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Dexamethasone for Acute Asthma Exacerbations in Children: A Meta-analysis

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KEY WORDS

dexamethasone, prednisone, prednisolone, asthma, status asthmaticus

ABBREVIATIONS

CI—confidence interval
ED—emergency department
IM—intramuscular
PO—per os
RR—relative risk

Dr Gorelick conceptualized the study; Drs Gray, Keeney, Morrison, Levas, Kessler and Hill conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, and drafted the initial manuscript; Dr Jackson participated in study design, carried out the initial analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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abstract



BACKGROUND AND OBJECTIVE: Dexamethasone has been proposed as an equivalent therapy to prednisone/prednisolone for acute asthma exacerbations in pediatric patients. Although multiple small trials exist, clear consensus data are lacking. This systematic review and meta-analysis aimed to determine whether intramuscular or oral dexamethasone is equivalent or superior to a 5-day course of oral prednisone or prednisolone. The primary outcome of interest was return visits or hospital readmissions.

METHODS: A search of PubMed (Medline) through October 19, 2013, by using the keywords dexamethasone or decadron and asthma or status asthmaticus identified potential studies. Six randomized controlled trials in the emergency department of children ≤ 18 years of age comparing dexamethasone with prednisone/prednisolone for the treatment of acute asthma exacerbations were included. Data were abstracted by 4 authors and verified by a second author. Two reviewers evaluated study quality independently and interrater agreement was assessed.

RESULTS: There was no difference in relative risk (RR) of relapse between the 2 groups at any time point (5 days RR 0.90, 95% confidence interval [CI] 0.46–1.78, $Q = 1.86$, $df = 3$, $I^2 = 0.0\%$, 10–14 days RR 1.14, 95% CI 0.77–1.67, $Q = 0.84$, $df = 2$, $I^2 = 0.0\%$, or 30 days RR 1.20, 95% CI 0.03–56.93). Patients who received dexamethasone were less likely to experience vomiting in either the emergency department (RR 0.29, 95% CI 0.12–0.69, $Q = 3.78$, $df = 3$, $I^2 = 20.7\%$) or at home (RR 0.32, 95% CI 0.14–0.74, $Q = 2.09$, $df = 2$, $I^2 = 4.2\%$).

CONCLUSIONS: Practitioners should consider single or 2-dose regimens of dexamethasone as a viable alternative to a 5-day course of prednisone/prednisolone. *Pediatrics* 2014;133:493–499

Asthma affects >6 million children in the United States, making it the most common chronic disease of childhood.^{1,2} As such, asthma accounts for 2% of all ambulatory care and emergency department (ED) visits by patients <18 years of age.³ Asthma is a chronic inflammatory disease characterized by airway edema, bronchoconstriction and airway hyperresponsiveness. In addition to bronchodilators, corticosteroids are the cornerstone of therapy for acute asthma exacerbations. They systemically reduce inflammation, decrease mucus production, and enhance the effects of β -agonists.² National and international guidelines advise early administration of systemic corticosteroids for moderate or severe exacerbations and for mild exacerbations that do not immediately and completely respond to short-acting β -agonists.^{1,4}

Current treatment regimens consist of oral prednisone or prednisolone taken once or twice daily for 5 days. Oral (PO) or intramuscular (IM) dexamethasone has been proposed as an equivalent therapy. Potential advantages include a longer half-life requiring a shorter course, increased compliance with a single dose, and less vomiting with dexamethasone. Although multiple small trials exist, clear consensus data are lacking.

OBJECTIVE

The purpose of this systematic review and meta-analysis of randomized clinical trials is to determine whether PO or IM dexamethasone is equivalent or superior to a 5-day course of oral prednisone or prednisolone. The primary outcome of interest was unscheduled return visits (clinic visit, ED visit, or hospital admission) for acute asthma exacerbation in pediatric patients. Secondary outcomes included vomiting in the ED and vomiting at home.

METHODS

Trials were identified using PubMed (Medline) with search terms of “dexamethasone”

OR “decadron” AND “asthma” OR “status asthmaticus” in all search fields, including only human trials without language restriction. The final search was conducted on October 19, 2013.

Studies were included in the meta-analysis if they were a randomized controlled trial of treatment of acute asthma exacerbation in either an ambulatory or ED setting comparing dexamethasone with prednisone or prednisolone in children ≤ 18 years of age. Patients hospitalized during the initial study encounter were not included in the analysis of return visits. Articles were excluded at the title and abstract phase by 2 authors (M.L. and G.H.). Reference lists from review articles and those studies included in the meta-analysis were reviewed by hand without identification of additional articles meeting criteria.

Data were abstracted by 4 authors (G.K., M.P.G., A.M., M.L.) and all data were verified by a second author. Abstracted data included subject characteristics (age in months, gender, ethnicity), asthma severity score, treatment characteristics (number of albuterol treatments in the ED), adverse effects (vomiting), and clinical outcomes (hospitalization during initial ED visit, asthma score at ED discharge, subjective improvement, and relapse rate as defined by an unscheduled visit to a clinic, ED, or a hospitalization). Outcomes were extracted as either dichotomous or continuous variables based on study report.

Study quality of the included trials was assessed using the Cochrane risk of bias tool, the 6-question instrument created and validated by Jadad and colleagues, and 2 additional items describing the presence of industry sponsorship in the trial and whether intent to treat analysis was performed.^{5,6} Two reviewers (G.H. and E.K.) evaluated study quality independently.

Data were pooled using a fixed-effects model. Relapse rates were reported

at different time intervals and combined for meta-analysis only when similar time intervals were reported (5 days, 10–14 days, and 30 days). Differences between groups were tested using random effects meta-regression.⁷ Heterogeneity was assessed using the I^2 method.⁸ We assessed for small study effects (publication bias) using the methods of Peters et al⁹ for dichotomous outcomes and Egger et al¹⁰ for continuous outcomes. We examined the potential for undue influence of any given study by looking at the percentage of total weight to the final pooled results for each study and by examining meta-influence plots. Potential sources of heterogeneity were explored by using stratified analysis. All analyses were performed by using Stata version 12.1 (Stata Corp, College Station TX). This study was supported by a grant from the National Center for Advancing Translational Sciences, National Institutes of Health.

RESULTS

Our search identified 667 articles. Application of inclusion and exclusion criteria resulted in 6 studies that were included in our analysis (Fig 1).^{11–16} All of the included studies were performed in EDs and had a mean of 171 participants (range 15–272). All studies but one (Gordon et al¹²) defined relapse as an unplanned clinic visit, return ED visit, or an unplanned hospital admission related to their initial asthma exacerbation. Dexamethasone was given as a single IM dose in 3 studies,^{12,14,15} as a single oral dose in 1 study,¹¹ and as multiple oral doses in 2 studies^{13,16} (Table 1). Included studies were from the United States ($n = 5$) and Canada ($n = 1$). All studies were among children with a mean age of 53.2 (95% confidence interval [CI] 41.5–64.9) months. Participants were mostly boys (63.5%). One of the studies included a predominantly Hispanic population (80%).¹² Among the remaining studies, participants were

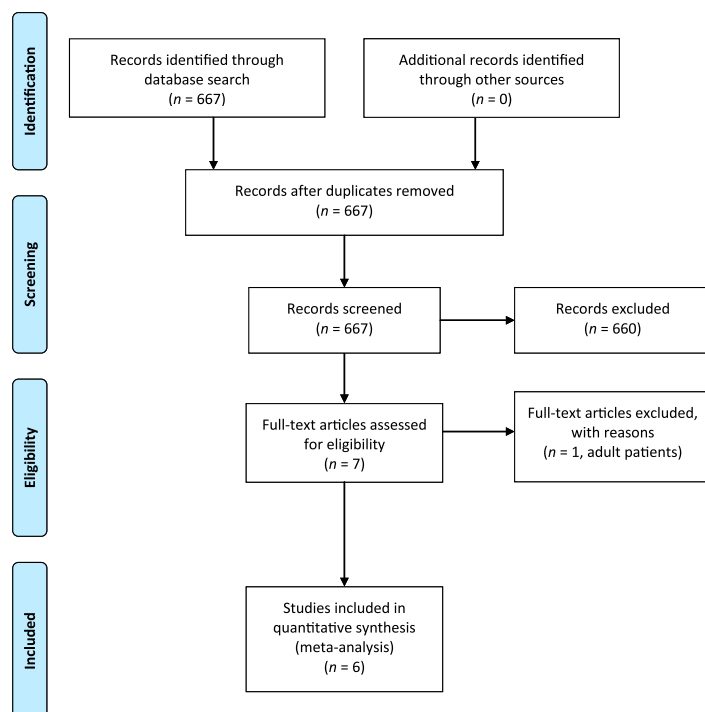


FIGURE 1
Study selection.

34.7% white and 37.9% African American. Study quality ranged from 3 to 8 on the Jadad scale (Table 1) and assessments using the results of the Cochrane risk of bias tool are presented in Table 2. Interrater agreement was excellent with a κ of 0.90.

In comparing the group receiving dexamethasone to prednisone, there were no differences at baseline in age (44.4 vs 56.7 months, $P = .66$), proportion of boys (63.6 vs 65.8, $P = .37$), or initial asthma severity score (standardized mean 3.5 vs 3.1, $P = .22$, 4 studies). There were no differences in the likelihood of improvement in asthma scores during the initial ED visit between groups (relative risk [RR] 1.01, 95% CI 0.93–1.10, $Q = 0.38$, $df = 2$, $I^2 = 0.0\%$), the number of albuterol treatments received in the ED (2.5, 95% CI 1.8–3.2 vs 2.7, 95% CI 1.9–3.5, P for difference = .87, 4 studies), or in post-treatment asthma severity scores (RR 1.38, 95% CI 0.0–2.81 vs 1.27, 95% CI 0.0–2.71, P for difference = 0.78). There was no difference in the average amount of improvement in asthma scores between

groups (standard mean difference 2.56, 95% CI 2.27–2.84 vs 2.30, 95% CI 2.03–2.56, P for difference = 0.56). There was no difference in rates of hospitalization during the initial ED visit (RR 0.91, 95% CI 0.66–1.26, $Q = 1.68$, $df = 4$, $I^2 = 0.0\%$).

In the dexamethasone group, there was a 6.6% (95% CI 0.3%–10.0%) relapse rate by 5 days, increasing to 13.8% (95% CI 11.3–16.4) by 2 weeks (Fig 2). In the prednisone/prednisolone group the 5-day relapse rate was 3.6% (95% CI 1.1%–6.2%), increasing to 11.9% (95% CI 0.9%–14.4%) by 2 weeks. There was no difference in relapse rate between the 2 groups at any time point (5 days RR 0.90, 95% CI 0.46–1.78, $Q = 1.86$, $df = 3$, $I^2 = 0.0\%$, 10–14 days RR 1.14, 95% CI 0.77–1.67, $Q = 0.84$, $df = 2$, $I^2 = 0.0\%$, or 30 days RR 1.20, 95% CI 0.03–56.93), although the 30-day relapse rate was reported in only 1 study.

Patients who received dexamethasone were less likely to experience vomiting in either the ED (Fig 3, RR 0.29, 95% CI 0.12–0.69, $Q = 3.78$, $df = 3$, $I^2 = 20.7\%$) or

at home (Fig 4, RR 0.32, 95% CI 0.14–0.74, $Q = 2.38$, $df = 2$, $I^2 = 4.2\%$).

The paucity of studies limited our ability to perform sensitivity analyses. There was no evidence of publication bias for any of our outcomes, including relapse rates (5 days: $P = .84$, 14 days: $P = .47$), hospitalization ($P = .75$), improvement in asthma severity scores ($P = .29$), vomiting in the ED ($P = .72$), or vomiting at home ($P = .93$). There was no evidence of undue influence on any of these outcomes from any particular study on meta-influence plots; no study contributed >29% of the total weight to any pooled analysis, suggesting lack of undue influence. Dexamethasone was administered orally in 3 studies and IM in 3 studies. However, the studies reported outcomes at different time points, making subanalyses tentative. There was no difference in likelihood of relapse for dexamethasone compared with prednisone/prednisolone, regardless of the route of dexamethasone administration ($P = .43$). Similarly, there were no differences for hospitalization ($P = .75$), or likelihood of improvement in asthma score ($P = .85$). Both PO and IM dexamethasone were associated with less vomiting in the ED (PO 0.32, 95% CI 0.11–0.91, IM 0.06, 95% CI 0.003–0.94). Route of administration accounted for only a small portion (26.7%) of the variance in this outcome. There was no difference in route of dexamethasone administration for vomiting at home ($P = .95$) with oral dexamethasone still resulting in less vomiting than prednisolone (RR 0.32, 95% CI 0.13–0.77), although the benefit was lost for the single trial of IM dexamethasone (RR 0.32, 95% CI 0.01–7.7).

CONCLUSIONS

This meta-analysis examined whether intramuscular or oral dexamethasone is equivalent or superior to a 5-day course of prednisone/prednisolone for acute asthma exacerbations in pediatric

TABLE 1 Included Studies

Author	Intervention ^a	Comparison ^a	Inclusion Criteria	Exclusion Criteria	Jadad Score
Single IM dose Gries, 2000 ¹⁴	Dexamethasone 1.7 mg/kg (max 36 mg) IM × 1 dose	Prednisone or prednisolone 1 mg/kg (max 20 mg) PO twice daily × 5 d	Age 6 mo–7 y, previous history of asthma, mild to moderate asthma exacerbation	Use of steroid in previous 2 wk, severe asthma exacerbation (requiring hospitalization), fever >101, or documented RSV infection	3
Gordon, 2007 ¹²	Dexamethasone 0.6 mg/kg (max 15 mg) IM × 1 dose	Prednisolone 2 mg/kg (max 50 mg) PO daily × 5 d	Age 18 mo–7 y, previous history of asthma, mild to moderate asthma exacerbation	Use of steroid in previous month, allergy to steroid, TB or varicella exposure, previous enrollment, major coexisting illness, O2 saturation < 88% on room air, pectus excavatum, or need for IV	4
Klig, 1997 ¹⁵	Dexamethasone 0.3 mg/kg (max 15 mg) IM × 1 dose	Prednisone 2 mg/kg (max 100 mg) PO × 1 dose then 1 mg/kg PO daily × 2 d	Age 3–16 y, previous history of asthma, mild to moderate asthma exacerbation	Use of steroid in previous month, oxygen saturation ≤ 95% on room air, significant recent hospitalization for asthma or ICU stay in the past year, 7 d of prednisone in past year, or major coexisting illness	3
Single Oral Dose Altamimi, 2006 ¹¹	Dexamethasone 0.6 mg/kg (max 18 mg) PO × 1 dose, placebo PO twice daily × 5 d	Prednisone or prednisolone 1 mg/kg (max 30 mg) PO × 1 dose, then 1 mg/kg PO twice daily × 5 d	Age 2–16 y, previous history of asthma and mild to moderate asthma exacerbation	Use of steroid in previous 2 wk, complete recovery after 1 bronchodilator, history of previous intubation or PICU admission, major coexisting illness, history of acute allergic reaction, active varicella, or HSV infections	8
Multiple Oral Doses Greenberg, 2008 ¹³	Dexamethasone 0.6 mg/kg (max 16 mg) PO once daily × 2 d	Prednisone 2 mg/kg (max 80 mg) PO × 1 dose, then 1 mg/kg (max 30 mg) PO twice daily × 4 d	Age 2–18 y, previous history of asthma, and acute exacerbation asthma	Use of steroid in previous month, history of intubation, varicella exposure, possible foreign body aspiration, major coexisting illness, significant respiratory distress, previous enrollment, no telephone for follow-up, or ≥2 episodes of emesis after steroid dose in ED	4
Qureshi, 2001 ¹⁶	Dexamethasone 0.6 mg/kg (max 16 mg) PO once daily × 2 d	Prednisone or prednisolone 2 mg/kg (max 60 mg) PO × 1 dose, then 1 mg/kg (max 60 mg) PO daily × 4 d	Age 2–18 y, previous history of asthma, acute exacerbation, and required at least 2 β-agonist treatments in ED	Use of steroid in previous 4 wk, history of intubation, varicella exposure, concurrent stridor, concern for intrathoracic foreign body, major coexisting illness, or need for immediate airway intervention	3

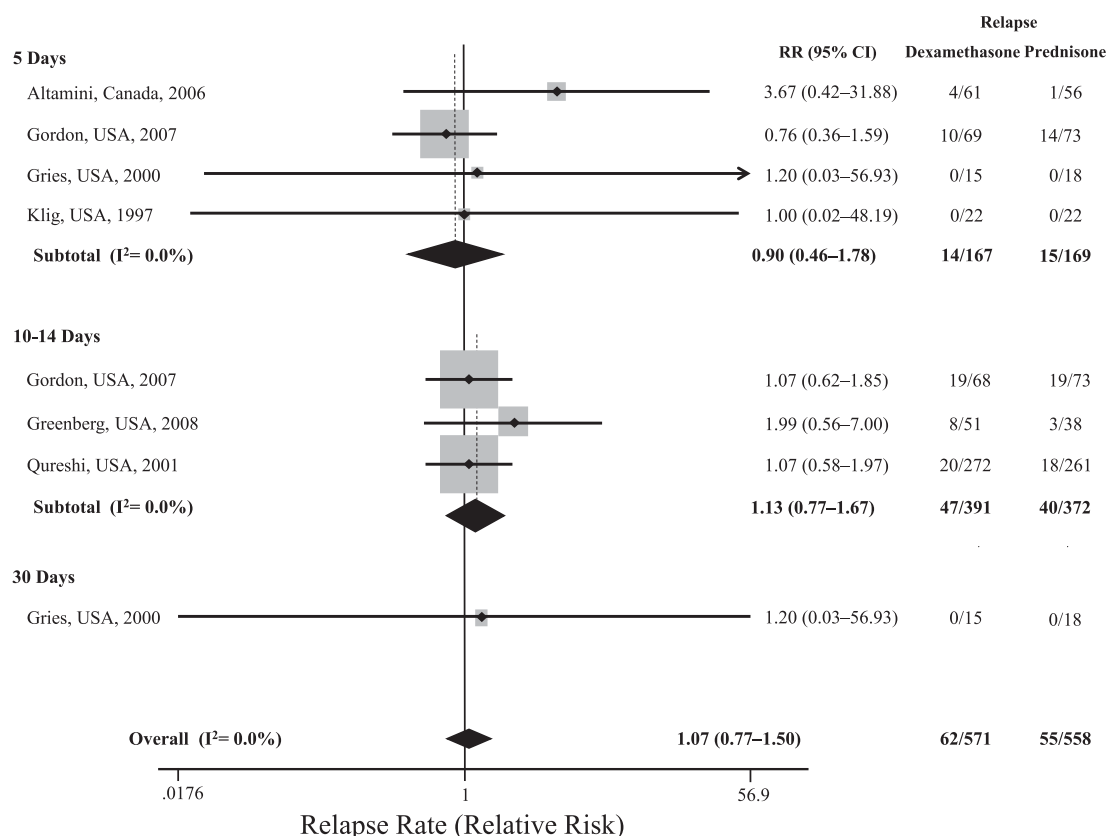
HSV, herpes simplex virus; max, maximum; RSV, respiratory syncytial virus; TB, tuberculosis.

^a First dose of medication provided in the ED.

TABLE 2 Cochrane Risk of Bias Quality Assessment

Study	Allocation Sequence Adequate	Allocation Concealed	Blinding of Participants	Blinding of Outcomes	Outcome Data Adequately Addressed	Free From Selective Outcome Reporting	Free From Other Problems
Altamimi ¹¹	Yes	Yes	Yes	Yes	No	Unclear	Yes
Gordon ¹²	Yes	Yes	No	No	Yes	No	Yes ^a
Qureshi ¹⁶	No	No	No	No	Yes	Unclear	Yes ^a
Greenberg ¹³	Unclear ^a	Unclear ^a	Yes	Unclear	No	Unclear	Yes
Gries ¹⁴	Unclear	Unclear	No	No	Yes ^a	Unclear	Yes
Klig ¹⁵	Unclear	Unclear	No	No	Yes	Unclear	Yes

^a Disagreement between reviewers.

**FIGURE 2**
Relapse rates.

patients discharged to home from the ED. Fixed effects methods increase the chance of finding differences. Finding no differences in a fixed effects model is a more conservative choice when comparing 2 different treatment options. The pooled results failed to demonstrate a statistically significant difference between the 2 therapies for the primary outcome of relapse rate to clinic, ED, or hospitalization, suggesting that the 2 therapies are equivalent.

Our decision to combine studies with different routes and dosing of dexamethasone

was an effort to increase generalizability. A subgroup analysis failed to show statistically significant differences regardless of the follow-up periods. The 4 studies that reported 5-day follow-up relapse rates all used a single dose of IM or PO dexamethasone.^{11,12,14,15} Five days was the most common follow-up duration and is the most clinically relevant period in which to detect treatment failure. This is supported by the fact that 5-day courses of oral corticosteroids have not been shown to be superior to 3-day courses for outpatient management of children with

acute exacerbations.¹⁷ There was no difference detected in studies reporting recurrence rates at 5, 10 to 14, or 30 days' follow-up.

Significantly fewer patients receiving dexamethasone vomited in the ED or at home after discharge. This finding has clinical significance for improving patient and parental satisfaction. The lower rate of vomiting with dexamethasone possibly reflects a difference in palatability that has been shown in previous studies.^{18,19} However, the group of studies that used oral dexamethasone

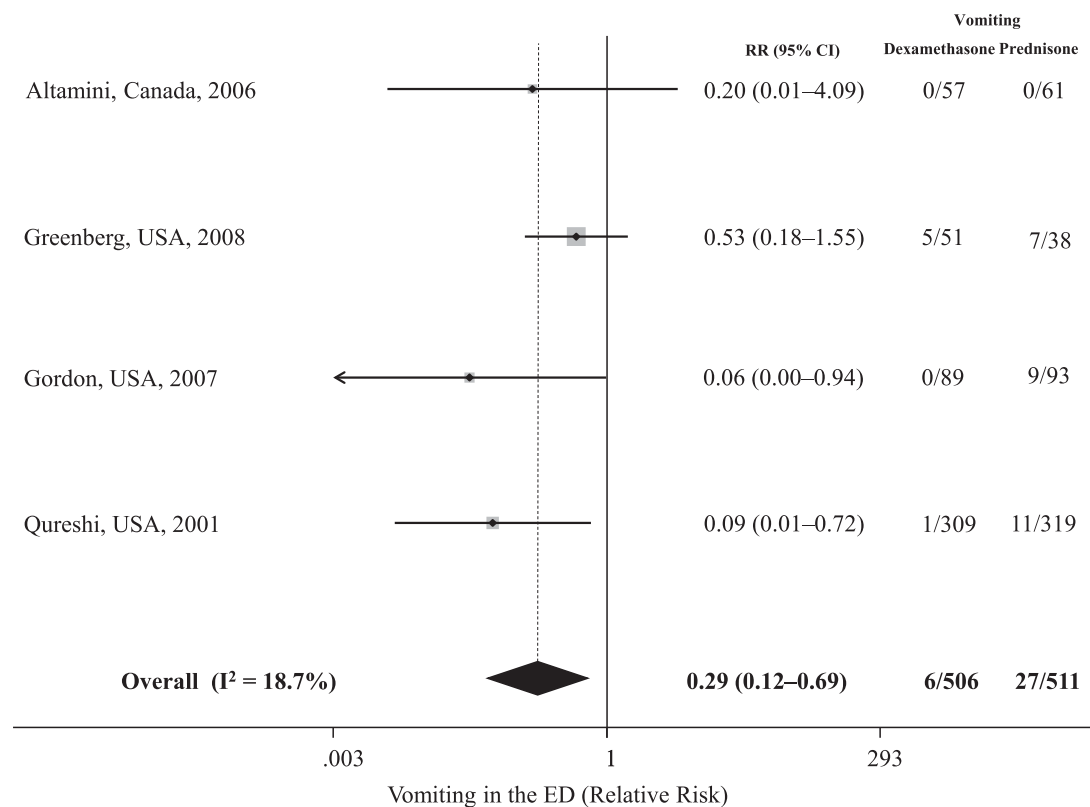


FIGURE 3
Vomiting in the ED.

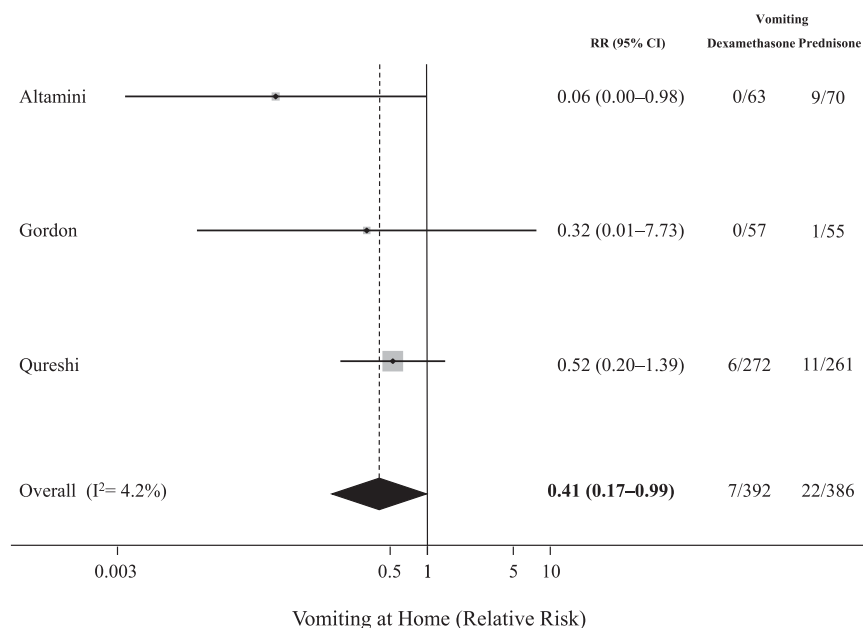


FIGURE 4
Vomiting at home.

was a heterogeneous group in that each used a different preparation for their oral medications. Additionally, single or 2-dose regimens may increase

compliance with systemic corticosteroid administration in acute asthma exacerbations compared with longer treatment courses.

There are potential limitations to this analysis, including publication bias and study quality. A systematic and comprehensive search of the published literature, as well as trial registries, was conducted to avoid bias. Two additional unpublished studies were identified. Attempts to contact the first and corresponding authors for all unpublished study results were unsuccessful in obtaining additional data for the meta-analysis. Unpublished clinical trials are more likely to confirm the null hypothesis and would support our pooled estimate for the primary outcome of interest. To further address possible study selection bias, we used 2 independent reviewers, had clear inclusion and exclusion criteria, and excellent interrater agreement. An additional limitation is that the paucity of trials made it difficult to examine important potential differences. For example, we were unable to address

whether IM and PO dexamethasone are equally effective, whether a single oral dexamethasone dose is equivalent to multiple doses, and whether there are differences in efficacy and palatability between different formulations of oral

prednisone/prednisolone. Furthermore, all our results are based on ED-based studies, and it is unclear whether this would translate to the ambulatory clinic setting. Future research should focus on these important questions.

Based on our findings, emergency physicians should consider single or 2-dose dexamethasone regimens over 5-day prednisone/prednisolone regimens for the treatment of acute asthma exacerbations.

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