Dexamethasone Compared to Prednisone for the Treatment of Children With Acute Asthma Exacerbations

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Abstract: Systemic corticosteroids are recommended in clinical practice guidelines for the treatment of acute asthma exacerbation based on evidence demonstrating reduced hospitalizations and improved outcomes after administration in the emergency department. Although prednisone and related oral preparations have been recommended previously, researchers have assessed dexamethasone as an alternative based on its longer biologic half-life and improved palatability. Systematic reviews of multiple small trials and 2 larger trials have found no difference in revisits to the emergency department compared to prednisone for dexamethasone given either as an intramuscular injection or orally. Studies of oral administration have found reduced emesis for dexamethasone compared to prednisone both in the emergency department and for a second oral dose, typically given 24 to 48 hours later. Studies assessing a single dose of dexamethasone have found equivalent improvement at follow-up but with some evidence of increased symptoms and increased need for additional corticosteroids compared to multiple doses of prednisone. Future research could further assess dexamethasone dose, formulation, and frequency and measure other related adverse effects such as behavior change. Consideration of baseline differences within the heterogeneous population of children requiring acute care for asthma may also guide the design of an optimal dexamethasone regimen.

Key Words: asthma, corticosteroids, dexamethasone, prednisone, prednisolone

(*Pediatr Emer Care* 2018;34: 53–60)

TARGET AUDIENCE

Physicians, nurse practitioners, and other providers who care for children with acute asthma exacerbations in a hospital or primary care setting.

LEARNING OBJECTIVES

After completing this CME activity, readers should be better able to:

- Describe the current published literature supporting the efficacy of corticosteroids for treating acute asthma during childhood.
- Compare the dosing, efficacy, and adverse effects of prednisone and dexamethasone for the treatment of acute asthma.
- Apply available evidence on corticosteroid treatment for acute asthma to design an appropriate emergency department treatment protocol.

OVERVIEW

Effective treatment with corticosteroids is a key component of high-quality care for children presenting to the emergency department (ED) for acute asthma exacerbation. Asthma is a leading cause of pediatric hospitalization, and systematic reviews of clinical trials have demonstrated a clear effect of corticosteroids on reducing admission and other measures of acute severity.[1] The anti-inflammatory effects of corticosteroids are synergistic with beta-agonist bronchodilators, and early clinical trials demonstrated that corticosteroids could have an effect within 2 to 4 hours.[2] When quality improvement projects have translated these findings and improved timeliness of corticosteroid treatment in practice, they have observed subsequent reductions in hospitalization rates and ED length of stay.[3] The National Asthma Education and Prevention Program (NAEPP) guidelines published by the National Institutes of Health recommend corticosteroids for "moderate or severe exacerbations or for patients who fail to respond promptly and completely to short-acting beta-agonist treatment."[4]

Despite the clear benefit of corticosteroids in ED asthma treatment, considerable uncertainty exists around the optimal formulation, dose, and duration of treatment. Published ED pathways commonly include a course of prednisone or prednisolone at 2 mg/kg for 5 days, based on early studies in which these doses were chosen somewhat arbitrarily.[2,5] As noted in the NAEPP guidelines, few comparative studies have assessed these regimens, and some evidence suggests that lower doses of 1 mg/kg may be as effective.[1] In addition, the population of patients presenting to the ED is heterogeneous, ranging from older children with chronic poorly controlled airway inflammation to young children with intermittent viral-induced wheezing. Children with poorly controlled asthma may require longer steroid courses and addition of inhaled corticosteroids, which both have been associated with improved asthma outcomes after asthma hospitalization.[6] For young children with intermittent asthma the evidence is less clear. Corticosteroids are not recommended for infants and toddlers with a first episode of viral bronchiolitis, and some researchers question efficacy of steroids in toddlers and with recurrent wheezing.[7] For these reasons, although "standard" courses of prednisone have been incorporated into treatment protocols, there is plenty of opportunity to improve the use of these medications through further research.

In recent years, studies have focused on use of dexamethasone as an alternative to prednisone. This research has been driven by recognition of the limitations of prednisone related to nonadherence, palatability, and other considerations. Studies of prescription filling in Medicaid populations have measured rates as low as 45%, with low rates of adherence even when prescriptions are filled.[8] If steroid prescriptions are commonly not being used after an ED visit, a longer acting preparation may be desirable. Palatability of oral prednisolone solutions is poor, even with newer, more costly preparations, with emesis rates ranging from 2% to

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The authors, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

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ISSN: 0749-5161

18%.[9,10] Dexamethasone offers the potential of an inexpensive, palatable corticosteroid with a longer effective action than prednisone. Over the past 2 decades, trials have compared different regimens of dexamethasone, starting with long-acting intramuscular preparations and moving to single-dose oral regimens. Results of these trials have been translated into clinical practice in many EDs. This review will summarize this active area of research with practical application for the provider or pediatric emergency care.

PHARMACOLOGY OF CORTICOSTEROIDS

The class of corticosteroids encompasses cortisol and its synthetic derivatives.[11] Cortisol is a hormone excreted by the adrenal cortex. The synthetic analogs include prednisolone, prednisone, methylprednisolone, and dexamethasone, among others.[11] Cortisol and its synthetic derivatives are typically used for their anti-inflammatory and immunosuppressant effects related to glucocorticoid activity, although mineralocorticoid effects are also variably present depending on the agent.[11] Corticosteroids have been shown to decrease inflammation in a multitude of ways including decreased production of inflammatory mediators, reversal of increased capillary permeability, and suppression of the immune system by reduction of activity and volume of lymphocytes.[11,12]

The long half-life of dexamethasone compared to prednisone refers to both plasma half-life and biologic half-life. Plasma half-life is the time that elapses before one-half of the serum concentration of a drug is eliminated from the body.[11] It reflects the rate of metabolism of the corticosteroid by the liver and is related to the duration of activity in the body.[11] The plasma half-life of dexamethasone is more than 300 minutes compared to more than 200 minutes for prednisolone and methylprednisolone.[11] Additionally, the plasma half-life has been shown to generally correlate with the relative anti-inflammatory potency of each corticosteroid (Table 1).[11]

Biologic half-life refers to time required for an agent to lose half of its biologic activity. For glucocorticoids, this is usually assessed by measuring the duration of hypothalamic-pituitary-adrenal (HPA) suppression.[11] Most studies evaluating dexamethasone for asthma exacerbations reference biologic half-life when determining comparative treatment courses of 1 to 2 doses of dexamethasone compared to 3 to 5 days of prednisone/prednisolone. The biologic half-life of prednisolone and methylprednisolone is approximately 12 to 36 hours compared to the biologic half-life of dexamethasone at 36 to 54 hours.[11] Onset of biologic effect is as important as duration in the ED setting, as admission decisions are typically made within several hours. Studies have demonstrated reduced admission rate and length of stay when corticosteroids are administered within the first hour after presentation.[3] Importantly,

TABLE 1. Oral Steroid Preparations and Their Pharmacologic Properties

Corticosteroid	Preparations Used for Asthma*	Strength	Dose	Flavor	Anti-inflammatory Potency (Compared to Cortisol)[12]	Plasma Half-life (minutes)[11]	Biologic Half-life (hours)
Prednisone	Concentrate (Prednisone Intensol)	5 mg/mL	1–2 mg/kg/d (max 60 mg/d) for 3–10 days	None	4	>200	12–36
	Solution	5 mg/5 mL		None			
	Tablet	1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg		NA			
Prednisolone	Solution: Generic Millipred, Pediapred, Veripred	15 mg/5 mL, 25 mg/5 mL, 5 mg/5 mL 10 mg/5 mL, 5 mg/5 mL 20 mg/5 mL		Grape raspberry	4	>200	12–36
	Syrup: generic	15 mg/5 mL					
	Tablet: Millipred	5 mg					
	Oral dispersible tablet: Generic, Orapred ODT	10 mg, 15 mg, 30 mg		Grape			
Methylprednisolone succinate	Injection: SOLU-medrol	(Per vial) 40 mg, 125 mg, 500 mg, 1000 mg, 2000 mg				>200	
Dexamethasone	Concentrate: Dexamethasone Intensol	1 mg/mL	0.3–0.6 mg/kg/dose (max 8–16 mg/dose) for 1–2 doses every 24–48 hours	None	25	>300	36–54
	Elixir: generic	0.5 mg/5 mL		Raspberry			
	Solution: Generic	0.5 mg/5 mL		None			
	Injection (given PO)	4 mg/mL, 10 mg/mL		None			
	Tablet: Generic	0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg		None			
	Intramuscular injection: Dexamethasone LA (dexamethasone acetate)	Manufacturer discontinued		None			

*Preparations listed refer to both brand and generic products.

dexamethasone has an onset of action of 1 to 2 hours after an enteral dose, which is comparable to that of enteral prednisolone/prednisone (1–2 hours) and intravenous methylprednisolone (1 hour).[13]

Adverse effects associated with steroids include osteoporosis, gastric ulceration and hemorrhage, pancreatitis, central nervous system effects including psychosis, hypertension, edema, precipitation of diabetes mellitus, hyperlipidemia, growth failure, and suppression of the immune and HPA systems.[11] Most of these are typically associated with long courses of corticosteroids; however, even short courses may have deleterious effects. Researchers have most thoroughly investigated the potential for short steroid bursts to cause HPA suppression. One study found that cortisol levels returned to baseline within 10 days after a 5-day course of 2 mg/kg per day prednisone. A second study showed that after a month of 2 mg/kg per day prednisone, morning cortisol levels returned to normal levels within 9 days after discontinuation. Both studies concluded that the HPA axis of children recovers rapidly from short-term, high-dosage glucocorticoid administration.[14,15]

DEXAMETHASONE VERSUS PREDNISONE/PREDNISOLONE IN THE LITERATURE

Multiple studies have explored the comparative effectiveness of dexamethasone and prednisone/prednisolone for the treatment of acute asthma. Several systematic reviews have found dexamethasone to be comparable to prednisone for clinical outcomes, with potential benefits in adverse effects such as emesis.[1,9] Keeney et al performed a systematic review and meta-analysis evaluating the use of dexamethasone compared to oral prednisone for pediatric patients presenting to the ED with asthma, focusing on return visits and hospital readmissions as primary outcomes. They found no significant difference between these corticosteroids in revisits within 5 days from initial presentation (relative risk [RR], 0.9; 95% confidence interval [CI], 0.46–1.78), the time point most commonly assessed in these studies. A Cochrane review performed by Normansell et al[1] comparing revisits in patients who received prednisolone or dexamethasone also showed no significant difference for pediatric patients (odds ratio, 0.85 [95% CI, 0.54–1.34] (Fig. 1). Meyer et al[16] also demonstrated no significant difference between dexamethasone and prednisone in unscheduled revisits (risk difference, 0.02; 95% CI, 0.02–0.05) or symptomatic improvement (risk difference, 0.98; 95% CI, 0.71–1.35).

Although the overall results have been consistent, studies have varied widely in the preparations and doses of corticosteroids evaluated (Table 2). The earliest studies compared prednisone in a standard 2 mg/kg oral dose to several different preparations of intramuscular dexamethasone,[3,4] Gries et al used dexamethasone acetate, a long-acting preparation with duration of action of 1 to 3 weeks. This study found similar clinical improvement in both prednisone and dexamethasone groups over 5 days, with no significant differences noted in asthma scores throughout the study period. Patients younger than 2 years were included in this study, however, introducing the possibility of misclassification with patients with bronchiolitis. Klig et al compared a 0.3 mg/kg dose of intramuscular dexamethasone (maximum, of 15 mg) to a 3-day treatment course of prednisone at 2 mg/kg per day in a study of 42 children. Patients in both groups were evaluated at 5 days from treatment, and all were found to have symptomatic improvement.[3] A later, similar study, by Gordon et al, used a dose of 0.6 mg/kg of intramuscular dexamethasone (maximum, 15 mg) and found no difference in asthma scores or revisits during the 4 days after ED discharge (difference, 1.8%; CI, −5.4% to 9.0%). All of these studies were small pilot studies with limited power to detect a difference and wide CIs for the results.

Larger studies have compared oral dexamethasone to oral prednisone and found similar results. Qureshi et al enrolled 628 children into a trial comparing a 2-dose oral dexamethasone regimen (0.6 mg/kg per dose, maximum of 16 mg) to a 5-day course of low-dose prednisone (2 mg/kg in the ED followed by 1 mg/kg daily at home). Rates of relapse within 10 days were comparable between dexamethasone and prednisone, 7.4% vs 6.9%, respectively.[9] Rather than providing all patients with medication at discharge, only those in the dexamethasone group were given their additional doses, resulting in a higher rate of noncompliance in the prednisone group that could have biased the results. Greenberg et al found concordant results in a similarly designed but smaller study with higher revisit rates and a trend toward higher rates in the dexamethasone group (16% vs 8% with prednisone, $P = 0.27$).

Fewer studies have assessed a single oral dose of dexamethasone. Altamimi et al assessed one dose of the intravenous solution given orally (0.6 mg/kg to a maximum of 18 mg) versus 1 mg/kg per day of prednisone given in the ED and twice per day at home for 5 days. This study, unlike the previous ones, included admitted patients and assessed the number of days to improvement in an asthma severity score or peak expiratory flow measurements. The average time to return to baseline was 5 days in each group, with no significant differences in this or other outcomes.

Most recently, Cronin et al assessed a single oral dose of dexamethasone at 0.3 mg/kg (maximum, 12 mg). The comparison prednisone dose was also lower than other studies at 1 mg/kg per day for 3 days. The primary outcome was the Pediatric Respiratory

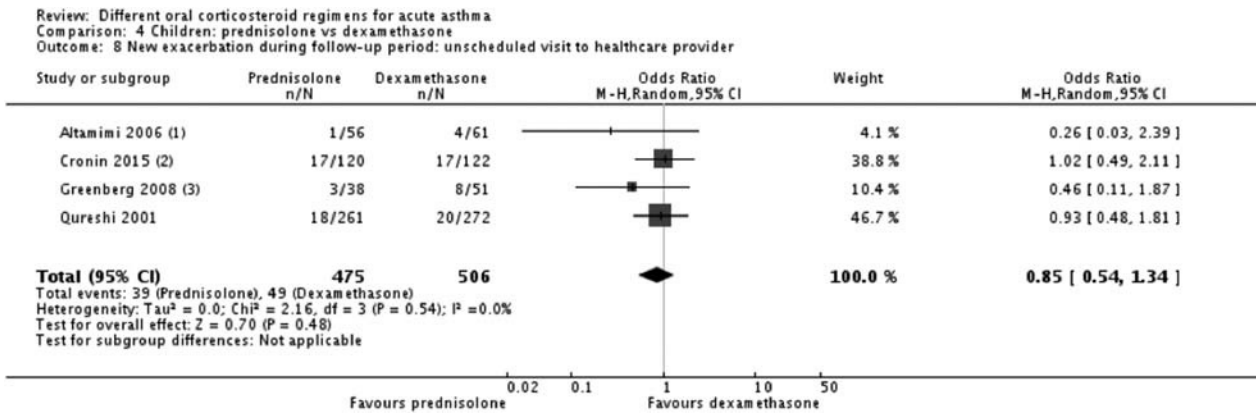

FIGURE 1. Forest plot from Normansell et al[1] Cochrane review comparing revisit rates for oral dexamethasone versus prednisone for acute asthma.

TABLE 2. Summary of Key Studies Comparing Dexamethasone and Prednisone for Acute Asthma

	Prednisone	Dexamethasone	Primary Outcome	Patient Population	Follow-up Duration	Findings
Klig et al,[17] 1997	Prednisone: 2 mg/kg/d × 3 days Max: 100 mg	Dexamethasone 0.3 mg/kg Max: 15 mg IM single dose	Clinical asthma score (Pulmonary Index score) and relapse rate	3–16 yrs	5 days	Dexamethasone is comparable treatment for mild to moderate pediatric asthma
Gries et al,[18] 2000	Prednisone: 2 mg/kg/d for 5 days Max: 40 mg	Dexamethasone acetate* 1.7 mg/kg Max: 36 mg IM single dose	Clinical asthma score Tolerance score	6 months to 7 years	14 days	Equally effective for mild to moderate exacerbations
Qureshi et al,[19] 2001	Prednisone 2 mg/kg × 1, 1 mg/kg/d × 4 days Max: 60 mg	Dexamethasone 0.6 mg/kg Max: 16 2 oral doses given as tablet	10-day relapse rate	2–18 years of age	11–14 days	Dexamethasone has similar efficacy and fewer adverse effects
Altimimi et al,[20] 2006	Prednisone 2 mg/kg/d for 5 days Max: 30 mg	Dexamethasone IV solution given orally, 0.6 mg/kg Max: 18 mg Single oral dose	Pediatric Self Assessment Score and Peak expiratory flow rate	2–16 years of age Included admitted patients	5 days	Dexamethasone is noninferior to prednisone
Gordon et al,[21] 2007	Prednisone 2 mg/kg/d for 5 days Max: 50 mg Patients who did not tolerate prednisone were treated with IV solumedrol before discharge	Dexamethasone phosphate 0.6 mg/kg Max: 15 mg IM single dose	Clinical asthma score (adaptation of pulmonary score)	18 mo to <7 years	14 days	No clinically significant difference for moderate exacerbations
Greenberg et al,[22] 2008	Prednisone 2 mg/kg/d for 5 days Max: 80 mg	Dexamethasone 0.6 mg/kg Max: 16 mg 2 oral doses given as capsules	10 day relapse rate	2–18 years of age	10 days	No difference in relapse rate
Cronin et al,[23] 2016	Prednisone 1 mg/kg/d for 6 days Max: 40 mg	Dexamethasone 0.3 mg/kg Max: 12 mg 1 oral dose given as tablets	Mean Pediatric Respiratory Assessment Measure score at day 4	2–16 years of age	14 days	Dexamethasone was noninferior to prednisone for treatment of acute asthma. Patients who received dexamethasone were more likely to require further treatment with steroids

*Not available for use in the United States.

IM, intramuscular.

Assessment Measure score assessed at day 4 after the ED visit, which was comparable between the 2 groups. However, 13.1% of patients who received dexamethasone required further treatment with systemic steroids within 14 days of enrollment compared to 4.2% of those in the prednisolone group (absolute difference, 8.9%; CI, 1.9%–16%). Additionally, patients in the dexamethasone group required more bronchodilators on days 4 and 5, when an observed difference between the groups might be expected.

These studies assessed a wide variety of adverse effects, including emesis, behavior change, and adrenal suppression. The study by Gries et al, which was unique in its use of dexamethasone acetate, used a formal tolerance score that evaluated both refusal and vomiting. Clinic visits were also used to assess for blood pressure changes, atrophy at the injection site, or weight gain. On day 14, adrenal function was assessed using a first-morning urine. Personality changes in both groups were assessed using symptom diaries. This study concluded that prednisone is poorly tolerated; in contrast, no significant adverse effects were noted for those who received dexamethasone.[4] Gordon et al also used intramuscular dexamethasone and assessed local injection effects such as swelling, tenderness, and erythema, which were present in up to 6% of patients. Thirteen percent of patients who received prednisone had at least one episode of vomiting the medication at home.

Among the oral dexamethasone studies, Qureshi et al assessed frequency of vomiting and observed a 3% emesis rate in the prednisone group compared to 0.3% for those who received dexamethasone ($P = 0.008$). Two percent of those who received dexamethasone vomited at home, as opposed to 4% of those who received prednisone. Altimimi et al measured abdominal pain, vomiting, headache, palpitations, and excessive urination in both groups with no significant mean difference noted. Greenberg et al measured emesis in the ED as a secondary outcome; 18% of patients in the prednisone group and 10% of patients in the dexamethasone group vomited in the ED, which was not a significant difference ($P = 0.24$). In the study by Cronin et al, nearly 6% of patients who received prednisone vomited within 30 minutes of the dose in the ED, compared to none in the dexamethasone group.

The only consistent trend across studies was a reduction in emesis. In their systematic review, Keeney et al[9] observed a decreased likelihood of vomiting both in the ED (RR, 0.29; CI, 0.12–0.69) and at home (RR, 0.32; CI, 0.14–0.74). Normansell et al[1] demonstrated a similar trend toward decreased odds of vomiting in patients who received dexamethasone (odds ratio, 3.05; 95% CI, 0.88–10.55). The most robust assessment of adrenal suppression was performed by Gries et al who used an atypical formulation and did not observe a statistically significant difference between the groups.

PRACTICAL APPLICATIONS AND FUTURE DIRECTIONS

Given the evidence base supporting dexamethasone as a comparable alternative to prednisone with better tolerance, many EDs have implemented it as part of standard asthma treatment protocols.[24,25] Future studies could evaluate the implementation of this change and measure the impact on outcomes. In addition to revisits and symptom scores, important outcomes to assess could include adverse events, cost, and parental preference. One cost effectiveness study using a decision analysis model found potential cost savings from using dexamethasone instead of prednisone.[26] A survey of parents at a single site documented preference for dexamethasone.[27] Further evaluation of these results in other populations after broader implementation would help support translating current research findings into national asthma guidelines.

One area for further exploration is the optimal dose and duration for dexamethasone. Multiple studies have used 0.6 mg/kg as the weight-based dose, although this corresponds to 3.8 mg/kg of prednisone using typical published equivalency ratios, almost twice the standard asthma dose. As previously described, the NAEPP guidelines note that there is no clear rationale for higher steroid doses being more effective, with doses of 1 mg/kg being considered acceptable (NAEPP). Studies in croup have found that lower doses of dexamethasone down to 0.15 mg/kg are as effective as the initial standard 0.6 mg/kg dose.[28] The most recent asthma study, by Cronin et al, used a 0.3 mg/kg/dose. Although some evidence of increased symptoms was observed compared to 1 mg/kg of prednisone, the study also used a single dexamethasone dose. As previously reviewed, the largest study of dexamethasone by Qureshi et al used a 2-dose regimen. Further large studies using a single dose would provide more evidence for efficacy of this approach. It is likely that other factors may need to be studied to fully explore this issue. Children with severe asthma or recent corticosteroid doses as well as concurrent illnesses and significant comorbidities were excluded from many of the studies of dexamethasone and may require a longer course.[18,19,21–23] Little evidence exists on the use of dexamethasone for patients hospitalized for asthma, although one retrospective review suggested that it may be used effectively for some patients in that setting.[29] In addition, the large population of young children with intermittent wheezing triggered by a viral infection are another subgroup worthy of study. Such studies should include measurement of adverse effects, such as behavioral changes, which may be an important consideration in deciding an optimal dose. In the absence of this evidence, one approach may be to prescribe or dispense a second dexamethasone dose and instruct the family to administer it only if the child has not improved.

Another key practical issue that requires further study is the optimal formulation of dexamethasone to administer. As previously noted, a variety of formulations have been used in studies, including intramuscular and oral preparations. Given the overall excellent tolerance of oral administration, a clear indication for an intramuscular injection is lacking. One approach to oral administration, used by Altimimi et al, has been to give the intravenous formulation of dexamethasone orally, mixed with syrup. Although well tolerated and supported by evidence for efficacy, many hospital pharmacies will not approve off-label use of an intravenous solution given orally when there is a commercial oral alternative. Unfortunately, the commercial oral solutions of dexamethasone are dilute, requiring high dose volumes, and not well tolerated. Other studies, including Qureshi et al and Cronin et al, have used oral tablets crushed and administered with applesauce or chocolate pudding. Dexamethasone tablets are readily available, easily crushed, and inexpensive; to accommodate administration, the dose can be rounded to 2 mg increments. Treatment protocols have incorporated straightforward weight-based categories to standardize this process.[24]

In summary, current published studies support the equivalence of dexamethasone compared to prednisone for the treatment of asthma in children well enough to be discharged from the ED. Oral dexamethasone seems to be well tolerated, with reduced emesis compared to oral prednisone. Many questions remain about the optimal dose, duration, and relative adverse effects of dexamethasone regimens. Many EDs have chosen to incorporate dexamethasone into standard treatment protocols using tablets or liquid preparations and focusing on early administration to achieve maximal benefit. Future research can assess implementation of these changes and determine an optimal approach for the large and heterogeneous population of children presenting with acute asthma exacerbation.

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