Herpes Zoster: It’s worse and better than you thought.

September 17, 2015
Objectives

- Review patho—physiology of herpes zoster (HZ)
- Review incidence and risk factors of HZ
- Review burden of HZ
- Review HZ recurrences
- Review prevention using HZ vaccine
Human Herpesviruses (HHV)

HHV family

Alpha-HHV
- HSV* (HHV-1, -2)
- VZV† (HHV-3)

Primary infection: varicella (chickenpox) *

Beta-HHV
- (HHV-6A, -6B)

Reactivation: herpes zoster (shingles) *

Gamma-HHV
- EBV‡ (HHV-4)
- CMV§ (HHV-5)

HHV family†


*HSV = herpes simplex virus
†VZV = varicella zoster virus
‡EBV = Epstein Barr virus
§CMV = cytomegalovirus

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HZ is common and burdensome

- 1 in every 3 people will develop HZ during their lifetime

- People living to age 85 years, have a 1 in 2 chance of developing HZ

- Both the incidence and the complication rates of HZ increase with age

- HZ causes a significant burden for affected individuals

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Diagnosis of Zoster

- Clinical findings
  - Distinctive unilateral, vesicular rash allows accurate diagnosis in the majority of cases.\(^1\)
  - In immunocompromised patients, zoster may be more severe, with cutaneous dissemination.\(^2\)
- Laboratory confirmation—but only so/so
  - Tzanck smear\(^3\)
  - Viral culture\(^3\)
  - Direct immunofluorescence assay\(^3\)
  - Polymerase-chain reaction\(^3\)

Zoster: Clinical Features

- Usually limited to 1 or 2 adjacent, unilateral dermatomes.\(^1\)
- “Grapelike” lesions clustered on an erythematous base.\(^2\)
- Lesions usually heal within 4 weeks.\(^1\)

Courtesy of the American College of Physicians
(www.acponline.org/shell-cgi/printhappy.pl/bioterro/smallpox_mimics.htm).

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Zoster: Latency and Reactivation

Posterior column spinal cord

Dorsal root ganglion

Site of VZV replication

Image courtesy of Thomas P. Habif, MD.
Zoster: Dermatomal Distribution

Asbury AK, et al. © 2001. Adapted with permission of McGraw-Hill.¹

VZV: Immune Response

- Cell-mediated immunity (CMI) plays a major role.¹
  - Clears virally infected cells
  - Limits viral replication at dermal sites
- Humoral immunity²
  - IgM, IgG, IgA are neutralizing antibodies.
- Immunity persists following disease.
  - Waning CMI with increasing age may contribute to reactivation of VZV as herpes zoster (shingles).³

Herpes Zoster by Worldwide Age

Worldwide Herpes Zoster by Age

- Hope-Simpson (UK)
- Brisson (UK)
- Gonzalez (France)
- Ultsch (Germany)
- Insinga (US)
- Yawn (US)
- Stein (Australia)
- Brisson (Canada)
- Jih (Taiwan)
- Choi (South Korea)

Annual Incidence (per 1,000 person-years)

Age

Referenced works:
- Araujo LQ et al. *Herpes* 2007;4 (supplement 2) 40A-44A.
HZ Incidence by age group and sex

Distribution of HZ Cases by Age

Preliminary data from Olmsted County, 2005.
The number of HZ cases was calculated by applying the Olmsted HZ incidence rates to the 2005 US population.
Distribution of HZ cases by age and immune status

Effect of Zoster on Activities of Daily Living

Prodromal pain mimics other conditions.

- Acute pain = lost work, play, sleep and prescription Rx
- PHN is a chronic neuropathic pain syndrome
- PHN can persist for months or years
- PHN occurs in 8%-30% of herpes zoster cases
  - 34%-73% in those over 70 yo

Health Care Use for HZ

- 30% of people with HZ make a visit for prodromal
- On average 3 ambulatory visits per HZ case
- 4% of HZ cases hospitalized
- > 70% of HZ cases receive antivirals
- Broad use of opiates, but also of antidepressants, anticonvulsants
  - HZ-related pain resistant to treatment
- Health care use due to HZ increases with age

**Prodromal Phase of Zoster**

- Pain and paresthesia may precede the vesicular rash.\(^1\)
  - Sensations range from itching to severe lancinating pain.\(^1,2\)
  - 40% of patients experience pain >4 days before eruption.\(^2\)
  - Prodrome common in persons >60 years of age.\(^1\)
  - Pain may mimic other conditions \(^1,3\)

- Constitutional symptoms\(^2\)
  - Headache, malaise, fever

Therapy for acute HZ

Anti-viral therapy—little reduction in pain

<table>
<thead>
<tr>
<th>Day 5</th>
<th>Day 15</th>
<th>Day 25</th>
<th>Day 45</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>91%</td>
<td>81-87%</td>
<td>80%</td>
<td>69-76%</td>
<td>72%</td>
</tr>
<tr>
<td>55-86%</td>
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<tr>
<td>51%</td>
<td>39-46%</td>
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<tr>
<td>29%</td>
<td>24-28%</td>
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</tbody>
</table>
Therapy for acute HZ

Pain Medications:

OTC---modest effect

Opioids---side effects
  constipation
  loss of balance--falls
  patient concerns

Antidepressants
Neuroleptics

Often too little, too late
Pain duration >90 days by age group

Pathophysiology of PHN

Postherpetic Neuralgia (PHN)

PHN is a chronic neuropathic pain syndrome that persists or recurs in the dermatome affected by Zoster.¹

Definitions of PHN vary, and have included²
• Any pain persisting after healing of zoster lesions
• Pain persisting 1 month after rash onset
• Pain persisting 3 months after rash onset

Therapy for PHN

- Pain medication
- Antidepressants
- Neuroleptics
- TENS
- Injections

- Often limited relief and many adverse effects
Spectrum of Sensory Abnormalities in PHN

- Spontaneous pain<sup>1</sup>
  - Continuous or paroxysmal
    - Burning, stabbing, shooting
- Stimulus-evoked pain<sup>2</sup>
- Partial sensory deficit<sup>1</sup>
- Parasthesias/dysesthesias<sup>2</sup>
- Autonomic instability may occur<sup>1</sup>
  - Signs include sweating, erythema

Risk Factors for PHN¹

- Older age
- More severe acute zoster pain
- Greater rash severity
- Greater sensory abnormalities during acute zoster
- Prodrome prior to zoster rash

Impact of PHN

- Clinical observations include\(^1\):
  - Depression and other psychological distress
  - Physical, occupational, and social impairments resulting from constant pain

Non-pain Complication rates by age

Zoster Ophthalmicus

Image courtesy of Charles E. Crutchfield III, MD. Crutchfield Dermatology, Eagan, MN.


Image courtesy of Dr. Dubin’s collection (www.skinatlas.com).
Scarring: Ophthalmic Zoster

Recurrences

- 1669 HZ cases: mean follow up 7.3 years
- 105 HZ recurrences in 95 individuals
  - 7 people had 2 recurrences and 1 had 4 (IC)
- The recurrence rates at 8 years were:
  - 7.2% (95% CI, 5.4-9.0) for women
  - 4.5% (95% CI, 2.8-6.2) for men
- 55% of the recurrences in the same site
- HZ recurrences noted 3 months to 10 years later

2. Epstein 1980.
Risk factors for HZ recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Multivariate Cox Regression Hazard ratio (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50</td>
<td>0.42 (0.2, 0.8) p = 0.006</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.45 (0.4, 1.1) p = 0.10</td>
</tr>
<tr>
<td>Immune-compromised</td>
<td>1.64 (0.9, 2.9) p = 0.09</td>
</tr>
<tr>
<td>Pain duration 30 days or more in the initial episode.</td>
<td>1.57 (0.9, 2.6) p = 0.08</td>
</tr>
<tr>
<td>Age&gt;50 and Pain&gt;=30 days (interaction)</td>
<td>5.81 (2.3, 15.0) p = 0.0003</td>
</tr>
</tbody>
</table>

HZ Recurrence Rate by Immune Status

HZ Recurrence Rate by Pain Status

Clinical Summary:

HZ is common and has a large disease burden
1 in 3 adults by age 80
Acute pain as well as PHN, eye and other issues
30% of people visit MD before the rash
Recurrence rates similar to occurrence rates

Complications can last days to a life time

Prevention is possible
Better at younger ages---start vaccine at 50

Decrease in risk of PHN goes beyond HZ prevention
Breakthrough cases have less PHN
Zostavax for prevention:

- Live attenuated
- Lypolized—frozen
- Must be reconstituted
- Short useable period after mixing

- Approved for use in non-immune compromised age 50 and older
- Single dose
Randomization of Subjects in the Shingles Prevention Study (SPS)

Subjects enrolled 38,546

Adverse Event (AE)
Substudy: 6,616

Cell-Mediated Immunity
Substudy: 1,395

Age 60 to 69 years
20,747

Zoster vaccine 10,378
Placebo 10,369

Age ≥70 years
17,799

Zoster vaccine 8,892
Placebo 8,907

SPS: Efficacy of ZOSTAVAX® on Herpes Zoster Incidence Compared With Placebo by Age Group

- Vaccine efficacy for the prevention of herpes zoster was highest in those subjects 60 to 69 years of age and declined with increasing age.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo Cases</th>
<th>ZOSTAVAX Cases</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–69 yrs</td>
<td>334</td>
<td>122</td>
<td>64% (95% CI: 56–71)</td>
</tr>
<tr>
<td>70–79 yrs</td>
<td>261</td>
<td>156</td>
<td>41% (95% CI: 28–52)</td>
</tr>
<tr>
<td>≥80 yrs</td>
<td>47</td>
<td>37</td>
<td>18% (95% CI: 29–48; NS)</td>
</tr>
</tbody>
</table>

ZEST: Overall Efficacy of ZOSTAVAX® on Herpes Zoster Incidence Compared With Placebo

22,439 Adults 50 – 59 years

Zostavax immunization 11,220

- HZ 30 Cases
- No HZ 11,190

Control 11,219

- HZ 99 Cases
- No HZ 11,120

Efficacy 69.8% (54.1-80.6)

Summary: ZOSTAVAX® is Highly Effective in Reducing the Incidence of Herpes Zoster and positive effects to Postherpetic Neuralgia

Overall Incidence of Herpes Zoster (HZ) In patients 50-59 y.o.¹

- Placebo: 99
- ZOSTAVAX: 30

70% Reduction
95%(CI: 54-80)

Overall Incidence of Herpes Zoster (HZ) In patients ≥60 y.o.²

- Placebo: 642
- ZOSTAVAX: 315

51% Reduction
95%(CI: 44-58)

Overall % of Zoster cases with Postherpetic Neuralgia (PHN) In patients who develop HZ postvaccination ≥60 y.o.

- Placebo: 12.5
- ZOSTAVAX: 8.6

39% Reduction
95%(CI: 7-59)

ZOSTAVAX has demonstrated a favorable safety profile

- The incidence of serious adverse events (SAEs) was comparable to placebo
- The most common adverse event is injection site reactions

ZOSTAVAX has demonstrated

- a significantly higher varicella-zoster virus gpELISA antibody GMT at 6 weeks post-vaccination compared with placebo

* ZOSTAVAX is not indicated for prevention of PHN

* Number of Herpes zoster cases

# Injection-Site and Systemic Adverse Experiences

Reported by vaccine report card in ≥1% of adults who received ZOSTAVAX or placebo (0 to 42 days postvaccination) in the AE monitoring substudy of the Shingles Prevention Study

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>ZOSTAVAX® (n = 3,345)</th>
<th>Placebo (n = 3,271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema*</td>
<td>33.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Pain/tenderness*</td>
<td>33.4%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Swelling*</td>
<td>24.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Warmth</td>
<td>1.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.4%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

*Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0–4 postvaccination.
Prevention Summary

Prevention is possible

Age 50 and older
Immunocompetent

Future to bring killed vaccine
Immunocompromised
How to Improve Vaccination Rates

- Know the rules
- Establish protocols/standing orders
- Make strong recommendations
- If your office cannot vaccinate, refer
- Partner with pharmacists and pharmacies
- Partner with public health vaccinators
- Be captain of the immunization ship!
Know The Rules: 2015 ACIP Adult Immunization Schedule

Recommended Adult Immunization Schedule—United States - 2015

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE GROUP</th>
<th>19-21 years</th>
<th>22-26 years</th>
<th>27-49 years</th>
<th>50-59 years</th>
<th>60-64 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>1 dose annually</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)*</td>
<td>Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Varicella</td>
<td>2 doses</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Female*</td>
<td>3 doses</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Male*</td>
<td>3 doses</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Zoster*</td>
<td>1 dose</td>
<td></td>
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</tr>
<tr>
<td>Measles, mumps, rubella (MMR)*</td>
<td>1 or 2 doses</td>
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<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)*</td>
<td>1-time dose</td>
<td></td>
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<tr>
<td>Pneumococcal polysaccharide (PPSV23)*</td>
<td>1 or 2 doses</td>
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<tr>
<td>Meningococcal*</td>
<td>1 or more doses</td>
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<tr>
<td>Hepatitis A*</td>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B*</td>
<td>3 doses</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)*</td>
<td>1 or 3 doses</td>
<td></td>
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</tr>
</tbody>
</table>

*Covered by the Vaccine Injury Compensation Program

CDC Advisory Cmte. on Immunization Practices.
Take an aggressive approach!

- Your recommendation is key
  - 88% of consumers said they were likely to get vaccinated if recommended by their doctor*

- Standing orders are one of the most effective ways to increase vaccination

- Utilize EMR to your advantage
  - Use automatic reminders
  - Some can run the daily patient list for immunizations that are due; have staff administer on arrival
  - Use patient portal
Protocols/Standing Orders

- Delegate! Get your staff involved
  - Have them ask about vaccination status when doing vital signs or medication reconciliation
  - They can provide vaccine information to patient
  - Establish standing orders for automatic administration of all vaccines, not just flu

- Appoint an office champion to spearhead patient identification and vaccination efforts

- Free download of standing order forms at www.immunize.org/standing-orders
Provider Recommendation Can Overcome Negative Attitude Among Patients

Vaccination Rates Among High Risk Patients With Negative Attitudes

MD, medical doctor.
If Your Office Cannot Vaccinate, Refer

- Know the rules.

- In Missouri, pharmacists can only provide vaccinations recommended by the ACIP
  - HZ vaccine after age 60
  - They have more hours of service than MD offices
  - Primary reason for referral may be Medicare Part D
  - Up to age 65 using private insurance—in office?
  - Can they vaccinate below that age with prescription?

- What are the rules for public health vaccinators?
Barriers

“But I’m too busy”
  • What makes immunizing your patient less important than other disease issues or giving therapy for other conditions?

“It’s too costly to stock all these vaccines”

“But its frozen”

“But it has to be reconstituted”

“But it expires in 60 minutes”
Barriers

- Reimbursement for adult vaccines better than for pediatric ones
- Can bill $30-$96 above vaccine cost in addition to vaccine administration cost per vaccine
- Many companies will provide vaccines up to 90 days before payment is due—can bill for them by then!!
- Most companies will buy back outdated/damaged product or freezer failures
Not

How important is it to me?

But

How important is it for patients?

And

How can I make it happen?