Prevention and Treatment of Seasonal Influenza

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What to expect

http://www.michigan.gov/mdch

Objectives

- Describe the differences between available influenza vaccines and preferred vaccines for different patient groups
- Understand who, what, when, and for how long when it comes to antiviral therapy for influenza
- Recommend treatment strategies for oseltamivir for hospitalized patients with influenza
Vaccines

• Who gets it?
  – All patients ≥ 6 months of age without contraindications!
    • Severe allergic reaction to vaccine component
    • Allergy to egg protein (for most)
    • Severe illness in past following vaccination is precaution

• When should they get it?
  – Three weeks ago
  – Unvaccinated individuals should be encouraged as long as virus is circulation in community

Vaccine options

<table>
<thead>
<tr>
<th>Type</th>
<th>Type Approval</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent inactivated (IIV4)</td>
<td>Fluarex/FluLaval ≥ 3 yrs</td>
<td>Adds 4th strain, B/Brisbane/60/2008-like</td>
</tr>
<tr>
<td>Trivalent inactivated (IIV3)</td>
<td></td>
<td>Many different products, age range based on formulation, Intradermal option as well.</td>
</tr>
<tr>
<td>Cell culture based IIV3</td>
<td>Fluvelx ≥ 18 yrs</td>
<td>NA</td>
</tr>
<tr>
<td>High dose IIV3</td>
<td>Fluzone High-Dose ≥ 65 years</td>
<td>Only approved for elderly</td>
</tr>
<tr>
<td>Recombinant trivalent (RIV3)</td>
<td>Flubok 18-49 years</td>
<td>No egg protein in product</td>
</tr>
<tr>
<td>Live, attenuated, quadrivalent (LAIV4)</td>
<td>FluMist 2-49 years</td>
<td>Preferred in children 2-8 years of age</td>
</tr>
</tbody>
</table>

Key patient populations

• Pediatrics (6 months through 8 years)
  – 2 doses (≥ 4 weeks apart) their first season
    • Usually
    – LAIV preferred (ages 2-8)
      • Increased protection, but don’t withhold vaccination until available
      • Data supports up to 6 years of age, but helps keep consistency in vaccine schedules

• Elderly
  – High dose vaccine?
    • Conflicting evidence that decreased response to standard vaccine

• Should I push for the quadrivalent?
High dose vs standard dose vaccine in patients ≥ 65 years

- Phase IIIb-IV, RCT comparing IIV-HD vs IIV-SD (high dose has 4 times the hemagglutinin).

<table>
<thead>
<tr>
<th></th>
<th>IIV-SD</th>
<th>IIV-HD</th>
<th>Relative Efficacy</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory confirmed influenza</td>
<td>1.9%</td>
<td>1.4%</td>
<td>24.2% (9.7 – 36.5)</td>
<td>200</td>
</tr>
<tr>
<td>Laboratory confirmed influenza by strain in vaccine</td>
<td>0.7%</td>
<td>0.5%</td>
<td>35.4% (12.5 – 52.5)</td>
<td>500</td>
</tr>
</tbody>
</table>

$4,000 – 10,000 per case of influenza prevented....

BUT.... Higher response is similar to reduction that would be expected in younger population.


About that quadrivalent vaccine....

<table>
<thead>
<tr>
<th>Respiratory Virus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>2009 A/H1N1pdm</td>
<td>0</td>
</tr>
<tr>
<td>Influenza A/H3</td>
<td>1</td>
</tr>
<tr>
<td>Influenza B</td>
<td>3</td>
</tr>
</tbody>
</table>

Michigan Department of Community Health Update Oct 29 2014

Treatment...

- Two classes of antivirals
  - Adamantanes
  - Neuraminidase inhibitors
- And one of them does not work.....

| TABLE 1: Summary of antiviral resistance among influenza strains worldwide. December 2010* |
|-----------------------------------------------|---|---|---|
|                               | 2009 H1N1 | 2012 | 8 |
| Adenovirus (not recommended currently) | Resistant | Resistant | No activity |
| Oseltamivir                        | Susceptible | Susceptible | Susceptible |
| Zanamivir                         | Susceptible | Susceptible | Susceptible |

MMWR Jan 2011; 60 (1)
Neuraminidase inhibitors

• Products
  – Oseltamivir (oral)
  – Zanamivir (inhalation, IV*)
  – Peramivir (IV*)

• Mechanism of action
  – Competitive inhibitor of viral neuraminidase
  – Prevents new virus particles from being released by infected (host) cell
  – Mechanism is basis for need to start ASAP in infection

A word about zanamavir

• Indicated for chemoprophylaxis (≥ 5 years of age) and treatment (≥ 7 years of age)
• Administered as oral inhalation by using plastic device given with medication
• Not recommended in patients with underlying airway disease!!
• No evidence in treating more complicated disease
  – No real role in hospital (maybe ED?)

Oseltamivir for chemoprophylaxis

• Useful adjunct to influenza vaccination
  – 70-90% effective in preventing influenza after exposure
• Widespread use not recommended due to concerns for resistance
• Consider use after exposure for
  – Persons at high risk for influenza complications
  – Immunosuppressed
  – LTCF during outbreaks at the facility
• Alternatively- monitor for signs and symptoms and start therapy ASAP if occur
Other chemoprophylaxis considerations

• Duration: For the entire duration of potential exposure and then 7 days after
• If taking after vaccination the recommended duration is for two weeks (until antibodies should develop)
• Generally NOT recommended if ≥ 48 hours have elapsed since first exposure to infectious person
• Recommended during outbreaks amongst high risk individuals in institutional settings
  – For periods at risk there are some evidence for long term exposure (4-6 weeks), but many unknowns……

Oseltamivir: Treatment

• The benefits of treatment
  – Shorten the duration and MAY reduce complications
  – Benefit is the greatest when started ASAP, especially within 48 hours
• Recommended for suspected or confirmed influenza in patients who
  – Are hospitalized
  – Have severe, complicated, or progressive illness
  – Are at high risk for influenza complications
• Clinical judgment based on patient specific factors for others

High risk for complications

• Children ≤ 2 years of age
• Adults ≥ 65 years of age
• Patients with chronic comorbidities
• Immunosuppressed
• Pregnant or postpartum women
• Patients ≤ 19 years of age on long-term aspirin
• American Indians/Alaskan Natives
• Morbidly obese
• Nursing home or other LTCF patients
Initiation of treatment

- As soon as possible after onset of illness!!
  - Ideally within 48 hours of disease onset
- In severe, complicated, progressive, or hospitalized patients
  - Select data suggest clinical benefit in hospitalized patients even day 4-5 after onset
- Pregnant patients
  - Preferably ASAP, but still benefit seen 3-4 days after onset (less benefit as time went on)

Other important considerations

- Decisions for treatment should NOT wait for diagnostics!!
- Influenza can still occur if vaccinated
- If considering therapy for a previously healthy, symptomatic, non high risk outpatient
  - Only if treatment can be initiated within 48 hours
  - MIGHT be a small benefit in pediatrics (one day reduction in symptoms) up to 72 hours

Lots of room for improvement

Considerations for hospitalized patients

• Remember— the (good) literature for antiviral recommendations comes from uncomplicated influenza
• Because of this…
  – No FDA approved regimens for this setting
  – The 48 hour rule for initiation doesn’t necessarily hold true
  – Duration of therapy should be driven by the clinical scenario, not the 5 days standard course

Because of this…

• Some experts have recommended a higher dose (150 mg twice daily) in high risk patients
  – Critically ill (PK issues?)
  – Obese patients
• Pharmacokinetic and clinical data do NOT support this
  – In critically ill patients with orally or enterically administered oseltamivir
    • Adequate absorption with standard doses providing therapeutic blood levels
    • Limited data suggest no improved outcomes with higher doses
  – Data indicate that exposure to oseltamivir carboxylate (active metabolite) is same in obese and non-obese patients receiving same dose
• Importantly though, higher doses appear safe

If your patient cannot tolerate oral

http://www.cdc.gov/flu/professionals/antivirals/intravenous-antivirals.htm
Considerations if your patient is failing therapy

• Most likely related to course of the disease
  – Acute lung injury, Severe sepsis, etc
• However, important considerations
  – Oseltamivir resistance?
    • Consider obtention and switch to IV zanamivir
  – Ventilator and fluid management
  – Secondary bacterial pneumonia?
    • Notably MRSA

Summary

• Vaccination and chemoprophylaxis both effective measures at preventing influenza
  – Vaccination recommended for almost all
• High dose influenza vaccination might offer some additional protection, but cost-effectiveness remains to be seen
• In general, the earlier you can start antiviral therapy the better efficacy you will see
  – But some extended benefit might be seen in more severely ill patients
• Data lacking to support higher dosing in obese, critically ill patients- but dose appears safe

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