Update on Herpes Zoster

ACIP Meeting
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National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention
Herpes Zoster Outline

- Clinical manifestations
- Epidemiology
- Prevention
  - Currently recommended vaccine: Zostavax
  - New investigational vaccines: V212 & HZ/su
Natural History of Varicella Zoster Virus (VZV)

Chicken Pox (Varicella)

Shingles (Herpes Zoster)

Primary VZV Infection

VZV Latency in Dorsal Root Ganglia

Spinal Cord

Reactivation

Herpes Zoster

Herpes Zoster (HZ): Clinical Manifestations

Courtesy of NIAID

Courtesy of CDC

Courtesy of CDC/Robert Sumpter
Clinical Symptoms of HZ: Rash

- Unilateral, involving 1-3 adjacent dermatomes
- Arises over ~5-7 days
- Resolution in ~5-25 days
- Occasional consequences
  - Secondary bacterial infections
  - Transmission of VZV to susceptibles

Photo Courtesy of CDC
Clinical Symptoms of HZ: Pain

• About 90% of HZ episodes associated with pain or discomfort
• Pain is variable in character and intensity
• Pain precedes rash onset in ~84% of cases
  ▪ Typically 1-5 days-- but can be weeks
  ▪ Diagnostic dilemmas
Clinical Manifestations of HZ: Herpes Zoster Ophthalmicus (HZO)

- Involvement of ophthalmic division of trigeminal nerve (~15% of HZ cases)
- Can cause chronic complications and sometimes, loss of vision

Courtesy of MN Oxman UCSD/San Diego VAMC.
Clinical Manifestations of HZ: Post Herpetic Neuralgia (PHN)

- Prolonged pain at least 90 days following resolution of rash
- 10-18% of HZ patients will go on to have PHN
- May persist for months to years & may be incapacitating
- PHN prevention
  - antivirals +/- steroids
  - shorten duration of HZ but do not conclusively reduce risk of PHN
- PHN treatment- multiple modalities
  - partial, inconsistent efficacy
  - side effects, especially in the elderly
Letter from a patient with PHN:

“My shingles post herpetic neuralgia is still painful seven years after my shingles episode. My PHN is worse than my cancer and chemotherapy… [it] has made me depressed and suicidal in the past”
Epidemiology

Herpes Zoster
Epidemiology of HZ in U.S.

• Annual rate ~4 cases per 1000 population
• About 1 million cases in the U.S. annually
• Lifetime risk of developing HZ: ~ 1:3
• Age-adjusted rates appear to be increasing
Epidemiology of HZ: Risk Factors

- Older age
  - Dominant factor driving incidence
- Immunosuppression
  - Blood malignancies, bone marrow transplant, or HIV, increase risk up to 50-fold
  - Increased severity: disseminated disease and hospitalization

**Underlying Mechanism:**

reduced cell mediated immunity

allows VZV reactivation/progression to HZ
Epidemiology of HZ in U.S.

HZ Incidence by Age, 2000-1

HZ rate per 1,000 person-years

Age in years

0-14 15-29 30-39 40-49 50-59 60-69 70-79 >80

In singa et al., J Gen Intern Med. 2005, 20:748-53 (MarketScan administrative data)
Epidemiology of HZ in U.S.

PHN Incidence by Age, 1996-2001

PHN = 90 days of pain.

Epidemiology of HZ in U.S.

Adapted from Harpaz, ID week, 2015
Epidemiology of HZ in U.S.

Adapted from Harpaz, ID week, 2015
Prevention

Herpes Zoster Vaccines
Herpes Zoster Vaccine: Zostavax

- Licensed by FDA in 2006
  - >38,500 non immunocompromised adults ≥60 years old
  - Median follow-up 3.1 years
  - Live-attenuated Oka-strain VZV (≥14X titer in Varivax)
  - Vaccine efficacy: 51% vs. HZ, 67% vs. PHN
- Safety
  - Serious adverse events not more common in vaccinated group
  - Local reactions more common in vaccine group
Zostavax Efficacy by Age – HZ & PHN

Adapted from Oxman et al. Shingles Prevention Study, 2005
Zostavax Efficacy for PHN by Duration of Pain

Vaccine Efficacy (%)

Oxman et al. Shingles Prevention Study, 2005
Zostavax: ACIP Policy

• 2008: Zostavax recommended by ACIP
  ▪ 1 dose for adults ≥60 years
  ▪ Contraindicated in immunocompromised

• 2011: No change to ACIP recommendation following FDA age expansion to 50-59 yr olds
  ▪ Vaccine shortages (now resolved)
  ▪ Higher herpes zoster disease burden in people ≥60 years

• 2013: ACIP affirmed recommendation for adults 60 years and older
  ▪ Waning of immunity
Zostavax: Duration of Protection against HZ

Oxman et al. NEJM, 2005, **STPS** (Short Term Persistence Study) Schmader et al, CID 2012, **LTPS** (Long Term Persistence Study, Morrison et al, CID 2015)

*Control group modeled using age and calendar year to account for secular increase in HZ incidence*
Zostavax: Duration of Protection against HZ

Effectiveness of HZ Vaccine by Years After Vaccination
Kaiser Permanente Southern California, 2007-2015

Tseng, et al., JID, 2016
Zostavax Uptake

HZ Vaccine Uptake (%), Adults ≥60

Zoster Vaccine Uptake

Why has uptake been sluggish?

- Price
- Storage & handling (frozen vaccine)
- Supply shortages (resolved)
- Medicare Part D reimbursement
- Lower prioritization of adult vaccines
- General fragmentation of preventive care for seniors

Vaccine Specific Factors

System Factors
New Vaccines: HZ/su (GSK)

- VZV Glycoprotein E + adjuvant system
  - 2 doses, 2 months apart
  - Refrigerator stable

- Phase III RCT in >30,000 non-immunocompromised adults ≥50 yrs
  - 1o Endpoint: Prevention of HZ
  - 2o Endpoints: Prevention of PHN, Safety and Reactogenicity
New Vaccines: HZ/su

• Vaccine efficacy for prevention of HZ:
  ▪ 97% for 50-59 years old
  ▪ 91% for 80 years and older

• Vaccine efficacy of ≥85% maintained after 4 years, all age groups

• Highly reactogenic
  ▪ 79% of vaccine recipients report a reaction to the vaccine (placebo= 30%)
  ▪ 12% of vaccine recipients report grade 3 reactions (symptoms that interfere with daily life) (placebo=2%)
New Vaccines for Immunocompromised

- **V212 (Merck):** inactivated formulation of Zostavax
  - 4-dose series in persons ≥18 years old
  - Ongoing phase 3 efficacy trials

- **HZ/su (GSK):** glycoprotein E + adjuvant
  - 2 dose series in persons ≥18 years old
  - Ongoing phase 3 efficacy trials
Conclusions

• The epidemiology of HZ is changing— we don’t fully understand why
• ~28% of adults ≥ 60 yrs have been vaccinated with Zostavax
• Vaccines to prevent varicella and HZ are reducing the amount of circulating VZV in our population
• 2 New vaccines for the prevention of Herpes Zoster are being evaluated
Thank You
## Herpes Zoster Work Group

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