Acute Respiratory Illnesses in Children

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Pediatric Hospitalist
I have no actual or potential conflicts in relation to this presentation.

I will be referring to some industry products in regards to non-invasive respiratory support options for pediatric patients.
Objectives

Discuss the diagnostic evaluation and management of bronchiolitis & community-acquired pneumonia

Discuss non-invasive respiratory support for these conditions

Review some of the commonly encountered diagnostic & therapeutic dilemmas
Bronchiolitis

- Most common cause of hospitalization among infants during the 1st year of life

- 1 in 5 infants of each birth year cohort require outpatient medical attention during the first year of life for RSV

- ~ 100,000 bronchiolitis admissions / year in the US for estimated cost of $1.73 billion

https://www.morethanacold.co.uk/
Illustration by: Hélène Desputeaux
“A young child (0 – 18 months old) with bronchiolitis typically presents during the winter months after 2-4 days of low-grade fever, nasal congestion, rhinorrhea and sx of lower respiratory tract infection as manifested by grunting, nasal flaring, intercostal / subcostal / supraclavicular retractions, inspiratory crackles and expiratory wheezing.”

- NEJM 2016
**Bronchiolitis – Pathophysiology**

Reference
Many viruses that infect the respiratory system cause similar signs and symptoms

<table>
<thead>
<tr>
<th>Virus</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>50-80</td>
</tr>
<tr>
<td>Human rhinovirus</td>
<td>5-25</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>5-25</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>5-10</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>5-10</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>5-10</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>1-5</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Seasonality of viral infections is relevant
Bronchiolitis – Microbiology

- nucleic acid amplification tests ↑ detection of viruses…
- “co-infections” with multiple viruses are frequently seen

Studies have shown that at least 1 respiratory virus can be found in up to 30% of children < 6 years old who have no respiratory symptoms.

1) Asymptomatic colonization
2) Incubation before clinical infection
3) Prolonged viral shedding post-infection
Bronchiolitis – RSV

- Enveloped single-stranded RNA virus of the *Paramyxoviridae* family.

- RSV reinfection occurs throughout life, despite induction of both antibody and T-cell responses after primary infection.

- Poor understanding of the mechanisms limiting the induction of long-lasting immunity has delayed the development of an effective vaccine.
Bronchiolitis – Clinical Course

- Variable and dynamic

- Proper assessment requires serial exams over a period of observation – after nasal suctioning

Reference
Bronchiolitis – High Risk Patients

- Infants <3 months old
- Hx of prematurity (<32 weeks)
- Chronic Lung Disease
- Immunodeficiency
- Congenital Heart Disease
- Neuromuscular Disorders
Apnea in Bronchiolitis

- Apnea is a life-threatening complication of bronchiolitis
- Incidence of apnea has varied from 1-24% in different studies

Retrospective cohort study of ~700 infants hospitalized with bronchiolitis
- Inpatient apnea identified in 19 patients (2.7%, 95% CI: 1.7 - 4.3%)

All patients who had apnea were identified by the following 3 “high-risk” criteria:
1. Born full-term (≥ 37 weeks) and currently < 1 month old
2. Born preterm (<37 weeks) and < 50 weeks postmenstrual age
3. Child’s parents or a clinician had witnessed apnea before admission

Reference
Caffeine for the Treatment of Apnea in Bronchiolitis?

A Cochrane review and meta-analysis of 6 RCTs showed that methylxanthines (i.e., theophylline or caffeine) are effective in treating apnea of prematurity

- ↓ # of apnea events
- ↓ need for mechanical ventilation

Proposed mechanism of action
- increased central respiratory drive
- increasing chemoreceptor sensitivity to carbon dioxide
- improved skeletal muscle contraction

Assessment:
Single center RCT enrolled 90 infants diagnosed with viral bronchiolitis who presented to a pediatric ER with history of apnea or observed apnea

*Patient:* Infants ≤ 4 months old with bronchiolitis

*Intervention:* IV dose of caffeine (25 mg/kg in 15 ml D5W)

*Comparison:* 15 ml normal saline

*Outcome(s):* time until a 24-hour apnea-free period

Mean duration to a 24-hour apnea-free period was 28.1 hrs (caffeine group) vs. 29.1 hours (placebo group).

**Recommendation**
A single dose of caffeine citrate did not significantly reduce apnea episodes associated with bronchiolitis

NNT = 452

**Reference**
No available treatment shortens the course of bronchiolitis or hastens the resolution of symptoms.
Bronchiolitis – Supportive Therapies

**NOT Recommended**

- short-acting β2-agonists
- racemic epinephrine
- systemic glucocorticoids
- ribavirin
- chest physiotherapy
- antibiotics

- Testing for viral causes*
- Chest X-ray*

**2014 AAP Clinical Practice Guideline**

- Nasal saline drops and suctioning
- Supplemental oxygen to keep SpO2 >90%
- IV or NG fluids if unable to maintain hydration orally
- May consider nebulized hypertonic saline if hospitalized (RCTs with inconsistent findings)
Bronchiolitis – Supportive Therapies

**Standard Nasal Cannula (“Low Flow”)**

- 100% oxygen through bubbler humidifier at rate of 0 – 4 LPM
- FiO2 varies from 25-40% depending on RR, TV and extent of mouth breathing
- Flow > 2 LPM is irritating to nares unless heated & humidified

**Heated, Humidified High Flow Nasal Cannula (HFNC)**

- Heated and humidified oxygen via special devices at rates up to 8 LPM in infants and 60 LPM in adults
- Better tolerated than face mask in terms of comfort
- ↓ RR, work of breathing and better oxygenation
High Flow Nasal Cannula

- Provides low-level positive pressure (PEEP) and aids in lung recruitment
- Provides CO2 “washout” of respiratory physiologic dead space
- Warmth and humidity keep secretions moist and improve mucociliary clearance
RAM Cannula & CPAP

- Designed by neonatologist for use in premies as alternative to nasal CPAP

- Has softer, thinner walled prongs with larger nasal prong inner diameter → results in lower airflow resistance with reduced nasal trauma
Complications of HFNC or RAM CPAP

Nasal irritation

Abdominal distension

Pneumothorax
Community-Acquired Pneumonia
Does this child have pneumonia?

**Case 1**

18 month old male with no significant PMHx presents to PCP with 1 day history of fever and cough. Parents report decreased PO intake for past 24 hours. Attends daycare.

Vital Signs: Temp 38.5°C, RR 48,
SpO2 93% on room air

Exam: Awake, alert with no signs of respiratory distress. He has diffuse crackles (R > L) with no wheezes. Other findings from his exam are normal.

**Case 2**

2 year old female with no significant PMHx presents to PCP with 4 days of fever and cough. Parents report decreased PO intake for the past 24 hours and they have noticed difficulty breathing. Attends daycare.

Vital Signs: Temp 38.5°C, RR 35,
SpO2 93% on room air

Exam: Awake, alert with no signs of respiratory distress. She has crackles in right lower posterior chest. Other findings from her examination are normal.
Community-Acquired Pneumonia (CAP)

- Pneumonia is the single greatest cause of death in children worldwide

- In the developed world, the annual incidence of pneumonia is ~3-4 cases per 100 children <5 years old

- There is no universally accepted and practical reference standard for diagnosis of pediatric CAP

Reference
## CAP - Diagnosis

**Depends on who you ask**

<table>
<thead>
<tr>
<th>World Health Organization (WHO)</th>
<th>British Thoracic Society</th>
<th>Infectious Disease Society of America (IDSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough or difficulty breathing and age-adjusted tachypnea</td>
<td>Persistent or repetitive fever $&gt; 38.5$ or $101.3$ with chest retractions and increased respiratory rate</td>
<td>Presence of signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside the hospital</td>
</tr>
<tr>
<td>2 – 11 mo: RR $\geq 50$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 5 yo: RR $\geq 40$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 5$ yo: RR $\geq 20$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CAP – Clinical Features

• Signs / Symptoms
  – Fever
  – Cough
  – Tachypnea
  – Dyspnea
  – Chest pain (adolescents)
  – Abdominal pain
  – Crackles / Rales
  – Diminished breath sounds
  – Wheezing
  – Grunting (infants)
  – Nasal flaring
  – Chest wall retractions (infants)
  – Hypoxemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency in children with radiographic evidence of pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>95%</td>
</tr>
<tr>
<td>Abnormal temperature</td>
<td>91%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>75%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>70%</td>
</tr>
<tr>
<td>Chest wall retractions</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Radiographic Findings</strong></td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td>58%</td>
</tr>
<tr>
<td>Alveolar or interstitial infiltrate</td>
<td>51%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>13%</td>
</tr>
</tbody>
</table>

CAP - Pathophysiology

Anatomic & Mechanical Barriers
- Upper respiratory tract nasal hairs & turbinate architecture to trap particles
- Mucociliary clearance of secretions
- Epiglottic reflex to prevent aspiration and cough to expel things that may be aspirated
- Complex respiratory airway branching

Humoral Immunity
- Secretory IgA is major immunoglobulin produced in upper airways and has antibacterial / antiviral activity
- IgG and IgM enter airways via transudation from blood and opsonize bacteria, activate complement and neutralize toxins.

Phagocytic Cells
- Alveolar macrophages are first line of cellular defense.
- Interstitial macrophages
- Intravascular macrophages

PNEUMONIA
Invasion of lower respiratory tract by a pathogenic organism that alters, inhibits or overpowers these host defenses

Cell-Mediated Immunity
- Lymphocytes play critical role in producing antibodies, cytotoxic activity and cytokine production to fight off viruses and intracellular microorganisms.
• Historically, CAP was largely considered a bacterial process
  – *Streptococcus pneumoniae*
  – *Haemophilus influenzae, type b*
  – *Streptococcus pyogenes*
  – *Staphylococcus aureus*

• Molecular diagnostics for viral respiratory pathogens have increased awareness of viral causes of CAP

Reference
Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children

Seema Jain, M.D., Derek J. Williams, M.D., M.P.H., Sandra R. Arnold, M.D.,
Krow Ampofo, M.D., Anna M. Bramley, M.P.H.,
Chris Stockmann, M.Sc., Evan J. Anderson, M.D.,
Wesley H. Self, M.D., M.P.H.,
Weston Hymas, M.S., Joshua M. Ferris, Ph.D.,
J. Herman Kasekam, M.D., Ph.D.,
Noel Lenny, Ph.D.,
David R. Hillyard, M.D.,
Min Levine, Ph.D.,
Stephen Lindstrom, Ph.D.,
Nanci Schindell, Ph.D.,
Jacqueline M. Katz, Ph.D.,
Dean Erdman, Dr.P.H.,
Deann Schneider, M.D.,
Lauri A. Hicks, D.O.,
Richard G. Wunderink, M.D.,
Kathryn M. Edwards, M.D.,
Andrew T. Pavia, M.D.,
Jonathan A. McCullers, M.D.,
and Lyn Finelli, Dr.P.H., for the CDC EPIC Study Team*

Reference
DESIGN:
Prospective population-based surveillance study. Eligible for study if <18 years old and…
1) hospitalized with CAP between Jan 2010 – June 2012
2) resided in 1 of 22 counties which comprised the study catchment areas of participating children’s hospitals (Nashville, Memphis, Salt Lake City)
3) had a CXR performed within 72 hrs before or after admission

RESULTS:
2,638 children were enrolled in the EPIC study.
Of the patients who had both radiographic evidence of pneumonia and blood / respiratory specimens available for bacterial + viral testing…

- Either viral or bacterial pathogen detected 81% cases
- Viral pathogen detected 73% cases
- Bacterial pathogen detected 15% cases
- Both viral + bacterial pathogen detected 7% of cases

Reference
Major Findings of the EPIC Study

1. Pathogen (viral or bacteria) was detected in 81% of children
   – viruses alone were detected in 66% of children

2. Most commonly detected pathogens were viruses
   – RSV 28%
   – Rhinovirus 27%
   – Human metapneumovirus 13%
   – Adenovirus 11%

3. Typical bacterial accounted for 8% of CAP overall
   – Streptococcus pneumoniae 5%
   – Staphylococcus aureus 1%
   – Streptococcus pyogenes 1%

4. Atypical bacteria was much more common in older children
   – Mycoplasma pneumoniae detected in 19% of children > 5 yo compared to only 3% in younger children

Reference
Children ≤ 4 years old had virus as sole pathogen in ~50% of cases and concurrent viral detection in an additional 15-25% of cases.

Reference
## Etiology of CAP by Age

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Viral Pathogens</th>
<th>Bacterial Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>RSV, Influenza</td>
<td>Group B streptococcus, Streptococcus pneumoniae</td>
</tr>
<tr>
<td>3 months – 5 years</td>
<td>RSV, Influenza, Parainfluenza, Human metapneumovirus</td>
<td>Streptococcus pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>Influenza, Adenovirus, Rhinovirus</td>
<td>Bacteroides, Mycoplasma pneumoniae, Streptococcus pneumoniae, Staphylococcus aureus, Bordetella pertussis, Streptococcus pyogenes (GAS), Chlamydia trachomatis, Haemophilus influenza type b</td>
</tr>
</tbody>
</table>
### Complications Associated with CAP

#### Pulmonary
- Pleural effusion or empyema
- Lung abscess
- Bronchopleural fistula
- Necrotizing pneumonia
- Acute respiratory failure

#### Metastatic Disease
- Meningitis
- CNS abscess
- Pericarditis
- Endocarditis
- Osteomyelitis
- Septic arthritis

#### Systemic
- SIRS → Sepsis
- Hemolytic Uremic syndrome

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**Right upper lobe lung abscess**

**Reference**

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**Necrotizing Pneumonia**

**a)** CXR, Day #1

**c)** CXR, Day #8

**Reference**
• Significant overlap in clinical symptoms

• Typical CXR findings DO NOT distinguish between viral and bacterial causes

• Acute-phase reactants (ESR, CRP, PCT) cannot be used as sole determinant to distinguish between viral and bacterial causes
CAP – Diagnostic Testing

**Outpatient (limited testing)**

**Recommended Actions**
- Pulse oximetry should be performed.
- Obtain respiratory viral testing.

**Choose Wisely:**
- Do not obtain blood culture in a nontoxic, fully immunized child.
- CXR is not necessary at initial visit. Obtain if significant respiratory distress or hypoxemic.
- Blood culture and CBC rarely change treatment course.

**Inpatient**

**Recommended Actions**
- Pulse oximetry should be performed.
- Obtain respiratory viral testing.
- Blood cultures should be obtained in hospitalized children with moderate-severe CAP.
- CBC, ESR, CRP may provide useful information for clinical management.
- CXR (PA + lateral) should be obtained in all hospitalized children with CAP.
In children < 5 yo, the majority of CAP will be due to viral pathogens and no antibiotic treatment is indicated.

**Outpatient**

1st line Therapy: Amoxicillin x 7 - 10 days
Alternative(s) 2nd/3rd Gen Cephalosporin

**Inpatient**

1st line Therapy: Ampicillin

Not fully immunized, severe disease → substitute a 3rd Generation Cephalosporin → + Vancomycin or Clindamycin if concern for *Staphylococcus aureus*
What about *Mycoplasma pneumoniae*?

- Frequent cause of CAP in school-aged children and adolescents

- **What does a positive PCR test for *Mycoplasma* mean?**
  - The CDC EPIC Study showed *Mycoplasma pneumoniae* was detected in 8% of children with pneumonia and fewer than 1% of controls
  - A cross-sectional, observational study from the Netherlands found higher rates of *Mycoplasma pneumoniae* in asymptomatic children

- Azithromycin is largely ineffective against other bacterial causes of CAP but is the 2nd most commonly prescribed antibiotic in outpatient pediatrics.
What about *Mycoplasma pneumoniae*?

- Studies have failed to consistently demonstrate a benefit of using macrolide therapy in children with pneumonia.

- However, existing clinical practice guidelines still recommend macrolide antibiotics for treatment of children (school-aged and adolescents) in an outpatient setting. - IDSA 2011

Reference
"Secondary" Bacterial Pneumonia

Presence of a preceding viral respiratory tract infection is an important risk factor in the pathogenesis of bacterial pneumonia.

Child with viral URI symptoms.

Begins to show clear clinical improvement.

Abrupt worsening of clinical status.

Chest X-ray*

Bacterial Superinfection

Public health evidence of this viral-bacterial interplay

- Severe pneumococcal pneumonia has been associated with outbreaks of influenza
- Pneumococcal vaccines decrease the morbidity of influenza infections
Does this child have pneumonia?

**Case 1**

18 month old male with no significant PMHx presents to PCP with 1 day history of fever and cough. Parents report decreased PO intake for past 24 hours. Attends daycare.

Vital Signs: Temp 38.5°C, RR 48, SpO2 93% on room air

Exam: Awake, alert with no signs of respiratory distress. He has diffuse crackles (R > L) with no wheezes. Other findings from his exam are normal.

Dx: Bronchiolitis
No CXR, no labs. Flu PCR (if winter)
Teach family nasal saline / suctioning
Anticipatory guidance

**Case 2**

2 year old female with no significant PMHx presents to PCP with 4 days of fever and cough. Parents report decreased PO intake for the past 24 hours and they have noticed difficulty breathing. Attends daycare.

Vital Signs: Temp 38.5°C, RR 35, SpO2 93% on room air

Exam: Awake, alert with no signs of respiratory distress. She has crackles in right lower posterior chest. Other findings from her examination are normal.

Dx: Pneumonia (mild)
No CXR, no labs. Flu PCR (if winter)
No antibiotics as < 5 yo
## Take Home Points

### Bronchiolitis

- Influenza testing during appropriate season
- Supportive cares only
  - nasal suctioning
  - fluid hydration
  - supplemental oxygen
- Do not order CXR
- Do not administer albuterol or racemic epinephrine in the office (unless admitting to the hospital)

### Community-Acquired Pneumonia

- Limited outpatient evaluation is appropriate for mild disease (pulse ox + respiratory viral testing).
- Viruses > > > Bacteria as cause of CAP in children
- Concerns whether treating *Mycoplasma pneumoniae* with a macrolide is effective at all
- 1st line treatment should be 7 – 10 days of Amoxicillin