Office of Evidence Based Practice (EBP) – Epinephrine (IM) for Asthma in the ED/UCC

Specific Care Question

For the child who presents to the Emergency Department or Urgent Care Center (ED/UCC) should epinephrine 1:1000 IM be considered in a severe exacerbation with impending respiratory failure?

Question Originator

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

Literature Summary

Background. Standard treatment for asthma exacerbations is short-acting beta$_2$-agonists (SABA) and oral systemic corticosteroids (Plus, 2017, December 11). The Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention (2018, p. 84) makes a strong recommendation that epinephrine be used for confirmed food allergy, and is indicated in, along with standard therapy, for asthma exacerbation associated with anaphylaxis and angioedema. GINA states epinephrine "is not a routinely indicated for other asthma exacerbations" (GINA, 2018, p. 84). Patients should be identified as high risk, and the education concerning the difference between anaphylaxis and asthma exacerbation should occur regularly (GINA, 2018, p. 65). The Expert Panel Report-3, Guidelines for the Diagnosis and Management of Asthma (NAEP-EPR-3, 2007) recommends against epinephrine as a quick-relief medication in children < 12 years of age (NAEP-EPR- 3. 2007, p. 317), youths > 12 years of age (NAEP-EPR-3 2007, p. 350), and during exacerbations (NAEP-EPR-3, 2007, p. 386). The primary reasons are there is no proven benefit over aerosol medication and in high doses there is potential for excessive cardiac stimulation (NAEP-EPR-3, 2007, p. 317).

Study characteristics. The search for suitable studies was completed on April 24, 2018. Amanda Nedved, MD reviewed the 39 titles and abstracts found in the search and identified no articles believed to address the question. On June 8, 2018, two additional searches, expanding the search date back to 1980, were performed. The first search centered on studies with adults as subjects and yielded 67 studies. The second search filtered for pediatrics studies only and yielded 18 studies. Duplicates were removed, and 92 articles addressed the question (39 from the original search plus 53 from the latter two searches. Amanda Nedved, MD and Irene Walsh, MD reviewed the additional 53 studies and selected 13 studies by reviewing title and abstracts. Following an in-depth review evaluating intervention, comparison, and outcomes reported four studies were selected to provide evidence for this question. Three RCTs compared epinephrine with SABA versus SABA alone for the outcome peak expiratory flow rate (PEFR) at 20 minutes (Becker, Nelson, & Simons, 1983; Kornberg, Zuckerman, Welliver, Mezzadri, & Aquino, 1991; Sharma & Madan, 2001). Becker et al. (1983) provided figures with no data; therefore, it could not be included in the meta-analysis. Becker et al. (1983) also reported on the outcome Adverse Events. Schwartz, Lipton, Warburton, Johnson, and Twarog, (1980) compared epinephrine to terbutaline with an outcome of FEV_1 (% predicted) at 20 minutes.

Key results. Our parent guideline (GINA, 2018, p. 84) recommends EPI IM in addition to conventional therapy for an asthma exacerbation associated with anaphylaxis and angioedema. We make a conditional recommendation to consider epinephrine 1:1000, IM, 0.1 mg, (EPI IM) for the patient in the ED with an asthma exacerbation that is not responding to conventional treatment. If the patient is not responding to conventional therapy, the use of EPI IM likely outweighs any adverse side effects. EPI IM may decrease risk of intubation and mechanical intubation. When epinephrine, 0.1 mg (1:1000) (IM), was added to treatment with SABA improvement in PEFR at 20 minutes after treatment was not significantly different from treatment with SABA alone (Becker et al., 1983; Kornberg et al., 1991; Sharma & Madan, 2001), see Table 2 and Figure 3. When epinephrine was compared to terbutaline, change in FEV_1 (% predicted) was not different (Schwartz et al., 1980), see Figure 5.

Summary by Outcome

Pulmonary Function. Three studies (*N* = 121) compared epinephrine to SABA (Becker et al., 1983; Kornberg et al., 1991; Sharma & Madan, 2001) and one study (*N* = 124) compared epinephrine to terbutaline (Schwartz et al., 1980). The evidence is graded as very low for both comparisons. Risk of bias was very serious as subjects, study personnel, or outcomes assessors were not blinded, or it was not reported if they were blinded. Per protocol analysis was performed, see Figure 2. Imprecision is very serious as there is a small number of studies, with a small number of subjects for both

comparisons. Sample size was not calculated in the studies, it is unknown if the sample was adequate to detect a difference in this outcome. For the two studies comparing epinephrine to SABA, Kornberg et al. (1991) and Sharma and Madan, (2001), the change % predicted PERF from baseline was not statistically different when subjects were treated with epinephrine 0.1 mg (IM) versus those treated with SABA nebulized (NEB), *MD* = 0.02. 95% CI [-0.29, 0.32]. Becker et al. (1983) reported there was not significant difference between groups treated with epinephrine 0.1 mg/kg, maximum 0.4 ml) versus those treated with SABA (INH) in FEV_1 at 15 minutes post treatment. A summary statistic was not provided. Schwartz et al., (1980) reported no difference in % predicted FEV1 when epinephrine was compared with terbutaline *MD* = 2.6, 95% CI [-10.34, 5.14], see Figure 5.

Adverse Events. One study (*N* = 40) reported on adverse events (Becker et al., 1983). The evidence is graded as low. Risk of bias is low in this study (see Figure 2), however, imprecision is very serious. There were no adverse events (nausea, vomiting, tremor, headache, palpitations, excitement, and pallor) in the SABA group, but 10 subjects in the epinephrine group reported at least one adverse event. Adverse events are not the primary outcome, it is uncertain if there were enough subjects to detect a difference on this outcome. A summary statistic was not reported, see Figure 4.

Search Strategy and Results (see PRISMA diagram)

April 24, 2018 PubMed

Specific study types:

Search: ("Asthma"[tw] OR "status asthmaticus") AND ("Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[tw] OR "emergency department"[tw] OR "accident and emergency"[tw] OR "Acute Disease"[Mesh] OR exacerbation[All Fields] OR attack[All Fields]) AND "Epinephrine"[tw] AND ("humans"[MeSH Terms] AND (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR "Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR systematic[sb]) AND English[lang] AND (child OR children OR childhood OR pediatr* OR paediatr*) AND ("2010"[PDAT] : "2018"[PDAT])) 15 results

All study types:

Search: ("Asthma"[tw] OR "status asthmaticus") AND ("Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[tw] OR "emergency department"[tw] OR "accident and emergency"[tw] OR "Acute Disease"[Mesh] OR exacerbation[All Fields] OR attack[All Fields]) AND "Epinephrine"[tw] AND ((child OR children OR childhood OR pediatr* OR paediatr*) AND ("2010"[PDAT] : "2018"[PDAT])) 33 results

June 8 2018 PubMed

Pediatrics only:

("Asthma"[tw] OR "status asthmaticus") AND ("Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[tw] OR "emergency department"[tw] OR "accident and emergency"[tw] OR "Acute Disease"[Mesh] OR exacerbation[All Fields] OR attack[All Fields]) AND "Epinephrine"[tw] AND ("humans"[MeSH Terms] AND (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR "Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR systematic[sb]) AND English[lang] AND (child OR children OR childhood OR pediatr* OR paediatr*) AND ("1960"[PDAT] : "2010"[PDAT])) 18 results

All ages:

("Asthma"[tw] OR "status asthmaticus"[All Fields]) AND ("Emergency Service, Hospital"[Mesh] OR "Emergency Nursing"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Emergency Medicine"[tw] OR "emergency department"[tw] OR "accident and emergency"[tw] OR "Acute Disease"[Mesh] OR exacerbation[All Fields] OR attack[All Fields]) AND "Epinephrine"[tw] AND ("humans"[MeSH Terms] AND (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR "Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR systematic[sb]) AND English[lang] AND ("1960"[PDAT] : "2018"[PDAT])) 67 results

Studies Included in this Review (in Alphabetical Order)

Becker et al. (1983)

Kornberg et al. (1991)

Schwartz et al. (1980)
Sharma and Madan, (2001)

Studies Not Included in this Review with Exclusion Rationale (in Alphabetical Order)

Author (YYYY)	Reason for exclusion
Biagini and Myers (2015)	Doesn't answer the question
Brandstetter et al. (1980)	Doesn't answer the question -- dose comparison study
Gotz et al. (1981)	Doesn't answer the question -- dose comparison study
Hon and Leung, (2017)	Systematic review that references papers already excluded
Indinnimeo, Chiappini, Miraglia Del Giudice, & Italian Panel for the Management of Acute Asthma Attack in Children, (2018)	Make a recommendation to not use epinephrine based on GINA (2015), EPR-3 (2007) and British Thoracic Society, SIGN guideline (2016)
Karetzky (1980)	Doesn't answer the question -- dose comparison study
Mondal et al. (2014)	Studied inhaled epinephrine
Schwartz et al. (1980)	Doesn't answer the question
Turnbull et al. (2010)	Case report
Wade and Chang, (2015)	IV epinephrine

Method Used for Appraisal and Synthesis

The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize the XXX included studies. GRADEpro GDT (Guideline Development Tool) is the tool used to create the Summary of Findings Tables for this analysis.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

Librarian responsible for the literature search:

Keri Swaggart, MLIS, AHIP

EBP Scholar's responsible for analyzing the literature

Kelly Huntington, RN, BSN, CPN
Kim Robertson, MBA, MT-BC
Hope Scott, RN CPEN
Rhonda Sullivan, MS, RD, LD

EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this Document

Nancy H. Allen, MS, MLS, RD, LD, CPHQ

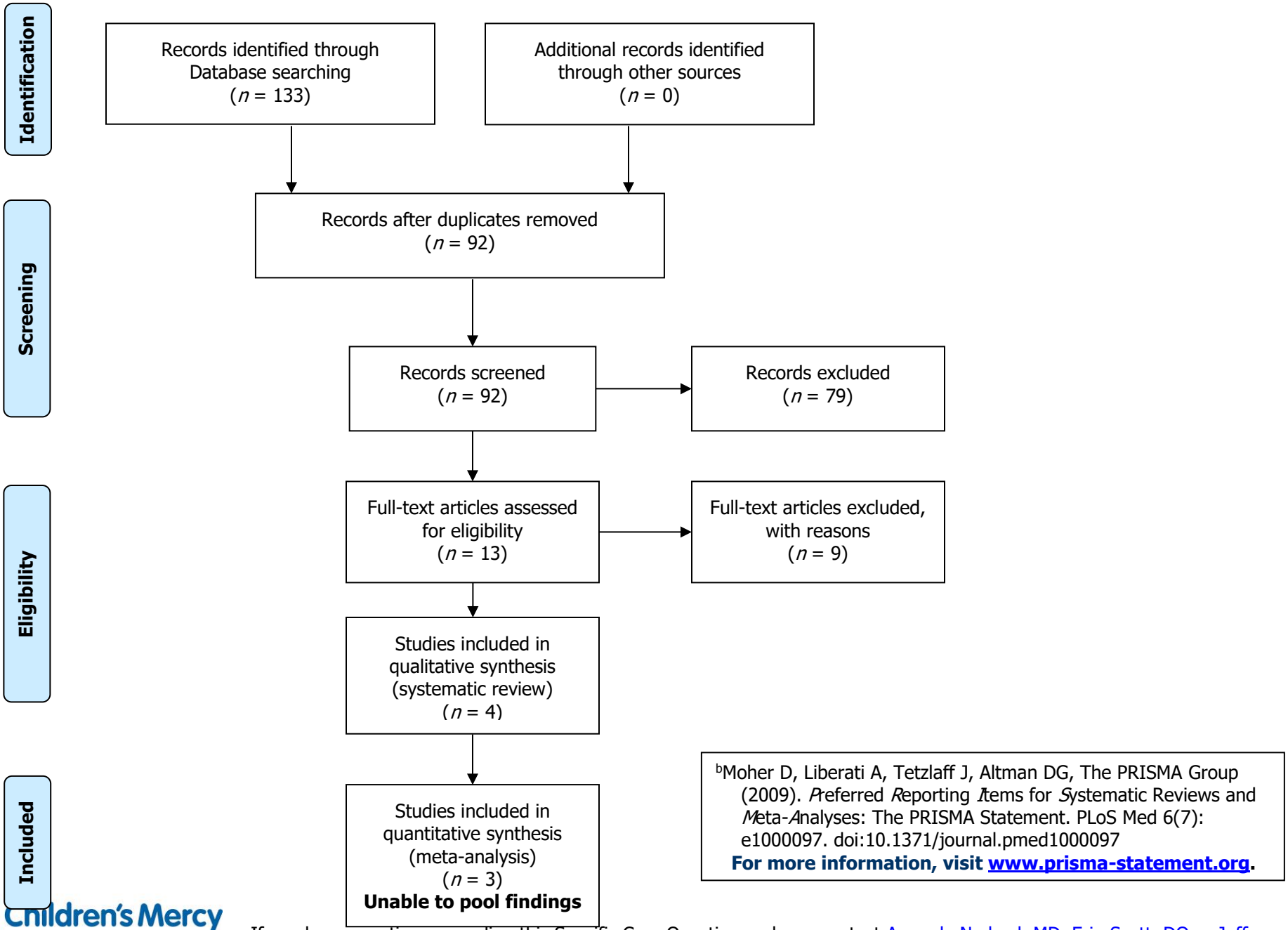
Acronyms Used in this Document

Acronym	Explanation
ED	Emergency department
EPR-3	Expert Panel Report-3, Guidelines for the Diagnosis and Management of Asthma
FEV_1	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
IM	Intramuscular

INH	Inhaled
MD	Mean Difference
NEB	Nebulized
PEFR	Peak expiratory flow rate
SABA	Short acting $beta_2$ agonist
SIGN	Scottish Intercollegiate Guidelines Network
UCC	Urgent Care Center

Date Developed/Updated: October 2018

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[b]



[b]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure ***2 Risk of Bias Summary***

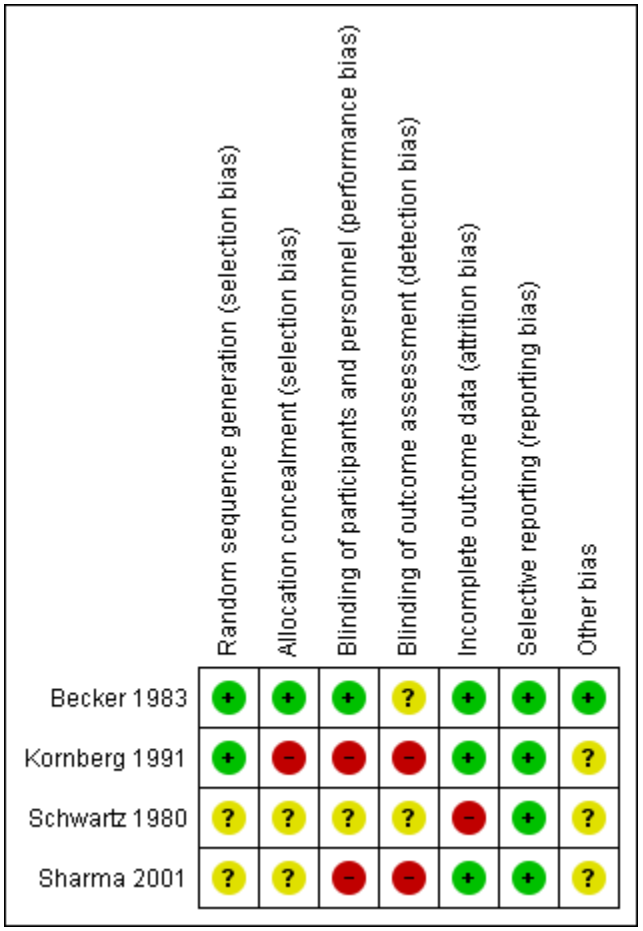


Table 1
Grade Profiles

Subcutaneous Epinephrine Compared to Nebulized SABA for Asthma Exacerbation in the ED/UCC											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Neb SABA	**With Sub q Epi**		**Risk with Neb SABA**	**Risk difference with Sub q Epi**
Percent predicted PEFR change from baseline											
81 (2 RCTs)	very serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	39	42	-	The mean percent predicted PEFR change from baseline was **0**	MD **0.02 higher** (0.29 lower to 0.32 higher)
Adverse events											
40 (1 RCT)	not serious	not serious	not serious	very serious [c]	none	⨁⨁◯◯ LOW	0/20 (0.0%)	10/20 (50.0%)	**OR 41.00** (2.18 to 770.08)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Neither study blinded personnel, participants, or outcome assessors.
b. There is only two included studies, and a low number of subjects for this comparison *N* = 81.
c. There is only one study that reported this outcome, with a total of 40 subjects. There were zero adverse events in the SABA group.

Epinephrine Compared to Terbutaline for Asthma Exacerbation in the ED/UCC											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Terbutaline	**With Epinephrine**		**Risk with Terbutaline**	**Risk difference with Epinephrine**
Percent predicted FEV1											
124 (1 RCT)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	64	60	-	The mean percent predicted FEV2 was **0**	MD **2.6 lower** (10.34 lower to 5.14 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Poorly reported study. Selection bias (randomization, and allocation concealment), performance (blinding of participants and personnel), and detection bias (blinding of outcome assessment are not discussed, and per protocol analysis was performed.

b. Comparison includes one study with 124 subjects.

Table *2*
Characteristics of Studies

Becker 1983

Methods	Double blind randomized control trial
Participants	**Setting:** Children's Hospital at the University of Manitoba in Winnipeg Canada **Randomized into study:** *N = 40* • **Group 1:** Epinephrine subcutaneously *n = 20* • **Group 2:** Inhaled salbutamol *n = 20* **Completed Study:** *N = 40* • **Group 1:** Epinephrine subcutaneously *n = 20* • **Group 2:** Inhaled salbutamol *n = 20* **Gender, males:** • **Group 1:** Epinephrine subcutaneously *n* = (60%) • **Group 2:** Inhaled salbutamol *n* = (65%) **Age, years** (mean) (SE): • **Group 1:** Epinephrine subcutaneously 10.4 $\pm$ 0.7 • **Group 2:** Inhaled salbutamol 10.6 $\pm$ 0.7 **Inclusion Criteria:** • Children ages 6-17 years • Came to the emergency room because of acute asthma during September and October 1981 • Previously documented reversible airway obstruction by pulmonary function testing • Had not received treatment for the acute episode within 2 hours **Exclusion Criteria:** • No previously documented reversible airway obstruction by pulmonary function testing • Received treatment for the acute episode within 2 hours **Power Analysis:** Not reported
Interventions	• **Group 1:** Epinephrine subcutaneously (1:1000, 0.01 ml/kg, maximum 0.4 ml) + inhaled saline • **Group 2:** Inhaled salbutamol (0.5% solution, 0.02 ml/kg, maximum 0.4 ml) + injected saline
Outcomes	Primary outcome(s): • Efficacy and safety of inhaled salbutamol and subcutaneous epinephrine Safety outcome(s): adverse effects including nausea, vomiting, tremor, headache, palpitations, excitement and pallor seen in 10 of 20 patients given epinephrine and no adverse effects were seen in the group given salbutamol and other than sinus tachycardia no arrhythmias were noted
Notes	• There was no significant difference between groups in improvement in percent FEV_1/FVC 30 minutes after therapy • No significant difference between groups in pulmonary index, respiratory rate, heart rate, and diastolic blood pressures 30 minutes after therapy • No significant difference between groups in the outcome of acute episode with regard to treatment, admission at initial visit, return to emergency room, subsequent admission on return, or total number of admission within seven days

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Group assignment by a pharmacist who was not treating the patient
Blinding of participants and personnel (performance bias)	Low risk	Each participant received a placebo of saline injection or inhaler, a nurse covered the injection site with gauze to prevent observation of presence or absence of skin blanching from injection
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	All completed the study
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Kornberg 1991

Methods	Prospective, randomized, controlled trial, ED
Participants	**Setting:** Children's Hospital of Buffalo pediatric emergency department between November 1987 and June 1988 **Randomized into study:** *N* = 43 • **Group 1 (Sus-Phrine + albuterol):** *n* = 20 • **Group 2 (Albuterol alone):** *n* = 23 **Completed study:** *N* = 43 • **Group 1 (Sus-Phrine + albuterol):** *n* = 20 • **Group 2 (Albuterol alone):** *n* = 23 **Gender, males:** *N* = 22 • **Group 1 (Sus-Phrine + albuterol):** *n* = 8 • **Group 2 (Albuterol alone):** *n* = 14 **Age, years (mean):** 8.9 • **Group 1 (Sus-Phrine + albuterol):** 9.6 +/- 3.5 • **Group 2 (Albuterol alone):** 8.2 +/- 3.8 **Inclusion criteria:** • Diagnosis of asthma according to the criteria of the American Thoracic Society • Acute asthma presentation • > 6 years of age **Exclusion criteria:** • History of cardiac disease

	• Chronic pulmonary disease aside from asthma • Current use of SABA **Power analysis:** Power analysis PEFR and respiratory rate was conducted. Using an alpha = 0.05 (two-sided) and a beta 0.20 (one-sided), study sample size would detect an additional improvement in the predicted PEFR of 10% and a decrease of 5 breaths per minute (with 80% assurance) for Group 1.
Interventions	**Group 1 (Sus-Phrine + albuterol):** • Single subcutaneous injection of Sus-Phrine, 0.005 ml/kg, to a maximum dose of 0.15 ml at enrollment • Nebulized, non-pressurized albuterol 2.5 mg in 3 ml of normal saline within 5 minutes of enrollment **Group 2 (Albuterol alone):** • Nebulized, non-pressurized albuterol 2.5 mg in 3 ml of normal saline within 5 minutes of enrollment Both groups received albuterol treatments every 20-30 minutes as clinically necessary after initial enrollment therapy.
Outcomes	**Primary outcomes:** Recorded at pre-treatment, 20 minutes and 2 hours • Clinical score • PEFR - best of three readings were accepted. • Respiratory rate • Heart rate
Notes	Only patients who were six years and over were given PEFR testing resulting in the following: • **Group 1 (Sus-Phrine + albuterol):** *n*= 17 • **Group 2 (Albuterol alone):** *n= 14* Sus-Phrine contains 5 mg of epinephrine per 1 ml, compared to 1 mg per ml for standard epinephrine solution for subcutaneous injection. Eighty percent of the available epinephrine in Sus-Phrine is in a suspension that is absorbed over six to eight hours. The remaining 20% is available in the rapidly absorbing form. **Results:** PEFR, % predicted (percentage of increase compared to pretreatment data) at 20 minutes **Sus-Phrine + albuterol, PEFR, % predicted:** 13% +/- 2.2% **albuterol alone, PEFR, % predicted:** 15% +/- 2.3% The difference in PEFR % predicted was not statistically different, nor was clinical score, respiratory rate decrease, or heart rate decrease at either 20 minutes or 2 hours after administration.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Coin toss was used to randomize participants in to group
Allocation concealment (selection bias)	High risk	Study was not blinded
Blinding of participants and personnel (performance bias)	High risk	Study was not blinded

Blinding of outcome assessment (detection bias)	High risk	Study was not blinded
Incomplete outcome data (attrition bias)	Low risk	Reported an all stated outcomes
Selective reporting (reporting bias)	Low risk	Reported on all participants
Other bias	Unclear risk	

Schwartz 1980

Methods	Randomized Controlled Trial
Participants	**Setting:** Four month study conducted in the Emergency Ward at the Children's Hospital Medical Center in Boston, MA **Randomized into study:** *N* = 280 • **Group 1:** Epinephrine, Did not report • **Group 2:** Terbutaline sulfate, Did not report • **Group 3:** Isoetharine hydrochloride, Did not report **Completed Study:** *N* = 269 • **Group 1:** Epinephrine *n* = 66 • **Group 2:** Terbutaline sulfate *n* = 76 • **Group 3:** Isoetharine hydrochloride *n* = 127 **Gender, males:** • **Group 1:** Epinephrine, Did not report • **Group 2:** Terbutaline sulfate, Did not report • **Group 3:** Isoetharine hydrochloride, Did not report **Age, years (mean):** • **Group 1:** Epinephrine, Did not report • **Group 2:** Terbutaline sulfate, Did not report • **Group 3:** Isoetharine hydrochloride, Did not report **Inclusion Criteria:** • Diagnosis of acute asthma • Between the ages of 5 and 21 years • Came to the Emergency ward **Exclusion Criteria:** • Received parenteral therapy for the present attack • Were in "impending respiratory failure" • Pregnant • Experiencing their first attack of asthma **Power Analysis:** Did not report
Interventions	• **Parenteral Treatment Protocol** ○ **Group 1**

	▪ Epinephrine (1mg/mL concentration) was administered at 15-minute intervals to a total of three doses (0.01 mg/kg, with a maximum dose of 0.4mL) ○ **Group 2** ▪ Terbutaline sulfate (1mg/mL concentration) was administered at 15-minute intervals to a total of three doses (0.01 mg/kg, with a maximum dose of 0.4mL) ○ **Both Group 1 and Group 2** ▪ When required, further therapy was provided by inhaled isoetharine hydrochloride (Bronkosol). After two doses of isoetharine, aminophylline was administered intravenously (5 to 7 mg/kg during 20-minute period), if clinically indicated. Ten minutes after completion of the aminophylline administration, a decision regarding discharge or admission to hospital was made by the house officer and senior resident in charge of the emergency ward • **Inhalation** ○ **Group 3** ▪ Inhalation of 0.5 mL of isoetharine hydrochloride in 2 mL of saline solution delivered by intermittent positive pressure breathing (IPPB) using a respirator powered with 40% oxygen at a pressure of approximately 15 cm H_2O. ▪ Repeated when necessary for a total of three treatments at 20-minute intervals. ▪ Further therapy included up to two doses of a subcutaneous adrenergic agent and, if required, IV aminophyline ○ At any stage, treatment was discontinued, and the patient was discharged from the emergency ward when he/she was clinically judged to be free of asthma by resolution of respiratory distress and improvement in auscultatory findings
Outcomes	**Primary Outcomes** • Compare the efficacy of subcutaneous epinephrine with terbutaline sulfate • Compare routes of administration of adrenergic agents (subcutaneous vs inhaled) ○ Frequency of adverse side effects ○ Clinical outcomes (discharge disposition) ○ Clinical scores and FEV
Notes	

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Did not discuss
Allocation concealment (selection bias)	Unclear risk	Did not discuss
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind coded vials

Blinding of outcome assessment (detection bias)	Unclear risk	Did not report
Incomplete outcome data (attrition bias)	High risk	Used per protocol analysis
Selective reporting (reporting bias)	Low risk	All outcomes are reported on
Other bias	Unclear risk	The study appears to be free of other sources of bias

Sharma 2001

Methods	Prospective RCT
Participants	**Setting:** Emergency Department, India, Pediatrics **Randomized into study:** *N* = 50 • **Group 1, Subcutaneous epinephrine:** *n* = 25 • **Group 2, Nebulized salbutamol:** *n* = 25 **Completed Study:** *N* = • **Group 1, Subcutaneous epinephrine:** *n* = 25 • **Group 2, Nebulized salbutamol:** *n* = 25 **Gender, males:** (%) • Not reported **Age, years** (mean) (SD): • **Group 1, Subcutaneous epinephrine:** 11.08 (0.4) • **Group 2, Nebulized salbutamol:** 10.3 (0.5) **Inclusion Criteria:** • 6-14 years of age • acute exacerbation of asthma o Increase coughing o Inability to speak in a sentence o Inability to take a drink o Wheeze o Chest recession **Exclusion Criteria:** • Severe exacerbation, life-threatening o Cyanosis o Silent chest o Poor air entry o Inability to speak 3-4 words o PERF < 30%for height • Bronchodilator within 6 hours of prior to presentation • History of a prior intensive care unit admission for asthma .

	Power Analysis: Not reported
Interventions	Both groups received oxygen, and kept a minimum of four hours under observation • **Group 1, Subcutaneous epinephrine: 0.**01 ml/kg/dose of subcutaneous epinephrine 1:1000 (1 mg/ml), maximum 0.3 ml, to be repeated twice at 20 minute intervals • **Group 2: Nebulized salbutamol: 0**.03 ml/kg. dose (150 microgram/kg/dose) of 0.5% respiratory solution to a maximum of 1 ml (5 mg) per dose, repeated twice at 20 minute intervals
Outcomes	**Primary outcome(s):** % predicted PEFR **Secondary outcome(s):** Improvement in respiratory rate, heart rate, dyspnea, use of accessory muscles, auscultation, ability to drink and speak in a sentence
Notes	

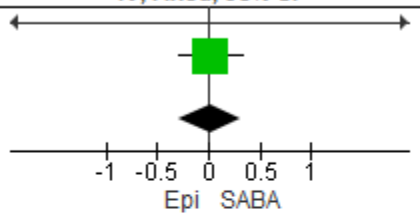
Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	State randomization, but do not describe method
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Not stated, although it would have been easy to blind subjects and personnel
Blinding of outcome assessment (detection bias)	High risk	Not stated, although it would have been easy to blind outcome assessors
Incomplete outcome data (attrition bias)	Low risk	All completed the study
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	

Figure 3.
Comparison: Epinephrine (IM) vs. SABA (NEB), Outcome: PEFR (% predicted) change from baseline

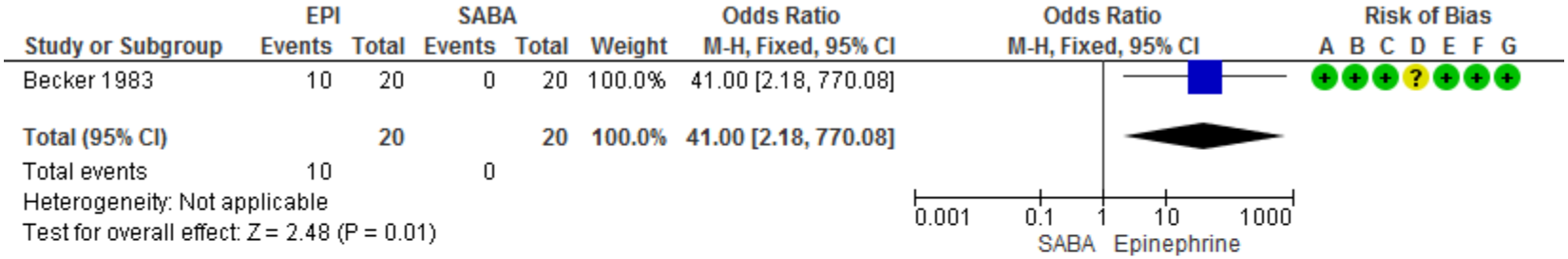
	Epi			SABA				Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**	**A B C D E F G**
Kornberg 1991	13	9.0708	17	15	8.6058	14	0.2%	-2.00 [-8.24, 4.24]		+ - - - + + ?
Sharma 2001	23.1	0.6	25	23.08	0.5	25	99.8%	0.02 [-0.29, 0.33]		? ? - - + + ?
Total (95% CI)			**42**			**39**	**100.0%**	**0.02 [-0.29, 0.32]**		

Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

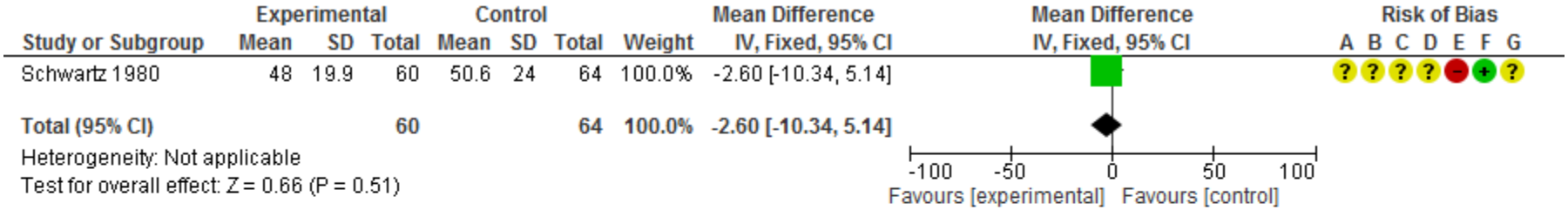
Figure 4.
Comparison Epinephrine (IM) vs. SABA (NEB), Outcome: Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5.

Comparison: Epinephrine versus Terbutaline, Outcome: FEV_1 % predicted at 20 minutes



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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