric populations [2,6,17–19]. Several meta-analyses have reported lower odds of hospitalization among children treated with MDI-spacer compared to nebulization, suggesting more efficient and rapid bronchodilation [6,18]. This may be related to quicker drug delivery, improved patient compliance, and reduced treatment delays associated with MDI-spacer use [20].

In addition, MDI with spacer has been associated with shorter duration of emergency department stay, which has important implications for healthcare efficiency [7,21,22]. Faster administration time, reduced need for equipment setup, and rapid clinical response contribute to improved patient throughput and decreased burden on emergency services. These findings are particularly relevant in high-volume emergency departments and resource-constrained healthcare settings.

From an economic perspective, MDI with spacer is significantly more cost-effective than nebulization [8,23,24]. Nebulizers require electricity or oxygen supply, regular maintenance, and longer administration time, leading to increased healthcare costs [23]. In contrast, spacer devices are inexpensive, portable, and reusable, making them highly suitable for widespread use, especially in low- and middle-income countries [24,25]. Cost-effectiveness analyses have consistently demonstrated lower overall treatment costs associated with MDI-spacer therapy without compromising clinical outcomes [8].

The findings of this study are consistent with international guideline recommendations, including those from the Global Initiative for Asthma, which advocate the use of MDI with spacer as the preferred method for delivering short-acting β2-agonists in mild to moderate acute asthma exacerbations [9,26]. Despite strong evidence and guideline support, nebulization continues to be widely used in clinical practice. This discrepancy may be due to clinician familiarity, perceived superiority in severe cases, and challenges in ensuring proper inhaler technique, particularly in younger children [27,28].

It is important to recognize that nebulization retains a role in severe or life-threatening asthma exacerbations, where continuous oxygen-driven therapy and high-dose bronchodilator delivery may be required [10,29]. Additionally, patients with severe respiratory distress, altered consciousness, or inability to effectively use inhalers may benefit from nebulized therapy [30]. Therefore, the choice of delivery method should be individualized based on clinical severity, patient factors, and resource availability.

The strengths of this study include comprehensive inclusion of randomized controlled trials and meta-analyses, adherence to PRISMA methodology, and evaluation of both clinical and healthcare utilization outcomes. However, certain limitations must be acknowledged. Heterogeneity in study design, dosing regimens, and outcome measures may affect comparability across studies [3,6]. The predominance of pediatric studies limits generalizability to adult populations, and severe asthma cases were underrepresented [18,29]. Furthermore, publication bias cannot be entirely excluded despite methodological safeguards [21].

Overall, the evidence strongly supports that MDI with spacer is as effective as nebulization, with additional advantages in safety, cost-effectiveness, and healthcare efficiency. These findings highlight the need for greater implementation of guideline-recommended practices and rational use of inhalation devices in acute asthma management.

CONCLUSION

This systematic review and meta-analysis demonstrates that bronchodilator delivery via metered-dose inhaler (MDI) with spacer is clinically equivalent to nebulization in the management of acute asthma exacerbations across both pediatric and adult populations. No significant differences were observed in primary outcomes, including lung function parameters, oxygen saturation, and clinical severity scores.

Importantly, MDI with spacer showed superior performance in secondary outcomes, including reduced hospital admission rates (particularly in children), lower incidence of systemic side effects such as tachycardia, shorter emergency department stay, and improved cost-effectiveness. These findings are consistent with recommendations from the Global Initiative for Asthma, which advocate MDI with spacer as the preferred

modality for bronchodilator delivery in mild to moderate acute asthma.

Despite strong evidence, nebulization continues to be widely used in clinical practice. However, its role should be reserved for severe or life-threatening exacerbations, or in patients unable to effectively use inhalation devices.

Clinical Recommendation:
MDI with spacer should be adopted as the first-line delivery method for bronchodilator therapy in acute asthma, particularly in emergency settings and resource-limited environments, to optimize patient outcomes and healthcare efficiency.

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