Diagnosis of Seasonal and Pandemic Influenza

Michael Klepsar, Pharm.D., FCCP
Professor
Ferris State University
College of Pharmacy

Objectives

• Given a patient case, be able to identify signs and symptoms associated with influenza and differentiate those from other respiratory diseases.
• Compare and various methods used to identify patients with influenza.
• Discuss the clinical utility of diagnostic methods for influenza.

Influenza Infections

• Each year 1-6% of the US population demonstrates serologic evidence of infection.
• Risk of severe influenza and complications is higher at extremes of age and among those with various underlying medical conditions.
Persons at Higher Risk for Influenza-Related Complications

- Children <5 years
- Adults >65 years
- Persons with immunosuppression
- Women who are pregnant or postpartum
- Persons <18 years receiving long-term aspirin
- American Indians/Alaska Natives
- Morbidly obese (BMI ≥40)
- Residents of nursing homes
- Persons with chronic diseases:
  - Pulmonary (including asthma)
  - Cardiovascular (not just HTN)
  - Renal
  - Hepatic
  - Hematologic (including sickle cell)
  - Metabolic (including diabetes)
  - Neurologic (including cerebral palsy, seizures, stroke, mental retardation, muscular dystrophy, and spinal cord injury)


Influenza Virus - Clinical Course

- 1-4 days of incubation.
- Abrupt onset of symptoms
  - Fever (100-104°F), chills, headache, myalgia - persist for ~3 days
  - Respiratory symptoms may persist 3-4 days after fever subsides.
- Duration of infectivity is 5 days after illness onset for adults. Children shed virus for several days before onset to ≥10 days after onset of symptoms.
- Convalescence 1-2 weeks.

Influenza Virus - Clinical Course

Peak viral titers

Infection Timeline

- Exposure to virus
- Incubation period
- Peak viral load
- Symptom onset
- Symptoms peak
- Convalescence

Differential Diagnosis

<table>
<thead>
<tr>
<th>Influenza</th>
<th>Pneumonia</th>
<th>Cold</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>1-4 days</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

**Symptoms**
- Influenza: Fever, cough, rhinitis, myalgias, malaise
- Pneumonia: Fever, cough, dyspnea, rips, chest discomfort
- Cold: No or low-grade fever, cough, sneezing, sore throat
- Heart Failure: Cough, shortness of breath, no fever

**Significant findings**
- Influenza: Radiological findings, cultures
- Pneumonia: Look at medication list.
- Cold: Look for lower extremity edema.
- Heart Failure: Look at medication list.


Making a Diagnosis: Influenza-Like Illness

- Fever (≥100°F [37.8°C]) and a cough and/or a sore throat in the absence of a known cause other than influenza.
- Good predictive value among healthier adolescents and adults (79%-88%).
- Worse in children <5 years (65%), hospitalized adults (51%), adults with chronic lung disease (41%).
- As the prevalence of disease decreases the positive predictive value (PPV) decreases.

Making a Diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Test time</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Culture</td>
<td>3-10 days</td>
<td>Gold standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenza has influence on treatment decisions</td>
</tr>
<tr>
<td>Immunofluorescence</td>
<td></td>
<td>Requires specialized equipment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable sensitivity and specificity</td>
</tr>
<tr>
<td>Real Time-PCR</td>
<td>1-6 hours</td>
<td>Does not always detect viable virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most appropriate for hospitalized patients</td>
</tr>
<tr>
<td>Rapid Diagnostic Tests</td>
<td>&lt;0.5 hours</td>
<td>Suboptimal sensitivity and specificity</td>
</tr>
</tbody>
</table>
Real Time-PCR

- Detects viral RNA in respiratory specimens.
- May get false positive following recent administration of LAIV.
- Not available for outpatient or emergency department use.
- Expensive.

Rapid Influenza Diagnostic Tests

- Identify viral antigens in respiratory specimens.
- Suboptimal sensitivity and sensitivity
  - Sensitivities 50%-70% (False negatives)
  - Specificities 90%-95% (False positives)

Sensitivity vs. Specificity

- High Sensitivity
  - Low Specificity
- Low Sensitivity
  - High Specificity
Rapid Influenza Diagnostic Tests

- Easy to perform and relatively inexpensive.
- Select screening population carefully to optimize positive predictive value.
- Clinical utility
  - Collect specimens as early in illness as possible
  - Should not be the sole factor upon which to base therapy

Positive Predictive Value

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patients with the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low PPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High PPV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Making a Reliable Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity for Seasonal H1N1</th>
<th>Sensitivity for Seasonal H3N2</th>
<th>Sensitivity for Novel H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Culture/PCR</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Rapid Diagnostic Test*</td>
<td>27%-80%</td>
<td>27%-83%</td>
<td>40%-69%</td>
</tr>
<tr>
<td>Presumptive Diagnosis*</td>
<td>43%-78%</td>
<td>43%-78%</td>
<td>43%-75%</td>
</tr>
</tbody>
</table>

*Predictive value depends on the prevalence of influenza in the community.
Sensitivity: percentage of persons with the disease who have positive test results.
Rachel

- Rachel is a 64-year-old female who comes to the pharmacy in December complaining of a terrible headache and feeling tired.
- Symptoms started today. First thing noted was headache.

- Social history:
  - Smokes 1-2 cigarettes daily
  - Has about one drink daily

- Family history:
  - Lives with husband

- Medications
  - Advair Diskus twice daily
  - Albuterol as needed
  - Lisinopril 10 mg daily

Rachel

- Physical findings: Cough, headache, fatigue
- Vital signs:
  - Temp 102.3°F
  - BP 122/75 mmHg
  - Pulse 75 Beats/min
  - RR 24 Breaths/min
  - Pulse Ox 98%

Rachel

- What do we do next?
  - Ask if she has received the influenza vaccine this year.
    ✓ No.
  - Is there any information you would like in order develop a care plan?
    - Sporadic influenza activity has been reported in the community.
Rachel

- Symptoms of influenza-like-illness:
  - Cough (Yes)
  - Fever (Temp 102.3°F)
  - Body aches (No)

Making a Diagnosis: Influenza-Like Illness

- Fever (≥100°F [37.8°C]) and a cough and/or a sore throat in the absence of a known cause other than influenza.
- Good predictive value among healthier adolescents and adults (79%-88%).
- Worse in children <5 years (65%), hospitalized adults (51%), adults with chronic lung disease (41%).
- As the prevalence of disease decreases the positive predictive value (PPV) decreases.

Rachel

- Do you feel comfortable saying the patient has influenza?
- What else could be done at this time?
  - Refer to Emergency Department?
  - Refer to Primary Care Physician?
  - Conduct an RIDT?
• How confident are you that Rachel has influenza?
• How confident would you be that Rachel did not have influenza if the test were negative?
• What do you want to do with Rachel?