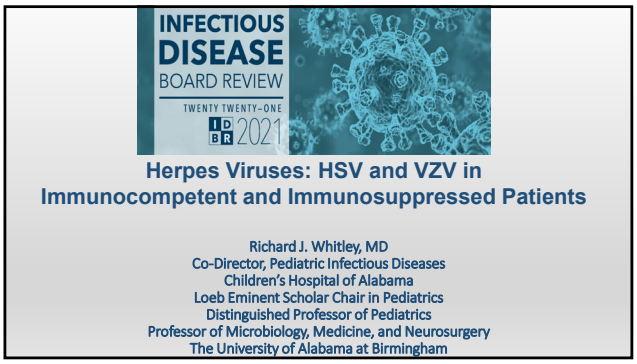
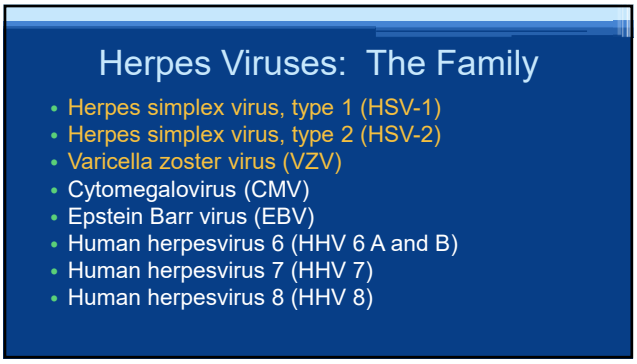
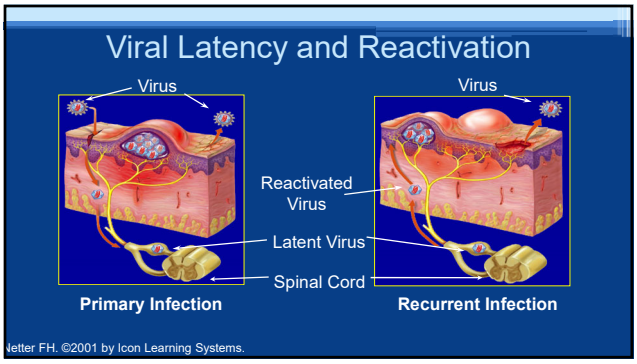
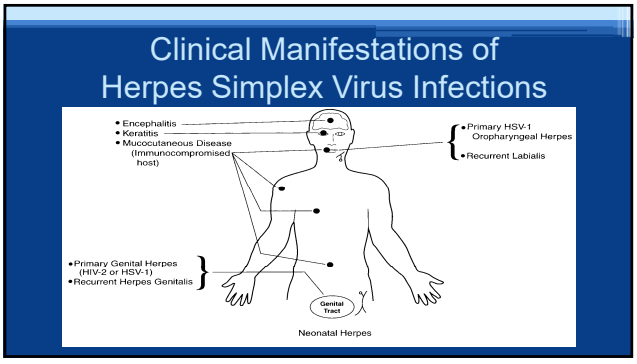
33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

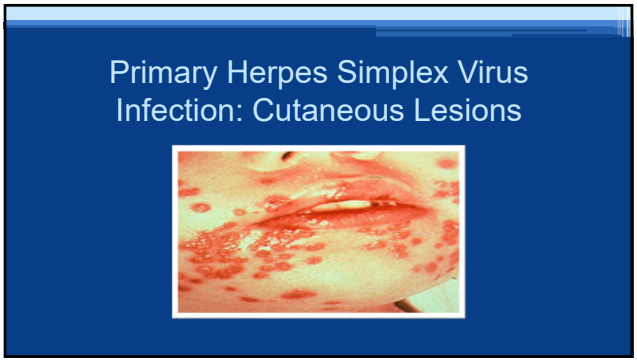
Speaker: Richard Whitley, MD











33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

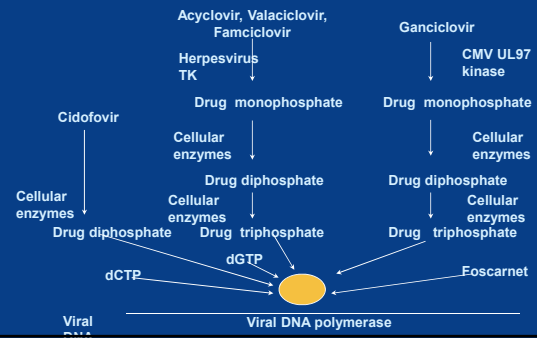
Speaker: Richard Whitley, MD

Herpes Simplex Labialis

Immunocompromised Host

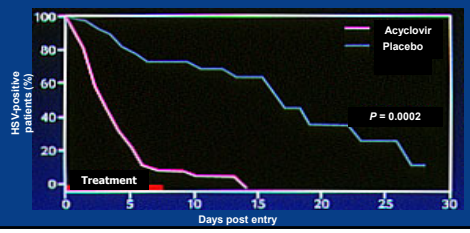
Most Widely Used Systemic Anti-HSV and VZV Drugs

- 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	

33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

Question #1

A 30 year old heart transplant has received acyclovir for the past 0 days with recurrent 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

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)

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

33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

Clinical Spectrum of HSV-2

HSV-2 Seroprevalence

Recognized Infection

10%

90%

Unrecognized and/or Asymptomatic Infection

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

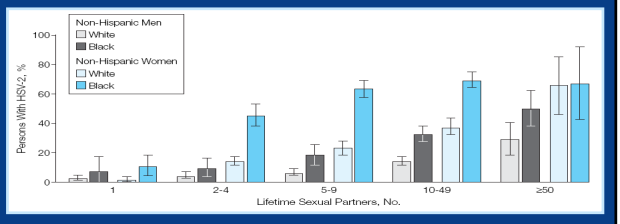
Changes in Weighted Herpes Simplex Virus 2 Seroprevalance Age 14 to 49 years

NHANES

	1988-1994		1999-2004		
	Sample Size	HSV-2 Seroprevalence (95% CI)	Sample Size	HSV-2 Seroprevalence (95% CI)	Change (95% CI)
Overall	9165	21.0	11,508	17.0	-19.0
Age Group					
14-19	1787	5.8	4650	1.6	-72.4
20-29	2750	17.2	2412	10.6	-38.4
30-39	2557	27.8	2251	22.1	-20.5
40-49	2061	26.3	2195	26.4	0

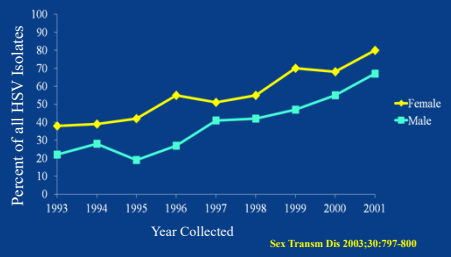
JAMA, August 23/30, 2006 Vol 296 No 8 pg 968

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



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

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



Sex Transm Dis 2003;30:797-800

Genital Herpes: Transmission

Men — Asymptomatic Recurrence ⇄ Women

Transmission — Symptomatic Recurrence → 30%

Transmission → 70%

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

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.

33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

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 Dr. Lee Gilbert, MD.

Question #2

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

Oral Antiviral Therapies

- Famciclovir [Famvir®]

500 mg 250 mg 125 mg

- Valaciclovir [Valtrex®]

1 g 500 mg

800 mg 600 mg 200 mg

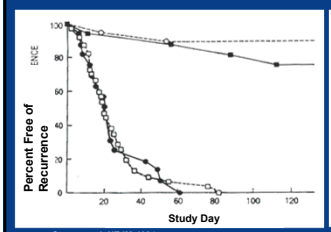
- Acyclovir [Zovirax®]

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline

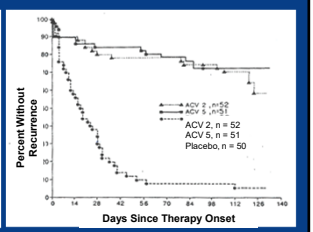
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	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)

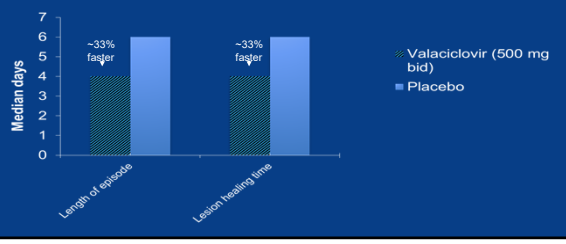
33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

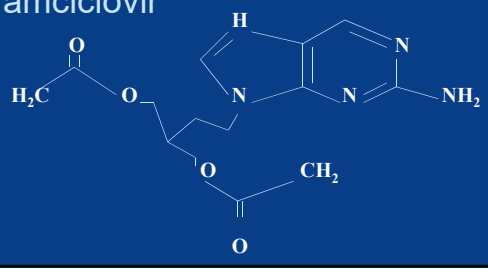
Acyclovir/Valacyclovir Kinetics

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

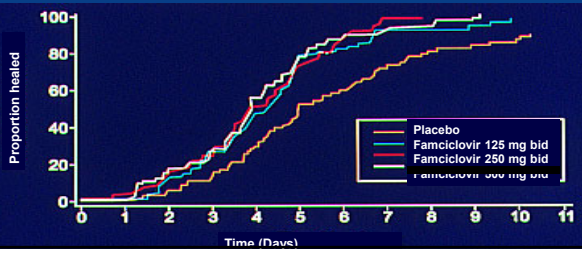
Therapy of Recurrent Genital Herpes: Duration of Disease



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

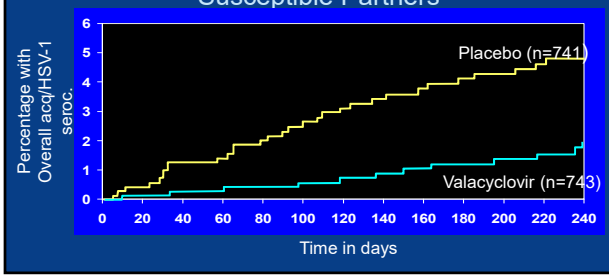
33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

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



Genital Herpes: CDC STD Guidelines

Recommended Treatment For Initial Episode

Acyclovir	400 mg orally three times a day for 7–10 days
ORAcyclovir	200 mg orally five times a day for 7–10 days
ORValacyclovir	1 g orally twice a day for 7–10 days
ORFamciclovir	250 mg orally three times a day for 7–10 days

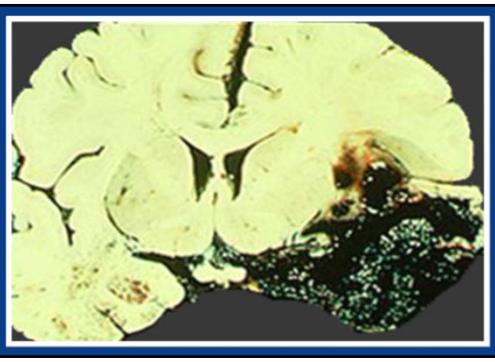
*Treatment can be extended if healing is incomplete after 10 days of therapy.

Recommended Treatment for Recurrent Episodes

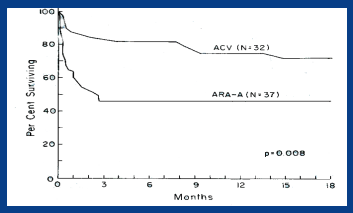
Acyclovir	400 mg orally three times a day for 5 days
OR Acyclovir	800 mg orally twice a day for 5 days
OR Acyclovir	800 mg orally three times a day for 2 days
OR Valacyclovir	500 mg orally twice a day for 3 days
OR Valacyclovir	1 g orally once a day for 5 days
OR Famciclovir	125 mg orally twice daily for 5 days
OR Famciclovir	1 gram orally twice daily for 1 day
ORFamciclovir	500 mg once, followed by 250 mg twice daily for 2 days

Suppressive Therapy for Recurrent Genital HSV: CDC Guidelines

Acyclovir	400 mg orally twice a day
OR Valacyclovir	500 mg orally once a day
OR Valacyclovir	1 g orally once a day
OR Famiciclovir	250 mg orally twice a day



Herpes Simplex Encephalitis Survival



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

33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

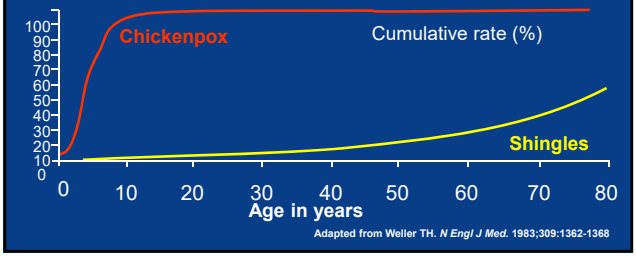
Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

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



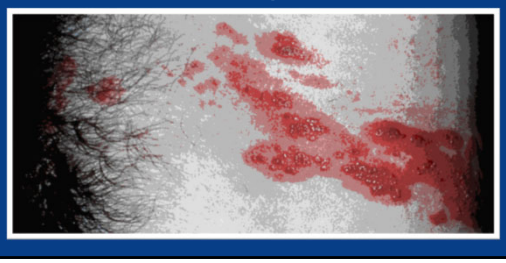
Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

CHICKEN POX: Is Therapy of Value

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



33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

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 #4 Stem

The patient has only the observed finding in the picture.

- **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

Hutchison's Sign

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

33 – 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**

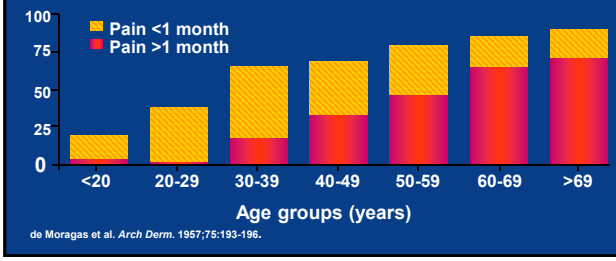
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

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

Prevalence and Duration of Pain



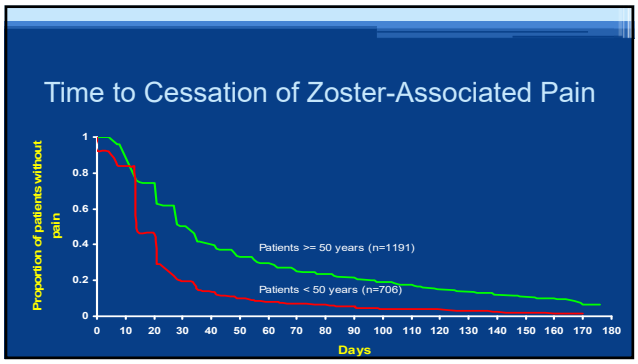
de Moragas et al. *Arch Derm.* 1957;75:193-196.

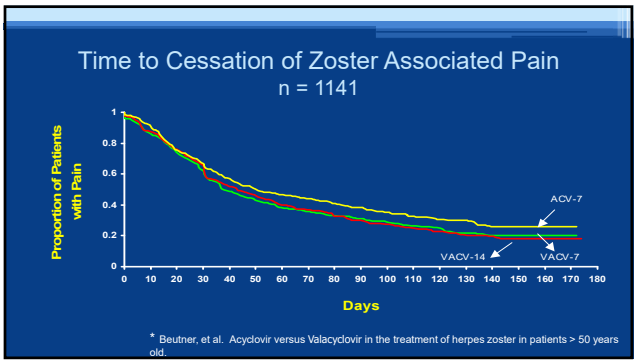
Goals of Therapy

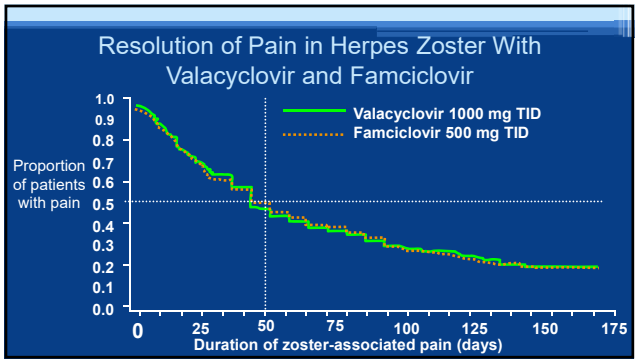
- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

33 – 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 6

A 32 year previously healthy female is referred by an ophthalmologist for treatment of acute retinal necrosis, diagnosed in her office earlier that day. You recommend which of the following as initial therapy:

- A. sulfadiazine and pyrimethamine
- B. ganciclovir IV
- C. acylovir PO
- D. acyclovir IV
- E. foscarnet IV

33 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

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

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