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SYSTEMATIC REVIEW **OPEN ACCESS**

Salbutamol and Corticosteroid Therapy in Preschool Wheeze: A Systematic Review

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Abstract:

Objective: The aim of the review is to determine the effectiveness of salbutamol as compared to salbutamol in combination with corticosteroids in the treatment of acute wheezing in preschool-aged children.

Methods: A systematic literature review was carried out in PubMed, Web of Science, and Scopus to retrieve peer-reviewed journal articles published between 2009 and October 2025. Inclusion criteria were original clinical studies assessing salbutamol-based interventions, with or without corticosteroid use, in preschoolers presenting with acute wheezing but untested with a formal diagnosis of asthma. Only peer-reviewed journal articles were considered, and unpublished data in clinical trial registries were not included.

Results: Fifteen studies were included, comprising randomised controlled trials, cohort studies, and observational studies conducted in various countries, including Chile, Egypt, Finland, Turkey, Italy, the Netherlands, and Israel. Several studies found that oral or inhaled corticosteroids, combined with salbutamol, decreased hospital admissions, improved the clinical severity scale, and reduced symptom duration, with minimal effects on cortisol. Nevertheless, no added value was reported in other studies.

Discussion: The variation in findings across studies appears to be due to heterogeneity in wheeze phenotypes, disease severity, timing of corticosteroid therapy, and route of administration, indicating that preschool children with wheeze do not respond uniformly to treatment.

Conclusion: Selective use of corticosteroids offers benefits for some preschool wheezing episodes, whereas universal administration risks unwanted complications. Further research should focus on biomarker-based interventions and standard treatment regimens to optimise outcomes.

INPLASY Registration Number: INPLASY2025100040.

Keywords: Salbutamol, Corticosteroids, Preschool wheeze, Heterogeneity, Corticosteroid therapy.

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1. INTRODUCTION

Wheezing is one of the most common respiratory symptoms among preschool children, with an estimated 30–40% experiencing at least one episode before the age of six [1]. These episodes, frequently triggered by viral infections, encompass different phenotypes, including episodic viral wheeze and multi-trigger wheeze [2]. While many children outgrow symptoms, some progress to develop asthma [3]. The heterogeneity of preschool wheeze complicates both diagnosis and treatment, particularly in the absence of definitive biomarkers and difficulty performing reliable lung function tests in young children [4, 5].

Short-acting beta-agonists (SABAs) such as salbutamol are widely accepted as first-line treatment for acute wheezing. However, debate continues regarding the role of corticosteroids in this population. Studies have shown variable outcomes, with some demonstrating reduced hospitalisation and improved clinical scores, particularly in children with atopic features or recurrent wheezing [6, 7], while others report no significant benefit or potential adverse effects, including cortisol suppression [8, 9]. Current guidelines remain inconsistent, with the Global Initiative for Asthma (GINA) recommending daily low-dose inhaled corticosteroids, followed by as-needed (PRN) use for preschool children with frequent viral-induced wheeze and interval asthma symptoms [10]. At the same time, the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) suggests their use in children less than 5 years old for 8-12 weeks as maintenance, given that they have asthma phenotypes [11]. Recent evidence from Lee *et al*. (2024) suggests that oral corticosteroids may reduce symptom severity and length of hospital stay [12], yet significant practice variation persists between institutions.

Despite widespread use, the optimal role of combining salbutamol and corticosteroids for preschool wheeze remains unclear. Previous studies report varied outcomes based on phenotype, dosing, route of delivery, and timing of administration. To address this gap, a systematic review wasconducted to synthesise current evidence comparing the effectiveness of salbutamol alone *versus* salbutamol combined with corticosteroids in managing acute wheezing episodes among preschool children without a formal asthma diagnosis. This review aims to inform clinical decision-making and provide guidance on the appropriate use of corticosteroids in this challenging population. The review focuses on findings reported in peer-reviewed journal articles, rather than on data from clinical trial registries or unpublished RCT databases.

2. MATERIALS AND METHODS

2.1. Review Framework

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The research question is as follows: Among preschool children presenting with acute wheezing but without a formal asthma diagnosis, does treatment with salbutamol combined with corticosteroids lead to better clinical outcomes compared to treatment with salbutamol alone? The review assessed whether salbutamol alone is sufficient or whether combining it with corticosteroids offers additional clinical benefit for preschool children presenting with acute wheezing . The protocol for this systematic review was registered with INPLASY (2025100040) and is available in full on inplasy.com (https://doi.org/10.37766/inplasy2025.10.0040).

2.2. Eligibility Criteria

The inclusion and exclusion criteria were established using the PICOS framework. The review focused on preschool children under 7 years of age who experienced episodes of wheezing, excluding established asthma diagnosis. The review included studies that investigated the use of salbutamol alone and/or in combination with corticosteroids, either systemic or inhaled. The review did not require the inclusion of a formal comparator group because it analysed the results reported from studies that utilised either treatment approach. This review compares results from different studies rather than within a single study; thus, the comparator element is conceptual. The outcomes evaluated across the included studies were symptom relief, the need for hospitalisation, and the occurrence of relapse. Eligible studies included original research articles such as randomised controlled trials (RCTs), cohort studies, retrospective chart reviews, and case series published in peer-reviewed journals.

Studies were included if they were conducted among preschool children with wheeze, evaluated salbutamol alone or with corticosteroids, were full English articles published in peer-reviewed journals between January 2009 and October 2025, and reported original primary research. Studies were excluded if they involved participants with confirmed asthma or were reviews, protocols, book chapters, case reports, or non-English publications.

2.3. Search Strategy and Study Selection

A comprehensive search was performed across three databases: PubMed, Web of Science, and Scopus. The search was limited to English-language articles published between January 2009 and October 2025 to ensure accurate interpretation of study methodology and reported outcomes. This review focused exclusively on studies with published outcomes in peer-reviewed, indexed journals to ensure methodological transparency and full reporting of study methods, as required for quality appraisal. Grey literature sources and clinical trial registries were not included in the primary search strategy. The search period began in 2009 to focus on contemporary clinical evidence reflecting current treatment strategies and diagnostic approaches for preschool wheeze, as earlier studies often used different disease classifications and treatment paradigms.

The search string used was: (“viral-induced wheeze” OR “preschool wheeze”) AND (salbutamol OR (salbutamol AND steroids)) AND (management OR treatment OR

outcomes) AND (paediatric OR children OR preschool). After a comprehensive search, duplicates were removed, and records were screened in two phases: titles and abstracts were assessed first, followed by a full-text review for eligibility.

The study selection process (Fig. **1**) identified 100 records, with 80 remaining after duplicate removal. Following title, abstract, and keyword screening, 38 were excluded. Full texts of 42 articles were retrieved, and 27 were excluded for reasons including reviews, book chapters, protocols, non-English language, asthma-related populations, consensus methodology, or out-of-scope age groups. Ultimately, 15 studies were included in the systematic review.

2.4. Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form developed for this review. The variables extracted included study characteristics, population characteristics, salbutamol administration method and treatment duration, corticosteroid type and route of administration, treatment regimen, including dose, comparator groups, and reported clinical outcomes such as symptom improvement, hospitalization rates, relapse rates, and lung function measurements. Important key findings of each study were also derived. The two reviewers discussed and agreed on any discrepancies in the extraction process. The data obtained are summarized in Table **1**, which provides an organized overview of the characteristics, treatment methods, and results of the included studies.

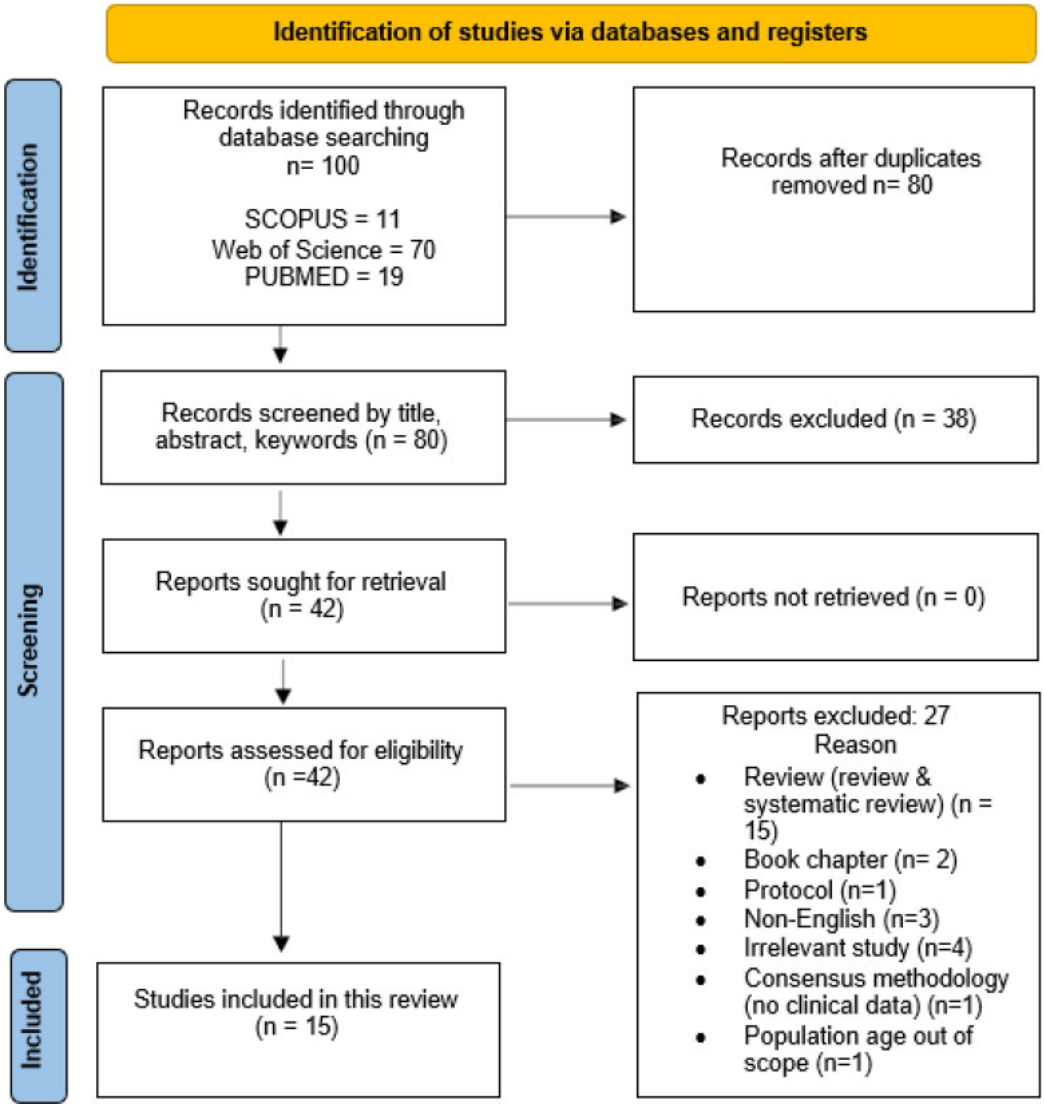

Fig. (1). PRISMA flow diagram.

2.5. Methodological Quality Appraisal and Risk of Bias Assessment

The methodological quality of the included studies was assessed across 11 domains using the Modified McMaster Critical Review Form for Quantitative Studies [13]. Each domain was rated, resulting in a total score ranging from 0 to 11. The appraisal was carried out by two reviewers who performed the appraisal on their own; inter-rater reliability was established using the Cohen Kappa (κ) value [14], and any discrepancies were solved by agreement.

Moreover, the overall methodological appraisal was complemented by a risk-of-bias assessment conducted with design-specific tools. The Cochrane Risk of Bias tool version 2 (RoB 2) [15] was used to evaluate randomized controlled trials for bias, assessing five domains: randomization process, deviations from intended inter-ventions, missing outcome data, measurement of the outcome, and selection of the reported result.

The evaluation of non-randomized and observational studies was based on the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool [16], which assesses bias in 7 areas, including bias due to confounding, bias in the selection of participants, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported result.

Each of the RoB 2 domains was rated as low risk, some concerns, or high risk, whereas the ROBINS-I domains were rated as low risk, moderate risk, severe risk, or no information provided, according to the tool guidance. The risk-of-bias assessments were conducted independently by two reviewers, and any disagreements were resolved through discussion.

2.6. Data Synthesis

A quantitative meta-analysis was deemed unsuitable due to the considerable clinical and methodological heterogeneity across the included studies. Heterogeneity was noted across various aspects, including variation in wheeze phenotypes, corticosteroid type, dose regimen, and outcome definition. Thus, a narrative synthesis was used to synthesize findings in line with PRISMA 2020 guidelines.

Narrative synthesis aimed to provide a summary of the studies' characteristics, treatment strategies, and reported clinical outcomes. Such outcomes were symptom improvement, hospitalization rates, clinical severity scores, lung function measurements, relapse rates, and reported adverse events. Where appropriate, the findings were compared across studies to detect patterns in treatment efficacy, safety, and possible phenotype-specific reactions.

3. RESULTS

3.1. Study Selection and Characteristics

The 15 included studies, published between 2009 and 2025, encompassed randomised controlled trials, prospective and retrospective cohort studies, and observational studies. Studies were conducted in Chile, Egypt, Finland, Turkey, Italy, the Netherlands, and Israel, with approximately 265,000 children included across all studies. The total population count excluded one survey study [17], which detailed treatment practices in 50 emergency departments (EDs) without specifying individual patient data. Salbutamol was administered *via* metered-dose inhalers (MDIs) with spacers and nebulisers. Corticosteroids included oral prednisolone, intravenous methylprednisolone, oral or intravenous dexamethasone, and inhaled budesonide, beclomethasone, or fluticasone, with treatment durations ranging from single doses to 16-week courses. Key characteristics of included studies are summarised in Table **1**.

3.2. Quality Appraisal and Inter-Rater Reliability

The 15 studies were rated using the Modified McMaster Critical Review Form for Quantitative Studies [13] and classified in accordance with the OCEBM hierarchy of evidence (Oxford Centre for Evidence-Based Medicine, 2011) [18]. The McMaster scores ranged from 8 to 11, indicating moderate to high methodological quality. Table **S1** in the supplementary material summarises the agreed scores following reviewer consensus and level of evidence. The inter-rater reliability between the two reviewers resulted in a Cohen's Kappa (κ) of 0.73, which is indicative of substantial and significant agreement [14]. General inter-rater reliability of reviewers is provided in Supplementary Table **S2**.

3.3. Risk of Bias

Across the included studies, the overall risk of bias varied according to study design. Initial methodological appraisal using the Modified McMaster Critical Review Form indicated moderate to high methodological quality across the studies. To provide a domain-specific assessment of potential methodological bias, the risk of bias was further evaluated using established tools appropriate to the study design. Randomized controlled trials were assessed using the RoB2 tool, while non-randomized and observational studies were evaluated using the ROBINS-I tool.

Among the randomized trials, the RoB2 assessment indicated that most studies demonstrated a low risk of bias across key domains, including deviations from the intended intervention, missing outcome data, and outcome measurement. However, several studies raised concerns about the selection of reported results, particularly due to the absence of trial registration or prespecified analysis protocols. For example, one study conducted a post hoc analysis of randomized trial data without adjustment for multiple comparisons, which may increase the risk of selective reporting. Overall, six randomized studies were judged to have a low overall risk of bias, while three studies presented some concerns (Supplementary Table **S3**). A graphical summary of the RoB2 assessment is presented in Supplementary Fig. (**S1**), which illustrates that the majority of domains were rated as low risk across the included randomized trials, with selective reporting representing the most frequent source of concern.

Table 1. Summary of included studies evaluating salbutamol alone *versus* salbutamol combined with corticosteroids in preschool children with wheeze.

No	Study Details: Author, Year, Country	Population	Salbutamol Administration Method	Salbutamol duration	Steroid Type	Steroid Administration Method	Treatment Details (Dose)	Comparison	Outcomes	Key Findings
1	Ater *et al.*, 2012, Israel [19]	41 children Inclusion: aged 1-6 years presenting to ED with acute wheezing episodes, clinical severity score (CS) ≥ 6 (institutional score).	Nebuliser	Every 20 minutes in ED, then as needed	N/A	N/A	Hypertonic saline (HS) group: 4 mL hypertonic saline 5% + salbutamol nebulisation	Hypertonic saline 5% (HS, n=16) *vs* Normal saline (NS, n=25), both	Primary: Length of stay (LOS); Secondary: Admission rate, CS	The HS group had significantly shorter LOS (mean 3.1±2.7 days *vs* 9.6±16 days, $p<0.001$) and lower admission rates (6.3% *vs* 32%, $p=0.027$)
2	Bannier *et al.*, 2022, Netherlands [6]	89 children aged 2-4 years with wheezing symptoms (from Asthma Detection and Monitoring (ADEM) study cohort of 202)), and followed up until 6 years old. Exclusion: no current symptoms, not able to stop inhaled corticosteroids (ICS)	Inhaled	For symptomatic relief during the study period (8 weeks)	Beclomethasone extrafine	Inhaled	Salbutamol as needed + beclomethasone 100 µg twice daily for 8 weeks, then salbutamol as needed + without ICS for 8 weeks	Crossover trial: 8 weeks ICS *vs* 8 weeks without ICS (plus salbutamol as needed)	Primary: Exhaled volatile organic compounds (VOCs) analysis; Secondary: Clinical response (≥30% symptom reduction and/or ≥10% airway resistance improvement)	ICS significantly altered exhaled breath profiles (20 VOCs discriminated pre/post-ICS with 73% sensitivity, and 67% specificity). 46/89 children (52%) were steroid-responsive
3	Ciftci *et al.*, 2021, Turkey [20]	70 preschool patients (2-5 years) who presented to the paediatric emergency department with acute wheezing Inclusion: recurrent wheezing (at least twice), (occurring at least twice). Exclusion: chronic diseases, drug use within the last month, marked infiltration on chest X-ray.	Inhaled	All received during acute episode treatment, then follow-up evaluation	Systemic steroids	Intravenous/oral	Steroid therapy was added for patients with severe asthma exacerbation and those who continued to require treatment after initial therapy	Evaluation of Clinical Asthma Score (CAS) and Asthma Severity Score (ASS) to predict steroid therapy needs and hospitalisation	Primary: Validation of CAS and ASS for predicting steroid therapy needs and hospitalisation. Secondary: Correlation between scoring systems and treatment outcomes	Both CAS and ASS scoring systems were significantly correlated and could predict the use of steroid therapy and hospital admission after exacerbation. CAS cut-off of 4.4 had 84.2% sensitivity and 63.6% specificity; ASS cut-off of 4.4 had 64.7% sensitivity and 78.8% specificity for predicting hospitalisation.
4	Clavenna *et al.*, 2014, Italy [21]	521 children aged 1-5 years with ≥1 episode of viral wheezing in the past 12 months, no/minimal asthma-like symptoms in between respiratory illnesses. Exclusion: steroid hypersensitivity, ICS/ oral corticosteroids (OCS) used in the preceding month, chronic respiratory diseases	Nebuliser	As needed for rescue medication during the 10-day treatment period	Beclomethoasone	Nebuliser	nebulised salbutamol/ nebulised beclomethasone/ OCS as rescue+ 400 µg twice daily for 10 days	Beclomethasone 400 µg (n=264) *vs* placebo (n=261) twice daily for 10 days during upper respiratory tract infection (URTI) episodes	Primary: Incidence of viral wheezing during 10-day treatment; Secondary: Wheezing severity, need for medical care, parental symptom scores, treatment compliance	No significant difference in wheezing incidence: 18/264 (6.8%) beclomethasone *vs* 29/261 (11.1%) placebo (RR 0.61, 95% CI 0.35-1.08, $p=0.09$). 63% of parents found the treatment helpful, with no group differences
5	Csonka *et al.*, 2021, Finland [17]	Survey of 50 emergency rooms (from 100 surveys sent). Inclusion: serving paediatric patients in Finnish municipalities with>10,000 inhabitants. Exclusion: Swedish speaking	Survey of practices - variable nebulisers *vs* pressurized metered-dose inhaler (pMDI) & valve-holding chamber (VHC)	Variable protocols across units (repeated 3-4 times with 20 minutes interval/ every 2-4 hours interval/3 times during 1 hour)	N/A	N/A	Variable dosing schemes for salbutamol; most common: 6 puffs (0.6mg) for <25kg, 8 puffs (0.8mg) for >25kg	Cross-sectional survey of emergency treatment practices for preschool wheezing-salbutamol route of administration	Survey outcomes: Device choice, administration techniques, face mask use, salbutamol dosing, staff training, written action plans	Poor adherence to guidelines: >50% used nebulisers, only 13% gave salbutamol as single puffs, >30% lacked face mask criteria, 62% continued treatment despite poor cooperation, only 20% trained staff on mask seal, 28% provided written action plans

(Table 1) contd.....

No	Study Details: Author, Year, Country	Population	Salbutamol Administration Method	Salbutamol duration	Steroid Type	Steroid Administration Method	Treatment Details (Dose)	Comparison	Outcomes	Key Findings
6	Gileles-Hillel *et al*., 2021, Israel [8]	234 children aged 1-7 years hospitalized with acute wheezing episodes. Inclusion: previously healthy, treated with dexamethasone/beclomethasone. Exclusion: wheeze due to other diseases- viral croup/foreign body, *etc*, chronic illness, history of prematurity < 34 weeks	Inhaled	Duration of hospitalisation (variable, typically 2-4 days of less than 4 hours intervals)- did not specifically say salbutamol (bronchodilator)	Betamethasone *vs* Dexamethasone	Oral	Betamethasone: variable dosing; Dexamethasone: variable dosing (cumulative prednisolone-equivalent doses compared)	Case-control study: Betamethasone group (n=89) *vs* Dexamethasone group (n=145)	Primary: LOS; Secondary: Clinical severity scores, demographic parameters, comorbidities	No significant difference in LOS between groups (betamethasone median 2.54 *vs* dexamethasone 2.50 days, p=0.049, but not clinically significant). Betamethasone achieved a similar clinical response with a lower cumulative steroid dose (3.76 *vs* 1.86 mg/kg prednisolone-equivalent, p<0.001)
7	Levine *et al*., 2019, Israel [22]	262,900 (from 689171) children from the Clalit Health Services database born 2005-2012 with asthma-like symptoms; subset analysis of those receiving controller therapy during 2005-2012. Inclusion: children prior to age 3, at least one of: a) ≥3 wheezing, b) ≥ 1 inhaled bronchodilator, c) ≥ 2 courses of systemic steroids in 1 year. Exclusion: healthy children with no asthma-like symptoms, chronic diseases, and being born premature.	Varied - inhaled corticosteroids, leukotriene receptor antagonists (LTRA), combination therapies	3-12 months of controller therapy	Various ICS types and LTRA	Inhaled and oral administration	Various dosing regimens for chronic controller therapy	Retrospective database analysis comparing healthcare utilization in different treatment groups	Primary: Healthcare utilization (emergency visits, hospitalisations); Secondary: Treatment patterns, medication persistence, exacerbation rates	Significant reduction in emergency department visits and hospitalisations in children treated with controller therapy. ICS showed greater effectiveness than LTRA in reducing exacerbations. Combination therapy most effective for severe cases
8	Mallol *et al*., 2009, Chile [23]	44 infants (age < 2 years old, mean age 52 weeks) with recurrent wheezing (more than 3 episodes) and family history of asthma completed the study; Exclusion: birth weight <2.5kg, oxygen requirement in neonatal period, cystic fibrosis, cardio-pulmonary malformations, neurological impairment, chronic diseases, systemic corticosteroids, or registered hospital admissions in preceding 2 months	Inhaled (pMDI + spacer)	As needed for rescue medication throughout the 3-months study period	Fluticasone propionate	Inhaled (pMDI + valved holding chamber)	Fluticasone propionate 375 µg (3 puffs of 125 µg) once daily in the morning for 3 months using Aerochamber Plus; plus salbutamol 200 µg prn for cough or wheezing	Fluticasone 375 µg once daily (n=21) *vs* placebo (n=23), both groups received salbutamol 200 µg prn	Primary: Lung function (forced expiratory flows FEF_{50}%, FEF_{75}%, FEF_{25-75}%) measured by raised volume rapid thoracic compression (RVRTC) technique; Secondary: Number of wheezing exacerbations, parental reporting of disease improvement, symptom-free days, plasma cortisol levels	The fluticasone group showed a significant increase in forced flows (FEF_{50}%, FEF_{75}%, FEF_{25-75}%; p<0.001), significantly fewer physician-diagnosed wheezing episodes (0.35 *vs* 1.08, p<0.002), a significant decrease in parent-reported wheezing episodes per month (p<0.03), and a higher percentage of parents reporting clinical improvement (95.2% *vs* 30.4%, p<0.001). No significant change in plasma cortisol levels or linear growth between groups
9	Mecklin *et al*., 2011, Finland [24]	303 children age 1-to-5-year old with acute bronchial obstruction Exclusion: Children with croup, foreign body, or pneumonia as a second diagnosis	Nebulisers *vs* MDIs with spacers	During treatment period;(nebulisers group: once or twice at 30-60 minutes intervals, MDI with spacer group: 4 times with 20 minutes. Both groups are reexamined and given more as necessary)	N/A	N/A	N/A	Salbutamol *via* nebulisers *vs*. Salbutamol *via* MDIs with spacers	Hospitalisation rate, LOS, ED stay duration	No significant difference in hospitalisation rates (~50% both groups). No difference in LOS. Children with MDIs stayed longer in ED- Change from nebulisers to MDIs with spacers was successful

(Table 1) contd.....

No	Study Details: Author, Year, Country	Population	Salbutamol Administration Method	Salbutamol duration	Steroid Type	Steroid Administration Method	Treatment Details (Dose)	Comparison	Outcomes	Key Findings
10	Mecklin *et al*., 2012, Finland [25]	310 children aged 1-5 years with preschool wheeze	MDI with spacers	4 times at 20 minutes intervals, reexamined and given more as necessary	N/A	N/A	Salbutamol *via* MDI with spacers	ED visits during 4-month study period	Hospitalisation rate, mean LOS	96% of children with preschool wheezing were treated with salbutamol using MDIs with spacers in the ED The hospitalisation rate was 51%, and all but one were treated with MDIs with spacers Mean LOS: 2.48 days Administration of salbutamol using MDI with spacers became an established emergency treatment
11	Papi *et al*., 2009, Italy [26]	276 preschool children (ages 1-4 years) with frequent wheezing (documented history of at least 3 episodes in the previous 6 months) were recruited during an acute wheezing episode; 267 completed the study. Exclusion: severe exacerbations requiring systemic glucocorticoids, chest infection or hospitalisation in the previous 4 weeks, treatment with inhaled glucocorticoids or methylxanthine in the previous 4 weeks, oral glucocorticoids in the previous 8 weeks	Nebuliser	As-needed rescue medication throughout the 12-week treatment period	Beclomethasone dipropionate (BDP)	Nebuliser	Three treatment groups for 12 weeks: (1) BDP 400 µg/vial b.i.d. + salbutamol 2500 µg/vial prn; (2) Placebo b.i.d. + BDP/salbutamol combination (800 µg BDP + 1600 µg salbutamol/vial) prn; (3) Placebo b.i.d. + salbutamol 2500 µg/vial prn. All delivered with Clenny aerosol nebuliser with a tight-fitting face mask	Regular BDP (n=110) *vs* prn BDP/salbutamol combination (n=110) *vs* prn salbutamol (n=56)	Primary: Percentage of symptom-free days during 12-week period; Secondary: Daily symptom scores (wheeze, cough, shortness of breath), nocturnal awakenings, rescue medication use, exacerbation frequency, salivary cortisol level in subgroup equally distributed among the 3 groups	Regular BDP had significantly higher symptom-free days (69.6% ± 20.89) compared to prn salbutamol (61.0% ± 24.83; p=0.034), but prn combination (64.9% ± 24.74) was not significantly different from prn salbutamol. Regular BDP reduced daytime and nighttime symptoms and nocturnal awakenings compared to placebo. Time to first exacerbation was longer in the regular BDP group (p=0.03 *vs* both other groups). No differences found between children with or without risk factors for asthma (p>0.05). Values of morning salivary cortisol did not change from baseline in any group
12	Papi *et al*., 2011, Italy [27]	166 pre-school children (ages 1-4) with multiple-trigger wheezing (history of recurrent wheezing with at least 3 episodes in the previous 6 months), recruited during an acute wheezing episode not requiring hospitalisation or systemic corticosteroids	Nebuliser	As needed (prn) during the 1-week treatment period	Beclomethasone dipropionate (BDP)	Nebuliser	Post-hoc analysis of 1-week treatment data from larger 12-week trial (Papi 2009). BDP 400 µg b.i.d. + salbutamol 2500 µg prn *vs* placebo b.i.d. + salbutamol 2500 µg prn	Nebulised BDP 400 µg b.i.d. + salbutamol 2500 µg prn (n=110) *vs* placebo b.i.d. + salbutamol 2500 µg prn (n=56)	Primary: Percentage of symptom-free days in first week; Secondary: Cough score, wheeze score, shortness of breath score, nocturnal awakenings, rescue medication use	BDP group had significantly higher symptom-free days at 1 week (54.7% *vs* 40.5%; p=0.012), with 35% relative difference. The difference reached significance by day 6 (12.3% difference; p=0.035). Cough score significantly reduced in the BDP group (0.11 *vs* 0.39; p=0.048), reaching significance at day 5. Mean salbutamol use is lower in the BDP group but not significant (0.26 *vs* 0.34 nebulisations/day; p=0.366). No differences between children with/without asthma risk factors

(Table 1) contd.....

No	Study Details: Author, Year, Country	Population	Salbutamol Administration Method	Salbutamol duration	Steroid Type	Steroid Administration Method	Treatment Details (Dose)	Comparison	Outcomes	Key Findings
13	Razi *et al*. (2017), Turkey [7]	100 children, aged 6 months to 6 years. Inclusion: had at least 3 episodes of wheezing within a year, moderate acute wheezing episodes. Exclusion: Previous systemic corticosteroid use, high ICS dose (budesonide) or changes in 2 months, other diseases	Nebuliser	Initial phase: at 0, 20, and 40 minutes Follow-up phase: at 80, 120, and 180 minutes	Budesonide	Inhaled	All patients received IV methylprednisolone initially and salbutamol nebulisation throughout	Budesonide nebulisation (n=50) *vs* placebo/normal saline nebulisation (n=50)	Primary: Discharge rates, pulmonary index score (PIS), oxygen saturations (O2, heart rate	Cumulative hospitalisation rate at 120 min: 72% placebo *vs* 44% budesonide (not statistically significant), Expected mean discharge times: 200.4 min budesonide *vs* 185.3-215.5 min placebo, Median PIS at 240min was significantly lower in the budesonide group *vs*. placebo (p<0.05), Addition of budesonide nebulisation may decrease the admission rate of preschool children with moderate to severe acute wheezing
14	Taha ., 2021, Egypt [28]	104 children total, aged 1 month to 2 years. Subdivided into asthma-prone *vs* non-asthma-prone groups. Inclusion: Diagnosed by a history of upper respiratory symptoms followed by tachypnea, cough, and chest wheeze. Exclusion: Cardiac, renal disease, cystic fibrosis, bronchopulmonary dysplasia, or any other chronic disease, O2 < 85%, Wang Clinical Severity Score (WCSS) >8, pediatric intensive care unit (PICU) admission, previous treatment with bronchodilators <4H, systemic steroids < 48H	Nebuliser	Repeated every 6 hours until improvement and hospital discharge	N/A	N/A	Salbutamol + normal saline *vs* salbutamol + hypertonic saline	Salbutamol + normal saline *vs* salbutamol + hypertonic saline	WCSS over 9 days, Hospital LOS, treatment response	Both groups showed improvement in WCSS, hypertonic saline showed faster improvement, and < hospital LOS was equally effective in both asthma and non-asthma-prone patients.
15	van de Kant (2011) Netherlands [4]	200 children with recurrent wheeze, 93 children in the analysis age, ranging from 2 to 4 years old (studied prospectively until 6 years old),	Inhaled	As needed for symptom relief during the 8-week treatment period.	Beclamethasone extrafine	ICS- 8 weeks	All patients received salbutamol + inhaled corticosteroids	Clinical response patterns, biomarker: fractional exhaled nitric oxide (FeNO) and solutes of exhaled breath condensate (EBC), differences in airway resistance, inflammatory markers, predictive markers	Primary: FeNO levels, airway resistance measurements, inflammatory markers in EBC. Secondary: symptoms score, lung function parameters, treatment response	After ICS treatment: airway resistance showed mild improvement, FENO levels varied between wheeze phenotypes (higher in asthmatic *vs* viral wheeze), and inflammatory markers were different

In the non-randomized, observational studies, the ROBINS-I assessment indicated moderate risk of bias in most, with two classified as having serious risk of bias, primarily due to confounding and non-randomized study designs. Bias due to confounding and participant selection was commonly rated as moderate, reflecting the inherent limitations of observational study designs. In contrast, the classification of interventions was generally assessed as low risk. Moderate risk was also observed in outcome measurement and reporting domains, largely due to reliance on retrospective data sources, clinician-reported outcomes, and the absence of pre-registered protocols. Overall, four observational studies were rated as moderate risk, while two were rated as serious risk of bias (Supplementary Table **S4**). The ROBINS-I domain distribution is summarised in Supplementary Fig. (**S2**),

which shows that confounding and participant selection contributed most substantially to the overall bias ratings among non-randomized studies.

Taken together, although the methodological quality of the included studies was generally acceptable according to the McMaster appraisal, the domain-specific bias assessments highlight limitations related to confounding, selective reporting, and observational study design.

3.4. Clinical Effectiveness Outcomes

Seven studies reported significant or phenotype-specific improvements in clinical outcomes, including reduced symptom burden, hospitalisation, or lung function, when corticosteroids were added to salbutamol [6-8, 20, 23, 26, 27]. Conversely, one study [21] did not show benefits, and one [4] was primarily a biomarker exploration study lacking evidence of clinical efficacy. For example, Razi *et al*. found that hospitalisation decreased by 72% to 44%, and PIS improved ($p < 0.001$) [7]. Three studies [23, 26, 27] reported more symptom-free days and better lung function with usual inhaled corticosteroids, with Clavenna *et al*. [21] reporting no significant difference compared with placebo. Regarding modes of salbutamol delivery, three studies [17, 24, 25] did not demonstrate significant differences in efficacy between nebulizers and MDIs with spacers; however, MDIs were more practical and were used more widely (in 96% of cases). The use of adjunct hypertonic saline therapy combined with salbutamol [19, 28] improved oxygenation and reduced hospital stay, particularly in asthma-prone infants. Corticosteroids were used orally, intravenously, or by inhalation; systemic routes were most effective in acute distress, whereas inhalation forms helped with recurrent wheeze. Two studies investigated steroid response biomarkers: one reported that FeNO and exhaled markers were poor predictors [4], whereas Bannier *et al*. [6] identified 20 volatile organic compounds with a predictive accuracy of about 70%.

3.5. Safety and Adverse Events

In all studies, there were minimal adverse effects of corticosteroids. No cortisol suppression or growth impairment occurred with inhaled corticosteroids [23, 26]. The combination of inhaled corticosteroids and salbutamol was consistently safe in the short term. However, adverse events were not consistently reported across all studies, and long-term endocrine or metabolic effects remain insufficiently explored.

4. DISCUSSION

This systematic review summarised 15 studies comprising approximately 265,000 preschool children with acute wheezing to determine whether the use of salbutamol alone or in combination with corticosteroids is effective. The results showed broad heterogeneity in treatment outcomes; some studies demonstrated a clear benefit of combination therapy, while others showed no effect or even harmful effects. These divergent results underscore the complexity of managing preschool wheeze and highlight the urgent need for phenotype-specific treatment approaches rather than universal protocols.

Among the included studies, there was significant variation in the effect of combining corticosteroids with salbutamol. Various studies have reported short-term benefits in symptoms and hospitalisation rates, but others have not found significant benefits or only slight benefits compared with salbutamol monotherapy. This inconsistency is probably due to variations in disease severity, the timing of corticosteroid initiation, and the underlying wheeze phenotype. The evidence indicates that corticosteroid addition therapy is most effective for moderate-to-severe or recurrent wheezing, but salbutamol is adequate in mild cases caused by a virus. The results presented by Razi *et al*. [7] indicated that nebulised budesonide with salbutamol had a significant effect on reducing hospitalisation rates and PIS within two hours. Similarly, Ciftci *et al*. [20] found that intravenous or oral systemic corticosteroids reduced CAS and predicted reduced admissions in children with recurrent wheeze. Levine *et al*. [22] also demonstrated that inhaled corticosteroid-based management decreased emergency visits and hospitalisations compared with bronchodilator-only management. The effectiveness of corticosteroids in preschool wheeze is also supported by a recent individual participant data meta-analysis by Lee *et al*. [12], which found that oral corticosteroids reduced the severity score at 4 hours post-treatment, with the effect most pronounced among preschoolers with asthma risk factors.

Symptom-free days and lung function have also been found to increase with regular inhaled corticosteroids, as reported by Papi *et al*. [26-27] with beclomethasone dipropionate and Mallol *et al*. [23] with fluticasone propionate, without affecting cortisol levels or growth. These results align with previous literature indicating that early corticosteroids are effective in the management of multi-trigger wheeze to prevent exacerbations and improve long-term control [29-30]. In contrast, Clavenna *et al*. [21] found no significant efficacy of corticosteroids *versus* placebo in mild- or virus-associated wheeze, indicating that corticosteroids are not necessarily effective.

Identifying which children respond to corticosteroids remains a major clinical challenge. Bannier *et al*. [6] identified exhaled volatile organic compounds that could distinguish between steroid-responsive and non-responsive patients with good sensitivity and specificity. This non-invasive modality with validation could inform clinicians to restrict corticosteroid therapy only to individuals who are likely to respond without exposing them to causes of unwarranted exposures. Conversely, the conventional signs of inflammation have demonstrated poor predictive capabilities. Van de Kant *et al*. [4] reported that, despite differences in FeNO levels among wheeze phenotypes, these did not predict corticosteroid response, indicating that preschool wheeze is characterized by different inflammatory mechanisms other than asthma. The European Respiratory Society (ERS) position statement endorsed the same findings, concluding that phenotype-specific biomarkers, such as blood eosinophils and aeroallergen sensitization, can identify ICS-responsive

subgroups, highlight the limitations of FeNO in preschoolers, and call for a biomarker-guided approach [2]. Another recent comprehensive review of phenotype/endotype heterogeneity also explained why treatment response varies dramatically across these groups of children and found that only ~25% of preschoolers fit the classical atopic/eosinophilic phenotype [31]. A review of 3 clinical trials examining preschool wheeze phenotypes found that higher eosinophilic counts were associated with higher exacerbation and hospitalisation rates, and that when inhaled corticosteroids were initiated daily, this was associated with decreased exacerbations thereafter [32].

Another review had conflicting findings on the use of FeNO in preschool wheeze. It may be useful in classifying types of preschool wheezing and evaluating the risk of later asthma or impaired lung development. However, data on the added benefit of FeNO over clinical factors are inconsistent, although high FeNO levels in schoolchildren have been shown to predict asthma development and slower growth in lung function over time [33]. Further research to demonstrate the utility of exhaled breath analysis in phenotype-based, larger populations would enhance precision-based therapy and clinical decision-making. Treatment heterogeneity is also explained by genetics. This is supported by a 2024 review [34] that examined studies on the genetics of preschool wheeze. One of these studies examined CDHR3 [35], which identifies the Rhinovirus C receptor, IL33, and the 17q locus, which includes the GSDMB and ORMDL3 genes. The 17q locus is the strongest wheeze and childhood-onset asthma locus and has been shown to interact with many environmental factors, including smoking and infections. Another study looked into the ANXA1 gene [36], which was recently associated with early-onset, persistent wheeze.

The use of corticosteroids to combat the inflammation is also relevant in preschool wheeze. A multi-omics study in 2025 [37] showed that the inflammation-dominant phenotype in preschool wheeze, compared with the epithelial remodeling-dominant phenotype that progresses to asthma, supports endotype-based treatment in this group. On the other hand, not all preschool wheeze is an allergic wheeze phenotype; a study examining the immunological aspects of preschool wheeze found that the majority are non-atopic (88% *vs* 11%), and this group accounts for two-thirds of health care utilisation [38]. This emphasised the undertreatment of non-atopic preschool wheeze with proper management, such as corticosteroids. Even for the episodic viral wheeze phenotype, intermittent or continuous inhaled corticosteroid use reduced the risk of viral-induced wheezing in preschool children [39].

Clinical outcomes also depend on the delivery methods and formulation. The study by Mecklin *et al*. [24-25] demonstrated that MDIs with spacers are equally effective as nebulisers and have greater practicality, portability, lower cost, and reduced risk of infection. Csonka *et al*. [17] reported that over 50% of emergency departments continue to use nebulisers with an insufficient match between evidence and practice. Another 2020 non-inferiority trial introduced a novel device: a portable MESH nebulizer for delivering ICS and salbutamol. It has similar clinical efficacy to MDI with a spacer but a lower acceptance rate and usability [40]. Therefore, educational interventions and standardised treatment regimes are required to enhance evidence-based utilisation of MDIs with spacers. Similarly, for corticosteroid formulations, Gileles-Hillel *et al*. [8] reported that betamethasone was equally effective as dexamethasone with lower cumulative steroid exposure, whereas prednisolone was associated with increased vomiting. By optimising corticosteroid selection, it is possible to improve compliance and minimise adverse effects, thereby enhancing patient comfort and clinical outcomes.

The current findings are consistent with international guidelines, which remain cautious about the use of corticosteroids in the treatment of preschool wheeze. According to the GINA guideline [10], corticosteroids should be used in the frequent or severe phenotypes of wheezing or high-risk asthma, whereas the BTS/SIGN [11] restricts their use to severe or hospital-level cases only. These findings align with earlier trials that have shown no significant benefit of oral corticosteroids in mild-to-moderate exacerbations [41-42]. Similarly, a recent review [12] demonstrated reduced wheezing severity and hospitalisation with corticosteroid use, supporting the positive outcomes observed in several studies included in this review. Nevertheless, previous reviews [43-44] summarised that corticosteroids could only have a useful role in moderate-to-severe exacerbations, not in routine viral wheeze. This conservative perception is supported by the existing synthesis, which emphasises that treatment must be customised to the wheeze pattern, frequency, and the likelihood of asthma.

The heterogeneity of treatment response is also affected by age. It is still clinically challenging to differentiate between early asthma and transient viral-related wheeze. The GINA guidelines [10] recognise these diagnostic uncertainties and suggest using age-based factors to determine corticosteroid use. Even children under 2 years were found by Mallol *et al*. [23] to respond positively to inhaled corticosteroids, and no exclusion criterion should be based solely on age in the presence of risk factors. The available information comparing corticosteroid effectiveness across distinct age groups, however, is limited, limiting the ability to provide age-based guidance. Future research should categorise subjects into age subgroups to define differences in developmental responses to therapy. Lastly, hypertonic saline adjunct therapy has been proven to be beneficial. Ater *et al*. [19] and Taha *et al*. [28] have shown that the combination of hypertonic saline and salbutamol reduces hospitalisation and symptom alleviation, especially in children predisposed to asthma. These findings are also supported by a recent review on the effectiveness of hypertonic saline and salbutamol combination, which showed reduced hospital length of stay and severity scores in preschool wheeze [45]. The proposed mechanism of hydration of the airway surface, mucociliary clearance,

and reduced oedema is biologically plausible, and the lack of side effects supports its clinical application.

In short, this review demonstrates that the management of preschool wheeze requires a personalised approach, grounded in evidence. Salbutamol is only effective in mild cases of the virus, and its effectiveness depends on certain phenotypes and corticosteroid severity. The management can be further optimised with emergent biomarkers, optimal inhalation techniques, and add-on treatments like hypertonic saline. It is essential to employ safer, more accurate, and more productive approaches to provide preschool wheeze care in future phenotype-stratified trials and to use clear criteria to develop guidelines.

5. CLINICAL IMPLICATIONS

This review highlights the need for a personalised and practical approach to managing preschool wheeze. Although preschool wheezers have heterogeneous pathologies, detecting these populations and treating them effectively is important to prevent asthma in later life. One significant pathology contributing to this is bacterial growth. An ERS congress in 2024 highlights that 50% of severe wheezers have positive BAL bacterial cultures when stable (Moraxella catarrhalis, H. influenzae predominant). Epithelial remodeling and H. influenzae infection are associated with a severe trajectory, and the report suggests that targeting dysbiosis with antibiotics/bacterial lysates may prevent asthma progression [46].

Based on the available evidence, a phenotype-oriented approach appears most appropriate. In children with mild episodic viral wheeze, salbutamol remains the preferred first-line treatment, and routine corticosteroid use is not consistently supported. In contrast, in children with moderate-to-severe, recurrent, or likely multi-trigger wheeze, particularly those with atopic features or a family history of asthma, corticosteroids may provide additional benefit when used selectively.

Salbutamol is the first-line intervention for all children with acute wheezing and should be administered *via* MDI with a spacer rather than a nebuliser, as it is equally effective and more convenient. Moderate-to-severe episodes that are unresponsive to initial bronchodilator treatment should receive corticosteroid therapy, particularly in children with recurrent wheeze and asthma risk factors, including atopy, a family history of asthma, or symptoms unrelated to viral infections. Rapid intervention in the emergency can shorten recovery and reduce hospital stay.

The route of corticosteroid administration should be determined by the clinical severity and recurrence pattern. Systemic therapy is recommended for severe acute attacks, while inhaled corticosteroids are used for recurrent episodes, with the lowest cumulative dose employed to minimize adverse effects. Notably, clinicians are advised to use the minimum effective cumulative steroid dose to reduce possible adverse effects. The existing evidence does not support the routine use of corticosteroids in all preschool wheezers, as non-selective prescribing can lead to unnecessary exposure to corticosteroids with no established benefits. Future advances in biomarker-guided therapy may enable clinicians to identify corticosteroid-responsive phenotypes more accurately and to implement safer, more targeted treatment strategies.

6. STRENGTHS AND LIMITATIONS

The primary strength of this review is its systematic and comprehensive synthesis of the current evidence on preschool wheeze in children who have not yet received an established asthma diagnosis, thereby filling an essential gap in the literature. The findings are informative, as they include studies conducted in various countries and healthcare settings, which are applicable across clinical settings. Also, this variety of RCTs and observational studies enables the review to include evidence of both controlled experimental studies and clinical practice.

A number of limitations, however, must be recognized. To begin with, the inclusion studies showed substantial heterogeneity in study design, patient populations, treatment regimens, corticosteroid type, dosing regimens, and outcome measures. This heterogeneity prevented direct comparability among the studies and precluded a quantitative meta-analysis. Second, not every study clearly differentiated between types of wheeze. In many studies, phenotype classification was either absent or defined by different criteria, preventing meaningful subgroup analysis across studies. This limitation restricts the ability to draw phenotype-specific conclusions regarding treatment responsiveness. Also, the non-asthmatic preschool wheeze remains clinically difficult to define, and the inconsistent findings may have been due to differences in diagnostic criteria across studies.

Moreover, many of the studies included were single-centre or institution-specific, which can introduce selection bias based on local clinical practices, patient populations, and healthcare resources. Consequently, the results might be inadequate in reflecting on wider paediatric populations in various healthcare systems. In addition, most studies were conducted in high- or middle-income countries with well-equipped healthcare systems. As such, the extent to which these findings can be generalised to low-resource settings where access to inhalation devices, corticosteroid preparations, or specialist paediatric care may be constrained must be approached with caution.

The other limitation concerns reporting safety outcomes. The effects of corticosteroid use on adverse effects were inconsistently reported across studies, potentially leading to an underestimation of harms. In addition, the study was limited to peer-reviewed articles published in English and omitted grey literature and clinical trial registries, which can introduce publication and language bias and may miss ongoing or unpublished studies that have not yet been reported in peer-reviewed journals. Lastly, many of the included studies had relatively short follow-up periods, so it was not possible to determine long-term treatment outcomes and safety profiles.

Future research should focus on properly designed, adequately powered randomized controlled trials using standard outcome measures and more precise phenotypic classification of wheeze. In addition, better reporting of adverse events and long-term follow-up will further inform clinical decision-making in the management of preschool wheeze. Future updates should also consider searching clinical trial registries to identify ongoing or unpublished studies, thereby reducing the risk of publication bias.

CONCLUSION

To conclude, while corticosteroids may provide clinical benefit when combined with salbutamol in selected preschool children with acute wheezing, particularly in moderate-to-severe cases or those with asthma risk factors, routine use in all wheezers is not supported and may expose children to unnecessary adverse effects. The considerable heterogeneity in treatment responses reflects the diverse pathophysiology underlying preschool wheeze and highlights the limitations of one-size-fits-all approaches. Future directions should focus on establishing dependable tools to detect responders at the point of care, such as biomarker-based phenotyping, and further improving the methods and formulations of corticosteroid delivery. Individualized clinical decisions should be made until this is available, based on disease severity, recurrence, and risk factors, to balance efficacy with safety in this susceptible age group.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: N.A. and N.N.: Contributed to the conception and design of the study; N.A., H.M., and N.N.: Contributed to data acquisition, analysis, and interpretation; N.N.: Contributed to data analysis and interpretation; N.A.: and N.N.: Drafted the article; N.A., H.M., and N.N.: Critically revised the article for important intellectual content. All authors have read and approved the final version of the article. N.N. takes responsibility for the paper as a whole.

LIST OF ABBREVIATIONS

ASS = Asthma Severity Score
BDP = Beclomethasone Dipropionate
BTS = British Thoracic Society
CAS = Clinical Asthma Score
CS = Clinical Severity Score
EBC = Exhaled Breath Condensate
ED = Emergency Department
ERS = European Respiratory Society
FEF = Forced Expiratory Flow
FeNO = Fractional Exhaled Nitric Oxide
GINA = Global Initiative for Asthma
HS = Hypertonic Saline
ICS = Inhaled Corticosteroids
LOS = Length of Stay
LTRA = Leukotriene Receptor Antagonists
MDI = Metered-Dose Inhaler
NS = Normal Saline
OCS = Oral Corticosteroids
PIS = Pulmonary Index Score
PRN = As Needed
SABA = Short-Acting Beta-Agonists
SIGN = Scottish Intercollegiate Guidelines Network
VOC = Volatile Organic Compound
WCSS = Wang Clinical Severity Score

CONSENT FOR PUBLICATION

Not applicable.

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PRISMA guidelines and methodology were followed.

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The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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