Office of Evidence Based Practice – Dose of Glucocorticosteroids for Asthma in the ED/UCC

Specific Care Question:

For the child who presents with mild, moderate, or severe asthma symptoms to the Emergency Department (ED) or Urgent Care Center (UCC) what is the optimal dose (including maximum dose) of glucocorticosteroids to improve asthma symptoms, reduce admission to the hospital, and decrease length of stay in the ED/UCC?

Question Originator:

The Asthma in the Emergency Department/ Urgent Care Center Clinical Practice Guideline Team

Literature Summary

Background. There is a difference in the maximum dose of steroid medications in the parent guideline (GINA, 2018) for this update and the maximum dose that was used in the previous CM Asthma CPG (2011). To make sure the dose we use for this update is correct, we conducted a search for studies on this topic, looking for maximum steroid doses. The *Global Strategy of Asthma Management and Prevention* (2016) was selected as the parent guideline for this CPG. For asthma exacerbation in children they recommend the following maximum doses of CS:

Age	Severity	Medication and Dose
5 years and younger	Severe or life threatening	Prednisolone 2 mg/kg (max 20 mg for < 2 years; max 30 mg for 2-5 years)
	Mild or moderate	Prednisolone 2 mg/kg (max 20 mg for < 2 years; max 30 mg for 2-5 years)- After up to 2 hours after SABA administration, and still requiring treatment.
5-12 years	All severities	1-2 mg/kg (max 40 mg)
> 12 years	All severities	1 mg/kg (max 50 mg)

However, the previous US National Guideline (NAEP-EPR-3, 2007) and Lexi-Comp (*Lexicomp Online* 2017) give the following recommendation for CS in asthma exacerbation, and they reference each other for the dosing recommendation:

Age	Medication and Dose
Children < 12	1-2 mg/kg in 2 divided doses (maximum 60 mg/d)
All > 12 years	40-80 mg/d in one or 2 divided doses

Study Characteristics. A literature search was conducted 4/19/2019. Irene Walsh MD and Erin Scott, DO reviewed the 80 studies to assess if there was research on the optimal maximum dose of CS for children and adolescents who present to the ED/UCC. Eighteen

were read closely to determine if maximum dose of CS was reported. Additionally, eighteen unique studies from a recent systematic review/meta-analysis (Normansell, Kew, & Mansour, 2016) on CS use in asthma exacerbation were appraised for CS maximum dosing. In all, three studies reported on maximum dose, and the maximum dose ranged from 50-60 mg. (Bhogal et al., 2012; Davis, Burke, Hogan, & Smith, 2012; Krebs, Flood, Peter, & Gerard, 2013). However, none of these studies were specifically looking for an optimal dose.

Key Results:
Based on high quality evidence, the GINA (2018) guideline, the Asthma in the ED/UCC Team makes a strong recommendation to keep prednisone/prednisolone dosing at 2 mg/kg for all three levels of asthma exacerbations. For children with mild exacerbations that do not respond to initial therapy, a strong recommendation is made to consider CS administration (GINA, 2018). Based on low quality of the Asthma in the ED/UCC Team makes a recommendation for maximum dose of prednisone/prednisolone of 60 mg/d (see Table 1 for dose ranges) (Qureshi et al., 2001).

For dexamethasone, there is no established lowest effective dose; the duration and number of doses is also not known. See Table 1 for the doses used across trials that studied dexamethasone in pediatric asthma exacerbations. Dexamethasone doses ranged from 0.15 to 1.7 mg/kg, maximum dose ranged from 10-36 mg/d and number of doses ranged from one to two days. The Asthma in the ED/UCC Team recommends 0.6 mg/kg/d of dexamethasone (Altamimi et al., 2006; Ducharme et al., 2015; Gordon et al., 2007; Greenberg et al., 2008; Qureshi et al., 2001). A maximum dexamethasone dose of 12 mg/day times 1-2 doses is recommended by the Asthma in the ED CPG Team (Cronin et al., 2016). These dose recommendations agree with the U.S. National Asthma Guideline (NAEP-EPR-3, 2007) and Lexi-Comp, a drug information database (*Lexicomp Online* 2017).

No studies assessing optimal dosing of CS were identified, therefore a meta-analysis for prednisone/prednisolone or dexamethasone dosing could not be performed.

EBP Scholar's responsible for analyzing the literature:
Teresa Bontrager, RN, BSN, MSNed, CPEN
Jennifer Foley, RT(R)(N), CNMT
Kori Hess, PharmD
Kelly Huntington, RN, BSN, CPN
David Keeler, RN, BSN, CPN
Erin Lindhorst, MS, RD, LD
Helen Murphy, BHS RRT AE-C
Katina Rahe, RN, BSN, CPN
Robert Rhodes, MHA, RRT-NPS
Hope Scott, RN CPEN
EBP team member responsible for reviewing, synthesizing, and developing this literature:
Nancy H Allen, MS, MLS, RD, LD
Jacqueline A Bartlett, PhD, RN
Jarrod D Dusin MS, RD, LD, CNSC

Search Strategy and Results:
PubMed
Search: ((("Asthma" OR asthma[tw]) AND ("Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[Mesh] OR "emergency department"[tw] OR "Acute Disease"[Mesh] OR exacerbation[tw] OR attack[tw])) AND (("Dexamethasone"[Mesh] OR "Dexamethasone Isonicotinate"[Mesh] OR "Methylprednisolone"[Mesh] OR "Methylprednisolone Hemisuccinate"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR corticosteroid[tw] OR "pregnadienediols"[Mesh] OR "pregnadienetriols"[Mesh]) AND ("Injections, Intramuscular"[Mesh] OR "Administration, Oral"[Mesh] OR "Infusions, Intravenous"[Mesh] OR "Injections, Intravenous"[Mesh] OR "administration and dosage "[Subheading]))) AND (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR Comparative Study[ptyp] OR "Cohort Studies"[Mesh] OR systematic[sb]) AND (infant OR child OR paediatr* OR pediatr* OR adolescent OR adolescence OR children) AND ("2010/01/01"[PDAT] : "2017/12/31"[PDAT]) (80 results)

Studies included in this review: 9
Arulparithi et al. (2015)
Bhogal et al. (2012)
Cronin et al. 2012)
Davis, Burke, Hogan, & Smith, (2012)
Krebs, Flood, Peter, & Gerard, (2013)
Normansell, Kew, & Mansour, (2016)
Keskin et al. (2016)
Wyatt, Borland, Doyle, & Geelhoed, (2015)
Zemek et al. (2012)

Studies <u>not</u> included in this review with rationale for exclusion: 10

Author/Year	Reason for Exclusion
Andrews, Wong, Heine, & Scott Russell, (2012)	This is a cost study
Chen et al., (2013)	This is an inhaled corticosteroid study; oral corticosteroids were given as a rescue treatment
Ducharme et al. (2014)	This is a protocol only- results have not been published
Edmonds, Milan, Brenner, Camargo, & Rowe, (2012)	This does not answer the question. It evaluates inhaled corticosteroids
Fernandes et al., (2014)	This does not give dosing information
Knapp, Hall, & Sharma, (2010)	This does not give dosing information

Meyer, Riese, & Biondi, (2014)	This is a systematic review
Visitsunthorn, Lilitwat, Jirapongsananuruk, & Vichyanond, (2013)	This does not give dosing information
Vuillermin et al. (2010)	Does not answer the question, pertains to parent-initiated corticosteroids
Williams, Andrews, Heine, Russell, & Titus, (2013)	This does not answer the question. It is a CS duration study

Acronyms Used in this Document:

Acronym	Explanation
CPG	Clinical Practice Guideline
CS-	Corticosteroids
ED/UCC	Emergency Department/ Urgent Care Center
EPR-3- (NAEP-EPR-3, 2007)	Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
GINA	*Global Strategy of Asthma Management and Prevention*, 2018
SABA-	Short acting beta-agonist such as albuterol

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5), was used to assess the bias? of the nine included studies.

Updated: August 2017

Characteristics of included studies:
Arulparithi et al., 2015

Methods	Randomized double-blind placebo-controlled trial
Participants	**Setting:** Pediatric ED in South India from May 2008 to November 2010 **Randomized into study:** *N* = 61 • Group 1- (beclomethasone): *n* = 30 • Group 2- (oral steroids): *n* = 31 **Completed Study:** N=61

	• Group 1- (beclomethasone): *n* = 30 • Group 2- (oral steroids): *n* = 31 **Gender %Male:** • Group 1 (beclomethasone) :57% (17/30) • Group 2 (oral steroids): 48% (15/31) **Age, years (mean):** • Group 1- 7.8 (1.93) • Group 2- 7.14 (1.93) **Inclusion Criteria:** • Children ages 5-12 years presenting with acute asthma exacerbation **Exclusion Criteria:** • First wheezing episode • Life threatening asthma • Received oral steroids in last 7 days • Children on high dose inhaled corticosteroid (ICS) ○ 1000mcg or more of beclomethasone or budesonide per day or 500mcg or more of fluticasone per day) • Concurrent cardiopulmonary disease • Immunodeficiency • Diabetes • Allergy to corticosteroids • Exposure to varicella in previous 21 days **Power Analysis:** not given
Interventions	**Group 1:** • Three doses of salbutamol (0.15 mg/kg) and 800mcg budesonide mixed in same nebulizer chamber at intervals of 20 minutes • Single dose of placebo tablets **Group 2:** • Three doses of salbutamol (0.15 mg/kg) along with placebo solution mixed together in same nebulizer chamber at intervals of 20 minutes • Single dose of oral steroids (2mg/kg) **Both groups:** • Assessed every 20 minutes for up to one hour with vital signs (HR, RR, o2 sat) • Peak flow done at one and four hours • Fitness for discharge assessed at the end of 2 hours using clinical severity score ○ Score of 0 or 1 for HR, RR, dyspnea, accessory muscle use, wheezing
Outcomes	**Primary:**

	• Efficacy of nebulized budesonide in treatment of acute asthma
	  ○ vital signs
	  ○ fitness for discharge

Notes	Both physicians and patients were blinded to treatment.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generation
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes used
Blinding of participants and personnel (performance bias)	Unclear risk	Patients and clinicians were blinded regarding drugs
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias)	Unclear risk	Intention to treat
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Small sample size Power analysis was not performed

Bhogal et al., 2012

Methods	Cohort study
Participants	**Participants**: Children (2-17 years) presenting to the ED with and asthma exacerbation between September-December 2006 (N=406) **Setting**: Montreal Children's Hospital **Number complete**: 406 patients **% male**: 63% **Inclusion criteria**: 2 to 17 years, with a diagnosis of an acute exacerbation treated with 1 or more albuterol nebulizations in the ED, had moderate or severe obstruction as documented by a baseline PRAM score of 5-12 **Exclusions**: Chronic illness (i.e. cystic fibrosis, bronchopulmonary dysplasia, cardiac or renal diseases), acute illness for which the administration of systemic corticosteroid was indicated (i.e. croup) or contraindicated (i.e. varicella) and ongoing oral corticosteroids use on presentation

	Power analysis: 406 patients with moderate or severe asthma receiving either early or delayed therapies
Interventions	Three groups: 1. Early administration of systemic corticosteroids w/in 75 minutes (n=205) 2. Delayed administration > 75 minutes (n=133) 3. No administration (n=68) • For moderate asthmatics: 1 or more nebulizations of albuterol (0.03 mL/kg of 5% albuterol solution and a dose of prednisone or prednisolone (1 mg/kg; maximum dose = 50 mg) • For severe asthmatics: 3 nebulizations of 0.03 mL/kg of albuterol and 1 mL of 250 mcg ipratropium bromide and 1 mg/kg of prednisone or prednisolone (although 4 to 8 mg/kg of intravenous hydrocortisone was occasionally administered
Outcomes	**Primary outcome:** Admission (defined as hospital admission or time from triage was greater than 6 hours) **Secondary outcomes:** Length of treatment (time between first and last nebulized albuterol therapy) and relapse (return visit to ED for acute asthma within 72 hours of discharge)
Notes	-Asthma score not measured -Doses of corticosteroids not measured The authors report values for the three groups and therefore multiple comparisons were created, the last comparison combined the Delayed and Not Given data sets for the outcomes of Admission and Relapse. This action could not be accomplished for the outcome Length of Active Treatment, hours

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	High risk	Random sequence generation was not used due to study design
Allocation concealment (selection bias)	Unclear risk	Not disclosed
Blinding of participants and personnel (performance bias)	Unclear risk	Authors report that healthcare clinicians were not aware of the ongoing study
Blinding of outcome assessment (detection bias)	Low risk	The assessed outcomes were binary in nature and could not be influenced by the outcome assessor
Incomplete outcome data (attrition bias)	Low risk	Authors report all data were analyzed
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	Study design

Cronin et al., 2012

Methods	Randomized, open-label, non-inferiority trial
Participants	**Setting:** Tertiary urban pediatric ED in Dublin, Ireland, July 2011 to June 2012 **Randomized into Study:** 245 enrollments involving 226 patients. (19 patients were reenrolled but were within inclusion criteria) • Treatment group n=123 • Control group n=122 **Completed Study:** • Treatment group n=120 • Control group n=115 **Age:** 2-16 years **Gender:** • Treatment group: 61.8% male • Control group: 74.6% male **Inclusion Criteria:** • History of asthma • Presenting with asthma exacerbation **Exclusion Criteria:** • Critical or life-threatening asthma • Known TB exposure • Active varicella or herpes simplex infection • Documented concurrent RSV infection • Fever > 39.5 degrees C • Use of oral corticosteroids in the previous four weeks • concurrent stridor • Galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption • Significant co-morbid dx: lung, cardiac, immune, liver, endocrine, neurologic or psychiatric **Power Analysis: S**ample size of 232 subjects (105 in each group with an estimated 10% loss to follow-up) required to reject the null hypothesis
Interventions	**Treatment Group:** Oral dexamethasone (single dose of 0.3 mg/kg, maximum dose 12mg) **Control Group:** Oral prednisolone (1mg/kg for 3 days, maximum dose 40mg per day)
Outcomes	1. Day 4 Asthma score (PRAM) 2. Hospital Admission
Notes	• Patients who vomited dose of either steroid within 30 minutes of administration received a second dose. If patient vomited second dose within 30 minutes of administration, no further dosages were administered but remained in study to perform an intention-to-treat analysis

	• Included in study were those patients who were hospitalized • Authors identify that including patients after hospital admission may be a confounding factor as treatment may differ from home treatment

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Numeric codes generated in random permuted blocks of 12 subjects. The recruiting clinician took the next available numbered envelope from the pre-randomized pack of study envelopes contained in a locked storage cupboard in the ED
Allocation concealment (selection bias)	Low risk	• Central allocation by pharmacy • Sequentially numbered, opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk	Since treatment group received 1 dose of medication and control group received doses over subsequent 2 days, it was impossible to blind participants
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome measures were assessed by physician blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Seven percent of the patient population dropped from the study; however, even with study dropouts both groups had greater than the needed sample size of 105 participants
Selective reporting (reporting bias)	Unclear risk	Intention-to-treat analysis was performed

Davis, Burke, Hogan, & Smith, 2012

Methods	Retrospective Cohort Study
Participants	**Participants**: Children between the ages of 2 and 18 years who presented to the ED with an acute asthma exacerbation and received oral prednisone or dexamethasone in the ED between 1 January 2007 and 31 December 2007 **Setting**: Connecticut Children's Medical Center in Farmington, CT, USA. **Completed Study:** 882 • **Treatment group, Corticosteroid <60 min group:** n=477, 54% • **Control group, Corticosteroid >60 min group**: n=405, 46% **Gender:** • **Treatment group:** 62.9% male • **Control group:** 61% male **Age, years (CI)** • **Treatment group:** 6.7 (6.3-7.1) • **Control group:** 6.7 (6.3-7.1)

	Inclusion Criteria: • Children between the ages of 2 and 18 years who presented to the ED with an acute asthma exacerbation and received oral prednisone or dexamethasone **Exclusion Criteria**: • Children who did not receive oral corticosteroids in the ED • Had significant medical co-morbidities. Co-morbidities include cystic fibrosis, congenital heart disease, and bronchopulmonary dysplasia • Were already on corticosteroids prior to arriving in the ED • Children who received any corticosteroids other than oral route • Children who vomited and subsequently received a second dose intravenously or intramuscularly • Children who returned to the CCMC ED with an asthma exacerbation within 7 days, data from subsequent visit was not included **Power Analysis**: Not specified by the authors

Interventions	Patients treated according to an Asthma Treatment Algorithm based on severity of exacerbation (Mild, Moderate, and Severe)
	Mild: Treat with beta-agonists (MDI treatment) and consider prednisone or equivalent (2 mg/kg - max 60 mg)
	Moderate: Treat with both beta-agonist (short treatment with ipratropium then long treatment) and prednisone/prednisolone (2 mg/kg - max 60mg) or Dexamethasone (1 mg/kg - max 12-16 mg)
	Severe: Treat with both beta-agonist (Short treatment with Ipratropium then long treatment) and prednisone/prednisolone (2 mg/kg - max 60mg) or dexamethasone (1 mg/kg - max 12-16 mg) and consider ancillary medications
	• MDI treatments (with spacer)
	  ○ Weight (Dose) Notes
	  ▪ ≤ 10 Kg: 4 puffs Use facemask or mouthpiece
	  ▪ ≥ 10 Kg: 8 puffs Use mouthpiece
	• Short Albuterol Treatments
	  ○ Weight; Medication, Dosing albuterol (mg), ipratropium (500 µg/vial)
	  ▪ ≤ 10 Kg, albuterol 2.5 mg, ipratropium 1 vial
	  ▪ ≥ 10 Kg, albuterol 5 mg, ipratropium 1 vial
	• Long Albuterol Treatments
	  ○ Weight, Albuterol (mg), Total Volume (with NS)
	  ▪ ≤ 10 Kg, albuterol 10 mg, 8 mL
	  ▪ ≥ 10 Kg, albuterol 20 mg, 8 mL

Outcomes	**Primary Outcome -** Length of Stay**:** • Corticosteroid <60 min group: 157 minutes • Corticosteroid >60 min group: 182 minutes **Secondary Outcome -** Dose of Steroids**:**

	Prednisone/prednisolone 2mg/kg with a maximum of 60 mg. Dexamethasone 1 mg/kg with a maximum of 12-16mg. MDI treatments (with spacer) Weight (Dose) Notes ≤ 10 Kg 4 puffs Use facemask or mouthpiece ≥ 10 Kg 8 puffs Use mouthpiece Short albuterol Treatments Weight albuterol (mg) ipratropium (500 µg) ≤ 10 Kg 2.5 1 vial ≥ 10 Kg 5 1 vial Long albuterol Treatments Weight albuterol (mg) Total Volume (with NS) ≤ 10 Kg 10 8 mL ≥ 10 Kg 20 8 mL
Results	**Length of Stay:** • **Primary** ○ Corticosteroid <60 min group: 157 minutes ○ Corticosteroid >60 min group: 182 minutes • **Secondary:** • We compared children treated with dexamethasone (n = 101) to those treated with prednisolone (n = 781) with the primary outcome- LOS (Figure 3). There was a 19-minute decrease in mean LOS for children who received dexamethasone compared with prednisolone (95% CI: 4–35), p = 0.016. If dexamethasone was administered within the first 60 minutes of triage, the mean LOS decreased by 34 minutes (95% CI: 7–60), p = 0.013 • The impact of albuterol timing on LOS was also evaluated. Subjects who did not receive any albuterol were excluded from the analysis. All subjects who received a corticosteroid (either dexamethasone or prednisolone), within and after 60 minutes, were subdivided by the timing of the first albuterol treatment, either within or after 60 minutes from triage. Within the group of children who received corticosteroids within 60 minutes, we found no significant difference in LOS when albuterol was administered within 60 minutes or after 60 minutes (p = 0.66)

Keskin et al., 2016

Methods	Cohort Study
Participants	**Participants:** Children between the ages of 6-18 with history of asthma presenting with an asthma exacerbation **Setting:** Gaziantep University, Turkey. Pediatric Allergy and Asthma Unit, January 2009-April 2010 **Number Complete:** N = 94

	Percent of Male Subjects: 66% (62/94) **Group 1:** Nebulized fluticasone propionate (FP) (n=59) **Group 2:** Oral prednisone (P) (n=35) **Inclusion criteria:** 1) Child between ages of 6-18 2) Asthma exacerbation defined as increased symptoms of cough, wheezing, shortness of breath or chest tightness and albuterol use. 3) Moderate or severe asthma score (Qureshi F scale, published by NIH, interrater reliability is good) **Exclusion criteria:** 1) Fever 2) Fine rales with auscultation 3) Asthma score < 8 4) Use of systemic corticosteroid within 3 weeks prior to study 5) Those receiving inhaled corticosteroid at dose of >/= to 1000 mcg/day of budesonide or equivalent 6) Signs of systemic disease other than asthma 7) History of intubation for asthma exacerbation
Interventions	All children received two nebulized albuterol (dosed at 0.15 mg/kg) treatments 20 minutes apart. After the first hour of treatment, albuterol was given hourly until a decision was made to admit or discharge the patient Asthma scores were assessed before any treatment was started, including administration of a steroid, and then hourly during the first four hours of treatment prior to administration of nebulized albuterol **Group 1:** 4000 mcg of nebulized *fluticasone propionate (FP)* **Group 2:** 1mg/kg dose of *oral prednisone (P)* After discharge: ***Group 1 (FP):*** treated with *inhaled FP* at a dose of 1000 mcg/daily with a pressurized meter dose inhaler and spacer **Group 2 (*P*):** treated with *oral prednisone* 1mg/kg per day for 6 days
Outcomes	**Primary outcome:** Changes in exhaled breath condensate (EBC) Ctys-LTs and 8-isoprostane levels after four hours of single high-dose FP or oral prednisone. **Secondary outcome:** Asthma Scores four hours after treatment
Results	• Changes in exhaled breath condensate Ctys-LTs and 8-isoprostane levels after four hours of single high-dose FP or oral prednisone. *No significant changes found.* • Asthma Scores four hours after treatment ○ *Fluticasone propionate group* showed improvement of asthma score from 9 (8,10) to 6 (5,7), $p < 0.0001$. ○ *Oral prednisone group* showed improvement of asthma score from 10 (9,10) to 6 (5,8), $p < 0.0001$. *Here at CMH, dose oral prednisone at 2mg/kg for initial single dose and for a 4 (more) day burst after an asthma exacerbation."

Krebs, Flood, Peter, & Gerard, 2013

Methods	Retrospective Chart review examining 2 periods
Participants	**Setting**: ED of a 190-bed, not-for-profit, urban, tertiary care pediatric hospital, with an annual ED census of 47,000 visits, USA **Participants**: Chart review examined 2 periods, March 1 to May 31, 2008 (pre-protocol implementation) and March 1 to May 31, 2009 (post-protocol implementation). During these periods, all patients younger than 21 years treated in the ED with a primary diagnosis of asthma were subject to chart review **Number Complete**: 766 patients (393 pre-protocol and 373 post-protocol patients) **Gender, Males:** • **Pre-protocol:** 230 • **Post-protocol:** 242 **Age, Mean years (SD):** • **Pre-protocol:** 8.1 (4.6) • **Post-protocol:** 7.6 (4.7) **Inclusion Criteria:** Disposition diagnoses of, or containing, the following terms were used to identify patients: • asthma, acute asthma, status asthmaticus, cough-variant asthma, and reactive obstructive airway disease **Exclusion Criteria:** • Younger than 2 years • First reported episode of wheezing • Comorbid conditions including unrepaired congenital heart disease, sickle cell disease, cystic fibrosis, pneumonia, and patients who did not receive albuterol during the ED visit
Interventions	**Pre-Protocol Implementation:** • No formalized scoring system used to assess asthma severity • Continuous nebulized albuterol (CNA) versus intermittent nebulized albuterol (INA) dosing, ipratropium administration, and steroid administration were determined on an individual basis by treating physician **Post-Protocol Implementation:** • Asthma severity determined using a modified Wood and Downes clinical asthma score (CAS) ○ CAS <3 receive INA delivered over 15min (2.5mg for pts <20kg, 5mg for pts ≥20kg) ○ CAS ≥3 receive CNA with ipratropium delivered over 1 hour (10mg albuterol per 250mcg ipratropium for pts <20kg, 20mg albuterol/500mcg ipratropium for patients ≥20kg) and 2mg/kg of oral or IV steroid (maximum dose 60mg). ○ CAS determined by triage nurse and appropriate treatment pathway initiated ○ Placed on continuous pulse oximetry

	○ Based repeated CAS, patients continue to receive albuterol treatments as per the protocol until a disposition is determined, either home or admission (CAS of 3 or greater are required to receive 3 full hours of CNA before admission level is determined)
Outcomes	Adverse Events, ED length of stay (LOS), return visits to ED within 7 days
Results	• No significant adverse drug effects, including tachyarrhythmia and symptomatic hypokalemia, were identified during the 2 study periods • ED LOS, mean (SD), min: ○ Pre-protocol 187.2 (105.5) ○ Post-protocol 217.8 (115.6) *P=<0.01* • Return visit to our ED w/in 7 days: ○ Pre-protocol 12 (3.1) ○ Post-protocol 6 (1.6) *P=0.19*

Wyatt, Borland, Doyle, & Geelhoed, 2015

Methods	Randomized, single-blind, controlled equivalence trial
Participants	**Setting:** Princess Margaret Hospital for Children in Australia; June 2007 to January 2011 Randomized into study: n = 416 • Group 1: salbutamol (SABA) + prednisolone + ipratropium: n = 209 • Group 2: salbutamol + prednisolone; n = 207 **Received allocated intervention**: n = 410 • Group 1: n = 205, (174 analyzed) • Group 2: n = 205 (173 analyzed) **Gender, males (%):** • Group 1: n = 105 (60.3%) • Group 2: n = 110 (63.6%) **Age, years (median):** • Group 1 = 4.3 • Group 2 = 4.1 **Inclusion Criteria**: Age 2-15 years, acute wheezing illness of moderate severity (according to National Asthma Council Australia), previous history of asthma or first presentation **Exclusion Criteria:** Oxygen saturations less than 90%, cyanosis, inability to speak secondary to breathlessness, silent chest or abnormal conscious state, chronic respiratory illness, received ipratropium in the preceding 6 hours Power: 173 subjects per arm are needed to show 15% difference with 80% power
Interventions	**Group 1:** • Salbutamol 100 mcg/puff x 3 doses (6 puffs per dose for 2-5 years; 12 puffs for 6-12) • Oral prednisolone 1 mg/kg x 1 dose

	• Ipratropium 21 mcg/puff x 3 doses (4 puffs per dose for 2-5 years; 8 puffs for 6-12) **Group 2:** • Salbutamol 100 mcg/puff x 3 doses (6 puffs per dose for 2-5 years; 12 puffs for 6-12) • Oral prednisolone 1 mg/kg x 1 dose
Outcomes	**Primary Outcome:** • Hospital admission rates **Secondary Outcomes:** • Admission to emergency observational unit vs. inpatient ward • Adverse events
Notes	• Authors stated this was an intent-to-treat trial but only analyzed subjects who received allocated intervention, met inclusion criteria, and were not missing any data. Therefore it is a per-protocol analysis • Not all subjects received prednisolone due to a change in prescribing guidelines during the trial; 94.8% in group 1 and 91.9% in group 2 received steroids • Primary outcome measure included both emergency observation unit (>4hr emergency care) AND inpatient admissions; other hospitals may not have considered emergency observational unit as "admissions" since they were not technically inpatient ○ criteria for inpatient admission included oxygen requirement or unable to be discharged from emergency observational unit within 24 hours • No criteria for admission was specified • Primary investigator was out of the country for 18 months during trial • Admission rate was considerably higher than expected (or predicted) for both groups (actual 67.1% vs. pre-trial prediction of 40-44%) • Subjects with "language difficulties" were not approached for enrollment

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized using blocked computerized random number generation
Allocation concealment (selection bias)	Low risk	Treatment assignments concealed in opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk	Placebo option was not available so only physicians were blinded to treatment; blind was likely adequate to maintain provider neutrality
Blinding of outcome assessment (detection bias)	Low risk	No blinding of outcome assessment but outcome measurement (admission rates) unlikely to be affected by blinding

Incomplete outcome data (attrition bias)	High risk	Authors stated they used intent-to-treat but actually analyzed per-protocol. Only 83% of subjects randomized to the either the intervention or control arm were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes were reported as expected but definition of admission seems inappropriate; would have liked to have seen statistical analysis of emergency observational unit vs. inpatient ward admissions
Other bias	Unclear risk	Not sure how much bias the notes above introduce, but there are a number of concerns

Zemek et al., 2012

Methods	Time-Series Controlled Trial (Before and After Initiation of a Medical Directive Permitting Triage Nurse Initiation of Oral Steroids)
Participants	**Setting:** The ED in Children's Hospital of Eastern Ontario, Canada- a tertiary hospital **Before / After Participant Groups:** • **Group 1: After Intervention:** Nurse-initiated intervention phase, n = 308 • **Group 2: Before intervention:** Physician-initiated intervention phase, n = 336 **Completed Study:** • **Group 1:** Nurse-initiated phase n = 308 • **Group 2:** Physician-initiated phase n = 336 **Male gender, *n* (%) :** • **Group 1:** Nurse-Initiated phase males n = 199 (64.6) • **Group 2:** Physician-initiated phase males n = 225 (67.0) **Mean age, years (SD):** • **Group 1:** Nurse-Initiated phase: 5.9 (3.8) • **Group 2:** Physician-initiated phase: 6.3 (3.6) **Inclusion Criteria:** • Aged 2 to 17 years • History of asthma defined by physician diagnosis or third or greater episode of wheezing responsive to $ß_2$ agonists • Moderate to severe acute asthma exacerbation Pediatric Respiratory Assessment Measure (PRAM) score $\geq$ 4 **Exclusion Criteria:** Children with the following: • PRAM score < 4 • Chronic lung disease (e.g., bronchopulmonary dysplasia, cystic fibrosis); • Chronic cardiac, metabolic, neuromuscular disorders;

	• Those who had undergone tracheostomies or in whom treatment with steroids or inhaled ß$_2$ agonists were contraindicated (e.g., patients on beta-blockers or those with known hypersensitivity to salbutamol, ipratropium bromide, or dexamethasone, or a history of adrenal suppression); • Those who had exposure to varicella in the preceding 3 weeks, in the absence of immunization; • Those who required immediate life-sparing resuscitation; • And those who had received treatment with oral steroids in the previous 14 days. **Power Analysis:** Sample size calculated 242 patients per group
Interventions	**Group 1:** Physician initiated phase (4 months immediately before introducing triage nurse initiated corticosteroids) • Children with moderate exacerbations (PRAM score of 4–7) received 3 salbutamol treatments by metered-dose inhaler during the first hour and continued hourly treatment as needed. • Children with severe exacerbations (PRAM score $\geq$ 8) received 3 salbutamol plus ipratropium bromide nebulizations for the first hour and continued hourly salbutamol treatment as needed. Physicians were encouraged to prescribe oral corticosteroids for patients with moderate and severe exacerbations. **Group 2:** Triage initiated phase 4 months subsequent to the introduction of triage nurse initiated corticosteroid • PRAM score of 1–3: Patient will be managed per the initial bronchodilator medical directive only (the authors did not describe this directive) • PRAM score of 4–11: Patient will be managed per the initial bronchodilator medical directive (see first point under Group 2 below) and receive 1 dose of oral dexamethasone (0.3 mg/kg per dose, with maximum dose of 12 mg). The dose of dexamethasone will be given immediately after the first bronchodilator treatment and before the second dose of the initial 3 back-to-back bronchodilator treatments. (Specifically, the patient will receive the first inhaled treatment, then oral dexamethasone, then the second inhaled treatment, and then the third inhaled treatment.) • PRAM score of 12: Notify physician immediately.
Outcomes	**Primary outcome(s):** • Time to clinical improvement (Time spent in the ED between arrival and a persistent reduction of the PRAM score by greater than or equal to 3 points over 2 assessments). **Secondary outcome(s)** • Total time in the ED, admission rate, time to mild status (defined as PRAM score persistently less than or equal to 3, indicative of overall improvement in discharged patients), and ED return visits for asthma over 7 subsequent days. **Potential confounders:** • Previous hospitalizations, age, concurrent viral illness, such as upper respiratory tract infection, tobacco smoke exposure, and degree of severity at presentation.
Results	• Children in the triage nurse–initiated phase improved significantly earlier compared with those in the physician initiated phase, with a median difference of 24 minutes between phases (95% CI: 1–50

	minutes; 158 minutes [interquartile range: 139–177] vs 182 minutes [interquartile range: 168–202]; *P* = .04 • Forty-one patients were admitted before PRAM score improvement of greater than or equal to 3, so they were censored in the analysis (median time to censoring was 536 minutes in physician-initiated vs 593 minutes in nurse-initiated phase). • The physician-initiated phase had a higher proportion with preceding upper respiratory tract infections. • Significant efficiency gains were associated with the nurse-initiated phase: ○ Hospital admission was significantly less likely, ○ Children received steroids faster, ○ Children improved to mild status faster, ○ Children had an earlier time to discharge • This strategy could optimize the function of multidisciplinary teams and have a significant impact on the burden of asthma in Emergency Departments. **Description of procedure: (includes dosing)** a. Identify patients in the ED with breathing difficulties and a history of asthma, as per the asthma critical pathway inclusion/exclusion criteria b. Complete a respiratory assessment by using PRAM and baseline vital signs, and document on the asthma critical pathway and/or triage document c. Weigh the patient and document on the asthma critical pathway and/or triage document d. Determine the treatment regimen based on the patient's PRAM e. PRAM score of 1–3: Patient will be managed per the initial bronchodilator medical directive only. f. PRAM score of 4–11: Patient will be managed per the initial bronchodilator medical directive and receive 1 dose of oral dexamethasone (0.3 mg/kg per dose, with maximum dose of 12 mg). The dose of dexamethasone will be given immediately after the first bronchodilator treatment and before the second dose of the initial 3 back-to-back bronchodilator treatments. (Specifically, the patient will receive the first inhaled treatment, then oral dexamethasone, then the second inhaled treatment, and then the third inhaled treatment.) PRAM score of 12: Notify physician immediately e. Any questions regarding the appropriateness or dosage of dexamethasone should be discussed with the physician before administration. f. If at any time the patient no longer responds appropriately to treatment or deteriorates, immediately notify the physician

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