Bronchiolitis: State of the Mess

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Anthony Arredondo, DO has no relationships with commercial companies to disclose

Objectives
At the end of this presentation, an engaged audience member will be able to:
1. Describe the basic pathophysiology and epidemiology of bronchiolitis
2. Describe and understand the basis of current management
3. Outline the latest guidelines and how local management may differ and why
4. Discuss future directions for bronchiolitis clinical improvement and research

Outline
- First reports of bronchiolitis
- Pathophysiology
- Epidemiology - national and local
- A common case of bronchiolitis
- 2014 AAP Guidelines
  - Diagnosis
  - Management
- Local data and guideline modifications
- Future directions


A brief history of bronchiolitis
1901: Luther E Holt: provided first description including basic epidemiology
1940s: viral cause suspected, steam, oxygen, supportive care, “as many opinions as authors”
1950s: theory on H. flu as cause put forth
1960s: RSV identified
1970s: small, uncontrolled trials of both alpha and beta-agonists show little effect
1980s: ribavirin developed specifically to target RSV
1990s: beginning of explosion of clinical trials evaluating long used therapies
2000s: Guidelines published, beginnings of quality improvement, research on long-term outcomes emerging
2010s: Supportive care mainstay, some consensus developing

First activity
- What is bronchiolitis?
- Find a neighbor, and try and define bronchiolitis in 1-2 sentences. You have 1 minute.
- After discussing, post your response:
American Academy of Pediatrics definition

- Constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by an increased respiratory effort and wheezing in children less than 2 years old

Bronchiolitis pathophysiology

- RSV invades epithelial cells of respiratory tract, forms syncytial cells, cells die
- First the ciliated cells, then columnar basal cells
- Swelling and mucus build-up in the bronchioles along with plugs of alveolar debris and fibrin
- Necrosis of respiratory epithelium, subsequent proliferation of epithelium without cilia
- All in context of maternal antibodies

Epithelial sloughing with exudates and fibrin

Baboon model

Day 1

Day 3

Day 5

RSV Inv (10x)

RSV Inv (40x)

Day after inoculation


Bronchiolitis epidemiology

- The most common cause of bronchiolitis is respiratory syncytial virus (RSV)
- Other major causes include influenza, para-influenza, rhinovirus, metapneumovirus and others
- Nearly universal infection - 95% of children infected with RSV by 2 years of age
- 1.5 million outpatient visits
- Bronchiolitis is the leading diagnosis at hospitalization for infants under 1 year of age
- RSV responsible for 40-50% of hospitalizations
- Results in approximately 150,000 hospitalizations per year at a cost of over $500 million
- 3% of all infants in the US will be admitted for bronchiolitis


http://www.dshs.state.tx.us/RSV/disease/rsv-data.aspx

Current local epidemiology

Hayes A et al. CDC MMWR. 2014.
Local (UHS) Epidemiology

Cases based on ICD-9/10 diagnoses for bronchiolitis during the admission

Annual Bronchiolitis Hospitalizations

Since 2000 – things have flattened out

Which of the Following is the MOST Likely Cause for the Increase in Hospitalization for Bronchiolitis?

1. Climate change related RSV distribution shifts
2. Shifting parental attitudes about respiratory distress
3. Increased use of X-ray, pulse oximetry and ED services
4. Increased severity of illness with weaker children (immune and general fortitude)
5. A nefarious plot by bulb suction manufacturers

Testing the testing hypothesis:

- Otherwise healthy infants aged 4 weeks to 12 months with mild to moderate bronchiolitis and true oxygen saturations of 88% or higher
- Randomly allocated to either true saturation (ie, true saturation values displayed) or altered saturation (ie, saturation measurements displayed were 3 points higher)

Pulse oximetry:

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Test Name</th>
<th>Average Oxygen Saturation (mm Hg)</th>
<th>Average Heart Rate (BPM)</th>
<th>Difference (mm Hg)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Control</td>
<td>88.5 ± 5.7</td>
<td>127 ± 15</td>
<td>88.5 ± 5.7</td>
<td>0.58</td>
</tr>
<tr>
<td>02</td>
<td>Oximetry</td>
<td>92.0 ± 5.2</td>
<td>133 ± 14</td>
<td>92.0 ± 5.2</td>
<td>0.29</td>
</tr>
<tr>
<td>03</td>
<td>Treatment</td>
<td>95.0 ± 4.8</td>
<td>139 ± 14</td>
<td>95.0 ± 4.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Our patient

- 3 m/o healthy male infant strolls into the office
- Wheezing, nasal congestion, and poor feeding reported by parent; low grade fever at home
- T 100.8°F, HR 160, RR 60, SaO2 90% on RA
- Infant in moderate respiratory distress, intercostal and subcostal retractions, wheezing in all lung fields, cap refill <3 sec

For the patient described, what tests would you order?

Find a neighbor, and discuss. You have 1 minute.

After discussing, post your response:

www.pollev.com/pediatric

Options (choose 1 or more, any combination):
1. History and physical
2. Chest x-ray
3. CBC
4. Respiratory viral panel/rapid RSV test
5. Basic chemistry

Overview of AAP 2014 Guidelines

- Incorporated data since 2006 guidelines published (significant contributions in last 10 years on clinical outcomes)
- Children with underlying respiratory illnesses such as recurrent wheezing, chronic neonatal lung disease, neuromuscular disease or cystic fibrosis, and those with hemodynamically significant heart disease are excluded from management recommendations


Diagnosis and Severity

- Recommendation 1a: Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination
- Recommendation 1b: Clinicians should assess risk factors for severe disease, such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency, when making decisions about evaluation and management
- Severity:
  - Clinical Respiratory Score: respiratory rate, retractions, Activity/feeding, Auscultation, O2 sats
  - Variability—serial observation
  - Upper airway obstruction
  - Appropriate follow up

Radiography and labs

- Recommendation 1c: When clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic or laboratory studies should not be obtained routinely

AAP Recommends against routine use
- Multiple cohort studies have shown that less than 1% of the time, CXR will yield alternate diagnosis
- Increased risk for atelectasis (25% of hospitalized infants)
- If don't get chest x-ray = cost savings (~$50 per patient) and decrease rate of unnecessary antibiotics due to false positives on X-ray

CBC

- AAP recommends against routine use
- Based on limited utility in predicting serious bacterial infection
- In RSV+ bronchiolitis, rate of +blood/urine cultures similar in those with normal WBC versus elevated (from 15-30K) – about 5% regardless of WBC count


Respiratory viral panel testing

- Reasonable from standpoint of cohorting in the hospital
- Indicated if taking palivizumab
- May be reasonable in <3 mo if febrile
- Less reasonable if used to reassure parents
- Costs about $60-100 depending on test
- Emerging research suggests some co-infections may have prognostic value

Our patient

- 3 mo otherwise healthy male described before, now admitted to the hospital after given albuterol in the clinic x 1 with no improvement
- Wheezing, nasal congestion, and poor feeding reported by parent; low grade fever at home
- T 100.8°F, HR 180, RR 62, SaO2 88% on RA
- Infant in moderate respiratory distress, intercostal and subcostal retractions, wheezing in all lung fields, cap refill <3 sec

For our patient, what treatment options would you normally consider in your setting?

- Find a neighbor, discuss the above. You have 1 minute.
- After discussing, post your response:
  - Choose 1 or more of the following:
    - Albuterol
    - Racemic epinephrine
    - Steroids
    - IV/NG fluids
    - Hypertonic saline (3%)
    - Antibiotics
    - Chest physiotherapy

Role of β-agonists in Bronchiolitis (albuterol)

- Recommendation 2: Clinicians should not administer albuterol to infants and children with a diagnosis of bronchiolitis (Evidence quality B)
- Pathology in bronchiolitis is NOT β-agonist reversible airway obstruction
- Several meta-analyses and systematic reviews showed:
  - May improve clinical score (varies, not a validated measure of the efficacy of bronchodilators)
  - No effect: disease resolution, need for hospitalization, or length of stay
- 30 trials reviewed with 1992 infants (12 countries):
  - Heterogeneity in design
  - No clinical benefit
- Greater adverse outcomes: cost, tachycardia, tremors


RSV Bronchiolitis

- Bronchocentric Infiltrates
- Epithelial sloughing with exudates and fibrin
Racemic epinephrine
- Rationale: potential benefit of alpha-agonist effect in reducing mucosal edema (versus primarily beta-agonist effect of albuterol)
- Recommendation 3: Clinicians should not administer epinephrine to infant and children with a diagnosis of bronchiolitis (Evidence quality B)
- May potentially be used as a rescue agent in severe disease (formal study still needed however)
- Transient effect (systematic review vs placebo):
  - Reduced hospitalizations on the day of the ED visit but not overall
  - 2 large, multicenter randomized trials (vs albuterol or placebo):
  - No improvement in length of stay or other inpatient outcomes
  - Large multicenter trial (vs placebo):
  - Lack of efficacy
  - Longer length of stay with fixed schedule vs PRN

Hypertonic saline
1) Osmotic flow into the mucus layer to rehydrate the airway surface liquid
1) Reduces edema in airway wall
2) Increases mucociliary clearance
3) Causes sputum induction and cough

Data summary
- Recommendation 4a: Nebulized hypertonic saline should not be administered in the emergency department (Evidence quality B)
- Recommendation 4b: Clinicians may administer nebulized hypertonic saline to infants and children hospitalized for bronchiolitis (Evidence quality B; Weak recommendation)
- Hypertonic vs. normal saline - 500 patients in 6 trials in inpatients:
  - Decreased clinical score by 1
  - Decreased length of stay by 1 day
- 380 patients in 4 trials (1 outpatient and 3 ED):
  - No change in admission (under-powered)
- Most of the trials included in the Cochrane review:
  - Settings where typical length of stay was > 3 days
  - In the US, the average length of stay is 2.4 days
  - May not be generalizable
- More recent trials did not report improvement in length of stay

But is it safe?
- Major concern: bronchospasm
- Both retrospective and prospective studies:
  - Safe without bronchodilator
  - Similar rate of adverse events
- Cochrane review examining 1090 infants enrolled in trials showed no severe adverse effects
- Favorable safety profile for nebulized 3% in bronchiolitis

Corticosteroids
- It’s an ‘itis’ – so it makes sense, right?
Well…
- 17 randomized trials have been done with 2536 patients
  - Both inhaled and oral steroids tested
- No effect: admission rates or length of stay
- Recommendation 5: Clinicians should not administer systemic corticosteroids to infants with bronchiolitis in any setting

Oxygen supplementation
- Recommendation 6a: may choose not to give if O2 sats > 90% in bronchiolitis
- Oxygen saturation - poor predictor of respiratory distress
- O2-Hb dissociation curve: small increases in PaO2 are associated with marked improvement in O2 sats when initially < 90%
- Transient hypoxemia - common in healthy infants
- 1 study of 64 infants between 2 weeks and 6 months, 60% went below 90% (as low as 88%)
- 1 of the new approaches: HFNC
  - Improves physiologic measures of respiratory effort
  - Generates CPAP
  - Reduces WOB and may decrease need for intubation
  - PTX- reported complication

Fernandes RM, Hartling L. Glucocorticoids for Acute Viral Bronchiolitis in Infants and Young Children. JAMA. 2014;312(1):87-88.
Continuous pulse oximetry

- Recommendation 6b: may choose not to use continuous pulse oximetry
- Excessively used in bronchiolitis as a proxy for respiratory distress
- CO2: greater impact on respiratory drive
- Overly dependent: less effective surveillance
- Accuracy is poor, especially between 76-90%
- Cyanosis: only accurate identifier of hypoxic children
- Pneum: exms of measurement (fall off easily)
- Retrospective study: 1 in 4 incurred unnecessarily prolonged hospitalization, outside of other symptoms
- Transient hypoxemia: normal phenomenon

Chest Physiotherapy

- If problem is plugging of small airways and not clearing secretions...
- Incredibly popular – especially in France!
- 9 trials, different techniques → no significant effect
- Recommendation 7: Should not use chest physiotherapy for bronchiolitis

Antibacterials

- Recommendation 8: Clinicians should not administer antibacterial medication unless a strong suspicion of a concomitant bacterial infection
- Studies:
  - Fever w/o identifiable source: risk of bacteremia as high as 7%
  - Viral syndrome: even lower, <1%, of bacterial infection of CF or blood
  - Supported by a systematic review of serious bacterial infections between 30-90 days of age
- Judged empirically if requiring intubation and mechanical ventilation for respiratory failure

Nutrition and hydration

- Recommendation 9: Administer NG or IV fluids for infants with bronchiolitis who cannot maintain hydration orally
- Pending level of respiratory distress
  - RR > 60-70 bpm: feeding compromised
  - 1/3 of those hospitalized require fluid replacement
  - Large randomized trial in AUS and NZ
  - No significant difference: ICU admission, ventil support, adverse events
  - NG: higher success rate of insertion
  - Parental satisfaction scores did not differ
  - Isotonic fluids appears to be safer

Summary of treatment recommendations:

1. Do as little as possible
2. If anything, use hypertonic saline, oxygen, and/or fluids
3. “All bronchial therapy is futile” – William Osler, MD on deathbed from influenza

How do our patients compare to guidelines?

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall Total Patients</th>
<th>More Than 5 Diagnoses</th>
<th>5 or fewer Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months (Median)</td>
<td>8.4 (14.64)</td>
<td>10.1 (16.4)</td>
<td>11.6 (11.12)</td>
</tr>
<tr>
<td>LOS (Median)</td>
<td>3.0 (6.0)</td>
<td>5.0 (9.0)</td>
<td>11.0 (11.0)</td>
</tr>
<tr>
<td>Number of Diagnoses (Median)</td>
<td>7.5 (11.25)</td>
<td>11.0 (11.25)</td>
<td>11.0 (11.25)</td>
</tr>
<tr>
<td>NM: None of 5 Diagnoses</td>
<td>8 (65)</td>
<td>10.1 (65)</td>
<td>11.6 (65)</td>
</tr>
<tr>
<td>Age, months (Median)</td>
<td>4.8 (11.1)</td>
<td>11.1 (2.8)</td>
<td>11.1 (2.8)</td>
</tr>
<tr>
<td>LOS (Median)</td>
<td>2.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td>3.0 (2.0)</td>
</tr>
<tr>
<td>Number of Diagnoses (Median)</td>
<td>3.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td>3.0 (2.0)</td>
</tr>
</tbody>
</table>
Latest data on 3% saline:
- Double-blind, controlled parallel-group study of infants admitted with bronchiolitis, comparing 3% HS with 0.9% normal saline (NS) from November 2011 through June 2014.
- The setting was an urban, tertiary care children's hospital with 136 beds and ~400 infants with bronchiolitis annually.

So what to do?

Our guidelines
- Where to find: Sunrise order set (Pediatric Bronchiolitis) or homepage: Clinical Protocols: Pediatrics

Future directions:
1. Better algorithms for predicting the course of illness
   - Established guidelines for most patients vs individualized therapy
   - Ultrasound, co-infections
2. Emphasis on parent satisfaction/patient-centered outcomes in all research (ie, not LOS as the only measure)
3. Studies in children previously excluded by most studies and guidelines
4. Hypertonic saline studies in the outpatient setting and in hospitals with shorter LOS
5. More studies on nasogastric hydration
6. Oxygen: strategies for monitoring oxygen saturation, high-flow
7. RSV vaccine and antiviral agents
   - Baboon model, newer antiviral agents

Guidelines: content

Individual future directions (last poll):
- Go to www.pollie.com/pediatric
- As result of participating in this grand rounds, I will now:
  1. Try to change my practice to be more in line with the suggested guidelines
  2. Not change my practice at all (I already practice very similar to the guidelines)
  3. Not change my practice at all (my patients are too different from the guidelines in some way)
  4. I was on my phone the whole time. I do not understand the rheology of mucus
  5. I don’t believe the data reflect the truth, I love albuterol, and I have to do something!
  6. Dedicate my life to the research of RSV
Acknowledgements

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