Respiratory Viral Infections: Focus on Influenza

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Bryn A Boslett, MD
Division of Infectious Diseases
University of California, San Francisco

Outline
• Influenza
  • Epidemiology & Pathogenesis
  • Clinical presentation
  • Diagnostics
  • Treatment
• Prevention
• Non-influenza respiratory viruses
  • Parainfluenza, RSV, Adenovirus
  • Avian influenza, Coronavirus, Measles

Disclosures
• None

Case 1
34yo woman with history of migraine presents to clinic in June with “cold symptoms” for 2 days – runny nose, watery eyes, mild cough and sore throat. Exam remarkable for temp 100.4F (38C), rhinorhea, clear lungs. What is the most likely etiology?

1. Group A Strep (GAS)
2. Influenza
3. Respiratory syncytial virus (RSV)
4. Rhinovirus
5. Seasonal allergies
**Epidemiology of Respiratory Viruses**


**Respiratory Viral Comparison**

* = immunocompromised

<table>
<thead>
<tr>
<th>Virus</th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Fall</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td></td>
<td>Ribavirin + IVIG or palivizumab*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td>Cidofovir*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus</td>
<td></td>
<td>None</td>
<td></td>
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</tr>
</tbody>
</table>


**Case 1 continued…**

What is your next step?

1. Obtain a CXR
2. Obtain respiratory virus testing
3. Obtain a rapid strep test for GAS
4. Start antibiotics (azithro, doxycycline, etc)
5. Supportive care recommendations

The Case for antibiotic stewardship

- Overuse of antibiotics is the single most important driver in antibiotic resistance, and contributes to rising healthcare costs
- Most antibiotics prescribed in the US are for acute respiratory tract infections, ~50% of these prescriptions are inappropriate
- Physician and patient education, computerized clinical decision support, and financial incentives have historically produced only modest reductions in prescription rates

Outpatient antibiotic use, 2000 - 2010

- Broad-spectrum antibiotic prescriptions doubled, 2000 – 2010
- 30% of prescriptions deemed unnecessary

Effect of Behavioral Interventions

47 primary care practices from three health systems, examined for decision-making around antibiotics for respiratory tract infections.

Three different behavioral interventions –
- **Accountable justification**: Free text response needed to justify the treatment decision. Statement included in the medical record.
- **Peer comparison**: Clinicians ranked from highest to lowest in inappropriate prescribing within each region, rankings sent via emails.
- **Suggested alternatives**: EHR pop-up intervention with “inappropriate prescribing” alert, suggestions for alternative treatments

Mean antibiotic prescribing rates change

- Accountable justification – 16.3% decrease (p = <0.001)
- Peer comparison – 18.1% decrease (p = <0.001)
- Suggested alternatives – 16% decrease (p = 0.66)
- Control arm – 11% decrease

Procalcitonin (PCT)

- Peptide released from cell during bacterial infections
  - Correlated with infection severity
  - Assay takes ~30 min to run and costs ~$25
- Two main uses found to be effective in studies:
  - Prevention of initiation of antibiotics (outpatient/ED)
  - shortened duration of antibiotics (ICU)
- Most data exists for respiratory tract infections
PCT effect on antibiotic prescribing

<table>
<thead>
<tr>
<th>Setting</th>
<th>Abx initiation</th>
<th>Abx duration, days median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>64% vs 84%</td>
<td>7 (4–10) vs 10 (7–13)</td>
</tr>
<tr>
<td>Outpatient*</td>
<td>23% vs 63%</td>
<td>7 (5–8) vs 7 (6–8)</td>
</tr>
<tr>
<td>ED</td>
<td>73% vs 88%</td>
<td>7 (4–10) vs 10 (7–12)</td>
</tr>
<tr>
<td>ICU</td>
<td>100% vs 100%</td>
<td>8 (5–15) vs 12 (8–18)</td>
</tr>
</tbody>
</table>

*Mainly trials of URI, bronchitis, COPD exacerbation

Case 2

68yo man with history of diabetes presents to clinic in January with fever, cough and malaise. Temp of 102.2°F (39°C), HR 100, other VS normal. His lungs are clear. What is your next step?

1. Obtain respiratory virus testing
2. Obtain a CXR
3. Start oseltamivir (Tamiflu®)
4. Start antibiotics (azithro, doxycycline, etc)
5. All of the above
6. Some combination of the above

Epidemiology of Respiratory Viruses

You decide to order a diagnostic assay for viral infection.

The best possible test would be:

1. Direct fluorescence antibody (DFA)
2. Rapid antigen detection
3. Respiratory viral PCR
4. Viral culture
**Diagnostics Comparison**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Turn-around</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Culture</td>
<td>++</td>
<td>Slowest</td>
</tr>
<tr>
<td>PCR</td>
<td>+++</td>
<td>Fast</td>
</tr>
<tr>
<td>DFA</td>
<td>++</td>
<td>Fast</td>
</tr>
<tr>
<td>Rapid Ag</td>
<td>+</td>
<td>Fastest</td>
</tr>
</tbody>
</table>

- **Case 2 continued...**

You send an NP swab for rapid antigen detection and respiratory viral PCR, which will take two days. You also obtain a CXR, shown here.

- **Diagnostic sampling**

  - **Upper tract samples:**
    - NP aspirates or swab > nasal swab > throat swab
    - Collect samples preferably within 5 days of onset (shedding is after 5d)

  - **Lower tract samples:**
    - Collect both upper and lower tract specimens in critically ill patients!
    - Lower tract can be (+) even if viral shedding is no longer detectable in the upper tract

  "Viral infections come with diverse CXR possibilities: normal, consolidation, diffuse infiltrates, etc"

  [www.radiology.vcu.edu](http://www.radiology.vcu.edu)
Case 2 continued…

The rapid antigen test is negative for influenza A and B. Your next step:

1. Azithromycin x 5 days
2. Oseltamivir while awaiting PCR
3. Send home with strict return instructions
4. Send to the ED for admission

Two days later, respiratory PCR (+) for influenza

Based on what we know about this current influenza season, what is the most likely influenza subtype in our patient?

1. Influenza A (H1N1)pdm09
2. Influenza A (H3N2)
3. Influenza A (H7N9)
4. Influenza B
Influenza mortality rate is up to 2.7x higher in H3N2 years.

Back to our case...

You call your patient to inform him of the results, but his wife answers the phone and tells you that he was hospitalized last night, in the ICU. His latest CXR is shown. What is the most likely etiology?

1. Influenza viral pneumonia
2. *H. influenzae*
3. *S. aureus*
4. *S. pneumoniae*
5. *S. pyogenes*
Microbiologic diagnosis (EPIC study)

- 2488 adults hospitalized with community acquired pneumonia
- No microbiologic dx found in 62% of cases
- Viruses +/- bacterial co-infection in 27%

Complications of Influenza

- Viral pneumonia
  - Up to 20% mortality, in severe cases
- Secondary bacterial pneumonia
  - Influenza "primes" lung tissues for bacterial superinfection
  - Direct viral damage, disrupts mucus barrier, upregulates adherence receptors
  - S. pneumoniae, S. aureus > S. pyogenes > H. influenzae, gram (-) rods

Treatment

In addition to broad-spectrum antibiotics, you would recommend:

1. No antiviral treatment – he is outside of the therapeutic window
2. Oseltamivir 75 mg PO BID x 5 days
3. Oseltamivir 150 mg PO BID x 10 days
4. Peramivir 600 mg IV x1
5. Zanamivir 10 mg inhaled BID x 5 days

Available treatments for Influenza

- Adamantanes: amantadine, rimantidine
  - M2 ion channel blockers – prevents viral uncoating
  - Influenza A only
  - Resistance widespread = Not Reliable
- Neuraminidase inhibitors: oseltamivir, zanamivir, peramivir
  - Drugs of choice
  - Active against A + B
Neuraminidase comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage</th>
<th>Renal dose?</th>
<th>Can use if intubated?</th>
<th>Contra-indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>75mg/10bid x 5-7d</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>N/V in ~30%</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>10mg IV x 5d</td>
<td>No</td>
<td>No</td>
<td>Underlying resp disease, asthma, COPD</td>
<td>Bronchospasm, cough</td>
</tr>
<tr>
<td>Peramivir</td>
<td>800mg IV x 1</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Dose-reduction (rinse), neuropathy</td>
</tr>
</tbody>
</table>

*Note courtesy of Jen Babik, MD, PhD*

Peramivir

- Intravenous neuraminidase inhibitor (NAI), FDA approved Dec 2014
- 600 mg IV daily
- Outpatients: Single dose duration of symptoms by 21 hrs
- Hospitalized patients: no advantage with daily dose x 5 days, in addition to standard of care (but SOC included a NAI in two-thirds of patients)
- No adequately powered studies comparing outcomes of peramivir vs other NAIs

> Consider for use if malabsorption concern, or poor response to alternative NAI


Timing, Duration, Dose

- Greatest benefit ≤ 48 hrs, but potential benefit > 48 hrs
- 48 hrs chosen based on healthy outpatient data
- Observational studies: Antivirals improved outcomes up to 5 days after symptom onset

Survival by Time of Antiviral Initiation, 2009 H1N1 Pandemic, California

Start Rx while awaiting test results!
Timing, Duration, Dose

- Optimal dose still unclear
  - RCT: 150 mg vs 75 mg BID – no difference for Influenza A
  - Trial was 75% children, did not include critically ill or immunocompromised
- Optimal duration still unclear
  - 5 days vs. longer?

Definitely treat: (even >48 hrs)
- All inpatients
- Outpatients with severe disease or at risk for complications:
  - Ages <2 or >65
  - Chronic disease (cardiopulmonary, diabetes, kidney disease, etc.)
  - Immunocompromised
  - Pregnant or recent post-partum
  - American Indians/Native Alaskans
  - Morbidly obese (BMI ≥40)
  - Residents of chronic care facilities

Consider:
- Healthy outpatients within 48 hrs
- Critically ill, immunocompromised:
  - High-dose oseltamivir (150 mg PO BID)
  - Treatment extension to 10 days or more
  - Use of alternative NAI

IDSA and CDC recommendations

Conflicting Data

- Multiple observational trials show
  - Illness duration, hospitalizations and pneumonia for all groups with NAIs
- 2014 Cochrane meta-analysis: No impact on hospitalization, not enough data on complications. Excluded many high-risk groups.

However...

- 2015 meta-analysis (most complete data from manufacturer):
  - Duration of illness by 21% (~24 hrs) for laboratory-confirmed infection
  - Antibiotic prescription for lower respiratory tract infection, by 44%
  - Risk of hospital admission for any cause, by 63%

CDC, Influenza Antiviral Medications: Summary for Clinicians, January 9, 2015.

Influenza Vaccine
Uptake of influenza vaccine amongst healthcare workers (HCW)

- HCW influenza vaccination coverage estimate for the 2014–15 season was 77.3%
- Rate of 96% attained when employers require vaccination – controversial policy
- Uptake lowest among medical assistants/aides (64%) and HCW in long-term care settings (64%)
- Offering vaccination at the workplace at no cost was associated with higher vaccination coverage.

Influenza vaccine in pregnant women

- 2014–15 influenza season: 50% of pregnant women vaccinated
- Recommendation and offer of vaccine by a primary provider significantly increased uptake
- Main reason for refusal was concern about harmful effects of vaccine on the fetus

Weekly distribution of live births and stillbirths, doses of seasonal trivalent influenza vaccine, and laboratory-confirmed influenza cases during cohort study period.

Adjusted risk of stillbirth was 51% lower among vaccinated women compared with unvaccinated women.

Oral Influenza Vaccine?

- Phase-1 RCT of oral recombinant influenza vaccine using a non-replicating adenovirus vector expressing hemagglutinin
- 92% in the treatment group (11/12) developed titers
- Durability of response was >6 months
Case 3

28yo woman with no significant medical history presents to clinic in April with a severe cough and fever for 2 days. She mentions that she recently returned from a backpacking trip across Asia. What are you worried about in this patient?

1. Avian influenza H5N1
2. Avian influenza H7N9
3. Influenza A
4. Middle Eastern Respiratory Syndrome (MERS)
5. I need more information

Highly Pathogenic Avian Influenza H5N1

- 1997: H5N1 → humans (Hong Kong)
- 2004-2005: Epidemics in poultry, some human cases
- Today: Highly Pathogenic Avian Influenza (HPAI H5N1)
  - >800 people infected, minimal human-human transmission
  - 16 countries (Asia, Middle East, Africa)
  - Most cases: Egypt, Vietnam, Indonesia
  - No USA cases to date
  - 60% mortality

Coronavirus: MERS Co-V

- 2012: Middle East Respiratory Syndrome (MERS Co-V)
  - All cases linked to Arabian peninsula
  - Outbreaks from returning travelers – South Korea in May 2015
  - (186 infected, 36 deaths)
  - Spread via respiratory droplets, but close contact needed
  - Mortality rate 30-40%

Avian influenza: H7N9

- March 2013: H7N9 virus first detected in humans
- March 2015: 667 cases and 229 deaths (thru Oct 2015)
- China, Malaysia, Canada
- Poultry-human transmission
- Limited human-to-human transmission (17 family clusters)
When to Suspect Avian Flu / MERS
• Fever plus respiratory symptoms, **AND**
• Travel to endemic area within past two weeks
  ➔ Obtain serum and NP samples if possible
  ➔ CDC/DPH can instruct on isolation and arrange for specimen testing

Respiratory Viral Summary
• **Timing:**
  • Influenza – Oct through April, generally
  • Other resp viral illnesses vary by season – some active year-round
• **Ways to Dx:**
  • Resp Viral PCR > DFA > Rapid test
  • High suspicion = don’t trust a (-) test result or normal CXR
• **Treatment:** For influenza, time = life!
  ➔ In high-risk pts, don’t wait for results. Start a NAI (oseltamivir, others)
  ➔ Earlier is better, but Rx even >48hrs in inpatients, high-risk pts
• For other resp viral illness, generally no Rx (unless immunocompromised)

Respiratory Viral Summary
• Prevention:
  • Influenza vaccination for all (ages >6mo, no contraindication)
  • Especially important for healthcare workers, pregnant women
  • Imported viruses: Take a travel history!

Thank You!