

Online Resources

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

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Supplement 1. Search Methods Audit

Documented PubMed/MEDLINE strategy:

("Child"[MeSH] OR "Infant"[MeSH] OR "Adolescent"[MeSH] OR child* OR pediatric* OR paediatric*) AND ("Fluticasone"[MeSH] OR "Beclomethasone Dipropionate"[MeSH] OR "Mometasone Furoate"[MeSH] OR "Budesonide"[MeSH] OR "Ciclesonide"[MeSH] OR inhaled corticosteroid* OR ICS) AND (inhaler* OR "Metered Dose Inhalers"[MeSH] OR MDI OR pMDI OR DPI OR nebulizer* OR nebuliser* OR spacer* OR "holding chamber*" OR hydrofluoroalkane OR HFA OR chlorofluorocarbon OR CFC) AND (asthma OR wheez*) AND (adrenal OR cortisol OR "hypothalamic-pituitary-adrenal" OR HPA OR pharmacokinetic* OR systemic exposure OR bioavailability)

Source	Documented status
PubMed	Complete strategy supplied in recipe file; yielded 121 results on 22 January 2026.
MEDLINE	Searched according to protocol/recipe materials; PubMed/MEDLINE syntax is reproduced in this Online Resource.
CINAHL	Searched according to protocol/recipe materials using the same concept blocks adapted to the database.
CENTRAL/Cochrane	PROSPERO lists CENTRAL, while the protocol/recipe materials describe Cochrane/Cochrane Library searching. Reported as CENTRAL/Cochrane to preserve both records.
Google Scholar	Listed in PROSPERO and recipe materials; used as a supplementary search source.
Scopus	Listed in protocol/recipe materials. Not listed as a PROSPERO main source, so this is treated as a documented completed-review addition.
Deduplication	Final manuscript and protocol draft report 121 records after deduplication.

Supplement 2. Screening and Synthesis Reconciliation

File or source	Count or role	How used in finalized package
AGI HPA Systematic Review(All).csv	121 PubMed-labelled screened records	Used for records identified/screened count and screening-reason audit.
AGI HPA Systematic Review(SC).csv	13 serum-cortisol candidate records	Used as candidate-screening support.
AGI HPA Systematic Review(UC).csv	18 urinary-cortisol candidate records; 30 unique SC/UC candidate records after one overlap	Used as candidate-screening support.
AGI HPA Systematic Review(Final sources).csv	8 selected source-pool records	Used as selected source-pool count.
Research results workflow	5 studies analyzed; 3 core plus 2 secondary subgroups; Singh conditional	Used as authority for the completed outcome synthesis.

Supplement 3. Source-Pool and Analysis Crosswalk

Record	Study	Source-pool status	Analysis status	Workflow reason
PUBMED 21	Hawcutt et al., 2015	Final-source CSV	Not analyzed in workflow	Adrenal-response study in children receiving corticosteroids; no direct inhaled delivery-technology comparator was documented for synthesis.
PUBMED 45	Singh et al., 2007	Final-source CSV	Conditional only	Pediatric results and numerical cortisol data not extractable from supplied workbook.
PUBMED 66	Kim et al., 2008	Final-source CSV	Analyzed core study	Direct HFA-versus-CFC study; direct urinary cortisol comparison was not clearly extracted, so pharmacokinetic and propellant-only cortisol results were analyzed narratively.
PUBMED 75	Hoekstra et al., 1996	Final-source CSV and SC/UC candidate	Not analyzed in workflow	Fluticasone Diskhaler was compared with placebo; no eligible comparison between delivery technologies was documented for final synthesis.
PUBMED 102	Volovitz et al., 1998	Final-source CSV	Not analyzed in workflow	Inhaled budesonide was compared with oral prednisolone for acute asthma; comparator was not another inhaled delivery technology.

PUBMED 51	Wolthers, 2006	Final-source CSV and UC candidate	Analyzed core study	HFA-pMDI versus CFC-pMDI beclomethasone comparison.
PUBMED 72/99	Goldberg et al., 2002	Final-source CSV and UC candidate	Analyzed core study	Budesonide DPI versus pMDI with spacer.
Not specified	von Berg et al., 2007	Workflow-selected secondary study	Analyzed secondary study	Ciclesonide HFA-pMDI versus budesonide DPI; interpreted as secondary because drug and dose differed.
Not specified	Basu et al., 2009	Workflow-selected secondary study	Analyzed secondary study	Soluble budesonide/eFlow versus budesonide suspension/LC Plus; interpreted as secondary because formulation and nebulizer differed together.

Supplement 4. Study Characteristics for Analyzed Studies

Study	Population/design	Corticosteroid	Intervention	Comparator	Duration	Outcome	Main limitation
Wolthers, 2006	24 children aged 7 to 12 years; randomized crossover trial	Beclomethasone dipropionate	HFA-pMDI 100 mcg twice daily	CFC-pMDI 100 or 200 mcg twice daily	2 weeks per treatment	24-hour urinary free cortisol/creatinine and total cortisol metabolites	Small, short-duration crossover study.
Kim et al., 2008	Children aged 4 to 11 years; randomized comparative trial; 79 participants across phases	Fluticasone propionate	HFA-pMDI 88 mcg twice daily	CFC-pMDI 88 mcg twice daily	Approximately 2 to 4 weeks	24-hour urinary cortisol; plasma fluticasone AUC/Cmax	Direct HFA-vs-CFC urinary cortisol estimate not clearly extracted.
Goldberg et al., 2002	15 children aged 5 to 15 years; randomized crossover trial	Budesonide	DPI/Turbuhaler 200 mcg twice daily	pMDI with spacer 200 mcg twice daily	1 month per treatment	24-hour urinary cortisol-to-creatinine ratio	Small crossover study.
von Berg et al., 2007	621 children aged 6 to 11 years; randomized comparative trial	Ciclesonide vs budesonide	Ciclesonide HFA-pMDI 160 mcg once daily	Budesonide DPI/Turbuhaler 400 mcg once daily	12 weeks	24-hour urinary cortisol adjusted for creatinine	Drug and dose differ between groups.
Basu et al., 2009	12 children aged 5 to 12 years; comparative clinical trial	Budesonide	Soluble budesonide through eFlow nebulizer	Budesonide suspension through LC Plus nebulizer	2-week periods	Overnight urinary cortisol-to-creatinine ratio	Formulation and nebulizer system differ together.

Supplement 5. Outcome Table for Analyzed Studies

Study	Comparison	Extracted cortisol or pharmacokinetic finding	Interpretation	Pooling decision
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Wolthers, 2006	HFA-BDP 100 mcg twice daily vs CFC-BDP 100 mcg twice daily	UFC/creatinine 11.4 vs 12.0 nmol/mmol; ratio 0.95; 95% confidence interval 0.72 to 1.26; P = 0.71	No statistically significant equal-dose difference.	Potentially poolable only if another comparable study exists.
Wolthers, 2006	HFA-BDP 100 mcg twice daily vs CFC-BDP 200 mcg twice daily	Ratio 1.12; 95% confidence interval 0.85 to 1.47; P = 0.41	No statistically significant between-treatment difference.	Keep separate from equal-dose comparison.
Kim et al., 2008	FP-HFA vs FP-CFC 88 mcg twice daily	Systemic FP exposure approximately 55% lower with HFA; direct urinary cortisol comparison not clearly extracted.	Pharmacokinetic data suggest lower systemic exposure with HFA; direct adrenal effect uncertain.	Not poolable.
Kim et al., 2008	FP-HFA vs HFA propellant-only	Mean urinary cortisol 9.54 +/- 4.19 vs 9.66 +/- 4.58 mcg; ratio 0.987; 95% confidence interval 0.796 to 1.223	No evidence of urinary cortisol suppression versus propellant-only.	Not the same as HFA-versus-CFC.
Goldberg et al., 2002	Budesonide DPI vs pMDI plus spacer	Baseline 0.038 +/- 0.012 mcg/mg; DPI 0.028 +/- 0.012, P = 0.018; pMDI plus spacer 0.037 +/- 0.019, P = 0.78	DPI associated with suppression from baseline; pMDI plus spacer was not.	Not poolable unless similar study exists.
von Berg et al., 2007	Ciclesonide HFA-pMDI vs budesonide DPI	24-hour urinary cortisol adjusted for creatinine measured; numerical results require full-text extraction.	Relevant but confounded by drug and dose.	Do not pool with same-drug comparisons.
Basu et al., 2009	eFlow soluble budesonide vs LC Plus suspension budesonide	Overnight urinary cortisol-to-creatinine measured; workbook states no significant difference.	No detected significant adrenal effect in current extraction.	Do not pool with pMDI or DPI comparisons.

Supplement 6. Risk-of-Bias Support

Study	Likely design from supplied extraction	Recommended tool/status	Overall judgment
Wolthers, 2006	Randomized crossover trial	RoB 2-style traffic-light screen	Some concerns.
Kim et al., 2008	Randomized comparative/pharmacokinetic trial	RoB 2-style traffic-light screen	Some concerns.
Goldberg et al., 2002	Randomized crossover trial	RoB 2-style traffic-light screen	Some concerns.
von Berg et al., 2007	Randomized comparative trial	RoB 2-style traffic-light screen	Some concerns.
Basu et al., 2009	Comparative clinical trial	RoB 2-style traffic-light screen	Some concerns.

Supplement 7. Protocol-Comparison Table

Topic	PROSPERO plan	Completed-review method	Match?	Reporting location
Information sources	CENTRAL, CINAHL, Google Scholar, MEDLINE, PubMed; supplementary searches planned.	Completed materials also name PubMed, MEDLINE, CINAHL, Scopus, and Cochrane/CENTRAL. Full PubMed syntax is reproduced; other syntax logs were not reproduced in files supplied to Codex.	Partial	Methods and Online Resource 1.
Screening	At least two independent screeners or person/machine combination.	Counts and exclusion categories supplied; reviewer process follows protocol and user-confirmed completed workflow.	Yes	Methods: Study-selection process.
Extraction	At least two people/person-machine combination; author contact for missing data.	Independent extraction completed by four reviewers; two additional reviewers available for disagreement review. Initials are listed on the title page.	Yes	Methods: Data-extraction process.
Risk of bias	RoB 2, JBI, ROBINS-I as design appropriate.	Completed RoB 2-style traffic-light screen used across five domains.	Partial	Methods/Results Risk of bias; Online Resource 1.
Synthesis	Narrative synthesis if fewer than three comparable studies.	Narrative synthesis used because comparisons were heterogeneous.	Yes	Methods: Synthesis methods.
Certainty	GRADE planned.	No completed GRADE table supplied.	No	Discussion limitations/readiness report.

Supplement 8. Excluded Full-Text Studies

The completed PRISMA count uses 14 full-text reports assessed, five included studies, and nine full-text exclusions. The eight-record source-pool CSV is retained as an audit trail rather than as the final analysis set. The available files documented the reasons shown in the source-pool crosswalk above; any additional full-text exclusion details should be retained with the screening file archive.

Supplement 9. Search Record Retention Checklist

Retain final database exports and screening files with the manuscript records.

Record database name, platform, coverage dates when available, exact search date, search strategy, and yield.

Retain deduplication notes supporting the final 121-record count.

Keep the final screening decisions, exclusion categories, and source-pool crosswalk together with the extraction file.

If the authors later run a pre-submission search refresh, update PRISMA counts, exclusion records, extraction, risk-of-bias assessment, synthesis, and references before submission.

Supplement 10. Reference Verification Table

Ref	Citation	DOI/source status
1	Robinson JD, Angelini BL, Krahnke JS, Skoner DP	10.1517/14740338.1.3.237
2	Zollner EW	10.1111/j.1399-3038.2007.00539.x
3	Kowalski ML, Wojciechowski P, Dziewonska M, Rys P	10.2500/aap.2016.37.3912
4	Ahmet A, Mokashi A, Goldbloom EB, et al	10.1136/bmjpo-2019-000569
5	Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D	10.1136/adc.87.6.457
6	Lipworth BJ	10.1016/S1081-1206(10)62914-6
7	Goldberg S, Algur N, Levi M, et al	10.1016/S1081-1206(10)63432-1
8	Fink RS, Pierre LN, Daley-Yates PT, Richards DH, Gibson A, Honour JW	10.1210/jc.2002-020287
9	Brodie M, McMurray A, Crofton PM, Bath L, Cunningham S	10.1007/s00431-006-0260-7
10	Tran DT, Chen Y, Zheng Y, et al	10.1002/iid3.1315
11	Wolthers OD	10.1111/j.1399-3038.2006.00460.x
12	Kim KT, Milgrom H, Yoon YK, et al	10.1177/0091270007309704
13	Goldberg S, Einot T, Algur N, et al	10.1016/S1081-1206(10)62103-5
14	von Berg A, Engelstatter R, Minic P, et al	10.1111/j.1399-3038.2007.00538.x
15	Basu K, Nair A, Williamson PA, Mukhopadhyay S, Lipworth BJ	10.1016/S1081-1206(10)60365-1
16	Singh D, Tutuncu A, Lohr I, Carlholm M, Polanowski T	10.5414/cpp45485
17	Hawcutt DB, Jorgensen AL, Wallin N, et al	10.1111/cen.12655
18	Hoekstra MO, Grol MH, Bouman K, et al	10.1164/ajrcm.154.4.8887604
19	Volovitz B, Bentur L, Finkelstein Y, et al	10.1016/S0091-6749(98)70276-3
20	Amirav I, Mansour Y, Tiosano T, et al; Ipros Network	10.1136/adc.88.6.527
21	Priftis KN, Papadimitriou A, Anthracopoulos MB, Fretzayas A, Chrousos GP	10.1159/000216191
22	Gangadharan A, McCoy P, Phyto A, et al	10.2147/JAA.S142874
23	Kannisto S, Korppi M, Remes K, Voutilainen R	10.1210/jcem.85.2.6336
24	Priftis KN, Papadimitriou A, Gatsopoulou E, Yiallourous PK, Fretzayas A, Nicolaidou P	10.1183/09031936.06.00071905
25	Wood Heickman LK, Davallow Ghajar L, Conaway M, Rogol AD	10.1159/000489125