RESPIRATORY VIRAL INFECTIONS

Infectious Diseases in Clinical Practice
February 2014

Jennifer Babik, MD, PhD
Division of Infectious Diseases
University of California, San Francisco

Disclosures

• NONE

Learning Objectives

• To know the main clinical, diagnostic, and therapeutic principles for managing influenza infection
• To know the basic clinical and treatment approach to other common respiratory viruses

Respiratory Viruses are Common in Hospitalized Patients

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>HCAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Influenza</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>RSV</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Choi et al, Am J Respir Crit Care 2012, 186:325.

Case #1

63 y/o woman with h/o breast CA is admitted January 2014 with fever, cough, and shortness of breath. An NP swab rapid influenza PCR is positive for influenza.

What is the most likely influenza subtype?

1. Influenza B
2. Influenza A (H3N2)
1. Influenza A(H1N1)pdm09
Influenza

• From the Italian word meaning “influence” because it was thought that the stars and planets caused and controlled diseases

Influenza Types

• Influenza A
  • Infects humans, mammals (pigs), birds
  • Subtypes based on type of hemagglutinin (H) or neuraminidase (N) present
  • 18 possible H subtypes, 11 possible N subtypes

• Influenza B
  • Infects humans only
  • No subtypes

• Influenza C
  • Causes only mild disease in humans
  • No subtypes

Influenza Nomenclature

• Influenza A/mallard/Memphis/123/95 (H5N1)

Antigenic Variation

Antigenic Drift

• Influenza A or B
• Caused by point mutations
• Minor changes
• Leads to annual flu epidemics

Antigenic Shift

• Influenza A only
• Caused by major change in viral genome (e.g., reassortment)
• These major changes can result in a new HA subtype
• Can lead to pandemics because humans have little to no immunity to the new HA

Gene Reassortment

Terminology

• Epidemic: confined to one location
  • Seasonal influenza
  • Influenza A, influenza B
  • Results from antigenic drift

• Pandemic: global outbreak
  • When a population has limited immunity to a virus
  • Sustained human-to-human spread → global transmission
  • Influenza A only
  • Results from antigenic shift
Prior Pandemics

**H1N1 (Spanish)**
- 1918
- 50 million deaths worldwide

**H2N2 (Asian)**
- 1957
- 70,000 deaths in the US

**H3N2 (Hong Kong)**
- 1968
- 34,000 deaths in the US


Pandemic H1N1 (“Swine Flu”)

8000-18000 deaths in the US


Influenza Transmission

- Transmitted via:
  - Respiratory droplets
  - Fomites (infective for 2-8h)
- Incubation 1-4 days
- Adults are infections from 1 day prior to sx onset until 5-7 days after (☉ in kids)

Back to the Case...

63 y/o woman with a h/o breast CA admitted with fever, cough, and shortness of breath and found to have influenza A (H1N1)pdm09.

Which is the most predictive of influenza?

1. Sudden onset fever + myalgias
2. Sudden onset fever + headache
3. Sudden onset fever + cough
Influenza: Are any Symptoms Predictive?

- In studies looking at pts ≥ 60 yrs old, the strongest predictors were:
  - Acute onset of both fever and cough (LR 5.4)
  - Fever (LR 3.8)
  - Malaise or (LR 2.6)
  - Myalgias (LR 2.4)

- In studies without age restriction
  - There were no strong positive predictors
  - Absence of fever, cough, congestion were negative predictors (LR<0.5)

Influenza: Clinical

<table>
<thead>
<tr>
<th>Signs/Sx in patients with pH1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>SOB</td>
</tr>
<tr>
<td>Fatigue/weakness</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Rash/urticaire</td>
</tr>
<tr>
<td>Myalgias</td>
</tr>
<tr>
<td>HA</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>


Influenza in Immunocompromised Hosts

- Less likely to have:
  - Fever
  - Cough, SOB
  - Chills/sweats

- More likely to have:
  - Decreased appetite
  - Abnormal pulmonary exam/CXR
  - Need for hospitalization
  - Need for mechanical ventilation
  - Higher mortality
  - Longer viral shedding (median 8 vs 5d, mean 19 vs 6 d)


Back to the case...

She starts requiring more oxygen while in the ED and so gets a CT scan.

Centilobular nodules indicate:

1. Influenza PNA
2. Secondary bacterial PNA
3. Either

CXR Findings in Influenza

- Of hospitalized adults with influenza, 40-60% have an abnormal CXR
- Infiltrates are:
  - Bilateral 60-70%, unilateral 30-40%
  - Consolidations in 75-90%
  - Interstitial thickening 60%
- ~8% of patients with PNA by CT scan have a normal CXR

Chest CT Findings in Influenza PNA

- GGO 90%
- Consolidations 66%
- Centrilobular nodules 60%
- Tree-in-bud 22%


Pathology of Influenza PNA

- Capillary thrombosis
- Alveolar necrosis and hemorrhage
- Necrotizing bronchitis and bronchiolitis


Case #2

A 35 year old man is admitted with 5 days of fever and cough and progressive respiratory distress. He is intubated but rapidly deteriorates and is started on ECMO. Rapid influenza PCR from an NP swab is negative.

What is the next appropriate test?

1. Rapid influenza antigen test
2. Repeat NP swab for influenza PCR
3. Nasal wash for influenza PCR
4. Lower tract sampling for influenza PCR

Diagnosis

- Rapid antigen tests (point-of-care) and DFA testing:
  - ~50-70% sensitive (a lot of false negatives during flu season!)
  - >90% specific
- PCR testing (test of choice):
  - ~95% sensitive and specific
- Samples:
  - NP aspirates or swabs
  - Collect samples preferably within 5 days (as shedding is after 5d)
  - In critically ill patients: collect both upper and lower tract specimens as lower tract samples can be positive even if viral shedding is no longer detectable in the upper tract


Case #2 Continued

He gets an endotracheal aspirate and the sample is positive for influenza A.
Would you give him antivirals?

1. No antivirals (he is out of the treatment window)
2. Oseltamivir 75mg PO bid x 5 days
3. Oseltamivir 150mg PO bid x 10 days
4. Zanamavir 10mg inhaled daily

Antivirals

M2 Inhibitors
- Amantadine, rimantidine
- Influenza A only
- Widespread resistance

Neuraminidase Inhibitors
- Oseltamivir, Zanamavir
- Influenza A and B
- Drugs of choice

Neurominidase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage</th>
<th>Renally dose?</th>
<th>Can use if intubated?</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>75mg PO bid</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>N/V in ~10%</td>
</tr>
<tr>
<td>Zanamavir</td>
<td>10 mg/2 inhalations, daily</td>
<td>No</td>
<td>No</td>
<td>Underlying respiratory disease (e.g., asthma, COPD)</td>
<td>Bronchospasm, cough</td>
</tr>
</tbody>
</table>

Timing of Oseltamivir in Outpatients

- Effect of oseltamivir <48h after symptom onset in healthy adults:
  - Symptoms by ~1 day
  - Conflicting data on the effect on influenza complications (e.g., PNA), hospitalizations, and mortality
  - The earlier therapy is started ➔ the greater the effect
  - Why 48hrs?: viral replication is largely controlled by most healthy outpatients by 48 hours
  - Recent RTC showing Rx for up to 72h after illness onset ➔ sx by ~1d and viral shedding (mostly children)


Timing of Oseltamivir in Inpatients

- >40% of patients hospitalized with influenza present at >48 hrs after symptom onset
- Multiple studies have shown a mortality benefit for treating inpatients:
  - Treatment within 48hrs ➔ mortality by 50-65%
  - Treatment seems to be effective even out to 5-6 days
  - But earlier is better: each day in delay increases risk of death by 20%


Timing of Rx: Better Late than Never

Treatment ➔ mortality, even up to 5 days after symptom onset

Treatment: High Dose Oseltamivir?

- Some experts recommend using high dose oseltamivir (150mg PO bid x 5-10 days) in immunocompromised or critically ill patients.
- 2 recent RTCs in Asia of high vs regular dose oseltamivir x 5d:
  - One study was in adults, the other mostly in kids (all hospitalized).
  - Mostly immunocompetent, <10% required mechanical ventilation.
- Results: No difference in viral clearance, mortality, duration of fever, use of O2, ICU admission or intubation, LOS.
  - One study: more rapid viral clearance for influenza B with high dose.
  - High dose oseltamivir was well tolerated.


Treatment Summary: Who to Treat?

- All inpatients and patients with severe, complicated disease irrespective of timing of symptom onset.
- All outpatients at risk of complications irrespective of timing of symptom onset.
- Ages <2 or >65.
- Chronic disease (cardiopulmonary, diabetes, kidney disease, etc).
- Immunocompromised.
- Pregnant or post-partum (within 2 weeks).
- American Indians/Native Alaskans.
- Morbidity obese (BMI ≥40).
- Residents of nursing homes or chronic care facilities.
- Consider in healthy outpatients on a case-by-case basis if <48-72h.


High Dose Oseltamivir: When to use?

- There seems to be no benefit in hospitalized patients who are immunocompetent non-ICU patients.
- Strongly consider high dose treatment in:
  - Immunocompromised.
  - Critically ill.
  - Patients with influenza B.
- Can consider prolonging the treatment duration depending on clinical response (although no data for this).
- At UCSF we use oseltamivir 150mg PO bid x 10 days in all critically ill and immunocompromised patients.

WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses, 2010.

ECMO for Severe H1N1

- Why ECMO?
  - Young patients, low comorbidities, likelihood of reversible ALI.
- Meta-analysis of 8 case series with 266 patients who received ECMO:
  - Average age 36y/o.
  - Obesity 39%, DM 11%, asthma or COPD 11%, peri-partum 20%.
  - Mortality 8-65%.
- Bottom line: it is feasible and effective although mortality benefit is unclear.

Zangrillo et al, Critical Care 2013, 17:R30.

What is your next step?

1. Change to IV oseltamivir.
2. Change to IV peramivir.
3. Send to the DPH for resistance testing.

Case #2 Continued

After 10 days his influenza PCR is still positive. You decide, although there is no data one way or another, to treat him for an additional 7 days since he is critically ill. However, he remains critically ill and his PCR continues to be positive.
What if my patient doesn’t get better?

- Consider resistance (especially critically ill or immunocompromised patients who may shed for weeks and thus are at higher risk of resistance) – send to DPH or CDC
- Consider whether PO absorption is adequate
- Alternative: IV zanamivir available via urgent EIND approval from GSK and the FDA (will treat oseltamivir resistant pandemic H1N1) http://www.cdc.gov/flu/professionals/antivirals/intravenous.html
- IV peramivir and IV oseltamivir are currently not available via clinical trial, compassionate use, or Emergency Use Authorization

Case #3

An otherwise healthy 39 year old man developed sudden onset of fever, myalgias, and HA.

He improved slightly after 2 days but then began to again have high fevers, developed a new cough, and started having progressive shortness of breath.

He presented to the ED and was found to have a large RLL pneumonia but vitals were stable. Rapid influenza PCR was negative.

Secondary Bacterial Pneumonia

- How common is it?
  - <3% of all cases of influenza
  - ~10% of all patients hospitalized for influenza
  - 20-30% of critically ill patients or deaths
- Clinical:
  - Classic: near resolution of influenza sx and then 4-7 days later there is recurrence of sx/development of PNA
  - Reality: these patients can present on ~day 5 of illness with symptoms that look like severe influenza (ie, without a period of improvement)

Antiviral Resistance 2013-2014

Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since October 1, 2013

<table>
<thead>
<tr>
<th>Oseltamivir</th>
<th>Peramivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>A H3 (H1N2)</td>
<td>6%</td>
</tr>
<tr>
<td>B</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oseltamivir</th>
<th>Peramivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>A H3 (H1N2)</td>
<td>6%</td>
</tr>
<tr>
<td>B</td>
<td>5%</td>
</tr>
</tbody>
</table>

Secondary Bacterial Pneumonia

- Viral infection leads to:
  - Epithelial cell dysfunction and death ➔ bacterial adhesion, invasion
  - Impairment of mucociliary clearance of bacteria for the lungs
- Get infection by colonizers of the nasopharynx:
  - S. pneumoniae ~40-50%
  - S. aureus ~30-40% (~ in critically ill)
  - Group A Streptococcus 5-25%
  - Others: H. influenzae, other GNs

Case #4

A 75 year old man just returned from a trip to China where he was visiting family. He was feeling unwell on his trip home and then next day is admitted with high fevers and a rapidly progressive pneumonia. He is intubated and requiring high levels of oxygen. His family in China sell chickens at stall at a local outdoor market.

You call the DPH asking them to check for:

1. Influenza A (H3N2v)
2. Influenza A (H7N9)
3. Hantavirus
4. Human metapneumovirus

Avian Flu: H5N1

- 650 cases in Asia, Africa, the Pacific, Europe, the Near East  → 386 deaths
- Jan 8, 2014: 1st case in the Americas (Canada) in a traveler from China
- Most cases are a result of direct or close contact with sick or dead infected poultry
- Rare person-to-person spread, not sustained

CDC, Highly Pathogenic Avian Influenza A (H5N1) in People, 2014.

Factors Affecting Bird-Human Transmission

- Poultry markets

Avian Flu: H7N9

- 250 cases reported in China since March 2013 with case fatality rate 22%
- Most cases are thought to be secondary to contact with infected poultry
- Limited person-to-person spread in rare circumstances but not sustained

WHO, Background and summary of human infection with influenza A(H7N9) virus, January 2014.
Swine Flu

- When swine flu viruses sporadically infect humans, they are called variant viruses (denoted by a "v" at the end of the subtype name)
- H3N2v most common (340 cases since 2011, 1 death)
- Human infections usually occur in people with exposure to infected pigs (e.g., at agricultural fairs)
  - Limited person-to-person spread

Swine Flu in Hawaii?

Case #4

84 y/o woman with ESRD on HD gets admitted with 2 days of fever and prominent wheezing. Her rapid influenza is negative.

This is most likely to be:

1. Adenovirus
2. CMV
3. RSV
4. Human metapneumovirus

RSV in Adults

- Winter seasonality – affects up to 10% of adults annually
- A common cause of CAP in adults (2.5-5%)
- Usually thought of as mild but can be severe especially in elderly or immunocompromised
- Clinical:
  - Fever, cough, runny nose, wheeze
  - Bacterial co-infection in 12%

RSV: Imaging

- CXR findings:
  - Normal in 50%
  - Consolidation 24%
  - GGO 20%
  - Unilateral 82%

RSV in Adults

- Compared with influenza:
  - More comorbidities
  - Fever less common (but still in 75%)
  - Wheezing and dyspnea more common

- Mortality rate:
  - 10% in elderly
  - Higher in immunocompromised patients (>50% in HSCT patients)

- Treatment only in immunocompromised: ribavirin +/- antibody therapy (IVIG or palivizumab)

Parainfluenza

- Parainfluenza 3 is most common type in adults (PIV-1 and PIV-2 cause croup in kids)

- Seasonality is spring-summer

- Clinical:
  - Fever, cough, SOB, wheeze
  - Causes URI, bronchiolitis, bronchitis, and pneumonia

Parainfluenza

- CXR findings:
  - Normal in 40%
  - Lobar consolidation 27%
  - Diffuse infiltrates 32%

- Can be severe in immunocompromised patients

- No treatment clearly effective (ribavirin, DAS-181)

Human Metapneumovirus

- Epidemiology:
  - First identified in 2001, closely related to RSV and parainfluenza
  - Seems to be as common as RSV and influenza (~4% of CAP)
  - Seasonality: winter-spring

- Clinical:
  - 40-70% of infections are asymptomatic
  - URI symptoms, cough, wheeze
  - Usually afebrile
  - CXR infiltrate in 27%
  - Can be severe, especially in high risk populations

- Treatment: case reports of using ribavirin + IVIG (like RSV)

Adenovirus

- Can cause severe PNA in immunocompromised and rarely in immunocompetent

- Adenovirus serotype 14 recently recognized as being able to cause severe PNA

- The classical features of adenoviral infection (pharyngitis, conjunctivitis, rash, diarrhea) may be absent

Adenovirus

- Diagnosis:
  - Some respiratory viral panel PCR assays are only ~60% sensitive for adenovirus (because the primers miss some serotypes)
  - If high suspicion, also send the serum PCR (> sensitivity)

- Treatment: can consider cidofovir
Thank you!