RSV Bronchiolitis in Children
The Bird’s Eye View

Nidal El-wiher, M.D. & Steve Lauer PhD MD
Department of Pediatrics
University of Kansas Medical Center
April 19th 2012
Case

10 mo male admitted to PICU early am, 3 days of URI, low grade fever, 1 day of respiratory distress, NP swab was + for RSV

Physical Exam: VS: HR 170, RR: 68/min, SaO2 87-90% on RA, BP 87/44, Tm 99.8

Coarse breath sounds, decrease air entry in the bases and LLL field, expiratory wheezes bilaterally, intercostal retractions, no murmur, CRT 2-3 sec.
Case

Patient was suctioned placed on 1L/min NC to maintain O2 sat > 92%, and started on the following regimen

- Albuterol Q2 hr and Q 4 hr prn
- NP suction Q 2 hr and prn
- Orapred 1 mg/kg BID
- As CXR showed LLL haziness patient was started on Ceftriaxone Q 24hr
- IVF started at maintenance
2 hrs later a different PICU attending started round and the following changes happened

- Albuterol/orapred was D/C
- Hypertonic saline wash Q4 hr was started
- Pulmozyme BID was started too

So PICU team had different questions about the reason of changing the management???
Objectives

- Review symptomatology of RSV Bronchiolitis
- Review Epidemiology
- Going to the basic
- Discuss the current therapeutic approach using EBM
- Discuss future therapy
- Interventions at KUMC
Definition
American Academy of Pediatrics

Acute bronchiolitis:

A constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children < 2yr of age
Clinical Manifestations

- Prodrome of URI
- Tachypnea
- Respiratory distress
- Poor feeding
- Apnea
- Wheezing in 30% of infected infants
Differential Diagnosis for Wheezing in Infants

- Viral bronchiolitis
- Pulmonary infections (*Mycoplasma, Chlamydia, TB*)
- Laryngotracheomalacia
- Foreign body, esophageal or aspirated
- Gastroesophageal reflux
- Congestive heart failure
- Vascular ring
- Allergic reaction
- Cystic Fibrosis
- Mediastinal mass
- Bronchogenic cyst
- Tracheo-esophageal fistula

Zorc J et al. Bronchiolitis: Recent Evidence on Diagnosis and Management. *Pediatrics* 2010;125;342-349
Extra-pulmonary manifestations of RSV

**CVS**
- Myocarditis
- MAT, VT
- Complete heart block

**CNS:**
- Central apnea (16-21%)
- Seizures (up to 6.6% pts admitted to PICU)
- Feeding or swallowing difficulties

**Endocrine**
- Elevated ADH, prolactin and GH
- Hyponatermia (1/3 pt admitted to PICU)

**Liver:**
- Hepatitis (up to 50% of pts on ventilator)
- Reyes Syndrome

**Others**
- Thrombocytopenia
- Conjunctivitis
- Scarlatiniform rash

Eisenhut, M et al. Extrapulmonary manifestations of severe RSV infection – a systematic review. *Critical Care* 2006, 10:R107
Epidemiologic features

- All children become infected with RSV within 2 yrs after birth
- 1-3% require hospitalization*
- RSV infection is the cause of 50-90% of hospitalization for Bronchiolitis
  - 5-40% of these for pneumonia
  - 10-30 % of these for tracheobronchitis

- 2009, a prospective population-based study showed that the yearly rate from RSV alone for infants <6 mo was
  - 17 hospitalizations
  - 55 ED visits
  - 132 office visits per 1000 children*

* Hall, C. The Burden of respiratory Syncytial Virus Infection in Young Children. NEJM 360,6 Feb5, 2009
Epidemiologic features

The cost of hospitalization for RSV Bronchiolitis in Children < 1 y.o is estimated to be

> $700 Million/year*

Pathophysiology of RSV Infection
Respiratory Syncytial Virus

Enveloped RNA virus of the family of Paramyxoviridae
Single stranded genome

Pathogens in Bronchiolitis

RSV 80%

Parainfluenza, Influenza, Adeno, Rhino, and Enterovirus 20%

Pathogenesis

- Incubation period: 2-8 Days
- Spread to lower airway within 1-3 Days
- Necrosis and sloughing of the epithelium of the small airways with edema and loss of cilia
- Collection of desquamated epithelial cells, neutrophils and lymphocytes within the airway, cellular infiltration and edema around the airway and increased secretion of mucus
- Obstruction of small airway
Pathogenesis

Mucus secretion

Necrosis Sloughing and edema

Peribronchial cellular infiltration

Obstruction of the flow

Smooth muscle

V/Q mismatch
Pathophysiology

Inflammation

Mucus production

Airway obstruction

\( R_{aw} \)

Hyperinflation
Air trapping

Increase RR
Increase WOB
Increase dead space
V/Q mismatch

\( \uparrow FRC, RV, TLC \)

\( \downarrow V_T \)
Histology

*Breese, C et al. RSV and Parainfluenza Virus, NEJM Vol, 344, No.25 June 21,2001
Management

Mild/ Moderate
- Oxygen
- NP Suction
- Fluid Replacement
- Bronchodilators?
- Corticosteroids?
- Hypertonic saline?
- Pulmozyme?
- Chest physiotherapy?

Severe
- Heliox
- CPAP/BiPAP
- Mechanical ventilation
- Surfactant
- ECMO
- Antiviral agents?
- Antibacterial agents

19
THE PATIENTS KNOW MORE ABOUT THEIR DISEASES THAN ME. I MUST GET FASTER MODEM, HIGHER SPEED INTERNET ACCESS THAN THEM.
Management

“Oxygen, administered by means of a small tent, gives these patients with cyanosis definite relief, and is the treatment upon which we have to rely for the most severely ill infants”

AAP Recommendation

- Supplemental oxygen is indicated if SpO2 < 90% persistently in previously healthy infants

- Infants with a known history of hemodynamically significant heart or lung disease and premature infants require close monitoring as the oxygen is being weaned
I need to do something!

- Chest X-ray
- Bronchodilators
- Corticosteroids
- Hypertonic saline
- rhDNase
- Chest therapy
6 month old with respiratory distress
CXR

- Hyperinflation and patchy infiltrates
- Focal atelectasis
- Flattened diaphragm
- Increased AP diameter
- Peribronchial cuffing

- Alternative diagnoses
  - Lobar pneumonia
  - CHF
  - Foreign body aspiration
In 265 nontoxic appearing infants with typical bronchiolitis, CXR results were inconsistent with clinical diagnosis only in 2 (0.75%) patients.

Does obtaining CXR increase the use of antibiotics?

2.6% prior to obtaining X-ray to 14.7% after viewing the X-rays

CXR is not recommended routinely by the AAP
Diagnostic test

- Antigen tests of nasal washings
  sensitivity 87-91%, specificity 96-100%

- Cultures less sensitive 60%, but are 100% specific

- Diagnostic test useful...
  - To clearly define cause
  - For cohorting when admitted to hospital
Bronchodilators

*Decreased airway diameter and wheezing are secondary to:*

- Increased secretion production
- Sloughing of injured airway epithelium to lumen
- Mucosal and interstitial edema
- Bronchoconstriction mediated by humoral and neurogenic mechanisms

Bronchodilators

- Racemic Epinephrine
- Albuterol
- Levalbuterol
Randomized, double-blind, controlled trial compares nebulized epinephrine with placebo in 194 infants admitted to four hospitals in Australia, with a clinical diagnosis of bronchiolitis.
- No significant differences between in the hospital LOS (P=0.16) or the time until the infant was ready for D/C (P=0.86)
- Among infants who required oxygen and IVF, the time until the infant was ready for D/C was significantly longer in the epinephrine group than in the placebo group (P=0.02)
- No significant changes in the RR, BP, or respiratory effort scores from before each treatment to after each treatment.
- HR was significantly increased after each tx with epinephrine (P=0.02 to P< 0.001)
### TABLE 5. Results From Cochrane Collaboration Meta-analysis Comparing Bronchodilators to Placebo for Children With Bronchiolitis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies Pooled (No.)</th>
<th>Characteristics of Included Trials</th>
<th>N in Treatment Group/Total</th>
<th>Results</th>
<th>Trials (No.) Including Patients With Recurrent Wheeze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in clinical score</td>
<td>8</td>
<td>4 nebulized beta agonist trials, 2 nebulized ipratropium trials, 1 epinephrine injection trial, 1 combination bronchodilator trial</td>
<td>211/394</td>
<td>0.29 OR (95% CI, 0.19, 0.45), favoring treatment</td>
<td>7/8</td>
</tr>
<tr>
<td>Rate of hospitalization</td>
<td>4</td>
<td>4 nebulized beta agonist trials</td>
<td>97/187</td>
<td>β agon 19.6% placebo 24.4% OR 0.76 (0.38, 1.53)</td>
<td>1/4</td>
</tr>
<tr>
<td>Length of stay if hospitalized</td>
<td>3</td>
<td>1 nebulized or oral beta agonist trial, 2 beta agonist +/- ipratropium trials</td>
<td>130/177</td>
<td>0.118 hours weighted mean difference, favoring placebo (95% CI, -0.311, 0.547)</td>
<td>0/3</td>
</tr>
</tbody>
</table>
## TABLE 6. Randomized Clinical Trials Comparing Nebulized Epinephrine to Placebo in Children With Bronchiolitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wainwright et al., 2003</td>
<td>194 hospitalized patients &lt; 12 months with first episode wheeze; 66% RSV positive, ~50% each group mod-severe illness</td>
<td>Nebulized epinephrine every 4 hours × 3</td>
<td>Length of stay: Epi(^a) = 58.8 hr, Placebo = 69.5 hr</td>
<td><em>Length of stay: Epi(^a) = 58.8 hr, Placebo = 69.5 hr</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time until ready to discharge: Epi(^a) = 46.5 hr, Placebo = 47.7 hr</td>
<td><em>Time until ready to discharge: Epi(^a) = 46.5 hr, Placebo = 47.7 hr</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (\text{O}_2) required: Epi(^a) = 54.0 hr, Placebo = 58.8 hr</td>
<td><em>Time (\text{O}_2) required: Epi(^a) = 54.0 hr, Placebo = 58.8 hr</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resp effort score 60 minutes after each epi neb: No differences between groups at any point</td>
<td><em>Resp effort score 60 minutes after each epi neb: No differences between groups at any point</em></td>
</tr>
<tr>
<td>Patel et al., 2002</td>
<td>98 hospitalized patients &lt; 12 months with first time wheeze, 67% RSV positive</td>
<td>Nebulized epinephrine every 1-6 hours</td>
<td>Length of stay: Epi(^a) = 59.8 hrs, Placebo = 63.3 hrs</td>
<td><em>Length of stay: Epi(^a) = 59.8 hrs, Placebo = 63.3 hrs</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean time to (\text{RDAI} \leq 4): Epi(^a) = 34.6 hrs, Placebo = 36.8 hrs</td>
<td><em>Mean time to (\text{RDAI} \leq 4): Epi(^a) = 34.6 hrs, Placebo = 36.8 hrs</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean time to (\text{SaO}_2) 25.0 hrs, Placebo = 36.6 hrs</td>
<td><em>Mean time to (\text{SaO}_2) 25.0 hrs, Placebo = 36.6 hrs</em></td>
</tr>
<tr>
<td>Abul-Ainine et al., 2002</td>
<td>39 hospitalized patients 30 days to 12 months old with moderate illness, 70% RSV positive</td>
<td>Nebulized epinephrine × 1</td>
<td>No statistical or clinically significant differences in (\text{RDAI}, \text{RR}, \text{SaO}_2) at 20, 40, 60 min post-treatment</td>
<td><em>Unclear allocation concealment</em></td>
</tr>
<tr>
<td>Kristjansson et al., 1993</td>
<td>34 hospitalized patients &lt; 18 months with clinical bronchiolitis with mod-severe illness</td>
<td>Nebulized epinephrine × 1</td>
<td>Mean oxygen saturation and clinical scores improved 60 minutes post epinephrine ((P &lt; .05))</td>
<td><em>Intention to treat violated</em> (\uparrow) <em>Included patients with recurrent wheezing</em></td>
</tr>
</tbody>
</table>
| Hariprakash et al., 2003| 75 outpatients 1 month to 1 year old with moderate illness, 48% RSV positive | Nebulized epinephrine × 2 at 30 min interval | Hospitalization rate (difference 12%, 95% CI 11% to 35%) \(\uparrow\) No statistically or clinically significant differences in \(\text{RDAI}, \text{RR}, \text{SaO}_2\) at 30, 60, 120 min post-treatment | *Data not collected on children not enrolled in trial* \(\uparrow\)  

\(^{a}\) Epi = Epi \text{nebulizer}
Epinephrine and Dexamethasone in Children with Bronchiolitis


- Multicenter, double-blind, placebo-controlled trial in which 800 infants (6 weeks to 12 months of age) with bronchiolitis who were seen in the ped ED assigned to one of four study groups.
The 1st group (the epinephrine–dexamethasone group) received 2 tx of neb epi and a total of 6 oral doses of dexamethasone.

The 2nd group (the epinephrine group) received neb epi and oral placebo.

The 3rd group (the dexamethasone group) received neb placebo and oral dexamethasone.

The 4th group (the placebo group) received neb placebo and oral placebo.

_The primary outcome was hospital admission within 7 days after the day of enrollment._
<table>
<thead>
<tr>
<th>Admission</th>
<th>No. of Patients (%)</th>
<th>Relative Risk (95% CI)</th>
<th>95% CI (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At enrollment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>36 (17.9)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Epinephrine and dexamethasone</td>
<td>23 (11.5)</td>
<td>0.65 (0.41–1.04)</td>
<td>(0.37–1.15)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>29 (14.6)</td>
<td>0.79 (0.51–1.23)</td>
<td>(0.47–1.34)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>31 (15.5)</td>
<td>0.85 (0.56–1.31)</td>
<td>(0.51–1.43)</td>
</tr>
<tr>
<td><strong>By day 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>53 (26.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Epinephrine and dexamethasone</td>
<td>34 (17.1)</td>
<td>0.65 (0.45–0.95)</td>
<td>(0.41–1.03)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>47 (23.7)</td>
<td>0.88 (0.63–1.23)</td>
<td>(0.59–1.32)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>51 (25.6)</td>
<td>0.96 (0.69–1.33)</td>
<td>(0.65–1.42)</td>
</tr>
<tr>
<td><strong>By day 22</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>54 (26.9)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Epinephrine and dexamethasone</td>
<td>37 (18.5)</td>
<td>0.69 (0.48–0.99)</td>
<td>(0.44–1.07)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>50 (25.1)</td>
<td>0.92 (0.66–1.27)</td>
<td>(0.62–1.36)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>53 (26.5)</td>
<td>0.98 (0.71–1.35)</td>
<td>(0.66–1.44)</td>
</tr>
</tbody>
</table>
Bronchodilators use in Bronchiolitis

Results of these studies are confounded by:

1- The variety of therapies

2- The outcome measures (ranges from short-term clinical scores obtained soon after treatment to broader clinical outcomes such as hospitalization or duration of illness)

3- Minute to minute change in clinical picture
AAP Recommendation

AAP recommendations is against the routine use of bronchodilators*

A carefully monitored trial of alpha or beta adrenergic medication is an option.

Inhaled bronchodilators should be continued ONLY IF there is a documented positive clinical response to the trial using an objective means of evaluation.

*Diagnosis and Management of Bronchiolitis, Subcommittee of AAP. Pediatrics Volume 118, Number 4, October 2006
Corticosteroids in Bronchiolitis

Studies* indicate that up to 60% of infants admitted to the hospital for bronchiolitis receive corticosteroids.


In 2004, a review by Cochrane Collaboration to 13 studies (~1200 pts) of the use of steroids for bronchiolitis showed no difference between steroids and placebo groups in:

- Respiratory rate
- O2 saturation
- Admission rates
- Length of stay
- Subsequent visits or readmission rates*

*Patel, H. et al. GC for acute viral bronchiolitis in infants and young children. Cochrane Database Sys Rev 2004;3
A double-blind, RT comparing a single dose of oral dexamethasone with placebo in 600 infants with a first episode of wheezing diagnosed in the ED as moderate-to-severe bronchiolitis
No significant difference in the rate of hospital admission, the respiratory status after 4 hrs of observation, or later outcomes
Meta-analysis of systemic steroid trials in bronchiolitis: Effect on duration of mechanical ventilation

Meta-analysis of systemic CS trials in bronchiolitis: Effect on hospital length of stay

<table>
<thead>
<tr>
<th>Study</th>
<th>dexamethasone</th>
<th>Control</th>
<th>WMD</th>
<th>Weight</th>
<th>WMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean(sd)</td>
<td>n</td>
<td>mean(sd)</td>
<td>(95%CI Random)</td>
</tr>
<tr>
<td>van Woensel 1997</td>
<td>7</td>
<td>11.00(1.86)</td>
<td>7</td>
<td>17.00(5.29)</td>
<td>-6.00[-10.15,-1.85]</td>
</tr>
<tr>
<td>van Woensel 2003</td>
<td>37</td>
<td>15.90(3.12)</td>
<td>45</td>
<td>14.60(3.04)</td>
<td>1.00[-2.76,4.76]</td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>44</td>
<td></td>
<td>52</td>
<td></td>
<td>-2.44[-9.30,4.42]</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=6.00 df=1 p=0.014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.70 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corticosteroid medications should not be used routinely in the management of bronchiolitis.
Randomized, double-blind, placebo-controlled trail of 75 pts with RSV bronchiolitis who received dose of 2.5 ml once daily for up to 5 days
There was significant improvement in the CXRs with the use of rhDNase compared to significant worsening in the placebo group.
A multicenter, randomized, double-blind, controlled trial, 225 O2 dependent infants admitted to the hospital for RSV bronchiolitis were randomly assigned to receive 2.5 mg BID of nebulized rhDNase or placebo until discharge.
Table 3—Length of Hospital Stay and Time Supplemental Oxygen Was Required, According to the Baseline Symptom Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>rhDNase</th>
<th>No. of Infants</th>
<th>Placebo</th>
<th>No. of Infants</th>
<th>Ratio of Geometric Means of rhDNase and Placebo Groups (95% Confidence Interval)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.4 (3.9–4.9)</td>
<td>111</td>
<td>3.8 (3.4–4.3)</td>
<td>111</td>
<td>1.14 (0.97–1.35)</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline symptom score ≤ 3§</td>
<td>3.9 (3.2–4.7)</td>
<td>46</td>
<td>3.4 (2.9–3.9)</td>
<td>56</td>
<td>1.15 (0.90–1.46)</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline symptom score ≥ 4</td>
<td>4.9 (4.2–5.7)</td>
<td>60</td>
<td>4.4 (3.6–5.2)</td>
<td>52</td>
<td>1.12 (0.89–1.42)</td>
<td>0.31</td>
</tr>
<tr>
<td>Time supplemental oxygen required, d‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.6 (2.2–3.1)</td>
<td>109</td>
<td>2.0 (1.6–2.4)</td>
<td>108</td>
<td>1.29 (0.99–1.67)</td>
<td>0.053</td>
</tr>
<tr>
<td>Baseline symptom score ≤ 3§</td>
<td>2.0 (1.5–2.7)</td>
<td>45</td>
<td>1.6 (1.2–2.2)</td>
<td>54</td>
<td>1.27 (0.84–1.93)</td>
<td>0.26</td>
</tr>
<tr>
<td>Baseline symptom score ≥ 4</td>
<td>3.2 (2.6–3.9)</td>
<td>59</td>
<td>2.6 (2.0–3.3)</td>
<td>51</td>
<td>1.24 (0.91–1.70)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
P = 0.09 (Mann-Whitney test)
Hypertonic Saline

- Breaks the ionic bonds within the mucus gel, thus reducing the degree of cross-linking
- Induces an osmotic flow of water into the mucus
- Stimulates ciliary beat
  - (increased prostaglandin E2)
- May reduce edema of the airway wall
- Causes sputum induction and cough
Four RCTs involving 254 infants with viral bronchiolitis (189 inpts and 65 outpts) compared nebulized 3% saline to nebulized 0.9% saline.
One study was a multi-center trial involving one hospital in the UAE and two hospitals in Canada (Kuzik 2007).

The other three studies were conducted by the same group of investigators in Israel (Mandelberg 2003; Sarrell 2002; Tal 2006).

In three trials (Mandelberg 2003; Sarrell 2002; Tal 2006), the patients received hypertonic saline inhalation in conjunction with bronchodilators.

In one trial (Kuzik 2007), the study protocol defined the use of nebulized HTN alone, but bronchodilators were added into the study solution in 60% of the treatments by attending physicians.
All three inpatient trials demonstrated a benefit of 3% saline in reducing the duration of hospitalization.

A statistically significant shorter mean length of hospital stay with a MD of \(-0.94 \text{ days}, P = 0.0006\) (25.9% reduction).

Rate of hospitalization:
The outpatient trial failed to demonstrate the efficacy of nebulized 3% saline in reducing the risk of hospitalization.
General Pediatric Hospital Care

vs.

PICU
Heliox

In 2002, Martinon-Torres and co-workers conducted a prospective study examined Heliox (70/30) delivered thru NRM in 38 infants with mod/severe RSV bronchiolitis.

Heliox therapy enhanced their clinical respiratory status.

This response occurred within the 1st hr and was maintained as long as heliox therapy continued.

In addition, PICU-LOS was reduced in heliox-treated patients.

Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: A prospective study and evidence review*

Daniel Levin, MD; Melissa Tribuzio, MD; Tamara Green-Wrzesinski, MD; Bethany Ames, MD; Sarah Radwan, MD; J. Dean Jarvis, RN; Therese Vaccaro, MD; John F. Modlin, MD

Prospective, descriptive study of 23 infants admitted to PICU with RSV and respiratory failure, and literature review.
The data suggest that >20% chance of bacterial pneumonia in otherwise low-risk infants with RSV and the use of empirical antibiotics for 24-48 hours pending culture results may be justified.
Surfactant in RSV infection

- Surfactant activity can be impaired in RSV infection:
  - Direct damage of type II pneumocytes
  - Inactivation of surfactant by protein-rich edema
  - Damage of the alveolo-capillary membrane may cause a loss of surfactant into interstitium and blood
  - Mechanical ventilation with large TV and high FiO2 can further damage alveolar surfactant*

Multicenter, randomized, controlled study in 6 PICU staffed by full-time intensive care physicians.

A total of 40 infants with RSV-induced respiratory failure requiring CNV were randomly assigned to either exogenous surfactant or conventional treatment.
PaO2/FiO2 comparison
Outcomes

- Duration of CMV was significantly shorter in the treated group [-1.2 day] \((p \leq 0.0001)\)

- The length of stay in the ICU was significantly shorter [-1.8 day] \((p \leq 0.0001)\) in the treated group

- No complications found in either group

- No infant was reintubated, none was treated with HFOV, iNO or ECMO

- All patients survived
**Meta-analysis of trials of surfactant in children with ARF: Duration of PICU stay**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Surfactant Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 RSV/Bronchiolitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luchetti (1998)</td>
<td>10</td>
<td>10.10 (1.20)</td>
<td>10</td>
<td>15.70 (1.50)</td>
<td>27.01</td>
<td>-5.60 [-6.79, -4.41]</td>
</tr>
<tr>
<td>Tibby (2000)</td>
<td>10</td>
<td>6.72 (3.48)</td>
<td>9</td>
<td>8.87 (5.35)</td>
<td>16.75</td>
<td>-2.15 [-6.26, 1.96]</td>
</tr>
<tr>
<td>Luchetti (2002)</td>
<td>20</td>
<td>6.40 (0.90)</td>
<td>20</td>
<td>8.20 (1.10)</td>
<td>28.15</td>
<td>-1.80 [-2.42, -1.18]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td>71.91</td>
<td>-3.31 [-6.39, -0.23]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 30.77, df = 2 (P < 0.00001), I² = 93.5%
Test for overall effect: Z = 2.10 (P = 0.04)

Meta-analysis of trials of surfactant in children with ARF: Duration of mechanical ventilation

Chest physiotherapy

- In a meta-analysis of 3 RCT of CPT in acute bronchiolitis, there was no effect on hospital LOS, supplemental oxygen requirements, or severity as measured by clinical score

Perrotta, C. et al. Chest physiotherapy for acute bronchiolitis in pediatric patients between 0 and 24 months old. *Cochrane Database of Systemic Reviews 2007 Issue 1*
Therapies showed no benefits

- Vitamin A

- Interferon A
Summary of Therapeutic Trials

- No sustained benefit of beta2-agonists
- No sustained benefit of corticosteroids
- No sustained benefit of rhDNase
- Potential benefit of hypertonic saline

– Cochrane Database
Future Therapies!! (maybe)

Macrolides antibiotics:
Antibacterial, immunomodulatory, anti-inflammatory

- One group in Turkey did a randomized double blind placebo controlled trial of 3 week course clarithromycin in the treatment of RSV Bronchiolitis

- Significant decreased hospital LOS, and level of IL-4, IL-8.

Vitamin D

the vitamin D receptor gene, have been associated with bronchiolitis and may link to preliminary evidence associating neonatal vitamin D levels with wheezing in young children.
Ribavirin

Systematic overview of 12 trails of ribavirin for RSV infection revealed that ribavirin may reduce duration of mechanical ventilation and hospital stay.

In addition, on the basis of a single study, the use of ribavirin may be associated with a decrease in the long-term incidence of recurrent wheezing following RSV disease.

Comparison Ribavirin versus placebo: Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peto.Fixed.95% CI</td>
<td></td>
<td>Peto.Fixed.95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hall 1985</td>
<td>2/30</td>
<td>1/29</td>
<td>26.7%</td>
<td>1.93 [0.19, 19.28]</td>
<td></td>
</tr>
<tr>
<td>Meert 1994</td>
<td>2/22</td>
<td>4/19</td>
<td>48.2%</td>
<td>0.39 [0.07, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Rodriguez 1987</td>
<td>1/20</td>
<td>1/10</td>
<td>15.8%</td>
<td>0.46 [0.02, 9.16]</td>
<td></td>
</tr>
<tr>
<td>Smith 1991</td>
<td>0/14</td>
<td>1/14</td>
<td>9.2%</td>
<td>0.14 [0.00, 6.82]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>86</strong></td>
<td><strong>72</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.56 [0.17, 1.84]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Treatment), 7 (Control)
Heterogeneity: Chisq = 1.79, df = 3 (P = 0.62); I² = 0.0%
Test for overall effect: Z = 0.96 (P = 0.34)
**Comparison  Ribavirin versus placebo: Length of hospitalization**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Guerguerian 1999</td>
<td>20</td>
<td>10.66 (5.21)</td>
<td></td>
<td>85.7 %</td>
<td>-1.63 [-4.81, 1.55]</td>
</tr>
<tr>
<td>Meert 1994</td>
<td>19</td>
<td>12.9 (9.7)</td>
<td></td>
<td>14.3 %</td>
<td>-3.30 [-11.10, 4.50]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>39</td>
<td>12.9 (9.7)</td>
<td></td>
<td>100.0 %</td>
<td>-1.87 [-4.81, 1.08]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0.0%

Test for overall effect: Z = 1.24 (P = 0.21)
Comparison Ribavirin versus placebo: Length of ventilation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Guerguerian 1999</td>
<td>20</td>
<td>4.26 (2.72)</td>
<td>21</td>
<td>5.26 (3.28)</td>
<td>90.3 %</td>
</tr>
<tr>
<td>Meert 1994</td>
<td>19</td>
<td>6.4 (6.9)</td>
<td>18</td>
<td>8.2 (10.1)</td>
<td>9.7 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>39</td>
<td>39</td>
<td></td>
<td>100.0 %</td>
<td>-1.08 [-2.83, 0.67]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0.0%
Test for overall effect: Z = 1.21 (P = 0.23)
Ribavirin

- Its use been limited because:

1- It is expensive

   (The cost of ribavirin in 2004 was approximately $1100 /day excluding administration costs)

2- A beneficial effect on clinical outcome remains unproved!
SUMMARY

General Pediatrics

- Oxygen is good, keep SaO2 > 91%
  - Or is it 90%? 92%???

- Suctioning of nasopharyngeal airway is good

- Bronchodilator may benefit some, but must assess each patient pre- and post- therapy

- Corticosteroids have no role

- Pulmozyme has no role but may improve xray findings
SUMMARY
PICU

- Hypertonic saline may decrease hospital stay
- Heliox will decrease work of breathing so use it in sicker pts
- Antibacterial agents are not recommended… unless as empiric for co-infection in patients with respiratory failure
- Surfactant may play a role in really sick kids
Interventions at KUH

- Education
- EMR Order sets

- Make it easy to do the right thing
- Make it hard(er) to do the wrong thing
Education

- Annual guideline-based education of residents, respiratory therapists and nurses

- Annual review of guidelines in hospitalist meetings
**Pediatric Bronchiolitis**

**General Orders**
- **Isolation**
  - Isolation Education
  - Airborne Isolation
    - Routine, Continuous starting Today at 0930 Until Specified

**Nursing Orders**
- **Activity**
  - Routine, Ongoing starting Today at 0930 Until Specified, NOTE: this will discontinue and replace the current order.
  - Activity level: Up ad lib

- **Vital Signs**
  - Routine, Q4H First occurrence Today at 0930

**Nursing Communication**
- **Weigh Patient**
  - Routine, Daily First occurrence Today at 0930 Until Specified
- **Length/Height**
  - Routine, Once First occurrence Today at 0930
- **Measure Circumference**
  - Routine, Once First occurrence Today at 0930
  - Body Part: Head
**CLINICAL PRACTICE GUIDELINE**

**Diagnosis and Management of Bronchiolitis**

Subcommittee on Diagnosis and Management of Bronchiolitis

Endorsed by the American Academy of Family Physicians, the American Academy of Cystic Fibrosis, and the American Thoracic Society

**ABSTRACT**

Bronchiolitis is a disorder most commonly caused in infants by viral lower respiratory tract infection. It is the most common lower respiratory infection in this age group. It is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchoconstriction.

The American Academy of Pediatrics convened a committee composed of primary care physicians and specialists in the fields of pulmonology, infectious disease, emergency medicine, epidemiology, and medical informatics. The committee partnered with the Agency for Healthcare Research and Quality and the RTI International-University of North Carolina Evidence-Based Practice Center to develop a comprehensive review of the evidence-based literature related to the diagnosis, management, and prevention of bronchiolitis. The resulting evidence report and other sources of data were used to formulate clinical practice guideline recommendations.

This guideline addresses the diagnosis of bronchiolitis as well as various therapeutic interventions including bronchodilators, corticosteroids, antiviral and antibacterial agents, hydration, chest physiotherapy, and oxygen. Recommendations are made for prevention of respiratory syncytial virus infection with palivizumab and the control of nosocomial spread of infection. Decisions were made on the basis of a systematic grading of the quality of evidence and strength of recommendation. The clinical practice guideline underwent comprehensive peer review before it was approved by the American Academy of Pediatrics.

This clinical practice guideline is not intended as a sole source of guidance in the management of children with bronchiolitis. Rather, it is intended to assist clinicians in decision making. It is not intended to replace clinical judgment or establish a protocol for the care of all children with this condition. These recommendations may not provide the only appropriate approach to the management of children with bronchiolitis.

**INTRODUCTION**

This guideline examines the published evidence on diagnosis and acute management of the child with bronchiolitis in both outpatient and hospital settings, including the roles of supportive therapy, oxygen, bronchodilators, antimicrobial agents, antibacterial agents, and antiviral agents and make recommendations to influence clinician behavior on the basis of the evidence. Methods of prevention...
THANK YOU