Joint Session with ACOFP and Cleveland Clinic: Managing Chronic Disease

Herpes Zoster: Diagnosis, Treatment and Prevention

Leonard Calabrese, DO
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Herpes Zoster: Diagnosis, Treatment and Prevention

• Biology & Epidemiology
• Clinical Aspects
• Treatment and prevention

Varicella Zoster Virus

• Family: herpesviridae
• Subfamily: alpha herpesviridae
• Ubiquitous
• 99+% of adults have immunologic memory
• Transmission: airborne; via fomites from skin lesions
• 2 clinical forms:
  - Varicella (primary)
  - Herpes zoster (reactivation)
History

- Molecular link between VZV and HZ first demonstrated by Stephen Straus (*NEJM* 1984)
- Latency in dorsal root ganglia molecularly demonstrated by Donald Gilden (*NEJM* 1990)

Rough estimates based on multiple studies expressed as cases per 1000 pt/ys

**Risk of HZ**

- **GENERAL RISKS** – AGE, F>M, trauma, recurrent 2-4%
- Incidence increasing globally over 50 years
- In the USA alone 1 million cases/yr
- Lifetime risk is about 20-30% with a 50% likelihood if survive to 85 yoa

*Patients with IMIDS are 2 x the risk of immunocompetent patients*
Incidence of HZ by Age Category 1945-2007*

*Population includes adults and children residing in Olmsted County, MN.


HZ
OI? Or Not?

Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance

K L Winthrop, 1 S A Novosad, 2 J W Badley, 3 L Calabrese, 4 T Chilles, 5 P Polgreen, 6 F Barrales, 7 M Lipman, 8 K Mariette, 9 O Lortholary, 10 M E Weiablatt, 11 M Saag, 2 J Smolen 12

Diagnosis & Treatment

Clinical

- Prodrome
  - Pain, itching, paresthesias
  - Dysesthesias, allodynia
- Rash
  - Papules → vesicles
  - Scab over in 7-10 days
- Limited to 1-3 dermatomes
- In most, resolution of skin lesions accompanied by decreased pain
- Complete resolution of pain in 4-6 weeks
Diagnosis

- Classic presentation with vesicular, dermatomal rash and neuralgic pain
- Papules to vesicles; 7-10 days’ 1-3 dermatomes
- Complete resolution 4-6 weeks
- Laboratory testing
  - For difficult diagnosis
  - PCR: high sensitivity and specificity

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Testing for Herpes Zoster</th>
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<tbody>
<tr>
<td>Test</td>
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<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>Direct immunofluorescent antigen staining</td>
</tr>
<tr>
<td>Virus culture</td>
</tr>
</tbody>
</table>

*NOTE: Diagnosis of herpes zoster is usually clinical, and testing is limited to atypical cases. Tests should evaluate fluid from vesicles.*

PCR, polymerase chain reaction.

Areas Typically Affected by HZ


By Henry Vandyke Carter - Henry Gray (1918)
Anatomy of the Human Body: Gray’s Anatomy, Plate 784.
### Diagnostic Challenges

- Prodromal pain may suggest other conditions, e.g., myocardial infarction, cholecystitis, appendicitis, migraine, trigeminal neuralgia
- Skin manifestations may be confused with HSV, contact dermatitis, impetigo, folliculitis, CA-MRSA, fungal infections
- Atypical HZ in immunized individuals
- HZ sine Herpete (2.4%) *(Hato Ann Neurol 2000)*

HSV, herpes simplex virus; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*.

### Complications of Acute HZ

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Ophthalmic</th>
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<tbody>
<tr>
<td>PHN</td>
<td>Stromal keratitis</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>Iritis</td>
</tr>
<tr>
<td>Cranial palsy</td>
<td>Retinitis</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Visual impairment</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>Episcleritis</td>
</tr>
<tr>
<td>Stroke*</td>
<td>Keratopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Visceral</th>
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</thead>
<tbody>
<tr>
<td>Bacterial superinfection</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Permanent scarring/changes</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>in pigmentation</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

Calabrese L et al Arth Rheum 2017
**PHN: Rates Increase with Age**


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**Severity of HZ and Duration of Chronic Pain in Adults Ages ≥ 50 y**


ZAP, zoster-associated pain.
**Other Complications of HZ**

- Zoster ophthalmicus
- Bacterial superinfection of HZ lesions
- Cranial and peripheral nerve palsies
- Disseminated zoster
- Visceral involvement
- Stroke
- Myocardial infarction


**HZ and Stroke**

**Older Era**

- **Children:** 1/15,000 varicella infections associated with stroke within 12 months
- **HZ of Cranial Nerve V (HZO)** associated with rare episodes of ‘contralateral hemiplegia’ weeks to months following HZ with evidence of direct vascular invasion
- **Severely immunocompromised individuals** may experience ischemic and hemorrhagic events with angiitis and evidence of direct viral invasion

Liesegang AA *Opt 2008*
Horan at al *Sem Ped Neurol 2012*
Grose, C *Ped Inf Dis J 2010*
• 2009 Kang et al (Taiwan National Health Research Database) found in 7760 HZ cases an adjusted hazard rate for stroke (1 yr follow up) of 1.31
• Six subsequent epidemiologic studies from Taiwan, Denmark, and UK each revealed significant associations with stroke following HZ ranging from 1.26 to 4.52 with varying influences: type of HZ, time of follow up, antiviral therapy, age, and CVD confounders
• No study has specifically examined immunosuppressed individuals for the association of stroke and HZ

Kang et al Stroke 2009
Lin Neurology 2010
Sreenivas S J Neuro Comm 2013
Breuer Neurology 2014
Langan CID 2014

HZ and Stroke
New Era >2009
Treatment of Acute HZ (Non Complex)

- Immunocompromised patients
  - Antiviral Therapy in ALL Patients Regardless if > 72hrs
    - Acyclovir 800mg 5 x day 7 days
    - Valacyclovir 1Gr 3x day 7 days
    - Famciclovir 500mg 3x day x 7 days
    - Brivudin
  - Reduce pain, promote healing, reduce shedding, PHN? (Cochrane data base 2009)
  - Treat Pain
    - Short acting narcotics, glucocorticoids(60mg prednisone with 10 day taper Whitely et al Ann Int Med 1996)
    - Other neuroleptic meds- tricyclics, gabapentin etc
Treatment Complex Zoster

- Hospitalization & IV antivirals
  - Complex cases – disseminated, CNS, visceral
- Herpes Zoster Ophthalmicus
  - Absolute indication for anti-virals, PO in uncomplicated forms
  - With ocular involvement ophthalmology consultation essential
  - Severe HZO hospitalization and IV anti-virals
- PHN – complex pain management

Prevention

Inn the Clinics Herpes Zoster Ann Int Med 2011
Zoster Vaccine Live

Indications and Contraindications

**Indications**
- ZOSTAVAX is indicated for vaccination of adults aged 50 years and older for
  - Prevention of herpes zoster (HZ)
  - Prevention of postherpetic neuralgia (PHN)
  - Reduction of acute and chronic HZ-assisted pain

**Contraindications**
- History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine
- Immunosuppression or immunodeficiency
- Active untreated tuberculosis
- Pregnancy
Cell-Mediated Immunity to VZV Decreases with Age

Skin Test Results

ELISPOT: interferon-γ enzyme-linked immunospot.

Herpes Zoster Vaccine: dosage and Administration

- (Zoster Vaccine Live [OKa/Merck]) is a lyophilized preparation of the Oka/Merck strain of live, attenuated VZV
- For subcutaneous administration
- Administered in a single dose of 0.65 mL
- Stored frozen
- Should be reconstituted immediately upon removal from freezer
- Diluent should be stored separately
- Discard reconstituted vaccine if not used within 30 minutes

(package insert) Whitehouse Station, NJ. Merck & Co, 2007
Disposition of SPS Subjects

Subjects enrolled (n=38,546)

Zoster vaccine (n=19,270)
- Terminated before study end
  - 793 (4.1%) Died
  - 57 (0.3%) Withdrew
  - 61 (0.3%) Lost to follow-up
- Completed study 18,359 (95.3%)

Placebo (n=19,276)
- Terminated before study end
  - 792 (4.1%) Died
  - 75 (0.4%) Withdrew
  - 52 (0.2%) Lost to follow-up
- Completed study 18,357 (95.2%)

Herpes Zoster Vaccine Trials: Summary

- Zoster vaccine efficacy¹ (age 60 +; no previous HZ)
  - 66.5% reduction in the incidence of PHN
  - 51.3% reduction in the incidence of HZ
  - 61.1% reduction in the HZ burden of illness (BOI)
- The clinical trials found an approximately 18% efficacy in people age 80 and older as compared with 64% efficacy in people age 60 through 69 years.
- Loss of efficacy over 5 years though no recommendations on re-vaccination

Vaccination Stimulates CMI

CMI, cell-mediated immunity.

Kaplan-Meier Estimates of the Cumulative Risk of Herpes Zoster by Herpes Zoster Vaccination Status

<table>
<thead>
<tr>
<th>Follow-up, y</th>
<th>Unvaccinated No. at risk</th>
<th>Vaccinated No. at risk</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>227,283</td>
<td>75,761</td>
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<tr>
<td>0.5</td>
<td>208,374</td>
<td>73,722</td>
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<tr>
<td>1.0</td>
<td>158,887</td>
<td>58,425</td>
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<tr>
<td>1.5</td>
<td>128,920</td>
<td>48,658</td>
</tr>
<tr>
<td>2.0</td>
<td>77</td>
<td>30</td>
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No. at risk, N."
Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older


ABSTRACT

Risk of Development of Herpes Zoster after Vaccination

Physician-Level Barriers

PCPs** Recommendations  
*HZ vs Other Adult Vaccines*

- HZ: 11 Recommend against, 47 Do not recommend, 41 Recommend, 4 Strongly recommend
- Tdap: 3 Recommend against, 20 Do not recommend, 76 Recommend, 4 Strongly recommend
- Pneumoccal: 5 Recommend against, 95 Do not recommend, 96 Recommend
- Influenza: 4 Recommend against, 96 Do not recommend, 96 Recommend

PCP-Level Barriers to Administering the HZ Vaccine*

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Responses (%)</th>
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<tbody>
<tr>
<td></td>
<td>Major Barrier</td>
</tr>
<tr>
<td>Cost concerns for my patients</td>
<td>53</td>
</tr>
<tr>
<td>Reimbursement challenges for my practice</td>
<td>52</td>
</tr>
<tr>
<td>Up-front costs of purchasing the vaccine for my practice</td>
<td>43</td>
</tr>
<tr>
<td>Need for my patients to pick up the vaccine at a pharmacy</td>
<td>23</td>
</tr>
<tr>
<td>Need to store the vaccine in the freezer in a sealed separate compartment</td>
<td>16</td>
</tr>
<tr>
<td>More pressing medical issues taking precedence over the vaccine</td>
<td>12</td>
</tr>
</tbody>
</table>

*Survey of 301 general internists and 297 family medicine physicians.

The Physician-Patient Disconnect
Results from Two Recent Surveys

“I talk to all of my patients about vaccines”
87%

“Yes, I regularly discuss vaccines with my HCP”
18%

“I occasionally discuss vaccines with my HCP”
31%

“I don’t recall ever discussing vaccines”
21%

Patient
Misconceptions/Questions

Common questions
• I already had shingles. Doesn’t that mean I’m immune?
• I never had chickenpox. Why would I need the shingles vaccine?
• My family member is immunocompromised. Can she catch shingles from me?

The best strategy for preventing complications of HZ is to prevent HZ
= Importance of HZ vaccination for all healthy adults ages ≥60 yo
All immunosuppressed rheumatology patients > 50 yo
Cleveland Clinic
Every life deserves world class care.