Author's response to reviews

Title: Racemic epinephrine during hospitalization improves acute respiratory distress but does not shorten length of stay for bronchiolitis: a randomized controlled clinical trial

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Author's response to reviews: see over
Dear Editor:

Thank you for your email of 23 February 2005 on MS 3079414895146875 – Racemic epinephrine during hospitalization…” in which you provided us with the reviewer comments and asked for a response. Please consider this communication that response. We appreciate the opportunity to revise the manuscript. Please note that trial registration is in progress and the number will be provided to you as soon as it is complete.

1. **Title.** The reviewer thought the title was misleading because they were not convinced that the statistically significant difference in the outcome measurement was clinically relevant. The reviewer suggested the title be changed to “Racemic epinephrine compared to salbutamol in hospitalized young children with bronchiolitis; a randomized controlled clinical trial.”

Title changed. Please see response to #14.

2. **Abstract.** The reviewer refers to the point about the clinical relevance of the two-point difference in the outcome measure (Please see response to No. 14)

3. **Methods.** The reviewer asks how the “feeding pattern” was operationalized for the purposes of the study, how breast-fed infants were assessed, if they were supporting body weights or urine specific gravity, and who reported this measure and how was it validated.

At enrolment and at the daily assessment the study nurse interviewed caregivers to determine the feeding pattern and whether it was normal, less than normal or if the child was unable to feed. This information has been inserted in a separate sentence in the methods. Caregiver report of this outcome was sought because feeding difficulty is a common reason for seeking medical advice in children with bronchiolitis. The parental report was not compared to urinary concentrating ability or change in total body weight.

4. **Reviewer Question:** How many children were eligible to enroll in the trial? How many were from the IWK and how many from the NB site? How many were not enrolled and for what reasons... a flow diagram would be helpful.

Ten children were enrolled at the Saint John site and 52 at the Halifax site; this has been added to the results. 245 children were screened who did not enroll: 46 did not meet inclusion criteria and in 34 parents refused consent. The rest were ineligible because of exclusion criteria. The most commons reason for exclusion was previous diagnosis of asthma (n= 58) and previous administration of systemic steroids (n= 44). This has been added to the results.

5. **How many research nurses measured the RDAI in study children?** Were inter-rater reliability checks performed? What were the results?
Two nurses at each site performed RDAI measurement. Nurses at the Halifax site were experienced with this respiratory status measurement in young children from other research studies and trained the Saint John nurses in its use. Mock assessments were done as part of that training and inter-rater reliability assessment conducted until adequate performance was achieved. Records of this training consist of lists of activities conducted and duration of training but not actual scores.

6. **What was the availability of the research nurse?** If enrolment could occur up to 24 hours after admission and we see that most children were only hospitalized for 1-3 days, then it may be that a substantial portion of children were exposed to the intervention for a brief period of time.

Enrolment occurred from 8 am to 8 pm. Enrolments begun by 8 pm would be completed that evening. Thus the enrolment process always started within 11 to 12 hours of admission. We have added the hours of research nurse coverage to the methods.

Medications received prior to enrolment were not reasons for exclusion other than those specified in the inclusion and exclusion criteria (See Methods).

7. **The author should verify and summarize the number of study doses received per group, per site and the duration enrolled in trial per group, per site.**
The mean number of study doses per group were 11.7 (epinephrine) and 14.6 (ventolin). This difference is not statistically significant. However, it should be noted that we did not intend for the treatment arms to have an identical number of doses since the randomization was to study drug every 1 to four hours, as required. If one arm had been clearly more efficacious fewer doses may have been required. The mean number of study doses per site was 12 (Halifax) and 19.4 (Saint John), a difference that is not statistically significant. Again, because there were two treatment arms at each site and random allocation one expects that practice variation should be distributed within each site equally to the two study arms. The mean study duration by treatment arm was epinephrine 2.16 days, ventolin 2.52 days.

8. **Was there a difference in results by study site? This is not mentioned or discussed in the paper. Must be included.**
There was no difference in wheezing score, total retraction score, total respiratory score oxygen saturation or duration of stay by study site. This sentence has been added to the results.

9. **Was there any contamination? If so, what was the magnitude?**
Contamination in this instance would be children in racemic epinephrine group receiving salbutamol or the latter group receiving racemic epinephrine. Once enrolled medications were given according to pre-printed study orders, which is mentioned in the methods. If the physician wished to control medication ordering then study participation would have been discontinued.

10. **Page 10, line 17 – please clarify what the comparison values represent.**
The sentence is the following: “On the third hospital day a significant difference in oxygen saturation was observed in children receiving racemic epinephrine (96.20% v.
93.80%, 98.80 v. 92.00 p = 0.03) but this difference was not significant when the two groups were compared over the entire hospital stay or on other days. “We have added “compared to salbutomol” to this sentence.

11. **Table 2 – baseline characteristics – should this table include p-values, CONSORT guidelines suggest not to include as with randomization should be fairly equal, for the authors to review and discuss.**

The purpose of randomization is to ensure known and unknown confounding factors are balanced across the treatment groups. A post-hoc comparison of individual known characteristics should therefore be unnecessary and is may, because of multiple comparisons, find a p value less than 0.05 by chance alone. We are delighted to exclude the column that lists p values.

12. **Figure 1 – Quite a wide variability in feeding by day both within and between groups, expected to see some discussion of these findings in discussion section. Reviewer notes R is replaced with RE in the legend and a discrepancy between the legend fill-in and the graph.**

The electronic version seems to have changed during submission, accounting for the discrepancy between the legend and the graph. With regard to the variability, it may be more efficient to present the feeding data at admission in the text. This has been revised accordingly in the text. The feeding data one week post-discharge is presented in Table 4 along with the other parental report results at that time.

13. **Discussion. Reviewer indicates it would be useful to look at the similarities/differences between the trials cited in references 24 and 25 and this trial, and notes the results were not so different but the interpretation is. The reviewer notes this type of discussion would be more relevant than the more didactic discussion of why there may have been a mathematically significant improvement in the epinephrine treated group.**

(Note: Reference 24 is Patel, reference 25 is Wainwright)

Ref 25 (Wainwright) allocated children to three doses of epinephrine. This difference is already noted in the discussion since we reference the trials that, like ours, provided epinephrine throughout the hospital stay. The text reads: “Our study is only the second [24] in which nebulized racemic epinephrine was provided throughout the hospital admission. Other trials have administered one to three doses spaced on one day only.”

With regard to the apparent didactic tone of the discussion, this was certainly not our intent. We would be happy to revise the relevant text that gives this impression with more editorial guidance.

14. **Clinical relevance of the findings must be addressed, particularly with the known limitations of the RDAI and the known difficulties in measuring respiratory distress in this patient group. (Variation over time in degree of respiratory distress.)**

There is no question about the difficulty inherent in the measurement of severity of respiratory symptoms and signs in infants. More recent research has focused on addressing this issue, but in asthmatic infants and toddlers, as opposed to (younger)
bronchiolitic infants. The RDAI was chosen because it is probably the most used and familiar of the scales used in this population and because it is heavily weighted by wheeze and retractions, arguably the most meaningful of signs (van der Windt, J Clin Epi 1994; 47:635). Even if one chooses to accept its validity, then one must choose between change in score, vs time to low score (e.g. ≤4) implying minimal distress. It is interesting to note that the largest changes in RDAI in a bronchiolitis study were seen in the study of Klassen et al. (J Peds 1991; 118:807) who compared salbutamol with placebo. In that study, the mean score fell by 2.75 at 30 minutes, and 3.75 at 60 minutes (impressive considering salbutamol might today be viewed as ‘placebo’ in a bronchiolitis treatment trial). The choice of a 4 point difference in RDAI on day 3 is admittedly arbitrary and relatively large, but not unrealistic. We speculated *a priori* that by virtue of its α-adrenergic effect, epinephrine might actually shorten duration of severe symptoms. This is based on the fact that plasma exudation is known to contribute to the airway obstruction in bronchiolitis, and that release of mediators *in situ* contributes to this leakage. Thus, by reducing mucosal blood flow, we hypothesized not only immediate relief of obstruction, but also shorter duration of illness. Measured SpO₂ was statistically significantly different on day 3, supporting our speculation. That this did not result in shorter hospital stay likely reflect other factors such as feeding issues. Note that this scenario differs from use of β-adrenergic treatment of acute asthma, in which no effect on underlying inflammation nor shortening of hospitalization would be expected; it is given purely for symptomatic relief.

15. **Reviewer notes that Wainwright also studied extended use in hospital with aerosols Q4h for the duration of hospitalization and asked that this be corrected in the discussion.** The methods section of the Wainwright paper (NEJM 2003;349, p 29 column 1) states “each infant was assigned one amber bottle containing 15 ml of clear, colorless solution containing either epinephrine …or vehicle…;the contents were sufficient for three doses of 4 ml with some margin of spillage.” The abstract states that these three doses were administered at four hour intervals, which would indicate that these were all given on the first day, not for the duration of hospitalization.

16. **If the feeding was as variable as it appears it was, then there needs to be some discussion of results, particularly as they were felt to be important enough to include in the diagram.** Diagram is deleted, see answer to question #3.

17. **Reviewer again discusses the clinical relevance of differences less than 2 in the RDAI outcome measurement and asks if this was thought to be a truly important group difference. If it was, reviewer asks that this be discussed and the “perspective of the results should reflect a statistical but not clinically relevant difference”.** Same issue as points #1, 2, 14. Please see response, #14.

18. **Major Compulsory Revisions.**
   a. **Change of title (see No. 1 above)**
   Title changed.
b. Reviewer states “given the multiple comparisons, need for evaluation of results by site, I think it would be reasonable for a statistician to review the manuscript.

Please note that we have a Masters trained statistician (Heather Joudrey) as a co-author who worked under the supervision of our center’s PhD statistician (Dr. Bruce Smith <bsmith.mathstat.dal.ca/~bruce/cv.html>).

Thank you for your careful review of our work. We hope these revisions address the concerns raised. Please do not hesitate to contact us for further information.

Sincerely,

Joanne Langley MD, FRCPC