Respiratory Viral Infections

Infectious Diseases in Clinical Practice
February 2018

Jennifer Babik, MD, PhD
Associate Clinical Professor
Division of Infectious Diseases, UCSF

Disclosures

- I have no disclosures.
Learning Objectives

By the end of this talk, you will be able to:

1. Recognize the key epidemiologic, clinical, and radiologic features of influenza and its complications.

2. Describe the different diagnostic tests, antiviral options, and vaccines available for influenza

1. Recognize the salient features and treatment options for the other common respiratory viruses.

Road Map

- Influenza
  - Epidemiology and vaccines (current season)
  - Clinical, Diagnosis, Treatment

- Other Respiratory Viruses
  - RSV
  - Parainfluenza
  - Human metapneumovirus
  - Adenovirus
  - Rhinovirus
Influenza

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

Fort Riley, Kansas, during the 1918 pandemic

Current Flu Season

Deaths and hospitalizations rise as flu season hits full swing

Kim Paisley, Special for USA TODAY  Published 4:26 p.m. ET Jan. 9, 2018 | Updated 8:59 a.m. ET Jan. 10, 2018

California hospitals face a ‘war zone’ of flu patients — and are setting up tents to treat them

To Your Health

This flu season is on track to be the worst in nearly a decade

In an ‘Intense’ Flu Season, Hospitalizations Are Rising. Here’s Why.

By DONALD G. NESBIE, Jr.  Jan. 3, 2018
How Bad is It Really?: Outpatient ILI Activity

FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Percentage of Visits for Influenza-like Illness (ILI) Reported by
the U.S. Outpatient Influenza-like Illness Surveillance Network (IILNet),
Weekly National Summary, 2017-2018 and Selected Previous Seasons

Influenza Hospitalizations (All Ages)

Highest rates in those >65 years
(as is true for most seasons)

Rate per 100,000

MMWR week
Week ending Jan 20

2009-10
2013-14
2015-16
2016-17
2017-18
2014-15
Influenza Mortality

**FLUVIEW**

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending January 6, 2018, as of January 25, 2018

% All Deaths Due to PNA/Influenza

- Epidemic
- Seasonal baseline

**Flu is Still Widespread (Less so in Hawaii!)**

2017-18 Influenza Season Week 3 ending Jan 20, 2018

CDC Fluview; 2017-2018 Influenza Season Week 3 ending January 20, 2018.
H3N2 is the Predominant Subtype This Year

Vaccine Effectiveness

- Vaccine effectiveness usually 40-50% and varies based on predominant circulating subtype
- CDC/IDSA: Do not use in decisions re: diagnosis or empiric treatment

Vaccine Effectiveness by Subtype

- Based on a meta-analysis 2004-2015:
  - Influenza B 54%
  - Seasonal H1N1 67%
  - Pandemic H1N1 61%
  - H3N2 33% (good match), 23% (poor match)

- Why lower for H3N2?
  - Antigenic drift and egg-adapted changes in H3N2 viruses are more likely to result in antigenic changes


What is the Vaccine Effectiveness This Year?

- Is it 10%? This was an Australian interim estimate against H3N2 circulating there

- CDC anticipates circulating H3N2 viruses are more similar to those from last season here (VE was 32%)

- CDC will issue an interim vaccine effectiveness estimate later in the season

Why Get a Flu Shot Even in Poor Match Years?

- CDC models: 10% efficacy in elderly prevents 13K admissions
- May be effective in preventing severe illness/complications
- Often more effective against other subtypes


Influenza Vaccines 2017-18 in Brief

- Flu vaccine for all people >6 months old
- Only injectable flu vaccines, with no recommendation on one injectable over the other
- No live attenuated influenza vaccine given concerns about poor efficacy
- What about the high dose vaccine for the elderly?
  - CDC/ACIP have no preference for one vaccine over the other
  - Most important thing is to just get any flu shot
  - Does induce stronger Ab response, provide better protection

Case #1

96 y/o F with COPD is admitted in March with 1 day of SOB, wheeze. No fevers or myalgias. She got the flu vaccine, and her son has a URI.

- Afebrile, HR 125, BP 90/60. WBC 11, lactate 6.
- What is your suspicion for influenza given lack of fever?

How Common is Fever in Influenza in the Elderly?

1. 10%
2. 35%
3. 60%
4. 90%
Classic Influenza Illness Script

- Incubation: 1-3 days
- Symptoms: acute onset of fever, cough, headache, sore throat, rhinorrhea, myalgias
- Symptom duration: 3-5 days

But What is the Data?

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients &gt;60 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Fever</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Cough</td>
<td>90%</td>
<td>20%</td>
</tr>
<tr>
<td>Fever and cough</td>
<td>65%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Key point: Fever, fever+cough less sensitive but more specific in elderly

What about other symptoms? Myalgia, chills, headache, sore throat, congestion: not sensitive or specific
Making a Clinical Diagnosis is Hard!

- In the ER/inpatient setting, the sensitivity of a provider’s clinical diagnosis for flu is only ~30-35%

Influenza in Immunocompromised Hosts

- Classic symptoms less likely
- More likely to have:
  - Need for hospitalization
  - Need for intubation
  - Higher mortality
- Longer viral shedding:
  - Median 8 vs 5 days
  - But 15% of ICH patients can shed for prolonged periods (>30 days)

Case #1 Continued

- Rapid influenza PCR positive for influenza A H3N2

- Is this severe influenza pneumonia or does she have a bacterial co-infection?
  - Her vitals: afebrile, HR 125, BP 90/60. WBC 11, lactate 6.

This Patient’s Sepsis is Most Likely Related To:

1. Primary influenza pneumonia

2. Secondary bacterial pneumonia

3. Could be either
Primary Influenza Pneumonia

- Occurs in ~40% of those hospitalized with influenza
- A severe illness!
  - 20% present with sepsis
  - 10% present with shock
  - 50% admitted to the ICU
  - 40% require mechanical ventilation
  - 25% develop ARDS
  - 20% mortality


Primary Influenza PNA: CXR Findings

- Infiltrates are:
  - Bilateral 60-70%
  - Unilateral 30-40%
  - Consolidations in 75-90%
  - Interstitial thickening 60%

- 8% have a normal CXR

**Chest CT in Influenza PNA: 3 Patterns**

- **GGO predominant**
- **Consolidations+GGO**
- **Centrilobular nodules+GGO**


---

**Secondary Bacterial Pneumonia**

- Likely responsible for most of the deaths from the 1918 pandemic

- How common is it now?
  - <3% of all cases of influenza
  - 10% of all inpatients
  - 20-30% of critically ill or deaths

Secondary Bacterial Pneumonia: Presentation

- **Classic:**
  - Period of improvement → recurrence symptoms 4-7 days later

- **Reality:**
  - Present on ~day 5 of illness without a period of improvement
  - Presentation indistinguishable from severe influenza pneumonia (no difference in symptoms, CXR, labs)


Secondary Bacterial Pneumonia: Etiology

- **Predominantly colonizers of the nasopharynx:**
  - *S. pneumoniae* ~40-50%
  - *S. aureus* ~30-40% (↑ in critically ill)
  - Group A Streptococcus 5-25%

- **Others:**
  - *H. influenzae*, other GNRs
  - Atypicals: *Mycoplasma, Legionella*

Influenza vs Bacterial PNA?

- **The problem:**
  - Severe influenza PNA and secondary bacterial PNA look the same

- **How to approach giving antibacterials?**
  - If severely ill → empiric ABx while cultures pending

- **When to stop?**
  - Cultures negative (before ABx)
  - Low suspicion for bacterial infection (negative or minimal changes on CXR)

Influenza and Myocardial Infarction

- Increased risk (6x) of MI in the week following influenza
- True to a lesser extent for other respiratory viruses
- Other studies have shown similar results
- Mechanism: ?acute inflammation, increased demand

Kwong et al, NEJM 2018.
Case #1 Continued

- She was treated with 2 days Abx (d/c’d when blood cultures were negative) and oseltamivir.

- Tenuous clinically but recovered fully, still doing well as an outpatient.

Case #2

A 35 year old man is admitted in January with 3 days of fever, cough and progressive respiratory distress.

- Rapid influenza antigen test in the ED is negative.
What is the Sensitivity of the Rapid Antigen Tests?

1. <25%
2. 30-50%
3. 50-70%
4. >90%

Diagnostic Tests for Influenza

Rapid Antigen Testing
- POCT in clinics, ERs
- ~50-70% sensitive
- >90% specific
- Cannot be used to exclude influenza during flu season
- New more stringent FDA requirements 1/2018

Molecular Assays
- ~95% sensitive and specific
- Test of choice
- Some assays can determine:
  - Influenza A vs B
  - Influenza A subtypes (seasonal H1N1, seasonal H3N2, pandemic H1N1)

### Which Patients Should Be Tested?

**Outpatients**
- Patients with high-risk conditions who will be considered for antiviral therapy

**Inpatients**
- All inpatients with an influenza-like illness or pneumonia
- Remember that not all patients with influenza will have fever (elderly, immunocompromised)

### Case #2 Continued

- Nasopharyngeal swab was positive by PCR for influenza A (seasonal H3N2).
- He was treated with oseltamivir and slowly recovered.
Case #3

A 34 y/o woman 28 weeks pregnant is admitted in January with 5 days of fever, cough, SOB and now has severe hypoxemic respiratory failure requiring intubation and 100% FiO2.

- Febrile to 38.1°C, WBC 15
- Nasopharyngeal swab for influenza PCR is negative

Should You Stop Empiric Oseltamivir?

1. Yes, it’s a great test
2. No, wait for a lower tract sample
Diagnosis: Samples

- **Upper tract samples:**
  - NP swab is optimal method
  - Note that shedding ↓↓ after 5 days

- **If critically ill: collect upper and lower tract samples**
  - Lower tract samples (BAL, mBAL, trach aspirate) can be positive even after upper tract viral shedding has stopped
  - **If high suspicion: do not stop empiric therapy until lower tract sample is negative**


Case #3 Continued

- **Empiric oseltamivir was continued while awaiting a lower tract sample**

- **Mini-BAL was PCR positive for influenza A (pandemic H1N1)**

- **But wait, she’s had symptoms for 5 days...should she still be treated?**
Would You Continue Her Antivirals?

1. No antivirals (she 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 bid x 5 days

Antivirals

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

Neuraminidase Inhibitors
- Oseltamivir, Zanamivir, Peramivir
- Influenza A and B
- Drugs of choice
**Neurominidase Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>75mg PO bid x 5 d (renally dose)</td>
<td>None</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>10mg INH bid x 5 d</td>
<td>Resp disease (asthma, COPD), cannot use if intubated</td>
<td>Bronchospasm Cough</td>
</tr>
<tr>
<td>Peramivir</td>
<td>600mg IV x 1</td>
<td>None</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

**Efficacy of Oseltamivir in Outpatients**

- Consistent across RCTs: \(\downarrow\) symptoms by \( \sim \) 24 hours
- Conflicting data on PNA, hospitalizations, mortality
  - Observational studies: \(\downarrow\) in PNA, hospitalizations
  - 2014 Cochrane: no effect on PNA, hospitalizations, death
  - 2015 meta-analysis (best data): \(\downarrow\) PNA, hospitalizations

Timing of Oseltamivir in Healthy Outpatients

- Most RCT participants had symptoms for ≤ 48h
  - 48h cutoff b/c replication usually controlled by this point
  - The earlier therapy is started → the greater the effect

- Treatment up to 72 hours?
  - RCT (kids): ↓ symptoms by ~1 day and ↓ viral shedding

Is Outpatient Oseltamivir Cost-Effective?

- Yes…assuming there is a benefit in preventing influenza complications and hospitalizations
Guidelines in Outpatients: Who to Treat?

- All outpatients at high risk for influenza complications (irrespective of time of symptom onset)
  - ≥ 65 years
  - Chronic pulm, CV, renal, hepatic, heme, neuro/developmental, and metabolic disorders (including diabetes)
  - Immunocompromised
  - Pregnant or postpartum (within 2 weeks after delivery)
  - American Indians/Alaska Natives
  - Morbidly obese (BMI ≥40)
  - Residents of chronic care facilities

- Can consider in healthy outpatients if <48h


Timing of Oseltamivir in Inpatients

- Treatment of inpatients at <48hrs of symptoms:
  - ↓ mortality by 50-65%
  - But >40% of pts hospitalized with influenza present at >48h

- Multiple studies show a mortality benefit at >48hrs, even out to 5 days

- But earlier is better:
  - Earlier treatment → lower mortality
  - Earlier treatment in elderly → shorter LOS, less need for SNF

Timing of Rx: Better Late than Never

Louie J CID 2012; 55: 1198-204

Timing of Rx: Better Late than Never

Louie J CID 2012; 55: 1198-204
Guidelines in Inpatients: Who to Treat?

- **All inpatients** with influenza irrespective of time of symptom onset.

- For suspected cases, **treat as early as possibly and do not delay therapy while awaiting lab confirmation.**

Duration of Therapy

- 5 days in most cases

- Can consider a longer course (e.g. 10 days) based on severity of illness and repeat RVP testing of lower respiratory tract samples
Peramivir (IV)

- FDA approved 2014 for adults with uncomplicated influenza and symptoms <48hrs

- When to use?
  - Any concerns for GI absorption of oseltamivir
  - Note: limited data that oseltamivir is well absorbed in obese and critically ill patients including those on CRRT and ECMO

- How to dose?
  - FDA approved for a single dose in uncomplicated influenza
  - UCSF guidelines: 5 days?


Influenza Treatment: Take-Home Points

- Who to treat?
  - Outpatients: All patients at high risk of complications.
  - Inpatients: All inpatients
  - For these high risk groups, treat irrespective of duration of symptoms, as early as possible, do not delay Rx while awaiting lab confirmation.

- Which drug?
  - Oseltamivir: drug of choice for most patients
  - Zanamivir: only if no COPD/asthma and not intubated
  - Peramivir: if need an IV option

- How long?
  - 5 days for most
  - Consider 10 days based on severity of illness and repeat PCR testing
Case #3 Continued

After 10 days her influenza PCR is still positive. You decide to treat her for an additional 7 days since she is critically ill. However, she remains critically ill and her PCR continues to be positive.

What is Your Next Step?

1. Change to IV oseltamivir
2. Start vancomycin and cefepime
3. Change to inhaled zanamavir
4. Send to the DPH for resistance testing
What If My Patient Doesn’t Get Better?

- **Consider oseltamivir resistance**
  - Especially critically ill or immunocompromised pts who may shed for weeks
  - Send to DPH or CDC
  - Rare (<1-2% of isolates over last 2 years)
  - If concerned for resistance → IV zanamivir available via urgent EIND approval from GSK and the FDA

- **Consider whether PO absorption is adequate** → if not, use IV peramivir

Case #4

A 75 y/o M no known lung disease is admitted in December for a “COPD exacerbation” due to SOB and wheezing.

- He is afebrile with a normal CXR.
- Steroids are started but he doesn’t improve after 2 days.
He most likely has:

1. Adenovirus
2. RSV
3. Parainfluenza-3
4. Cytomegalovirus

Rapid-Fire Respiratory Viruses

- Brief word on epidemiology
- RSV
- Parainfluenza
- Human metapneumovirus
- Adenovirus
- Rhinovirus
Respiratory Viruses are Common!

Most common viruses isolated (in order):
1. Rhinovirus
2. Influenza, parainfluenza, metapneumovirus, RSV, coronavirus
3. Adenovirus


Respiratory Virus Seasonality

<table>
<thead>
<tr>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Metapneumovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RSV in Adults

- **Clinical:**
  - Wheezing and dyspnea more common than flu
  - URI accounts for majority of disease overall
  - Mortality in elderly can approach 10%


RSV in Immunocompromised Patients

- **HSCT:**
  - 30-40% of patients with URI progress to LRTI
  - Mortality rates of up to 70-80%
  - Late airflow decline, bronchiolitis obliterans

- **Solid organ transplant:** overall better outcomes
  - Lung transplants highest risk
  - Up to 20% mortality, up to 60% bronchiolitis obliterans

Treating RSV PNA in Immunocompromised

![Graph showing progression from LRTI and mortality with different treatments](image)

- **Immunomodulator = IVIG**

### Ribavirin

- Synthetic guanosine nucleoside analogue that inhibits nucleic acid synthesis

- Available in 3 forms:
  - **Aerosolized**: previously standard of care
    - Toxicity: Bronchospasm, cough, dyspnea
    - Isolation: Teratogenic, HCW precautions
  - **IV**: poor outcomes in older studies, toxicity → hemolytic anemia, neutropenia, thrombocytopenia
  - **Oral**: what we use at UCSF, watch for hemolytic anemia

Marcelin et al, TID 2014
Who to Treat?

- Our protocol: oral ribavirin + IVIG for 2 weeks

- Which syndrome?:
  - In general we only treat pneumonia
  - We only treat URI in HSCT patients <1 mo from transplant

- Which patients:
  - HSCT, heme malignancy, solid organ transplant patients
  - Extrapolate to other types of immunocompromise?

Parainfluenza

- PIV-3 most common in adults (PIV-1, PIV-2 → croup in kids)

- Clinical:
  - Fever, cough, SOB, *wheeze*
  - URI, bronchiolitis, bronchitis, PNA
  - Can be severe in immunocompromised

- No treatment clearly effective
  - HSCT: No benefit with ribavirin in 2 retrospective studies
  - Solid organ transplant: some case reports of success with ribavirin, but no controls

Human Metapneumovirus

- **Clinical:**
  - 40-70% are asymptomatic
  - URI symptoms, cough, wheeze
  - Usually afebrile
  - Can be severe, especially in high risk populations

- **Treatment:**
  - Case reports of ribavirin + IVIG (like for RSV) in transplant patients


Adenovirus

- Can cause severe PNA in ICH host, rarely in immunocompetent

- Classic features of adenovirus infection (pharyngitis, conjunctivitis, rash, diarrhea) may be absent

- **Diagnosis:**
  - Some resp viral PCR assays only ~60% sensitive for adenovirus
  - If high suspicion, also send serum PCR ( Gibraltar sensitivity)

- **Treatment:** can consider cidofovir

Rhinovirus

- “Common cold”
- Often detected in CAP/HAP but pathogenicity unclear
- May predispose to bacterial superinfection
- HSCT patients with rhinovirus have similar outcomes as those without
- Treatment: supportive


Take-Home Points

1. The flu vaccine is usually 40-50% effective (and lower for H3N2) but even when low, you should still recommend it!
2. Influenza pneumonia is common and can be severe
3. POCT rapid antigen test cannot rule out influenza given low sensitivity
4. Treat all inpatients with influenza irrespective of time of symptom onset
5. Other respiratory viruses are common in CAP and HAP
Thank You!

- Questions?