

Cost-effectiveness of salbutamol via metered-dose inhaler with spacers versus nebulizers in children with asthma exacerbation in middle income country

Jittawat Witnalakorn,¹ Aroonwan Preutthipan,¹ Oraluck Pattanaprteep,² Wiparat Manuyakorn¹

Abstract

Background: Previous studies have demonstrated that salbutamol administration via metered-dose inhaler with spacer (MDI-S) is as effective as using a jet nebulizer (NEB) for treating children experiencing asthma exacerbation. However, a paucity of research focuses on the direct medical costs associated with each mode of salbutamol administration for asthma exacerbation.

Objective: This study aims to compare the effectiveness and direct medical costs of salbutamol administration via MDI-S versus NEB.

Methods: A retrospective cohort study was conducted on the medical records of children under 18 years old presenting with mild to moderate asthma exacerbation. Clinical responses to salbutamol administration were assessed using the Ramathibodi Pediatrics Asthma Scores. The costs and clinical outcomes (i.e., Asthma score and hospitalization averted) were compared using the Incremental Cost-Effectiveness Ratio (ICER) from a hospital perspective.

Results: The study included 95 medical records from 72 children, with 33 records of MDI-S and 62 records of NEB. Both the MDI-S and NEB groups showed significant reductions in asthma scores post-treatment. Children with moderate asthma exacerbation treated with MDI-S had a lower hospitalization rate than those treated with NEB (20% vs 57.5%, $p = 0.034$). The cost-effectiveness analysis indicated that the MDI-S group incurred lower costs and was considered cost-saving compared to the NEB group, with an ICER of -4.60 US dollars per one-point improvement in asthma score and -20.07 US dollars per hospitalization averted.

Conclusions: Salbutamol administration via MDI-S offers clinical effectiveness comparable to NEB and is more cost-effective.

Key words: Acute asthma, Direct medical cost, Aerosol therapy, ICER, Children

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Affiliations:

¹ Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

² Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Corresponding author:

Wiparat Manuyakorn
Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University
270 Rama 6 Road, Phayathai, Rachathewi, Bangkok, 10400, Thailand
E-mail: mwiparat@hotmail.com

Introduction

Salbutamol is the first-line treatment for acute asthma exacerbation, with administration options including Metered-Dose Inhaler with spacer (MDI-S) and nebulization (NEB), both providing comparable clinical benefits.^{1,2} MDI-S is associated with additional advantages, such as reduced hospitalization rates and overall cost savings, particularly in emergency room (ER) and inpatient department (IPD)

settings.³ Despite the benefits of MDI-S, NEB remains the preferred treatment method for pediatric asthma exacerbations in many hospitals and medical centers, including those in Thailand. NEB is often seen as the cornerstone of therapy in acute care settings. On the other hand, salbutamol via MDI-S is more commonly prescribed for outpatient or ambulatory management. Moreover, during resource constraints, it is crucial to consider not only treatment outcomes but also the efficiency of healthcare spending. Cost-effectiveness analysis, a type of economic evaluation method, assesses the trade-offs between costs and clinical outcomes, enhancing transparency in healthcare decision-making. This method compares incremental costs to additional clinical outcomes, which, in this study, include (1) improvement in asthma scores and (2) avoidance of hospitalization, which are displayed as the incremental cost-effectiveness ratio (ICER). Previous studies have demonstrated the cost-effectiveness of MDI-S in pediatric populations, but there has been a lack of analysis specifically comparing these methods in middle-income countries like Thailand. Such analyses are crucial to guide national health policies and ensure the most efficient allocation of resources. Furthermore, during aerosol therapy, nebulization generates aerosols, posing a risk of virus transmission. Consequently, it is recommended that salbutamol be administered through MDI-S during the COVID-19 pandemic to minimize the risk of COVID-19 virus transmission.⁴ The current study aims to assess the cost-effectiveness of administering salbutamol

through MDI-S versus NEB for the acute care treatment of children experiencing acute asthma exacerbations in a Thai hospital perspective.

Materials and Methods

Electronic medical records of children diagnosed with ICD-10 codes J45 (Asthma) and J46 (Status asthmaticus) from the outpatient and emergency departments at the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, from January 1, 2020, to June 30, 2023, were reviewed. Children presenting with acute wheezing from conditions other than asthma exacerbation or those with severe asthma exacerbation were excluded from the study. All consecutive cases who met the inclusion criteria during the study period were enrolled. The enrollment flow chart is summarized in **Figure 1A**. Asthma exacerbation severity was categorized as mild if the score was 0-3, moderate, 4-6, and severe if the score was 7-12 using Ramathibodi Pediatrics Asthma Scores.⁵ Physicians routinely followed the hospital's "Pediatric Asthma Exacerbation Guideline" for managing children with acute asthma exacerbation, as summarized in **Figure 1B**. The clinical effectiveness of both treatments was evaluated by the improvement in Ramathibodi Pediatrics Asthma Scores and the aversion of hospitalization. The Human Rights and Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (COA. MURA2022/188) approved the current study.

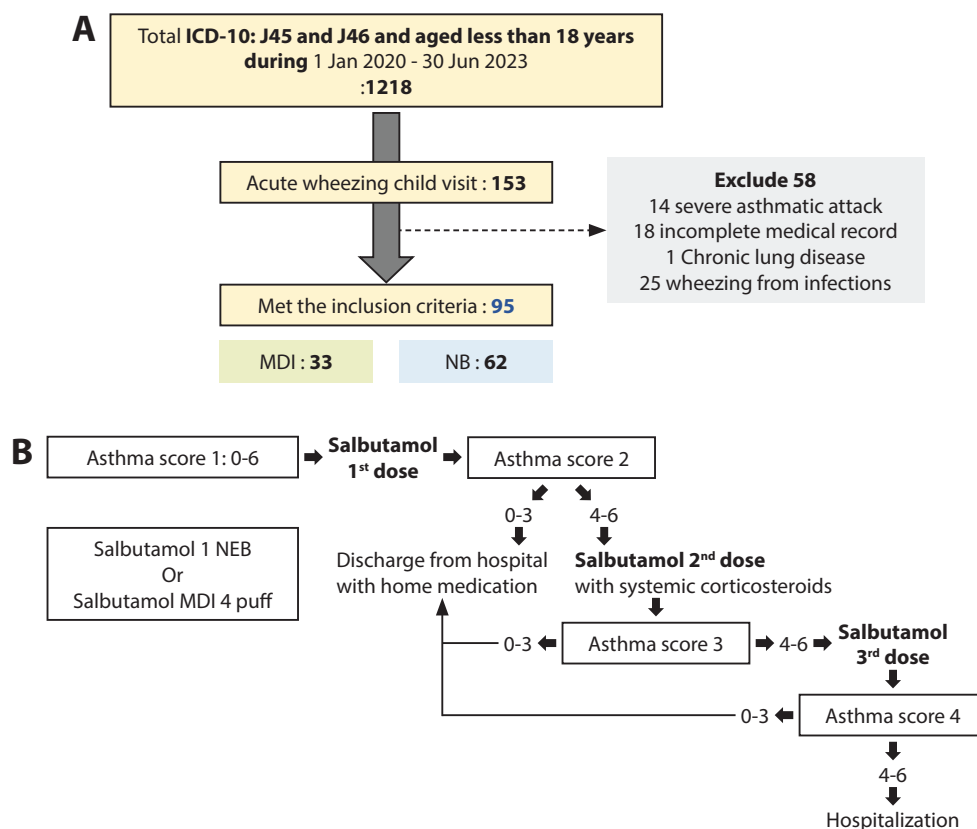


Figure 1. A) Flow chart of subject screening and enrollment. B) Asthma exacerbation treatment guideline.

Cost-effectiveness analysis

The cost-effectiveness analysis involved calculating the ratio of the reduction in asthma scores and the aversion of hospitalization after salbutamol administration to the total direct medical treatment costs per hospital visit. The treatment costs from the hospital invoice of any healthcare plans were included and categorized into the following components: 1) Drugs: Short-acting β_2 agonists (salbutamol) and corticosteroids (hydrocortisone, prednisolone, budesonide). 2) Equipment: Oxygen monitoring devices and infusion/syringe pumps. 3) Nursing Fees: Costs associated with nursing care. 4) Medical Supplies: Nebulizer masks, syringes, extension tubes, and spacers. All costs were adjusted to the 2023 price level using the consumer price index from the Ministry of Commerce’s database in Thai Baht and then converted to US dollars based on the exchange rate provided by the Bank of Thailand on January 3, 2023 (1 US dollar = 34.56 Thai Baht).⁶ Since disposable homemade spacers⁷ were used throughout the study period. The cost of the spacer was estimated at 10 US dollars, based on the average price of commercially available spacers at the study hospital. The cost-effectiveness of MDI-S compared to NEB therapies was evaluated using the ICER which was calculated as the cost difference between the two treatment methods divided by the improvement in asthma scores and by the aversion of hospitalization. Two equations were constructed as follows:

$$\text{ICER for the improvement of asthma score} = \frac{\text{Cost}_{\text{MDI-S}} - \text{Cost}_{\text{NEB}}}{\text{asthma score}_{\text{MDI-S}} - \text{asthma score}_{\text{NEB}}}$$

$$\text{ICER for the aversion of hospitalization} = \frac{\text{Cost}_{\text{MDI-S}} - \text{Cost}_{\text{NEB}}}{\text{hospitalization}_{\text{MDI-S}} - \text{hospitalization}_{\text{NEB}}}$$

A one-way sensitivity analysis was conducted by varying each parameter individually to its minimum and maximum values to assess the impact on the ICER and determine the robustness of the cost-effectiveness results and presented as tornado diagrams.

Statistical analysis

Data were analyzed using STATA version 14 and MS Excel with TreePlan addins. The analysis of treatment response over time within each treatment group was conducted using multilevel mixed-effects linear regression. This method allowed for assessing changes in asthma scores over time while accounting for the repeated measures within patients. The comparison of hospitalization rates between the MDI-S and NEB groups was performed using the chi-square test. This test was used to determine if the two groups had a statistically significant difference in hospitalization rates.

Direct medical costs between the MDI-S and NEB groups were compared using the Mann–Whitney U test. This non-parametric test was chosen due to its ability to compare differences between two independent groups when the data do not necessarily follow a normal distribution.

Results

A total of 95 medical records from 72 children were reviewed, comprising 33 records of MDI-S and 62 records of NEB. There were no significant differences in mean age, sex, inhaled corticosteroid usage, or baseline heart rate between the MDI-S and NEB groups. The median (IQR) pre-bronchodilator asthma score in the NEB group was significantly higher than that in the MDI-S group [4.5 (1-6) vs. 3 (1-5), $p = 0.001$]. However, when categorized by mild and moderate severity, there were no significant differences in the median (IQR) pre-bronchodilator asthma scores between the MDI-S and NEB groups (Table 1).

Table 1. Baseline characteristics of enrolled children.

	MDI-S (N = 33)	NEB (N = 62)	p-value
Age (month): Mean \pm SD	89.5 \pm 41.8	87.6 \pm 41.8	0.443
Sex: Male : N (%)	18/33 (54.6)	41/62 (66.1)	0.268
Previously/current ICS: N (%)	19 (57.6)	36 (58.1)	0.963
Heart rate: bpm, Mean \pm SD	121.3 \pm 20.0	130.0 \pm 20.5	0.909
Severity of asthma exacerbation			
• Mild: N (%)	23 (70)	22 (35.5)	0.001
• Moderate: N (%)	10 (30)	40 (64.5)	
Baseline asthma score: median, (min, max)			
• Mild	2 (1,3)	2 (1,3)	0.816
• Moderate	5 (4,6)	5 (4,6)	0.114

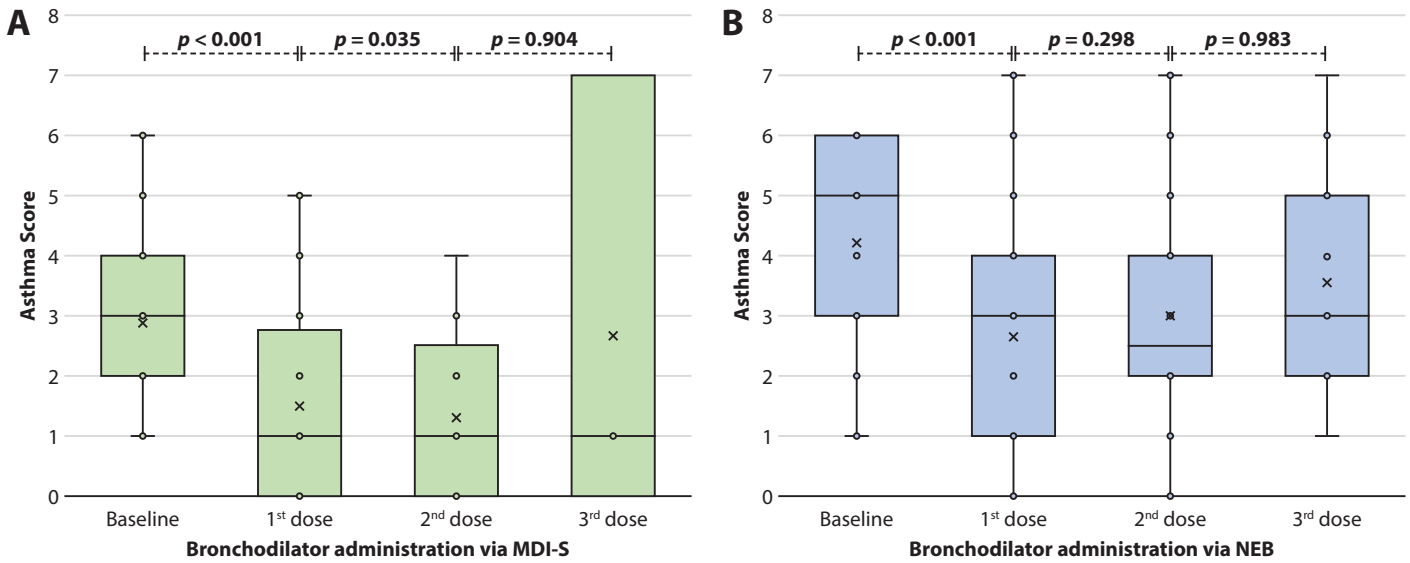


Figure 2. Changes in asthma score after salbutamol treatment. A) MDI-S and B) Nebulization.

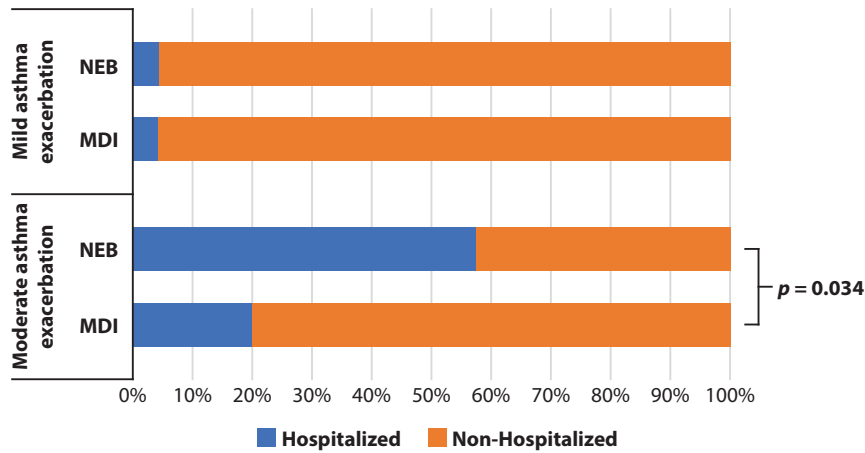


Figure 3. Hospitalization rate in children with mild vs. moderate asthma exacerbation.

Clinical outcomes after bronchodilator treatment with MDI with spacer (MDI-S) and nebulizer (NEB)

Asthma scores significantly improved after treatment in the MDI-S and NEB groups (Figure 2). The hospitalization rates for children with mild asthma exacerbation were similar between the MDI-S and NEB groups (4.3% vs. 4.5%). However, for children with moderate asthma exacerbation, the hospitalization rate was significantly lower in the MDI-S group compared to the NEB group (20% vs. 57.5%, $p = 0.034$) (Figure 3). Children in the MDI-S group tended to spend less median (min, max) time in the treatment room compared to those in the NEB group, though this difference did not reach statistical significance [80 (15, 260) vs. 105 (30, 300) minutes, $p = 0.08$].

Cost-Effectiveness Analysis

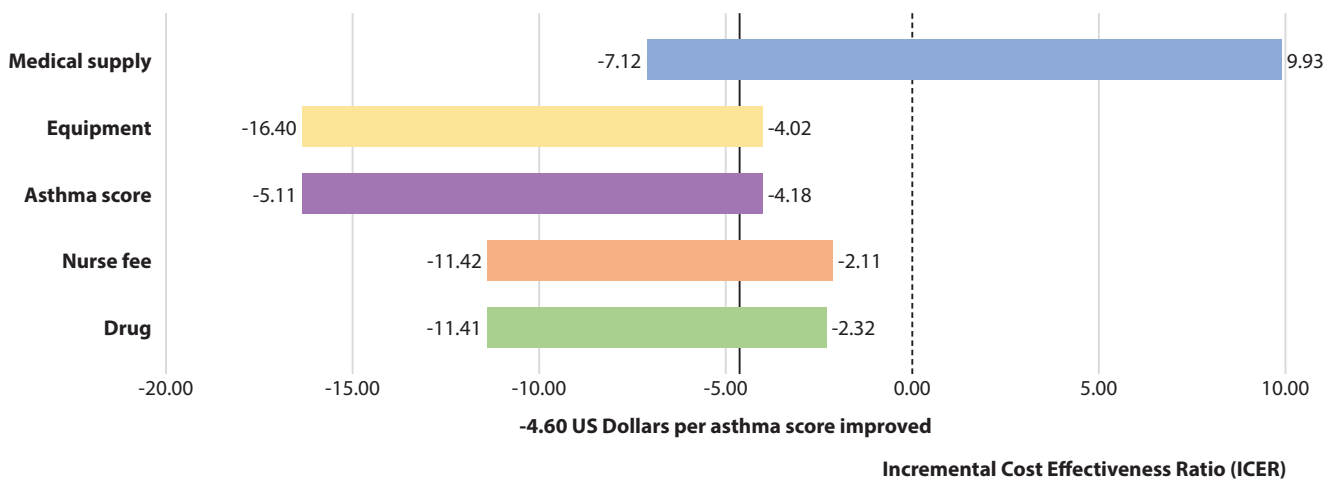
The treatment cost comparisons between MDI-S and NEB revealed that patients using MDI-S incurred significantly lower equipment costs and nurse fees but had considerably higher medical supply costs ($p = 0.001$). While children receiving MDI-S tended to have lower total costs compared to those receiving NEB, this difference did not reach statistical significance [17.87 (15.02, 29.58) vs. 27.60 (15.97, 39.01), respectively] (Table 2). The incremental cost of MDI-S compared to NEB was -6.09 US dollars. Meanwhile, the incremental outcomes included a 1.32-point improvement in asthma scores and a 0.30 reduction in hospitalizations. To evaluate cost-effectiveness, the ICER was calculated.

Table 2. Comparison of the direct medical costs per hospital visit for treatment between MDI-S and NEB.

Direct medical costs per hospital visit (US\$)	MDI-S	NEB	p-value
• Drug	2.45 (1.79, 6.47)	4.70 (1.65, 8.23)	0.26
• Equipment	0 (0, 0)	2.98 (0, 5.95)	< 0.001
• Nurse fee	2.95 (2.20, 5.35)	7.43 (6.14, 10.42)	< 0.001
• Medical supply	10 (10, 15.25)	7.55 (3.87, 13.51)	0.001
• Total cost	17.87 (15.02, 29.58)	27.60 (15.97, 39.01)	0.107

Data present as median (IQR)

A) Asthma score improved



B) Hospitalized avert

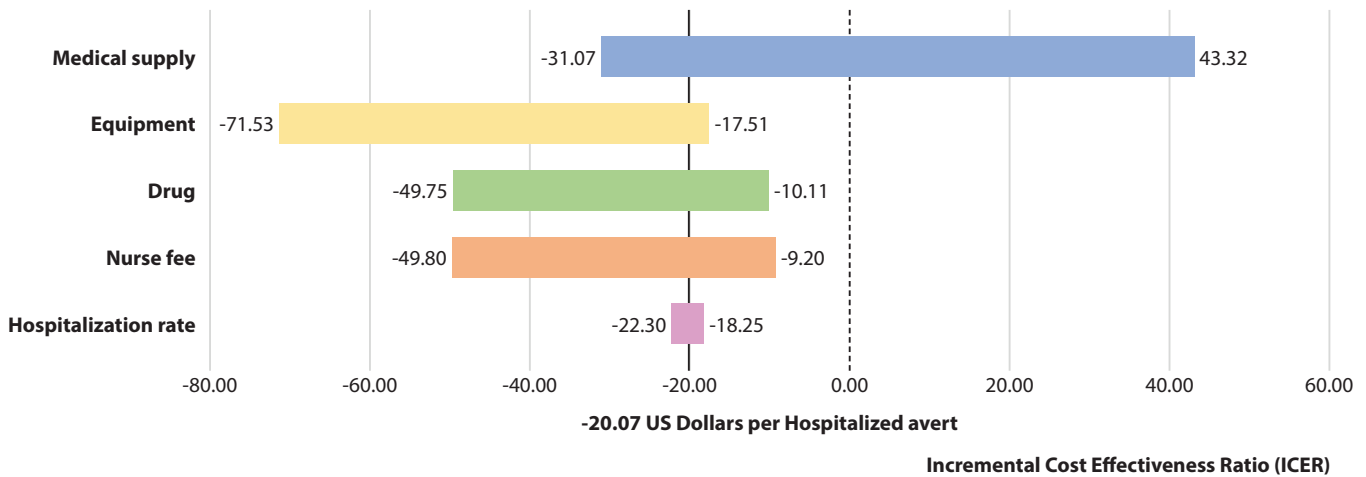


Figure 4. One-way sensitivity analysis-Tornado diagram. The ICER value was shown on the X-axis, and the solid line showed the ICER when all parameter mean values were used (each parameter presented on the Y-axis). ICER at 0 was the dashed line; any value on the left (ICER below 0) indicated cost savings and greater benefit at lower cost. A) asthma score improved. B) hospitalization averted.

The ICER, which reflects the cost difference between the two treatments divided by the improvement in asthma scores, was -4.60 US dollars per one-point improvement in asthma scores (derived from -6.09/1.32) and -20.07 US dollars per one hospitalization averted (derived from -6.09/0.30), indicating that MDI-S was cost-saving compared to NEB. A one-way sensitivity analysis (Figure 4) was conducted to explore each parameter's uncertainty affecting cost-effectiveness. The ICER value was shown on the X-axis, and the solid line showed the ICER when all parameter mean values were used (each parameter presented on the Y-axis). ICER at 0 was the dashed line; any value on the left (ICER below 0) indicated cost savings, greater benefit at lower cost. The figures showed that medical supply and equipment costs were the first and second greatest effects on ICER for both outcomes. Only when the cost of medical supplies raised to the maximum value, the ICER would move to a positive number, indicating non-cost savings.

Discussion

The present study has demonstrated the comparable effectiveness of salbutamol delivery via MDI-S and nebulizer in children with mild to moderate asthma exacerbation. Children receiving salbutamol delivery via MDI-S tended to have a lower percentage of hospitalization and spend less time in the hospital, consistent with previous research findings. A recent meta-analysis reported better clinical outcomes, as assessed by the pulmonary index score, in children with acute asthma exacerbation treated with salbutamol delivery via MDI-S compared to nebulization.⁸ Similarly, children treated with salbutamol via MDI-S for asthma exacerbation in the emergency department showed similar hospitalization rates compared to those treated via nebulization.⁹ A randomized, double-blind, placebo-controlled study involving children aged 1-4 years with moderate to severe asthma exacerbation demonstrated a lower hospitalization rate in children receiving salbutamol via MDI-S.¹⁰ Our subgroup analysis of children with moderate asthma exacerbation further supported these findings, showing a lower percentage of hospitalization among those who received salbutamol via MDI-S. An observational study conducted in Canada, focusing on children aged 1-7 years presenting with acute wheezing at the pediatric emergency department, also found that treatment with MDI-S versus NEB was associated with a 4.4% reduction in hospitalization rates.³

These results support the use of MDI-S as an effective and potentially preferable treatment option for children with asthma exacerbation, offering comparable or better clinical outcomes and potentially reducing the need for hospitalization.

The present study revealed that children receiving salbutamol via MDI-S incurred lower direct medical costs in equipment and nurse fees than those receiving nebulization. In addition, our study is the first to calculate ICER for treating acute asthma exacerbation by comparing salbutamol delivery via MDI-S vs. Nebulization. Previous studies have consistently reported lower treatment costs for children receiving salbutamol via MDI-S for acute asthma

exacerbation. Research conducted in emergency department settings^{3,10,11} and hospital settings^{8,12} has shown that MDI-S is associated with reduced direct medical costs compared to nebulization. These findings highlight the potential economic benefits of using MDI-S to treat acute asthma exacerbation in children. By reducing direct medical costs, MDI-S may contribute to more efficient resource allocation and healthcare utilization, ultimately benefiting patients and healthcare systems.

Our findings underscore the clinical and economic advantages of using metered-dose inhalers with spacers (MDI-S) over nebulizers (NEB) for administering salbutamol in children with mild to moderate asthma exacerbations. Both treatment modalities were equally effective in reducing asthma scores; however, MDI-S was associated with significantly lower hospitalization rates for moderate asthma exacerbations and incurred lower direct medical costs, particularly in nurse fees and equipment expenses. Conversely, the cost of medical supplies, primarily driven by the expense of the spacer, was slightly higher in the MDI-S group. Despite this, the cost-effectiveness analysis demonstrated that MDI-S provides substantial cost savings, with an ICER of -4.60 US dollars per one-point asthma score improvement and -20.07 US dollars per one hospitalization averted, establishing MDI-S as a cost-saving alternative to NEB. These findings indicate that MDI-S is not only clinically effective but also a more cost-effective option for healthcare providers. Our study supports the broader adoption of MDI-S for pediatric asthma management in both emergency and hospital settings, particularly in resource-limited environments where cost considerations are critical. Future research should explore long-term outcomes and strategies for broader implementation to further validate and expand upon these findings.

However, our study has several limitations. First, it employed a retrospective design, inherently susceptible to biases and limitations, such as incomplete or inaccurate documentation. Second, the study was conducted at a single medical center, potentially limiting the generalizability of the findings to other settings or populations with differing healthcare systems and practices, particularly in countries with varying healthcare infrastructures. Third, the study period, from January 1, 2020, to June 30, 2023, coincided with the COVID-19 pandemic and post-pandemic period. While healthcare utilization measures related to the prevention of viral transmission likely did not influence the direct medical costs assessed, only the direct medical costs associated with asthma exacerbation treatment were included, excluding costs related to viral transmission prevention. Fourth, the pre-bronchodilator asthma scores in the NEB group were higher than those in the MDI-S group, reflecting more severe exacerbations in the NEB group. However, when categorized by mild and moderate severity, there were no significant differences in the median (IQR) prebronchodilator asthma scores between the MDI-S and NEB groups. Additionally, a lower hospitalization rate was observed among children with moderate exacerbations in the MDI-S group compared to the NEB group. This difference is unlikely to impact the cost-effectiveness analysis significantly.

Lastly, the calculation of direct medical costs may not have captured all relevant expenses or fully reflected the total economic impact of asthma exacerbation treatment, such as indirect costs, hospitalization expenses, or long-term healthcare utilization.

In conclusion, salbutamol administration via MDI with spacer is an effective and economically advantageous approach for treating children with asthma exacerbations, warranting consideration as a preferred method in clinical practice.

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