RESEARCH PAPER

A Systematic Review and Meta-Analysis Comparing Continuous versus Intermittent Nebulized Salbutamol in Children with Severe Asthma Exacerbation

Elbarraa Ebrahim Reihan Abujabal[1], Mohamed Mahmoud Rashad Fouad[2]
[1] MBBS, University of West Kordufan & Master of Pediatric Medicine from Lincoln University
[2] Professor of Pediatrics, Faculty of Medicine, Benha University
Corresponding author's Email: albarraareihan198@gmail.com

Abstract
Background: Severe exacerbations of Asthma in children are a major cause of emergency visits and hospital admissions. Nebulized short-acting β2-agonists, particularly salbutamol (albuterol), are the cornerstone of acute management. Although both intermittent and continuous nebulization strategies are widely used. This systematic review and meta-analysis aim to compare the continuous versus intermittent nebulization of salbutamol in children with severe asthma.
Methods: A comprehensive literature search was conducted for studies published from inception up to April 2026 using PubMed, Scopus, Cochrane, and Web of Science databases, focusing on studies comparing continuous and intermittent nebulization of salbutamol in children with severe asthma. The outcomes were asthma score at 2, 4 hours, length of hospital stay, and side effects (vomiting and tremors). The risk of bias was assessed using the RoB 2 tool for randomized trials, and meta-analytical techniques were employed to calculate pooled effect sizes and statistical significance.
Results: There were no significant differences between continuous and intermittent nebulized salbutamol in asthma scores at 2 and 4 hours. Length of hospital stay was also comparable between both groups. In addition, no significant differences were observed in adverse effects, including vomiting and tremors. Overall, heterogeneity across the included outcomes ranged from moderate to high.
Conclusion: Continuous nebulized salbutamol did not show significant superiority over intermittent nebulization in children with severe asthma exacerbation, with both strategies demonstrating comparable efficacy and safety.
Keywords: Continuous, Intermittent, Nebulization, Salbutamol, Albuterol, Asthma, Children, Meta-Analysis
How to cite this article: Elbarraa Ebrahim Reihan Abujabal1 Mohamed Mahmoud Rashad Fouad2. A Systematic Review and Meta-Analysis Comparing Continuous versus Intermittent Nebulized Salbutamol in Children with Severe Asthma Exacerbation. Int J Drug Deliv Technol. 2026;16(80s):641-647. DOI: 10.25258/ijddt.16.80s.78.

Introduction

Asthma involves inflammation that affects the airways, and leads to bronchial hyperreactivity, narrowing of airways, structural changes in airway walls, and increased production of mucus [1]. Asthma remains an important public health issue, significantly affecting the quality of life for many affected individuals [2].

Asthma is a major global health issues, affecting around 300 million people, and causing about 1,000 deaths daily. Asthma affects around 260 million people globally, causing around 0.5 million deaths annually. The global mortality rate for pediatric asthma varies, ranging from 0.1-0.7 deaths/100,000 [3]. The most frequently observed symptoms among children experiencing asthma include flare-ups, chest tightness, wheezing, and shortness of breath [4].

Inhaled short-acting β2-adrenergic agonists (SABAs), particularly Salbutamol (also known as Albuterol), are the first-line bronchodilators recommended by international guidelines such as the Global Initiative for Asthma [5]. These agents exert their therapeutic effect by stimulating β2-adrenergic receptors on airway smooth muscle, leading to increased intracellular cyclic adenosine monophosphate (cAMP) levels and subsequent smooth muscle relaxation [6].

Additionally, β2-agonists may enhance mucociliary clearance and inhibit mediator release from mast cells, contributing to their rapid clinical efficacy [7]. Delivery of salbutamol via nebulization is particularly advantageous in children with severe exacerbations, as it does not require coordinated inhalation and allows administration of higher drug doses over a sustained period [8].

Intermittent nebulization with SABA, salbutamol 0.15–0.3 mg per kg, every one to 4 hours is the current first-line recommendation for hospitalized children with asthma exacerbation [9]. However, children with severe asthma exacerbation may have suboptimal responses to first-line treatment and eventually require an escalation to more aggressive therapy (eg, continuous nebulization, intravenous salbutamol, or intravenous magnesium sulfate) [10]. Admission to the pediatric intensive care unit (PICU)

is crucial for delivering and monitoring for side effects of these therapies [11].

When progression to lifethreatening respiratory failure occurs, endotracheal intubation and mechanical ventilation are needed. The results are asthma complications, prolonged hospital stays, and increased expenditures. Prolonged PICU admission is also a very stressful experience and can be associated with post-traumatic stress disorder for both children and their parents [12].

Continuous nebulization with SABA, salbutamol 10–25 mg per hour or 0.5–1 mg per kg per hour, has been recommended for children with asthma exacerbation who did not show adequate response to the first-line intermittent nebulization [13]. Continuous use of Salbutamol inhalation has been shown to be more effective than sporadic administration [14]. It was reported that some children with severe asthma exacerbation usually ended up with continuous nebulization therapy [15].

Given these inconsistencies, a comprehensive synthesis of the available evidence is warranted. A systematic review and meta-analysis offers a robust methodological framework to quantitatively evaluate the comparative effect of continuous versus intermittent nebulized salbutamol in this clinical context. By integrating data from multiple studies, such an analysis can enhance statistical power, reduce uncertainty, and provide more precise estimates of treatment effects, thereby informing evidence-based clinical decision-making.

Therefore, the present study aimed to systematically review and meta-analyze the existing literature comparing continuous and intermittent nebulized salbutamol in children with severe asthma exacerbations.

Methods

We performed a systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Protocol for this review was registered with the PROSPERO database

Search strategy

Using the PubMed, Scopus, Cochrane, and Web of Science databases, a thorough literature search was carried out to find papers comparing continuous and intermittent nebulization of salbutamol in children with severe asthma that had been published up from inception until April 2026.

This meta-analysis and systematic review was structured according to the PICO framework. Population (P): Pediatric patients (<18 years old) with severe asthma. Intervention (I): continuous salbutamol. Comparison (C): intermittent salbutamol. Outcome (O): asthma score at 2, 4 hours, length of hospital stay, and side effects (vomiting and tremors).

Search Strategy and Study Selection

The search strategy included combinations of Medical Subject Headings (MeSH) terms and keywords with Boolean operators (AND, OR) were used to refine the search: ("continuous") AND ("intermittent" OR " sporadic") AND ("nebul*" OR "aerosol*" OR "inhal*") AND ("Albuterol" OR "salbutamol" OR "beta-2 agonist" OR "short-acting beta agonist" OR "SABA") AND ("child*" OR "pediatric" OR "paediatric" OR "infant*") AND ("asthma" OR "status asthmaticus" OR "wheezing").

The titles and abstracts of the studies were used for screening after the duplicates were removed. Eligibility was determined by full-text reviews according to inclusion and exclusion criteria. To record the steps of screening and selecting, we utilized the Preferred Reporting Items for Systematic Reviewers and Meta-Analyses (PRISMA) flow diagram.

Inclusion Criteria: Research was considered for inclusion if it fulfilled the following criteria: 1. studies that have been published. 2. Research contrasting continuous with intermittent nebulized salbutamol (albuterol). 3. Pediatric patients with severe asthma.

Exclusion Criteria: 1. Dealing with poorly specified or non-existent main endpoints. 2. Studies using animals or cadavers. 3. Case reports, case series, reviews, editorials, or conference abstracts without accessible full text. 4. Studies that did not directly compare continuous versus intermittent nebulized salbutamol, or those involving different bronchodilators or combination therapies where the independent effect of salbutamol could not be determined

Study Selection

Two reviewers manually screened the studies based on title and abstract then another two reviewers screened them based on full text, with subsequent verification by an independent reviewer to ensure accuracy and resolve disagreements.

Data Extraction

From each included study, two reviewers retrieved pertinent material, which was then confirmed by a third reviewer to guarantee correctness.

Extracted data included year of publication, country of origin, study design, sample size, patient demographics.

Quality assessment

The Cochrane risk-of-bias tool for randomized trials (ROB2) was used to assess the risk of bias of the included studies [16]. The risk of bias resulting from the randomization procedure, missing outcome data, risk of bias in outcome assessment, and risk of bias in the selection of the reported result are the five primary domains that this instrument assesses.

These standards were used to evaluate each study. The quality assessment was carried out by two separate reviewers, and any disagreements were settled by discussion.

Outcomes

Primary outcomes was asthma score at 2 hours. Secondary outcomes were asthma score at 4 hours, length of hospital stay, and side effects (vomiting and tremors).

Data Synthesis and statistical analysis

Mean difference (MD) with 95% Confidence Intervals (CIs) were pooled for continuous outcomes and risk ratio (RR) for dichotomous outcomes. A P value greater than 0.05 was considered statistically significant for overall effect estimates. The DerSimonian and Laird random-effects model was applied. Heterogeneity was assessed using the Cochran Q test and I^2 statistics, with p <0.10 and I^2 $>50\%$ considered indicative of significant heterogeneity, following Cochrane's guidelines. Statistical analyses were performed using Review Manager (REV-Man) Version 5.4.

Results

Study Selection

Initially, 108 articles were found. In order to determine eligibility, 72 papers were screened based on their titles and abstracts after 36 research were eliminated as duplicates. Ten of these studies were found to be appropriate for full-text review. After full text screening, four studies were eliminated. This review ultimately comprised seven papers. Comorbidities were accounted for in all of the trials. The complete process of choosing a research is shown in **Figure 1.**

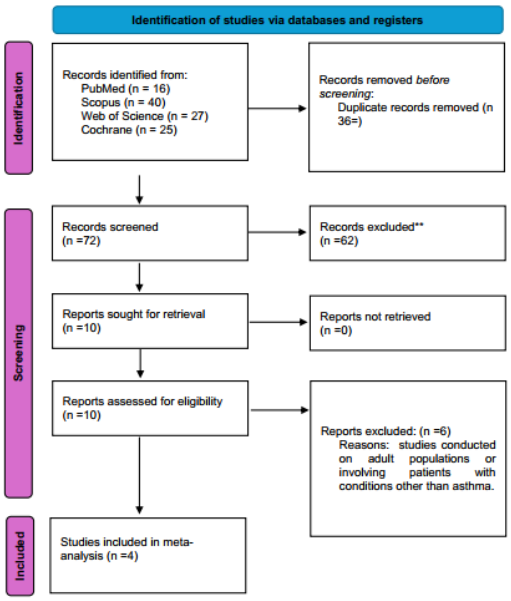

Figure 1: PRISMA flow diagram depicting the selection of the included articles

Quality assessment

To evaluate the included studies' risk of bias, the Cochrane risk-of-bias tool for randomized trials (ROB2) was used. Certain research showed some issues.

There was only one study that showed some concerns while 6 studies were of low risk as demonstrated in **Table 1, Figure 2.**

Table 1: Risk of bias assessment using RoB 2 tool

	Papoet al.,1993 [17]	**Khine etal., 1996** [18]	**Kulalert et al., 2020** [13]	**Zulqarnain et al., 2026** [14]
Domain				
Potential bias due to the randomization procedure	Low	Low	Low	Low
Impairment as a result of divergence from planned actions	unclear	unclear	unclear	unclear
Due to lacking outcome data, there is bias	Low	Low	Low	Low
Potential for bias in outcome assessment	Low	Low	Low	Low
Potential for bias in the chosen outcome	Low	Low	Low	Low
Overall	Low	Low	Low	Low

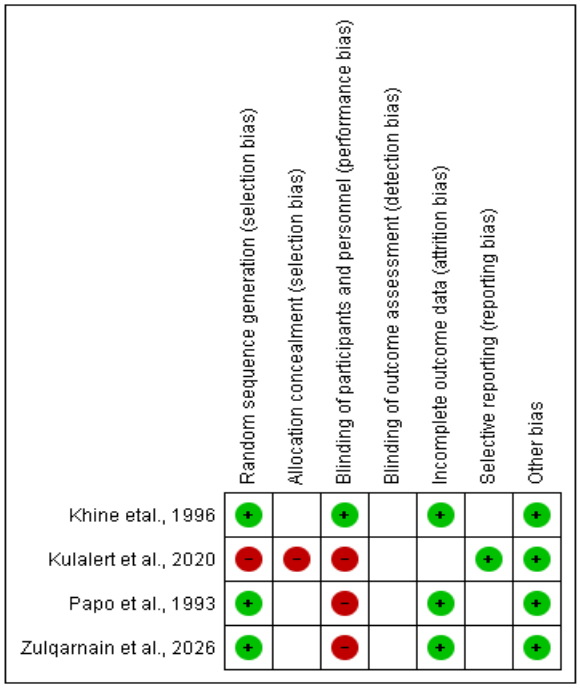

Figure 2: Risk of bias assessment of the included articles

Characteristics of included studies

The included studies and their characteristics are shown in **(Table 2).** The analysis encompassed a total of 319 patients with 160 patients received continuous nebulized salbutamol while 159 received intermittent nebulized salbutamol.

Table 2: Characteristics of the included studies

Author	Country	Number of patients in (Continuous group)	Number of patients (Intermittent group)	Mean Age (years) (mean ± SD)		Gender (M/F)	
				Continuous	Intermittent	Continuous	Intermittent
Papo et al., 1993 [17]	USA	9	8	N/A	N/A	M:5 F:4	M:5 F:3
Khine etal., 1996 [18]	USA	35	35	7.17±3.83	6.58±4.17	M:27 F:8	M:25 F:10
Kulalert et al., 2020 [13]	Thailand	56	56	5.87±4	5.8±4	M:33 F:23	M:33 F:23
Zulqarnain et al., 2026 [14]	Pakistan	60	60	8.11±1.8	7.98±1.5	M:33 F:27	M:35 F:25

M: Male, F: Female.

Outcomes

Three studies [14, 17, 18], revealed that the asthma score at 2 hours was insignificantly different between both groups (MD=-36, 95%CI: -0.95:0.24, p=0.24) with I2=87%. **Figure 3**

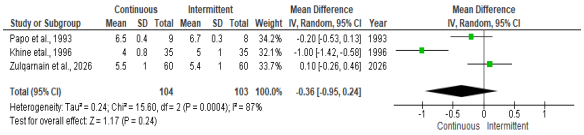

Figure 3: Forest plot comparing Asthma score at 2 hours between continuous and intermittent nebulized salbutamol

Two studies [14, 17], revealed that the asthma score at 4 hours was insignificantly different between both groups (MD=-39, 95%CI: -1.37:0.59, p=0.44) with I2=93%. **Figure 4**

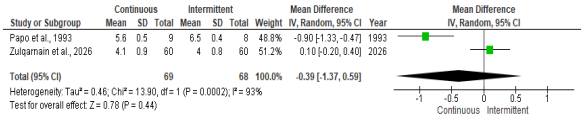

Figure 4: Forest plot comparing Asthma score at 4 hours between continuous and intermittent nebulized salbutamol

Three studies [13, 14, 17], revealed that the length of hospital stay was insignificantly different between both groups (MD=-18.34, 95%CI: -45.13:8.44, p=0.18) with I^2=86%. **Figure 5**

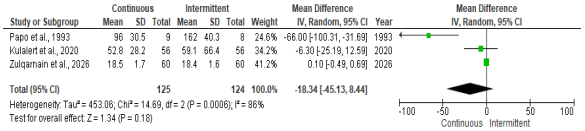

Figure 5: Forest plot of comparing length of hospital stay between continuous and intermittent nebulized salbutamol

Three studies [13, 14, 18], revealed that the vomiting was insignificantly different between both groups (RR=0.66, 95%CI: 0.11:4.02, p=65) with I^2=34%. **Figure 6**

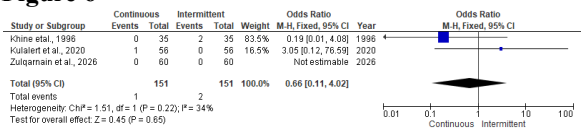

Figure 6: Forest plot of comparing the vomiting between dexmedetomidine and magnesium sulfate

Two studies [14, 18], revealed that the tremors was insignificantly different between both groups (RR=0.48, 95%CI: 0.14:1.62, p=24). **Figure 7**

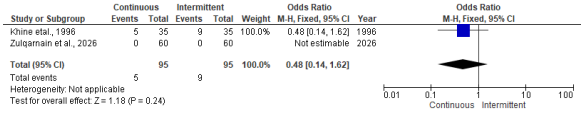

Figure 7: Forest plot of comparing the tremors between dexmedetomidine and magnesium sulfate

Heterogeneity

The observed asymmetry in the forest plots, especially in the primary outcomes, indicates the potential presence of publication bias or other biases, such as methodological heterogeneity among the studies. A leave-one-out sensitivity analysis was performed under a random-effects model for all outcomes with high heterogeneity, which was applied to all endpoints, except tremor.

Discussion

This systematic review and meta-analysis compared continuous versus intermittent nebulized salbutamol in children with severe asthma exacerbation. The pooled analysis demonstrated no statistically significant differences between both treatment strategies regarding asthma score at 2 and 4 hours, length of hospital stay, vomiting, or tremors.

Although continuous nebulization has traditionally been considered a more aggressive therapeutic approach for severe asthma, the current findings suggest that its clinical superiority over intermittent nebulization remains uncertain in pediatric patients.

One possible explanation for the absence of significant differences in asthma scores is that both regimens ultimately deliver the same pharmacologically active β2-agonist with a rapid onset of action. Salbutamol effectively relaxes bronchial smooth muscle regardless of whether it is delivered continuously or intermittently, especially when adequate dosing is achieved early during exacerbation management [7]. Therefore, intermittent nebulization administered at frequent intervals may provide bronchodilation comparable to continuous administration in many children with severe asthma.

Another explanation may relate to variability in disease severity among the included studies. Although all studies involved severe asthma exacerbations, the exact definitions of "severe asthma" differed between trials. Some studies included children with impending respiratory failure, whereas others enrolled patients with moderate-to-severe symptoms only. This variation may have diluted any measurable advantage of continuous nebulization and contributed to the substantial heterogeneity observed in the pooled analyses.

The present findings are partially consistent with the randomized trial by Papo et al. **[17]**, which reported no major clinical advantage of continuous nebulized albuterol compared with intermittent therapy in children with status asthmaticus. Similarly, Khine et al. **[18]** found that both regimens resulted in comparable clinical improvement and adverse event profiles. These studies support the concept that intermittent administration may be sufficient for many pediatric patients when delivered appropriately and monitored carefully.

In contrast, Zulqarnain et al. [14] suggested that continuous nebulization produced faster symptomatic improvement in children with acute severe asthma. Continuous administration theoretically maintains more stable bronchodilator concentrations within the airways, preventing fluctuations in β2-receptor stimulation that may occur with intermittent dosing. This sustained bronchodilation could be particularly beneficial in patients with severe airflow limitation or poor aerosol penetration secondary to mucus plugging and airway edema.

Furthermore, Kulalert et al. [13] reported favorable outcomes with continuous nebulization as first-line therapy in hospitalized children with severe asthma exacerbation. Their propensity score matching analysis suggested potential reductions in treatment failure and escalation of care. One explanation is that continuous delivery may reduce periods of untreated bronchospasm between intermittent doses, especially in children with rapidly recurring symptoms after temporary improvement.

Despite these theoretical benefits, the pooled analysis did not demonstrate shorter hospitalization duration with continuous nebulization. Several factors may explain this finding. Hospital discharge decisions are often influenced by institutional protocols, physician preference, oxygen requirements, and social factors rather than bronchodilator regimen alone. Consequently, length of hospital stay may not accurately reflect the isolated therapeutic effect of salbutamol delivery strategy.

The analysis also demonstrated no significant differences in adverse effects, including vomiting and tremors, between both groups. Salbutamol-related side effects are primarily dose-dependent and mediated through systemic β2-adrenergic stimulation. Although continuous nebulization may theoretically increase systemic exposure, careful dose titration and monitoring in hospitalized children likely minimized clinically important toxicity [19]. Additionally, the relatively small sample sizes of the included studies may have limited the ability to detect rare or subtle adverse events.

An important finding in this meta-analysis was the high heterogeneity observed in several outcomes, particularly asthma scores and hospital stay. Multiple factors may explain this heterogeneity. First, there were differences in nebulization protocols, including salbutamol dose, duration of administration, and intervals between intermittent treatments. Second, asthma severity scoring systems varied among studies, reducing comparability across trials. Third, co-interventions such as systemic corticosteroids, oxygen supplementation, magnesium sulfate, and anticholinergic therapy differed between institutions and may have influenced clinical outcomes independently of nebulization strategy.

The small number of included studies and limited overall sample size also reduce the certainty of the pooled estimates. Some studies were conducted decades ago, when asthma management protocols and supportive care differed substantially from current pediatric practice. Advances in emergency care, earlier corticosteroid administration, and improved monitoring may reduce the incremental benefit of continuous nebulization seen in older trials.

Evidence from adult studies provides additional perspective. Besbes-Ouanes et al. [20] demonstrated that continuous nebulized salbutamol improved pulmonary function more rapidly than intermittent therapy in adults with acute severe asthma. Similarly, Lin et al. [21] reported greater short-term improvement in airflow parameters with continuous administration.

These adult findings may suggest a physiological advantage of continuous bronchodilation during severe airway obstruction. However, extrapolation to pediatric populations should be performed cautiously because children differ from adults in airway anatomy, aerosol deposition, respiratory mechanics, and β2-receptor responsiveness.

Another possible explanation for the discrepancy between adult and pediatric findings is that adults with severe asthma often have more fixed airway remodeling and chronic airflow limitation, potentially making sustained bronchodilator delivery more beneficial. In contrast, children generally have more reversible airway obstruction and may respond adequately to intermittent therapy alone.

The current meta-analysis has several strengths. It systematically synthesized available pediatric evidence comparing two commonly used salbutamol delivery strategies. Additionally, the inclusion of randomized and comparative studies improved the comprehensiveness of the analysis. The use of PRISMA methodology and ROB2 quality assessment further strengthened methodological rigor.

Nevertheless, several limitations should be acknowledged. First, the number of included studies was relatively small, limiting statistical power. Second, substantial heterogeneity was present across multiple outcomes. Third, variations in dosing regimens, asthma severity definitions, and supportive treatments may have influenced pooled estimates. Fourth, publication bias could not be excluded due to the small number of studies available for each outcome. Finally, some included studies were older and may not fully represent current pediatric asthma management practices.

Overall, the findings of this meta-analysis suggest that continuous nebulized salbutamol does not provide statistically significant clinical advantages over intermittent nebulization in children with severe asthma exacerbation. However, continuous nebulization may still be valuable in selected patients with severe bronchospasm, inadequate response to intermittent therapy, or impending respiratory failure. Future large-scale, multicenter randomized controlled trials using standardized asthma severity scores and uniform treatment protocols are needed to better define which pediatric patients may benefit most from continuous nebulized salbutamol.

Conclusions

Continuous nebulized salbutamol was not associated with better clinical outcomes compared with intermittent nebulized salbutamol in children with severe asthma exacerbation, as both approaches showed similar effects on asthma severity scores, length of hospital stay, and adverse events. Therefore, intermittent nebulization remains an effective and safe treatment option, while continuous nebulization may be reserved for selected severe or refractory cases.

References

1. Figueiredo IAD, Ferreira SRD, Fernandes JM, Silva BAD, Vasconcelos LHC, Cavalcante FA. A review of the pathophysiology and the role of ion channels on bronchial asthma. Front Pharmacol. 2023;14(9):123-65.
2. Kasse T, Zenebe S, Agegnehu Y, Lonsako AA. Factors influencing health-related quality of life in children with asthma: insights from Addis Ababa public hospitals. Front Public Health. 2025;12 (1):621-54.
3. Serebrisky D, Wiznia A. Pediatric asthma: A global epidemic. Ann Glob Health. 2019;85(1):412-57.
4. Jones H, Lawton A, Gupta A. Asthma attacks in children-challenges and opportunities. Indian J Pediatr. 2022;89(4):373-7.
5. Bloom CI, Cabrera C, Arnetorp S, Coulton K, Nan C, van der Valk RJ, et al. Asthma-related health outcomes associated with short-acting β2-agonist inhaler use: an observational UK study as part of the SABINA global program. Adv Ther. 2020;37(10):4190-208.
6. Abbas GH, Ahmed F, Iqbal R, Henna F, Khouri ER, Smeenk FW, et al. A 10-year interval of cardiovascular effects of albuterol in asthma management: Graphical review. Curr Res Pharmacol Drug Discov. 2025;9(7):100-36.
7. Marques L, Vale N. Salbutamol in the Management of Asthma: A Review. Int J Mol Sci. 2022;23(22):521-47.
8. Lemaçon C, Lopes AA. Inhalers or nebulisation of salbutamol in childhood asthma exacerbations in emergency departments. Respir Med. 2025;243(7):108-52.
9. Abdelgadir IS, Mudawi K, Hamud A, Tonbari A, Alhaji A, Salem R, et al. Second-line treatment option for children aged 18 years and under with an acute severe asthma exacerbation: a systematic review and meta-analysis of randomised controlled trials. Arch Dis Child. 2025;110(12):948-54.
10. Leung JS. Paediatrics: how to manage acute asthma exacerbations. Drugs Context. 2021;10(5):12-7.
11. Özdemir A, Ersoy M, Aydoğdu AK. Once or consecutive administration of inhaled salbutamol in children with acute asthma exacerbation: Is an additional dose beneficial? Pediatr Pulmonol. 2024;59(12):3190-6.
12. Joseph A, Ganatra H. Status Asthmaticus in the Pediatric ICU: A Comprehensive Review of Management and Challenges. Pediatr Rep. 2024;16(3):644-56.

13. Kulalert P, Phinyo P, Patumanond J, Smathakanee C, Chuenjit W, Nanthapisal S. Continuous versus intermittent short-acting β2-agonists nebulization as first-line therapy in hospitalized children with severe asthma exacerbation: a propensity score matching analysis. Asthma Res Pract. 2020;6(4):6-18.
14. Zulqarnain A, Fayyaz A, Zafar S, Fatima B. Continuous versus intermittent nebulization of salbutamol in acute Severe asthma in children under 12 years of age. Pak J Med Sci. 2026;42(1):185-90.
15. Gayen S, Dachert S, Lashari BH, Gordon M, Desai P, Criner GJ, et al. Critical care management of severe asthma exacerbations. J Clin Med 2024;13(3):859-65.
16. Mukherjee K, Das A, Basunia SR, Dutta S, Mandal P, Mukherjee A. Evaluation of Magnesium as an adjuvant in Ropivacaine-induced supraclavicular brachial plexus block: A prospective, double-blinded randomized controlled study. J Res Pharm Pract. 2014;3(4):123-9.
17. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med. 1993;21(10):1479-86.
18. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. Acad Emerg Med. 1996;3(11):1019-24.
19. Elgassim M, Abdelrahman A, Saied ASS, Ahmed AT, Osman M, Hussain M, et al. Salbutamol-induced QT interval prolongation in a two-year-old patient. Cureus. 2022;14(2):512-26.
20. Besbes-Ouanes L, Nouira S, Elatrous S, Knani J, Boussarsar M, Abroug F. Continuous versus intermittent nebulization of salbutamol in acute severe asthma: a randomized, controlled trial. Ann Emerg Med. 2000;36(3):198-203.
21. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emerg Med. 1993;22(12):1847-53.