

Adrenal Suppression and Systemic Bioavailability Across Inhaled Corticosteroid Delivery Technologies in Children With Asthma: A Systematic Review

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Abstract

Background and Objective: Inhaled corticosteroids (ICS) are central to pediatric asthma treatment, but systemic exposure may suppress the hypothalamic-pituitary-adrenal (HPA) axis. This systematic review evaluated whether different ICS delivery technologies are associated with different systemic bioavailability or adrenal suppression in children with asthma.

Methods: A PROSPERO-registered review identified pediatric asthma studies comparing defined delivery technologies and reporting cortisol, adrenal, or pharmacokinetic outcomes. The supplied records documented 121 screened records, 14 full-text reports assessed, an eight-record source pool, and five studies carried into completed outcome analysis.

Results: The five analyzed studies had a nominal combined sample of 751 participants. Three core studies addressed hydrofluoroalkane (HFA) versus chlorofluorocarbon (CFC) pressurized metered-dose inhalers and budesonide dry-powder inhaler versus pressurized metered-dose inhaler with spacer. Two secondary studies addressed ciclesonide HFA delivery versus budesonide dry-powder inhaler and nebulized budesonide systems. Meta-analysis was not performed because drug molecule, dose, formulation, device, spacer or nebulizer use, duration, and outcome timing differed substantially.

Conclusions: Available pediatric evidence is limited and does not support a broad assumption that one delivery-device class is consistently safer for adrenal suppression. Interpretation should separate pharmacokinetic exposure from biochemical adrenal outcomes and should account for drug, dose, formulation, delivered dose, and measurement method. PROSPERO: CRD420261460607.

1 Introduction

Inhaled corticosteroids (ICS) are a main controller therapy for children with persistent asthma, but systemic absorption can occur despite intended local airway delivery. Systemic glucocorticoid exposure may suppress the hypothalamic-pituitary-adrenal (HPA) axis, and biochemical suppression may be clinically silent until illness, injury, or surgery exposes impaired cortisol reserve [1–5].

Delivery technology is relevant to drug metabolism and pharmacokinetics because the labeled dose is not necessarily the dose deposited in the lung or swallowed from the oropharynx. Hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC) pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), spacer-assisted pMDIs, valved holding chambers, and nebulizer systems differ in aerosol generation, particle behavior, inspiratory-flow dependence, coordination requirements, and airway deposition [6, 7]. Those differences may affect both asthma control and systemic corticosteroid bioavailability.

In children, the device effect is especially difficult to separate from technique and development. A pMDI can deliver inconsistently when actuation and inhalation are poorly coordinated. A spacer or valved holding chamber can reduce oropharyngeal deposition but may also change the fraction available for

lung absorption. DPIs require sufficient inspiratory flow, while nebulizer systems vary by formulation, residual volume, particle output, and treatment time. These details matter because device selection, technique education, spacer care, and adherence support can alter delivered dose without changing the prescription label.

Adrenal outcomes are also methodologically heterogeneous. Urinary cortisol, urinary free cortisol corrected for creatinine, overnight urinary cortisol-to-creatinine ratios, morning serum cortisol, stimulation testing, and pharmacokinetic measures such as area under the concentration-time curve (AUC) and maximum concentration (C_{max}) are related but not interchangeable [8–10]. This review therefore separates pharmacokinetic exposure from biochemical adrenal effect and avoids treating every cortisol measure as the same outcome.

This systematic review asks whether different ICS delivery technologies in children with asthma are associated with different systemic bioavailability or adrenal suppression. The review emphasizes device-related interpretation while recognizing that corticosteroid molecule, dose, formulation, duration, technique, and outcome method can confound device comparisons.

2 Methods

2.1 Protocol and Registration

The review was registered in PROSPERO (CRD420261460607) as a systematic review of systemic bioavailability and adrenal suppression across ICS delivery technologies in children with asthma. The PROSPERO record lists CENTRAL, CINAHL, Google Scholar, MEDLINE, and PubMed as planned information sources and describes independent selection, extraction, and design-specific risk-of-bias assessment. Protocol and workflow differences are reported in Online Resource 1.

2.2 Eligibility Criteria

Eligible studies enrolled children or adolescents with asthma who received an ICS through a defined delivery technology and reported at least one adrenal, cortisol, or pharmacokinetic outcome. Eligible technologies included pMDIs using HFA or CFC propellants, DPIs, pMDIs with spacers or valved holding chambers, and nebulizer systems. Eligible corticosteroids included fluticasone propionate, beclomethasone dipropionate, budesonide, ciclesonide, or another ICS when the comparison involved delivery technology.

The workflow separated direct and indirect device evidence. Same-drug, same-dose device comparisons were considered the most directly informative for device effects. Studies were retained as secondary device-technology evidence when a device contrast was accompanied by differences in drug, dose, or formulation, but those comparisons were not interpreted as isolating the device effect.

2.3 Information Sources and Search Strategy

The completed-review materials report searches of PubMed/MEDLINE, CINAHL, Scopus, and the Cochrane Library/CENTRAL; the PROSPERO registration also lists Google Scholar. The supplied appendix includes the full PubMed search syntax and the protocol states that the search algorithm was applied across the listed databases. The search strategy combined pediatric terms, ICS terms, device or administration terms, asthma terms, HPA-axis or adrenal-suppression terms, and trial or cohort design terms.

The PubMed strategy yielded 121 records on 03 August 2026. The completed results report 121 records after deduplication across the combined database search. Non-English studies were excluded according to the protocol materials.

2.4 Study-Selection Process

The uploaded screening files documented 121 screened records. The final-source file listed eight selected source-pool records. The research workflow then narrowed the completed outcome analysis to five studies: Wolthers, Kim et al., and Goldberg et al. as core synthesis studies, with von Berg et al. and Basu et al. presented in secondary device-technology subgroups [11–15]. Singh et al. was marked as conditional because pediatric results and numerical cortisol data were not extractable from the supplied workbook [16].

This report follows that workflow distinction by using the eight-record source pool as an audit trail and the five workflow-selected studies as the completed qualitative synthesis. The reason for choosing five rather than eight was methodological: the five analyzed studies had usable pediatric asthma data and a delivery-technology comparison that could be placed into the protocol-defined core or secondary synthesis groups; the remaining source-pool records did not provide extractable pediatric delivery-technology outcome data for this synthesis structure.

The eight-record source pool was therefore broader than the final analyzed evidence set. It included records that were useful during screening because they addressed pediatric adrenal safety, inhaled corticosteroids, or candidate delivery questions, but the completed synthesis required both an eligible pediatric asthma population and a comparison that could inform delivery-technology interpretation. Hawcutt et al. addressed adrenal responses in children receiving corticosteroids but was not a direct delivery-technology comparison. Hoekstra et al. evaluated fluticasone propionate versus placebo through a Diskhaler rather than comparing two eligible delivery technologies. Volovitz et al. compared inhaled budesonide with oral prednisolone for acute asthma, so the comparator was not another inhaled delivery technology. Singh et al. compared HFA and CFC budesonide pMDIs but the workflow states that pediatric cortisol results were not extractable. Amirav et al. was present in the source pool, but the completed workflow did not place it in the core HFA/CFC, DPI/spacer, or secondary nebulizer synthesis groups [16–20].

2.5 Data-Extraction Process

Data were independently extracted using a standardized extraction form by four reviewers. Disagreements were resolved through discussion, with two additional reviewers available for disagreement review. Extracted fields included study design, participant age, corticosteroid molecule, delivery device, propellant or nebulizer system, dose, treatment duration, cortisol or pharmacokinetic outcome, numerical results when available, interpretation, and pooling decision.

2.6 Outcomes

The primary outcome was biochemical adrenal suppression measured with urinary cortisol-based outcomes, including 24-hour urinary cortisol, urinary free cortisol corrected for creatinine, overnight urinary cortisol, and urinary cortisol-to-creatinine ratios. Secondary outcomes included morning serum cortisol, dynamic adrenal testing, AUC, Cmax, and other pharmacokinetic or HPA-axis outcomes when extractable.

2.7 Risk-of-Bias Assessment

Risk of bias was assessed with a Cochrane RoB 2-style traffic-light screen across randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. The completed chart used low risk, some concerns, and high risk labels. Because all overall judgments were some concerns, risk of bias was incorporated into interpretation rather than used to exclude studies.

2.8 Synthesis Methods

A structured narrative synthesis was used. Meta-analysis was not performed because fewer than three sufficiently comparable studies were available for any single device contrast, and the studies differed in corticosteroid molecule, nominal dose, formulation, inhaler or nebulizer technology, spacer or chamber use, treatment duration, participant characteristics, cortisol outcome, pharmacokinetic outcome, and outcome timing. Pooling these comparisons would have combined clinically non-interchangeable effects.

3 Results

3.1 Study Selection

The supplied records document 121 screened records and 14 full-text reports assessed. Nine full-text reports were excluded, and five studies met final eligibility criteria for qualitative synthesis. The uploaded final-source CSV listed an eight-record source pool, but the research workflow narrowed the completed analysis to five studies because three source-pool records did not provide an analyzable pediatric ICS delivery-technology comparison with extractable cortisol, adrenal, or pharmacokinetic data for the final synthesis. Figure 1 summarizes the completed study-selection flow.

This selection decision was not based on study quality alone. It reflected the protocol hierarchy that prioritized direct same-drug delivery comparisons and allowed secondary analysis only when a delivery-

technology contrast remained clinically interpretable despite differences in molecule, dose, or formulation. The final five studies therefore represent the records that could support the review question without stretching contextual adrenal-safety papers into device-comparison evidence.

3.2 Study Characteristics

The five analyzed studies were published between 2002 and 2009 and had a nominal combined sample of 751 participants: 79 in Kim et al., 24 in Wolthers, 15 in Goldberg et al., 621 in von Berg et al., and 12 in Basu et al. [11–15]. Table 1 summarizes the analyzed study designs, delivery-technology comparisons, and key interpretation. The usable adrenal-outcome sample may be lower than the nominal randomized sample in some studies, so the total should be treated as a descriptive source-pool count rather than a pooled analytic denominator.

Corticosteroids included fluticasone propionate, beclomethasone dipropionate, budesonide, and ciclesonide. Delivery technologies included HFA-pMDIs, CFC-pMDIs, DPIs, spacer-assisted pMDIs, and nebulizer systems. Outcomes included 24-hour urinary cortisol, urinary free cortisol corrected for creatinine, overnight urinary cortisol-to-creatinine ratio, and pharmacokinetic exposure measures.

Table 1
Study characteristics and key findings for the five analyzed studies

Study	Population/design	Delivery-technology comparison	Key finding or interpretation
Wolthers, 2006 [11]	24 children aged 7 to 12 years; randomized crossover trial	Beclomethasone HFA-pMDI vs CFC-pMDI	No statistically significant urinary free cortisol/creatinine difference at equal dose or versus higher-dose CFC comparator.
Kim et al., 2008 [12]	Children aged 4 to 11 years; randomized comparative/pharmacokinetic trial; 79 participants across phases	Fluticasone HFA-pMDI vs CFC-pMDI	HFA formulation showed lower systemic fluticasone exposure; direct HFA-versus-CFC urinary cortisol effect was not clearly extracted.
Goldberg et al., 2002 [13]	15 children aged 5 to 15 years; randomized crossover trial	Budesonide DPI vs pMDI with spacer	DPI was associated with lower urinary cortisol-to-creatinine from baseline; pMDI plus spacer was not.
von Berg et al., 2007 [14]	621 children aged 6 to 11 years; randomized comparative trial	Ciclesonide HFA-pMDI vs budesonide DPI	Secondary comparison only because corticosteroid molecule and dose differed in addition to delivery technology.
Basu et al., 2009 [15]	12 children aged 5 to 12 years; comparative clinical trial	Soluble budesonide/eFlow vs budesonide suspension/LC Plus	No significant overnight urinary cortisol-to-creatinine difference reported; formulation and nebulizer system differed together.

Abbreviations: CFC, chlorofluorocarbon; DPI, dry-powder inhaler; HFA, hydrofluoroalkane; LC Plus, PARI LC Plus nebulizer; pMDI, pressurized metered-dose inhaler.

3.3 Risk of Bias

The risk-of-bias traffic-light table rated every analyzed study as having some concerns overall (Table 2). Kim et al. was rated low for randomization and deviations but some concerns for missing data, outcome measurement, and reporting. Wolthers and Goldberg et al. were rated some concerns for randomization and reporting but low for deviations, missing data, and outcome measurement. Von Berg et al. was rated low for randomization, deviations, and outcome measurement, with some concerns for missing data and reporting. Basu et al. was rated some concerns for randomization, deviations, missing data, and reporting, and low for outcome measurement.

Table 2 Risk-of-bias traffic-light status across domains

Study	Randomization	Deviations	Missing data	Outcome measurement	Selective reporting	Overall
Kim et al., 2008	L	L	S	S	S	S
Wolthers, 2006	S	L	L	L	S	S
Goldberg et al., 2002	S	L	L	L	S	S
von Berg et al., 2007	L	L	S	L	S	S
Basu et al., 2009	S	S	S	L	S	S

Abbreviations: L, low risk of bias; S, some concerns; H, high risk of bias. No overall high-risk judgments were displayed.

3.4 Findings by Delivery-Technology Comparison

HFA versus CFC pMDI evidence came from Wolthers and Kim et al. [11, 12]. Kim et al. evaluated fluticasone propionate 88 mcg twice daily in children aged 4 to 11 years. The extraction reports approximately 55% lower systemic fluticasone exposure by AUC and approximately 26% lower Cmax with HFA compared with CFC delivery. The available urinary cortisol data compared fluticasone HFA with an HFA propellant-only period and did not show urinary cortisol suppression, but the direct HFA-versus-CFC urinary cortisol effect was not clearly extracted.

Wolthers evaluated beclomethasone dipropionate by HFA- and CFC-pMDI in 24 children aged 7 to 12 years. At 100 mcg twice daily, urinary free cortisol-to-creatinine values were 11.4 versus 12.0 nmol/mmol, ratio 0.95, 95% confidence interval 0.72 to 1.26, $P = 0.71$. HFA 100 mcg twice daily versus CFC 200 mcg twice daily produced ratio 1.12, 95% confidence interval 0.85 to 1.47, $P = 0.41$. These comparisons did not show a statistically significant between-device difference in urinary free cortisol [11].

Goldberg et al. compared budesonide DPI with budesonide pMDI plus spacer at 200 mcg twice daily in a randomized crossover study of 15 children aged 5 to 15 years [13]. The extraction reports baseline urinary cortisol-to-creatinine ratio 0.038 mcg/mg, decreasing to 0.028 mcg/mg after DPI treatment, $P = 0.018$, and remaining similar after pMDI plus spacer treatment at 0.037 mcg/mg, $P = 0.78$. This was the clearest same-drug, same-dose device signal, but it came from a small crossover study.

The two secondary technology studies were not interpreted as isolated device comparisons. Von Berg et al. compared ciclesonide HFA-pMDI 160 mcg once daily with budesonide DPI 400 mcg once daily in 621 children, so corticosteroid molecule and nominal dose differed in addition to device [14]. Basu et al. compared soluble nebulized budesonide delivered by eFlow with budesonide suspension delivered by LC Plus in 12 children; the workbook states no significant overnight urinary cortisol-to-creatinine difference, but formulation and nebulizer system differed together [15].

The eight-record source pool also contained Hawcutt et al., Singh et al., Hoekstra et al., Volovitz et al., and Amirav et al. [16-20]. Three of these were not part of the completed five-study analysis because the workflow did not identify them as analyzable delivery-technology comparisons for the synthesis. Singh et al. was specifically marked conditional because pediatric results and numerical cortisol data were not extractable from the supplied workbook. Hawcutt et al. and Hoekstra et al. primarily informed adrenal-safety context rather than an analyzable device contrast. Volovitz et al. compared inhaled budesonide with oral prednisolone, which did not meet the final device-comparison synthesis structure. Amirav et al. appears in the source pool, but the completed workflow did not carry it forward into the analyzed nebulizer or inhaler-device comparisons.

4 Discussion

4.1 Principal Findings

The analyzed pediatric evidence is limited, heterogeneous, and not suitable for meta-analysis. It does not show that one broad ICS delivery category consistently produces greater adrenal suppression in children with asthma. Instead, systemic exposure appears to depend on interacting treatment and device factors: drug molecule, dose, formulation, delivered lung dose, spacer or chamber use, nebulizer system, treatment duration, and cortisol measurement method.

The most direct HFA-versus-CFC beclomethasone comparison did not show a statistically significant urinary cortisol difference at equal nominal doses. The fluticasone study suggested lower systemic exposure with HFA than CFC delivery, but the direct adrenal effect for that comparison was not extracted. The clearest device-related adrenal signal came from the small budesonide DPI versus spacer-assisted pMDI crossover study.

4.2 Relationship to Existing Evidence

These findings fit broader evidence that adrenal suppression from ICS is related to systemic glucocorticoid exposure rather than device class alone [1-3, 6, 21-24]. The review adds a delivery-technology and bioavailability focus but also shows that pediatric evidence is sparse and often confounded by drug, dose, or formulation differences.

4.3 Implications for Respiratory and Pharmacokinetic Practice

For clinicians and pharmacokinetic readers, the practical message is caution against assuming that one broad device class is always safer. Device selection should consider the child, drug, dose, spacer or chamber use, inspiratory-flow ability, adherence, and technique. Children receiving higher-dose or prolonged ICS therapy, multiple corticosteroid routes, or devices associated with greater delivered lung dose may warrant closer monitoring for possible systemic effects [4, 5, 25].

Respiratory-care and prescribing teams can reduce avoidable delivered-dose variability by checking actuation timing, inspiratory flow, spacer fit and cleaning, mask seal, nebulizer setup, and adherence barriers. The review does not show that technique optimization eliminates adrenal risk, but it supports treating device education as part of medication-safety practice.

4.4 Strengths and Limitations

Strengths include a focused pediatric asthma question, separation of core same-drug comparisons from secondary confounded technology comparisons, and use of the research workflow to explain why only five of eight selected source records were analyzed. Limitations are substantial: the analyzed evidence base is small; several samples are very small; outcomes are inconsistent; the search was built from multiple source materials with uneven database-level documentation; and the risk-of-bias chart remained a RoB 2-style traffic-light screen rather than a full published-domain support table.

4.5 Future Research

A major measurement gap is the lack of a practical, standardized way to assess HPA-axis suppression in children. Serum cortisol and dynamic stimulation testing can be difficult to obtain in pediatric asthma studies because blood sampling is burdensome, timing-sensitive, and may require specialized clinical supervision. Urinary cortisol is easier to collect in some settings, but it is an imperfect surrogate because collection completeness, creatinine correction, renal handling, assay method, and timing can affect interpretation [8-10]. Future research should prioritize child-feasible endocrine outcome methods that are reproducible, minimally invasive, clinically interpretable, and comparable across delivery-device trials.

Future pediatric studies should compare delivery technologies while holding corticosteroid molecule, nominal dose, formulation, and treatment duration constant. They should report standardized urinary cortisol methods, morning cortisol or dynamic adrenal testing when clinically appropriate, AUC, Cmax, adherence, inhalation technique, spacer or chamber details, and clinically relevant adrenal-insufficiency outcomes [22-24].

5 Conclusion

Available pediatric evidence does not demonstrate that one ICS delivery technology consistently produces greater adrenal suppression. Equal-dose HFA- versus CFC-beclomethasone showed no significant urinary cortisol difference, HFA fluticasone showed lower systemic exposure than CFC fluticasone but had uncertain direct adrenal comparison data, and a small budesonide crossover study suggested greater urinary cortisol suppression with DPI delivery than with pMDI plus spacer. Device-related interpretation remains limited by heterogeneity, small samples, non-extractable outcomes, and comparisons confounded by drug, dose, or formulation.

Statements and Declarations

Ethics approval: Not applicable. This systematic review used already published aggregate literature and did not involve new recruitment of human participants, access to identifiable private data, or collection of biological material.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

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Competing interests: No conflicts of interest were reported in the PROSPERO record for the listed review team members.

Data availability: The screening and extraction files used to prepare this review are available from the corresponding author on reasonable request.

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CRedit Author Contributions

Ayagiysan Kaneshan: Conceptualization, methodology, investigation, data curation, writing - original draft, project administration. Ral Vandenhoudt: Methodology, investigation, validation, data curation, writing - review and editing. Lenore Hooriani: Investigation, validation, data curation, writing - review and editing.

Review Process Details

Independent extraction was completed by AK, RV, LH, and Dr. SLM. Disagreement review included Dr. RW and Dr. DG.

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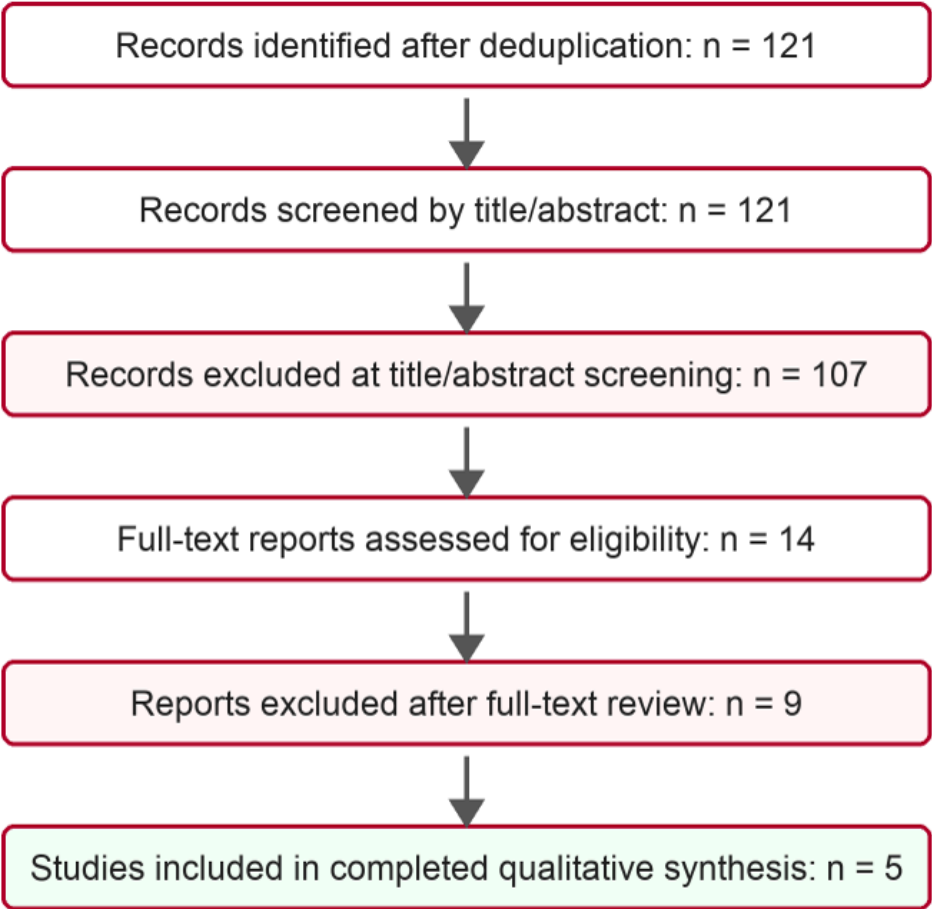
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Figures



Note. The eight-record source pool was retained as a screening audit; the completed workflow carried five studies into qualitative synthesis.

Figure 1

PRISMA 2020 flow diagram for study selection. Abbreviations: ICS, inhaled corticosteroid; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Supplementary Files

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