# Nebulised hypertonic saline in bronchiolitis: take it with a pinch of salt

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Nebulised hypertonic saline is attractive as a therapy for acute viral bronchiolitis. Thick and sticky secretions in oedematous airways induce breathlessness and poor feeding as a hallmark of the disease. Loosening secretions with this simple therapy could prevent admission to hospital, or speed recovery and discharge. In a condition with no current acute therapeutic options, this would be welcome indeed.[1 2] Hypertonic saline changes mucous rheology, and when used in cystic fibrosis, has good—if modest—effect.[3]

In bronchiolitis, hypertonic saline has had a promising start. Early trials demonstrated appealing benefits with reduction in length of stay by up to 25%.[4] A Cochrane review, last updated in 2013, concludes with a recommendation to use hypertonic saline in bronchiolitis to reduce length of stay in hospitalised patients.[5]

Hypertonic Saline in acute Bronchiolitis RCT and Economic evaluation (SABRE), printed in this issue,[6] is the largest reported study for the use of nebulised hypertonic saline infants hospitalised with bronchiolitis. Importantly, the study protocol challenges head on the difficulties with using a placebo control when testing a nebulised intervention. As it cannot be assumed that nebulised normal saline (0.9%) will have no clinical effect, the non-intervention arm in SABRE was the current standard of care in the UK—i.e., no regular use of epinephrine, salbutamol or 0.9% saline that were nebulised in all previous studies testing hypertonic saline in bronchiolitis. By necessity, that made the trial open label, which leaves a study open to criticism of potential confounding bias. In this case, however, the weight of evidence to date in favour of hypertonic saline and the desperate need for something to work in bronchiolitis, might suggest any anticipated bias would have been in favour of the intervention. Yet, the open label design did not favour the intervention: nebulised hypertonic saline did not change the length of time to fit to discharge and actual discharge. Not even with a persuasive hint of any effect.

Was the decision only to include infants with an oxygen requirement ($SpO_2$ ≤92%) a reason for the lack of response? Could use of hypertonic saline earlier in the course of the illness, before the small airways are excessively clogged with mucous be more successful? Certainly that is plausible, though this has not been considered a potential issue in previous studies,[7] with no benefit in some studies of moderate disease severity.[8] It also would have been helpful to extract time to regain adequate feeding as an outcome. This data was collected as part of the primary outcome but not reported and is an important milestone in infants recovering from bronchiolitis.[9] SABRE had a disappointingly poor follow-up of patients' symptoms up to 28 days—successful in only a third—although not impacting on the primary or key secondary outcomes, this should have been better within the infrastructure of this well-funded trial working within the UK medicines for children's framework. Given the lack of immediate benefit for hypertonic saline, an effect in the subsequent 28 days may not be anticipated—but the study cannot be considered to have provided an answer to a question it posed. Even taking into account these few considerations, the message from SABRE could not be more emphatic—for infants in hospital with acute viral bronchiolitis, nebulised hypertonic saline does not work.

So, why the significant contradiction between SABRE and last year's Cochrane review?

The answer probably lies in the pitfalls of systematic reviews and the great benefit of large, well-designed, appropriately funded trials in answering key clinical questions. Systematic reviews, Cochrane or otherwise, efficiently coalesce studies of varying design and presentation—functioning to manage the effect of bias for and against an intervention. That strength is also their weakness, as review methodologies typically cope poorly with study behaviours that are either clinically inconsistent or at times implausible. In particular, small early trials, especially with repeated trials from small groups of researchers, may unbalance the assumptions of random bias. In the case of hypertonic saline, an early study demonstrated a dramatic 25% reduction in length of stay,[4] (which is a great thing), but no effect on heart rate (which is higher with respiratory distress) or oxygen saturation (which is surely why they are in hospital[9]). Two further linked studies were in older children with bronchiolitis (possibly inconsistent with UK definitions)—length of stay was reduced in mild/moderate patients by 19%[10] and severe bronchiolitis by 25%.[11] However, discharge time for the mild/moderate control group at 7.4 days was more than twice the UK average across all disease severities (3 days), and infants with severe disease were discharged 24 h sooner than those with mild/moderate disease (who remained in hospital for 2–3 days following a non-significant clinical score of <2 in each group). The clinical practice in these studies seems inconsistent with current UK norms, yet presented within the forest plots of the Cochrane review they apply critical traction for the benefit of hypertonic saline over placebo. The irony for many reading this from a UK perspective is that these studies, comparing something we do not do (hypertonic saline) with something we do not do (nebulised normal saline, salbutamol or epinephrine) as a double-blind design, would grade much higher than SABRE from a trial design perspective.

Were SABRE standing alone against the weight of the Cochrane review it might continue to be considered on the aberrant side of the balance of evidence for this topic—except that SABRE joins a growing choir of recently published heavyweight randomised controlled trials providing a vocal crescendo against the use of hypertonic saline in bronchiolitis. In this *annus horribilis* of evidence on the use of hypertonic saline published since the Cochrane update, newer studies have presented an increasingly compelling case for lack of benefit; a study of 248 infants comparing 3% with 0.9% nebulised saline 4 hourly with Salbutamol found no benefit to hypertonic saline on length of stay or clinical scores[8]; in 292 infants given 8-hourly nebulised 0.9%, 3% or 6% saline with Salbutamol, there was no difference in time to discharge, improvement in oxygen saturation, feeding or clinical scores[12]; a study of 408 infants provided with

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0.9% or 3% saline nebulised in the emergency departments and then 8-hourly in those admitted to hospital, found reduced admission rates in those provided with 3% saline, but no effect on subsequent clinical scores or length of stay in those admitted to hospital.[13] By contrast, there was no difference in admissions from emergency departments in a study of 101 infants provided with 7% vs 0.9% saline and also no difference in clinical scores or length of stay in hospital for those admitted.[14] A defining study to hopefully inform the effects of hypertonic saline provided in emergency departments will be a study of 778 infants receiving two doses of 3% saline that has now completed recruitment but is yet to report (http://www.clinicaltrials.gov NCT01777347), however, with no previous consistent benefit demonstrated on short-term clinical scores, heart rate, respiratory rate and oxygen saturation, the outcome is not anticipated to be positive for hypertonic saline.

With hypertonic saline added to the pile of ineffective therapies for acute viral bronchiolitis,[1 2] what hope is there for infants with bronchiolitis? Moving the target to prevention or earlier intervention seems key. Respiratory Syncytial Virus (RSV) is the viral culprit in 80% of bronchiolitis. Monthly injections of the antiRSV monoclonal antibody palivizumab reduces admissions with RSV bronchiolitis and—pivotally—the frequency of subsequent wheeze episodes.[15] Unfortunately, palivizumab has limited effectiveness and applicability, but given its worldwide burden,[16] RSV is now the target of many pharmaceutical suitors.

RSV vaccine development was cautioned for many years by the severe enhanced disease experienced by toddlers provided with formalin-inactivated RSV vaccines developed in the 1960s.[17] But there is now fervent progress with up to 20 preclinical programmes moving to Phase I for an RSV vaccine and two vaccines under Phase II development: a live-attenuated immunisation of infants (MedImmune-559[18]) and a maternal immunisation by RSV F Protein nanoparticle (Novovax, press release only). So, while an effective vaccine for RSV remains elusive, the outlook is now more promising. At the same time, multiple emerging treatment therapies for RSV are in rapid competitive parallel development. GS-5806, an oral RSV fusion inhibitor has recently demonstrated the ability to reduce viral load and symptoms in infected adult volunteers—the first therapeutic agent to demonstrate this ability in humans.[19] Two further agents have active Phase 1 trials in infants with RSV this northern hemisphere winter. ALS-8176 is an oral nucleoside analogue (Alios, USA) and ALX-0171 a novel nebulised camelid antibody 'nanobody' (Ablynx, Belgium), both with good preclinical activity against RSV. With all three demonstrating good early safety in humans, there is very good hope for a therapeutic option for RSV in the near future.

So there are many reasons to be cheerful for the improving outlook for our poor infants with bronchiolitis—it just will not be by using nebulised hypertonic saline.

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## REFERENCES

1 Network SIG. Bronchiolitis in Children (SIGN 91). NHS Quality Improvement Scotland, 2006.
2 American Academy of Pediatrics Subcommittee on D, Management of B. Diagnosis and management of bronchiolitis. *Pediatrics* 2006;118:1774–93.
3 Elkins MR, Robinson M, Rose BR, *et al*. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354:229–40.
4 Mandelberg A, Tal G, Witzling M, *et al*. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest* 2003;123:481–7.
5 Zhang L, Mendoza-Sassi RA, Wainwright C, *et al*. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev* 2013;7:CD006458.
6 Everard ML, Hind D, Ugonna K, *et al*. SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax* 2014;69:1105–12.
7 Kuzik BA, Al-Qadhi SA, Kent S, *et al*. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr* 2007;151:266–70, 70 e1.
8 Sharma BS, Gupta MK, Rafik SP. Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: a randomized controlled trial. *Indian Pediatr* 2013;50:743–7.
9 Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. *Pediatrics* 2008;121:470–5.
10 Luo Z, Liu E, Luo J, *et al*. Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatr Int* 2010;52:199–202.
11 Luo Z, Fu Z, Liu E, *et al*. Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis. *Clin Microbiol Infect* 2011;17:1829–33.
12 Teunissen J, Hochs AH, Vaessen-Verberne A, *et al*. The effect of 3% and 6% hypertonic saline in viral bronchiolitis: a randomised controlled trial. *Eur Respir J* 2014;44:913–21.
13 Wu S, Baker C, Lang ME, *et al*. Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial. *JAMA Pediatr* 2014;168:657–63.
14 Jacobs JD, Foster M, Wan J, *et al*. 7% Hypertonic saline in acute bronchiolitis: a randomized controlled trial. *Pediatrics* 2014;133:e8–13.
15 Blanken MO, Rovers MM, Molenaar JM, *et al*. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013;368:1791–9.
16 Nair H, Nokes DJ, Gessner BD, *et al*. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;375:1545–55.
17 Chin J, Magoffin RL, Shearer LA, *et al*. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. *Am J Epidemiol* 1969;89:449–63.
18 Malkin E, Yogev R, Abughali N, *et al*. Safety and immunogenicity of a live attenuated RSV vaccine in healthy RSV-seronegative children 5 to 24 months of age. *PLoS ONE* 2013;8:e77104.
19 DeVincenzo JP, Whitley RJ, Mackman RL, *et al*. Oral GS-5806 activity in a respiratory syncytial virus challenge study. *N Engl J Med* 2014;371:711–22.