Objectives

- Review the available literature on the use of nebulized hypertonic saline in the treatment of acute viral bronchiolitis
- Review proposed mechanism(s) of action and safety profile for hypertonic saline in bronchiolitis

Background

- Viral bronchiolitis is the leading diagnosis at hospitalization for infants under 1 year of age
- It results in approximately 150,000 hospitalizations per year at a cost of over $500 million
- 3% of all infants in the US will be admitted for bronchiolitis

Pathology in bronchiolitis is not beta-agonist reversible airway obstruction

Little benefit gained from routine beta-agonist usage, no impact on admission rates or LOS, no impact on oxygen saturation (or a negative impact), minor and equivocal impact on respiratory scores

SO, DON'T JUST DO SOMETHING, STAND THERE, RIGHT?
And, along comes hypertonic saline


Early Studies

- Sarrell 2002 – outpatient trial (n=70), no impact on hospitalization rates, but + impact on respiratory scores, all treatments given with 5mg terbutaline

- Mandelberg 2003 – inpatient (n=52), +impact on both scores and LOS, all treatments given with 1.5 mg epinephrine

- Tal 2006- inpatient (n=41), +impact on both scores and LOS, all treatments given with 1.5 mg epinephrine

Leading to the Multicenter Trial


- Multicenter, Canada and UAE, inpatient (n=96), +impact on LOS with a 30% reduction amounting to about 1 day

Then, the Meta-analysis


- Analyzed the three Israeli studies and Kuzik

- Inpatient pooled results (3 studies, 189 patients) showed a 0.94 day decrease in LOS (CI 1.48 to 0.4)

Recent Studies – Luo 2009


- N=93 inpatients, 1.4 d decrease in LOS (6.4 vs. 4.8 days)

- At least a day off time to resolution of wheezing, cough and moist crackles…..whatever those are.

Recent Studies – Al-Ansari


- N=187, no impact on LOS (1.5 d), three arms comparing 5% to 3% to NS, with sig difference in severity scores at 48hr only for 5% vs. NS
Recent Studies – Luo 2010
- N=126 inpatients, 1.6 d decrease in LOS, at least 1 d decrease in other symptoms, this time it was 3% saline vs. NS without any bronchodilators prescribed.
- Only prior study to do this was Kuzik where about 30% of doses of 3% given without bronchodilators.

Emergency Dept Studies
- Grewal S, et al. Archives 2009. Candadian ED. (n=46) Two arms, epi + NS vs. epi + HS, and up to two doses. Outcome was RACS. Everybody got better.
- Anil AB, et al. Ped Pulm 2010. Turkish ED. (n=186) Five arm study, albuterol and epi combined with either NS or HS vs. NS placebo give twice. 120 mins duration. Everybody got better.

So why might this actually work?
- In vitro, HS increases airway surface thickness, decreases epithelial edema and improves mucus rheology and transport rates
- In vivo, HS increases mucociliary transport in normal subjects

Theory of dehydration of ASL
- It is proposed that mucociliary failure such as occurs in CF also occurs in severe bronchiolitis due to dehydration of the ASL
- Airway surface liquid (ASL) is the combined mucus layer (top) and the cell surface periciliary liquid
- This gets dehydrated and inspissated in CF with even minor insults

What might HS do in bronchiolitis?
- Hydrates the ASL
- Breaks ionic bonds in mucus layer which reduces cross linking
- Increases ciliary beat frequency by release of PGE2 (note higher conc. may decrease cbf)
- Causes conformational change in mucus by shielding negative charges thereby reducing repulsion
- Theoretically reduces edema in airway wall through flow of free water into the ASL
- Induces cough and moves out the sputum which is now better able to flow
Indirect Proof of Concept
- Nebulized distilled water makes a bad placebo
- Initial Ribavirin studies were done with distilled water as placebo, and then were not repeatable, ultimate conclusion was that the "placebo" was harmful whereas the medicine wasn't very useful………..

Indirect Proof of Concept
- NS may not be a placebo
- Many authors of negative studies have made this conjecture, everybody in these studies gets “significantly” better which makes them awfully hard to power when you are using respiratory scores as the outcome

Indirect Proof of Concept
- Sood N. Am J Respir Crit Care Med. 2003; 167:158-63 (proposed effects on ASL not concentration dependent but function of total NaCl delivered)
- Further hypothesized by both Anil and Mandelberg

But is it safe?
- Major concern was with bronchospasm
- In asthma studies HS has been used to demonstrate that a patient has asthma (i.e. suffers from a repeated pattern of reversible airway obstruction)
- Doses are generally much higher in asthma studies (concentrations of at least 4.5% and clear dose-response curve seen with increasing volumes)

Direct Evidence of Safety?
- Kuzik was the first to administer in bronchiolitis without beta-agonists but did not report clearly on this question
- Ralston and Hill retrospectively reported on safety profile with clear data on timing of doses of HS vs. beta-agonists
- Luo did a full RCT without beta-agonists
- Favorable safety profile for nebulized 3% in bronchiolitis is likely established
So what’s next?

- Currently a multicenter study in the US at CHLA and Oakland Children’s (with albuterol)
- Undoubtedly there will be more studies without albuterol in both the US and Canada
- Only in inpatients, outpatients, at home?
- Could you just use enough NS? No safety concerns, cheap, easy.