Dilemmas in Zoster Eye Disease

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HZO DILEMMAS...WHAT’S NEW?

- **Clinical Presentation:** Zoster Sine Herpete may be more common
- **Changing Epidemiology:** increasing incidence; decreasing age of onset
- **New Risk Factors:** family history; heart failure; TBI; DM; asthma; acute kidney disease; statin use
- **Complications:** VZV trigger for GCA?; stroke, heart disease, peripheral artery disease
- **Treatment Dilemmas:** chronic/recurrent; Zoster Eye Disease Study (ZEDS)
- **Prevention:** Debate over timing of live vaccine; new (non-live) vaccine available; gabapentin to prevent PHN
HZO CLINICAL PRESENTATION

- Reactivation of latent VZV acquired from chicken pox or vaccination

- Unilateral, vesicular rash, follows trigeminal dermatome
  - 74% prodrome with mod/severe stabbing pain

- Sine Herpete – dermatomal pain without rash
  - Diagnosis easily missed
  - Severe uveitis
  - DDx GCA important
62 YO CAUCASIAN FEMALE

- Right side scalp and forehead pain, photophobia, decreased vision x 2 days; first occurrence
- No jaw claudication, neck pain, weight loss, polymyalgia rheumatic, TVL, + malaise
- 20/40 PH 20/25 OD; 20/20 OS
- IOP 12 mmHg OD; 18 mmHg OS
- Slit lamp: 4+ cell; 2+ flare OD; quiet OS
- DFE normal OU
- Start topical prednisolone acetate 1% Q 1hr OD (shake well); homatropine BID OS
  - Sent for urgent ESR/CRP/platelet count – normal
  - Rash developed 2 days later – PO valacyclovir 1g TID x 7
HZO CLINICAL PRESENTATION

- HZO with or without eye involvement
- Can affect all ocular structures
- Hutchinson sign (nasociliary branch involvement) – high likelihood eye involvement
- In acute disease – can take up to 1 month for keratitis to occur
EPIDEMIOLOGY OF ZOSTER

- 1,200,000 new zoster cases per year in U.S.
  - ~20% HZO
- 95-99% > age 40 in U.S. seropositive for VZV
- 1 in 3 develop zoster; 1 in 2 > age 85
- 90% are NOT immunocompromised, but more common (~2X) and severe if immunocompromised
- Increasing incidence
- Decreasing age of onset
  - Highest number of cases in 50’s
ZOSTER IN CHILDREN

- Rare
- PHN rare
- Most cases in immunosuppressed or healthy children exposed to VZV in utero
- Most resolve without ocular sequelae
- VZV vaccinated children at lower risk for HZ
  - Chicken pox vaccination (Varivax®, Merck) program began 1995 in US
INCREASING INCIDENCE

- Veterans population
- Increase in U.S. people > age 40, with sharper increase > age 50

Age-specific rate of unique zoster cases (national data, by year)

INCREASING INCIDENCE

- Olmstead County, MN, 59% women
- >4-fold increase in all age groups
- Increase steady before and after varicella vaccination program

WHY INCREASE IN INCIDENCE?

- **Unknown**
- **Past hypotheses:**
  - Increased aging population
  - Use of varicella vaccination (1995) may lead to fewer “booster exposures”
  - Increase in zoster rate > rate of aging population, began before vaccination program initiated
  - Increased incidence in North America, Europe, Australia and Asia Pacific comparable to U.S., and started before vaccination programs
  - VZV (chicken pox) vaccine not widespread in Europe, yet zoster rates are similar to U.S.

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Increased Rates of Zoster Worldwide

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Cohen E. Herpes Zoster and the Zoster Eye Disease Study (ZEDS) [https://med.nyu.edu/research/zoster-eye-disease-study/physicians](https://med.nyu.edu/research/zoster-eye-disease-study/physicians)
Also supports decreasing age of onset

913 patients with HZO at Massachusetts Eye & Ear Infirmary

Significant age decrease from 61.2 years in 2007 to 55.8 years in 2013 (p=0.0119)

RISK FACTORS FOR REACTIVATION

- Declining cell-mediated immunity
  - Aging
  - Immune deficiency or suppression
- Female
- Family history (3X)
- Depression (4X)

- Stress (3X)
- Heart failure (2X)
- TBI (3X)
- DM, asthma, acute kidney disease, autoimmune disease
- Statin use (dose dependent)
Comlications: Ocular

- 20% develop serious eye disease
  - Corneal or eyelid scarring
  - Neurotrophic keratitis
  - Uveitis
  - Secondary glaucoma
  - Necrotizing retinal disease
High VZV antigen rates (74%) in temporal artery biopsies from giant cell + GCA patients compared to normal (8%)
- Artery adventitia > media > intima
- “VZV Vasculopathy” of temporal artery
- Suggest anti-viral treatment (4-12 weeks) in addition to steroids
VZV AND GIANT CELL ARTERITIS CONTROVERSY

- Conflicting Data: other studies unable to replicate or show clear correlation
- Overlap in histopathology/clinical signs suggest association but not necessarily causation
- Standard use anti-viral in GCA unproven treatment option – needs further study

England BR. Arthritis Rheumatol 2017;69:2351-2358
Ing EB. Clin Ophthalmol 2018;12:113-118
COMPLICATIONS: SYSTEMIC

- Post-herpetic neuralgia (PHN)
- Stroke
  - 2-4x increased risk after HZO vs. HZ
  - Increased risk especially in younger patients
  - Chronic, active VZV in cerebral arteries
- Heart Disease
  - Increased risk for MI < age 40
  - Increased risk for arrhythmia and coronary artery disease (mean age 46)
- Peripheral artery disease
POSTHERPETIC NEURALGIA

- Pain persisting 3 months after onset
- Most common complication; Risk for major depression
- Most common cause suicide from pain in people age 70+
- PHN risk factors
  - Older age, severity of acute pain, rash, HZO
- Occurs in ~30% HZO with eye involvement; mostly older age (65+)
POSTHERPETIC NEURALGIA

Pain-Diverse Symptoms
- Paresthesia
- Dysesthesia
- Hyperalgesia
- Alloodynia
- Damage to CNS and PNS

Pharmacological Treatments
- Lidocaine 5% patch 3 patches daily
- pregabalin (Lyrica®) 300-600mg TID
- gabapentin (Neurontin®) 150-300mg 2 or 3 divided doses
- amitriptyline 10-25 mg QD starting dose increased to 75-150mg per day
- Opioids or tramadol third+ line
Mallorca, Spain

134 patients, age 50+ with HZ, rash onset within 72 hrs, 4/10 pain

Determine efficacy and optimal dose gabapentin + valacyclovir + prn analgesics to prevent PHN

Prior studies show contradictory results
82 YO FEMALE WITH HZO

Severe (10/10) pain x 3 days; 20/30 OD, 20/20 OS; IOP/DFE Normal
Start Valacyclovir 1,000 mg TID x 10 days; artificial tears; referral to primary provider for pain management
2 WEEK FOLLOW UP

(initial presentation)

pregabalin (Lyrica®) for pain – although remains at 7/10
No ocular recurrences

For three years could not touch hair or face

Pain remained steady at 6/10 despite pregabalin; gabapentin; lidocaine patch; acupuncture; opioid therapy

Slept most of day (per son)
TREATMENT DILEMMAS
TREATMENT HZO

- Acutely: PO antivirals, ideally within 72 hours of rash onset
  - valacyclovir 1000 mg 3 x daily x 7-10 days
  - famciclovir 500 mg 3 x daily 7-10 days
  - acyclovir 800 mg 5 x daily x 7-10 days
    - Immunocompromised IV 15-20 mg/kg per day up to 30 mg/kg per day if disseminated
  - Very safe; may need renal dosing in renal disease
- Decreases risk chronic eye disease from 50% → 30%
- Does not reduce risk for PHN
- No standard treatment approach for HZO complications
58YO FEMALE WITH HZO AND RENAL DISEASE

- Tearing, rash x 1 day; first occurrence
- 20/20 OD, OS
- IOP: 14 mmHg OD 15mmHg OS
- DFE: normal OU
- Contacted nephrologist
  - Creatinine clearance 20 mL/min
  - Valacyclovir 1,000 mg q 24 hrs x 7 days (renal dosing)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal Dose</th>
<th>Creatinine Clearance 30-49 mL/min</th>
<th>Creatinine Clearance 10-29 mL/min</th>
<th>Creatinine Clearance &lt; 10 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valacyclovir</td>
<td>1,000 mg q 8hrs</td>
<td>1,000 mg q 12 hrs</td>
<td>1,000 mg q 24 hrs</td>
<td>500 mg q 24 hrs</td>
</tr>
<tr>
<td>Famiciclovir</td>
<td>Normal Dose</td>
<td>Creatinine Clearance 40-59 mL/min</td>
<td>Creatinine Clearance 20-39 mL/min</td>
<td>Creatinine Clearance &lt; 20 mL/min</td>
</tr>
<tr>
<td>Famiciclovir</td>
<td>500 mg q 8 hrs</td>
<td>500 mg q 12 hrs</td>
<td>500 mg q 24 hrs</td>
<td>250 mg q 24 hrs</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Normal Dose</td>
<td>Creatinine Clearance 10-25 mL/min</td>
<td>Creatinine Clearance 0-10 mL/min</td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>800 mg 5 x daily</td>
<td>800 mg q 8 hrs</td>
<td>800 mg q 12 hrs</td>
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8 MONTHS LATER…

- HZ epithelial pseudo-dendrites
  - No standard treatment
  - Can be persistent and/or recur months to years later
  - VZV+ with PCR analysis
  - PO antiviral, topical trifluridine, and topical steroids varying success
  - Topical ganciclovir 0.15% gel (Zirgan®) 5 x day until resolved then 2-3 x day for 1 wk – 2 months (tailor based on dz activity) successful in recurrent or persistent cases
RECURRENT AND CHRONIC HZO

- Exact rates unknown – some studies as high as 51% (tertiary uveitis clinic)
  - Risk factors for recurrence: uveitis, ocular hypertension, chronic disease, immunosuppression, females, older age, absence of zoster vaccination
- Due to chronic, active infection and/or immune response
  - Chronic epithelial keratitis PCR+ for VZV
  - Chronic iritis anterior chamber is PCR+ for VZV
  - Anti-viral and steroids useful
    - Steroid use to tx ocular inflammation - often require prolonged treatment; have rebound inflammation and require long, slow taper
RECURRENT AND CHRONIC HZO

- No evidence based guidelines supporting suppressive, PO anti-viral treatment in chronic/recurrent disease
- 2010 Survey 100 corneal specialists
  - 30% used prolonged treatment with antiviral
**ZOSTER EYE DISEASE STUDY (ZEDS)**

- NEI funded, randomized, placebo controlled trial
- First patient enrolled October 2017
- 60 sites
- 1,050 adult, immunocompetent, past HZO with typical rash; epi, stromal, endothelial keratitis and/or iritis within one year prior to enrollment
- Enroll over 3 years; complete in 5 years
- Similar design as HEDS Acyclovir Prevention Trial
- 1 year 1000 mg daily valacyclovir vs. placebo follow-up every 3 months for 18 months

(Coordinating center: NYU Langone Health)

https://med.nyu.edu/research/zoster-eye-disease-study/physicians
ZEDS

Primary Endpoint
- Determine if suppressive valacyclovir, compared to placebo, will delay time to new or worsening disease
  - Epithelial keratitis
  - Stromal keratitis without ulceration
  - Endothelial keratitis
  - Iritis
  - Stromal keratitis with ulceration

Secondary Endpoints
- Determine if suppression persists 6 months after discontinuing treatment
- Determine if suppression reduces incidence, severity, and/or duration of PHN

https://med.nyu.edu/research/zoster-eye-disease-study/physicians
Zoster Eye Disease Study

Participants Screened | Participants Enrolled/Randomized
---|---
135 | 95

As of October-12-2018

Countdown To End of Enrollment

438d 2h 44m 41s
PREVENTION

ZOSTER VACCINES
ZOSTER VACCINES

- Live Zoster Vaccine (ZVL; Zostavax®, Merck)
  - FDA approved for immunocompetent age 50+ since 2011 (age 60+ since 2006)
  - CDC recommended for immunocompetent age 60+ since 2008
  - 1 dose

- Recombinant Zoster Vaccine (RZV; Shingrix®, GlaxoSmithKline)
  - FDA approved October 2017 for age 50+
  - CDC recommended for immunocompetent age 50+
  - 2 doses; 2-6 months apart
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Shingrix (recombinant zoster vaccine [RZV], GlaxoSmithKline [GSK])</th>
<th>Zostavax (zoster vaccine live [ZVL], Merck)</th>
</tr>
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<tbody>
<tr>
<td><strong>Vaccine Type</strong></td>
<td>Inactivated recombinant, adjuvanted (non-live)</td>
<td>Live attenuated</td>
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</tbody>
</table>
| **Vaccine Composition**| Supplied as 2 components:  
1. lyophilized glycoprotein E antigen  
2. AS01B adjuvant suspension                                                                 | Supplied as 2 components:  
1. lyophilized vaccine  
2. sterile water diluent                                                                 |
| **Storage**            | • Refrigerate both the vaccine and diluent at +36° to +46°F (2° to 8°C)  
• DO NOT FREEZE. Do not use if frozen                                                                 | • Freeze the vaccine at -58°F to -5°F (-50°C to -15°C)  
• Store diluent separately at room temperature (no warmer than +77° (25° C), or in the refrigerator at +38°F to 46°F (2° C to 8°C) |
| **Preparation**        | • Reconstitute the vaccine with the diluent supplied by the manufacturer  
• Administer immediately after reconstitution or refrigerate and use within 6 hours  
• Discard reconstituted vaccine if not used within 6 hours | • Upon removal of vaccine from the freezer, reconstitute the vaccine with the diluent supplied by the manufacturer  
• Administer immediately after reconstitution  
• Discard reconstituted vaccine if not used within 30 minutes |
| **Administration**     | • Intramuscular (IM) injection into the deltoid region of the upper arm, with a 1- to 1.5-inch needle                         | • Subcutaneous (SQ) injection into the upper outer triceps area, with a 5/8" needle  |
| **Dosage**             | 2-dose series, spaced 2 to 6 months apart  
0.5ml/dose  
Arrange appointment/remind patient of second dose | Single dose  
0.65ml/dose |
| **Recommended groups** | • 50 years and older, immunocompetent adults  
Those who previously had shingles or got Zostavax  
Shingrix is the preferred shingles vaccine | • 60 years and older, immunocompetent adults  
Those who previously had shingles  
May be used, for example, if a person prefers Zostavax or requests immediate vaccination and Shingrix is unavailable |

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/faqs.html
The CDC states SHINGRIX is:

- Recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years

- Recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL)

- Preferred over ZVL for the prevention of herpes zoster and related complications
SHINGLES PREVENTION STUDY

- Randomized, placebo controlled trial
- 1998-2004 (3 yrs follow up)
- 38,546 immunocompetent adults
- 51% decreased incidence of HZ with Zostavax®
  - Varied by age: 63% age 60-69 vs. 37% age 70+
  - Effect on disease severity greater in age 70+
  - 71% age 50-59
  - Schmader Clinical Infectious Diseases 2012;54(7):922-928
- 66% decrease post-herpetic neuralgia

Oxman et al. NEJM 2005;352(22):2271-2285
SHINGRIX® CLINICAL TRIALS

- Two-part, phase III randomized, placebo controlled clinical trials
  - ZOE-50 and ZOE-70
- 29,305 immunocompetent adults
- 97% decreased incidence HZ age 50-59
  - 91% decrease in PHN
- 97% decreased incidence HZ age 60-69
  - 91% decrease in PHN
- 90% decrease incidence HZ age 70+
  - 90% decrease in PHN

**DURATION OF EFFICACY**

- Zostavax® protection wanes after 8 years
  - Case-control study 180,000 age 60+ immunocompetent adults
  - Yr 1: 69%  Yr 3-6: 33%  Yr 8: 4%
  - Morrison Clin Infect Dis 2015;60:900-909
- Need for booster vaccination is unclear
- Questions surround timing of vaccination
  - Currently no data for age 50-59
  - Younger age group may have longer duration of efficacy compared to older age groups
  - Li et al. Vaccine 2015;33(12):1499-1505
- Shingrix® efficacy 84% at 4 years, but past 4 years uncertain (currently under study)
ZOSTAVAX (ZVL) VACCINE CONTRAINDICATIONS

- Not given during acute episode of HZ
- Immuno-compromise
  - AIDS, leukemia, lymphoma, CA of bone marrow or lymphatic system, stem cell transplant
  - Immunosuppressive treatment
    - Prednisone > 20 mg/day x 2+ weeks; wait 1 month after discontinuing
    - Chemotherapy; wait 3 months after discontinuing
    - Immune modulation therapy (e.g. antitumor necrosis factor drugs); wait 1 month after discontinuing
- Anaphylactic reaction to gelatin, neomycin
- Pregnancy and breastfeeding
- Must be off anti-viral 1 day before and 2 weeks after

2. Cohen E. Herpes Zoster and the Zoster Eye Disease Study (ZEDS) https://med.nyu.edu/research/zoster-eye-disease-study/physicians
SHINGRIX VACCINE CONTRAINDICATIONS

- Allergic to component of vaccine
- VZV negative (get Varivax instead)
- May not be as effective if immunosuppressed
- CDC no recommendation for immunocompromised because excluded from studies
- Pregnancy/breast feeding: no recommendation
SHINGRIX AND IMMUNOCOMPROMISED

- ZOE-HSCT
  - Phase III randomized, placebo controlled trial
  - 1,721 immunocompromised (stem cell transplant 50-70 days prior) adults (age 18+)
    - < age 50
      - 71% efficacy
    - 50+
      - 67% efficacy

BARRIERS TO VACCINATION

- Cost
  - ~$175 Shingrix® (total for 2-dose series)
  - ~$200-250 Zostavax®

- Complex insurance coverage and reimbursement

- Production problems
  - Zostavax® (resolved in 2011)

- Lack of recommendation by physicians

https://www.cdc.gov/mmwr/volumes/66/ss/ss6611a1.htm
SUPPLY UPDATE

The accelerated adoption of SHINGRIX has led to an unprecedented level of demand.

Healthcare professionals have adopted SHINGRIX and are now vaccinating against shingles at a much higher rate than in previous years.

GSK projects to bring significantly more doses of SHINGRIX into the market in the second half of the year than in the first half of the year.

GSK expects to consistently release doses of SHINGRIX into the market every 2-3 weeks to provide a more predictable and reliable supply experience. As healthcare professionals are vaccinating with SHINGRIX at an unprecedented rate, ordering limits and allocations should still be expected and individual customer resupply experiences will vary.

While demand still exceeds supply, the increased and consistent supply should provide reassurance that patients will have an opportunity to complete the 2-dose series within the 2-6 month dosing window.

- The CDC has guidance on the 2-dose window for SHINGRIX—click here for full dosing information.

There have been no manufacturing issues and we are reaching all of our production goals.

Thank you again for your partnership and commitment to protecting appropriate patients from shingles. Please do not hesitate to contact GSK with any further questions. You may reach us at 1-800-772-9292 or contact your GSK Vaccines Representative today.
Recurrence of HZO post-vaccination

- Case-reports HZO recurrence 2-6 weeks post-vaccination (Zostavax®)
  - HZ kerato-uveitis with corneal perforation 2 weeks post-vaccination
  - HZ endothelitis (1 case); stromal keratitis (1 case) 3-5 weeks post-vaccination
    - Cohen E. Cornea 2015;34(10)S3-8
  - HZ acute retinal necrosis (2 cases) 6 days and 2 months respectively, post-vaccination
    - Immuno-suppressed patient post-renal transplant (vaccine contraindicated)
    - Other patient had end-stage renal disease (has been associated with lymphoid immune dysfunction)
    - Cohen E. Cornea 2015;34(10)S3-8

Zoster vaccine considered safe and immunocompetent adults age 50+ should receive vaccine even with history of HZO
Patients with h/o HZO should have an eye exam within several weeks before and after vaccination against herpes zoster, and adverse events should be reported.
Retrospective, cohort study

- 72,141 vaccinated (cohort 1) vs. 133,604 unvaccinated (cohort 2)
- Recurrent HZO: 2679 vaccinated (cohort 3) vs. 9421 unvaccinated (cohort 4)
- Did not find live vaccine being linked to recurrence of anterior-segment HZO
HZO AND VACCINE TIMING

- Wait unspecified amount of time after resolution of disease
- Wait until eruptions, acute and recurrent events resolved; chronic dz stable
- Report Vaccine Adverse Events to:
  Vaccine Adverse Events Reporting System (VAERS)
    - 1-800-822-7976
    - https://vaers.hhs.gov/
CONCLUSIONS

- More patients/younger age affect by potentially chronic disease
- Some patients may need prolonged course of treatment
- Discuss Zoster Vaccination with patients age 50 and older