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Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis

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ABSTRACT

Objective Adverse events (AEs) associated with short-term corticosteroid use for respiratory conditions in young children.

Design Systematic review of primary studies.

Data sources Medline, Cochrane CENTRAL, Embase and regulatory agencies were searched September 2014; search was updated in 2017.

Eligibility criteria Children <6 years with acute respiratory condition, given inhaled (high-dose) or systemic corticosteroids up to 14 days.

Data extraction and synthesis One reviewer extracted with another reviewer verifying data. Study selection and methodological quality (McHarm scale) involved duplicate independent reviews. We extracted AEs reported by study authors and used a categorisation model by organ systems. Meta-analyses used Peto ORs (pORs) and DerSimonian Laird inverse variance method utilising Mantel-Haenszel Q statistic, with 95% CI. Subgroup analyses were conducted for respiratory condition and dose.

Results Eighty-five studies (11 505 children) were included; 68 were randomised trials. Methodological quality was poor overall due to lack of assessment and inadequate reporting of AEs. Meta-analysis (six studies; n=1373) found fewer cases of vomiting comparing oral dexamethasone with prednisone (pOR 0.29, 95% CI 0.17 to 0.48; I^2=0%). The mean difference in change-from-baseline height after one year between inhaled corticosteroid and placebo was 0.10 cm (two studies, n=268; 95% CI −0.47 to 0.67). Results from five studies with heterogeneous interventions, comparators and measurements were not pooled; one study found a smaller mean change in height z-score with recurrent high-dose inhaled fluticasone over one year. No significant differences were found comparing systemic or inhaled corticosteroid with placebo, or between corticosteroids, for other AEs; CIs around estimates were often wide, due to small samples and few events.

Conclusions Evidence suggests that short-term high-dose inhaled or systemic corticosteroids use is not associated with an increase in AEs across organ systems. Uncertainties remain, particularly for recurrent use and growth outcomes, due to low study quality, poor reporting and imprecision.

Strengths and limitations of this study

- ► Examined safety outcomes associated with short-term corticosteroid use across multiple common acute respiratory conditions in young children.
- ► Broad range of adverse events (AEs) captured across organ systems.
- ► Inconsistent definitions, assessments and reporting of AEs.
- ► Extensive variation in corticosteroid formulations and dosages within and between studies.
- ► Did not examine long-term corticosteroid use (>14 days).

INTRODUCTION

Corticosteroids are the cornerstone of treatment for many common paediatric respiratory conditions including croup and asthma.[1–3] These conditions often result in presentation to urgent and emergency care settings, in otherwise healthy children. Previous studies examining corticosteroid use in chronic asthma have demonstrated the potential for short-term and long-term adverse events (AEs), particularly growth inhibition, bone disease and adrenal suppression.[4–6] While corticosteroids have demonstrated effectiveness for the acute treatment of many respiratory indications, clinicians are faced with considerable uncertainty regarding short-term safety, particularly among the youngest children.[1]

Previous systematic reviews have examined corticosteroids in preschool or school-aged asthma or wheezing[4 7 8]; however, most focused on efficacy and were restricted to randomised controlled trials (RCTs). These reviews also focused on a specific underlying condition, disease severity, or particular corticosteroid, and mostly for longer-term administration (eg, for recurrent, persistent or chronic asthma). Current guidance on systematic assessment of harms highlights the need to include data from observational studies when considering safety outcomes.[9] As well, it has been suggested that it may be useful to have a wider view of the evidence across a number of similar indications.[10] Recent knowledge synthesis approaches have studied specific safety outcomes across conditions to increase power, with the assumption that some safety outcomes are not confounded by condition.[10] Such a comprehensive approach to knowledge synthesis in this area is critical to inform treatment decisions, reduce practice variation and optimise management of young children who seek care due to acute respiratory illness.

The goal of this study was to synthesise evidence regarding the safety of short course corticosteroid use in young children (<6 years) with acute respiratory conditions.

METHODS

This review followed internationally recommended methods and standards for systematic reviews.[11–13] An a priori protocol was developed (available from authors).

Patient and public involvement

Patients and/or the public were not involved in the design or conduct of this systematic review.

Literature search

Original database searches were conducted September 2014 in Ovid Medline, the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library, and Ovid Embase. Additional sources included regulatory agency databases: Drugs@FDA, Health Canada's Drug Products Database and the European Medicines Agency's European Public Assessment Reports. Search strategies combined index terms and keywords for respiratory illnesses, children and drug classes identified in the Global Initiative for Asthma (GINA)[14] guidelines. Study design filters were applied to limit results to RCTs and observational studies. Update searches were executed in Medline and CENTRAL in February 2016, and then again in July 2017. Detailed search strategies are in online supplementary file 1.

Eligibility criteria

We included primary studies involving population (P): children up to six years old; intervention (I): treated with single or recurrent systemic (any dose) or high-dose inhaled (as defined by the GINA guidelines[14]) corticosteroids for up to 14 days; comparator (C): any comparator; outcome (O): any AE; timing (T): any timing; and, setting (S): any inpatient or outpatient setting providing care to children with an acute respiratory condition. See online supplementary file 2 for detailed eligibility criteria.

Given the lack of standardised terminology for safety, we gathered information on all potentially drug-related harm outcomes[15] from studies including, but not limited to: adverse drug reactions, adverse drug events, medication errors, side effects and potential adverse drug events. For consistency, these outcomes are referred to in the manuscript as AEs. Studies that did not report or mention AEs were excluded. Due to resource constraints and mean age of the studies, no attempt was made to contact study authors if no harms were reported in the text, or when there was potentially missing data; such efforts are unlikely to yield additional data.

Study selection

Two reviewers independently screened the titles and abstracts of all records using a priori selection criteria. Full texts of potentially eligible studies were reviewed by two reviewers independently using a standard form. Disagreements were resolved through consensus or consultation with a third reviewer.

Data extraction

One reviewer extracted data using a structured form, with verification by a second reviewer. Data were extracted on study characteristics (design features), patient characteristics (age, sex, baseline characteristics), respiratory conditions, interventions (type, dose, duration, route of administration, timing, cointerventions, rescue medications), outcomes (types and timing), care setting, funding sources and results.

AEs were extracted as reported by study authors and categorised using a published model based on organ systems (see Results section).[16] A panel of clinicians with specialties in paediatrics, emergency medicine, respiratory medicine and clinical pharmacology rated each AE in order of clinical severity independent of knowledge of the study results.

Assessment of methodological quality

Two reviewers independently assessed the methodological quality of studies using the McMaster Quality Assessment Scale for Harms (McHarm)[17]; disagreements were resolved through discussion.

Data synthesis

A comparative summary of AEs for studies with more than one treatment arm was presented to provide an overall picture of which interventions had a high risk of specific AEs. Risk differences were pooled using the DerSimonian Laird inverse variance random-effects method utilising the Mantel-Haenszel Q statistic. Binary data were also pooled using the Peto ORs (pORs) fixed-effects method.[18] Studies that reported at least one event in at least one treatment arm were included in the analysis of pORs and all comparative studies were used for analysis of RD. One AE (growth) was reported as a continuous outcome and data were pooled using a DerSimonian Laird inverse variance random effects method as a mean difference (MD; in cm). The I^2 statistic was presented to quantify the magnitude of statistical heterogeneity between studies; while the I^2 has the potential to be misinterpreted, it is the standard in the field and we chose to present the statistic for

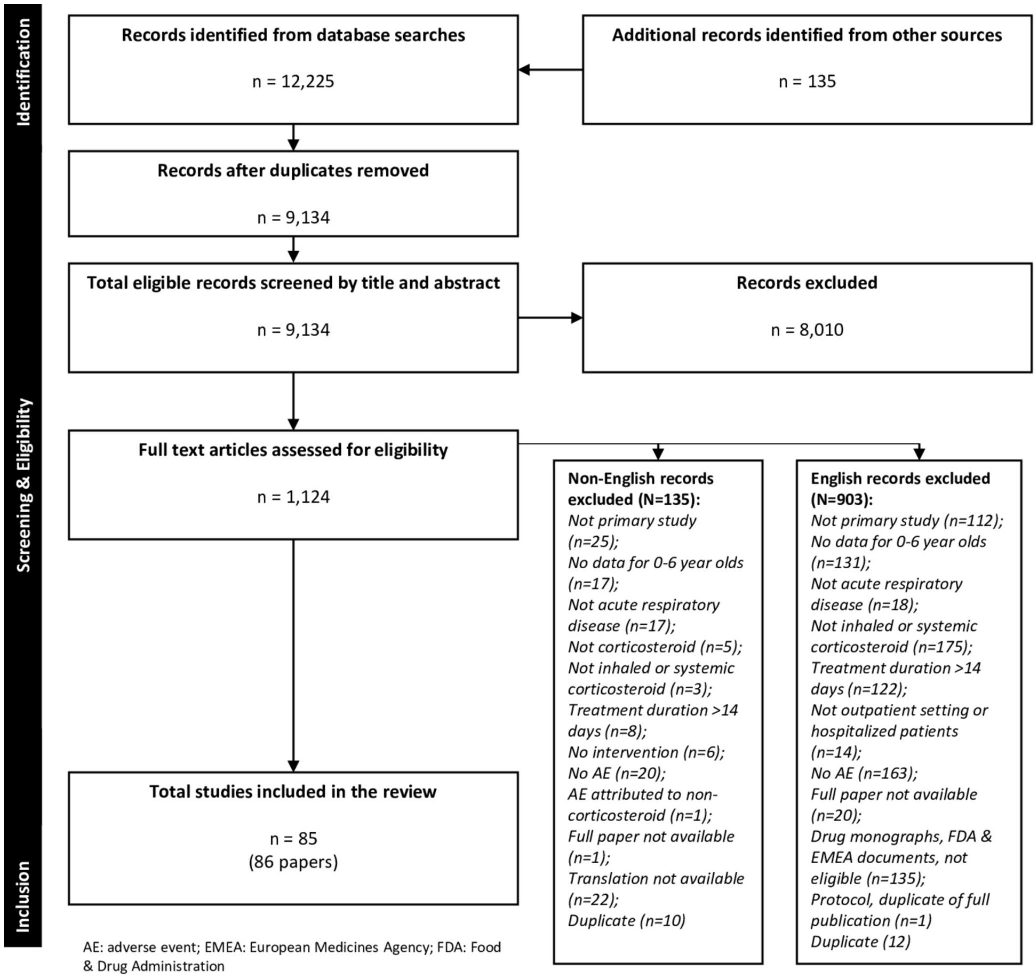

Figure 1 PRISMA study flow selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

informational purposes.[19] Subgroup analyses from study-level data were conducted for respiratory condition and dose (single vs multidose) using Cochran's Q (α=0.05) to detect statistical heterogeneity. Studies contributing no numerical data for analysis (eg, single arm studies, studies that reported no AEs overall) are summarised in online supplementary file 3. Assessment of small-study bias (for meta-analyses with at least eight studies) was planned using the funnel plot and Egger's test[20]; however, this was not conducted due to inadequate number of studies for each outcome. Analyses were conducted using Review Manager V.5.3 (Cochrane Collaboration).[21] Graphs were constructed using TIBCO Spotfire S+Workbench V.3.4.[22]

RESULTS

Database and grey literature searches yielded 9134 records. Eighty-six papers (85 studies)[23–108] involving 11 505 participants were included (figure 1). Characteristics of the included studies are in online supplementary file 3. There was large variation in corticosteroid type, dose, duration and route of administration, both for systemic and inhaled corticosteroids. Methodological quality of studies was poor overall due to inadequate reporting of how AEs were defined and collected (table 1; online supplementary file 4).

Adverse events

Results below are presented according to the categories in table 2. Figures 2, 3 and 4 display forest plots of AEs comparing systemic corticosteroid to placebo, inhaled corticosteroid to placebo, and systemic dexamethasone to another systemic corticosteroid, respectively. Results of meta-analyses and subgroup analyses are in online supplementary file 5, with effect estimates and 95% CIs. Forest plots from meta-analyses are in online supplementary file 6. There was large variation in the number of studies and number of patients with available data for meta-analysis across comparisons and outcomes. Further, for four safety outcomes there were no events in both study arms (double-zero) across studies. In most cases, the subgroup analyses by dose and condition did not differ substantially from the overall results. Studies reporting no AEs overall are summarised in online supplementary file 7.

Infections and respiratory system

The number of studies contributing to each meta-analysis ranged from one to seven (range 58–2178 children).

Table 1 Summary of methodological quality assessments

McHarm* criteria	Rating	No of studies (%†)
(1) Were the harms PRE-DEFINED using standardised or precise definitions?	Yes	6 (7)
	No	79 (93)
	Unsure	0
(2) Were SERIOUS events precisely defined?	Yes	2 (2)
	No	83 (98)
	Unsure	0
(3) Were SEVERE events precisely defined?	Yes	0
	No	85 (100)
	Unsure	0
(4) Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Yes	10 (12)
	No	75 (88)
	Unsure	0
(5) Was the mode of harms collection specified as ACTIVE?	Yes	46 (54)
	No	37 (44)
	Unsure	2 (2)
(6) Was the mode of harms collection specified as PASSIVE?	Yes	11 (13)
	No	73 (86)
	Unsure	1 (1)
(7) Did the study specify WHO collected the harms?	Yes	22 (26)
	No	63 (74)
	Unsure	0
(8) Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	Yes	20 (24)
	No	65 (76)
	Unsure	0
(9) Did the study specify the TIMING and FREQUENCY of collection of the harms?	Yes	39 (46)
	No	45 (53)
	Unsure	1 (1)
(10) Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes	6 (7)
	No	76 (89)
	Unsure	3 (4)
(11) Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Yes	80 (94)
	No	2 (2)
	Unsure	3 (4)
(12) Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Yes	24 (28)
	No	61 (72)
	Unsure	0
(13) Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Yes	16 (19)
	No	69 (81)
	Unsure	0
(14) Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	43 (51)
	No	39 (46)
	Unsure	3 (4)
(15) Did the author(s) specify the type of analyses undertaken for harms data?	Yes	10 (12)
	No	75 (88)
	Unsure	0

*Methodological quality of publications/studies as assessed by the McHarm scale.[17]
†Sum of percentages may not total 100 due to rounding.

Table 2 Number of studies and participants reporting adverse events*

Organ system	AE—category	AE—specific	No of studies	No of participants
Infection and respiratory GI	Severe infections		5	1235
	(1)	Sepsis	1	32
	(2)	Superinfection	2	354
	(3)	UTI	1	720
	(4)	Streptococcal infection	1	129
	Systemic infections		5	1635
	(1)	Fever	3	963
	(2)	Common viral/bacterial/fungal infection	2	792
	(3)	Varicella	3	1449
	Lung/trachea		10	2053
	(1)	Empyema	1	600
	(2)	Pneumonia	8	2051
	(3)	Respiratory distress	2	2
	Upper respiratory tract		14	2457
	(1)	Bacterial tracheitis	5	1023
	(2)	Sinusitis	2	849
	(3)	Croup	2	131
	(4)	Viral parotitis	1	27
	(5)	Pharyngitis	1	129
	(6)	Persistent cough	1	27
	(7)	Oral thrush	3	837
	(8)	Otitis media	4	1173
	(9)	Ear, nose, throat infection	3	862
	(10)	Nasal discharge	1	720
	(11)	Eye discharge	1	720
	Voice complaints		5	794
	GI bleeding		8	2669
	(1)	Bleeding	5	1577
	(2)	Gross hematochezia	1	118
	(3)	Occult blood in stools	2	292
	(4)	Dark stools	1	800
	Vomiting		27	6067
	(1)	Vomiting	24	5983
	(2)	Nausea	6	586
	(3)	Palatability	3	170
	Abdominal pain		5	1332
	Diarrhoea		8	1346
	(1)	Diarrhoea	7	1217
	(2)	Gastroenteritis	1	129
CNS and behaviour	Tremor/jitteriness		8	1274
	(1)	Tremor	7	1226
	(2)	Jittery	1	48
	Behaviour change		14	2078
	(1)	Violent behaviour	1	198
	(2)	Mood change	7	1430
	(3)	Hyperactivity	2	268
	(4)	Restlessness	3	297
	(5)	New sleep problems	3	408
	(6)	Emotional distress due to nebulizer mask	1	82
	(7)	Psychosis	1	1
	Headache		3	291

Continued

Table 2 Continued

Organ system	AE—category	AE—specific	No of studies	No of participants
Dermatological	Burn		1	198
	Integument		10	1954
	(1)	Hives	2	199
	(2)	Rash	8	1954
	(3)	Eczema	1	129
	(4)	Eye irritation	2	211
	(5)	Tongue irritation	1	82
	(6)	Positive weal	1	1
	(7)	Bleeding from ear	1	720
	Phlebitis		1	32
Endocrine/metabolic and musculoskeletal	Fluid and electrolyte abnormalities		7	1849
	(1)	Hyperkalemia	1	800
	(2)	Hyperglycemia	3	154
	(3)	Glycosuria	1	125
	(4)	Sodium retention	1	50
	(5)	Dehydration	1	720
	Growth		6	731
	Adrenal suppression		5	249
	Bone health		5	579
Cardiovascular	Arrhythmia		3	312
	(1)	Tachycardia	2	178
	(2)	Palpitations	1	134
	Hypertension		5	1491
	Congestive heart failure		1	50
General	General complaints		5	1146
	(1)	Dizziness	1	87
	(2)	Pallor	2	869
	(3)	Excessive urination	1	134
	(4)	Normal tooth eruption	1	56
	Haematology, gum bleeding		1	1
Immune system and oncology	Immunosuppression		4	147
	(1)	Immunosuppression	3	146
	(2)	Tumour cell proliferation	1	1

*Each adverse event was clustered into its related organ system; a panel of clinicians ranked each AE category and its corresponding adverse events in order of clinical significance/severity. The organ systems are presented in order of frequency of reporting, beginning with the most frequently reported (ie, infection and respiratory).
AE, adverse event; CNS, central nervous system; GI, gastrointestinal; URT, upper respiratory tract.

There were no statistically significant differences between: (1) *systemic corticosteroid compared with placebo* for severe infections,[30 74 96 99] systemic infections,[30 40 43 83] infections of the lung/trachea[30 40 54 74 96 98 105] and the upper respiratory tract,[30 43 54 65 67 74] and voice complaints[43] (estimated pORs between 0.15 and 1.26) and (2) *inhaled corticosteroid compared with placebo* for severe infections,[45] systemic infections,[43 45] lung/trachea,[45] infections of the upper respiratory tract[37 44 45 65–67] or voice complaints[37 43 100 101] (estimated pORs between 0.54 and 1.51). No study comparing *dexamethasone with another corticosteroid* reported infections or respiratory AEs.

Gastrointestinal tract

The number of studies contributing to each meta-analysis ranged from one to seven (range 97–3176 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for gastrointestinal (GI) bleeding,[30 32 40 65 83 87 105] vomiting,[30 38 40 42 70 81 83] abdominal pain[30] or diarrhoea[42 77 105] and (2) *inhaled corticosteroid and placebo* for GI bleeding,[65] vomiting[37 45 69 85 101] or diarrhoea.[37 45] Estimated pORs for both comparisons ranged from 0.89 to 1.10.

Meta-analysis of six studies (1373 children)[25 27 41 49 52 80] found fewer cases of vomiting in patients who received *dexamethasone compared with another corticosteroid*, although the number of events was small (12/663 vs 51/710 cases; pOR 0.29, 95% CI 0.17 to 0.48; I^2=0%). These studies focused on asthma (n=3),[27 41 80] croup (n=2)[49 52] or both (n=1)[25]; all compared oral dexamethasone with oral prednisone. No statistically significant difference was found for abdominal pain between *dexamethasone and another corticosteroid*.[25 27 52]

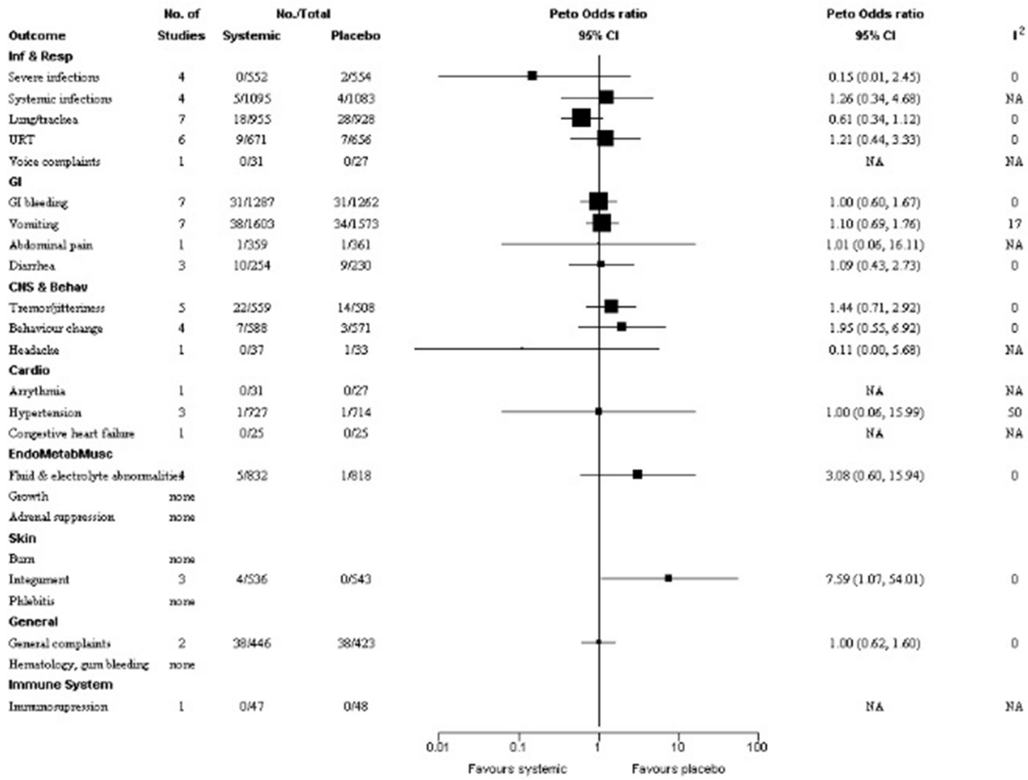

Figure 2 Forest plot of adverse events—systemic versus placebo.

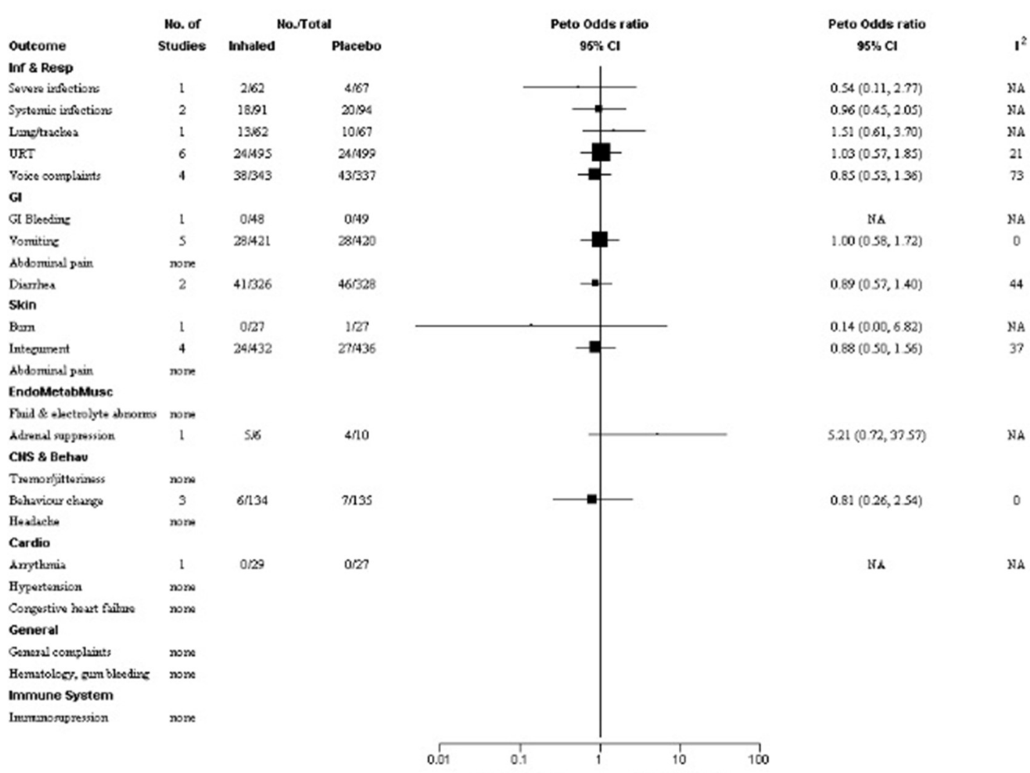

Figure 3 Forest plot of adverse events—inhaled versus placebo.

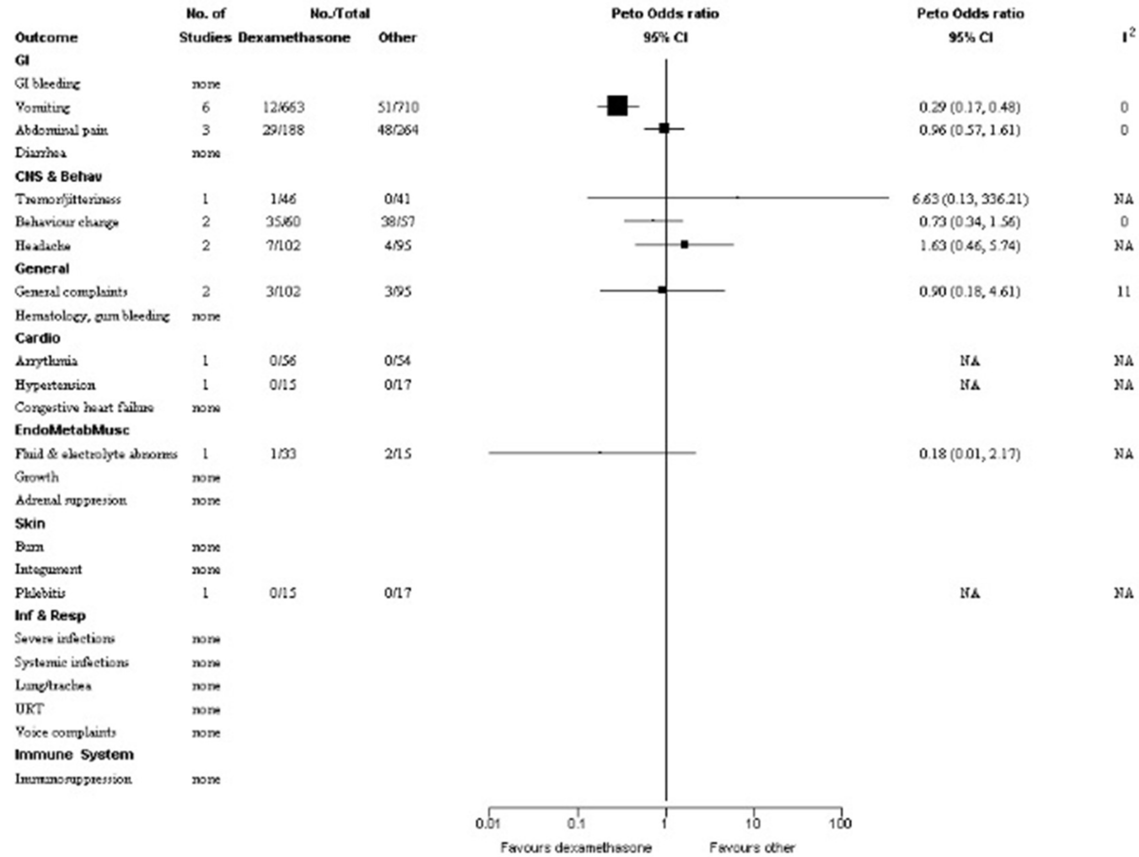

Figure 4 Forest plot of adverse events—dexamethasone versus other.

CNS and behaviour effects

The number of studies for each meta-analysis ranged from one to five (range 70–1159 children). The estimated pORs for the *systemic corticosteroid and placebo* were 1.44 for tremor/jitteriness,[38 55 70 77 83] 1.95 for behaviour change[30 42 67 77] and 0.11 for headache,[38] with no statistically significant differences. There were also no differences between *inhaled corticosteroid and placebo* for behaviour change[67 85 101]; and *dexamethasone and another corticosteroid* for behaviour change,[52 57] headache[27 52] or tremor/jitteriness,[52] the latter with an estimated pOR of 6.63 from a small study (n=87) with only one reported event.

Dermatologic conditions

The number of studies per meta-analysis ranged from one to four (range 32–1079 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for rash and hives,[30 42 67] albeit with an estimated pOR of 7.59 (4/536 vs 0/543; 95% CI 1.07 to 54.01) and (2) *inhaled corticosteroid and placebo* for rash,[37 45 85] hives[67] and burning sensation[68] (estimated pORs 0.88 and 0.14, respectively). No events of phlebitis were reported comparing *dexamethasone to another corticosteroid*.[57]

Endocrine/metabolic and musculoskeletal systems

There were no statistically significant differences for electrolyte abnormalities between *systemic corticosteroid and placebo* (estimated pOR 3.08)[30 47 83 102] and *dexamethasone to another corticosteroid* (estimated pOR 0.18).[102]

Pooled data for linear growth between *inhaled corticosteroid and placebo* included two studies (n=263) using recurrent doses for acute wheeze with follow-up at one year.[28 45] The estimated change-from-baseline height was small (MD 0.10 cm; 95% CI −0.47 to 0.67; I^2=9%). Five studies reported measurements of growth (height and weight) ranging from one to three years of follow-up, which could not be pooled due to heterogeneous interventions, comparators or outcome measurements.[29 31 45 58 71] Three studies included data on inhaled corticosteroid versus placebo. One RCT on asthma[58] (n=20) comparing budesonide and placebo found no signs of growth retardation by height measurements at 12 months or after up to six treatments. An RCT of episodic wheeze[29] (n=294) found height at three years of age was unaffected in children receiving budesonide or placebo. One RCT of inhaled fluticasone propionate at very high doses (1500 µg per day during upper respiratory infections) versus placebo in recurrent wheeze[45] reported additional outcome data on height that was not pooled in the meta-analysis mentioned above. There was a smaller mean change in height z score in the corticosteroid group over one year (MD −0.24; 95% CI −0.40 to −0.08; adjusted results).[45] Furthermore, mean weight was significantly lower at one-year follow-up in the fluticasone group (n=62) versus placebo (n=67); two children given fluticasone and one given placebo met criteria for 'failure to thrive'.[45] Finally, two small trials did not report group differences for other comparisons: total and mean height growth (at 8–19 months) for intravenous dexamethasone versus inhaled budesonide in asthma (n=18)[71]; weight and height gains at 2 years for theophylline and metaproterenol with or without systemic prednisone on prevention of wheeze during upper respiratory infections in asthma (n=32).[31]

Five studies reported on adrenal function/suppression, with few children contributing data for this outcome.[45 57 58 71 89] The RCT of high-dose inhaled fluticasone propionate versus placebo (99 children with data)[45] found no significant differences between groups in basal cortisol (baseline and 12 months). Another RCT in asthma reported no differences in serum cortisol and urinary cortisol/creatinine after 10 days of inhaled budesonide or placebo (16 children with data). A subgroup who received oral betamethasone (n=9) showed significant changes from baseline after three days, but no differences at 12–14 days.[58] Two studies included comparisons between different corticosteroids. One RCT[89] in acute asthma compared intravenous prednisolone (n=20) with nebulised budesonide (n=30) and found significant levels of suppressed serum cortisol in the prednisolone group, although not considered pathologic by the study authors. Although another RCT[57] comparing intramuscular dexamethasone with oral prednisone for asthma (n=32) found lower median urinary cortisol/creatinine in the former group at day 14, there was no statistically significant difference. An RCT[71] comparing intravenous dexamethasone (n=9) with inhaled budesonide (n=9) found no significant differences between groups from baseline for blood pressure and blood glucose measurements.

Five studies reported on bone health biomarkers, three of which compared inhaled corticosteroids and placebo; no pooled analyses were performed.[29 45 58 61 92] One RCT[29] compared inhaled budesonide (n=294) with placebo in episodic wheeze and found no effect on bone mineral density over three years. The RCT comparing high-dose inhaled fluticasone propionate with placebo (n=59 children with data) in viral wheeze[45] reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT[58] comparing inhaled budesonide with placebo (n=20) in asthma found transient decreased levels of bone and collagen markers post-treatment and in a subset of children who received oral betamethasone, with no difference between groups. A study of patients with acute respiratory illness[92] compared hydrocortisone (n=28), methylprednisone (n=21) and controls (n=51) and found decreased levels of osteocalcin and alkaline phosphatase in younger children 2 days post-treatment; these effects were reversed 12 days after treatment. A non-randomised controlled trial of 36 asthma patients[61] compared intravenous methylprednisolone of three different durations and found that all had decreasing levels of serum osteocalcin that correlated with increasing duration of treatment.

Cardiovascular system

No significant differences were found between *systemic corticosteroid and placebo* in three bronchiolitis studies reporting hypertension (estimated pOR 1).[32 40 83] Single studies with up to 110 children did not report events for arrhythmia[43] and congestive heart failure[47] (*systemic or inhaled corticosteroid* vs *placebo*); and arrhythmia[27] or hypertension[57] (*dexamethasone with another corticosteroid*).

General AEs/other symptoms

Meta-analyses included a total of two studies (range 197–869 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for pallor[70 83] and (2) *dexamethasone and another corticosteroid* for dizziness[52] or excessive urination.[27] No study comparing *inhaled corticosteroid with placebo* reported general AEs.

Immune system and oncology

One study (95 participants)[39] compared *systemic corticosteroid and placebo* and found no occurrences of immunosuppression. No other study reported immune system-related AEs.

DISCUSSION

This systematic review of studies in which short-course corticosteroids were administered to children under six years of age for acute respiratory conditions, included 85 studies involving more than 11 000 patients. These studies used a variety of delivery routes, doses, formulations and duration of corticosteroids. Overall, the evidence suggests that short-term corticosteroid use is not associated with a significant increase in AEs across organ systems. However, given the low quality of included studies, the heterogeneous and poor reporting of AEs, and the lack of precision of results, considerable uncertainties remain regarding the safety of high-dose inhaled or systemic corticosteroids for these indications in this age range.

A common concern when using corticosteroids in young children is effect on growth. Results from a single, small trial (n=129) of recurrent high-dose inhaled fluticasone propionate in wheezing preschoolers were heterogeneous across outcome measures, but suggested a small significant risk of growth suppression.[45] Observational data have also suggested that multiple corticosteroid bursts can increase the risk of growth suppression, fractures, bone mineral accretion and osteopenia in children with underlying respiratory disease.[5 6 109] Conversely, a pooled analysis using change-from-baseline linear growth did not find significant differences, although the other included study used a substantially lower equivalent dose of inhaled corticosteroid.[110] Further, results from individual studies reporting transient differences in bone and adrenal biomarkers are of unclear clinical relevance, particularly for previously healthy children and single use. This calls for caution and monitoring of linear growth, particularly when use of high-dose inhaled or systemic corticosteroid is recurrent.

We found no other statistically significant differences between systemic or inhaled corticosteroid and placebo, or between dexamethasone and other systemic corticosteroid, including subgroup analyses by respiratory condition or dose, for AEs across organ systems. Due to small sample sizes and low number of events, these results should be interpreted with caution. While we found increased pORs when comparing systemic corticosteroids for behavioural outcomes such as tremor/jitteriness and behaviour change, there were wide CIs around estimates. No study examined neurodevelopmental outcomes after corticosteroid administration; ideally, studies should assess children for potentially related long-term AEs using validated instruments in this domain. Results from case series and case reports added anecdotal evidence of rare cases of hypersensitivity, infection or behavioural AEs, which have been described.[111 112] While the estimated increased pOR for rash and hives was close to statistical significance, no other differences were found in systemic or severe infections as well as immunosuppression.

This review did not ascertain a clear safety advantage between systemic or inhaled corticosteroids compared with placebo. When comparing between different systemic corticosteroids, evidence favoured oral dexamethasone over oral prednisone for vomiting (pOR 0.029; 95% CI 0.17 to 0.48; I^2=0%). Differences in palatability and tolerability between corticosteroids are well known to parents, healthcare providers and researchers, and can influence adherence to medication in children.[113] Further, different specific formulations of corticosteroid (eg, prednisolone tablets vs prednisolone syrup) have been shown to influence taste and vomiting.[25] However, cost and access to better tolerated formulations may be problematic. Subgroup analyses also found no significant differences between groups by respiratory condition or dose (single vs multiple) for these outcomes. Due to extensive variation in dosing within and across studies, we were unable to analyse data or draw further conclusions with respect to dosage or differences between specific molecules. It should be noted that among the eight RCTs[35 43 46 51 65 67 71 89] directly comparing systemic and inhaled routes of corticosteroid administration, none contributed meaningful data for meta-analysis. The decision to initiate corticosteroid and the selection of drug, dose and mode of administration must consider these uncertainties on harms, as well as existing evidence on comparative potency and clinical effectiveness. The risk–benefit rationale is less established for repeated acute use in younger children, such as in recurrent wheezing.[114]

Strengths and limitations

We conducted a comprehensive systematic review of the literature following rigorous methods, including grey literature, to minimise potential for publication and selection bias. We examined safety outcomes across multiple acute respiratory conditions using 'baskets' of outcomes in each organ system to increase our ability to detect rare events and the precision of our estimates.[16] This approach is reflective of clinical practice where corticosteroids are used across many respiratory diseases, even if the evidence base is not entirely robust for children. A recent systematic review also assessed the toxicity of short-course oral corticosteroids in children across clinical conditions.[115] However, there was scarce overlap in respiratory conditions across included studies, and authors mostly provided estimates of the incidence of AEs within treatment groups rather than comparative treatment effects. Studies in adults have also adopted similar approaches to estimate incidence rates of AEs. For example, findings from a recent retrospective cohort in adults showed a significant increase in rates of sepsis, venous thromboembolism and fracture.[116]

This review was limited by the quality of the primary literature, particularly regarding the definition, assessment and reporting of AEs. This underscores the challenges researchers encounter when attempting to synthesise safety data due to sparse and poor reporting,[117] and highlights the urgent need to enhance detection and reporting of AEs. For example, it is worthwhile noting that 26 studies reported 'no AEs' or 'no significant AE' which could not be included in pooled estimates; this may be a reflection of these studies being under-powered to detect statistically significant findings (especially for rare AEs) and/or AEs that may or may not be considered of special interest and/or clinically important. Such blanket statements are problematic for interpretation, highlighting the need for study authors to clearly report AEs of interest pre-study and post-study conduct. Common nomenclature (eg, www.meddra.org) and standardised approaches to collection of AE data should be implemented to help draw comparisons across studies. Further, safety reporting was not a primary focus of the studies, AEs were rarely defined a priori, and methods for ascertaining AEs were usually absent. While the McHarm scale is recommended to be used in conjunction with other quality assessment tools to evaluate the broader elements of study quality, we used it exclusively to assess methodological quality since the primary focus of this review was on AEs. The AEs reported typically reflect what is detected by a healthcare provider; it is difficult to discern what is reported by patients as well as what patients consider important. The duration of surveillance of most studies was insufficient to detect many of the long-term AEs potentially associated with corticosteroid use. Although the present study suggests that single doses of systemic or inhaled corticosteroids may result in few AEs, recurrent courses may lead to long-term risks, as cumulative dosing has been shown to be a determinant of safety.[109] Finally, there was variation within and across studies with respect to maintenance corticosteroids, and concomitant and rescue medications. Due to the variation in corticosteroids and extensive range of AEs reported (including when a single study contributes to an outcome or in cases of zero events, where meta-analysis was not feasible or meaningful) among varied study designs of overall poor quality, we did not attempt to rate the quality of the body of the evidence using the Grading of Recommendations Assessment, Development and Evaluation[118] approach.

CONCLUSION

This is the most comprehensive systematic review to date examining the safety of corticosteroids for managing acute respiratory conditions among young children, an age group of great clinical concern. While the existing evidence suggests that short-term high-dose inhaled or systemic corticosteroids is not associated with an increase in AEs across organ systems, uncertainties remain due to low quality of studies, poor reporting and lack of precision of results. Importantly, these results can help guide future research in the collection and reporting of AEs, particularly concerning measures of growth and behavioural outcomes; this in turn is needed to help inform shared decision-making between clinicians and parents/caregivers of young children.

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