Updates in the Treatment and Prevention of Herpes Zoster and Postherpetic Neuralgia

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Burden of Illness

Have you ever been grabbed by a burning demon in your face? I have. It's called "Shingles". Shingles is a disease that strikes more than a half-million Americans every year.

It took three days of blinding pain for someone in the medical profession to recognize what I had.

Quote Rosemary Appleton zoster patient who developed post herpetic neuralgia
Childhood Immunization

- Varicella zoster immunization occurs in children – long term protection unknown
- Adults have been administered 2 doses the VZV vaccine post household exposure with a 70% efficacy
- Risk of developing herpes zoster after disease vs. vaccination unknown
Herpes Zoster (HZ)

- Painful or itching rash that is on one side of body or face with dermatomal distribution
VZV BECOMES LATENT IN THE NERVE GANGLIA

CHICKEN POX

REACTIVATES YEARS LATER

SHINGLES
HZ risk

- Seropositive for VZV
- Advancing age
  - 2.5 per 1,000 ages 20-50
  - Double
    - 5 per 1,000 ages 50-60
  - Double
    - 10 per 1,000 ages over 65
HZ risk

Also due to:
- Immune compromise
- Stress
- Major depression
Role of Immunity

- Normal/adequate anti-varicella zoster virus antibodies are present – not antibody mediated immunity
- Cell-mediated immunity
Life-span VZV immunity

- Pre VZV exposure
- Initial VZV exposure
- Aging
- Vulnerability

- Cell mediated immunity
- Antibody levels
- Viral latency
Viral presence at dermal/epidermal layer
sprojects.mmi.mcgill.ca/dermatology/vesicle5.jpg
Ascent up sensory nerves to sensory ganglion
www.merck.co.za/.../images/962_herpes_zoster.jpg
DERMATOMES
Herpes Zoster

- Reactivation of dormant varicella zoster virus
- 2-3 out of 10 people in the USA will develop herpes zoster in their lifetime
- More than 1 million people each year
Herpes Zoster

Herpes Zoster: Clinical Course or Natural History

Prodrome

Acute Illness

Vesicles

Ulcus Crust

Reepithelialization

Long-Term Complications

Patients (%)

0

50

100

Zoster Rash and Acute Pain

Time After Onset

PHN

PHN=postherpetic neuralgia.
Adapted from Hope-Simpson RE. Geriatrics. 1967;22:151-159.
Prodrome

- Headache
- Photophobia
- Malaise
- Dermatomal pain and itching can happen weeks before rash
- Viremia likely cause
Rash

- Red
- Maculopapular
- Unilateral
- Dermatomal
- Typically T3-L4

Rash phase is contagious through direct contact (15% household transmission rate)
Healing

- 2-4 weeks with frequent scarring/pigment changes
- Resolution of pain/discomfort in most cases
Complication

- Significant prodrome
- Severe pain
- Severe rash
Complications

- Postherpetic Neuralgia (PHN)
- 17% pain 3 months after crusting occurs
- 5% pain 6 months after crusting occurs
- Each year age increment increases risk to PHN by 9%
Postherpetic Neuralgia (PHN)

Inflammatory infiltrate around dying neurons
PHN

Quality of life impact equal or greater than impact of
- Diabetes
- Heart failure
- Heart attack
- Depression
PHN

- Drug dependency
- Depression
- Suicide

Assess patients for ADLs and psychologic comorbidities
Not your grandkids vaccine!

- Live attenuated virus
- Oka/Merck
The Varicella Zoster Vaccine

Study design

- Randomized, double-blinded, placebo-controlled
- Large 38,546 subjects 60 years of age or older
- Cases of herpes zoster were diagnosed by both clinical and laboratory criteria
- Pain and discomfort measured repeatedly
- More than 95% of subjects completed 3.12 year median surveillance
End Point 1

Burden of Illness (BOI) due to Herpes Zoster

- BOI Defined as
  
  “Incidence, severity and duration of associated pain and discomfort”
End Point 2

Incidence of postherpetic neuralgia (PHN)
Diagnosis

- Clinically “suspected cases of herpes zoster”
  - Unilateral rash with no alternative diagnosis

- Confirmed/not confirmed by PCR, culture or clinical diagnosis by 5 physician evaluation committee
Incidence

- 957 confirmed cases of zoster
- 642 among placebo recipients
- 315 among vaccine recipients

Reduced incidence of herpes zoster by 51.3% (P<0.001)
Endpoint 1 – Burden Of Illness

Zoster Brief Pain Inventory area under curve against time for 182 days after rash occurs

Subjects with poorer initial health status experienced worse BOI

Zoster vaccine reduced BOI by 61.1% (P<0.001)
End point 2 - PHN

- Neuropathic pain syndrome persisting after the dermatomal rash has healed
  - Frequency and severity of PHN increases with increasing age

**PHN incidence was reduced by 66.5%**

\( P < 0.001 \)
Result Summary

- Immunized individuals greater than 60 developed herpes zoster half as often
- Immunized individuals experience 60% less pain, severity and duration
- Immunized individuals develop PHN 1/3 as frequently and have milder cases
Adverse Effects

42 days following vaccine
- 7 confirmed cases of HZ in immunized patient and 24 in the placebo group
- Site reaction was greater in the immunized group (pain, pruritis, swelling)
- Severe events
  - Immunized – 1 case of AE asthma, 1 case PMR
  - Placebo – 1 case anaphalactoid reaction (ate peanuts), 1 case PMR, 1 case Goodpasture Syndrome
Treatment

Antivirals

Subjects diagnosed with herpes zoster received famciclovir and pain management.

- Given shortly after initial occurrence, antivirals may reduce severity and duration of herpes zoster outbreak.
- Does not reduce frequency of PHN.
- May reduce duration of PHN.
Treatment

- Steroid plus antiviral
  - Added steroid may reduce pain and inflammation
  - No reduction in PHN
  - Not instead of antiviral
Pain Management

- Neurontin
- Pregabalin
- Lidocaine patches
- Tricyclic Antidepressants
- Narcotics
- Nerve Blocks - not yet indicated
- Combination therapy likely to be needed
Main Points

- VZV vaccine is highly effective in adults aged 60 or greater
- VZV vaccine appears safe
- A single vaccination at age 60 appears adequate to boost cell-mediated immunity for a typical lifespan
Main Points

- Early and accurate diagnosis of herpes zoster allows for intervention

- Antiviral therapy within first 72 hours may reduce duration and severity of PHN

- Management techniques for HZ and PHN must be individualized and comprehensive
Resources

NEJM, Volume 352;2271-84, June 2005, Oxman, Levin, et.al

www.aapa.org.member, MedCases 2004

Current treatment and future strategies, 2006, M. Levin

www.famvir.com/hcp/about/zoster
Shingles & the eye: 3 cases
herpes zoster ophthalmicus, HZO
Case 1

Age 70y, female
Burning around left forehead
2 days later vesicles left forehead, more painful
Eye dept contacted for advice
Systemic famvir 7days 500mg tid
(could have used high dose oral acyclovir)
Checked in eye dept 3 weeks later, vesicles going, pain going, eye quiet
Case 1 cont.
Case 2

- Age 65y, male
- On systemic steroids for asthma
- Burning around left forehead
- 2 days later vesicles left forehead, more painful
- Eye dept contacted for advice
- Systemic famvir 7days 500mg tid
- Start immediately...the earlier the better
- Checked in eye dept 3 weeks later, vesicles still present, painful, eye quiet
- 3 months later, uveitis, neuralgia++
Case 2 cont

(a different patient)
Case 2 cont

Anyone immuno-suppressed, intravenous acyclovir (check renal function) for first week, oral maximum dose 1 week..give immediately diagnosis made, the earlier the better

If very ill with a severe attack of HZO, treat similarly.
Case 3

- Age 80y, male
- Cannot close left eye
- Deaf left ear (when asked)
- Vesicles left ear
- Treatment for HZ
- Treat corneal exposure
- Long term corneal problems, (although improved a lot)
HZO, herpes zoster ophthalmicus

Attacks
- Older people
- If immuno-suppressed MUCH more severe

Begins
- Burning forehead
- Neuralgia-like pain (burning pain), intensity fluctuates
- Days later.....Rash
The prodromal phase of HZO includes an influenza-like illness with fatigue, malaise, and low-grade fever that lasts up to one week before the rash over the forehead appears. About 60 percent of patients have varying degrees of dermatomal pain in the distribution of the ophthalmic nerve.

Erythematous macules appear along the involved dermatome, rapidly progressing over several days to papules and vesicles containing clear serous fluid and, later, pustules. These lesions rupture and typically crust over, requiring several weeks to heal completely.”
HZO: guide, mild attacks

- contact/recurrence
- vague illness
- Neuralgia (dermatome)

Nose NOT affected
...gets better, eye spared

Crusts over

vesicular rash (dermatome)

Skin may develop cellulitis
...bacterial...antibiotics

Neuralgia and parasthesia settle over 1 year
HZO: guide, severe attacks with eye affected

Nose affected
...ocular inflammation
(this is debated)

Scleritis
...may continue for a year

Uveitis,
3 weeks after onset

Needs topical steroids, cycloplegics, treat glaucoma
HZO: guide, severe attacks cont.

- acute retinal necrosis or retinitis
- Can get any ocular pathology without the rash
- Diagnosed by anterior chamber paracentesis and PCR analysis
- Particularly in HIV patients
- Differentiate from CMV retinitis

Symptoms: blurred vision and/or pain in one/both eyes. Need to dilate pupils to look
HZO: very severe attacks

Severe skin lesions, nasty cellulitis

CVA, hemiplegia, Cranial nerve problems (Tolosa Hunt Syndrome), may cross dermatome, many other problems
HZO, post herpetic neuralgia

- Prevent many by prompt treatment with antivirals, safe, well tolerated
- Analgesics, often not very effective,
- Tricyclics may help, but may not be effective
- Gabapentin is now recommended by many experts
- Expert pain advice helpful...pain can be very **severe**
- Pain, burning, parasthesia/numbness,
- Episodic, disturbs sleep
- Lots of support needed/treat depression etc
HZO: treatment summary

Symptoms of parasthesia in ophthalmic dermatome

Treat (even if uncertain), Eg famvir or high dose acyclovir (intravenous if ill)

Eye: if white & quiet & good sight may get uveitis ~3 weeks
? Tip of nose affected

Treat other problems (secondary infection, systemic illness etc)

• Ramsey Hunt…corneal exposure
• Scleritis
• retinitis if HIV+ve
• Secondary glaucoma
• CVA, cranial nerve palsy

Long term:
• Post-herpetic neuralgia
• Continued ocular inflammation
Ramsey Hunt syndrome: One patient's story

My life changed forever when I suddenly became ill with severe ear pain and flu-like symptoms in October 1992. I was always healthy up to this time. I went to bed