Bronchiolitis & Hypertonic Saline

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Objectives

• Discuss management implications of the 2014 AAP Bronchiolitis Guidelines
• Evaluate data regarding patient outcomes with Hypertonic Saline use in Bronchiolitis
• Describe the pathophysiology and clinical use of Hypertonic Saline in Bronchiolitis
Bronchiolitis

• Caused by viral lower respiratory tract infection
  – RSV common cause (76%)
    • 90% of children infected by 2 yo
    • 40% with lower respiratory symptoms
  – Rhinovirus (39%), metapneumovirus, influenza (10%), adenovirus, coronavirus (2%), parainfluenza (1%)

• Acute inflammation, edema, and necrosis of epithelial cells in small airways

• Increased mucus production

• Natural History
  – 2 days of rhinorrhea, nasal congestion and cough
  – Progressing increased work of breathing
Bronchiolitis

- Season time and duration based on location
- December through April here
- Variations in care
- Clinical scoring different in studies
  - Respiratory Rate
  - Respiratory Effort
  - Severity of Wheezing
  - Oxygenation
How should we manage bronchiolitis?

THE GUIDELINES
Guideline Criteria

- 1-23 months
- Excluded:
  - Immunodeficiency
    - HIV
    - Solid organ or stem cell transplant
  - Underlying Respiratory Illness
    - Recurrent Wheezing
    - Chronic Lung Disease (Neonatal)
    - Neuromuscular Disease
    - Cystic Fibrosis
  - Congenital Heart Disease (Hemodynamically significant)
    - On medications to manage congestive heart failure
    - Mod-severe pulmonary hypertension
    - Cyanotic Heart Disease
AAP Guidelines 2006

• Clinical Diagnosis
  – Recommendation 1a
  – Through History and Physical
  – Should NOT routinely order labs or imaging
    • Evidence level B (preponderance of benefit over harm, observational studies consistent)

• Risk Factors
  – <12 weeks old
  – Prematurity
  – Cardiopulmonary disease
  – Immunodeficiency
AAP Guidelines 2006

• Bronchodilators should not be routinely used
  – Recommendation 2a
  – Albuterol/Salbutamol
  – Epinephrine/Adrenaline
  – Evidence level B (RCTs with limitations and expert opinion; preponderance of harm of use over benefit)

• Trial of Bronchodilator
  – Recommendation 2b
  – Continue if documented response
  – Evidence level B (RCTs with limitations and expert opinion; balance of benefit over harm)
AAP Guidelines 2006

• Corticosteroids should not be used
  – Recommendation 3
  – Evidence level B (RCTs with limitations and expert opinion; preponderance of risk over benefit)

• Ribavirin should not be used
  – Recommendation 4
  – Evidence level B (RCTs with limitations and expert opinion; preponderance of risk over benefit)

• Antibacterial medications only for use for coexistence of bacterial infection
  – Recommendation 5
  – Evidence level B (RCTs and observational studies; preponderance of benefit over harm)

• Clinicians should assess hydration
  – Recommendation 6a
  – Evidence level X (clear predominance of benefit over harm)
AAP Guidelines 2006

• Chest Physiotherapy should not be used routinely in the management of bronchiolitis
  – Recommendation 6b
  – Evidence Level B (RCTs with limitations; preponderance of harm over benefit)
  – Cochrane review of 3 RCTs found no clinical benefit
    • Vibration
    • Percussion
  – Benefit for nasal suction
    • No benefit for deep suction
AAP Guidelines 2006

• Supplemental Oxygen indicated if oxyhemoglobin saturation is persistently below 90%
• Supplemental Oxygen may be discontinued if Spo2 at or above 90%
  – Infant is feeding well
  – Minimal respiratory distress
• Recommendation 7a
• Evidence level D (expert opinion and reasoning; some benefit over harm)
Oxyhemoglobin dissociation curve showing percent saturation of hemoglobin at various partial pressures of oxygen.

Subcommittee on Diagnosis and Management of Bronchiolitis Pediatrics 2006;118:1774-1793

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AAP Guidelines 2006

• As the child’s clinical course improved, continuous measurement of Spo2 is not routinely needed
  – Recommendation 7b
  – Evidence level D (expert opinion; balance of benefit and harm)

• Infants at high risk require close monitoring
  – Recommendation 7c
  – Evidence level B (observational studies with consistent findings; preponderance of benefit over harm)
AAP Guidelines 2006

• Synagis may be administered to specific infants in 5 monthly doses starting in Nov/ Dec
  – Chronic Lung Disease
  – Congenital Heart Disease
  – Recommendation 8a & 8b
  – Evidence level A (RCT; preponderance of benefit over harm)
AAP Guidelines 2006

• Hand decontamination is the most important step in prevention of RSV spread
  – Recommendation 9a
  – Evidence level B (observational studies with consistent results; strong preponderance of benefit over harm)

• Alcohol-based rubs preferred
  – Recommendation 9b
  – Evidence level B (observational studies with consistent results; preponderance of benefit over harm)

• Clinicians should education families on hand sanitation
  – Recommendation 9c
  – Evidence level B (observational studies; preponderance of benefit over harm)
AAP Guidelines 2006

• Infants should not be exposed to smoke
  – Recommendation 10a
  – Evidence level B (observational studies with consistent results; strong preponderance of benefit over harm)

• Breastfeeding is recommended to decrease risk of lower respiratory tract infection
  – Recommendation 10b
  – Evidence level C (observation studies; preponderance of benefit over harm)

• Clinicians should inquire about CAM
  – Recommendation 11
  – Evidence level D (expert opinion; some benefit over harm)
Evaluation

Bronchiolitis

- Chest X-ray
- Labs
- Hydration Status
- Continuous Pulse Ox?
Treatment

Bronchiolitis

- Hydration
- Albuterol
- Epinephrine
- Ipratropium
- Corticosteroids
- Ribavirin
- Chest Physiotherapy
- Antibiotics
- Oxygen
Prevention

Bronchiolitis

Hand washing

Breast feeding

No Smoking

Synagis

Smoking
Did this change clinical decisions?

- Analyzed data from Pediatric Health Information System 2004-2012
- 41 pediatric hospitals with 130,262 patients
Diagnostic and treatment utilization over 3 time periods from 41 hospitals (n = 37 907).

CBC, CXR, RSV trends had P value < .001.

Steroids and bronchodilators trends had P value < .001. Antibiotics had P value = .007.

Kavita Parikh et al. Pediatrics 2014;133:e1-e7
AAP Guidelines 2014

• Clinical Diagnosis & Severity
  – Recommendation 1a & 1b
  – Through History and Physical
  – Should NOT routinely order labs or imaging
    • Evidence level B

• Risk Factors
  – <12 weeks old
  – Prematurity
  – Cardiopulmonary disease
  – Immunodeficiency
Risk Factors

• **Respiratory Rate**
  – Counted over 1 minute
  – Regular RR- low risk for significant illness
    • Negative Likelihood Ratio 0.5
  – RR >70 bpm increase risk

• **Pulse oximetry to detect hypoxemia**
  – Perceived need for oxygen predictive of:
    • Increased LOS
    • ICU admission
    • Mechanical Ventilation
Risk Factors

• Apnea
  – <1 month old
  – <48 weeks corrected for premature infants
  – No association between specific virus and apnea
AAP Guidelines 2014

• Bronchodilators should not be routinely used
  – Recommendation 2 & 3
  – Albuterol/Salbutamol
  – Epinephrine/Adrenaline
  – Evidence level B

• Trial of Bronchodilator
  – Recommendation 2b
  – Continue documented response
  – Evidence level B (RCTs with limitations and expert opinion; balance of benefit over harm)
Albuterol

- Multiple studies show bronchodilators may improve clinical scores
  - Clinical scores not validated
- No evidence for:
  - Improving disease resolution
  - Hospitalization
  - Length of Stay
- Adverse events: tachycardia & tremor
- Cost
- Unable to identify population that may benefit
Epinephrine

- No evidence for:
  - Length of Stay
  - Outcomes
- Increased Length of Stay if scheduled and not as needed
- Potential use as rescue medication
- Reduced hospitalization on day of ED visit but not overall
  - Hartling et al
AAP Guidelines 2014

• Hypertonic Saline should not be administered in the emergency center
  – Recommendation 4a
  – Evidence level B
• Hypertonic Saline may be administered in hospital
  – Recommendation 4b
  – Evidence Level B (Weak; randomized control trials with inconsistent findings)
Hypertonic Saline

- Increasingly studied
- Studies demonstrated decreased length of stay
  - When > 72 hours
  - Average length of stay 58 hours
- 3% Hypertonic Saline
- Improved symptoms after 24 hours of use
- Studies with and without concurrent bronchodilators
AAP Guidelines 2014

• Corticosteroids should not be used
  – Recommendation 5
  – Evidence level A
AAP Guidelines 2014

• Supplemental Oxygen indicated if oxyhemoglobin saturation is persistently below 90%

• Supplemental Oxygen may be discontinued if Spo2 at or above 90%
  – Infant is feeding well
  – Minimal respiratory distress

• Recommendation 6

• Evidence level D (expert opinion and reasoning; some benefit over harm)
Oxygen

• 60% of healthy infants 2 weeks to 6 months had transient oxygen desaturations <90% ¹
  – Down to 83%

• 1 in 4 patients had increased length of stay for perceived need for oxygen when continuous pulse oximetry used ²

Oxygen

• Home oxygen in areas with high altitude
• Humidified, heated, high-flow nasal cannula
  – Evidence for reduced work of breathing
  – Study in Australia with decreased intubations rates
  – No randomized control trial
  – Complication: pneumothorax
AAP Guidelines 2014

• May choose not to use continuous pulse oximetry
  – Recommendation 6b
  – Evidence level D (expert opinion; balance of benefit and harm)

• Infants at high risk require close monitoring
  – Recommendation 7c
  – Evidence level B (observational studies with consistent findings; preponderance of benefit over harm)
AAP Guidelines 2014

- Chest Physiotherapy should not be used routinely in the management of bronchiolitis
  - Recommendation 7
  - Evidence Level B
  - Cochrane review of 6 RCTs found no clinical benefit
    - Vibration
    - Percussion
  - 1 study showed benefit for passive expiratory technique
  - Benefit for nasal suction
    - No benefit for deep suction
AAP Guidelines 20114

• Antibacterial medications only for use for coexistence of bacterial infection
  – Recommendation 8
  – Evidence level B

• Clinicians should assess hydration and use NG/IV as needed
  – Recommendation 9
  – Evidence level X
AAP Guidelines 2014

• Synagis may be administered to specific infants in 5 monthly doses starting in Nov/ Dec
  – Chronic Lung Disease
  – Congenital Heart Disease
  – Recommendation 10
  – Evidence level A (RCT; preponderance of benefit over harm)
AAP Guidelines 2014

• Hand hygiene should be completed
  – Recommendation 11a
  – Evidence level B

• Alcohol-based rubs preferred
  – Recommendation 11b
  – Evidence level B
AAP Guidelines 2014

• Infants should not be exposed to smoke & clinicians should discuss this
  – Recommendation 12
  – Evidence level B/ C

• Breastfeeding is recommended to decrease risk of lower respiratory tract infection
  – Exclusive for 6 months
  – Recommendation 13
  – Evidence level B

• Clinicians should educate families on diagnosis, treatment and prevention
  – Recommendation 14
  – Evidence level C
Evaluation

Bronchiolitis

Chest Xray

Labs

Hydration Status

Continuous Pulse Ox
Treatment

Bronchiolitis

- Hydration
- Hypertonic Saline
- High-Flow Nasal Cannula
- Epinephrine
- Ipratropium
- Corticosteroids
- Ribavirin
- Chest Physiotherapy
- Oxygen
- Antibiotics
- High-Flow Nasal Cannula
- Albuterol
- Hypertonic Saline
Prevention

- Hand washing
- Breast feeding
- No Smoking
- Synagis
What are the patient outcomes?

HYPERTONIC SALINE
Difficult to Assess Data

• No adequate placebo for Hypertonic Saline studies
  – Sood et al demonstrate Airway Surface Liquid changes with 0.9% Saline

• Multiple randomized trials with conflicting data
  – Variable Severity Scores
  – Variable doses and other medications
    • Albuterol, Epinephrine, 0.9%
History

• First trial in 2002
• Multiple trials
• 2013 Cochrane Review by Zhang et al
  – Found it was safe to use Hypertonic Saline with bronchodilators
  – Decreased LOS
  – Decreased Clinical Severity Score
• Multiple more trials
Hypertonic Saline Systematic Review

• Systematic review published online 9/28/2015
• Used 0.9% saline as control when reviewing articles
  – Some trials with albuterol and epinephrine
  – Some alone
  – Saline 0.9%, 3% (19 trials), 5%, 6%, 7% (2-4 mL)
• 24 trials included by criteria
• Heterogeneity

Hypertonic Saline Systematic Review

• Length of stay difference not as large
• 5 trials demonstrated improved Clinical Severity Scores on 1st day
• Effect greater on decreased hospitalization in trials with ≥3 doses and with virology testing
• Improved outcomes in studies with higher selection bias, difference between groups not statistically significant
• No significant difference in rate of readmission
• No change in oxygenation

Hypertonic Saline Systematic Review

• Safety
  – 14 trials without any adverse events
    • 81.3% with bronchodilators
    • 18.7% alone
  – 7 trials with 1+ adverse events
    • 26% with bronchodilators
    • 74% alone
• Only 1 serious adverse event with bradycardia and desaturation resolved in 1 day
  – HS alone
• Reported adverse events: coughing fits, vomiting, diarrhea, parental concern, hoarse voices, bronchospasm, desaturation, agitation

Hypertonic Saline Systematic Review

• Decreased length of stay
  – Statistically significant
  – 1/3rd the length reduction as 2013 (-0.45 days)

• Could reduce risk of hospitalization by 20%
  – Statistically significant
  – Less than 2013 (but not statistically significant)

• Mild to moderate bronchiolitis

Effects of nebulized HS on reduction of LOS among inpatients.

Effects of nebulized HS on reducing the risk of hospitalization among outpatients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Events1</th>
<th>N1</th>
<th>Events2</th>
<th>N2</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarrell 2002</td>
<td>2</td>
<td>33</td>
<td>3</td>
<td>32</td>
<td>0.65 (0.12, 3.62)</td>
<td>1.13</td>
</tr>
<tr>
<td>Grewal 2009</td>
<td>8</td>
<td>23</td>
<td>13</td>
<td>23</td>
<td>0.62 (0.32, 1.20)</td>
<td>7.50</td>
</tr>
<tr>
<td>Anil 2010</td>
<td>1</td>
<td>75</td>
<td>1</td>
<td>74</td>
<td>0.99 (0.06, 15.48)</td>
<td>0.44</td>
</tr>
<tr>
<td>Ipek 2011</td>
<td>5</td>
<td>60</td>
<td>8</td>
<td>60</td>
<td>0.63 (0.22, 1.80)</td>
<td>2.98</td>
</tr>
<tr>
<td>Florin 2014</td>
<td>22</td>
<td>31</td>
<td>20</td>
<td>31</td>
<td>1.10 (0.78, 1.55)</td>
<td>26.81</td>
</tr>
<tr>
<td>Jacobs 2014</td>
<td>22</td>
<td>52</td>
<td>24</td>
<td>49</td>
<td>0.86 (0.56, 1.32)</td>
<td>17.79</td>
</tr>
<tr>
<td>Wu 2014</td>
<td>61</td>
<td>211</td>
<td>84</td>
<td>197</td>
<td>0.68 (0.52, 0.89)</td>
<td>43.33</td>
</tr>
<tr>
<td>Overall (I-squared = 2.4%, p = 0.407)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.80 (0.67, 0.96)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for overall effect Z = 2.40 (p = 0.01)

NOTE: Weights are from random effects analysis

<table>
<thead>
<tr>
<th>Study ID and Country</th>
<th>Setting</th>
<th>Inclusion Criteria of Participants</th>
<th>RSV Positivity</th>
<th>Intervention and Control</th>
<th>Treatment Regimen</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Anṣari 2010, Qatar</td>
<td>Outpatient (ED)</td>
<td>Infants ≤18 mo with moderate to severe bronchiolitis, defined as a prodromal history of viral RTI followed by wheezing and/or crackles and Wang CSS of ≥4.</td>
<td>56.1% (96/171)</td>
<td>−5 mL 3% saline + 1.5 mg epinephrine (n = 58)</td>
<td>Saline solutions given on enrollment and every 4 h thereafter.</td>
<td>− Primary: Wang CSS at 48 h. - Secondary: Wang CSS at 24 and 72 h, LOS in ED, revisit to ED, AEs.</td>
</tr>
<tr>
<td>Anil 2010, Turkey</td>
<td>Outpatient (ED)</td>
<td>Infants 6 wk to 24 mo with first episode of bronchiolitis, defined by symptoms of upper RTI and presence of bilateral wheezing and/or crackles on auscultation and Wang CSS between 1 and 9.</td>
<td>NA</td>
<td>−4 mL 3% saline + 1.5 mg epinephrine (n = 39)</td>
<td>Saline solutions given at 0 and 30 min.</td>
<td>− Primary: Wang CSS at 0, 30, 60, 120 min. - Secondary: SAO₂ in room air and heart rate at 0, 30, 60 and 120 min, AEs.</td>
</tr>
<tr>
<td>Everard 2014, England and Wales</td>
<td>Inpatient</td>
<td>Children &lt;12 mo with diagnosis of bronchiolitis defined as apparent viral RTI with airway obstruction (hyperinflation, tachypnea, and subcostal recession) and widespread crepitations, needing O₂ with SaO₂&lt;92%.</td>
<td>84% (179/212)</td>
<td>−4 mL 3% saline + HS given every 6 h until primary outcome achieved</td>
<td>Standard care (n = 149)</td>
<td>- Primary: fit for discharge (75% of usual intake and SaO₂ ≥92% for 6 h at room air). - Secondary: actual time to discharge, readmission within 28 d from randomization, healthcare usage, duration of respiratory symptoms postdischarge, ITQoL, AEs.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Location</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Outcomes</td>
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<tr>
<td>Florin 2014, USA</td>
<td>Outpatient (ED)</td>
<td>Children &lt;24 mo with first episode of bronchiolitis, defined as first episode of wheezing associated with signs and symptoms of upper RTI and respiratory distress measured by RDAI score between 4 and 15.</td>
<td>NA</td>
<td>-4 mL 3% saline (n = 31) -4 mL 0.9% saline (n = 31)</td>
<td>One dose of saline solutions given at 0 min. - Primary: RACS at 1 h after inhalation. - Secondary outcomes: vital signs, SaO₂, hospitalization rate, physician clinical impression, parental assessment, AEs.</td>
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</tr>
<tr>
<td>Grewal 2009, Canada</td>
<td>Outpatient (ED)</td>
<td>Children 6 wk to 12 mo with diagnosis of bronchiolitis, defined as first episode of wheezing and symptoms of viral RTI, initial SaO₂ 85%–96% and initial RDAI score ≥4.</td>
<td>82.2% (37/45)</td>
<td>-2.5 mL 3% saline + 0.5 mL 2.25% racemic epinephrine (n = 24)</td>
<td>One dose saline solutions given at 0 min. - Primary: RACS 0–120 min, change in SaO₂ 0–120 min. - Secondary: admission to hospital, return to ED, AEs.</td>
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</tr>
<tr>
<td>Ipek 2011, Turkey</td>
<td>Outpatient (ED)</td>
<td>Children &lt;2 y with history of preceding viral upper RTI followed by wheezing and crackles on auscultation and Wang CSS between 4 and 8.</td>
<td>NA</td>
<td>-4 mL 3% saline + 0.15 mg/kg salbutamol (n= 30) -4 mL 0.9% saline + 0.15 mg/kg salbutamol (n= 30) -4 mL 3% saline (n = 30) -4 mL 0.9% saline (n = 30)</td>
<td>Saline solutions given at 0, 20, 40 min. - Primary: Wang CSS, use of corticosteroid, hospitalization, clinical assessment 48–72 h. - Secondary: SaO₂, respiratory rate, heart rate.</td>
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</tr>
<tr>
<td>Jacobs 2014, USA</td>
<td>Outpatient (ED)</td>
<td>Children 6 wk to &lt; 18 mo with bronchiolitis defined as viral RTI and first episode of wheezing, Wang CSS ≥4 and SaO₂&gt;85%.</td>
<td>60.3% (41/68)</td>
<td>-3 mL 7% saline + 0.5 mL 2.25% racemic epinephrine (n = 52) -3 mL 0.9% saline + 0.5 mL 2.25% racemic epinephrine (n = 49)</td>
<td>One dose of saline solutions given at 0 min. - Primary: Wang CSS before and after treatment and at disposition. - Secondary: hospitalization rate, proportion of admitted patients discharged at 23 h, LOS, AEs.</td>
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<tr>
<td>Kuzik 2007, Abu Dhabi and Canada</td>
<td>Inpatient</td>
<td>Children ≤18 mo with history of preceding viral upper RTI, wheezing or crackles on chest auscultation, plus either SaO₂ of 94% in room air or significant respiratory distress as measured by RDAI score ≥4.</td>
<td>68.8% (55/80)</td>
<td>-4 mL 3% saline (n = 47)</td>
<td>3 doses given every 2 h, followed by every 4 h for 5 doses, followed by every 6 h until discharge. - Primary: LOS defined as time between study entry and time at which the infant either reached protocol-defined discharge criteria (RDAI score &lt; 4 and SaO₂ ≥95% in room air for 4 h) or discharged by attending physician, whichever came first. - Secondary: AEs.</td>
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</tr>
<tr>
<td>Li 2014, China</td>
<td>Outpatient (Ambulator care unit)</td>
<td>Children 2–18 mo with first episode of bronchiolitis (Wang y care unit) CSS ≥4).</td>
<td>NA</td>
<td>-2 mL 3% saline (n = 42) -2 mL 5% saline (n = 40) -2 mL 0.9% saline (n = 42)</td>
<td>Saline solutions given twice daily for 3 d. - Primary: Wang CSS 24, 48, 72 h after treatment. - Secondary: AEs.</td>
<td></td>
</tr>
<tr>
<td>Luo 2010, China</td>
<td>Inpatient</td>
<td>Wheezing infants with mild to moderate viral bronchiolitis, measured by Wang CSS.</td>
<td>69.9% (65/93)</td>
<td>-4 mL 3% saline + 2.5 mg salbutamol (n= 50) -4 mL 0.9% saline + 2.5 mg salbutamol (n= 43)</td>
<td>Saline solutions given every 8 h until discharge. - Primary: Wang CSS, cough, pulmonary moist and crackles, Wang CSS, AEs.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Inpatient/Outpatient</td>
<td>Study Population</td>
<td>Intervention</td>
<td>Dosing</td>
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<tr>
<td>Luo</td>
<td>2011</td>
<td>China</td>
<td>Inpatient</td>
<td>Children &lt;24 mo with first episode of wheezing diagnosed as moderate to severe bronchiolitis according Wang CSS.</td>
<td>−4 mL 3% saline (n = 57) −4 mL 0.9% saline (n = 55)</td>
<td>3 doses given every 2 h, followed by every 4 h for 5 doses, followed by every 6 h until discharge.</td>
</tr>
<tr>
<td>Mandelberg</td>
<td>2003</td>
<td>Israel</td>
<td>Inpatient</td>
<td>Children ≤12 mo with clinical presentation of viral bronchiolitis, temperature &gt;38°C and SaO₂ ≥85%.</td>
<td>−4 mL 3% saline + 1.5 mg epinephrine (n = 27) −4 mL 0.9% saline + 1.5 mg epinephrine (n = 25)</td>
<td>Saline solutions given every 8 h until discharge.</td>
</tr>
<tr>
<td>Miraglia</td>
<td>2012</td>
<td>Italy</td>
<td>Inpatient</td>
<td>Children under 24 mo with diagnosis of bronchiolitis, defined as first episode of wheezing and clinical symptoms of viral RTI, SaO₂&lt;94% in room air and significant respiratory distress measured by Wang CSS.</td>
<td>−7 mL 3% saline + 1.5 mg epinephrine (n = 52) −7 mL 0.9% saline + 1.5 mg epinephrine (n = 54)</td>
<td>Saline solutions given every 6 h.</td>
</tr>
<tr>
<td>Ojha</td>
<td>2014</td>
<td>Nepal</td>
<td>Inpatient</td>
<td>Children &gt;6 wk to &lt;24 mo with first episode of bronchiolitis defined as wheezing associated with upper RTI, tachypnea, increased respiratory effort, clinical scoring of respiratory distress ≥4 and SaO₂≥85%.</td>
<td>−4 mL 3% saline (n = 36)</td>
<td>Saline solutions given every 8 h until discharge.</td>
</tr>
<tr>
<td>Pandit</td>
<td>2013</td>
<td>India</td>
<td>Inpatient</td>
<td>Children 2–12 mo with acute bronchiolitis defined as short history of cough with or without fever &lt;7 d and first episode of wheezing.</td>
<td>−4 mL 3% saline + 1 mL adrenaline (n= 51) −4 mL 0.9% saline + 1 mL adrenaline (n= 49)</td>
<td>3 doses given every 1 h, followed by every 6 h until discharge.</td>
</tr>
<tr>
<td>Sarrel</td>
<td>2002</td>
<td>Israel</td>
<td>Outpatient (Ambulatory care unit)</td>
<td>Children ≤24 mo with clinical presentation of mild to moderate bronchiolitis and SaO₂ &lt;96%.</td>
<td>−2 mL 3% saline + 5 mg terbutaline (n= 33)−2 mL 0.9% saline + 5 mg terbutaline (n= 32)</td>
<td>Saline solutions given every 8 h for 5 d.</td>
</tr>
<tr>
<td>Sharma</td>
<td>2012</td>
<td>India</td>
<td>Inpatient</td>
<td>Children 1–24 mo with moderate (Wang CSS 3–6) acute bronchiolitis defined as first episode of wheezing with prodrome of upper RTI.</td>
<td>−4 mL 3% saline + 2.5 mg salbutamol (n= 125)−4 mL 0.9% saline + 2.5 mg salbutamol (n= 123)</td>
<td>Saline solutions given every 4 h until discharge.</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting</td>
<td>Population</td>
<td>Clinical Presentation</td>
<td>Treatment</td>
<td>Primary Outcome</td>
<td>Secondary Outcome</td>
</tr>
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</tr>
<tr>
<td>Tal 2006, Israel</td>
<td>Inpatient</td>
<td>Children ≤12 mo with clinical presentation of viral bronchiolitis leading to hospitalization and ( \text{SaO}_2 \geq 85% ).</td>
<td></td>
<td>(-4) mL (3%) saline + 1.5 mg epinephrine ((n = 21))</td>
<td>Primary: LOS (discharge decided by attending physician), Wang CSS.</td>
<td>- Secondary: radiograph score, AEs.</td>
</tr>
<tr>
<td>Teunissen 2013, The Netherlands</td>
<td>Inpatient</td>
<td>Children 0–24 mo with moderate to severe (Wang CSS ≥3) bronchiolitis defined as upper RTI with wheezing, tachypnea, and dyspnea.</td>
<td></td>
<td>(-4) mL (3%) saline + 2.5 mg salbutamol ((n = 84))</td>
<td>Primary outcome: LOS defined as time between the first dose of medications and clinical decision to discharge (protocol-defined discharge criteria: no supplemental (\text{O}_2), no tube-feeding or intravenous fluids).</td>
<td>Secondary: transfer to ICU, duration of supplemental (\text{O}_2) or tube-feeding, AEs.</td>
</tr>
<tr>
<td>Tinsa 2014, Tunis</td>
<td>Inpatient</td>
<td>Children 1 to 12 mo with diagnosis of bronchiolitis, defined as first episode of wheezing associated with acute RTI and Wang score ≥3.</td>
<td></td>
<td>Saline solutions given every 4 h until discharge.</td>
<td>Primary: Wang CSS at 30, 60 and 120 min.</td>
<td>Secondary: LOS (discharge criteria: no supplemental (\text{O}_2), adequate fluid intake, Wang CSS &lt;3), AEs.</td>
</tr>
<tr>
<td>Wu 2014, USA</td>
<td>Outpatient (ED)</td>
<td>Children &lt;24 mo with first episode of bronchiolitis during bronchiolitis season.</td>
<td></td>
<td>(-4) mL (3%) saline ((n = 211))</td>
<td>Primary: admission rate, LOS.</td>
<td>Secondary: RDAI score, need for supplemental therapy, AEs.</td>
</tr>
<tr>
<td>NCT01276821</td>
<td>Outpatient (ED)</td>
<td>Children 6 wk to 2 y with bronchiolitis defined as first episode of wheezing and Wang CSS between 1 and 9.</td>
<td></td>
<td>Saline solutions given every 20 min to a maximum of 3 doses.</td>
<td>Primary: Wang CSS at 30, 60, 120 min.</td>
<td>Secondary: (\text{Sao}_2), respiratory rate, heart rate at 30, 60, 120 min, transfer to ICU, discharge rate after 120 min, revisit to ED within 1 wk, AEs.</td>
</tr>
<tr>
<td>NCT01488448</td>
<td>Inpatient</td>
<td>Children 0–12 mo admitted to hospital with a diagnosis of bronchiolitis.</td>
<td></td>
<td>Saline solutions given every 4 h until discharge.</td>
<td>Primary: LOS.</td>
<td>Secondary: readmission within 30 d, transfer to ICU, AEs.</td>
</tr>
<tr>
<td>NCT01238848</td>
<td>Inpatient</td>
<td>Children 1–24 mo hospitalized for first episode of bronchiolitis, with severity score ≥5 and oxygen saturation ≥97%.</td>
<td></td>
<td>Saline solutions given every 8 h until discharge.</td>
<td>Primary: LOS.</td>
<td>Secondary: duration of supplemental (\text{O}_2), AEs.</td>
</tr>
</tbody>
</table>
Hypertonic Saline RCT

- Multicenter Randomized Control Trial published 2014 followed by Systematic Review August 19, 2015
- Performed in UK hospitals, included in Zhang et al review
- Differing definitions of “acute bronchiolitis” between countries
- No change in length of stay
- Minimal adverse events
Hypertonic Saline RCT

- Systemic review demonstrated decreased length of stay by 0.3 days but given heterogeneity not believed to be significant
- Additional articles to Zhang et al from other countries
- Came to different conclusion that Hypertonic Saline does not decrease length of stay
Cumulative survival plot for time to being declared fit for discharge.

Mark L Everard et al. Thorax 2014;69:1105-1112
“THE ONLY TRUE WISDOM IS IN KNOWING YOU KNOW NOTHING.”

Socrates
Bronchiolitis

- Hydration
- Hypertonic Saline
- Hydration
- High-Flow Nasal Cannula
- Albuterol
- Epinephrine
- Ipratropium
- Corticosteroids
- Ribavirin
- Antibiotics
- Oxygen
- Chest Physiotherapy
- Hypertonic Saline
- Oxygen
HYPERTONIC SALINE

What is the pathophysiology & use in infants and children?
Airway Mechanisms

- **ASL** Airway surface liquid
  - **PCL** Periciliary liquid
  - **ML** Mucus layer
- **Cilia**
- **MC** Mucus clearance
  - **MCC** Mucociliary clearance
- **Hydration**
  - Extracellular ATP
  - CFTR
  - ENaC

Fig. 1. Postulated mechanism in vivo, explaining ASL dehydration in RSV bronchiolitis as compared to normal and CF: (A) normal, (B) mild RSV bronchiolitis: (C) severe RSV bronchiolitis, (D) during viral infection in CF. This figure was modified particularly for RSV bronchiolitis, with the permission and the courtesy of Randell SH and Donaldson SH, both from the University of North Carolina at Chapel Hill.

Proposed RSV affects

- RSV depletes extracellular ATP through ATPase
  - Shear stress naturally occurring with inflation and deflation increases ATP -> hydration
- Leads to dehydration of ASL
  - Increased Na absorption (ENaC)-> decreased Cl secretion
  - Increased water in submucosa
- Ciliary damage
- Increased Cytokines
- CFTR overcome
- Cellular damage
- Clinical findings: mucus plugging, airway obstruction, hyperinflation, atelectasis

Can we re-hydrate the Airway Surface Liquid?

• In vitro, Hypertonic Saline increases ASL hydration
• In vivo, Hypertonic Saline increases mucus transport rate
Fig. 2. Simplified scheme assuming only osmotic forces to control water transport.

Hypertonic Saline Effects

• Decreased mucus cross-linking
• Increased ciliary beat frequency
  – Prostaglandin E2
• Absorb water from submucosa
• Cause cough
Hypertonic Saline

• Use of 3-7% saline found to be safe in children and infants
• Volume used 2-4 mL based on study/ location and if bronchodilator present
• Monitor for bronchospasm
Conclusion

• Discuss management implications of the 2014 AAP Bronchiolitis Guidelines
• Evaluate data regarding patient outcomes with Hypertonic Saline use in Bronchiolitis
• Describe the pathophysiology and clinical use of Hypertonic Saline in Bronchiolitis
References

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- Jacobs JD, Foster M, Wan J. 7% Hypertonic Saline in Acute Bronchiolitis: A Randomized Controlled Trial. Pediatrics 2014: 133, 1 e8 -e13
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