A Randomized Trial of Single-Dose Oral Dexamethasone Versus Multidose Prednisolone for Acute Exacerbations of Asthma in Children Who Attend the Emergency Department

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Study objective: In acute exacerbations of asthma in children, corticosteroids reduce relapses, subsequent hospital admission, and the need for ß$_2$-agonist bronchodilators. Prednisolone is the most commonly used corticosteroid, but prolonged treatment course, vomiting, and a bitter taste may reduce patient compliance. Dexamethasone has a longer half-life and has been used safely in other acute pediatric conditions. We examine whether a single dose of oral dexamethasone is noninferior to prednisolone in the emergency department (ED) treatment of asthma exacerbations in children, as measured by the Pediatric Respiratory Assessment Measure (PRAM) at day 4.

Methods: We conducted a randomized, open-label, noninferiority trial comparing oral dexamethasone (single dose of 0.3 mg/kg) with prednisolone (1 mg/kg per day for 3 days) in patients aged 2 to 16 years and with a known diagnosis of asthma or at least 1 previous episode of ß$_2$-agonist–responsive wheeze who presented to a tertiary pediatric ED. The primary outcome measure was the mean PRAM score (range of 0 to 12 points) performed on day 4. Secondary outcome measures included requirement for further steroids, vomiting of study medication, hospital admission, and unscheduled return visits to a health care practitioner within 14 days.

Results: There were 245 enrollments involving 226 patients. There was no difference in mean PRAM scores at day 4 between the dexamethasone and prednisolone groups (0.91 versus 0.91; absolute difference 0.005; 95% CI −0.35 to 0.34). Fourteen patients vomited at least 1 dose of prednisolone compared with no patients in the dexamethasone group. Sixteen children (13.1%) in the dexamethasone group received further systemic steroids within 14 days after trial enrollment compared with 5 (4.2%) in the prednisolone group (absolute difference 8.9%; 95% CI 1.9% to 16.0%). There was no significant difference between the groups in hospital admission rates or the number of unscheduled return visits to a health care practitioner.

Conclusion: In children with acute exacerbations of asthma, a single dose of oral dexamethasone (0.3 mg/kg) is noninferior to a 3-day course of oral prednisolone (1 mg/kg per day) as measured by the mean PRAM score on day 4. [Ann Emerg Med. 2015;■:1-9.]

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INTRODUCTION

Background

Asthma is a major cause of pediatric morbidity and mortality.[1,2] In acute exacerbations, corticosteroids reduce relapses, subsequent hospital admission, and the need for ß$_2$-agonist bronchodilator therapy.[3] The British Guideline on the Management of Asthma[4] recommends commencing oral prednisolone early for children presenting with exacerbations of asthma and, if they are discharged, continuing treatment for up to 3 days.

Prednisolone is a relatively short-acting corticosteroid with a half-life of 12 to 36 hours, thereby requiring a multiple-dose regimen.[5] A prolonged treatment course, unpleasant bitter taste, and vomiting may reduce patient compliance.[6] In one study, caregivers of children with asthma reported compliance to the prescribed course of oral corticosteroid therapy only 64% of the time.[7] In contrast, dexamethasone is a long-acting corticosteroid with a half-life of 36 to 72 hours[5] and is used safely in children with croup and bacterial meningitis.[5,8,9]

There are currently 7 published randomized controlled trials and a meta-analysis comparing dexamethasone with prednisolone in the treatment of acute asthma exacerbations in children.[10-17] There are limitations to each of the trials in

Editor's Capsule Summary

What is already known on this topic

Single-dose dexamethasone is an alternative to a short course of prednisone to treat an asthma exacerbation.

What question this study addressed

Is treatment of children with an acute asthma exacerbation with single-dose dexamethasone (0.3 mg/kg) inferior to prednisolone (1 mg/kg per day) as measured by the Pediatric Respiratory Assessment Measure score at day 4?

What this study adds to our knowledge

In this open-label trial of 245 children aged 2 to 16 years, a single dose of dexamethasone was not inferior to prednisolone.

How this is relevant to clinical practice

Given the potential for increased compliance, clinicians should consider a single dose of oral dexamethasone for the emergency treatment of a child with an asthma exacerbation.

terms of study design, sample size, and dosing regimen, and the age of patients enrolled varied between studies. In addition, the lack of consistent and reliable outcome measures makes the results difficult to interpret.

Importance

If effective, a single-dose corticosteroid regimen may overcome the challenges of poor compliance associated with a multiple-dose corticosteroid regimen for acute asthma exacerbation in children.

Goals of This Investigation

We hypothesized that a single dose of oral dexamethasone was noninferior to prednisolone for 3 days in the treatment of acute exacerbations of asthma in children, as measured by the Pediatric Respiratory Assessment Measure (PRAM) at day 4.

MATERIALS AND METHODS

Study Design and Setting

From July 2011 to June 2012, a randomized controlled trial was conducted in the emergency department (ED) of Our Lady's Children's Hospital, Crumlin in Dublin, Ireland, a tertiary pediatric hospital with an annual ED census of 35,000.

Selection of Participants

Eligible participants were children aged 2 to 16 years with a history of asthma who presented to the ED with an acute asthma exacerbation. A history of asthma was defined as either at least 1 previous episode of $ß_2$-agonist–responsive wheeze or a previous diagnosis of asthma, made by a pediatrician or clinician of comparable experience. An exacerbation of asthma was defined as acute asthma that prompts ED assessment, with any or all of the following clinical features: dyspnea, wheeze, acute cough, increased work of breathing, increased requirement for $ß_2$-agonist from baseline use, or SaO_2 less than 95%.

Children with a critical or life-threatening asthma exacerbation, active varicella or herpes simplex infection, documented concurrent infection with respiratory syncytial virus, temperature greater than 39.5°C, use of oral or intravenous corticosteroids in the previous 4 weeks, concurrent stridor, galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption, a history of tuberculosis exposure, or significant comorbid disease were also excluded. A critical or life-threatening asthma exacerbation was defined (as per the Our Lady's Children's Hospital, Crumlin ED asthma guideline) as patients displaying 1 or more of the following clinical features: confused or drowsy, maximal accessory muscle use or recession, poor respiratory effort (including bradypnea), exhaustion, silent chest, cyanosis, SaO_2 less than 90% in air, marked tachycardia, unable to verbalize normally (ie, different from baseline verbal ability), and pneumothorax.

Before the study commenced, the research team conducted training sessions for all ED nurses and emergency physicians on good clinical practice guidelines and on all aspects of the study, including the use of the PRAM score.[18,19] After eligibility for inclusion in the study was confirmed, informed consent was obtained from the parent or legal guardian. In all cases where appropriate, informed assent was obtained from the patient.

We used a randomization design achieved by generating numeric codes in random permuted blocks of 12 subjects. The randomization process was designed by the study statistician (G.C.) and was kept in a locked storage cupboard in the hospital's pharmacy department. The recruiting clinician took the next available numbered envelope from the prerandomized pack of study envelopes contained in a locked storage cupboard in the ED. This envelope contained the subject identification number of each enrolled patient and stated to which treatment arm they were assigned.

Interventions

This was an open-label study. Enrolled patients were randomized to receive a single dose of oral dexamethasone 0.3 mg/kg (maximum dose 12 mg) (DEX) or a 3-day

course of once-daily prednisolone 1 mg/kg per day (maximum dose 40 mg) (PRED). Prednisolone 5-mg tablets (Prednesol, Phoenix Labs, Co, Meath, Ireland) and dexamethasone 2-mg tablets (Organon Ireland Ltd, Swords, Co, Dublin, Ireland) were used. Tablets were either swallowed whole or dissolved in water for younger patients. The dose of prednisolone was rounded off to the nearest 5 mg and the dose of dexamethasone was rounded off to the nearest 2 mg, and the next pack of study medication with that dose was taken. Study packs were prepared by the study clinical trials pharmacist (J.H.).

After randomization and administration of the day 1 dose (day 1=day of enrollment), and before discharge from the ED, the parents or legal guardians of patients randomized to the PRED group were instructed on how to appropriately store the remaining study drug. Patients who vomited the medication in the ED within 30 minutes of administration received a second dose. If the patient vomited again within 30 minutes of the second dose, then no further dose was administered, but the patient remained in the study and his or her data were analyzed on an intention-to-treat basis. If a patient randomized to the PRED group was admitted to the hospital, a member of the research team (J.J.C. or S.M.) was responsible for supplying the prednisolone dose on days 2 and 3. These doses were dispensed from the study medication pack. Patients presenting to our ED with an exacerbation of asthma were treated according to a specific asthma guideline (Figure E1, available online at http://www.annemergmed.com).

Patients and their parents or legal guardians were advised to receive regular inhaled bronchodilators according to a written asthma action plan detailing "step-down" $ß_2$-agonist treatment and were supplied with an asthma diary on discharge. Patients were requested to bring their study packs and diary with them for the day 4 assessment. Inhaled corticosteroids were not routinely prescribed for patients being discharged from the ED who were not receiving this medication before being enrolled in the trial. The dosing of $ß_2$-agonist for study patients admitted to the hospital from the ED was at the discretion of the relevant inpatient medical team.

Methods of Measurement

Study patients were reviewed by a member of the research team in the ED on day 4. If their attendance was not possible on this day, a review was arranged for either day 3 or 5. Participants or parents were contacted by the research team (J.J.C. or S.M.) by telephone on day 14 to further assess the secondary outcomes. Scripted questionnaires were used for both the day 4 and telephone interviews.

Outcome Measures

The primary outcome measure was the mean PRAM score at day 4. The score consists of 5 components and has a maximum total of 12 points: suprasternal retractions (0 to 2), scalene muscle contraction (0 to 2), air entry (0 to 3), wheezing (0 to 3), and SaO_2 (0 to 2). This was performed by a senior physician blinded to treatment allocation. Patients and families were instructed not to reveal treatment allocation to the clinician measuring the PRAM score on day 4. The PRAM score was chosen as the primary outcome because it is a validated, responsive, and reliable tool to objectively determine asthma severity in children aged 2 to 16 years (Table 1).[18,20] We had considered using relapse, ie, an unscheduled return to a health care practitioner, as the primary outcome as it had been used in some other studies in this area.[14,15,17] However, a patient who consults his or her family physician with a continuing cough or mild wheeze and one who returns to ED in extremis, requiring ICU admission, can each be considered as a single relapse. Using the PRAM score is more likely to differentiate between different severities of relapse. Furthermore, deterioration or lack of improvement in asthma symptom severity, which is measured by PRAM, is a hallmark of relapse. PRAM has also been used for a recent study comparing prednisolone and placebo for preschool viral-induced asthma in the emergency care setting.[21] Previous studies comparing dexamethasone and prednisolone have also used an acute asthma score as their primary outcome.[10-12] However, to our knowledge this is the first study comparing dexamethasone and prednisolone to use the PRAM score as the primary outcome measure.

Table 1. The Pediatric Respiratory Assessment Measure (PRAM).[18]

	Score			
Signs	**0**	**1**	**2**	**3**
Suprasternal muscle contraction	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/ silent chest with minimal air entry
SaO_2, %	≥95	92–94	<92	

*In case of asymmetry, the worst lung is rated. Mild exacerbation=1 to 3; moderate, 4 to 7; and severe, 8 to 12.

Secondary outcome measures were change in PRAM score from ED arrival to follow-up, PRAM score at ED discharge, hospital admission from the ED on day 1, ED length of stay (measured as time of ED registration to time of ED departure or transfer to a hospital inpatient ward), unscheduled visits to a health care provider (for example, pediatricians, emergency physicians, or primary care physicians) for asthma or respiratory symptoms within 14 days of study enrollment, readmission to the hospital after discharge and within 14 days of study enrollment, administration of further systemic corticosteroids (apart from study medication) within 14 days of study enrollment, and the number of salbutamol therapies administered after enrollment. The incidence of vomiting within 30 minutes of study medication was compared between the 2 groups. School days and parental workdays missed and days of restricted activity were also analyzed.

All clinical data were verified and validated, and all resultant data queries were resolved. All data were extracted as SPSS data sets (version 20.0; SPSS Inc, Chicago, IL) for statistical analysis.

Patients were monitored for adverse events (serious and nonserious) throughout the entire period that they were involved in the study.

Primary Data Analysis

The sample size calculation comparing dexamethasone and prednisolone at day 4 assumed that dexamethasone is noninferior to prednisolone if the mean PRAM score at day 4 for the DEX group was not more than 1 point higher than for the PRED group. Assuming a similar effectiveness for dexamethasone and prednisolone, a sample size of 210 (105 subjects per group) would be sufficient to conclude noninferiority with a probability (power) of 90%. This assumes a type I error rate of 0.05, a noninferiority margin of 1 unit on the PRAM score, and a standard deviation (SD) of 2.4. A different sample size calculation was included when the trial was registered with ISRCTN in 2010 (original published protocol). However, the calculation included here was finalized before ethics committee and regulatory body approval and before the commencement of patient enrollment.

We aimed to recruit a sufficient number of patients to allow a loss to follow-up rate of 10%. An interim analysis was not included in the statistical analysis plan. Data are presented as means with SDs, and effect sizes are expressed as mean difference with 95% confidence intervals (CIs) to compare differences between the groups. Significance was set at the 5% level. The primary outcome was also calculated for each unique patient excluding reenrollments. A descriptive analysis of the patients enrolled multiple times was performed. A post hoc subgroup analysis, stratified according to age, was also performed.

This study was performed in accordance with good clinical practice guidelines, the EU CT Directive 2001/20/EC, GCP Commission Directive 2005/28/EC, the Declaration of Helsinki (2008), and with all other local regulatory requirements.[19] Risk analysis was carried out as part of protocol development. Conduct of the study was approved by the Health Research Ethics Committee at Our Lady's Children's Hospital, Crumlin, and by the Irish Medicines Board.

A more detailed methodology has been published.[22]

RESULTS

Characteristics of Study Subjects

We screened 836 individual patient presentations (CONSORT diagram, Figure E2, available online at http://www.annemergmed.com). Of 354 potentially eligible presentations, 250 patients underwent randomization. One patient withdrew after randomization but before the administration of any study medication. There were 4 protocol violations resulting in exclusion from the study: a grandparent signed the consent in one case, and 3 patients had exclusion criteria that had been mistakenly overlooked at enrollment. The remaining 245 enrollments involved 226 patients. There were 19 reenrollments, with 14 patients being enrolled twice (14 reenrollments), one 3 times (2 reenrollments), and one 4 times (3 reenrollments). No reenrollment was within 4 weeks of a previous enrollment. Treatment allocation was chosen randomly at each enrollment. Ten patients received both medications on one occasion, 4 were enrolled to the PRED group twice, one to the PRED group twice and DEX once, and one to the DEX group thrice and to the PRED group once. The review took place on day 4 for 61 of 120 patients (50.8%) in the DEX group and 65 of 115 patients (56.5%) in the PRED group, on day 3 for 25 (20.8%) of the DEX group and 23 (20.0%) of the PRED group, and on day 5 for 34 (28.3%) of the DEX group and 27 (23.5%) of the PRED group.

Baseline demographic characteristics, except for sex distribution, were similar between the 2 groups (Table 2). There were significantly more male patients in the PRED group (74.6% versus 61.8%; P=.03). There was no significant difference between the study groups in symptom duration or in the PRAM score at initial ED clinical assessment.

Main Results

The mean PRAM score (with a range of 0 to 12 points) at day 4 for the DEX and PRED groups was 0.91 (SD

Table 2. Baseline characteristics of patients.

Characteristic	DEX (n=123)	PRED (n=122)	Statistical significance
Age, mean (SD), y	5.65 (3.52)	5.76 (3.22)	
Sex (% male patients), male: female ratio	76:47 (61.8)	91:31 (74.6)	*P*=.03*
Medical history			
Previous ED attendances for asthma exacerbations, mean (SD)	3.42 (5.79)	4.01 (6.01)	
Previous hospital admissions for asthma exacerbations, mean (SD)	1.02 (2.89)	1.00 (2.64)	
Asthma, No. (%)	73 (59.3)	88 (67.2)	
Eczema or atopy, No. (%)	64 (52.0)	50 (41.0)	
Family history, No. (%)			
Asthma	90 (73.2)	77 (63.1)	
Eczema or atopy	57 (46.3)	51 (41.8)	
Regular medications, No. (%)			
Inhaled corticosteroids	74 (60.2)	75 (61.5)	
LRA	10 (8.1)	4 (3.3)	
LABA	4 (3.3)	7 (5.7)	
Daily salbutamol use	27 (22.0)	21 (17.2)	
Salbutamol as required	86 (69.9)	89 (73.0)	
Episode characteristics			
Duration of symptoms, No. (%)			
0–6 h	4 (3.3)	7 (5.7)	
6–12 h	11 (8.9)	9 (7.4)	
12–24 h	10 (8.1)	10 (8.2)	
1–3 days	64 (52.0)	75 (61.5)	
>3 days	34 (27.6)	21 (17.2)	
Doses of ß-agonist administered out-of-hospital, mean (SD)	3.45 (2.32)	3.25 (2.12)	
Baseline PRAM score at ED arrival, mean (SD)	4.38 (2.53)	4.51 (2.35)	Mean difference −0.13 (95% CI −0.74 to 0.49)

LRA, Leukotriene receptor antagonist; *LABA*, long-acting $ß_2$-agonist.
*χ^2 Test.

1.16) and 0.91 (SD 1.52), respectively (a graphic representation of the primary outcome result is included in Figure E3, available online at http://www.annemergmed.com). The mean difference in these scores was –0.005 (95% CI –0.35 to 0.34). Table 3 shows the primary outcome for all patients enrolled in the trial, including the breakdown for patients aged 2 to 5 years and those older than 5 years, male and female patients, and patients with different levels of asthma exacerbation severity. For each of these subgroups, there was no significant difference in the primary outcome, or in the PRAM score at ED discharge, between the 2 trial arms.

The mean change in PRAM score from arrival in the ED to review at day 4 was similar between the trial arms (3.48 [SD 2.66] for the DEX group and 3.51 [SD 2.59] for the PRED group; mean difference –0.38; 95% CI –0.71 to 0.64). There was no significant difference in PRAM scores at discharge from the ED between the 2 groups (DEX 1.01 [SD 1.58] versus PRED 0.99 [SD 1.69]; mean difference 0.02; 95% CI –0.39 to 0.43) or in ED length of stay (DEX 4.31 hours [SD 1.7] versus PRED 4.18 hours [SD 2.11]; mean difference 0.13 hours; 95% CI –0.63 to 0.71 hours). There was no significant difference in the number of patients who were admitted to the hospital from the ED on the day of enrollment, in the length of hospital stay for that admission, or in terms of the requirement for a return health care provider visit (Table 4).

There were 3 patients (2.5%) in the DEX group and 1 patient (0.8%) in the PRED group who were discharged on day 1 from the ED and required hospital admission at a later stage within 2 weeks of trial enrollment (absolute difference 1.6%; 95% CI –1.6% to 4.9%).

In total, 16 children in the DEX group (13.1%) received further systemic steroids in the 14 days after enrollment compared with 5 in the PRED group (4.2%; absolute difference 8.9%; 95% CI 1.9% to 16.0%). Patients who received further steroids were older (mean age=6.0 years; SD 3.71) and had higher mean PRAM scores (initial PRAM score=5.43 [SD 2.34]; PRAM score at ED discharge=3.14 [SD 2.56]; PRAM score at day 4=1.48 [SD 1.60]). Of the 34 patients who were admitted from the ED on day 1, 9 of 18 in the DEX group (50.0%) and 3 of 16 in the PRED group (18.75%) received further steroids as inpatients (absolute difference 31.25%; 95% CI –1.3% to 63.8%). There was no significant difference between the trial arms in this subgroup in terms of demographic and clinical characteristics, length of admission, or number of daily salbutamol treatments participants received as inpatients (Table 5).

Seven patients in the PRED group (5.7%) vomited within 30 minutes of the dose of steroid on day 1 in the ED compared with none in the DEX group (absolute difference –5.7%; 95% CI –9.9% to –1.54%). Seven patients vomited after the prednisolone dose on day 2, and 6 vomited after the dose on day 3. A total of 14 patients vomited after at least 1 dose of prednisolone. No other

Table 3. Primary outcome (χ^2 test).

Day 4 PRAM Scores	DEX Mean (SD)	PRED Mean (SD)	Mean Difference (95% CI of Difference)
All patients	0.91 (1.16) n=120	0.91 (1.52) n=115	−0.005 (−0.35 to 0.34)
All patients excluding reenrollments	0.92 (1.15) n=110	0.92 (1.55) n=108	0 (−0.36 to 0.36)
Patients ≥6 y	1.00 (1.14) n=44	0.81 (1.58) n=43	0.19 (−0.40 to 0.77)
Patients 2–5 y	0.86 (1.16) n=66	0.98 (1.54) n=65	−0.12 (−0.59 to 0.35)
Male patients	0.94 (1.23) n=67	0.86 (1.31) n=83	0.085 (−0.328 to 0.498)
Female patients	0.88 (1.03) n=43	1.12 (2.186) n=25	−0.236 (−1.016 to 0.543)
Mild exacerbation*	1.00 (1.26) n=49	0.79 (1.23) n=43	0.209 (−0.307 to 0.725)
Moderate exacerbation*	0.81 (1.104) n=48	0.85 (1.615) n=55	−0.042 (−0.591 to 0.507)
Severe exacerbation*	1.00 (0.913) n=13	1.80 (2.201) n=10	−0.800 (−2.197 to 0.597)

*A mild exacerbation refers to a PRAM score between 1 and 3 at initial ED assessment; moderate, 4 and 7; and severe, 8 and 12.

adverse events attributable to the study medications were noted.

There was no significant difference between the trial arms in the number of $ß_2$-agonist inhaler treatments administered in the ED (DEX 3.13 [SD 1.00] versus PRED 3.14 [SD 1.02]; mean difference –0.01; 95% CI –0.26 to 0.24). However, on days 4 and 5 postenrollment, patients in the DEX group received more doses of $ß_2$-agonist than those in the PRED group (Figure). There was no significant difference in $ß_2$-agonist administration between the groups on any other day postenrollment.

There was no difference between the study groups in the number of days of restricted activity, the number of school days missed, and the number of parental workdays missed (Table 4).

LIMITATIONS

This randomized controlled trial has some limitations. First, this was an open-label study, and foreknowledge of the intervention may have introduced bias and limited the trial's internal validity. However, the primary outcome used is an objective measure, which was assessed by a physician blinded to treatment allocation, therefore strengthening the trial's internal validity.

Second, there were significantly more male patients in the PRED group, raising the possibility of selection bias.

Table 4. Secondary outcomes.

	DEX	PRED	Difference (95% CI of Difference)
Hospital admission from the ED on day 1, n/N (%)	18/123 (14.6)	16/122 (13.1)	1.5 (−7.2 to 10.3)
Length of admission, mean (SD), days	2.33 (1.24) (n=18)	2.69 (1.74) (n=16)	−0.35 (−1.40 to 0.69)*
Return visit to health care provider within 14 days, n/N (%)	17/122 (13.9)	17/120 (14.2)	−0.2 (−9.1 to 8.6)
Hospital admission post–ED discharge within 14 days, n/N (%)	3/122 (2.5)	1/120 (0.8)	1.6 (−1.6 to 4.9)
Further systemic steroids administered, n/N (%)	16/122 (13.1)	5/120 (4.2)	8.9 (1.9 to 16.0)
Further systemic steroids administered on inpatient basis (if admitted on day 1), n/N (%)	9/18 (50.0)	3/16 (18.75)	31.25 (95 CI −1.3 to 63.8)
Number of days of restricted activity, mean (SD)	4.53 (4.05) (n=112)	4.28 (3.46) (n=111)	0.25 (−0.70 to 1.20)*
Number of subjects who missed >1 school day, n/N (%)	58/76 (76.3) (N/A=46)	56/76 (73.7) (N/A=44)	2.6 (−11.3 to 16.6)
Number of school days missed, mean (SD)	2.54 (2.36)	2.14 (2.10)	0.40 (−0.31 to 1.12)*
Number of subjects for whom >1 parental workday was missed, n/N (%)	44/109 (40.4) (N/A=13)	42/111 (37.8) (N/A=9)	2.5 (−10.5 to 15.6)
Number of parental workdays missed, mean (SD)	0.91 (1.66)	0.64 (0.99)	0.27 (−0.09 to 0.64)*

N/A, Not applicable.
*Mean difference (95% CI of the difference).

Table 5. Patients admitted to the hospital.

	DEX (n=18)	PRED (n=16)	Mean Difference (95% CI of Difference)
Male patient, No. (%)	11 (61.1)	12 (75.0)	
Age, mean (SD), y	5.22 (3.13)	5.32 (2.98)	
Known diagnosis of asthma, No. (%)	9 (50.0)	10 (62.5)	
Regular use of inhaled corticosteroids, No. (%)	13 (72.2)	11 (68.8)	
Number of previous ED attendances, mean (SD)	1.89 (2.30)	3.75 (4.20)	
Number of previous hospital admissions, mean (SD)	0.61 (0.85)	1.13 (2.16)	
Initial PRAM score, mean (SD)	6.44 (1.98)	6.06 (2.05)	0.38 (−1.03 to 1.79)
PRAM score at ED discharge to mean (SD)	4.11 (1.64)	4.31 (2.55)	−0.20 (−1.68 to 1.28)
Mean hospital LOS, days	2.33	2.73	0.495
$ß_2$-Agonist bronchodilator administered by metered-dose inhaler (mean number of doses per day), mean (SD)	3.19 (1.76)	3.71 (2.01)	−0.53 (−1.94 to 0.88)
Nebulized $ß_2$-agonist bronchodilator (mean number of doses per day), mean (SD)	2.20 (2.01)	2.00 (2.41)	0.20 (−1.59 to 1.99)
Patients who received further steroids during their hospital stay, No. (%)	9 (50.0)	3 (18.7)	31.3 (−1.3 to 63.8)

LOS, length of stay.

This is, however, unlikely because the interventions studied have no demonstrable sex difference.

Third, inclusion of patients admitted to the hospital in our analysis may be considered a confounding factor because treatment after hospital admission may differ from home treatment. This is unlikely to have significantly affected the internal validity of this trial because the number of participants admitted to the hospital was similar between the study groups.

Fourth, although parents and patients were asked to note any missed doses of prednisolone in their asthma diary and to bring empty packets with them to the day 4 review, compliance was self-reported and we were reliant on the accuracy of their reporting for this outcome.

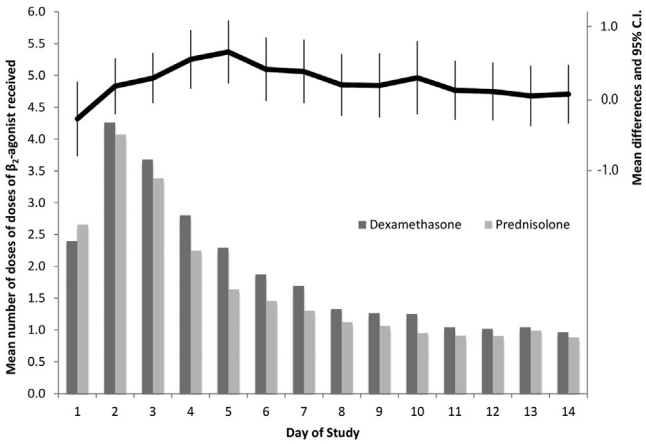

Figure. Mean number of doses of β_2-agonist received by both groups for each day from day of enrollment (day 1) to day 14, including mean differences and 95% CIs (vertical lines).

DISCUSSION

Dexamethasone has emerged as a potential alternative to prednisolone in the treatment of acute asthma exacerbations in children.[10-17] In a noninferiority randomized controlled trial, we found that in children with acute asthma exacerbations, a single dose of oral dexamethasone (0.3 mg/kg) is noninferior to a 3-day course of oral prednisolone (1 mg/kg per day), as measured by the primary outcome, the PRAM score on day 4. To our knowledge, this is the first randomized controlled trial comparing dexamethasone with prednisolone for acute asthma exacerbations in children that used study drug doses similar to those used in routine clinical practice in Ireland, the United Kingdom, and Australasia.

We also found no significant difference between the study groups in the hospital admission rate, ED length of stay, and PRAM score at ED discharge. More patients in the DEX group received additional steroid therapy during the 2-week study period after trial enrollment. Although this may reflect an increased requirement for extra steroid treatment compared with that of patients in the PRED group at the doses used in this study, it is possible that it reflects traditional physician preference for prednisolone, given that the physicians who reviewed patients in this study during the 2-week period had the discretion to prescribe other steroids as they believed clinically appropriate. Despite the fact that there was no significant difference between the 2 study arms in terms of asthma severity at the review appointment and in terms of unscheduled returns to a health care provider, more patients in the DEX group received further steroids. Further supportive evidence that clinician preference may be responsible for the administration of additional steroids

is derived from the finding that, of the patients admitted to hospital, more patients in the DEX group received further steroids in addition to the study medications despite no difference between the 2 groups in terms of baseline characteristics, the amount of $ß_2$-agonist administered, and PRAM scores on ED arrival and at ED discharge to a hospital ward (Table 5).

There are currently 7 published randomized controlled trials comparing dexamethasone and prednisolone for the treatment of acute asthma exacerbations in children.[10-12,14-17] However, there are limitations to each of these trials in terms of study design, sample size, and dosing regimen. The first of these studies compared nebulized dexamethasone with oral prednisolone.[16] Even though no difference was found between the comparator interventions, the external validity of this study is limited by the fact that it is accepted standard practice in most jurisdictions to administer systemic, rather than nebulized, corticosteroids for acute asthma in children. Three of the other 6 published randomized controlled trials compared intramuscular dexamethasone with oral prednisolone.[11,12,14] Although these 3 studies found no demonstrable difference between the comparator interventions, intramuscular injection is likely to cause significant distress in children. The remaining 3 published randomized controlled trials compared oral dexamethasone with oral prednisolone,[10,15,17] and all 3 were conducted in the United States, where both the dosing and duration of treatment vary from what is usual practice in Ireland, the United Kingdom, and Australasia.[23] A dose of 2 mg/kg and a 5-day course of prednisolone is typically used in the United States, whereas the most commonly used guideline in the United Kingdom and Ireland on the management of asthma recommends a 3-day course of 1 mg/kg.[4] Chang et al,[24] in a study of 201 children aged 2 to 15 years, found no difference between 3- and 5-day courses of prednisolone 1 mg/kg in children with acute exacerbations of asthma who were not hospitalized.[24]

Another challenge in the interpretation of the published randomized controlled trials is that the age of participants varies between studies. Asthma is not usually diagnosed in a patient younger than 2 years because of the prevalence of bronchiolitis in this age group. To limit phenotypic variability, ideally all trials should recruit a relatively homogeneous age group of acute asthma exacerbations and recruit patients up to aged 16 years.

There is also a lack of consistent and validated outcome measures in these previous studies. Three randomized controlled trials comparing dexamethasone with prednisolone each used a different asthma score as the primary outcome, and 2 of these studies used composite primary outcome measures.[10-12] To our knowledge, this is the first study to use the PRAM score as the primary outcome measure in a randomized controlled trial comparing dexamethasone with prednisolone. The PRAM is an objective score based on clinician findings on examination as opposed to self-reported symptoms, thus reducing recall bias.[18]

Keeney et al[13] conducted a meta-analysis and combined results for relapse rates when similar intervals were reported by the included studies. They found no difference in relapse rate at any point during follow-up. Patients who received dexamethasone were less likely to vomit both in the ED (relative risk 0.29; 95% CI 0.12 to 0.69) and at home (relative risk 0.32; 95% CI 0.14 to 0.74). There was also no difference in hospitalization or likelihood of improvement in asthma score.

Dexamethasone has been shown to be significantly more palatable than prednisolone to children presenting to the ED with exacerbations of asthma.[25] No patient in our study vomited after administration of dexamethasone, whereas 14 patients vomited after the administration of at least 1 dose of the 3-day prednisolone course.

In conclusion, this randomized controlled trial of steroids in children with acute asthma who attended the ED found no significant difference between a single dose of oral dexamethasone (0.3 mg/kg) and a 3-day course of oral prednisolone (1 mg/kg per day). However, more patients in the DEX group were treated with further steroids during the study. According to our findings, it may be possible to safely use a single dose of oral dexamethasone to simplify the ED treatment of children with acute asthma exacerbation.

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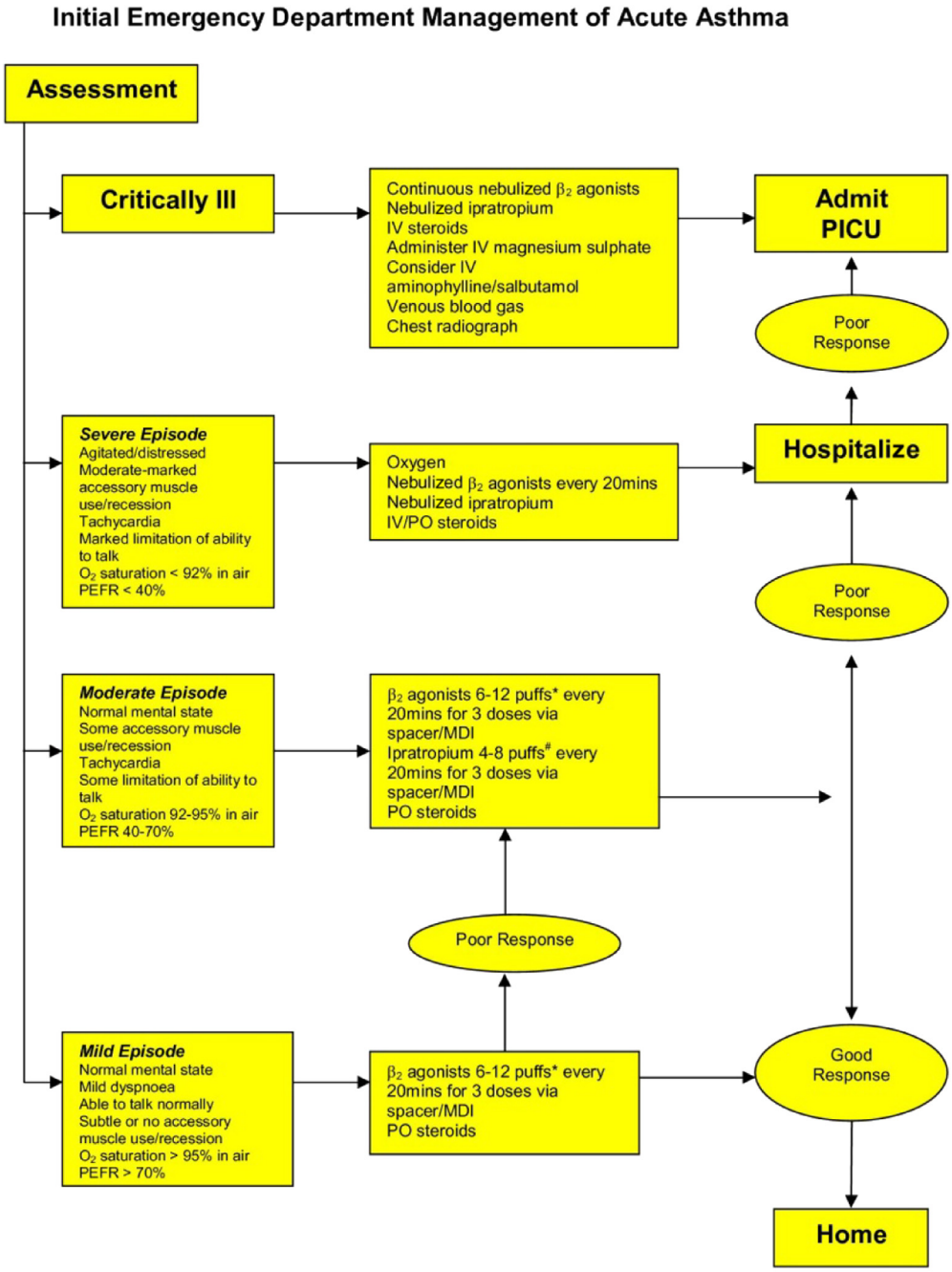

Figure E1. Our Lady's Children's Hospital, Crumlin ED asthma guideline. *PICU,* Pediatric intensive care unit; *PEFR,* peak expiratory flow rate; *MDI,* metered-dose inhaler.

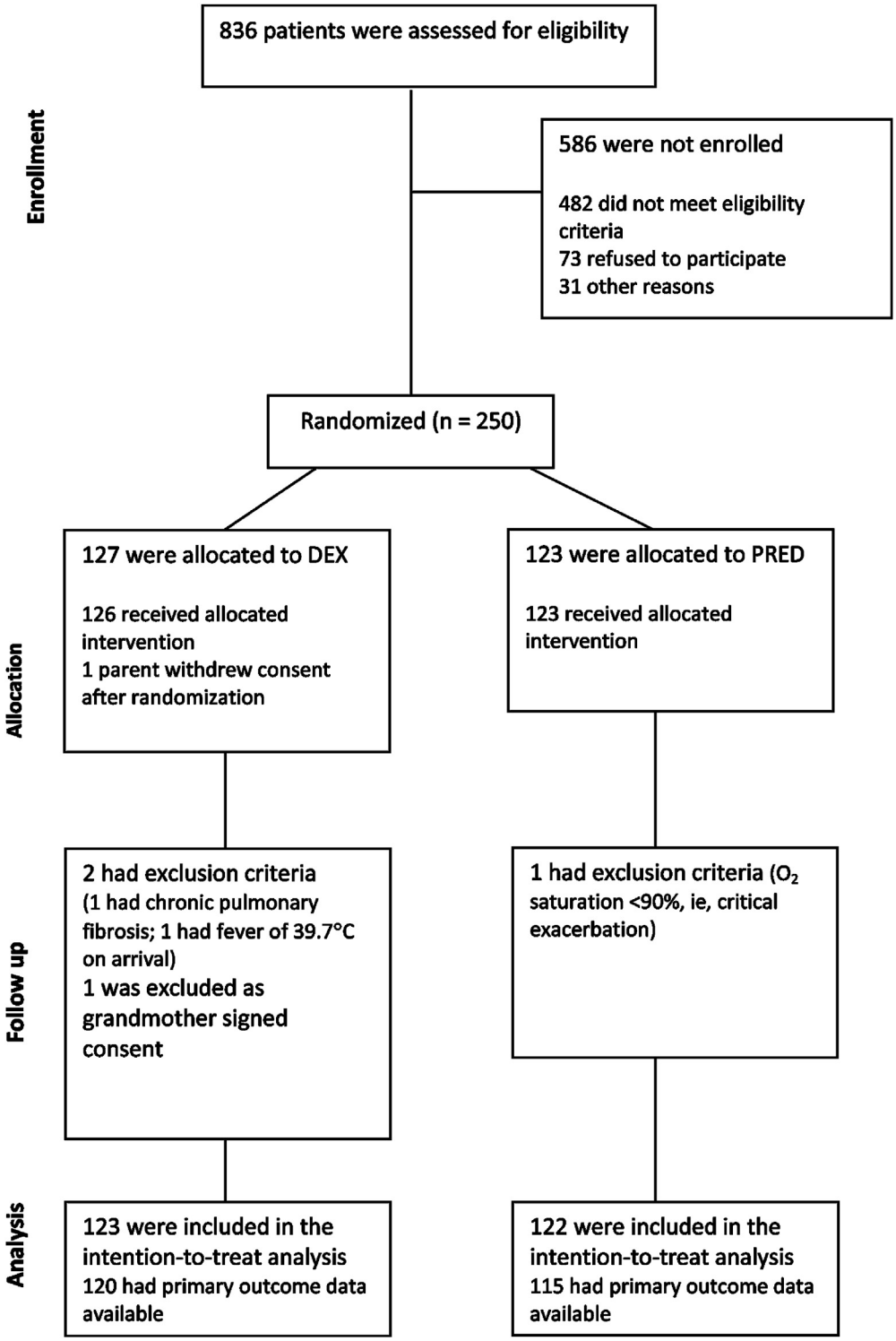

Figure E2. Enrollment and outcomes.

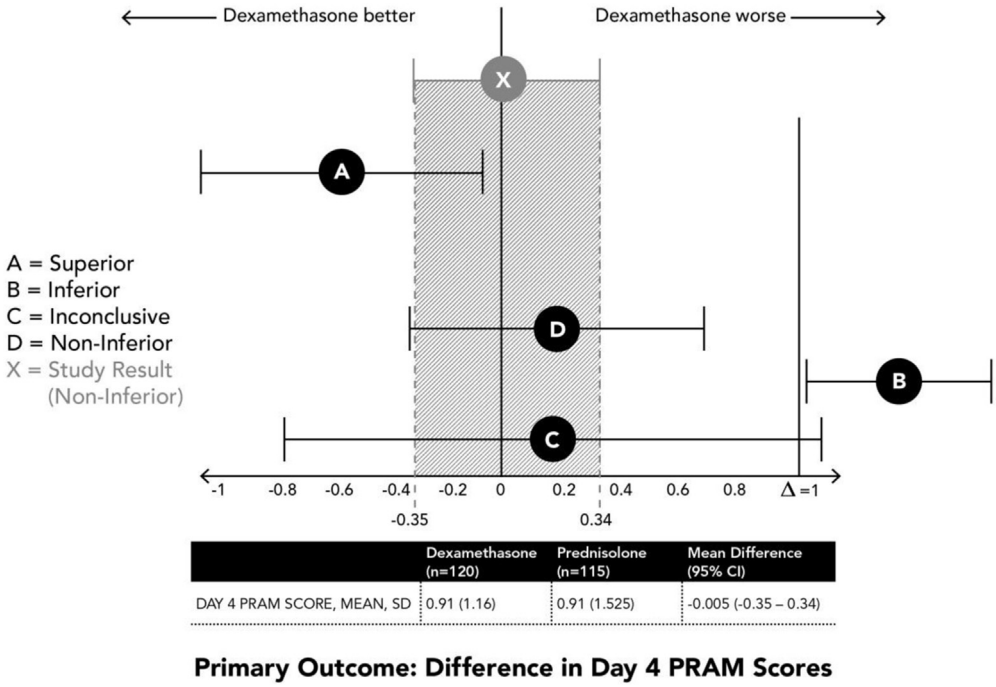

Figure E3. Forest plot. A, B, C, and D are theoretical examples of different types of results for a noninferiority trial (after Piaggio et al[26]). X shows the primary outcome result in this study).