

What Is the Dose of Systemic Corticosteroids for Severe Asthma Exacerbations in Children?

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THE QUESTION OF THE most appropriate dose of systemic corticosteroids for the treatment of acute exacerbations of asthma has been unanswered for years. Obviously, one needs to give enough to be effective but not in excessive doses that might produce adverse effects. The current NHLBI, National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3) guidelines recommend 1 mg/kg/day in 2 divided doses of prednisone equivalent until the patients peak expiratory flow (PEF) is 70% of predicted normal for children coming to the emergency department or who are hospitalized; and 1–2 mg/kg/day prednisone or prednisolone equivalent with a maximum 60 mg daily for 3–10 days for outpatient bursts.¹ Why the difference? Why a possibly higher dose for outpatients? The previous guidelines recommended higher doses for hospitalized patients (1 mg/kg every 6 h for 48 h, then 1–2 mg/kg/day with a maximum of 60 mg in 2 divided doses until PEF reached 70% of predicted normal.² Why was this recommendation changed?

A brief history of the EPR recommendations is in order and is diagrammed in the figure. On review of the literature for the 1991 EPR1, only 3 randomized, double-blind, placebo-controlled trials (DB-RCT) in a total of 133 children hospitalized for severe acute asthma were found.^{3–5} Two studies demonstrated somewhat better outcomes in the corticosteroids groups (improved PaO₂ at 24 h and no patients requiring breaking the study code and given open label corticosteroids³; and more rapid improvement in forced expiratory flow between 25% and 75% of forced vital capacity).⁴ The prednisolone equivalent doses used were 1.75 mg/kg loading dose intravenously followed by a continuous infusion of 44 mg/kg/day³ and a 2 mg/kg loading dose intravenously followed by 1 mg/kg every 6 h.⁴ The third trial in 39 children who received intravenous hydrocortisone every 4 h in the first 24 h at a prednisone equivalent dose of 4.5 mg/kg/day and then prednisone 1 mg/kg twice daily for the duration of hospitalization reported no difference in hospital length of stay or PEF at discharge.⁵ However, they did report significantly fewer relapses in the following 3 months and marginally greater PEFs on the second day of therapy. An additional DB-RCT in 16 inpatients of a residential facility found more rapid improvement in PEFs and decreased

need for nebulized bronchodilators with 2 mg/kg/day prednisone divided every 6 h for 72 h.⁶ One non-blinded RCT in only 19 children receiving hydrocortisone intravenously every 6 h in a prednisone equivalent dose of 7 mg/kg/day found no benefit for the corticosteroid.⁷ A DB-RCT of a single dose of 1.5–2 mg/kg prednisone (based on weight as patients received either 30 mg or 60 mg based on age) or placebo in 140 children reported significantly more patients discharged at 4 h after the intervention (30% versus 3%) and greater improvement in clinical scores and PEF.⁸ The only DB-RCT non-placebo dose-ranging study compared 20 mg/kg/day versus 200 mg/kg/day prednisone equivalent divided every 6 h.⁹ Two outpatient DB-RCTs encompassing 86 children reported using doses of 1–2 mg/kg/day prednisolone in varying schemes (tapering doses for 3 days and constant dose daily for 7 days) reported improved symptom scores and PEFs and reduced hospitalizations and decreased relapse within 1–2 weeks.^{10,11} While a smaller trial of 28 patients using a tapering dose beginning at 1–2 mg/kg/day and tapering by 4 mg/day over 8 days reported nonsignificant differences favoring prednisone,¹² 2 of the studies gave the same milligram dose to all patients so the milligram per kilogram dose varied based upon weight of the patients and was estimated using average weight for age. The frequency of dosing was either not recorded,¹⁰ given once in the morning,¹² or twice daily.¹¹

Prior to the 1997 EPR2, only 2 additional DB-RCTs in hospitalized patients were published and they only assessed single doses of prednisone versus placebo.^{13,14} In the first study of 70 children more patients who received prednisone 2 mg/kg were ready for discharge at 4 h, the primary outcome variable than those receiving placebo (46% versus 18%).¹³ Three additional DB-RCTs evaluated single-dose therapy in infants and children (*N* = 237 total) presenting to the emergency department with acute asthma.^{15–17} One trial administered intramuscular methylprednisolone 4 mg/kg, one 2 mg/kg intravenous methylprednisolone, and the other oral prednisone 2 mg/kg. Two demonstrated a reduction in hospitalizations but it only reached significance in the subset of more severe patients at presentation in the infants that received intramuscular therapy, while the intravenous study

showed no benefit. Two additional DB-RCTs of single oral doses prednisone ($N = 145$ total) administered at home (2 mg/kg) or in the clinic (1–2 mg/kg depending on weight) demonstrated modest benefits for the prednisone.^{18,19} Based upon these additional studies since the EPR1 small changes in dosage were recommended in the 1997 EPR2 (Fig. 1).

An extensive review of the literature for the 2007 EPR3 identified 2 meta-analyses of systemic corticosteroids in hospitalized children with asthma, one by the Cochrane Library, and one extensive, subjective review of systemic corticosteroids for acute asthma in children but no further placebo-controlled DB-RCTs.^{1,20–22} However, 2 trials exploring mode of administration and dosage were found.^{23,24} In the first 66 children 2–18 years old were administered either methylprednisolone (1 mg/kg) intravenously every 6 h or prednisone 2 mg/kg orally twice daily.²³ No difference was found for length of hospital stay or any clinical outcomes between intravenous and oral therapy similar to

that reported in adults. In the second 98 children received either 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg (maximum 60 mg) prednisolone once daily for the duration of hospitalization and an additional 3 days following discharge.²⁴ No differences in duration of hospitalization or rate of improvement in clinical scores, PaO_2 , or PEF were detected between treatments. Thus, we have the first study suggesting that lower doses than the usual 1–2 mg/kg daily are effective. Both meta-analyses suggested that systemic corticosteroids are more effective than placebo in hospitalized children with asthma.^{20,21} The Cochrane report stated that significantly more patients who received corticosteroids could be discharged within 4 h with a number needed to treat (NNT) of 3.²⁰ However, this finding is based upon only 2 studies including 210 patients total.^{8,13} Clinicians should feel comfortable with this recommendation because some single-dose studies in the emergency department preventing hospitalization provide confirmation for this finding.^{14–16}

Informative Trials*

Four inpatient DB-PC-RCT ($N = 2,733$ total)^{3–5,8}

Doses: 1.75 mg/kg LD, then 44 mg/kg/day infusion
2 mg/kg LD, then 1 mg/kg every 6 h
4.5 mg/kg first 24 h then 1 mg/kg twice daily
1–3 mg/kg single dose



Recommendations

EPR1 (1991) Inpatient

1–2 mg/kg/dose every 6 h

Four outpatient DB-PC-RCTs ($N = 130$ total)^{6,10–12}

Doses: 0.5 mg/kg every 6 h for 3 days
2 mg/kg day 1, 1 mg/kg day 2, 0.5 mg/kg day 3
1–2 mg/kg/day in 2 doses for 7 days
32 mg/kg day 1 (0.8–2 mg/kg) then taper by 4 mg/day



EPR1 (1991) Outpatient

1–2 mg/kg/day in 1 or 2 doses for 3–5 days, reassess in 3 days



Two inpatient DB-PC-RCTs ($N = 128$ total)^{13,14}

Doses: 2 mg/kg single dose
1 mg/kg single dose



EPR2 (1997) Inpatient

1 mg/kg/dose every 6 h then 1–2 mg/kg/day

Three ED DB-PC-RCTs ($N = 237$ total)^{15–17}

Doses: 2 mg/kg single dose oral
4 mg/kg single dose intramuscular
2 mg/kg single dose intravenous



EPR2 (1997) Outpatient

1–2 mg/kg/day for 3–10 days

Two outpatient DB-PC-RCTs ($N = 145$ total)^{18,19}

Doses: 2 mg/kg single dose
1 mg/kg single dose



Two inpatient DB-RCTs plus 2 meta-analyses

Doses: 1 mg/kg every 6 h intravenously versus 2 mg/kg orally twice daily ($N = 66$)²³
0.5, 1.0, 2.0 mg/kg orally once daily ($N = 98$)²⁴



EPR3 (2007) Inpatient

1 mg/kg/day (max 60 mg) in 2 doses until PEF is 70% predicted

One outpatient DB-RCT ($N = 86$)²⁵

Doses: 1 mg/kg/day versus 2 mg/kg/day in 2 divided doses



EPR3 (2007) Outpatient

1–2 mg/kg/day (max 60 mg) for 3–10 days

FIG. 1. Schematic of National Asthma Education and Prevention Program's Expert Panel Report (EPR) corticosteroid recommendations and informative studies. *Those trials that determined recommendations. Abbreviations: DB, double-blinded; PC, placebo-controlled; RCT, randomized clinical trial; LD, loading dose; ED, emergency department; EPR, National Asthma Education and Prevention Program's Expert Panel Report.

The other main outcome was that children receiving corticosteroids had significantly fewer relapses within 1–3 months (NNT = 3). Again, this finding was based upon only 2 studies that included only 84 total patients.^{4,5} One new outpatient DB-RCT compared 5-day courses of either 1 mg/kg/day or 2 mg/kg/day (maximum of 60 mg) prednisone each administered in 2 divided doses in 86 children of 2–16 years old.²⁵ The primary outcome of this study was the behavioral effects recorded by questionnaire with resolution of asthma symptoms at 2 weeks a secondary outcome. No difference in resolution of asthma was noted but the higher dose produced significantly greater anxiety and aggressive behavior in the children. Since the publication of EPR3 a large DB-RCT ($N = 201$) in children 2–15 years old presenting to an emergency department and not hospitalized, a 3-day versus 5-day course of 1 mg/kg prednisone were compared.²⁶ The proportion of patients who were symptom-free at 7 days (main outcome) and pediatric asthma quality of life at days 7 and 14 was not different either by intention-to-treat or per-protocol (those who completed entire study) analyses. Interestingly, the patients continued to have resolution of symptoms after 5 days.

Systemic corticosteroids other than prednisone or prednisolone have been used for acute asthma exacerbations. There are differences in relative potency (receptor binding affinity), pharmacokinetics, and biological duration of action; however, these differences have yet to yield clinically meaningful differences in efficacy compared to standard doses of prednisone or prednisolone.^{27–32} Prednisolone and prednisone are essentially the same drug as prednisone is the prodrug that is converted to prednisolone. Methylprednisolone is slightly more potent than prednisolone with greater lung penetration, but as stated previously methylprednisolone given intravenously every 6 h is no more effective than prednisone at the same milligram per kilogram dose administered twice daily.²³ These agents are generally preferred over cortisone and hydrocortisone due to their minimal mineralocorticoid effects. Since the EPR2 a number of trials comparing dexamethasone to prednisone have been instigated primarily due to concerns of adverse effects (nausea and vomiting) with oral prednisone and prednisolone and looking for a more palatable alternative or a means of assuring compliance (intramuscular repository injections).^{28–33} The first was a comparison of nebulized dexamethasone sodium phosphate solution 1.5 mg/kg versus a single dose of prednisone 2 mg/kg in the emergency department with each followed by 2 mg/kg/day prednisone in 2 divided doses for 5 days after discharge from the emergency department in 111 children 1–17 years old.²⁸ As dexamethasone is well absorbed orally as well as through the lung, it is not topically selective. If one considers the delivery from nebulizers to be 10% of the amount placed in the nebulizer plus another 5%–10% swallowed, the systemic dose of dexamethasone was approximately 0.2–0.3 mg/kg or 1–2 mg/kg prednisone equivalent. They reported significantly less vomiting with the dexamethasone than the prednisone (0% versus 15%) and fewer 48 h post-discharge relapses (0% versus 16%) for dexamethasone treatment. There were no differences in hospitalization rate or improvement in symptom scores. Interestingly, within the dexamethasone group there was a higher percentage of patients hospitalized in those using a face mask (33%) versus those using a mouthpiece (8%), which is known to reduce aerosol delivery in

half. Whether this was due to difference in delivery or just and increased risk of hospitalization in younger patients is unknown. A small single-blinded RCT compared single-dose intramuscular depot dexamethasone acetate 1.7 mg/kg to oral prednisone 2 mg/kg/day in 2 divided doses for 5 days in 32 patients 0.5–7 years old.²⁹ No significant differences were found between therapies. The depot injection, which is no longer available, was estimated to have a 72-h duration so the doses were estimated based upon prednisone equivalence of 2 mg/kg/day for 3 days. Three of 17 children refused 75% of their doses of prednisone and another 4 missed 30%–50%.²⁹ Two additional single-blinded RCTs compared single-dose intramuscular dexamethasone phosphate (either 0.3 mg/kg or 0.6 mg/kg) to prednisone 2 mg/kg for 3 or 5 days in 168 total patients 1.5–16 years old presenting to the emergency department.^{30,31} No significant differences were found for any outcomes. A large non-blinded RCT in 533 children 2–18 years old presenting to an emergency department compared 1 dose of oral dexamethasone 0.6 mg/kg for 2 days and prednisone 2 mg/kg followed by 1 mg/kg/day divided in 4 doses (maximum 60 mg) daily for 5 days.³² No difference in clinical outcomes were apparent despite more vomiting and more non-compliant parents in the prednisone group. However, parents had to fill a prescription for the prednisone and were given the second dose of dexamethasone in the emergency department to take home. After publication of EPR3, a follow-up DB-RCT in 89 children 2–18 years old presenting to an emergency department comparing 2 daily doses of dexamethasone 0.6 mg/kg with 2 mg/kg of prednisone followed by 5 days of 1 mg/kg/dose twice daily where all patients received their home medications in the emergency department.³³ No differences were found for 10-day relapse (primary outcome) or vomiting in the emergency department (secondary outcome). Finally a DB-RCT compared a single dose of oral dexamethasone administered in the emergency department with prednisolone 2 mg/kg/day in 2 divided doses for 5 days in 110 children 2–16 years old.³³ No significant differences were found for admission rate, improvement in symptom, scores, and side effects. Although there were slightly more patients in the dexamethasone group with unscheduled returns to the emergency department and admissions after initial discharge, these were very few (4 versus 1) so the clinical relevance was uncertain.

Based upon this brief review of the literature, it might appear as though the initial questions are merely academic particularly as short courses or “bursts” of oral corticosteroids are considered safe. But how safe are they? Reports of steroid-induced myopathy have only been reported in association with high doses of systemic corticosteroids (16 mg/kg/day prednisone) equivalent that are unnecessary.³⁴ However, adverse behavioral and psychological effects can occur rather commonly (1 in every 5–9 children treated for 5 days) and this can be significantly reduced by using 1 mg/kg/day as opposed to 2 mg/kg/day.²⁵ A 5-day course of 2 mg/kg/day produces a significant blunting of peak cortisol response to hypoglycemia at 3 days following the course but not at 10 days.³⁵ However, 1 study suggested children receiving 4 or more short bursts in a year have abnormal responses and are at risk for adrenal insufficiency.³⁶ However, this was a small study with only 10 children receiving 3 or more bursts. A larger cross-sectional study in 48 children who had adrenal axis testing 1 month since their last burst

(1–2 mg/kg/day for a median of 5 days) found no lasting effects on the cortisol response.³⁷ They did report a transient decrease in serum osteocalcin at without an apparent effect on bone mineral density (BMD) in children with a median exposure of 4 bursts (3–11) in the preceding year. However, both their unexposed and exposed group had lower than normal BMD z-scores. More recently, a long-term (median 7 years) prospective study of BMD in the Childhood Asthma Management Program (CAMP) reported a dose-dependent decrease in bone mineral accretion in boys that was associated with an increase in developing osteopenia in those receiving on average 2 bursts per year (180 mg prednisone over 4 days).³⁸ This is consistent with a large population (37,562 children receiving oral corticosteroids, median duration 5 days/burst, 78% for respiratory disease)-based study from the UK.³⁹ Children receiving 4 or more bursts had significant increased fracture risks as did patient who received 30 mg daily or more during their bursts. Thus, there is evidence of potential long-term consequences to excessive number of bursts as well as the dose used for the burst. Therefore, using lower doses for shorter periods of time appears to be a worthwhile strategy.

Whether shorter courses with the higher potency dexamethasone will be safer is completely unknown at this juncture. While prednisone and dexamethasone have similar elimination rates, the biological duration of action of dexamethasone is about 48 h compared to 24 h for prednisone.²⁷ However, this is a measure of their effect on the adrenal axis and may not translate directly to the antiasthmatic effect. In a study of single-dose prednisone in acute asthma in children, the duration of effect on PEF appeared to be only 5–8 h.⁸ Dosing frequency has been inadequately assessed. Although a number of mechanistic pharmacodynamic studies suggest that low frequent dosing may provide more efficacy than large single doses, once daily and multiple daily dosing studies in acute asthma appear to result in similar outcomes.²⁷ However, many of the studies tend to exclude those patients with more severe asthma exacerbations. In addition, twice daily dosing may reduce the amount of gastrointestinal intolerance but this has also not been assessed in well-controlled trials. However, due to these above factors, dividing the daily dose into 2 doses may be a better option.

Palatability of prednisone/prednisolone is a recognized problem as they are very bitter and may contribute to vomiting and nonadherence; however, there is little quality objective data to quantify the problem.^{40–43} One study of 159 caregivers of children 2–9 years old stated that 26% had trouble giving the oral corticosteroids and that only 64% time were they adherent for the duration of therapy.⁴¹ Caregivers were concerned about adverse effects 60% of the time. In 1 study of 78 children 3–8 years old a liquid banana-flavored oral solution was better tolerated than crushed tablets with lemonade or custard, 23% of patients receiving crushed tablets withdrew from the study due to repeated vomiting.⁴³ Dexamethasone has been reported in an open label study to result in fewer withdrawals due to vomiting but in 2 blinded trials where patients swallowed capsules or mixed each as a powder into applesauce or pudding or received identical flavored syrups there was no difference in vomiting.^{32,33,42} Obviously the use of intramuscular injection insures the patient receives the drug but that requires administration in the clinic or emergency department.

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