Appendix D

Question 5: Updated October 2016- For the child who presents with the symptoms of bronchiolitis should inhaled racemic epinephrine be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation

The AAP guideline recommends against the routine use of inhaled racemic epinephrine to treat acute bronchiolitis in both the inpatient and outpatient settings (Ralston et al., 2014). However, the Bronchiolitis CPG Team concludes the evidence is insufficient at this time to make a recommendation for against using racemic epinephrine.

The meta-analysis by Hartling et al., (2011) was analyzed using GRADEprofiler (GRADEpro). The evidence is GRADED as Moderate to Low quality. Risk of bias, specifically poorly reported allocation concealment and blinding were detected in the included studies. Studies were also inconsistent, which decreases confidence in the pooled results. Hartling et al., (2011) conclude that the evidence shows some reduction in hospital admission when children with bronchiolitis are treated with epinephrine. However, the short term of medication effect and the differences in timing of outcome measurements limit the quality of the evidence. There is no evidence to support the use of racemic epinephrine in the inpatient setting. See the GRADE table below.

In a series of studies (Skjerven et al., 2013, 2015) report on the same group of subjects who received either inhaled racemic epinephrine versus normal saline for acute bronchiolitis in the inpatient setting. In the first study, (Skjerven et al., 2013) LOS was not significantly between the two groups. In the second study (Skjerven et al., 2015), the same subjects were evaluated approximately 2 years later. For those who received racemic epinephrine at the acute bronchiolitis visit, a comparison was made between and went on to develop either recurrent bronchial obstruction, atopic eczema, or allergic sensitization and those who did not develop these conditions. The outcome was the LOS at the acute bronchiolitis visit. There was no difference in LOS between those who went on to develop atopic symptoms and those who did not.

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GRADEpro Table:

Quality assessment (Hartling et al., 2011)							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epinephrine vs placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Length of Stay (inpatients only) (range of scores: 2.45-2.9; Better indicated by lower values)												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	143	-	MD 0.35 lower (0.87 lower to 0.17 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Admission at enrollment or <24 hours (outpatient only (assessed with: Count)												
6	randomized trials	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/493 (12.6%)	93/502 (18.5%)[4]	RR 0.67 (0.5 to 0.89)	61 fewer per 1000 (from 20 fewer to 93 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Admissions overall up to 7 days (outpatient only) (assessed with: Count)												
3	randomized trials	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	none	88/437 (20.1%)	110/438 (25.1%)	RR 0.81 (0.63 to 1.03)	48 fewer per 1000 (from 93 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Outpatient clinical score at 60 minutes (Better indicated by lower values)												
6	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	490	485	-	MD 0.73 lower (1.13 to 0.33 lower)	⨁⨁⨁⨁ HIGH	CRITICAL

[1] One study had high risk for selective reporting bias.
[2] Poorly reported allocation concealment
[3] Poorly reported blinding technique
[4] Chose the mean baseline risk as the variation in risk was similar across studies (~20%), except one study where it was 75%. (Ralston 2005a)

[5] One study varied the saline concentration of the epinephrine carrier as well
[6] Low number of events

(Skjerven, et al, 2013)

Methods	An eight center, randomized double blind trial with a 2 by 2 factorial design; inpatients
Participants	**Setting:** Eight centers in Norway **Number randomized:** N= 404; n= 203 in the treatment group and n= 201 in the control group Enrollment only occurred as long as a physician and nurse were available. **Number completed:** N=321; n= 167 in the treatment group and n= 154 in the control group **Gender:** 59% male **Inclusion criteria:** moderate bronchiolitis (score of 4 or greater on a scale of 0-10, lower is better); less than 12 months old; **Exclusion criteria:** any serious cardiac, immunologic, neurologic, or oncologic disease; serious respiratory disease other than bronchiolitis; more than one previous episode of obstructive airway disease; symptoms of lower airway disease (i.e. coughing) for more than 4 weeks; treated with glucocorticosteriod within the previous 4 weeks **Power analysis:** 176 subjects in each medication group would provide a power of 80% at an alpha level of 0.05
Interventions	**Treatment group:** Weight based - 10 ml of racemic adrenaline dissolved in 0.9% saline to form a solution of 20 mg per mL • < 5 kg- 0.10 mL • 5 to 6.9 kg 0.15 mL • 7 to 9.9 kg, 0.20 mL • 10 kg or more 0.25 mL **Control group:** 0.9% saline alone
Outcomes	**Primary:** LOS- definition time from the first study inhalation until discharge from the hospital **Secondary:** clinical score 30 minutes after the first inhalation, use of nasogastric feeding,
Notes	Cannot enter data into data table. The difference in LOS in children who received RE (n=203) = 63.6 hours, Range [46.2-81.0[; while the range of those who received normal saline was 64.1 hours, range [49.8, 86.4]. The Difference = 4.5, 95% CI [-6.5-15.5] and is not significant p= 0.42 There was a significant difference between subjects who received either treatment on a "On Demand" schedule vs. a "Fixed" schedule. Here the Difference = 13.7, 95% CI [2.9, 2424].

Risk of bias table

Bias	Scholars' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Block of eight, assignment to one of four study groups- randomization occured at a central site 1. RE scheduled 2. Placebo scheduled 3. RE intermittent 4. Placebo intermittent
Allocation concealment (selection bias)	Low risk	Used a list of study number for use for consecutive assignment
Blinding of participants and personnel (performance bias)	Low risk	All treatments were prepared in an off-site pharmacy
Blinding of outcome assessment (detection bias)	Unclear risk	Author did not disclose
Incomplete outcome data (attrition bias)	Low risk	20% did not complete the study for various reasons, but the analyzed the primary outcome with intention to treat analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(Skjerven et al., 2015)

Methods	This is a follow up study of Skjerven 2013. Looking at the treatment response in infancy was different when subjects were ~ 2 years of age and had recurrent bronchial obstruction, atopic eczema, or allergic sensitization. It is an eight center, randomized double blind trial with a 2 by 2 factorial design; inpatients
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	• 5 to 6.9 kg 0.15 mL • 7 to 9.9 kg, 0.20 mL • 10 kg or more 0.25 mL **Control group:** 0.9% saline alone
Outcomes	**Primary:** LOS- definition time from the first study inhalation until discharge from the hospital, strafifed by subgroups identified 2 years later. Sub groups were patients with and without recurrent bronchial obstruction, atopic eczema, or allergic sensitization by 2 years of age
Notes	Cannot enter data into data table. When the data was re analyzed (~ 2 years) after the subjects could be separated into subgroups of those who had recurrent bronchial obstruction, atopic eczema, or allergic sensitization, no effect was seen in the LOS between those who developed atopic disease and received RE or not.

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Figures:

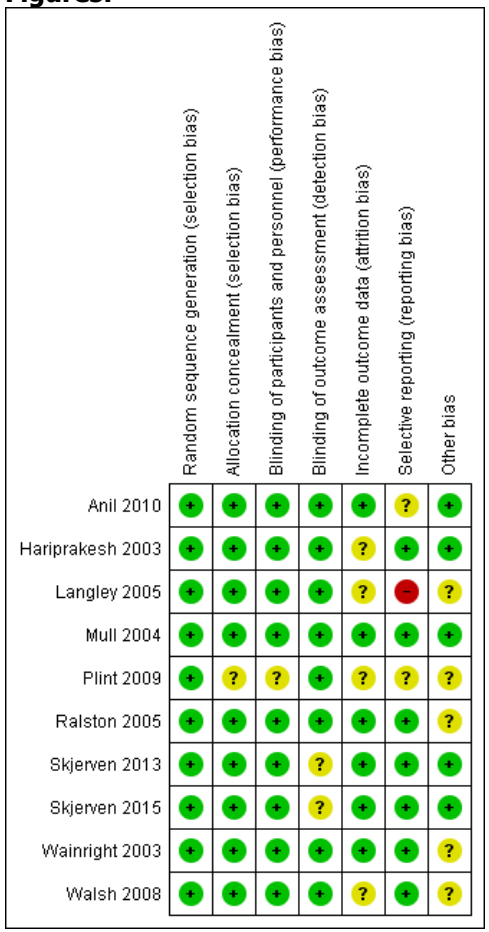

Figure: Risk of Bias Summary for included studies for racemic epinephrine and bronchiolitis.

Note: includes the following studies from Hartling, Wiebe, Russell, Patel and Klassen (2011) – Anil, 2010; Hariprakash 2003; Langley 2005; Mull 2004; Plint 2009; Ralston 2005: Wainright 2003; Walsh 2008. Skjerven 2013 and Skjerven 2015 were added to the meta-analysis for this guideline.

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Date: October 5 2016