

## What Works in Bronchiolitis?

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The spate of inquiries following the recent EURECA publication on hypertonic saline in bronchiolitis(1), prompts this communication on what works (and does not) in this condition.

### RELEVANCE

Bronchiolitis is diagnosed based on the first (or sometimes subsequent) episode of wheezing in infants, usually concomitant with a viral upper respiratory infection(2,3). In the context of our setting, it is always diagnosed clinically and no viral detection tests are performed. As it is (i) quite common, (ii) often frustrating to manage, and (iii) therefore open to a variety of (usually) futile management strategies, a systematic summary of current best evidence is relevant.

Another issue while summarizing evidence is, which outcomes should/could be regarded as relevant. This is important because different RCTs use different outcome measures, not all of which are clinically important. Often, dramatic effect-sizes for the 'less relevant' outcomes are extrapolated to more important outcomes. Therefore choosing appropriate outcome measures is paramount. For this EURECA review, clinically relevant 'hard outcomes' considered are (i) admission rate among out-patients, (ii) duration of hospitalization among in-patients, (iii) clinical cure (both groups), (iv) requirement of intensive care and (v) death(though rare); whereas measures such as improvement in clinical status, oxygenation parameters, symptom scores, time to improvement, etc are surrogate outcomes, hence regarded as less important.

The clinical question here is "In infants with bronchiolitis (population), which treatment(s) (intervention) result in improved/better/favorable outcome (outcome) compared to placebo/no intervention (comparison)".

### CURRENT BEST EVIDENCE

A Cochrane Library search on 31 December 2008 showed 7 Cochrane reviews, two protocols, seven other systematic reviews and 235 clinical trials on bronchiolitis. A search for additional randomized controlled trials (beyond the respective Cochrane review search dates) was undertaken in Pubmed and identified 76 citations. From each source of evidence, data on hard outcomes was extracted, (re)analyzed, critically appraised and are summarized below and in **Table I**.

*Inhaled epinephrine:* There is no benefit in terms of admission rate or duration of hospitalization; however subgroup analysis suggests that epinephrine has some benefit among outpatients; it has been aptly described as the "least ineffective" intervention(3). Similarly, there is no difference for surrogate outcomes including change in oxygen saturation, heart rate and respiratory rate, although epinephrine results in more favourable clinical score change from baseline.

*Inhaled bronchodilators:* There is no benefit of inhaled salbutamol for admission rate or duration of hospitalization. However, clinical score appears to be better with salbutamol, although another surrogate outcome (oxygenation) shows no difference.

**TABLE 1** INTERVENTIONS FOR BRONCHIOLITIS

Comparison	Outcome	
	Current best evidence	Results
<i>Admission rate among out-patients</i>		
Epinephrine vs placebo	Cochrane review (2 trials, $n=105$ ) and two additional RCTs ( $n=65, n=66$ ) (4-6)	No difference
Bronchodilator vs placebo	Cochrane review (5 trials, $n=224$ ) (7)	No difference
Epinephrine vs salbutamol	Cochrane review (4 trials, $n=228$ ) and two additional RCTs ( $n=65, n=66$ ) (4-6)	No difference
Ipratropium vs placebo	Cochrane review (1 trial, $n=31$ ) (8)	No difference
Systemic glucocorticoids vs placebo	2004 Cochrane review (3 trials) (9) and one additional RCT ( $n=600$ ) (10)	No difference
Hypertonic saline vs placebo	Cochrane review (1 trial, $n=70$ ) (11)	No difference
<i>Duration of hospitalization</i>		
Epinephrine vs placebo	Cochrane review (2 trials, $n=292$ ) (4)	No difference
Bronchodilator vs placebo	Cochrane review (5 trials, $n=314$ ) (7)	No difference
Epinephrine vs salbutamol	Cochrane review (2 trials, $n=131$ ) and one additional RCT ( $n=62$ ) (4,12)	No difference
Ipratropium vs placebo	Cochrane review (1 trial, $n=31$ ) (8)	No difference
Ipratropium + beta-2 agonist vs beta-2 agonist alone	Cochrane review (2 trials, $n=62$ ) (8)	No difference
Systemic glucocorticoids vs placebo	2004 Cochrane review (7 trials) (9) and two additional RCTs ( $n=600, n=174$ ) (10,13)	No difference
Hypertonic saline vs placebo	Cochrane review (3 trials, $n=189$ ) (11)	Duration shorter by 0.94 d with hypertonic saline
Surfactant vs placebo in ICU	Cochrane review (3 trials, $n=79$ ) (14)	No difference
Antibiotics vs placebo	RCT ( $n=21$ ), Clarithromycin used for three weeks (15)	Shorter duration with Clarithromycin (51 vs 88 hours)
Chest physiotherapy	Cochrane review (3 trials, $n=172$ ) (16)	No difference
Montelukast granules vs placebo	One RCT ( $n=53$ ) (17)	No difference

RCT: Randomized controlled trial; n: Number of participants in a RCT; ICU: intensive care units

*Inhaled epinephrine vs inhaled bronchodilator:* There is no difference in admission rate or duration of hospitalization, though subgroup analysis shows marginal benefit among outpatients. Change in clinical score at serial intervals, oxygenation parameters, serial measurements of heart rate and respiratory rate, also are not different between the groups. As both interventions show no difference when compared to placebo, it follows that neither is superior.

*Inhaled anticholinergics:* Compared to placebo, ipratropium does not show any benefit in admission rate, duration of hospitalization and also most surrogate outcomes (clinical improvement, oxygenation parameters, symptom score), except parental assessment of improvement. A combination of ipratropium with salbutamol (vs salbutamol alone) also does not show any benefit for various surrogate outcomes.

*Glucocorticoids:* This is no difference from placebo for hard outcomes and several surrogate outcomes (clinical scores, oxygenation parameters, respiratory rate, readmission rate). One recent RCT shows that a single dose of intravenous dexamethasone results in (statistically but not clinically significant) shorter duration of hospitalization and time for resolution of respiratory distress(13). Inhaled dexamethasone does not show any difference in clinical score and oxygenation compared to saline(18).

*Hypertonic saline nebulization:* Although the admission rate is no different compared to placebo, the duration of hospitalization is less by almost one day with hypertonic saline nebulisation. Clinical severity scores show variable results for inpatients and outpatients, on different days of measurement, but are mostly in favour of hypertonic saline. The limitations with hypertonic saline have been presented previously(1).

*Surfactant:* Surfactant does not reduce the duration of hospitalization, but results in shorter duration of ICU stay despite no significant reduction in the duration of ventilation.

*Antibiotics:* Clarithromycin decreases the duration of hospitalization as compared to placebo, but the single RCT showing this finding administered the antibiotic for three weeks(15). The Cochrane review on antibiotics included only one RCT on ampicillin versus placebo, but did not report any event in either arm(19).

*Chest physiotherapy:* This does not reduce the duration of hospitalization and there is no data on admission rate.

*Other interventions:* Two RCTs ( $n=140$ ,  $n=129$ ) on oral salbutamol versus placebo show that there is no difference in terms of clinical recovery/cure(20,21). One RCT on nasal phenylephrine versus placebo ( $n=41$ ) shows that there is no significant difference for outcomes such as oxygenation and clinical score(22). Similarly, inhaled furosemide is no different from placebo in terms of oxygenation parameters(23). One RCT comparing inhaled salbutamol with dexamethasone versus salbutamol alone shows that both are comparable for various

measures such as heart rate, respiratory rate respiratory distress scores and oxygenation(24). Montelukast does not reduce duration of hospitalization and measures such as clinical severity scores(17). There is no RCT comparing steam inhalation versus no inhalation. Interventions that are not available in India (heliox, ribavirin, vaccination) have not been considered in this review.

### CRITICAL APPRAISAL

Despite the widespread use of various interventions (singly and in combination) among infants with bronchiolitis, robust data represented by systematic reviews and RCTs are lacking in quantity and quality. Most trials highlight results showing superiority of intervention (compared to placebo) for a variety of outcomes that are not of high clinical priority; on the other hand limited data for clinically relevant (hard) outcomes do not speak in favour of any of the interventions. Many trials (and even systematic reviews) are under-powered (small sample size), leading to the disappointing conclusion that more research is required for most interventions. It should be noted that there is no robust evidence even for the so-called recommended standard treatment (oxygen and fluids) in bronchiolitis(2,3,25).

### EXTENDIBILITY

An important issue in extending evidence from the research setting to the bedside, is whether 'bronchiolitis' defined in various RCTs (and systematic reviews) matches our perception of the condition. Fortunately, this is not a problem as most RCTs included infants with a clinical diagnosis of bronchiolitis (almost exactly as we would in the local setting), very few included viral studies to confirm the presence of the usual causal viruses and almost none used less well-defined terminology such as 'viral wheeze' etc. In addition, many RCTs included infants prior to hospital admission (outpatients) and very few were conducted in the setting of an intensive care unit. Thus, although most trials were not conducted in developing countries, the inclusion criteria were similar to those routinely used. Therefore the evidence can be extended to our setting.

### EURECA CONCLUSIONS IN THE INDIAN CONTEXT

- None of the interventions commonly used in bronchiolitis is backed by robust evidence of benefit for clinically significant outcomes.

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