Review and Update: Upper Respiratory Tract Infections

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Streptococcus pyogenes - GAβHS

- Group A streptococcus (GAβHS) – wide range of bacterial clinical syndromes
  - Pharyngeal carrier
  - Pharyngitis with no sequelae or only local sequelae
  - Immunologic: RF, glomerulonephritis
  - Invasive disease: osteomyelitis, bacteremia
  - Toxin-mediated: STSS, scarlet fever

Our Focus Today: GAβHS Pharyngitis

- GAβHS – 15-30% of acute pharyngitis in children
- 5-11 years – highest incidence of GAβHS pharyngitis
- Temperate climates – winter and early spring
- Short incubation period (2-5 days)
- Transmission occurs with close contacts via inhalation of organisms in large droplets or by direct contact with respiratory secretions

Table 1. Estimated global burden of group A streptococcal disease.

<table>
<thead>
<tr>
<th>Disease, population</th>
<th>Annual no. of cases</th>
<th>Annual no. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>616,026,000</td>
<td>...</td>
</tr>
<tr>
<td>Less-developed countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>423,406,000</td>
<td>...</td>
</tr>
<tr>
<td>Adults</td>
<td>192,616,000</td>
<td>...</td>
</tr>
<tr>
<td>More-developed countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>22,835,000</td>
<td>...</td>
</tr>
<tr>
<td>Adults</td>
<td>39,000,000</td>
<td>...</td>
</tr>
<tr>
<td>Impetigo</td>
<td>111,200,000</td>
<td>...</td>
</tr>
<tr>
<td>Acute poststreptococcal glomerulonephritis</td>
<td>472,000</td>
<td>5000</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>470,000</td>
<td>349,1208</td>
</tr>
<tr>
<td>Invasive disease</td>
<td>925,000</td>
<td>103,000</td>
</tr>
</tbody>
</table>

In the US, there are 3.1–3.8 cases of invasive disease per 100,000
Exudative Pharyngitis

Nonexudative Pharyngitis

Pathophysiology

- Disease: 2-3 weeks
- Nose/throat droplet contact → Endothelial infection
- Nose/throat colonization
- Protective type-specific immunity (> 120 types) → Re-infection
Obtaining a Throat Culture for Diagnosis of Streptococcal Pharyngitis

- 90-95% sensitivity of detecting GAβHS
- Specimen collection
- If no GAβHS growing after 24 hours, should re-incubate plate
- Bacitracin test

Rapid Antigen Detection of GAβHS

- Generally, specificity is ≥ 95%
- Sensitivity is variable
  - Latex agglutination
  - EIA
  - Optical immunoassays/DNA probes

Laboratory Testing for GAβHS Pharyngitis: Throat Culture

- 90-95% sensitivity of detecting GAβHS
- Specimen collection
- If no GAβHS growing after 24 hours, should re-incubate plate
- Bacitracin test

Table 1. Non-GAβHS Pharyngitis

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-hemolytic streptococci: Group C, G</td>
<td>Epstein-Barr</td>
</tr>
<tr>
<td>Corynebacterium diptheriae</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>Arcanobacterium haemolyticum</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Chlamydomphila pneumoniae</td>
<td>Influenza</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Parainfluenza</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Rhinovirus</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>Coronavirus</td>
</tr>
<tr>
<td>Coxiella burnetti</td>
<td>Respiratory syncytial</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td></td>
</tr>
</tbody>
</table>
Distinguishing Viral vs. GA$\beta$HS Pharyngitis

- GAS
  - Abrupt onset,
  - Abdominal pain,
  - Palatal petechiae,
  - Uvulitis,
  - Tender LAD

- Viral
  - Exudative Pharyngitis,
  - Throat pain,
  - HA,
  - Fever

G$\beta$HS CARRIER

Treatment

- Median self-resolution of pharyngitis = 4 days
- Tx at $\leq$ 9 days, decreases risk of ARF; no $\Delta$ AGN
- Antibiotic of choice is penicillin (if pills) x 10D
  - Benzathine penicillin G, $6 \times 10^5$ units x 1 IM if $\leq$ 27 kg and $1.2 \times 10^6$ if $>28$ kg

How Good is H&P at Distinguishing Between Viral and G$\beta$HS Pharyngitis?

- 10 experienced physicians
- Asked to predict presence of GAS pharyngitis by H & P
- Of 308 obtained cultures, 4.9% were positive for GAS
- Physicians overestimated the probability of a positive culture for GAS in 81% of their patients.

Treatment

- Amoxicillin $25$ mg/kg/dose, $750$ mg, twice/D $\times 10$D
- cefdinir $14$ mg/kg/dose, $600$ mg, once/D $\times 10$D
- cefixime $8$ mg/kg/dose, $400$ mg, once/D $\times 10$D
- OR
- cefpodoxime $10$ mg/kg/day, $200$ mg, twice/D $\times 5$D
- cefdinir $14$ mg/kg/day, $600$ mg, twice/D $\times 5$D
- azithromycin $12$ mg/kg/day, $500/250$ mg, once/D $\times 5$D

- Penicillin allergy: clarithromycin, cephalexin, or clindamycin
**Influenza Virus: Types**

- Three types: A, B, and C
- Type A: Pandemics, epidemics, seasonal outbreaks
- Type B: Epidemic, outbreaks
- Type C: Similar to common cold, not significant

**The Influenza Virus**

- Influenza Type A
  - Matrix protein
  - Segmented RNA genome
  - Neuraminidase (NA)
  - Hemagglutinin (H1/H2)
- Influenza A: 15 subtypes of Hemagglutinin antigen
- 9 subtypes of Neuraminidase antigen
- Influenza B: no subtypes of either

**Lifecycle**

- Steps
  - Attachment – Hemagglutinin
  - Uptake – Hemagglutinin
  - Uncoating
  - RNA replication, protein synthesis
  - Assembly
  - Budding and release - Neuraminidase

**Burden of Influenza**

- Morbidity:
  - 26-50 million cases/year in U.S.A.
  - 300,000 hospitalizations/year
- Mortality, especially in elderly
  - 20,000-50,000 excessive deaths annually
- Economic costs
  - $3-5 billion in healthcare costs
  - $12 billion in severe epidemic
Epidemiology in Children

- Highest rates of infection are in children
  - infants and preschool (24-30%)
  - school-age (30-45%)
- Within a family unit, the predictor for flu activity is the presence of a school-age child
- Children are central to introduction of influenza into a unit and spread in the community


Clinical Manifestations

Pediatric Clinical Picture: Infants and Toddlers 2-5 y/o

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Frequency</th>
</tr>
</thead>
</table>

Influenza Infection: Acute Cardiopulmonary Hospitalizations

- These rates in young children exceed those commonly seen in elderly persons

Source: AAP. Pediatrics 2002;110:1246-52

* Includes infants <6 months of age.
Pediatric Clinical Picture: Children > 5 y/o

**Presentation**

**Frequency**

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### Diagnostic tests for influenza

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Type of specimen</th>
<th>Time to result</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu culture</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>5–11 days*</td>
<td>No</td>
</tr>
<tr>
<td>Immuno-fluorescent</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>2–4 hours</td>
<td>No</td>
</tr>
<tr>
<td>Reverse transcription</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>1–2 days</td>
<td>No</td>
</tr>
<tr>
<td>Serologic testing</td>
<td>A and B</td>
<td>Peripheral blood</td>
<td>&gt; 2 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Enzyme immunoassay (EIA)</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>2 hours</td>
<td>No</td>
</tr>
</tbody>
</table>

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### Rapid diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Type of specimen</th>
<th>Time to result</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu CREA (Chromogenic assay)</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>&lt; 30 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flu CREA A/RI</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>&lt; 30 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid Flu A/B test (Chlamydiavirus)</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>&lt; 30 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid Flu A/B test (Chlamydiavirus)</td>
<td>A and B</td>
<td>Nasopharyngeal swab</td>
<td>&lt; 30 minutes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**ACIP Risk-Based Pediatric Influenza Immunization Guidelines 2004-07**

All children 6-59 months, 5-18 y/o at high risk* due to underlying medical conditions1,2, and contacts

- Lung (asthma)
- Cardiac disease
- Sickle cell disease
- HIV/AIDS suppression
- Metabolic diseases (diabetes)
- Long-term aspirin therapy


*Increased risk of hospitalization due to pneumonia, respiratory conditions, heart failure and myocarditis.*

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Pediatric Influenza Vaccines: Indications

- **Trivalent inactivated vaccine (TIV)**
  - Approved for use in the U.S. for many decades
  - Immunization against selected virus strains in any person aged ≥6 months with and without risk factors

- **Live, attenuated influenza vaccine (LAIV*)**
  - Approved for use in the U.S since 2003
  - Immunization against selected virus strains in healthy persons 2 to 49 years

  * Also known as cold-adapted intra-nasal vaccine (CAIV)

Neuraminidase Inhibitors: Zanamivir and Oseltamivir

- **Neuraminidase**
  - Site where sialic acid is cut from receptor
  - Invariant in all influenza types A and type B

- **Neuraminidase inhibitors**
  - Selective inhibition of viral neuraminidase
  - “Plug” or block catalytic site
  - Prevent release of new viruses

Summary of currently licensed neuraminidase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age approved for treatment</strong></td>
<td>≥ 1 year</td>
<td>≥ 7 years</td>
</tr>
<tr>
<td><strong>Age approved for prevention</strong></td>
<td>≥ 1 year</td>
<td>≥ 5 years</td>
</tr>
<tr>
<td><strong>Dosage form</strong></td>
<td>Capsule or liquid suspension</td>
<td>Diskhaler</td>
</tr>
<tr>
<td><strong>Benefits if started ≤ 48 hrs</strong></td>
<td>Reduces illness 1.5 days</td>
<td>Reduces illness 1.25 days</td>
</tr>
<tr>
<td><strong>Major adverse reactions</strong></td>
<td>Nausea, vomiting</td>
<td>Bronchospasm, headache</td>
</tr>
</tbody>
</table>

Conclusions

- Throat culture remains an important tool for diagnosing streptococcal pharyngitis and other etiologies of pharyngitis
- Therapeutic choices for GAβHS have increased, but with the caveat of some high regional resistance to macrolides

Conclusions

- Immunization remains the best prevention
  - Trivalent inactivated vaccine licensed for children ≥ 6 month of age
  - In addition to high risk children, routine immunization of healthy children 6-60 months now recommended
  - CAIV now licensed for healthy individuals 2-49 y/o
- Oseltamivir and Zanamivir are effective for treatment of type A and type B influenza

Epidemiology of RSV Bronchiolitis

- Infection uniform by age 2 years
- RSV causes 80% of winter bronchiolitis
- Wheezing in 10-20% of RSV infections
- 0.5-1.5% of infected infants hospitalized

Bronchiolitis

Whooping Cough

Katalin Koranyi, MD
Professor of Pediatrics
Department of Pediatrics
College of Medicine
The Ohio State University
Nationwide Children’s Hospital
Epidemiology of RSV Bronchiolitis

- Peak age of hospitalization: 1-6 months
- Underlying cardiopulmonary disease in 40% of infants hospitalized
- Increasing rates of hospitalization

Clinical Findings in Bronchiolitis

- Preceding URI with fever
- Tachypnea (RR > 40/min)
- Cough
- Wheezing and rales
- Intercostal retractions
- Hypoxia
- Relative hypercarbia

Bronchiolitis: Usual Viral Agents

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial virus</td>
<td>44-65%</td>
</tr>
<tr>
<td>Parainfluenza viruses</td>
<td>14-26%</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>2-13%</td>
</tr>
<tr>
<td>Influenza viruses</td>
<td>1-4%</td>
</tr>
<tr>
<td>Other agents</td>
<td>1-10%</td>
</tr>
</tbody>
</table>

Diagnosis of Bronchiolitis

- Clinical findings
- Chest x-ray: air trapping, infiltrates, atelectasis
- NP wash for DFA, EIA, PCR, or culture
- CBC - no value
- Blood/urine cx - no value
- O₂ saturation

References:
1. Henderson FW et al. NEJM 1979;281:103
CXR or infant with bronchiolitis: air trapping, flattened diaphragms and patchy RUL infiltrate

Patients in whom palivizumab or RSV-IVIG is indicated at the start of RSV season

- < 2 yrs old with chronic lung disease & medical Rx in past 6 mos (O_2, diuretic, bronchodilator Rx, steroids)
- ≤ 28 wks gestation – up to 12 mos of life
- 28-32 wks gestation – up to 6 mos of life
- 32-35 wks - < 6 mos of life and risk factors: DCC, school-aged sibs, air pollutants, congenital airway anomalies, severe neuromuscular disease

AAP Policy Statement. Pediatr 2003;112:1442

Patients in whom palivizumab or RSV-IVIG is indicated at the start of RSV season

- < 24 mos of age with congenital heart disease (Palivizumab only):
  - On medication for congestive heart failure
  - Mod or severe pulmonary hypertension
  - Cyanotic heart disease

AAP Policy Statement. Pediatr 2003;112:1442

Bronchiolitis: Criteria for Hospitalization

- Sustained RR ≥ 60/min
- Ill or toxic appearance
- Fatigue, anxiety, difficulty feeding
- O_2 saturation ≤ 92% in room air
- Apnea
- Risk factors present for severe disease: age <2 mos, premature birth, CHD, CLD, immunodeficiency

AAP Policy Statement. Pediatr 2003;112:1442
Variation in the management of 601 infants < 1yr old hospitalized with bronchiolitis or RSV pneumonia in 10 pediatric hospitals from 5/1/95 to 9/30/96

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>27%</td>
<td>8-61%</td>
</tr>
<tr>
<td>β agonists</td>
<td>92%</td>
<td>82-100%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>64%</td>
<td>39-77%</td>
</tr>
<tr>
<td>Furosemide</td>
<td>9.5%</td>
<td>1-28%</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>2.5%</td>
<td>0-15%</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>27%</td>
<td>4-71%</td>
</tr>
<tr>
<td>% PICU admission</td>
<td>28%</td>
<td>19-56%</td>
</tr>
</tbody>
</table>

Wilson DF. Pediatr 2001;108:851

Debated Management Strategies

- Bronchodilator therapy
- Corticosteroid therapy
- Antiviral therapy

AAP Guidelines 2006

Accepted Management Strategies

- Isolation to prevent nosocomial spread
- Oxygen & Hydration
- Suction nasal secretions
- Feeding
- Monitor for complications
  - Apnea
  - Respiratory failure
  - Secondary bacterial infection

Summary: Bronchodilator Therapy

- Data supporting use of albuterol:
  - Limited
  - Mostly no benefit
- Racemic epinephrine:
  - Slight benefit in selected infants
  - Tachycardia is a side effect
Summary: Bronchodilator Therapy

- Albuterol or Racemic epinephrine:
  - If tried, the child should be carefully evaluated before and after therapy; if no benefit on wheezing, work of breathing, or oxygenation can be documented, discontinue use.
- 3% saline aerosol:
  - More beneficial than normal saline aerosol

Summary: Use of Steroids in Bronchiolitis

- Limited data suggest a minimal role if any in treating the child severe enough to warrant hospital admission.
- Although data may support a role for early steroid use in the ED or outpatient setting, the data are very limited and with many flaws limiting their reliability.

Pertussis: On the Rise

[Graph showing the increase in pertussis cases from 1922 to 2004]
Adolescents: High Percentage of Pertussis Cases (2004)*

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>14%</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>3%</td>
</tr>
<tr>
<td>1-4 yrs</td>
<td>11%</td>
</tr>
<tr>
<td>5-9 yrs</td>
<td>9%</td>
</tr>
<tr>
<td>10-19 yrs</td>
<td>37%</td>
</tr>
<tr>
<td>20+ yrs</td>
<td>27%</td>
</tr>
<tr>
<td>Unknown</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>


Clinical Features of Pertussis

- Incubation stage: 7 to 10 days (up to 21 days)
- Catarrhal stage: 1 to 2 weeks
  - Similar to minor upper respiratory infection with nonspecific cough
- Paroxysmal cough stage: 1 to 6 weeks
  - Coughing “fits,” heavy inspiration (whoops), post-tussive vomiting
- Convalescent stage: weeks to months
  - “100-day cough”

Pertussis Symptoms in Infants and Adolescents

Infants/Children
- Classic presentation more common
- Whoop may be absent in infants <6 months
- Vomiting and exhaustion commonly follow episode

Adolescents
- Less typical presentation
- Persistent cough (may last 100 days or more)
- Choking, vomiting, whooping may occur

Pertussis Morbidity in Infants and Adolescents

Infants
- Account for majority of hospitalizations and severe complications
- Incomplete or no immunization increases risk for complications
- Pneumonia, seizures, encephalopathy, death possible
- Majority of deaths in infants

Adolescents
- Severe complications less common
- 38% still coughing at 106 days
- 83% miss school
  - Mean number of missed days: 5.5
  - Range: 0.4 to 32 days

**Diagnosis of Pertussis**

- Usually based on history and physical examination
- Laboratory tests
  - Isolation of *B. pertussis* by culture
  - Polymerase chain reaction (PCR) testing
  - Direct fluorescent antibody (DFA) testing
  - Serologic testing
  - Elevated WBC count with lymphocytosis

**Treatment and Prophylaxis of Pertussis**

- **Recommended**
  - Erythromycin: 40-50 mg/Kg per day in 4 divided doses for 14 days; max 2 g/day, or
  - Azithromycin: 10 mg/Kg as a single dose on day 1 (max 500 mg); then 5 mg/Kg per day on days 2-5 (max 250 mg/day). For under 6 months of age 10 mg/Kg per day for 5 days, or

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**Factors Contributing to Increasing Incidence of Pertussis**

- Improvements in diagnosis and surveillance
  - Increased awareness of pertussis among healthcare professionals?
  - Increased recognition of symptoms?
  - Enhanced case reporting to health departments?
- Waning vaccine-induced immunity
  - Vaccine-induced immunity wanes 5-10 years following last DTA
### Strategies to Reduce Incidence of Pertussis

- Infant vaccination
  - Timely
  - Complete
- Tdap vaccines for adolescents and adults to eliminate reservoirs of infection
- Tdap—2 vaccines available
  - Boostrix: 10-18 y.
  - Adacel: 11-64 y.

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### Conclusions Pertussis

- Disease is on the rise
  - Adolescents: reservoirs
- Adolescent Tdap vaccine available and should be given
- Antibiotics indicated for
  - Treatment of persons with pertussis
  - Prophylaxis of exposed persons
  - Resp. isolation in hospital: after 5 days of Rx
  - Return to school: after 5 days of Rx

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### Tdap vaccination in adolescents and adults

1. Age 19-64 and ≥10 years since last tetanus booster
2. Any age adult with close contact with children <12 months of age
3. Women before becoming pregnant
4. Women immediately post-partum
5. Health-care workers