Bronchiolitis and Respiratory Syncytial Virus (RSV) in Children: Helping the Wee Wheezer

William Sonnenberg, MD, FAAFP

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Dr. Sonnenberg earned his medical degree from the University of Pittsburgh and completed his family medicine residency at McKeensport Hospital in Pennsylvania. A past president of the Pennsylvania Academy of Family Physicians, he has been in private practice in the Titusville area since 1983. In 2017, he was a featured speaker about pneumonia and inflammatory bowel disease in three editions of the AAFP’s FP Audio™. His lectures at national meetings have been selected for publication by Audio-Digest seven times. 2019 marks his 12th time presenting at the AAFP’s annual meeting.
Learning Objectives

1. Identify the risk factors for bronchiolitis and the indications and modalities for aggressive treatment including hospitalization utilizing AAP guidelines.

2. Utilize comprehensive, evidence-based, and cost-effective strategies for the evaluation of bronchiolitis including rapid testing and radiographic studies.

3. Prescribe appropriate prevention strategies including appropriate use of palivizumab for children who are at increased risk for bronchiolitis.

4. Council parents/families regarding appropriate supportive care for patients who have bronchiolitis.

Audience Engagement System

Step 1

Step 2

Step 3
Key Guidelines from AAP and AAFP

- The diagnosis of bronchiolitis and assessment of disease severity should be based on history and physical examination. Laboratory and radiologic studies should not be routinely ordered for diagnosis.
- Risk factors for severe disease such as age < 12 weeks, premature birth, underlying cardiopulmonary disease, or immunodeficiency should be assessed when making decisions about evaluation and management of children with bronchiolitis.
- Bronchodilators (albuterol, salbutamol), epinephrine, and corticosteroids should not be administered to infants and children with the diagnosis of bronchiolitis.
- Nebulized hypertonic saline should not be administered to infants with the diagnosis of bronchiolitis in the emergency department. Nebulized hypertonic saline may be administered to infants and children hospitalized for bronchiolitis.
- Antibiotics should not be used in children with bronchiolitis unless there is a concomitant bacterial infection.
- Supplemental oxygen is not necessary in children and infants with a diagnosis of bronchiolitis if \(\text{SpO}_2\) exceeds 90%.

https://www.aafp.org/patient-care/clinical-recommendations/all/bronchiolitis.html

Audience Engagement Question #1

- Which of the following is a criteria for diagnosis of bronchiolitis
  a. Presence of RSV
  b. Age under 2
  c. Abnormal chest x-ray
  d. Hypoxia
Key Guidelines from AAP and AAFP

• Continuous pulse oximetry is optional for infants and children with bronchiolitis.
• Chest physiotherapy should not be used in the management of bronchiolitis.
• Palivizumab prophylaxis should be administered during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity (<32 weeks gestation who require >21% $O_2$ for the first 28 days of life).
• To prevent spread of respiratory syncytial virus (RSV), hands should be decontaminated before and after direct contact with patients, after contact with inanimate objects in vicinity of patient, and after removing gloves. Alcohol rubs are the preferred method for hand decontamination. Clinicians should educate personnel and family on hand sanitation.
• Infants should not be exposed to tobacco smoke.
• Exclusive breastfeeding for at least 6 months is recommended to decrease the morbidity of respiratory infections.

Viral URI followed by increased respiratory effort and wheezing

Less than age 2
Scope of Problem

- Most common lower respiratory tract infection in infants younger than age 2
- 60% of LRTI's in first year of life
- Leading cause of hospitalization in younger than age one
- Hospitalizations have declined from 2000 to 2010
- 4500 deaths/yr 1985 to ≈ 12 deaths/yr now

The Lancet, Aug 20, 2016

Leading Cause of Infant Hospitalization

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Incidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV Bronchiolitis</td>
<td>220,379</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>181,662</td>
</tr>
<tr>
<td>Jaundice</td>
<td>87,826</td>
</tr>
<tr>
<td>Dehydration</td>
<td>73,250</td>
</tr>
</tbody>
</table>

## Epidemiology of Bronchiolitis

### Bronchiolitis Statistics
- 90% children 0-2 yrs infected with RSV
- 20% have lower respiratory infection
- 3% hospitalized
- 0.002% mortality

### Age at Presentation
- Peak age 2-5 months
- Mean age 3 months
- Rare in 1st month of life

### Sex Epidemiology
- Male : Female
  - Hospitalized infants 2:1
  - Milder RSV disease 1:1
- Sex influences expression of illness rather than attack rate
- Preschool and daycare increases risk

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Hall CB. RSV. Textbook of Pediatric Infectious Disease
Socioeconomic Factors

- Lower socioeconomic infants have increased risk of infection
- Higher socioeconomic infants tend to be older, thus have milder disease
- More hospitalized infants are lower socioeconomic
  - Daycare, crowded living quarters

Risk Factors

- Cigarette smoke exposure
- Younger than 6 months
- Crowded conditions
- Lack of breast feeding
- Premature before 37 weeks
- Birth order ≥ 2nd
Risk and Prematurity


Premature at High Risk

- Immature lung development
  - Altered airway anatomy
  - Reduced lung function through early childhood

- Immature immune system
  - Impaired humoral and cellular immunity
Interrupted Lung Development

Antibody Levels in Premature

Yeung CY, Hobbs JR. Lancet. 1968; 2:1167-70
Prematurity and RSV

RSV Hospitalization Rate by Gestational Age at Birth

(Stevens TP et al. Arch Ped Adoles Med 2000)

80% RSV admissions occur within 4 months discharge from NICU
**Honeymoon Period**

- 0-4 weeks of age
- Transplacental maternal antibody gives partial immunity
- Preterm infants may miss IgG transfer at full term

*Cunningham CK, McMillan JA, Gross SJ Pediatrics 1991*

Elective Caesarean Section

- 11% increase in hospital admissions for bronchiolitis
  - Records of 212,068 babies over a 10-year period
- No increase in pneumonia admissions

“Mandatory” Vitamin D Slide

- Prospective study on healthy term neonates
- Mean 25-OHD 82 nmol/L
- <50 nmol/L had 6 times risk of RSV LRTI in first year of life compared to those ≥ 75 nmol/L

Belderbos M et al. Pediatrics, May 9 2011, online
Maternal Asthma and Smoking

Maternal Smoking and Bronchiolitis

- United Kingdom prospective cohort study, 378 infants
- Doubles need for oxygen
- Five times risk of ventilator care
- Infants should not be exposed to cigarette smoke

Breast Feeding and Bronchiolitis

- Not breast feeding in first 4 months of life more than triples risk for hospitalization
- Exclusive breastfeeding for first 14 days protects against hospitalization (OR=0.21)
- Exclusive breastfeeding for at least 6 months is recommended to decrease the morbidity of respiratory infections


The Season for Wheezin?

- Generally November through April
- Parts of Florida, early as July 1

Pathology ofBronchiolitis

Pathogenesis

- Incubation 2-8 days
- Nose + lowerresp tract 1-3 days
- Worsening lower airwaydisease 3-5 days
- Some repairNext 2 weeks
- Complete repair4-8 weeks
Associated Conditions with RSV

Clinical Findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>98%</td>
</tr>
<tr>
<td>Fever</td>
<td>75%</td>
</tr>
<tr>
<td>Rhinorrhea, Wheezing</td>
<td>65-78%</td>
</tr>
<tr>
<td>Labored Respirations</td>
<td>73-95%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Occasionally</td>
</tr>
</tbody>
</table>

Fever

- Most have low grade fever lasting 2-4 days
- Height and duration does not correlate with disease severity
- Tends to disappear with progression to lower respiratory tract

Clinical Course of Bronchiolitis

Swingler et al. 2000
Pathology

- Bronchiolar mucosal inflammation
- Submucosa & adventitia edema
- Sloughed, necrotic epithelium and fibrin plug airway
- Airway trapping
- Atelectasis – lack collateral channels
- Little smooth-muscle constriction

Airway Debris
Airway Plugging

Histopathology

- Marked transmural cellular infiltrate
- Metaplastic changes
- Ulcerative changes
Apnea and RSV

- 20% of hospitalized infants with RSV previously
- 2.7%

Risk factors for apnea
- History of apnea
- < one month of age
- Post conception age of 48 weeks for premature

Frederic W. Bruhn (J. Pediatr. 1977;90:382-6

Bronchiolitis and Asthma?

- Retrospective study 90,341 children
  - 18% had bronchiolitis visit
  - 31% of those had childhood asthma dx
  - Adjusted odds ratio 1.86

- No clear answer – does bronchiolitis alter airways or are infants born predisposed to asthma and wheezing?
- Maybe rhinovirus more likely to result in asthma

http://news.vanderbilt.edu/2011/02/bronchiolitis-asthma-allergies/
The Viral Pathogens

Viral Causes of Bronchiolitis

Respiratory Syncytial Virus

- RNA virus
- Subtype A & B
- A more severe
- Strains shift each year
- Hardy virus
- Inhibits detoxifying enzymes that lessens oxidative stress

What Does Syncytial Mean?

- Surface F protein causes cells to merge call a Syncytium
- Fusion allows cell-to-cell viral spread
RSV Pathogenesis

- RSV damages airway epithelium
- RSV fuses to cell membrane and forms Syncytia, multinucleated cells
- Resistant to host defense mechanisms
- Syncytia eventually slough into airway lumen


RSV Transmission

- Direct inoculation of contagious secretions from the hands
- Large-particle aerosols into eyes and nose
- Rarely by mouth
- Cuddling transmits but not sitting nearby
RSV Transmission

<table>
<thead>
<tr>
<th></th>
<th>Percent Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing students sitting 6 feet from</td>
<td>0%</td>
</tr>
<tr>
<td>a child with bronchiolitis for 8</td>
<td></td>
</tr>
<tr>
<td>hours</td>
<td></td>
</tr>
<tr>
<td>Nurses holding an infant with RSV</td>
<td>70%</td>
</tr>
<tr>
<td>in their arms intermittently</td>
<td></td>
</tr>
<tr>
<td>Subjects touching bed clothes after</td>
<td>78%</td>
</tr>
<tr>
<td>an infant with RSV was removed from</td>
<td></td>
</tr>
<tr>
<td>the room</td>
<td></td>
</tr>
</tbody>
</table>

Hall, Ped Research : 1978

Human Metapneumovirus

- Same viral family as RSV
- Bronchiolitis, sometimes pneumonia
- 8% of LRTI's
- Peaks December to March, every other year
- Alternates with RSV
- Virtually all children exposed by age 5
Bocavirus

- Parvovirus, identified 2005
- Wheezing in infants, asthma exacerbations in general
- Winter months
- Maybe GI symptoms
- High rate (20%-50%) of coinfection with other respiratory viruses

Other Viruses

- Rhinovirus
  - Dual infections
  - Bronchiolitis in spring and fall
- Parainfluenza
- Influenza
- Adenovirus

Viral Coinfection

- 67% chance of RSV sole pathogen
- 30% of hospitalized children with bronchiolitis had coinfection
- Adenovirus usually had another virus
- Coinfection does not increase ICU admission but prolongs stay
  - RSV and HRV prolong stay 33%

Mansbach, ACEP News, Aug 2011

Diagnosis of Bronchiolitis
Audience Engagement Question #2

- Which of the following tests should be routinely ordered in the evaluation of bronchiolitis?
  a. Chest x-ray, PA and lateral
  b. RSV antigen
  c. CBC
  d. None of the above

Diagnostic Testing

- **Dx Based on H&P, no routinely ordered tests**
- Rapid antigen testing
  - Does not change management
  - 90% sensitive (best antigen test)
  - 96% specific
- Chest X-ray
- WBC – normal or slightly elevated

AAFP, 2014
Rapid RSV Testing and Antibiotic Use

• Reduced antibiotic use, RR = 0.36
• No change in length of visit or ancillary testing


Chest X-Ray?

• Study of 265 cases, 0.75% of CXR’s showed lobar consolidation
  – Low yield if O2 saturation > 92%
• Of value when:
  – Temp >38.4° in ED
  – Hypoxia < 90%
  – Previous cardiopulmonary disease
  – ICU or ventilator need
  – Atypical cases

Chest X-Ray

- Flattened diaphragm
- Bilateral atelectasis

Usual RSV X-Ray Findings

- Diffuse interstitial pneumonitis most common in all lobes
- Hyperaeration > 50%
- Peribronchial thickening
- Lobar or segmental consolidation 20-50%
- RUL, RML most common
Bilateral Perihilar Fullness

Hyperinflation
Hyperinflated
Flattened diaphragm

Immunity

- Natural immunity neither complete nor durable
- Mucosally restricted
- Recurrent infections common

Caroline Breese Hall, M.D. NEJM 2001; 344:1917-1928
Prevention of RSV

Prevention

- Frequent hand washing – alcohol wipes preferred
- Keep sick school-age children away from younger siblings (under 2 years of age)
- Minimize visitors with an infant
- Avoid crowded places
  - Malls, grocery stores
- If possible, avoid daycare during RSV season
**RSV Viability**

- Hard surfaces: 6 hours
- Rubber gloves: 90 minutes
- Skin: 20 minutes

**Breast Feeding – Always the Right Answer**

- Hazard ratio for no breast feeding: 1.57 at 12 months
- Risk for exclusive breast feeding similar to breastfed with formula

Lanari M et al. Early Hum Dev. 2013 Jun;89 Suppl 1:S51-7
Palivizumab

- Administer in first year of life
  - Hemodynamically heart disease
  - Chronic lung disease of prematurity
    - <32 weeks gestation who require >21% O$_2$ for the first 28 days of life

Palivizumab

- Monoclonal antibody to F protein of RSV
  - 55%↓ hospitalizations for preterm/chronic lung disease
  - 45%↓ hospitalizations for congenital heart disease
Cost-Effectiveness

- Kansas Medicaid Study
  - Reduced hospitalization – 0.47 odds
  - Shorter length of stay - 74%
  - Less inpatient costs - $703
  - No deaths in either group
- Costs 6.67 times as much as no treatment
- About $6,000 per season


Palivizumab and Wheezing in Healthy Preterm Infants

- Preterm 33 – 35 weeks,
- All otherwise healthy
- ≤ 6 months at start of RSV season
- Outcome: Wheezing in first year of life
- Relative reduction 61% wheezing days
- Respiratory episodes same, less coinfections

Maarten O. et al. NEJM 2013; 368:1791-1799
Palivizumab and Wheezing in Healthy Preterm Infants

Maarten O. et al. NEJM 2013; 368:1791-1799

Palivizumab: Wheezing 6 years Follow-up

- ≥ 3 doses of palivizumab
  - 15.3% treated v. 31.6% untreated wheezing
- No prevention of atopic asthma
- Nonrandomized
- Untreated group
  - More likely to have smoker in household
  - More family hx of asthma

Hiroyuki Mochizuki ; Satoshi Kusuda ; Kenji Okada ; Shigemi Yoshihara ; Hiroyuki Furuya ; Eric A. F. Simões. Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing. American Journal of Respiratory and Critical Care Medicine, February 2017
Does Palivizumab Prevent Asthma?

- 429 infants, GA 32-35 weeks randomized to prophylaxis or placebo
- No major effect on asthma or lung function at 6 years
  - 10.3% placebo v. 9.9% treated.


Palivizumab Points

- Does not prevent RSV infection but prevents LRI
- Can’t treat existing infection
- Reduces subsequent wheezing but not asthma
RSV Vaccination?

- Failed vaccine trial in 1968
  - Vaccinated:
    - 12/15 hospitalized, 2 deaths
  - Unvaccinated:
    - 1/19 hospitalized, no deaths
- Exaggerated immune response

Caroline Breese Hall, M.D. NEJM 2001; 344:1917-1928

Future Vaccine Strategies

- Overcoming RSV genetic variation
  - F component of RSV/A2 strain
  - Conserved region of the G protein BBG2Na
- Cold live, attenuated RSV
- Maternal immunization in third trimester
- 15 in development

Audience Engagement Question #3

- Which of these are indicated in the treatment of bronchiolitis?
  a. Nebulized albuterol
  b. Saline nose drops
  c. Narrow spectrum antibiotics
  d. Hypertonic saline in ER
Risk Factors for Severe Disease

• Age < 12 weeks
• Premature birth
• Underlying cardiopulmonary disease
• Immunodeficiency

Signs of Worsening

• More than 60 breaths/minute
• Labored breathing
  – Accessory muscles, retractions, cyanosis, flared nostrils
• Fewer wet diapers
• Worsening appearance
• Lethargy or toxic appearing

Diagnosis and Management of Bronchiolitis, was developed by the American Academy of Pediatrics and endorsed by the American Academy of Family Physicians.
Don’t Use These

• Bronchodilator
  – Albuterol
  – Salbutamol
• Epinephrine

• Corticosteroids
• Chest physiotherapy
• Antibiotics

Supportive Care

• Saline nose drops, bulb suctioning
• Frequent hand washing
• Limit visitors
• No cigarette exposure
• No antibiotics, antihistamines, decongestants, nasal vasoconstrictors
Inpatient Treatment

Hospitalization Rates

- 1-2% of all USA infants hospitalized with RSV
- 20-30% of premature infants are hospitalized with RSV disease
Indications for Hospitalization

• Age less than 3 months
• Gestational age less than 34 weeks
• Cardiopulmonary disease or immunodeficiency
• Respiratory rate higher the 70 breaths/min
• Wheezing and respiratory distress with $O_2$ saturations below 92% on room air
• Hypercarbia
• Atelectasis or consolidation on CXR

Predictors of Severity

**Increased Severity**

• Younger age
• Dehydration
• Work of breathing (retractions)
• Tachycardia (HR > 97% for age)

**Mild Disease**

• Adequate oral intake
• Age ≥ 2 months
• Hx of eczema
• Initial O2 sat of at least 94%
• Lower respiratory rate
• No Hx of intubation
• No or mild retractions

Don’t Use These

• Bronchodilator
  – Albuterol
  – Salbutamol
• Epinephrine

• Corticosteroids
• Chest physiotherapy
• Antibiotics

Clearly Effective Treatments

• Supportive care
• Hydration
• Supplemental oxygen

Pediatrics November 2014, VOLUME 134 / ISSUE 5
From the American Academy of Pediatrics Clinical Practice Guideline

Supportive

- Nasal suctioning to clear upper airway
- Monitor for apnea, hypoxemia, and impending respiratory failure
- Normalize body temperature
- Rehydrate with oral or intravenous fluids
- Monitor hydration status

IV Fluids

- Severe respiratory difficulties
- Respiratory rate greater than 80 beats per minute
- Fatigue during feeding

Oxygen

- Supplemental oxygen is not necessary if SpO₂ exceeds 90%
- Continuous pulse oximetry optional
  - Headbox or tent
- Mechanical ventilation if
  - PaCO₂ ≥ 55 mmHg
  - PaO₂ ≤ 70 on 60% O₂

High Flow Oxygen?

<table>
<thead>
<tr>
<th>Standard Flow</th>
<th>High-Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2 L/min</td>
<td>2 L/min/Kg for FIO₂ of 92% to 98%</td>
</tr>
<tr>
<td>Escalation of care 23%</td>
<td>Escalation of care 12%</td>
</tr>
<tr>
<td>Same LOS, stay in ICU, or duration of oxygen therapy</td>
<td></td>
</tr>
</tbody>
</table>

Franklin D et al. NEJM 2018; 378:1121-1131
CPAP

- Decrease work of breathing
- Decreased ventilator associated pneumonia
- Before endotracheal intubation

Intensive Care Med. 2008;34(9):1608

How Much O₂ and How Long?

- O₂ saturations improve 66 hours after other problems resolve
- Continuous oximetry reveals characteristic transient dips
- AAP suggest less intense oximetry as infants improve otherwise
- Home O₂ being studied

Pediatrics Vol. 125 No. 2 February 1, 2010 pp. 342-349
Choosing Wisely Campaign for Hospitalized Infants

- **No** CXR’s in childhood asthma or bronchiolitis
  - Radiation and false positives
- **No** bronchodilators in bronchiolitis
  - Minimal or no benefit
- **No** systemic steroids in children under 2
  - Harmful and no benefit
- **No** continuous pulse oximetry unless on O$_2$
  - Over diagnosis hypoxemia

Nebulized 3% Hypertonic Saline

- Improve mucociliary transit time in cystic fibrosis
- Osmotic hydration
- Double blind study of 127 patients showed no difference in LOS between 3% and saline
- **Don’t use in ER, may use inpatient**
  - Better with longer LOS

Montefiore Medical Center. "Common treatment for bronchiolitis ineffective at reducing length of hospital stay, study suggests." ScienceDaily. ScienceDaily, 6 May 2013
Antibiotics

- Frequently used because of fever, young age, concerns over secondary bacterial infection
- Secondary infection uncommon (0%-3.7%)
- Given to 50-80% of hospitalized infants
- Most common secondary infection is UTI
- Antibiotics should not be used in children with bronchiolitis unless there is a concomitant bacterial infection

Practice Recommendations

- Avoid daycare, older siblings, cigarettes, formula, poverty, prematurity, and crowds to lessen risk of bronchiolitis
- Transmission is mostly direct contact
- Most treatment is supportive; supportive, hydration and oxygen
- Palivizumab is indicated for certain premature infants during RSV season
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drbill@drbillfp.com

Questions