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

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Disclosures of Financial Relationships with Relevant Commercial Interests

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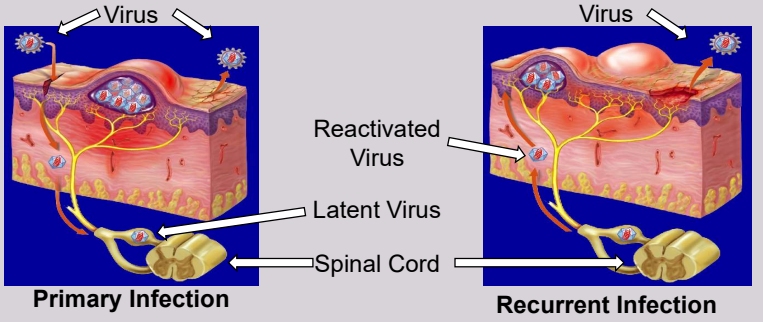
Herpes Viruses: The Family

- **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



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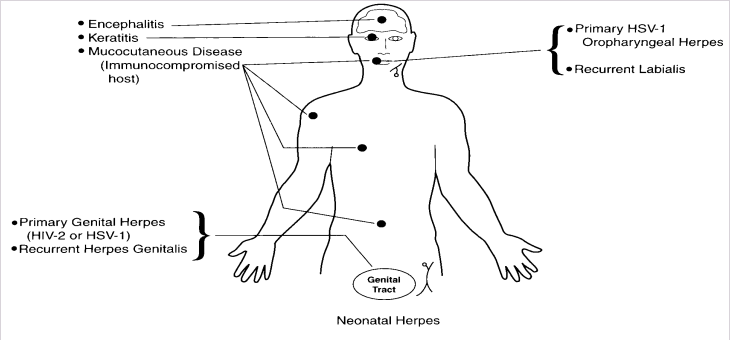
Clinical Manifestations of Herpes Simplex Virus Infections



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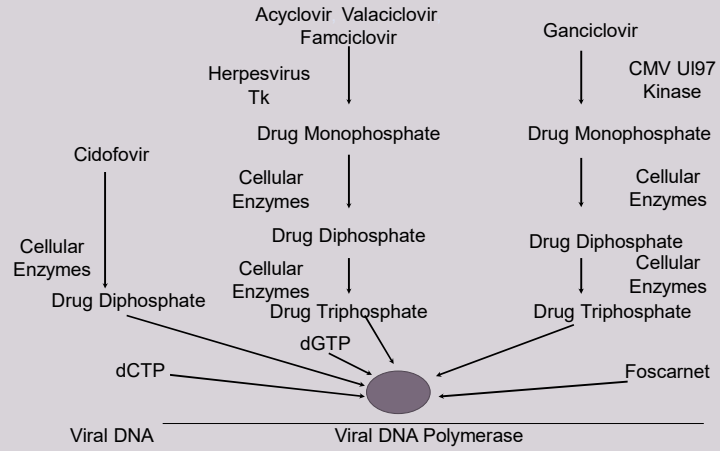
Primary Herpes Simplex Virus Infection: Cutaneous Lesions

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



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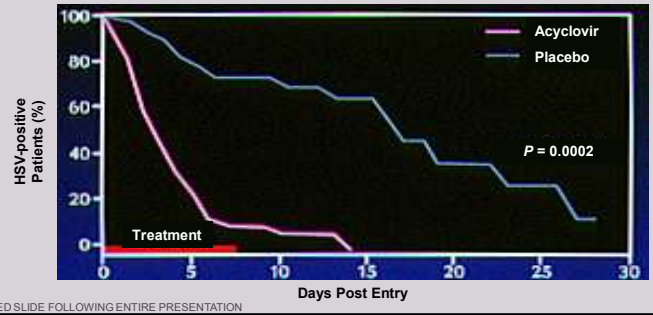
Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

Time To Cessation of Viral Shedding with Acyclovir



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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**	

Question #1

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.

What is the most likely cause for disease progression regarding a deficiency or alteration?

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

Question #1

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.

What is the most likely cause for disease progression regarding a deficiency or alteration?

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease

D. Thymidine kinase*

E. DNA polymerase

Question #2

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

Question #2

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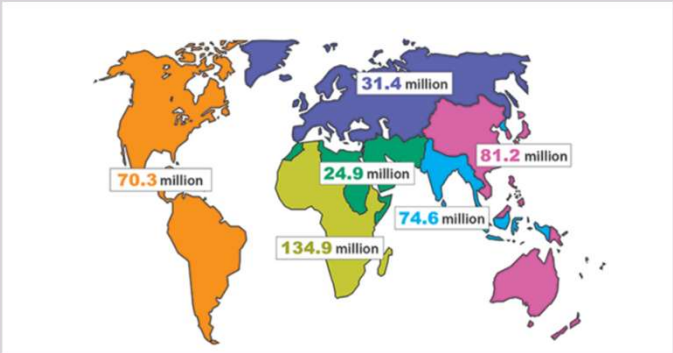
D. Give oral ganciclovir
E. Give intravenous foscarnet*

Answers 1 and 2

- 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)

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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

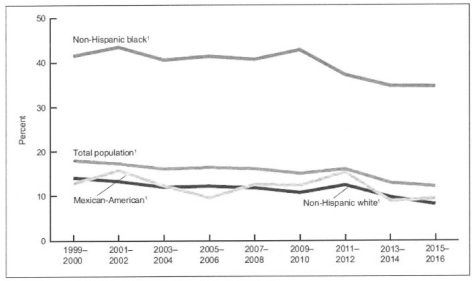
Early Healing of Vesicles, Erosions, or Ulcers

Clinical Spectrum of HSV-2

HSV-2 Seroprevalence

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

HSV-2 seroprevalence has decreased over time, overall and in all racial/ethnic groups



¹ Significant decreasing linear trend over time, p<0.05
NOTES: Age adjusted by the direct method to the 2000 US Census population, using age groups 14-19, 20-29, 30-39, and 40-49 years. Total population includes all race and Hispanic origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population.

McQuillan, et al. NCHS Data Brief 2018.

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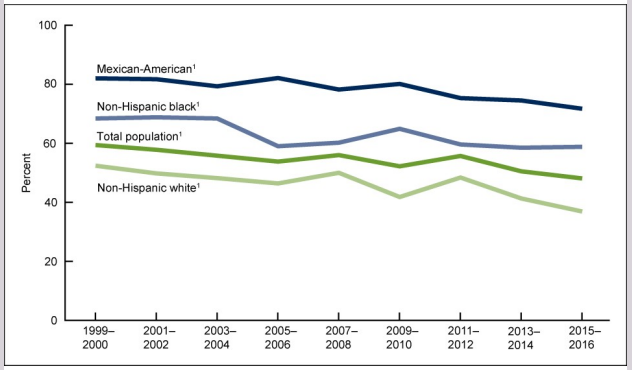
Figure 2. Trends in age-adjusted prevalence of herpes simplex virus type 1 among persons aged 14–49, for the total population and by race and Hispanic origin: United States, 1999–2000 through 2015–2016



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SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

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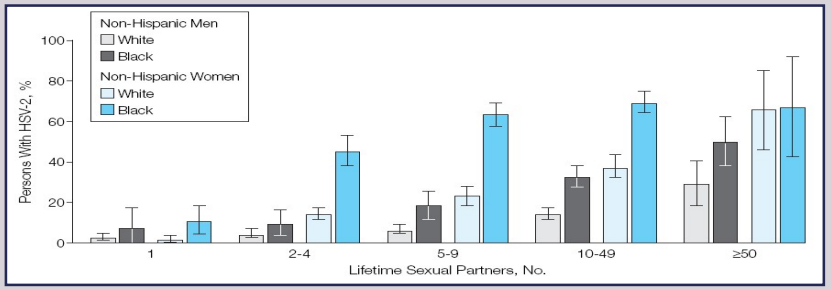
Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence

According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004



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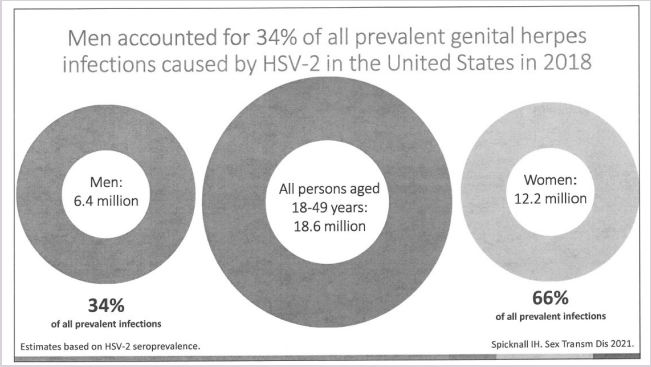
JAMA, August 23/30, 2006 Vol 296 No 8 pg 967



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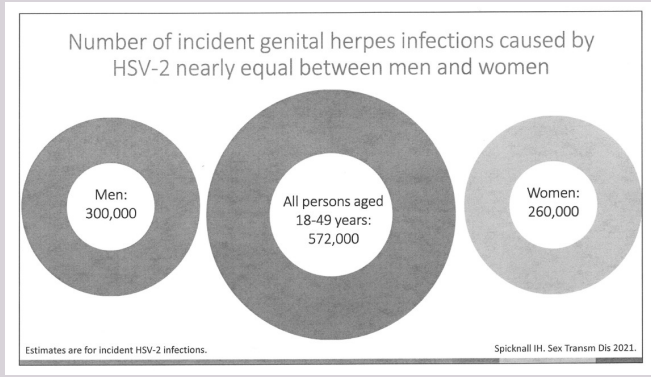

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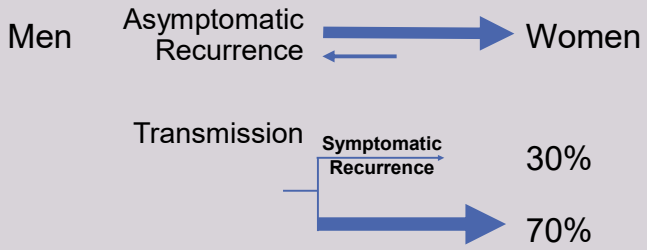
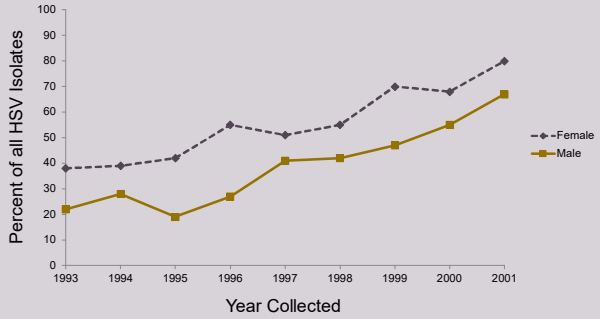
Genital Herpes Transmission



Corey L. *Sex Transm Dis*. 1994;21(S38-S44
Mertz GJ, et al. *Ann Intern Med*. 1992;116:197-202

HSV-1 Genital Isolates Among U.S. College Students



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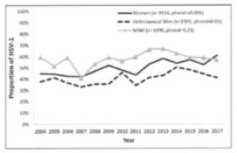
Sex Transm Dis 2003;30:797-800

Changing epidemiology of first episode genital herpes

Melbourne Sexual Health Center



In 2017, 54% of first episode genital herpes was due to HSV-1

Public Health-Seattle & King County

Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

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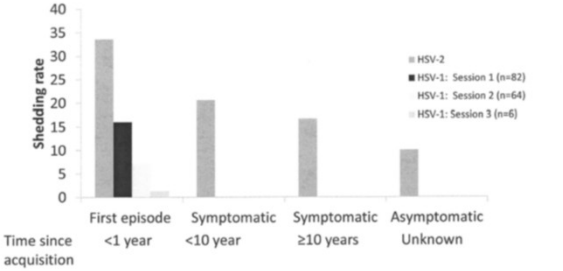
Genital Shedding Rate: HSV-2 vs. HSV-1



Johnston et al, ISSTDR 2019
Phipps et al, JID 2011
Tronstein et al, JAMA 2011

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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 #3

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

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C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab*

Answer #3

- 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 replaced 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 best performed by Western Blot (U. Washington).

Oral Antiviral Therapies

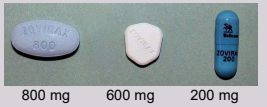
- **Famciclovir [Famvir®]**

500 mg 250 mg 125 mg

- **Valaciclovir [Valtrex®]**

1 g 500 mg

- **Acyclovir [Zovirax®]**



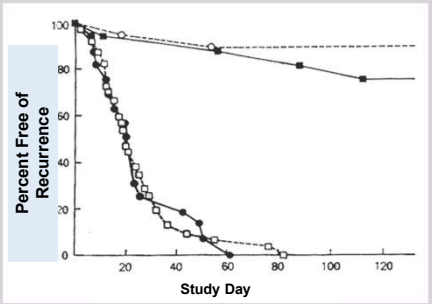
800 mg 600 mg 200 mg

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline

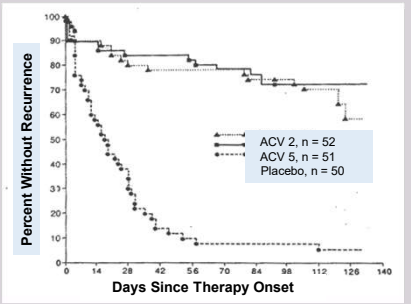
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	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

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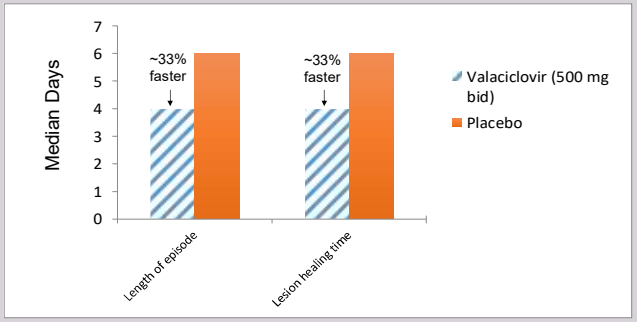
Second Generation Anti-Herpetic Medications

- 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



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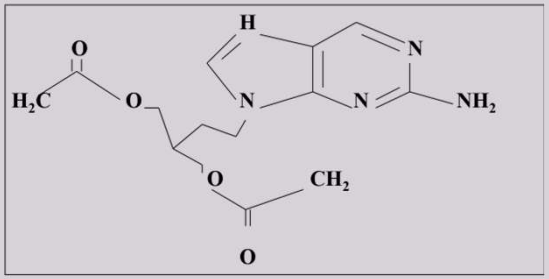
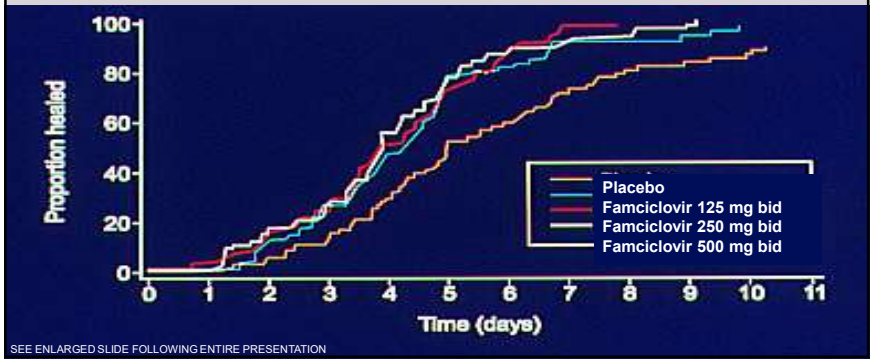
Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



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Shorter and Shorter Therapy

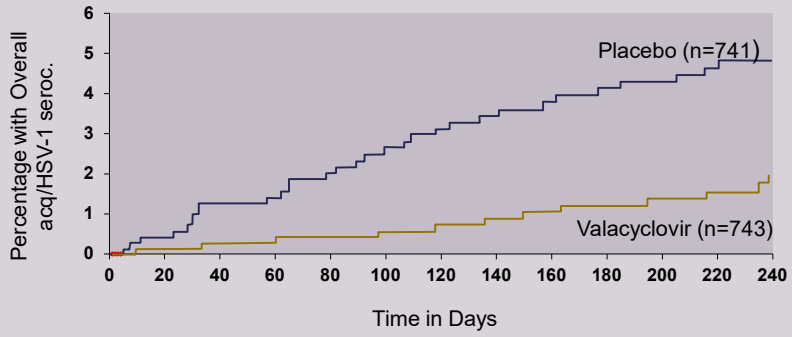
- **Genital Herpes**
  - Valacyclovir: three days
  - Famciclovir: one day
- **Labial Herpes**
  - Valacyclovir: two days
  - Famciclovir: one day

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



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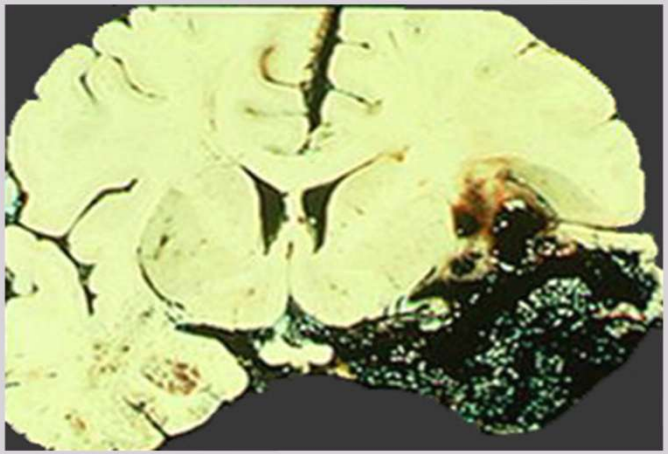
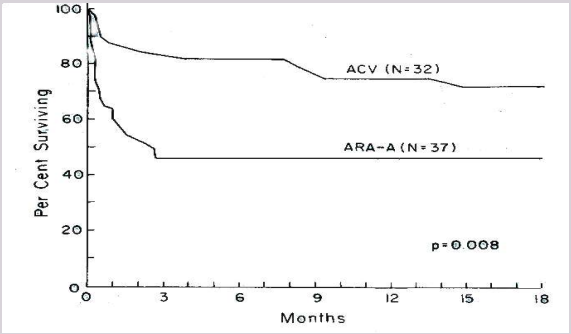


Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A) Vs. Acyclovir (ACV); P=0.008

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HSE Morbidity

Percent Patients Patient Normal/Mild Impairment

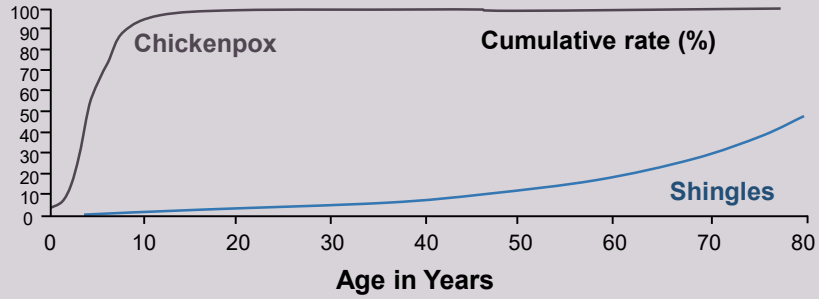
Age	Glasgow Coma Scale	
	<6	>6
<30	0	30
<30	0	36

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



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

Chicken Pox: Is Therapy of Value?

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

- What is the most likely diagnosis?
- 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 #4

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 #4

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 #4

- 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 #5

The patient has only the observed finding on his nose.

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

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 #5

The patient has only the observed finding on his nose.

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

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

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

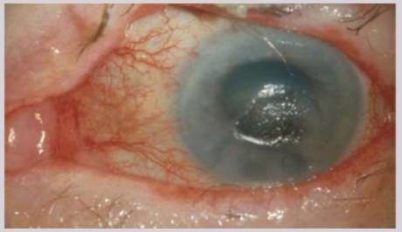
www.medscape.com

Answer #5

- This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e., ophthalmic branch of the trigeminal nerve, which innervates 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 Innervates the Tip of the Nose and the Cornea



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

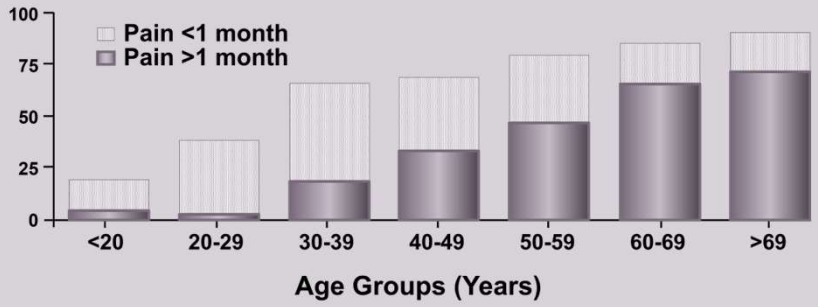
Natural History of Zoster in the Normal Host

- 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

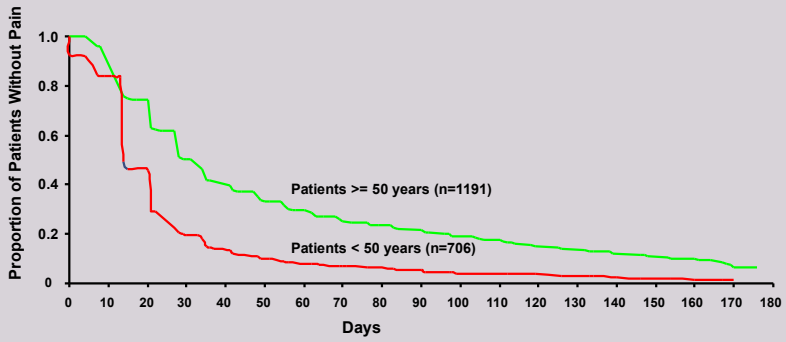


de Moragas et al. *Arch Derm.* 1957;75:193-196

Goals of Therapy

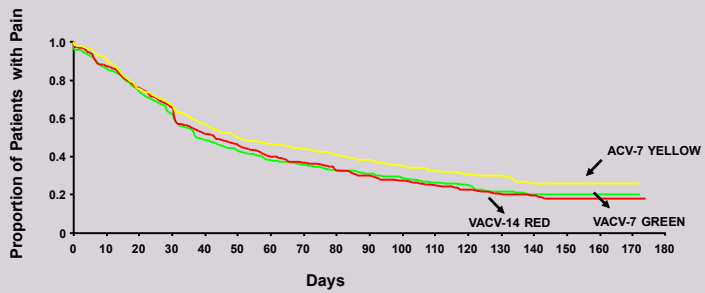
- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

Time to Cessation of Zoster Associated Pain



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

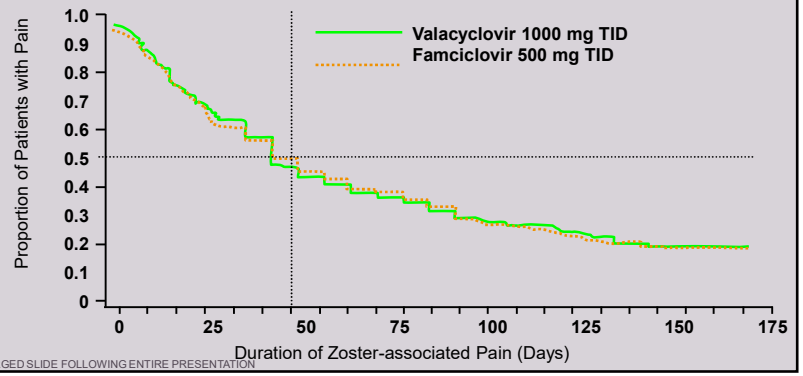
Time to Cessation of Zoster Associated Pain n=1141



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

Resolution of Pain in Herpes Zoster with Valacyclovir and Famciclovir



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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 #6

What is the most likely etiologic agent?

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

www.cdc.gov

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Answer #6

- 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)

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

Teaser: Vaccine is associated with decreased occurrence of Alzheimer's disease

Thank You

rwhitley@uabmc.edu