

St. Anthony's Fire: **Herpes Zoster in Older Adults and Implications for Vaccination**

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Clinical Case

- 65 y/o elderly male living in assisted living with his wife
- Known history of multiple strokes and coronary vascular disease
- Calls his primary doctor with severe chest pain and is referred to the ER for possible “angina”

Clinical Case

- Patient describes pain as burning across left chest – different from prior cardiac chest pain
- In the ER EKG is stable
- Pain not improved with nitroglycerin
- Cardiac work up is negative, but admitted for observation to cardiology service

Clinical Case

- Continued pain overnight
- Nurse notes new rash in the morning
- *“It’s weird.....it is only on one half of his body”*



Herpes Zoster of the Left Chest

Image from hardinmd.lib.uiowa

Introduction to Herpes Zoster

- Pathophysiology
- Epidemiology
- Clinical Manifestations
- Laboratory diagnostics
- Treatment
- Prevention

Historical

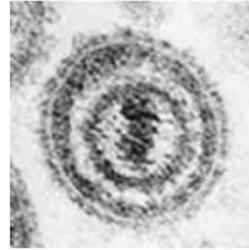
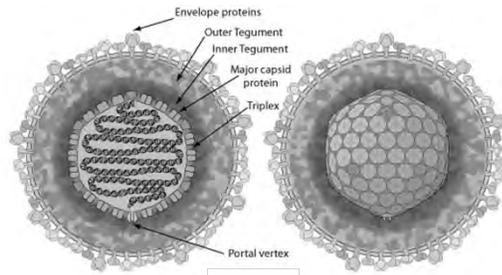
- **St. Anthony's Fire**
- ***Hezam innar*** ("belt of fire") in Arabic
- ***Baoisayaa daga*** ("big rash") in Hindi
- ***Helvetesild*** ("Hell's fire") in Norwegian
- ***Culebrilla*** ("Small viper [snake]") in Spanish

Isenheim Altarpiece



From Yawn Neurology 2013 and Gaillat CID 2011

Varicella Zoster Virus



EM image of VZV

- Alpha herpesvirus family
- Double stranded DNA virus
- Lipid envelope fuses to human cells during infection
- Only infects humans and causes **Chicken pox** and **Herpes Zoster**

Primary VZV Infection

- Exposure to virus by close personal contact will lead to disease in patient without prior history of VZV infection
- Route of infection is primarily by the respiratory route, but can also occur through direct contact with lesions
- After mucosal contact, the virus replicates and spreads to regional lymph nodes, resulting in a **primary viremic phase**.
- On days 4 to 6, the infection spreads to the liver, the spleen, and other cells within the reticuloendothelial system.
- **A secondary viremic phase** occurs at about day 9, with mononuclear cells transporting the virus to the skin and mucous membranes, causing the classic vesicular rash of primary disease - "**Chicken-pox**"

1. Sawyer J Infect Dis. 1994
2. Arvin Clin Microbiol Rev. 1996.
3. Sawyer J Infect Dis. 1992

Primary VZV Infection

- The **incubation period is typically 14 days.**
- The virus is detectable in the nasopharynx 1 to 2 days before the onset of the rash, and **patients are infectious prior to demonstrating classic rash of Chickenpox.**¹
- **Patients with primary disease are Highly contagious**
- Patients remain infectious for at least 5 days and until all lesions have crusted over.
- Patients who are immunocompromised may shed the virus for longer periods of time than normal hosts

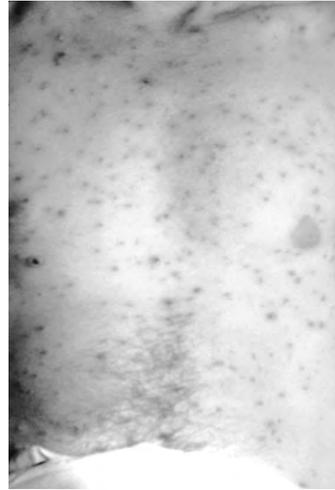


1. Sawyer J Infect Dis. 1992

Varicella Vaccination

- Varicella zoster virus (VZV) vaccines are recommended for all children in the US for prevention of varicella
- Live virus vaccine (Oka Strain)
- Given to healthy children at 12-15 months and the second at 4-6 years
 - 80-85% effective following first dose, ~95% with second
- Shown to be effective in preventing major varicella complications
- Can be given safely to adults who have no documented evidence of prior exposure to VZV

Chicken Pox (Varicella)



Chicken Pox (Varicella)



“Dew drop on a rose petal”

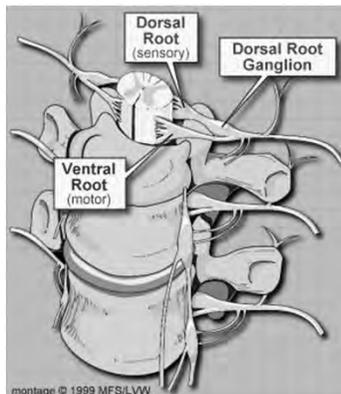


Photo Courtesy of CDC - Dr. K.L. Hermann

Chickenpox (Varicella)

- Generally a benign, self limiting disease in young children
- Fewer than ~ 50 deaths a year due to disease in children in the US (declining with vaccination)
- Rare complications in children:
 - Group A strep skin infections (e.g. Necrotizing fasciitis)
 - Invasive disease (e.g. pneumonia, encephalitis)

Following Primary Disease



- Develop VZV antibodies (humoral)
- Cell mediated immune responses to VZV (CD4 and CD8 effector and memory T-cells)
- VZV becomes latent in the dorsal root ganglia of the spinal cord (neurotropic)
- Multiple “mini” episodes of reactivation throughout life that are localized and do not lead to complications

montage © 1999 MFS/LWW

1. Cohrs J Med Virol 2008

Following Primary Disease



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- VZV becomes latent in the dorsal root ganglia of the spinal cord (neurotropic)
- Multiple “mini” episodes of reactivation throughout life that are localized and do not lead to complications
- VZV can be detected in saliva in asymptomatic astronauts¹ and some geriatric patients²

1. Cohrs J Med Virol 2008
2. Arvin JID 2011

How many of you have had Chicken pox?

- Reported history of either chicken pox or vaccination is not reliable¹ so important to check antibody titers
- Required in all healthcare workers to document antibodies or proof of vaccination
- May not recall or have developed subclinical infection

1. Wu J Hosp Infection 2012

How many of you have had Chicken pox?

- Reported history of either chicken pox or vaccination is not reliable¹ so important to check antibody titers
- Required in all healthcare workers to document antibodies or proof of vaccination
- May not recall or have developed subclinical infection
- **Important to check VZV serology if concerned about patients at risk**

1. Wu J Hosp Infection 2012

Chickenpox in Geriatric pts?

- The majority of patients have had prior exposure as children to VZV in the US – so disease is rare
- Estimated that 95% of elderly adults have acquired VZV and have detectable VZV antibodies
- Patients who grew up in Tropical countries may have lower rates of positive serology¹
- Primary varicella in older adults is much more severe than in children with increased rates of organ invasive disease such as pneumonia
- 55% of varicella mortality nationally occurs in adults >20²
- Exposure to grandchildren with primary disease can be major risk



Courtesy of Galvin and D'Alessandro

1. Pembrey PLOSone 2013
2. MMWR 1997

Primary Disease Take-home Points

- The majority of Geriatric patients have had prior exposure and have latent VZV (~95%)
- Serology is the best test for determining prior exposure, and reported history of vaccination and disease are known to be inaccurate
- Although only a small number at risk, primary disease (Chicken pox) in elderly patients can be very severe and life-threatening

Herpes Zoster / Shingles



Herpes Zoster is an Underrated Illness

- Nearly one million new cases of HZ occur in the US per year
- Significant morbidity in patients who develop post-herpetic neuralgia (PHN) or herpes zoster complications
- Costs associated with HZ are substantial in standard populations and geriatric populations^{1,2}
- **Elderly and Immunocompromised patients have significantly increased burden of disease and associated complications**

1. White, et al. Pharmacoeconomics. 2009;27:781-792
2. Wareham & Breuer. BMJ. 2007: 1211-1215.

Why is it called shingles?

From Middle English influenced by:

- Old French **sengle** (single, chingle, belt)

&

- Medieval Latin **cingulus** (translation of Greek zōstēr, girdle, shingles, from the fact that the inflammation often extends around the middle of the body), variant of Latin cingulum, girdle [from cingere, to gird.]



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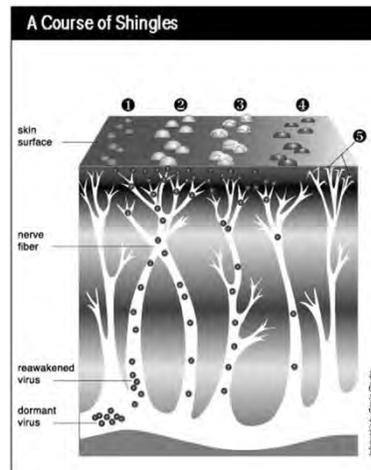
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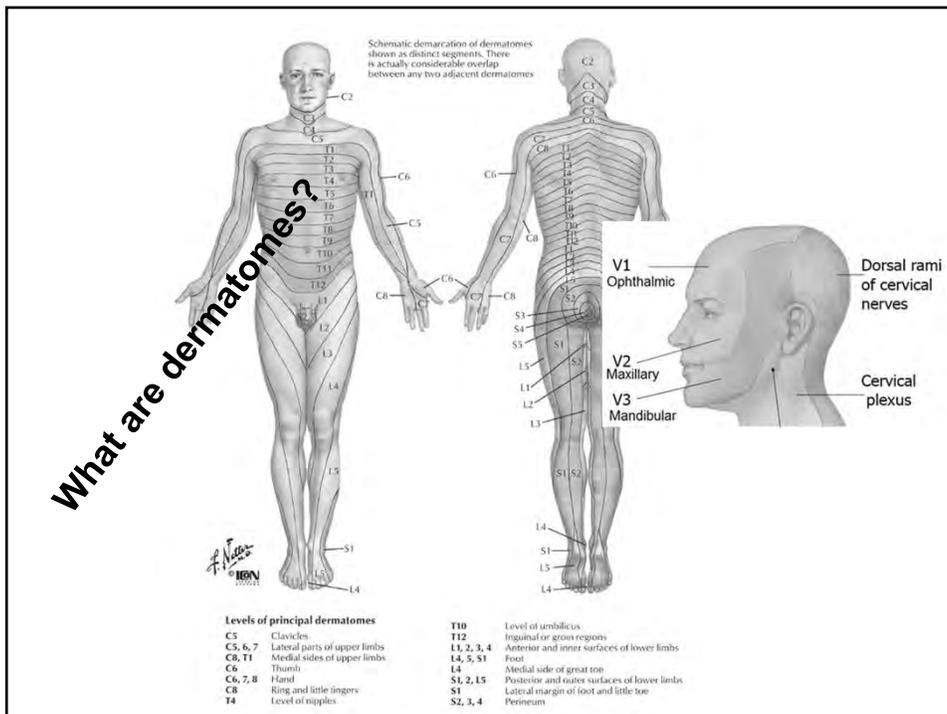
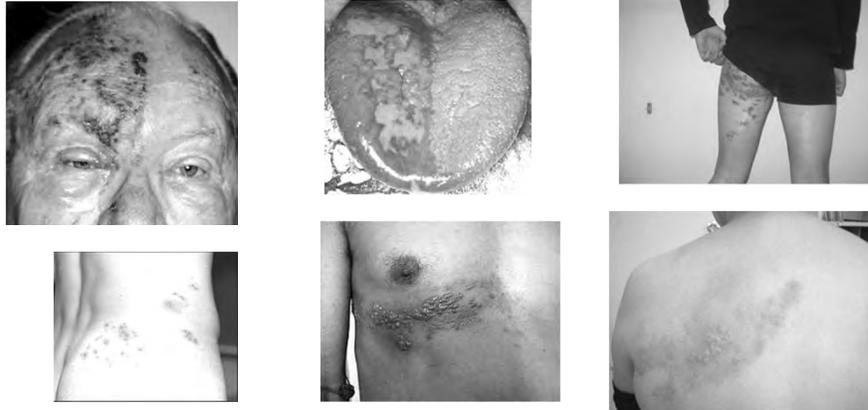


Pathogenesis of Herpes Zoster

- Virus reactivates from latent sites in nerves
- Travel along nerve endings and cause skin rash along nerve root



Reactivation Nerve Roots Dermatomes = Unilateral



Rash Not Always Obvious

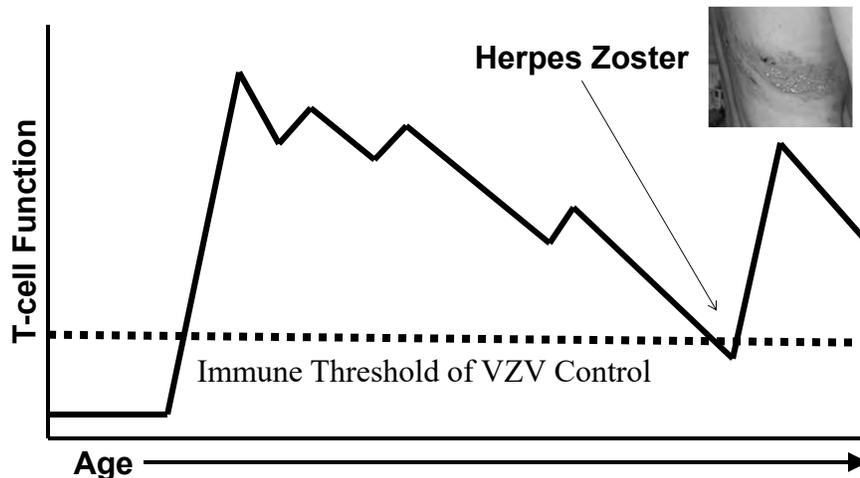


NECK

- Rashes can be more subtle
- “Spider or Bed Bug Bites”
- Irritation from clothes / or rash
- Still follow classic patterns of reactivation

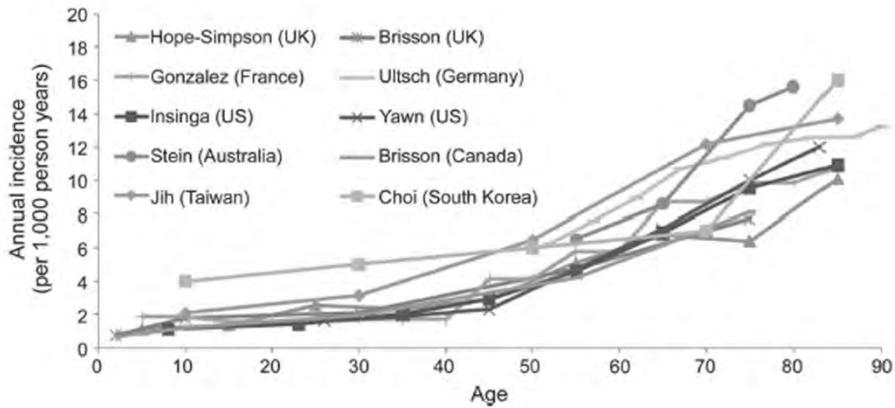
Chest

Pathogenesis of Reactivation



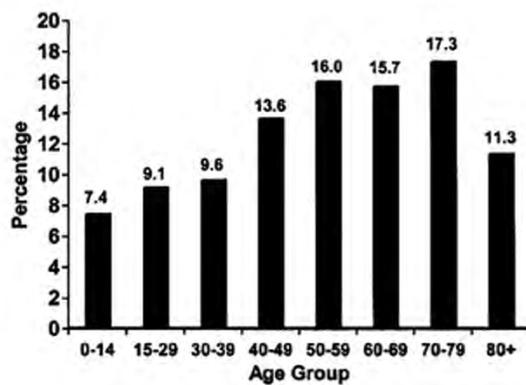
Burden of Herpes Zoster is Driven by Age

Figure Age-specific zoster incidence rates around the world



from Yawn Neurology 2013

Burden of Herpes Zoster is Driven by Age



**≥60 age group
make up 44%
of those who
develop
Shingles**

from Insinga JGIM 2005

Burden of Herpes Zoster is Driven by Age

Age	Males			Females		
	Person-Years	Cases	Rate per 1,000 Person-Years (95% CI)	Person-Years	Cases	Rate per 1,000 Person-Years (95% CI)
0 to 14	186,291	166	0.9 (0.8, 1.0)	177,660	231	1.3 (1.1, 1.5)
15 to 29	187,660	219	1.2 (1.0, 1.3)	189,916	308	1.6 (1.4, 1.8)
30 to 39	138,007	264	1.9 (1.7, 2.2)	161,668	336	2.1 (1.9, 2.3)
40 to 49	190,653	473	2.5 (2.3, 2.8)	228,677	740	3.3 (3.0, 3.5)
50 to 59	199,300	749	3.8 (3.5, 4.0)	229,801	1,240	5.4 (5.1, 5.7)
60 to 69	122,101	741	6.1 (5.6, 6.5)	135,162	1,037	7.7 (7.2, 8.1)
70 to 79	82,317	699	8.5 (7.9, 9.1)	96,958	993	10.3 (9.6, 10.9)
≥ 80	33,776	319	9.4 (8.4, 10.5)	54,450	637	11.7 (10.8, 12.6)
Overall†	1,140,105	3,630	2.6 (2.5, 2.7)	1,274,292	5,522	3.8 (3.7, 3.9)

Increasing rates per decade of life and more frequent in women

from Insigna JGIM 2005

Rates of Herpes Zoster are Increasing Nationally

- Due to **increasing immunosuppression**
- Aging population
- **Aging population that is increasingly immunocompromised**
- Vaccine use, does not appear to be a cause as rates are increasing in parts of the world where Varicella vaccine is not frequently used

Geriatric Diseases/Treatments Increase Risk

- Cancer
- Rheumatologic diseases
- Kidney and liver dysfunction
- Steroid use
- Stress or Injury
- Depression

Cancer



- Weakened immune systems increase risk from primary disease (hematologic cancer > solid tumor)
- Treatment markedly alters immune function and increases rates multi-fold
- Older age and being male were associated with a higher risk of HZ complications in HM patients; more advanced cancer stage was associated with HZ complications in STM patients¹
- Herpes zoster can be presenting symptom/disease at time of cancer diagnosis²

1. Tran Scand Infect Dis 2014
2. Iglar OpenMed 2013



Rates of HZ in RA in Administrative Databases

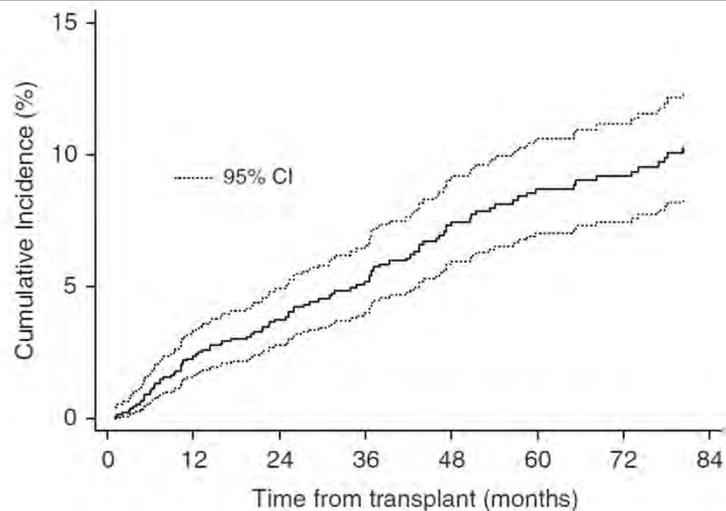
	Reference	Population	n	Rate per 1000 pt years
Gen Population	Donahue <i>Arch Int Med</i> 1995	Health organization database	500,408	2.15
	Mullooly <i>Epidemiol Infections</i> 2005	Kaiser Permanente	2,269,574	3.69
	Jumaan <i>CID</i> 2005	Large HMO database	--	3.47
	Insinga <i>J Gen Med</i> 2005	MarketScan database	2,808,160	3.2
RA	Wolfe <i>Rheumatology</i> 2006	National Databank for Rheumatic Diseases	10,614	13.2
	Smitten <i>Arthritis & Rheum</i> 2007	US and UK PharMetrics database	122,272	9.83
	McDonald <i>CID</i> 2009	VA administrative Database	20,357	9.96

Organ Transplant

- **Large single center study from Alberta¹**
 - 27.2 per 1000 patient years, approx 67% develop in the first year
 - Heart > Lung > Kidney > Liver
 - Risk factors for the group: receipt of induction therapy & antiviral therapy (other than for prophylaxis)
- **Multicenter VA cohort in US²**
 - Incidence rate 22.2 per 1000 patient years
 - Heart > Kidney > Liver
 - No change in rates between 1995-2007, though fewer early cases
- **Mayo Clinic Kidney Transplant Cohort³**
 - Incidence of 28 per 1000 patient years

1. Gourishankar AJT 2004
2. Pergam TID 2011
3. Arness TID 2008

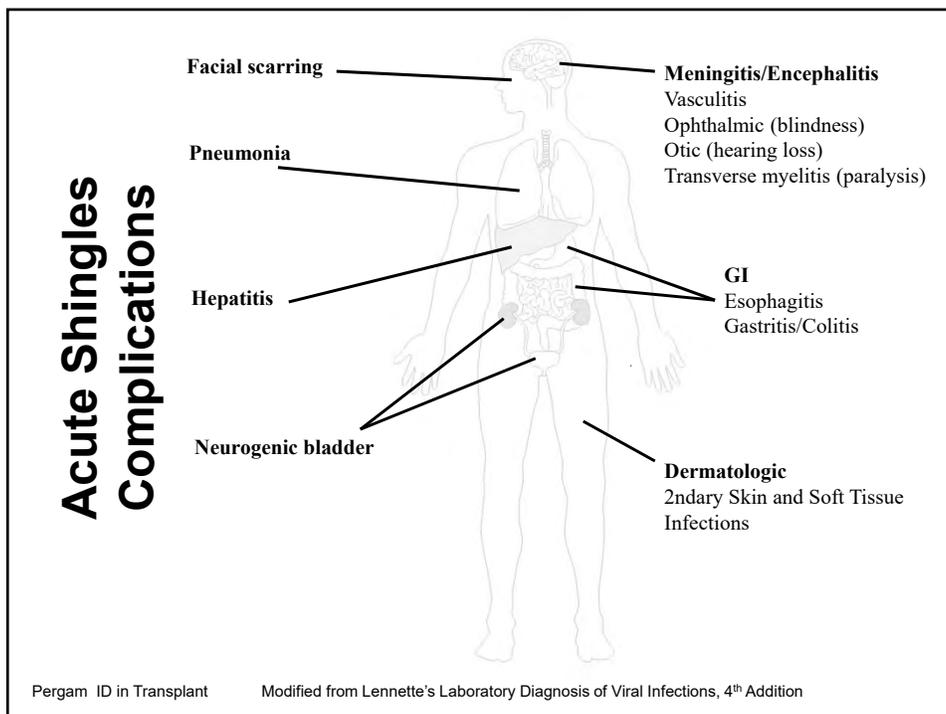
SOT and Zoster



1. Pergam TID 2011

Clinical symptoms

- Unilateral (“dermatomal rash”)
- Painful (burning/sharp)
- Itching
- Rarely involves more than one dermatome
- Even more infrequently is disseminated and leads to invasive disease



Zoster Ophthalmicus



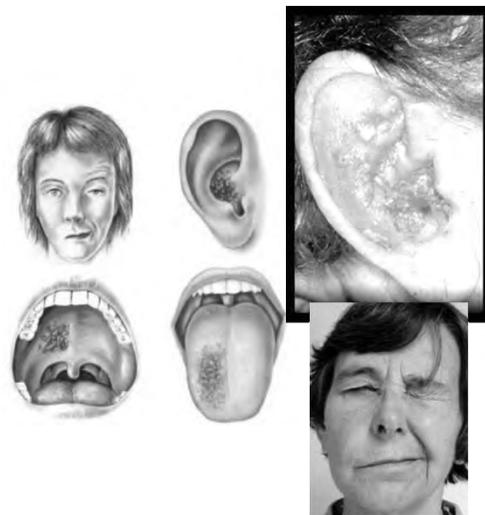
- Involvement of the Ophthalmic branch of the Trigeminal nerve



- Accounts for ~10-20% of all HZ cases¹
- Considered an **Ophthalmologic emergency** requiring immediate treatment to prevent keratitis and unilateral blindness

1. Raggiozino Medicine 1982

Zoster Oticus / Ramsey Hunt Syndrome



- Involvement of the geniculate ganglion which leads:
 - Paralysis of facial nerve (facial muscles)
 - Blisters on and in ear (less frequently tongue and roof of mouth)
- Complications include facial palsy, dysarthria, hearing loss, vertigo, etc.

Herpes Zoster Encephalitis

- Most dreaded complication of Herpes zoster
- **Not always associated with rash, or rash may appear after start of symptoms**
- More frequent in immunocompromised patients
- Can lead to severe vascular involvement and stroke – including ischemic infarcts
- High rates of mortality even with aggressive treatment

Complication: *Post-Herpetic Neuralgia*

- Pain that persists at site of zoster event
- Intermittent and light touch or the brush of clothing is sometimes perceived as being painful, a phenomenon called *allodynia*.
- Can occur post-Herpes Zoster, but defined as lasting >90 days after primary event
- Incredibly debilitating, leading to significant morbidity and depression in many patients
- Risk increases substantially in elderly patients (<60 = 5%, 60-69 = 10%, >80 = 20%)¹, and likely much higher in immunosuppressed patients
- Chronic pain can happen in up to 70% of elderly patients, not meeting definition of PHN

1. Sampathkumar Mayo Clin Proceeding 2009

Herpes Virus Diagnosis?

- **Clinical appearance**
- Unroof lesion and swab for:
 - Viral culture (slow – not used in acute disease)
 - Direct florescent antibody testing (DFA) faster
- VZV PCR from skin lesions **most accurate**, and from atypical sites when considering invasive disease CSF, blood or BAL fluid
- Serology tests are not useful for acute diagnosis
- Saliva has been shown to be method of detection (PCR)

TREATMENT

Treatment



- Antiviral therapy is the backbone of Herpes Zoster treatment:
 - **High-dose Acyclovir, Valacyclovir or Famciclovir** are the drugs of choice (look up doses)
 - Hastens resolution of symptoms and may limit complications – major benefit if given within 72 hours of symptoms
 - **IV should be given in high risk cases** (ophthalmic, otic, CNS, and or in immunocompromised patients)
- Calamine lotion to decrease itching
- Pain control
- Gabapentin to control neuropathic pain? Thought to provide minimal if any benefit¹

1. Dworkin Pain 2009

Steroids?

- Meta-analysis of 5 placebo-controlled trials evaluating acyclovir/valacyclovir compared with acyclovir/valacyclovir & steroids¹:
 - No benefit of combination therapy on quality of life or the incidence of PHN

1. He Cochrane Database Sys Review 2008

Treatment of PHN



- Very frustrating for patients and providers
- No clear therapy that has proven to be most effective at preventing symptoms:
 - Topical agents (Capsaicin / Topical Lidocaine)
 - Pain medications
 - Anti-depressants (tricyclics)
 - Anti-consultants (gabapentin, carbamazepine)
 - *Antiviral therapy provides no benefit*

Prevention



Prevention – Varicella Vaccine

- Data on herpes zoster following primary Varicella vaccine looks promising to date, as patients receiving vaccination are thought to have lower rates than those who naturally acquire VZV. ^{1,2}
- Some countries do not recommend varicella vaccination due to concerns that decreases in exogenous boosting from natural infection (i.e., children with varicella) will lead to increased risk for herpes zoster in adults.³
- Retrospective studies have shown conflicting results^{4,5}, and have been limited by notable increases in herpes zoster prior to the implementation of such childhood vaccination programs.⁶

1. Marin Pediatrics 2008
2. Harpaz MMWR 2008
3. Ojunjimi PlosOne 2013
4. Rimland CID 2010
5. Guris JID 2005
6. Russell Vaccine 2013

Prevention – Zoster Vaccines

- Two available vaccines:
 - **Zostavax (Merck):**
 - Live attenuated virus vaccine (similar to Varivax but higher dose)
 - Single dose
 - Recommended by ACIP for patients ≥60 years of age
 - **Shingrix (GSK):**
 - Adjuvanted subunit vaccine (not live)
 - Two doses
 - Recommended by ACIP for patients ≥50 years of age

Prevention – Zostavax

- Live virus vaccine similar to Oka Stain Varicella vaccine (Zostavax®), but 10-12 times the amount of live virus
- Given once in adults and recommended by the CDC for patients ≥60 years of age, although data has shown benefits and it is FDA approved from those ≥50 years of age²
- HZ vaccine has shown to decrease rates of HZ by ~51% patients over 60³
- Shows reductions in serious complications, including post-herpetic neuralgia (PHN) by 67%³
- Immunogenicity is less robust with increasing age but can still be given if >70⁴
- Waning immunity over time

1. Harpaz MMWR 2008
2. Schmader CID 2012
3. Oxman NEJM 2005
4. Veshkari Hum Vacc Immuno 2013

Prevention – Shingrix

- Adjuvanted subunit vaccine
- Recommended as first line by ACIP, because of enhanced efficacy
- Adjuvanted vaccine- can cause arm pain, low grade fever
 - Local AE with 1st dose does not predict AE with second dose
- Regardless of prior episode(s) of Zoster
- Regardless of whether/not rc'd Zostavax (min 2 months post)
- No need to: test and/or vaccinate vs. Varicella first to defer for 'at risk contacts'– no transmission

Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡	Rate of Herpes Zoster	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡	Rate of Herpes Zoster	
			no./1000 person-yr	no./1000 person-yr			no./1000 person-yr	no./1000 person-yr	% (95% CI)
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
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All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

* The total vaccinated cohort included all vaccinated participants for whom data related to efficacy end points were available. The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose. Efficacy was calculated by means of the Poisson method.

† P<0.001 for all efficacy comparisons with placebo. Vaccine efficacy in each age group was adjusted for region. Overall vaccine efficacy was adjusted for age group and region.

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Lal NEJM 2015

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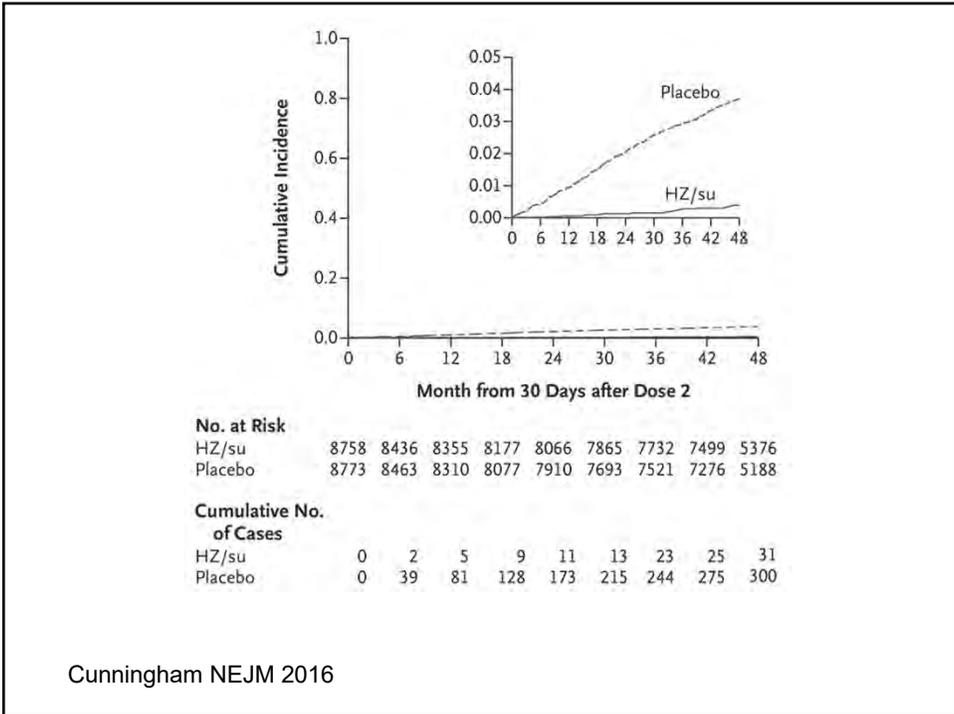
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Lal NEJM 2015



Vaccine Recs

- Shingrix recommend ≥ 50 years of Age
 - Make sure you can get second dose as efficacy not as good with only one dose
 - Data in immunosuppressed populations unknown but early data looks good – *data should be coming later this year
- Zostavax still an option but only for those ≥ 60 and not as effective in patients ≥ 70

Dooling MMWR 2018

Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

Kathleen L. Dooling, MD¹; Angela Guo, MPH¹; Manisha Patel, MD¹; Grace M. Lee, MD²; Kelly Moore, MD³; Edward A. Belongia, MD⁴; Rafael Harpaz, MD¹

Introduction

On October 20, 2017, Zoster Vaccine Recombinant, Adjuvanted (Shingrix, GlaxoSmithKline, [GSK] Research Triangle Park, North Carolina), a 2-dose, subunit vaccine

Methods

From March 2015 to October 2017, the ACIP Herpes Zoster Vaccines Work Group (Work Group; see acknowledgments for members and their affiliations) participated

Isolation



CDC recommends:

- Patients with herpes zoster should cover their lesions to prevent transmitting to at risk patients
- If **immunocompromised** then inpatients should be placed in **airborne and contact isolation** (N-95/PAPR)
 - Data suggesting that even immunocompetent patients may shed virus in respiratory tree during active dermatomal zoster¹
 - Patients with zoster in extremities found to shed VZV in saliva²

1. Lopez JID 2008
2. Gershon JID 2011

Exposed and At-Risk for Primary VZV?

- VariZig (Varicella specific antibodies)
- IVIG?
- Antiviral prophylaxis
- Varicella vaccination



Review guidelines with your ID and Infection Control Teams to prevent spread, as decisions based on exposure and risk to patient

Herpes Zoster is an Underrated Illness

- Nearly one million new cases of HZ occur in the US per year
- Significant morbidity in patients who develop post-herpetic neuralgia (PHN) or herpes zoster complications
- Costs associated with HZ are substantial in standard populations and geriatric populations^{1,2}
- **Elderly and Immunocompromised patients have significantly increased burden of disease and associated complications**

1. White, et al. Pharmacoeconomics. 2009;27:781-792
2. Wareham & Breuer. BMJ. 2007: 1211-1215.

Herpes Zoster Take-Home Points

- **Know the clinical signs and symptoms Herpes zoster and its associated rare complications**
- **Antiviral therapy should be started early, and remains the most effective treatment for Herpes Zoster**
- **Immunosuppressed and Geriatric populations are at highest risk for Herpes zoster complications**
- **Zoster vaccine should be given to eligible patients as it has been shown to substantially reduce burden of disease in patients >60**