Herpesviruses: The Tired, the Rashy, and the Ubiquitous

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Disclosures

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Educational Objectives

• Recognize the different presentations of human herpesvirus infections.

• Recommend testing for herpesvirus infections.

• Prescribe appropriate therapy for herpesviruses.
Definitions

herpes  
\( n \)  
a disease characterized by patches of vesicles

derived from the Greek  
\( \varepsilon \rho \pi \varepsilon \iota \nu \) (to creep)

originally applied to spreading vesicular lesions
Herpesviruses: basics

- enveloped DNA viruses
- icosahedral capsid (100 nm)
- virion spherical (120-200 nm)
- linear dsDNA 120-240 kbp (100+ proteins)
- large family, endemic in many animals
Image obtained from the Centers for Disease Control, Public Health Image Library.
Herpesviruses: life cycle (1)

• bind to receptors  
  - heparan sulfates, other molecules
• fuses with cell membrane
• capsid transported to nuclear pore
• uncoating of dsDNA
Herpesviruses: life cycle (2)

- cascade of gene expression
  - immediate-early genes
  - early genes
  - late genes
  - latency-associated transcripts (LATs)

- DNA synthesis enzymes
Herpesviruses: life cycle (3)

- new viral DNA coated with icosahedral capsid
- buds through nuclear membrane
- most cells die by lysis (18-72 hrs)
- some cells express lytic genes, some express latency genes
- level of latency transcripts determine recurrence rates?
Herpesviruses: life cycle (4)

• primary infection of longer duration
• most primary infection asymptomatic
• reactivation / secondary infection shorter
• most human → human transmission asymptomatic shedding to naïve hosts

• animal → human transmission asymptomatic vs. severe disease
Human Herpes Viruses

- HHV-1/2 \rightarrow Herpes Simplex Virus 1/2
- HHV-3 \rightarrow Varicella-Zoster Virus
- HHV-4 \rightarrow Epstein-Barr Virus
- HHV-5 \rightarrow Cytomegalovirus
- HHV-6 \rightarrow Roseolovirus
- HHV-7 \rightarrow Roseolovirus
- HHV-8 \rightarrow Kaposis Sarcoma-Associated Herpesvirus
Herpesviruses: classes (1)

• subfamily *Alphaherpesvirinae*
  - rapid growth cycle / cytolytic
  - genera
    *Simplexvirus* (HSV-1, HSV-2)
    *Varicellovirus* (VZV)

• target cells → mucoepithelial

• site of latency → neurons
Human Herpes Virus 1/2

Herpes Simplex Virus 1/2
- ~50% DNA homology
  - cross-protection?
- transmission by contact
  - infect mucosal / epithelial cells
- establish latency in sensory neurons
  - trigeminal ganglion
  - dorsal nerve roots
  - sacral ganglion
Human Herpes Virus 1/2

Herpes Simplex Virus 1/2

• incubation period 2-20 days

• ubiquitous human infections

• HSV-1 > HSV-2
Human Herpes Virus 1/2

HSV-1
- acquired in childhood
- 40-60% by 5 yo
- 70-90% by late adulthood

HSV-2
- acquired throughout life
- some perinatal transmission
- increases in adolescence
- 10-60% in adults

*Age-adjusted by using the 2000 U.S. Census civilian, non-institutionalized population aged 14-49 years as the standard.

NOTE: Error bars indicate 95% confidence intervals.
Genital Herpes—Initial Visits to Physicians’ Offices, United States, 1966–2011

Visits (in thousands)

Year

Primary Infection

• lesions vesicular (d1-7)
  → ulcerative (d7-14)
  → crusting / healing (d14-21)

Secondary Infection

• lesions vesicular (d1-2)
  → ulcerative (d3-4)
  → crusting / healing (d4-7)
Human Herpes Virus 1/2

Gingivostomatitis
- HSV-1 > HSV-2
- ulcerative oral disease
- gums / lips / tongue
- recurrence on lips (cold sores)
- posterior pharyngitis (teens / adults)
  - ¼ of pharyngitis in college
  - symptoms overlap EBV
Image obtained from the Centers for Disease Control, Public Health Image Library.
Human Herpes Virus 1/2

Vulvovaginitis / Genital HSV
• HSV-2 > HSV-1
• ulcerative genital lesions
• recurrence
• cervix often involved
  - source for perinatal transmission

• primary genital herpes
  HSV-1 > HSV-2 ?
Human Herpes Virus 1/2

Perinatal
- HSV-2 > HSV-1
- lesions at presenting part
- mother’s cervix often involved
- recurrence risk in future?
Human Herpes Virus 1/2

Encephalitis

• HSV-1 > HSV-2
  - reversed in neonates
• meningitis alone HSV-2 > HSV-1
  - associated with genital disease
• Mollaret meningitis
  - “benign” recurrent
Human Herpes Virus 1/2

Cutaneous
  • herpes gladiatorum
  • eczema herpeticum

Whitlow
  • nail biting

Ocular
  • keratitis
HSV: diagnosis

- Tzanck smear (obsolete)
- serology (unreliable / unhelpful)
- DFA (dependent on quality of specimen)

- culture of lesion or CSF

- PCR of lesion / CSF
  gold standard
Human Herpes Virus 3

Varicella-Zoster Virus
  • varicella (diminutive of variola)
  • zoster (Greek word: girdle)
• transmission by respiratory route
  • highly contagious (80-90% attack)
• establishes latency in neurons
  • most recurrences in dermatomes with most primary lesions?
Human Herpes Virus 3

Varciella-Zoster Virus

• incubation period 10-23 (14) days

• ubiquitous human infection
• was 8-9%/yr from 1-9yo
  (5% subclinical)
• higher rates in temperate zones
  vs tropical zones
Varicella Cases by Month: Antelope Valley, CA, 1995–2004

Image obtained from the Centers for Disease Control.
Human Herpes Virus 3

Primary: Varicella (chickenpox)

• prodrome (adults > children)
  → fever with crops of vesicular lesions (d1-2)
  → fever with evolution (d3-5)
  → crusting / healing (d5+)

• disease in adults often severe
Human Herpes Virus 3

Secondary: Zoster

- lesions localized (1-3 dermatomes)
  - vesicular / confluent (d1-3)
  - → crusting (d3-5)
  - → slow healing (d5-28)

- post-herpetic neuralgia 25-50% in those >50 yo
VZV: diagnosis

- usually a clinical diagnosis
- serology (unhelpful)
- DFA (dependent on quality of specimen)
- culture of lesion or CSF

- **PCR of lesion / CSF**
  gold standard
Herpesviruses: classes (2)

• subfamily *Betaherpesvirinae*
  - slow growth cycle / cytomegaly
  - genera
    *Cytomegalovirus* (CMV)
    *Roseolovirus* (HHV-6A/B, HHV-7)

• target cells → T cells (monocytes?)

• site of latency → T cells (monocytes?)
Human Herpes Virus 5

Cytomegalovirus
- originally called salivary gland virus
- largest of herpesviruses

- transmission via body fluids
  - saliva / urine / breast milk
  - evidence for sexual transmission
    - semen / CVL
- blood products (nosocomial)
- establishes latency in leukocytes
Human Herpes Virus 5

Cytomegalovirus

• incubation period unclear
• ubiquitous human infection
• ~1% congenital
• ~50% attack rate in breast milk
• 50-80% +ve in daycares
• adults with high SES 40-60% vs low SES >80%
Human Herpes Virus 5

Diseases: **Protean**

- most asymptomatic
- mononucleosis syndrome
  - heterophile antibody
- hepatitis / marrow suppression
- severe disease in AIDS
Human Herpes Virus 5

Diseases: **Congenital**

- most asymptomatic
- intracranial calcifications
- retinitis
- thrombocytopenia
- hearing loss
- mental retardation
  - role for therapy unclear / evolving
CMV: diagnosis

• serology (immune screen)

• culture of urine (shell vial)

• PCR of blood (viral levels)
Human Herpes Virus 6A/B, 7

HHV-6A / HHV-6B / HHV-7
- genetically distinct
  • transmission probably via body fluids
    • saliva
    • congenital
    • nosocomial
  • establish latency in T cells / monocytes / bone marrow stem cells (integration?)
Human Herpes Virus 6A/B, 7

HHV-6A / HHV-6B / HHV-7

- incubation period unclear
- ubiquitous human infections
- ~100% HHV-6 infected by 2 yo
- ~65% HHV-7 infected by 3 yo, but ~100% by 6 yo
Prevalence of HHV-6/7 Infections in British Children by Age

Human Herpes Virus 6A/B, 7

Primary disease: Exanthem subitum
• aka: roseola infantum, 6th disease
• fever (~3d), fine rash after fever breaks
• can be rash-less
• association with febrile seizures
  - definitive association with HHV-6B
  - strong evidence for HHV-7
  - not clear disease caused by HHV-6A
Human Herpes Virus 6A/B, 7

Recurrent disease: **Unclear**

- asymptomatic shedding common

- pityriasis rosea (HHV-7)?

- CNS reactivation in immunocompromised
HHV-6A/B, 7: diagnosis

• clinical diagnosis

• serology (not helpful in acute disease)

• culture (hard to get)

• PCR of blood / other fluids (only helpful in immunocompromised)
Herpesviruses: classes (3)

• subfamily *Gammaherpesvirinae*
  - variable growth cycle
  - malignant transformation potential
  - genera
    *Lymphocryptovirus* (EBV)
    *Rhadinovirus* (KSHV)

• target cells → B cells, epithelial cells

• site of latency → B cells
Human Herpes Virus 4

Epstein-Barr Virus
- recognized as a cause of infectious mononucleosis
  • transmission via body fluids
    - saliva
    - blood products (nosocomial)
  • establishes latency in B cells
Human Herpes Virus 4

Epstein-Barr Virus

- incubation period unclear
- ubiquitous human infection
- congenital rare / no clear disease
- childhood acquisition common
- 80-95% +ve in adults
Human Herpes Virus 4

Diseases: **Protean**

- most asymptomatic
  (increased symptoms with older age?)
- chronic active disease rare
- hepatitis / marrow suppression
- malignant disease
  - Burkitt lymphoma
  - Hodgkin disease
  - PTLD
Human Herpes Virus 4/5

Diseases: Infectious Mononucleosis

- highest incidence 15-19 yo
- heterophile antibody (after age 4-5)
- pharyngitis / lymphadenopathy
- fever
- hepatosplenomegaly (1-3 months)
- fatigue (1-3+ months)
EBV: diagnosis

• serology (specific antibodies)

• monospot (heterophile antibody)

• PCR of blood (viral levels)
<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>VCA IgM</th>
<th>VCA IgG</th>
<th>EA</th>
<th>EBNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infectious mononucleosis</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Late stage / recovery</td>
<td>falling</td>
<td>high</td>
<td>falling</td>
<td>rising</td>
</tr>
<tr>
<td>Previous infection</td>
<td>low / negative</td>
<td>positive</td>
<td>low / negative</td>
<td>positive</td>
</tr>
<tr>
<td>Reactivation</td>
<td>positive</td>
<td>high</td>
<td>high</td>
<td>positive</td>
</tr>
</tbody>
</table>
Human Herpes Virus 8

Kaposi Sarcoma-Associated Herpesvirus
- cause of Kaposi sarcoma

• transmission via body fluids
  - saliva / semen? / CVL?

• establishes latency in B cells
Human Herpes Virus 8

KSHV

- incubation period unclear
  - appears to have long delay from acquisition to sarcoma

- variable rates of infection
  - 0-20% in Asia, NA, Europe
  - >50% in Africa / Amazon
Human Herpes Virus 8

Disease: **Kaposi Sarcoma**
- disease of older adults
- disease of AIDS
- no clear disease states in childhood
- multicentric Castleman disease

Diagnosis: symptomatic
THERAPY
HHV: therapy

• drugs interfere with nucleic acid synthesis

• goals of therapy
  - reduce severity and duration of primary and recurrent outbreaks
  - prophylaxis of outbreaks
HHV: therapy

- guanosine analogs
  - acyclovir and valacyclovir
  - ganciclovir and valganciclovir
  - penciclovir and famciclovir
- phosphate analogs
  - foscarnet
- cytosine analogs
  - cidofovir
guanosine  HO  acyclovir  HO
valacyclovir

acyclovir
ganciclovir

guanosine
valganciclovir

ganciclovir
guanosine  HO  penciclovir  HO
famciclovir

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\begin{align*}
\text{H}_2\text{N} &\quad \text{H}_3\text{COCOCO} \\
\text{H}_2\text{N} &\quad \text{H}_3\text{COCOCO}
\end{align*}
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penciclovir

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{HO} \\
\text{H}_2\text{N} &\quad \text{HO}
\end{align*}
\]
HHV: therapy

• guanosine analogs
  - acyclovir and valacyclovir
  - ganciclovir and valganciclovir
  - penciclovir and famciclovir

• activated by viral thymidine kinase
  - variable activation by cellular enzymes
HHV: therapy: acyclovir

- studied in all age groups
- very effective given IV
- poor GI absorption (10-20%)
- saturable absorption (↓ bioavailability with ↑ dose)
- oral liquid formulation almost pure sugar
  - well tolerated
  - dental caries
HHV: therapy: valacyclovir

- prodrug (valine ester of acyclovir)
  - rapidly converted to acyclovir in bloodstream
- approved by FDA 1995
- under study in children
- 3-5x greater bioavailability

- do not use for CNS disease
HHV: therapy: famciclovir

• prodrug (analog of penciclovir)
  • converted to penciclovir by aldehyde oxidase
• approved by FDA 1994
• being studied in children
• ~75% bioavailability
• longer half-life intracellularly
HHV: therapy: ganciclovir

• similar to acyclovir but with activity against CMV
• much greater bone marrow toxicity
• valganciclovir $$$$$$
• utility in resistant HSV, CMV
• utility in congenital CMV unclear
### HHV: drug activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>HSV-1/2</th>
<th>VZV</th>
<th>EBV</th>
<th>CMV</th>
<th>HHV-6</th>
<th>HHV-7 KSHV</th>
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</thead>
<tbody>
<tr>
<td>acyclovir / valacyclovir</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
<td>?</td>
</tr>
<tr>
<td>penciclovir / famciclovir</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>ganciclovir / valganciclovir</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
<td>?</td>
</tr>
<tr>
<td>foscarnet</td>
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<td>?</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>cidofovir</td>
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<td>?</td>
<td>−</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>