# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*


**Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients**

**Richard J. Whitley, MD**
**Co-Director, Division of Pediatric Infectious Diseases**
**Loeb Eminent Scholar Chair in Pediatrics**
**Professor of Pediatrics, Microbiology, Medicine, and Neurosurgery**
**The University of Alabama at Birmingham**

**7/1/2024**

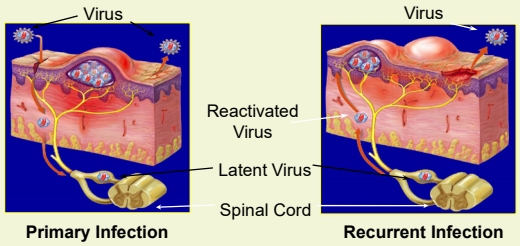

**Disclosures of Financial Relationships with Relevant Commercial Interests**

Steering Committee: NIAID COVID-19 Recover Study, NIAID Recover VITAL Study
Scientific Advisory Board: Treovir, LLC
Scientific Advisory Board: Altesa Biosciences
Member, Board of Directors at Evrys Bio
Member, Board of Directors at Virios Therapeutics
Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB

## Herpes Viruses: The Family

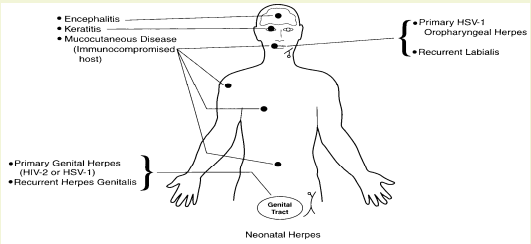
- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

## Viral Latency and Reactivation

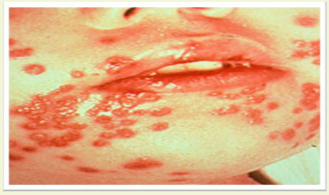



Netter FH. ©2001 by Icon Learning Systems.

## Clinical Manifestations of Herpes Simplex Virus Infections




## Primary Herpes Simplex Virus Infection: Cutaneous Lesions



# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

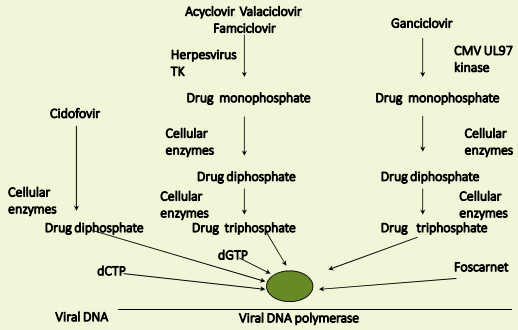
*Speaker: Richard Whitley, MD*

## Herpes Simplex Labialis

## Immunocompromised Host

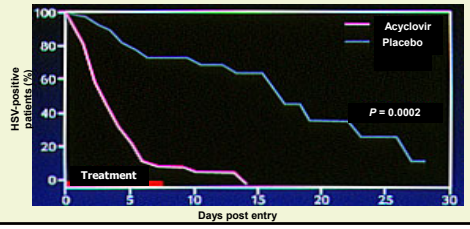
## Most Widely Used Systemic Anti-HSV and VZV Drugs

- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir




## Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

Time to cessation of viral shedding with acyclovir




## Acyclovir Prophylaxis for HSV Infection in BMT Patients

Acyclovir (250 mg iv/m2 /tid) or placebo for 18 days beginning 3 days before transplant

| Group | Number of Patients | Number of HSV Infections | P |
|---|---|---|---|
| Acyclovir | 10 | 0 | ~0.003 |
| Placebo | 10 | 7 | |

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Question #1

PREVIEW QUESTION

A 30 year old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive in spite of high-dose intravenous therapy. The most likely cause for disease progression is a deficiency or alteration of:

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

## Question #1a

PREVIEW QUESTION

Instead of healing, as shown on the last slide, the lesions progress despite antiviral therapy. The most likely cause for disease progression is a deficiency or alteration of:

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
**D. Thymidine kinase ***
E. DNA polymerase

## Question #1b

PREVIEW QUESTION

Which is the best treatment choice for this patient?

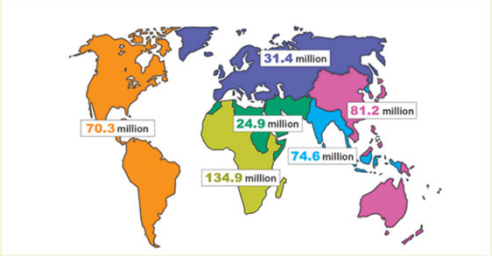
A. Give high-dose of intravenous acyclovir
B. Give intravenous ganciclovir
C. Give oral famciclovir
D. Give oral ganciclovir
**E. Give intravenous foscarnet ***

## Answer #1a and b

PREVIEW QUESTION

- Three types of acyclovir resistant viruses:
  - thymidine kinase negative
  - thymidine kinase altered substrate
  - DNA polymerase mutations
- All populations of HSV contain viruses with resistant genotypes
- Progressive disease has been limited to the immunocompromised host, especially HSCT recipients and those with poorly controlled HIV
- Three normal hosts with documented ACV resistant virus had disease progression

## Global Prevalence of HSV-2 Infection




Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Acyclovir Therapy of Genital Herpes

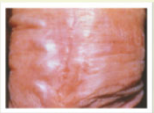
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

## Spectrum of HSV Clinical Presentation

First infection

Classical recurrence



Atypical recurrence

## Progression of Lesions

Early Redness/Swelling

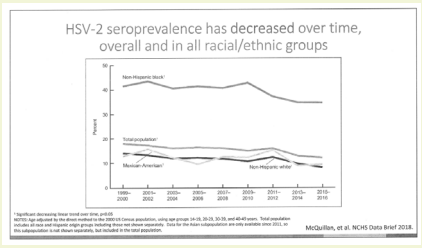
Thin-Walled Fluid-Filled Vesicles and Pustules

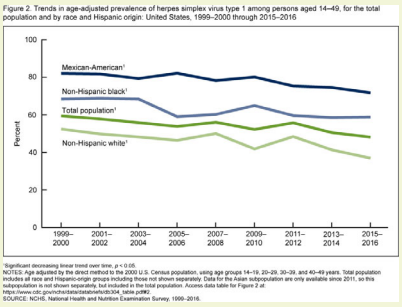
Early Healing of Vesicles, Erosions, or Ulcers

## Clinical Spectrum of HSV-2

HSV-2 Seroprevalence

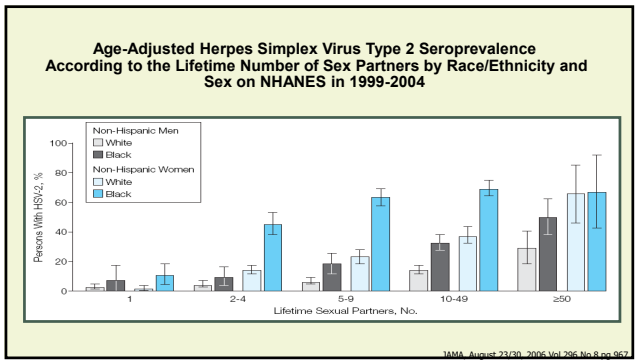

Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839.

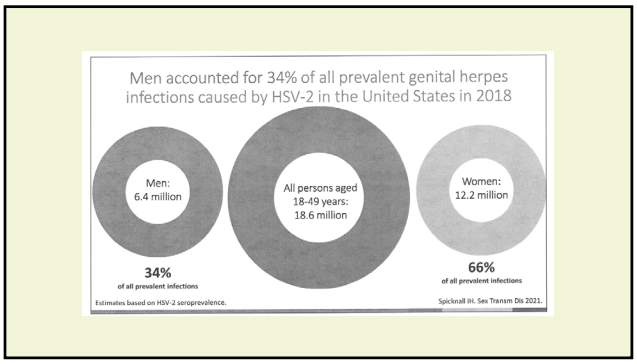


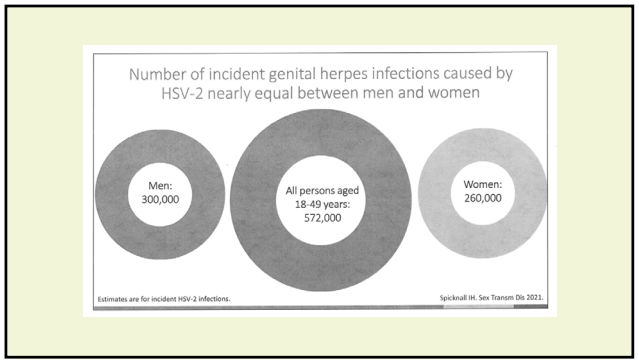



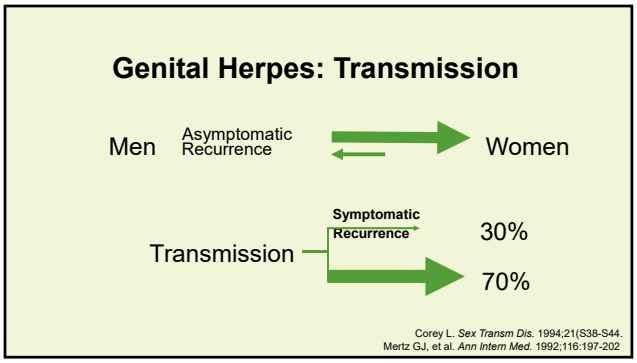
# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

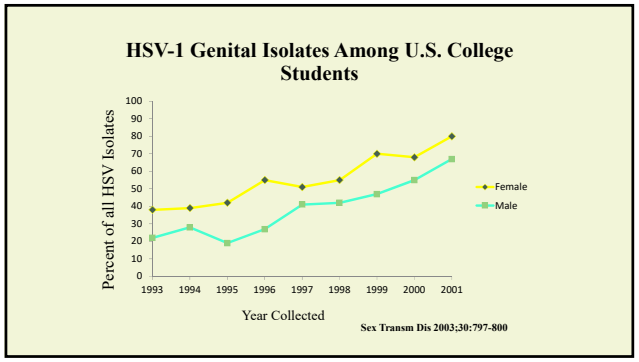
*Speaker: Richard Whitley, MD*

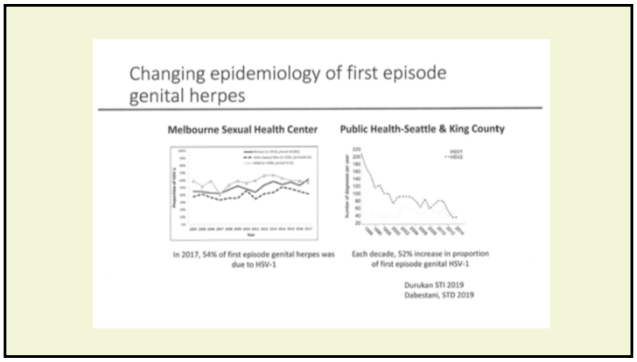


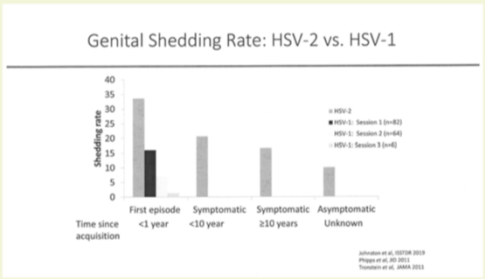



# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*




## Genital Herpes: Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

*Genital Herpes – A Clinician's Guide to Diagnosis and Treatment*. American Medical Association, 2001:1-20.
Whitley RJ, et al. *Clin Infect Dis*. 1998;26:541-555.

## Herpes Presenting as Ulceration

- **The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.**
- **What is the key to the diagnosis?**
  - **A. the fact that lesions recurred**
  - **B. site of involvement is not unusual**
  - **C. trauma can induce reactivation**

Photo courtesy of Jeffrey Gilbert, MD

## Question #2

PREVIEW QUESTION

**An 18 year old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.**

**Which of the following diagnostic tests is most likely to yield the specific diagnosis?**

- **A. Serum RPR**
- **B. Serum FTA-Abs**
- **C. Darkfield microscopy**
- **D. Glycoprotein-G 1 serum antibodies**
- **E. PCR on lesion swab**

## Question #2

PREVIEW QUESTION

**An 18 year old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.**

**Which of the following diagnostic tests is most likely to yield the specific diagnosis?**

- **A. Serum RPR**
- **B. Serum FTA-Abs**
- **C. Darkfield microscopy**
- **D. Glycoprotein-G 1 serum antibodies**
- **E. PCR on lesion swab ***

## Answer #2

PREVIEW QUESTION

- Historically, culture of HSV was the gold standard. Using daily cultures to detect viral shedding resulted in 4-7% of all days being positive.
- Use of PCR has supplemented culture and detects shedding in up to ~25% of days. More recent data show intermittent shedding on the same day.
- A culture isolate of virus is required to test for resistance
- Serology can be used to assess prior exposure to HSV. The distinction between HSV glycoprotein 1 and 2 is diagnostic.

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Oral Antiviral Therapies

- Famciclovir [Famvir®]


- Valaciclovir [Valtrex®]

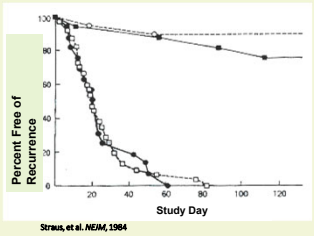

- Acyclovir [Zovirax®]


Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

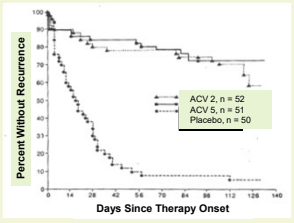
## Impact of Acyclovir Therapy on Primary Genital HSV Infection

| | Treatment Group (Days) | | | |
|---|---|---|---|---|
| | Acyclovir | Placebo | RR | P |
| Virus Shedding | 2.8 | 16.8 | 6.82 | 0.0002 |
| Pain | 8.9 | 13.1 | 2.00 | 0.01 |
| Scabbing | 9.3 | 13.5 | 2.21 | 0.004 |
| Healing | 13.7 | 20.1 | 1.83 | 0.04 |

## Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes




Straus, et al. *NEJM*, 1984




Douglas, et al, *NEJM*, 1984

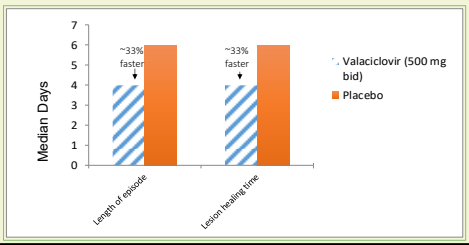
## Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

## Acyclovir/Valacyclovir Kinetics

| DRUG | DOSE | PHARMACOKINETICS | |
|---|---|---|---|
| | | $C_{max}$ (μg/mL) | Daily AUC (μg/mL•h) |
| VALTREX | 1 g 3x/d | 5.0 | 47 |
| Oral ZOVIRAX | 800 mg 5x/d | 1.6 | 24 |
| IV ZOVIRAX | 5 mg/kg 3x/d | 9.8 | 54 |
| | 10 mg/kg 3x/d | 20.7 | 107 |

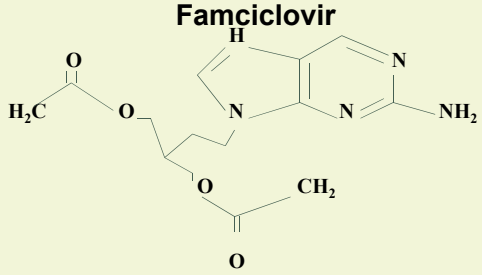
## Therapy of Recurrent Genital Herpes: Duration of Disease



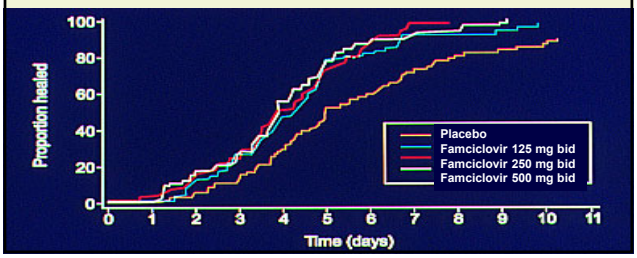
# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Famciclovir




## Famciclovir Therapy of Recurrent Genital Herpes




## Shorter and Shorter Therapy

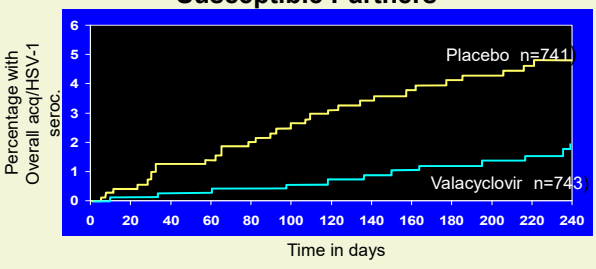
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

## Prevention of Person-to-Person Transmission

## Valacyclovir Prevention of HSV Transmission to Susceptible Partners

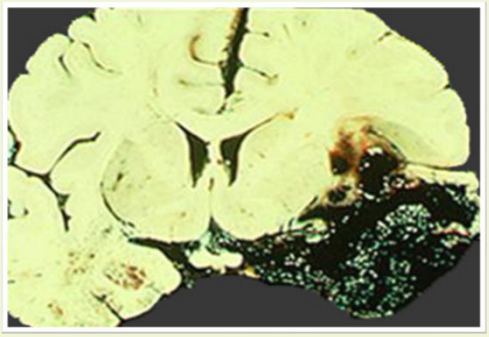
| Susceptible Partner | Val-ACV N = 743 | Placebo N = 741 | Total |
|---|---|---|---|
| No. acquired HSV-2 | 14 | 28 | 42 |
| No. acquired HSV-1 | 0 | 4 | 4 |
| No. developed clinical HSV-2 | 4 | 17 | 21 |

## Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners

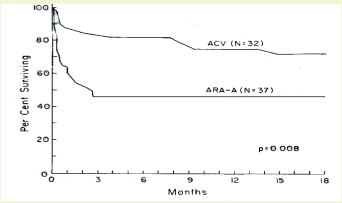


# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*



## Herpes Simplex Encephalitis Survival




**Vidarabine (ARA-A) vs Acyclovir (ACV); P=0.008**

## HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

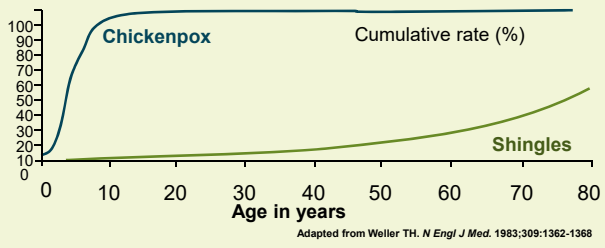
| Age | Glasgow Coma Scale | |
|---|---|---|
| | <6 | >6 |
| <30 | 0 | 60 |
| >30 | 0 | 36 |

## Sensitivity and Specificity of PCR

| | Biopsy Positive | Biopsy Negative |
|---|---|---|
| PCR Positive | 53 | 3 |
| PCR Negative | 1 | 44 |

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

## Varicella Zoster Virus Infection




Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

## CHICKEN POX: Is Therapy of Value?

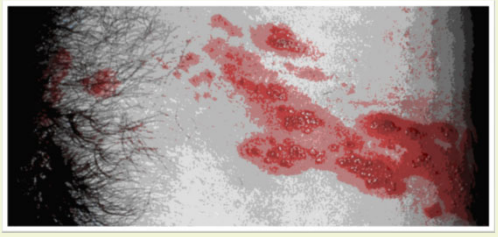
# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

| | Acyclovir (n=38) | Placebo (n= 38) | *P* |
|---|---|---|---|
| Time to maximum number of skin lesions (days) | 1.5 | 2.1 | 0.002 |
| Days of new lesion information | 2.7 | 3.3 | 0.03 |
| Time to onset of cutaneous healing (days) | 2.6 | 3.3 | <0.001 |
| Time to 100% crusting (days) | 5.6 | 7.4 | 0.001 |
| Maximum number of lesions | 268 | 500 | 0.04 |

## Thoracic Herpes Zoster



## Questions

1. What is the most likely diagnosis?
2. How would you prove the etiology?

## Answer

- Clinically this is herpes zoster
- The lesion shown is Tzank prep positive on skin scraping. The sensitivity of this test is only ~60% and, therefore, is not recommended
- Immunofluorescence is positive for VZV, having a sensitivity of ~80%.
- Preferably, PCR can be performed even when lesions are scabbed and has the highest sensitivity.

## Question #3

What complication would you be most concerned about?

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies

http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

## Question #3

What complication would you be most concerned about?

**A. Facial paralysis ***
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies

http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Answer: #3

- This patient has Ramsay Hunt syndrome (Herpes zoster oticus), caused by VZV reactivation in the geniculate ganglion, i.e. zoster of CN VII, presenting with severe ear pain and reduced hearing or deafness. When vesicle are seen in the auditory canal, abnormalities in cranial nerves VII, and sometimes VIII, IX or X, can occur. Thus A, facial paralysis is the best answer. Acyclovir is usually recommended although its not clear if it's effective. The facial paralysis is more severe and less likely to resolve than the usual HSV related Bells Palsy.
- Keratitis would be more typical of a lesion on the tip of the nose, or zoster ophthalmicus involving the CN V ophthalmic branch.
- Encephalitis can be caused rarely by VZV and would not be the best answer. Stroke syndromes due to carotid intimal involvement are associated with zoster, and often with cranial nerve V (trigeminal involvement), but are not offered as an answer
- Optic neuritis and oculomotor paralysis would be uncommon.

## Question #4 Stem

**The patient has only the observed finding on his nose.**

- **What is your most likely diagnosis?**
- **What is the name of this sign?**

www.medscape.com

## Question #4

What complication is it most likely to be associated with this illness?

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

www.medscape.com

## Question #4

What complication is it most likely to be associated with?

A. Deafness
B. Vertigo
C. Optic neuritis
D. **Keratitis** *
E. Stroke

www.medscape.com

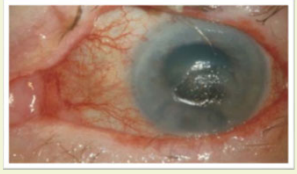
## Answer: #4

This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e. ophthalmic branch of the trigeminal nerve, which inervates the tip of the nose and the globe. After a prodrome of fever and headache for 1-4 days, patients develop a cutaneous rash. Days or up to 3 weeks later, the sclera and cornea can be involved. Thus, keratitis is the correct answer.

Deafness or vertigo would be more characteristic of geniculate ganglion (CN VII) involvement, i.e. Ramsay Hunt, which is a polyneuropathy involving the cranial nerve VII, and then often involves VIII, IX, X. Thus A and B are not the best answers.

## Hutchison's Sign

**Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea**



# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Zoster Ophthalmicus

## NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- Acute neuritis may precede rash by 48 - 72 hours
- Maculopapular eruption, followed by clusters of vesicles
- Unilateral dermatomal distribution

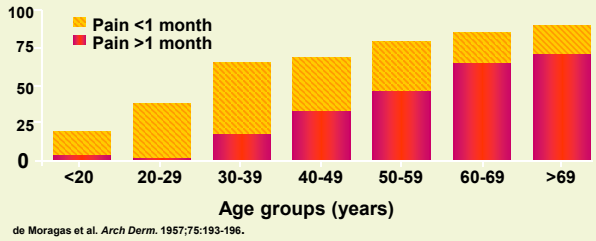
## NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- Events of healing:
  - Cessation of new vesicle formation: 3 - 5 days
  - Total pustulation: 4 - 6 days
  - Total scabbing: 7 - 10 days
  - Complete healing 2 - 4 weeks
- Cutaneous dissemination can occur dissemination is extremely rare
- Postherpetic neuralgia in 10% - 40% of cases

## Complications of Zoster

| Common | Uncommon |
|---|---|
| • Postherpetic neuralgia | • Cutaneous dissemination |
| • Ocular complications | • Herpes gangrenosum |
| • Ophthalmic zoster | • Hepatitis |
| • (uveitis, keratitis, scleritis, optic neuritis) | • Encephalitis |
| • Pneumonitis | • Motor neuropathies |
| • Scarring | • Myelitis |
| • Bacterial superinfection | • Hemiparesis (granulomatous CNS vasculitis) |

## Prevalence and Duration of Pain



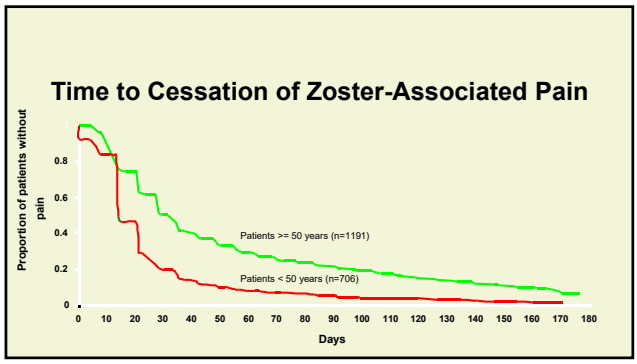

de Moragas et al. *Arch Derm.* 1957;75:193-196.

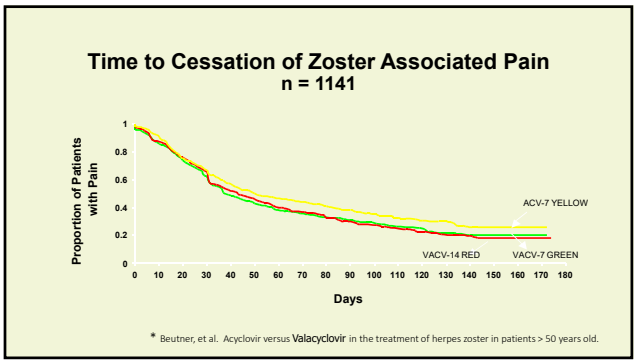
## Goals of Therapy

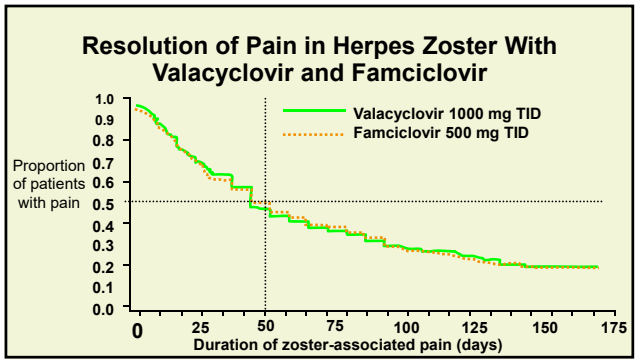
- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*




## Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

## Question #5

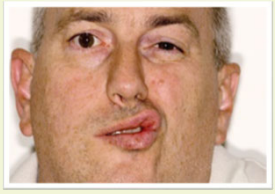
What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

## Question #5

What is the most likely etiologic agent?



A. **HSV ***
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

# 22 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

*Speaker: Richard Whitley, MD*

## Answer #5

- This patient has facial palsy, also known as Bells palsy. The most likely cause of this lesion is HSV. HIV and Lyme disease are less common causes. Answers d and e are not the best answer. Of note, Lyme is rarely the cause of Bells palsy unless there are other manifestations of Lyme disease.
- For typical facial palsy, prednisone is the preferred therapy, optimally given within 3 days of onset, for one week (prednisone 60-80mg qd). Acyclovir alone is not better than placebo, although there might be some rational (unproven) to add acyclovir to prednisone.
- Ganciclovir would be a therapy for CMV, a rare cause of facial paralysis and thus not the best answer.

## METHODS OF PREVENTING / MODIFYING VARICELLA

Pre-exposure: Oka varicella vaccine

Post-exposure: VZIG (now available in US)

Oka varicella vaccine
(<3 days after exposure)

Acyclovir
(7-14 days after exposure)

## Shingles Prevention Trial: Zostavax

**Attenuated, live virus (approved 2006)**

- **Efficacy but waning of immunity with time**
  - **Burden Of Illness 61.1% (51.1 – 69.1%)**
  - **Post-Herpetic Neuralgia 66.5% (47.5 – 79%)**
  - **Incidence of Herpes Zoster 51.3% (44.2 – 57.6%)**

## Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

**Thank You**
**rwhitley@uab.edu**