Herpes Zoster: Clinical Presentations

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Learning Objectives

• This program will enable participants to:
  – Describe the range of clinical presentations in patients who develop herpes zoster (HZ)
  – Appreciate the rationale for helping to prevent HZ disease
ZOSTAVAX® (Zoster Vaccine Live)

• ZOSTAVAX is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older.

• ZOSTAVAX is not indicated for the treatment of zoster or PHN.
SELECT SAFETY INFORMATION
ZOSTAVAX® (Zoster Vaccine Live)

• ZOSTAVAX is contraindicated in persons with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; with a history of primary or acquired immunodeficiency states including leukemia; lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or with AIDS or other clinical manifestations of infection with human immunodeficiency viruses. ZOSTAVAX is a live attenuated varicella-zoster vaccine and administration may result in disseminated disease in individuals who are immunosuppressed. ZOSTAVAX is also contraindicated in persons on immunosuppressive therapy. ZOSTAVAX is not indicated in women of childbearing age and should not be administered to pregnant females.
SELECT SAFETY INFORMATION
ZOSTAVAX® (Zoster Vaccine Live) (cont)

• Vaccine-related, injection-site and systemic adverse experiences in ≥1% of individuals in the Adverse Event Monitoring Substudy (AEMS), a subgroup of individuals from the Shingles Prevention Study (SPS) who received ZOSTAVAX (n=3,345), included headache (1.4%) and the following injection-site reactions: erythema (33.7%), pain/tenderness (33.4%), swelling (24.9%), hematoma (1.4%), pruritus (6.6%), and warmth (1.5%). Most of these adverse experiences were reported as mild in intensity.

• From Day 0 to 42 postvaccination, in the overall study population, serious adverse experiences (SAEs) occurred at a similar rate (1.4%) in subjects vaccinated with ZOSTAVAX or placebo. In the AEMS, the rate of SAEs was increased in the group who received ZOSTAVAX (1.9%) as compared to the placebo group (1.3%) from Day 0 to 42 postvaccination. Over the course of the entire study, in the overall study population, investigator-determined, vaccine-related serious adverse experiences were reported for two subjects vaccinated with ZOSTAVAX (asthma exacerbation and polymyalgia rheumatica) and three subjects who received placebo (Goodpasture's syndrome, anaphylactic reaction, and polymyalgia rheumatica).

• ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox).
Herpes Zoster
Epidemiology and Disease Burden of HZ

- Herpes zoster (HZ, “zoster,” or shingles) results from the reactivation of the varicella-zoster virus (VZV).
- Varicella-zoster virus infects about 99.5% of the population ≥40 years of age.
  - According to the US Centers for Disease Control and Prevention, all older adults are at risk for zoster.
  - There is no way to predict who will develop HZ.
- It is estimated that there are nearly 1 million new cases per year in the United States.
- Incidence and severity of zoster increase with advancing age.
  - Of the estimated 1 million new cases per year, approximately 40% to 50% occur in individuals ≥60 years of age.
  - By 85 years of age, approximately 50% of individuals will have had zoster.
  - About 1 in 3 persons will develop HZ.

Clinical Phases of HZ\textsuperscript{1–3}

Prodrome

- Several days or weeks after rash onset

Acute Rash

- 2–4 weeks

Chronic/Postherpetic Neuralgia (PHN)\textsuperscript{a}

- 30–180 days from rash onset

- Months to years

Potential Complications

\textsuperscript{a}Definitions of PHN vary from $\geq 30$ days to $\geq 180$ days after rash onset.

Pain is one of the most debilitating symptoms of HZ.\textsuperscript{1}

How does the pain compare to other conditions your patients may experience?
Comparison of Pain Scores for Various Conditions

Katz and Melzack compared total pain rating index scores from multiple studies of chronic pain and acute pain of diverse causes, using the Short-Form McGill Pain Questionnaire.

Signs and Symptoms of Prodromal and Acute HZ\textsuperscript{1,2}

**Rash**

- **Prodrome**
  - Dermatomal pain before rash onset

- **Acute HZ**
  - Evolution of Rash (Unilateral)
    - May have maculopapules and vesicles
  - Cessation of new vesicle formation
  - Pustulation
  - Scabbing
  - Cutaneous healing

- ~ Duration = 2–4 weeks

**Signs and Symptoms**

- Headache
- Photophobia
- Malaise
- Abnormal skin sensations
- Unbearable itching
- Pain (varying severity)\textsuperscript{3}
  - Aching
  - Burning
  - Stabbing
  - Shock-like
  - Provoked by trivial stimuli
  - Altered sensitivity to touch

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Complications of HZ

- Morbidity due to zoster is substantial
- In a population-based study in adults ≥22 years of age:
  - 10% of patients with HZ experienced nonpain complications
  - 10% of patients with HZ experienced a complication called PHN
- Complications can be:

  - **Neurologic**
  - **Ophthalmic**
  - **Cutaneous**
  - **Visceral** (rare)

\[a\] Complications other than pain for ≥30 days, such as ocular disease or motor neuropathies.
\[b\] PHN defined as at least 90 days of documented pain.

Neurologic Complications: PHN

PHN is the most common complication of zoster and can result in severe, chronic pain.¹

- Occurs in 10% to 18% of patients with HZ²
- May persist for months or occasionally even years³

A risk factor is older age.²

- In a population-based study of 1,669 patients with HZ aged ≥22 years, the percentage of patients who developed PHN increased from 5% in patients <60 years of age to 20% in patients ≥80 years of age⁴

Common features may include:

- Steady and intermittent pain⁵
- Allodynia (distressing and debilitating pain provoked by innocuous stimuli)¹⁵
  - Present in about 45% to 55% of acute HZ patients, but may affect up to 90% of patients with PHN¹⁵

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Other Complications of HZ

• Neurologic\textsuperscript{1,2}
  – Loss of sensation, cranial and motor neuron palsies, meningoencephalitis, encephalitis, hearing loss

• Ophthalmic\textsuperscript{1,2}
  – Herpes zoster ophthalmicus (HZO)
    • Occurs in 10% to 25% of patients with zoster
    • Visual impairment, ptosis, pain, facial scarring
    • Keratitis
      » Occurs in about two thirds of patients with HZO

• Cutaneous\textsuperscript{2}
  – Scarring, bacterial superinfection

• Visceral (rare)\textsuperscript{2}
  – Hepatitis, myocarditis, pericarditis, arthritis

Treatments for HZ and PHN

<table>
<thead>
<tr>
<th>HZ</th>
<th>PHN</th>
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| • Antiviral therapy\(^1\)  
  – Ideally antiviral therapy should begin within 72 hours of onset of symptoms | • Analgesics\(^1\)  
  – Non-narcotics  
  – Narcotics |
| • Analgesics\(^2\)  
  – Non-narcotics  
  – Narcotics | • Topical agents\(^1\)  
  • Anticonvulsants\(^1\)  
  • Consultation with a pain management specialist may be necessary\(^1\)  
  • Although PHN may resolve over time, some patients are refractory to all treatments\(^3\) |
| • Supportive care | |

Current strategies are only partially effective.\(^4\)

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Average annual estimates of reported shingles cases, treated cases, and ambulatory visits

Number in Millions

- Persons With Shingles Reports: 1.1
- Persons Treated for Shingles: 0.9
- Ambulatory Care Visits: 2.1

Clinical Presentations

Cases 1 and 2

About 1 in 3 persons will develop HZ.

The following are mock cases representing various phases and presentations of zoster.

Mock Case 1: Patient in Prodromal Phase of HZ

- A 63-year-old teacher with a 2-day history of tingling, unbearable itching, and pain on her left side complains of:
  - Headache, photophobia, and malaise

Mock Case 1: Patient in Prodromal Phase of HZ (cont)
Mock Case 1: Patient in Prodromal Phase of HZ (cont)

“I started having itching, pain, and tingling sensations on the left side of my chest. The itching lasted all day long. Even the creams and the medicines I took wouldn’t make the pain and itching go away. But pain and itching weren’t the only problems. I also had headaches and felt uncomfortable in general. On top of that, I was feeling sluggish and run down. It was awful. It was 2 days before the rash showed up.”
Mock Case 2: Patient in Acute Phase of HZ With Rash

- A 62-year-old manager with a 7-day history of pain, erythema, and clusters of clear vesicles
  - Unilateral, vesicular lesions not crossing the midline

Mock Case 2: Patient in Acute Phase of HZ With Rash (cont)

Dramatization
Mock Case 2: Patient in Acute Phase of HZ With Rash (cont)

“I was at work when I first felt the pain and itchiness on one side of my chest. At first, I thought it might have been bug bites. But as the days went on, I saw that I had blisters and a rash. I felt a constant sensation of tingling and pricking in my skin. At times, anything that touched my chest, even lightly, seemed to trigger excruciating pain. Nothing interested me. All I could focus on was the pain.”
Mock Case 2: Patient in Acute Phase of HZ With Rash (cont)

- A 62-year-old manager with a 7-day history of pain, erythema, and clusters of clear vesicles
  - Unilateral, vesicular lesions not crossing the midline
- Paresthesia and pain develop in affected regions
- The patient received antiviral treatment with limited effect, but pain subsided as the rash healed

Clinical Presentations

Cases 3 to 6

In a population-based study in adults ≥22 years of age:

- 10% of patients with HZ experienced nonpain complications\(^a\)
- 10% of patients with HZ experienced PHN\(^b\)

The following are mock cases representing various phases and presentations of zoster

\(^a\)Complications other than pain ≥30 days, such as ocular disease or motor neuropathies.
\(^b\)PHN defined as at least 90 days of documented pain.

Mock Case 3: Patient With PHN

- A 75-year-old retired woman with prior history of acute HZ, about 8 months before, complains of
  - Persistent pain\(^1\)
  - Persistent allodynia\(^2\) (pain at light touch) in affected regions

- Topical applications of lidocaine patches and other oral analgesics provide only a temporary, inconsistent relief\(^1\)

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Mock Case 4: Patient With Ophthalmic Zoster

- A 64-year-old architect comes for an office visit with vesicular lesions on the nose and forehead. He complains of severe unilateral pain on the right forehead.
- The concentration of lesions occurs in the region of the ophthalmic division of the trigeminal nerve.
- The eye involvement includes redness, pain, and decreased vision.

Mock Case 5: Patient With HZ Rash and Secondary Bacterial Infection

- A 75-year-old gardener presents with skin lesions that have been present for the past 7 days, scattered from his back around to his upper abdomen.
- The patient complains of having new onset fever with occasional chills.
- The skin lesions are itchy and painful, causing the patient to continuously scratch the area.
- On examination, the skin lesions are unilateral, not crossing the midline.
- The area around the lesions is inflamed and red.

Mock Case 6: Patient With Ramsay Hunt Syndrome\(^1\–^3\)

- A 62-year-old engineer presents with unilateral facial paralysis and rash on the right ear.
- On examination, the patient has erythematous swelling on the right ear canal and tender vesicles on the pinna—zoster oticus in the auditory canal and the pinna.
- The patient complains of pain, vertigo, and loss of hearing.
- There are also signs of facial paralysis characterized by widened palpebral fissure and decreased forehead wrinkling and smile on the right.

Need to Implement a Proactive Approach

• Current strategies are only partially effective for the therapeutic management of HZ and its complications
  
• Unmet needs
  – Fully effective treatment of HZ
  – Fully effective and sustained management of associated pain

• Morbidity due to HZ is substantial

• Proactive strategy
  – Focus on prevention of VZV reactivation through vaccination of patients at risk

ZOSTAVAX®
(Zoster Vaccine Live)
Indications and Usage

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SELECT SAFETY INFORMATION

ZOSTAVAX® (Zoster Vaccine Live) (cont)

• Transmission of vaccine virus may occur rarely between vaccinees and susceptible contacts.
• ZOSTAVAX is not indicated for prevention of primary varicella infection (chickenpox).
• Vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.
Benefits of ZOSTAVAX® (Zoster Vaccine Live) Against HZ

51% Reduction in Incidence of Zoster
(95% CI: 44%, 58%)

• Efficacy was evaluated in a placebo-controlled, double-blind clinical trial in which 38,546 subjects 60 years of age and older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276) and were monitored for the development of zoster for a median of 3.1 years (range 31 days to 4.9 years).
• Vaccine efficacy for the prevention of herpes zoster was highest for the subjects 60 to 69 years of age and declined with increasing age.

Benefits of ZOSTAVAX® (Zoster Vaccine Live) Against PHN Among Those Who Developed Zoster Postvaccination

39%* Reduction in Incidence of PHN Among Postvaccination Zoster Patients
(95% CI: 7%, 59%)

- Vaccine efficacy against PHN in subjects who developed zoster postvaccination was 55% in individuals 70–79 years of age; 5% (not significant) in individuals 60–69 years of age; and 26% (not significant) in individuals 80 years of age or older.
- Overall, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of herpes zoster.

*Age-adjusted estimate based on the age strata (60–69 and ≥70 years of age) at randomization.
Overview of Varicella-Zoster Virus (VZV) Identification Program (VZVIP)

**Description**
A collaborative program between Merck & Co., Inc., and Columbia University, New York, NY
Uses polymerase chain reaction (PCR) analysis to identify presence of wild-type VZV virus vs Oka/Merck vaccine VZV
Fulfills post-licensure regulatory commitments and assists in the post-marketing safety surveillance of the VZV-containing vaccines

**Eligibility**
Clinical specimens of interest for all VZV-containing vaccines [ie, VARIVAX® (Varicella Virus Vaccine Live), ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live), and ZOSTAVAX® (Zoster Vaccine Live)]:
- Herpes zoster (Shingles)
- All rashes (postvaccination and breakthrough varicella)
- Suspected secondary transmission
- Any serious adverse experience including but not limited to pneumonia, neurologic adverse experiences, death; also AEs involving inadvertent vaccination of immunocompromised patients
- Pregnant women who inadvertently receive a VZV-containing vaccine or who are exposed to a vaccinee, and who subsequently develop a varicella rash

Participation is voluntary. To report a case and obtain details about the VZVIP program, please contact the Merck National Service Center at 1-800-672-6372.

**Reporting of Results**
Merck sends letter reporting final PCR results to health care provider; may also call to discuss results in some cases
No charge to health care provider or patient
Advisory Committee on Immunization Practices (ACIP)

Current Guidelines
Selected ACIP Recommendations for Use of ZOSTAVAX® (Zoster Vaccine Live)

• Routine vaccination of all persons aged ≥60 years with 1 dose of zoster vaccine.
  – Vaccine should be offered at first available clinical encounter.
• Standing orders are a strategy to consider in connection with zoster vaccination.
• Routine vaccination for nursing home residents without contraindications should be considered in light of appropriate risk-benefit information.

Selected ACIP Recommendations for ZOSTAVAX® (Zoster Vaccine Live): Special Groups and Circumstances

- Persons anticipating immunosuppression
  - Vaccine given at least 14 days before initiation of immunosuppressive therapy, but 1-month wait may be advisable.
- Persons receiving antiviral medications
  - Discontinue medications at least 24 hours before administration of vaccine.
  - These medications should not be used for at least 14 days after zoster vaccine administration.
  - As stated in the Prescribing Information (PI) for ZOSTAVAX, concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.
- Persons on immunosuppressive therapy should not receive the vaccine for at least 1 month following discontinuation of such therapy.
- Persons with severe acute illness
  - Defer vaccination until recovery.
  - Vaccine can be administered to persons who have mild acute illness with or without fever.
  - In accordance with the PI for ZOSTAVAX, deferral of vaccination should be considered in acute illness, eg, in the presence of fever.

Good Adult Vaccination Practice: Zoster Vaccine

Strategies to promote zoster vaccination include:

- Linking delivery of zoster vaccine with other appropriate preventive-health interventions
- Standing orders
- Practice-based audits and/or physician reminder systems
- Vaccination for appropriate nursing home and long-term care residents without contraindications
- Vaccine documentation in patient’s medical records

Communicating Importance of Vaccination

Communicate effectively with patients

• Educate patients about the risks and benefits of vaccination.¹,²

• Vaccination rates may be improved by direct communication between providers and patients.²

• Vaccine recommendation by a health care provider is a key motivator for appropriate patients.¹

ACIP Recommendations for Adult Zoster Vaccination: Interactive Questions

Based on the ACIP recommendations, zoster vaccine

a) Should be offered to appropriate patients ≥60 years of age at first available clinical encounter

b) Should be given to nursing home residents without contraindications in light of appropriate risk-benefit information

c) Should be deferred in patients who have severe acute illness

d) All of the above
According to ACIP recommendations, strategies to promote zoster vaccine include:

- a) Linking delivery of zoster vaccine with other appropriate preventive health interventions
- b) Vaccination for appropriate nursing home and long-term care residents without contraindications
- c) Introducing standing orders to vaccinate appropriate patients
- d) All of the above
ACIP Recommendations for Adult Zoster Vaccination: Interactive Questions (cont)

**True or False**

According to ACIP recommendations, zoster vaccine can be administered to appropriate immunocompetent individuals anticipating initiation of immunosuppressive treatment if given a sufficient amount of time in advance of such therapy.
ACIP Recommendations for Adult Zoster Vaccination: Interactive Questions (cont)

True or False

According to ACIP recommendations, zoster vaccine can be administered to patients who are currently on antiviral medications.

As stated in the Prescribing Information for ZOSTAVAX, concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated.
Summary: Call to Action

- Incidence of HZ increases with age.\textsuperscript{1,2}
- About 1 in 3 persons will develop zoster during their lifetime.\textsuperscript{2}
- Unilateral, vesicular rash is a distinctive feature of zoster.\textsuperscript{2,3}
  - Symptoms may include altered sensitivity to touch, pain provoked by slight stimuli, and unbearable itching.\textsuperscript{2}
- Morbidity due to HZ can be substantial.\textsuperscript{2}
- Complications of zoster may be neurologic, ophthalmic, cutaneous, and, rarely, visceral.\textsuperscript{2}
  - The most common complication of zoster is PHN, which is a chronic, often severe and painful condition.
- Current strategies for zoster treatment and PHN pain management are only partially effective.\textsuperscript{3}
- ZOSTAVAX\textsuperscript{®} (Zoster Vaccine Live) is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older.
- ZOSTAVAX is not indicated for the treatment of zoster or PHN.

Summary: Call to Action (cont)

- Proactive strategy
  - Focus on prevention of VZV reactivation through vaccination of patients at risk.
- The ACIP recommends zoster vaccine for all appropriate persons ≥60 years of age who have no contraindications at first available clinical encounter.
- Vaccine recommendation by a health care provider is a key motivator for appropriate patients.
- Strategies to improve rate of zoster vaccination include:
  - Linking delivery of zoster vaccine with other appropriate preventive-health interventions;
  - Use of standing orders to vaccinate appropriate patients;
  - Vaccination for nursing home and long-term care residents without contraindications should be considered in light of appropriate risk-benefit information.

Before administering ZOSTAVAX® (Zoster Vaccine Live), please read the Prescribing Information and Patient Product Information available at this presentation.

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