Treatment of Viral Bronchiolitis and the Place of Hypertonic Saline

From Basic Science to Clinical Practice
Modern – 2013 understandings

A. Mandelberg

The Pediatric Pulmonary Unit.
Wolfson Medical Center, Holon, Israel
Noa – 3M Old baby

- Presenting: Fever, rhinitis, cough for 2 days
- Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.
- Anamnesis: Never wheezed, no family allergy/asthma
- CXR: Over-inflation, plate like atelectasis.
- PHI = Previously Healthy Infant
Natural Course ↔ treatments (why we fail so far)

Understanding the natural course/pathophysiology of acute viral bronchiolitis – explain why we fail so far - treating these babies

Mandelberg A, Amirav I; Pediatric Pulmonology. Jan 2010


Staat MA. Semin Resp Inf. 2002; 17:15
**Natural Course PHI**

- **Incubation** – 5d (to the first symptom)
- **Shedding Peak** – 4d in Previously Healthy Infants (PHI)
- **Cytokines/mediators/inflammation Peak** > 5d in PHI

Why we fail so far

- Anti viral agents (Ribavirin and Mono Clonal Ab) - futile in hospitalized PHI when - viral load $\downarrow$ while inflammation $\uparrow$ - causing all the damage.

- Steroids - anti-inflammatory $\downarrow$, but viral shedding $\uparrow$ - are unpredictable in these babies.

Natural Course changes by different populations, Risk Factors / treatments

• However, the natural course differs between previously healthy infants (PHI) and other populations.

• Some treatments which are futile in PHI, will be “the state of the art” in other populations.

Natural Course Changes by different populations, risk factors / treatments

• Immunocompromised infants (congenital, acquired or iatrogenic, BMT) with concomitant acute viral bronchiolitis
  – Increased viral ↑↑↑ shedding - 30-55d.
  – Benefit from Ribavirin and monoclonal antibodies

• Previously wheezing infants / or BPD / ↓TLR4…
  – More steroid and/or bronchodilator responsive

• Data on PHI in the acute phase should not be generalized to other populations.

Treatment disappointments

- Still, the mainstay of treatment for RSV - supplemental **oxygen** and **hydration**: (*,**,**,**

- RIBAVIRIN (inspired great hope): AAP stated: “*Ribavirin should be used”…
    Ventilated babies: Ribavirin **V** water-placebo → hospitalization↓ + ventilation↓ days.

- However, the “beneficial” effect of ribavirin could not be duplicated subsequently in PHI and only then was it appreciated that **distilled water** was not an appropriate placebo.

  ***** Schuh S. *J Pediatr* 2002;140:27
• AAP statement 1996: changed from “should be used” to “Ribavirin may only be considered for children with serious underlying disorders” #PHI

Mandelberg A, Pediatric Pulmonol. 2010
**TABLE 3  Treatment of acute viral bronchiolitis**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators</td>
<td>Should <strong>not</strong> be used routinely (individual trial may be justified)</td>
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<tr>
<td>INH steroids</td>
<td>Should <strong>not</strong> be used</td>
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<tr>
<td>Systemic corticosteroid</td>
<td>Should <strong>not</strong> be used</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist</td>
<td>Should <strong>not</strong> be used</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Should <strong>not</strong> be used</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Should <strong>not</strong> be used</td>
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<tr>
<td>Antiviral – Ribavirin</td>
<td>Should <strong>not</strong> be used</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>Should <strong>not</strong> be used</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>Should <strong>probably</strong> be used</td>
</tr>
</tbody>
</table>

*Medicine used in respiratory diseases only seen in children*
Hypertonic Saline in Viral Bronchiolitis and beyond – Does Hypertonic Saline "Hold Water?"

From Basic Science to Clinical Practice
Modern – 2013 understandings

A. Mandelberg

The Pediatric Pulmonary Unit.
Wolfson Medical Center, Holon, Israel
RSV-Bronchiolitis Treatment
(why we failed)

• These infants are wheezing but do not respond very well to anti-asthmatic treatment. - # Asthma
Pathophysiology

Bronchiolitis is a viral infection of the bronchiolar epithelium - subsequent: (*,**)

Profound sub-mucosal edema and mucus plugging

Increased secretion of mucin by exocytosis

Relative ASL Dehydration (↑mucin/water)

RSV- by ↑ATPases…absolute ASL dehydration (↑↑mucin/water↓) (***)

** Darville T. Pediatrics in Review. 1998; 19:55-61  
*** Randell SH AJRCMB 2006
Pathophysiology Oriented Treatment

- This called for a new treatment approach
- Aiming on Mucus clearance and **Hydration**
- Hypertonic saline
Hydration is the dominant variable governing MC

• In mice model: ENaC ↑ (ASL severe dehydration) resulted in spontaneous mortality of 60% by 30 d. [Mall M, 2004; Nat Med]

• So why CF patients “with lab evidence of severe ASL dehydration and ASL collapse” do not die so quickly?
  – Long periods of relative health during basal states. [Bucher RC AJPCCM 2010]

• Back to BASIC SCIENCE
Since airway epithelia are water permeable, water moves following Cl and Na to equalize electrolytes concentrations.

- ATP and its metabolite adenosine are probably the most important regulators hydrating the ASL.

CF cell – ↓CFTR - no response to adenosine is totally dependent on ATP.

Randell SH; Am J Respir Cell Mol Biol, 2006
Mandelberg A & Amirav I; Pediatric Pulmonol. 2010
Rundell’s model: A two separate layer structure

ASL (Airway Surface Liquid) = PCL + Mucus layer

PCL (Peri-Ciliary Liquid) = 7 micron

- The mucus layer acts as a fluid reservoir, it accepts or donates liquid to maintain apposition of the mucus layer inner surface with the tips of the cilia. Randell SH, 2006; AJRCMB

- However, in severe ASL dehydration, the ability of the mucus layer to “donate” water is exhausted – PCL COLLAPSE. [Tarran R, 2005; J Biol Chem]*
ASL, Old concept–New concept

- Old concept: In CF, (based on all \textit{static} EP cultures) – complete collapse of ASL (PCL+ML) Everywhere.
- "Why don’t they die quickly?"
- There is some wondrous compensatory mechanism - \textit{in-vivo only}.
- Actually, \textit{in vivo}, MCC in CF are functionally almost \textit{normal} (at birth and in most “non-insulted” respiratory regions during life)

\textbf{What is this compensatory mechanism - INVIVO only?}

[Bucher RC AJPCCM 2010]
[Randell SH, 2006;Am J Respir Cell Mol Biol;35;20]
The answer is

**ATP is paramount – but IN-VIVO only**

- **IN-VITRO** - in static cell cultures - Extra-cellular ATP concentration is negligible.

- However **IN-VIVO** the ATP concentration dramatically rises

*Why does ATP↑ rise INVIVO only?*

* [Tarran R, 2005; J Biol Chem]
• **Mechanotransduction**: A mechanism by which cell converts mechanical stimulus into chemical activity

- SHEAR STRESS \( (\tau = V \times Q / t \times I) \rightarrow ATP \) (extra-cellular)
- \([0.4-0.5 \text{ dyne/cm}^2]\) ~ the same in trachea, bronchi, bronchioles
- Shear stress is parallel to the ASA
- Increases due to inspiratory and expiratory movements (acceleration/deceleration)
- Only in vivo. (Not in static tissue cultures).

\[ V = \text{shear force at that location} \]
\[ Q = \text{first moment of area} \]
\[ t = \text{thickness in the material perpendicular to the shear} \]
\[ I = \text{second moment of area} \text{ of the cross section} \]
ATP = key signal during phasic motion (in vivo)

- Phasic motion of the airway wall (inflation/deflation – shear stress) - ATP↑ and Adenosine ↑. - increases ASL Ht
- When normal human airway epithelial cells cultures were subjected to phasic shear stresses in moving heated incubators, in a rate similar to tidal breathing, the height of ASL doubled.

CF airway epithelial cultures
- Phasic motion
  [Tarran R, 2005; J Biol Chem]

* [Tarran R, 2005; J Biol Chem]
ASL–VIRAL INFECTION INSULT

• Actually, in vivo, MCC in CF are functionally normal (at birth and in “non-insulted” respiratory regions during life)

• “Catastrophic” viral inf. Induce ASL dehydration and collapse

[Randell SH, 2006; Am J Respir Cell Mol Biol; 35; 20]
Disease exacerbations are due to intermittent catastrophic MC failures caused by **VIRAL** infections

- Viral infection up-regulates **ecto-ATPases**, depleting extracellular ATP – attenuating Cl secretion $\downarrow$ to and increasing Na movement from $\uparrow$ ASL - dehydration, MC $\downarrow$.

- **RSV** infection in **CF** epithelia under **phasic motion** condition (simulating in vivo conditions) causes ASL collapse,

- This is true not only in **CF**. **In normal** epithelia under **phasic motion**, **RSV still** causes (although less) **ASL dehydration** – probably depending on the severity of the infection.

[Tarran R, 2005; J Biol Chem]
Disease exacerbations are due to intermittent catastrophic MC failures caused by **VIRAL** infections

- Rundell: *Therapy to maintain ASL *hydration* is important in viral exacerbation of all chronic airway diseases. [Rundell 2006; AJRCMB]
Possible mechanisms for MC ↑ of HS

1. ASL Hydration and decreasing sub-epithelial edema by osmotic forces.

Mandelberg A, Pediatric Pulmonol. 2010
(2) Ionic bonds: **HS which is polar** shields the ionic bonds of mucin macromolecules causing ↓viscoelasticity
Pediatric Pulmonol. Jan 2010
Avigdor Mandelberg, MD1* and Israel Amirav, MD2

Hypertonic Saline or High Volume Normal Saline for Viral Bronchiolitis: Mechanisms and Rationale

Normal Mild/Moderate Bronchilitis

Severe bronchiolitis Viral infection in CF

Normal MCC = 60
Excess hydration MCC = 100

CaCC
ENaC
CFTR

Shear stress

Mild/Moderate Bronchilitis

Decreased MCC due to dehydrated ML

CaCC
ENaC
CFTR

Viral infection in CF

RSV → ATPase → ATP

CaCC
ENaC
CFTR

Possible cytotoxic effect

sub-epithelial edema

sub-epithelial edema
Clinical studies and outcomes using HS

Acute Viral Bronchiolitis
3% Hypertonic saline in RSV bronchiolitis

- **Objective:** To determine the utility of inhaled 3% hypertonic saline / epinephrine to shorten hospitalization stay and improve clinical scores in PHI hospitalized with acute viral bronchiolitis
- **Design:** Randomized, double blind, placebo-controlled trial.
  - 53 PHI - age (months): 2.9±2.1 with viral bronchiolitis
  - Received either - aerosol inhalation of 1.5 mg epinephrine / in 4mL saline–3% (treatment-group II, n=27).
  - Or aerosol inhalation of 1.5 mg epinephrine / in 4mL saline–0.9% (control-group I, n=25)
  - The above treatment was repeated 3 times every hospitalization day until discharge.

**RESULTS** - Using 3% saline shortened hospitalization stay by 25% * n=51

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Treatment</th>
<th>Group I (n = 24)</th>
<th>Group II (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>3% NaCl</td>
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<td></td>
</tr>
</tbody>
</table>

| DAYS         | 4±1.9          | 3±1.2           | \( P<0.05 \)      |

* $75,000,000 Direct Save / Year - USA

More experience – Second year + pooled meta-analysis of both years

- Second year experience: hospital stay↓ symptoms↓
- Pooled data: N=93 (48 - epinephrine 1.5mg/hypertonic saline 3% and 45 - epinephrine 1.5mg / normal saline combination). hospital stay↓ symptoms↓

<table>
<thead>
<tr>
<th>Second year data</th>
<th>Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.9% NaCl</td>
<td>3% NaCl</td>
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<tr>
<td>Group I</td>
<td>Group II</td>
<td></td>
</tr>
<tr>
<td>DAYS</td>
<td>3.5±1.7</td>
<td>2.6±1.4</td>
</tr>
</tbody>
</table>

IMAJ 8:169-173, 2006
More experience

• **Design:** Randomized, double blind, placebo-controlled trial.
  
  • **65 ambulatory infants**
    - milder bronchiolitis.
    - 12.5±6 months old

• **NaCl-3%/5mg-terbutaline (Treatment group)** is more effective in decreasing symptoms as compared to **NaCl-0.9%/terbutaline (Control group)**

Design: A prospective, randomized, double-blinded, controlled, multicenter trial (3 centers – 3 Years 2003-2006 study).

Nebulized 3% HS (treatment group) or 0.9% NS (control) - 9 INH / Day

Principal outcome: Length of stay (LOS)

Results: 26% reduction in LOS to 2.6±1.9 days, compared with 3.5±2.9 days in the NS group (P=0.5)

The treatment was well tolerated, with no adverse effects

Conclusions: The use of nebulized 3% HS is a safe, inexpensive, and effective.

\textit{(J Pediatr 2007;151:266-70)}
Nebulized hypertonic saline solution for acute bronchiolitis in infants

• First published in 2008, Issue 4
• Last published in 2013, Issue 7 - (adding more studies to a new full meta-analysis)
• no change to conclusions.
**Cochrane Review 2013**

Nebulized hypertonic saline solution for acute bronchiolitis in infants

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**Figure 2. Hypertonic saline versus 0.9% saline: length of hospital stay (days)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypertonic saline</th>
<th>0.9% saline</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelberg 2003</td>
<td>3</td>
<td>4</td>
<td>-1.00 [-1.87, -0.13]</td>
<td>2003</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6</td>
<td>3.5</td>
<td>-0.90 [-1.86, 0.08]</td>
<td>2006</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>2.6</td>
<td>3.5</td>
<td>-0.90 [-1.88, 0.08]</td>
<td>2007</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>6</td>
<td>7.4</td>
<td>-1.40 [-1.96, -0.84]</td>
<td>2010</td>
</tr>
<tr>
<td>Luo 2011</td>
<td>4.8</td>
<td>6.4</td>
<td>-1.80 [-2.08, -1.12]</td>
<td>2011</td>
</tr>
<tr>
<td>Giudice 2012</td>
<td>4.9</td>
<td>5.6</td>
<td>-0.70 [-1.25, -0.15]</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>254</strong></td>
<td><strong>246</strong></td>
<td><strong>-1.15 [-1.49, -0.82]</strong></td>
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</tbody>
</table>

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 7.18$, df = 5 ($P = 0.21$); $I^2 = 30\%$

Test for overall effect: $Z = 6.83$ ($P < 0.00001$)
Nebulized hypertonic saline solution for acute bronchiolitis in infants

**Figure 5. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 2**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypertonic saline Mean</th>
<th>SD</th>
<th>Total</th>
<th>0.9% saline Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
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<tbody>
<tr>
<td>1.4.1 Outpatients</td>
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<tr>
<td>Sarrell 2002</td>
<td>2.77</td>
<td>1.4</td>
<td>33</td>
<td>4.77</td>
<td>2.31</td>
<td>32</td>
<td>12.6%</td>
<td>-2.00</td>
<td>[-2.93, -1.07]</td>
<td>2002</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2.77</td>
<td>1.4</td>
<td>33</td>
<td>4.77</td>
<td>2.31</td>
<td>32</td>
<td>12.6%</td>
<td>-2.00</td>
<td>[-2.93, -1.07]</td>
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<td>Heterogeneity: Not applicable</td>
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<td>Test for overall effect Z = 4.21 (P &lt; 0.0001)</td>
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<td>1.4.2 Emergency department patients</td>
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<tr>
<td>Al-Ansari 2010</td>
<td>3.86</td>
<td>1.16</td>
<td>115</td>
<td>4.12</td>
<td>1.11</td>
<td>56</td>
<td>15.7%</td>
<td>-0.27</td>
<td>[-0.63, 0.09]</td>
<td>2010</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>3.86</td>
<td>1.16</td>
<td>115</td>
<td>4.12</td>
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<td>56</td>
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<td>Heterogeneity: Not applicable</td>
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<td>Test for overall effect Z = 1.47 (P = 0.14)</td>
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<tr>
<td>1.4.3 Inpatients</td>
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<tr>
<td>Mandelberg 2003</td>
<td>6.41</td>
<td>1.34</td>
<td>24</td>
<td>6.92</td>
<td>1.62</td>
<td>25</td>
<td>13.1%</td>
<td>-0.51</td>
<td>[-1.36, 0.34]</td>
<td>2003</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>5.35</td>
<td>1.34</td>
<td>20</td>
<td>6.45</td>
<td>1.62</td>
<td>1</td>
<td>13.9%</td>
<td>-0.09</td>
<td>[-1.36, 0.28]</td>
<td>2006</td>
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<tr>
<td>Luo 2010</td>
<td>2.22</td>
<td>1.11</td>
<td>50</td>
<td>3.89</td>
<td>1.5</td>
<td>43</td>
<td>14.9%</td>
<td>-0.60</td>
<td>[-1.07, -1.06]</td>
<td>2010</td>
</tr>
<tr>
<td>Luo 2011</td>
<td>3.55</td>
<td>1.11</td>
<td>57</td>
<td>5.98</td>
<td>1.62</td>
<td>55</td>
<td>15.2%</td>
<td>-2.40</td>
<td>[-2.89, -1.91]</td>
<td>2011</td>
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<tr>
<td>Gidwitz 2012</td>
<td>6.85</td>
<td>1.44</td>
<td>52</td>
<td>8.24</td>
<td>1.7</td>
<td>54</td>
<td>14.6%</td>
<td>-0.14</td>
<td>[-0.98, -0.81]</td>
<td>2012</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6.85</td>
<td>1.44</td>
<td>203</td>
<td>71.7%</td>
<td></td>
<td>197</td>
<td>-1.45</td>
<td>-1.45</td>
<td>[-2.06, -0.85]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.36; Chi² = 18.94, df = 4 (P = 0.0008); I² = 79%</td>
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<td>Test for overall effect Z = 4.74 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>351</td>
<td>71.7%</td>
<td></td>
<td>281</td>
<td>-1.32</td>
<td>-1.32</td>
<td>[-2.00, -0.64]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.73; Chi² = 56.78, df = 6 (P &lt; 0.00001); I² = 89%</td>
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<tr>
<td>Test for overall effect Z = 3.81 (P = 0.0001)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 18.98, df = 2 (P &lt; 0.0001), I² = 97%</td>
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</tbody>
</table>
Nebulized hypertonic saline solution for acute bronchiolitis in infants

Figure 5. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 2

- **1.4.1 Outpatients**
  - Sarrell 2002
    - Hypertonic saline: Mean = 2.77, SD = 1.4, Total = 33
    - 0.9% saline: Mean = 4.77, SD = 2.31, Total = 32
    - Weight: 12.6%
    - Mean Difference: -2.00 [-2.93, -1.07]
    - Year: 2002
  - Subtotal (95% CI): 33
  - Heterogeneity: Not applicable
  - Test for overall effect: Z = 4.21 (P < 0.0001)

- **1.4.2 Emergency department patients**
  - Al-Ansari 2010
    - Hypertonic saline: Mean = 3.86, SD = 1.16, Total = 115
    - 0.9% saline: Mean = 4.12, SD = 1.11, Total = 56
    - Weight: 15.7%
    - Mean Difference: -0.27 [-0.63, 0.09]
    - Year: 2010
  - Subtotal (95% CI): 115
  - Heterogeneity: Not applicable
  - Test for overall effect: Z = 1.47 (P = 0.14)

- **1.4.3 Inpatients**
  - Mandelberg 2003
    - Hypertonic saline: Mean = 6.41, SD = 1.4, Total = 24
    - 0.9% saline: Mean = 6.92, SD = 1.62, Total = 25
    - Weight: 13.1%
    - Mean Difference: -0.51 [-1.36, 0.34]
    - Year: 2003
  - Tal 2006
    - Hypertonic saline: Mean = 5.35, SD = 1.3, Total = 20
    - 0.9% saline: Mean = 6.45, SD = 1, Total = 1
    - Weight: 13.9%
    - Mean Difference: -1.10 [-1.82, -0.38]
    - Year: 2006
  - Luo 2010
    - Hypertonic saline: Mean = 2.2, SD = 1.1, Total = 50
    - 0.9% saline: Mean = 3.8, SD = 1.5, Total = 43
    - Weight: 14.9%
    - Mean Difference: -1.60 [-2.14, -1.06]
    - Year: 2010
  - Luo 2011
    - Hypertonic saline: Mean = 3.5, SD = 1.1, Total = 57
    - 0.9% saline: Mean = 5.9, SD = 1.5, Total = 55
    - Weight: 15.2%
    - Mean Difference: -2.40 [-2.89, -1.91]
    - Year: 2011
  - Guilde 2012
    - Hypertonic saline: Mean = 6.8, SD = 1.4, Total = 52
    - 0.9% saline: Mean = 8.2, SD = 1.7, Total = 54
    - Weight: 14.6%
    - Mean Difference: -1.40 [-1.98, -0.81]
    - Year: 2012
  - Subtotal (95% CI): 203
  - Heterogeneity: Tau² = 0.36; Chi² = 18.94, df = 4 (P = 0.0008); I² = 79%
  - Test for overall effect: Z = 4.74 (P < 0.00001)

- **Total (95% CI):**
  - Hypertonic saline: Mean = 71.7%
  - 0.9% saline: Mean = 85%
  - Weight: 100.0%
  - Mean Difference: -1.45 [-2.06, -0.85]

- **Favours hypertonic saline: 203**
- **Favours 0.9% saline: 197**

Test for subgroup differences: Chi² = 18.98, df = 2 (P < 0.0001), I² = 89.5%
Nebulized hypertonic saline solution for acute bronchiolitis in infants

• First published in 2008, Issue 4

• Last published in 2013, Issue 7 - no change to conclusions.

Authors’ conclusions

Current evidence suggests nebulised 3% saline may significantly reduce the length of hospital stay among infants hospitalised with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.

Plain Language Summary

The establishment of a therapeutic role for hypertonic saline solution may provide a cheap and effective therapy for these patients.

We included 11 randomised trials involving 1090 infants with mild to moderate bronchiolitis. All but one of the 11 trials are considered as high-quality studies with low risk of error (i.e. bias) in their conclusions. Meta-analysis suggests that nebulised hypertonic saline could lead to a reduction of 1.2 days in the mean length of hospital stay among infants hospitalised for non-severe acute bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations. No significant short-term effects (at 30 to 120 minutes) of one to three doses of nebulised hypertonic saline were observed among emergency department patients. However, more trials are needed to address this question. There were no significant adverse effects noted with the use of nebulised hypertonic saline when administered along with bronchodilators.

Given the clinically relevant benefit and good safety profile, nebulised hypertonic saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis.
נייר עמדה (2012)

נייר עמדה המשמש האיגוד היהודי לີרפואת הילד, האיגוד היהודי לفىרפואת הילדים והאיגוד הישראלי ליאיורוזוולוגים ברפואה.

• ממילויים על ציפולי עם מלך היופטרון 3% או 5% (עם בטח אוגניטיסים) ברחולים מארשדים בחרולים אם בחרולים ברוכניליטיס ויראלו.

• ברחולים מארשדים מבקר אşıפודיס בחרולים אם בחרולים ברוכניליטיס משרר סימפטומי – CS.
Beyond Does Hypertonic Saline Further "Hold Water?" in Older “asthmatic” children

New “hot” data
Hypertonic Saline and Acute Wheezing in Preschool Children
Dorit Ater, Hanita Shai, Bat-El Bar, Nir Fireman, Diana Tasher, Ilan Dalal, Ami Ballin and Avigdor Mandelberg

*Pediatrics*; originally published online May 21, 2012;
DOI: 10.1542/peds.2011-3376

**WHAT’S KNOWN ON THIS SUBJECT:** Most acute wheezing episodes in preschool children are associated with rhinovirus, which decreases extracellular adenosine triphosphate levels, leading to airway surface liquid dehydration and submucosal edema, which cause failure of mucus clearance. These children respond poorly to available treatments.

**WHAT THIS STUDY ADDS:** Hypertonic saline inhalation, a pro–airway surface liquid hydration therapy, significantly decreases both length of stay by 33% (1 day) and the absolute risk of hospitalization by 30% in preschool children presenting with acute wheezing episode to the emergency department.
Oral Dexamethasone for Bronchiolitis: A Randomized Trial
Khalid Alansari, Mahmoud Sakran, Bruce L. Davidson, Khalid Ibrahim, Mahmoud Alrefai and Ibrahim Zakaria
*Pediatrics* 2013;132;e810; originally published online September 16, 2013;

**WHAT IS KNOWN ON THIS SUBJECT:** Some infants presenting with bronchiolitis are later diagnosed with asthma. Corticosteroid treatment of all infants with bronchiolitis is not clearly efficacious.

**WHAT THIS STUDY ADDS:** We used infant eczema or asthma history in a first-degree relative to select patients with bronchiolitis for dexamethasone or placebo blinded treatment. Dexamethasone treatment of 5 days led to significantly earlier readiness for discharge from infirmary treatment.

• Asthma predictive index positive = Selective population
Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: Bronchiolitis, a leading cause of infant hospitalization, has few proven treatments. A few small studies have reported the beneficial effects of a mixture of 21% oxygen + 79% helium (Heliox). The 2010 Cochrane Review concluded that additional large randomized controlled trials were needed to determine the therapeutic role of Heliox in bronchiolitis.

WHAT THIS STUDY ADDS: The Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE) trial is the largest multicenter randomized controlled trial to date to investigate the efficacy of Heliox in acute bronchiolitis. The delivery method for Heliox therapy was found to be crucial to its efficacy.

CONCLUSIONS: Heliox therapy does not reduce LoT unless given via a tight-fitting facemask or CPAP. Nasal cannula heliox therapy is ineffective.

*Pediatrics* 2013;131:661–669
Clinical studies and outcomes in Airway Diseases using HS

800 infants – Pediatric Emergency Dep. Outcome – hospitalization rate within 7 D

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hospitalization Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=200</td>
<td>26.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Dexamethasone–1mg/kg and 0.6mg/kg-5 days</td>
<td>25.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine 1:1000 - 3cc</td>
<td>23.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Dexamethasone + Epinephrine</td>
<td>17.1%</td>
<td>p=0.07</td>
</tr>
</tbody>
</table>

Dexamethasone Cumulative dose = 4mg/kg/6days
9% (N=18) preventive hospitalization

Figure 3. Cumulative Admissions during the First 7 Days after the Initial Emergency Department Visit, According to Study Group.
Enrollment data represent all patients admitted at their initial visit to the emergency department, and data for day 1 represent patients admitted within 24 hours of this visit.
Nebulized hypertonic saline solution for acute bronchiolitis in infants

Figure 3. Hypertonic saline versus 0.9% saline: rate of hospitalisation.

37% reduction in hospitalization. However p=0.9
Noa – 3M old baby

- Presenting: Fever, rhinitis, cough for 2 days
- Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.
- Anamnesis: Premature-28W 1500gr, ventilated for 5 days, needed oxygen for 50 days. Family-no atopy
- CXR: Over-inflation, plate like atelectasis.

= Previously BPD (=CLD of NB)
### Recommendations

<table>
<thead>
<tr>
<th>Medicine Used in Respiratory Diseases Only Seen in Children</th>
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</thead>
<tbody>
<tr>
<td>Bronchodilators</td>
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<tr>
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<tr>
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<tr>
<td>Chest physiotherapy</td>
</tr>
<tr>
<td>Hypertonic saline</td>
</tr>
</tbody>
</table>
Noa – 3M old baby

- Presenting: Fever, rhinitis, cough for 2 days
- Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.
- Anamnesis: Post BMT 3 2 weeks ago. Family-no atopy.
- CXR: Over-inflation, plate like atelectasis.

= Immune deficient baby
### Recommendations

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</table>
Dafna – 7M old baby

• Presenting: Fever, rhinitis, cough for 2 days

• Exam: Dyspnea, wheezing, rales, crepitations, 65 BPM, retractions.

• Anamnesis: Previously recurrent wheezing.

  Family-mother-asthma+allergy.

• CXR: Over-inflation, plate like atelectasis.

• = Previously Infantile asthma
### Recommendations

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment of acute viral bronchiolitis</th>
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*Medicine used in respiratory diseases only seen in children*
Shiri – 7M old baby

- Presenting: Fever, rhinitis, cough for 2 days
- Exam: No Dyspnea, wheezing, mild rales, 40 BPM, no retractions.
- Anamnesis: Mother says “wheezing from birth, less at night. Family-no atopy.
- CXR: Over-inflation, plate like atelectasis.

= Persistent wheezing
### Recommendations

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Yosi – 2.5Y old boy

- Presenting: Fever, rhinitis, cough for 2 days
- Exam: Dyspnea, wheezing,, 60 BPM, retractions.
- Anamnesis: Never wheezed, no family allergy/asthma
- CXR: Over-inflation, plate like atelectasis.

= Viral triggered wheezing
### Recommendations

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*Medicine used in respiratory diseases only seen in children*
Hypertonic Saline in Viral Bronchiolitis and beyond – Does Hypertonic Saline "Hold Water?"

From Basic Science to Clinical Practice
Modern – 2013 understandings

A. Mandelberg

The Pediatric Pulmonary Unit.
Wolfson Medical Center, Holon, Israel
**Viruses** *(n - increase with molecular diagnosis)*

- Respiratory syncytial virus (RSV) is the most common approximately – 80%
- Rhinovirus
- Parainfluenza virus
- Human metapneumovirus
- Influenza virus
- Adenovirus
- Coronavirus
- Human bocavirus
- Using molecular diagnostics, more than one virus may occur in up to one-third of young children hospitalized with bronchiolitis
• family: paramixoviridae, enveloped, ss-RNA,
• two surface glycoproteins:
  – **F**: fusion, conserved
    – T1 response
  – **G**: attachment,
    – T2 response
  – strains A and B

**RSV burden**

- Virtually **all** children become infected with RSV within two years after birth, (*,****)
  - 50% - infected twice (****)

- **0.5-2%** require hospitalization (*,**,**,****)
  - 2/3 of the cost of annual RSV epidemics result of hospitalization (*)
  - N↑↑↑↑ In Infants < 1 y: annual hospitalization/1000 ↑ 2.4-fold, from 12.9 in 1980 to 31.2 in 1996 (***)

- In 1985 - 100,000 children were hospitalized with RSV infection in USA = $300 million. (*)

---

RSV burden - Risk factors

- 1% of PHI are hospitalized = largest “risk group” (up to 75% of hospitalized babies)
  - Calls for genetic/immunological markers

- Age < 6 weeks
- Premature infants
- BPD / CLD, CF
- Congenital Heart Disease
- Immunosuppressive disease / therapy
- Underlying conditions:
  - Cong anomaly, CP, metabolic Disease