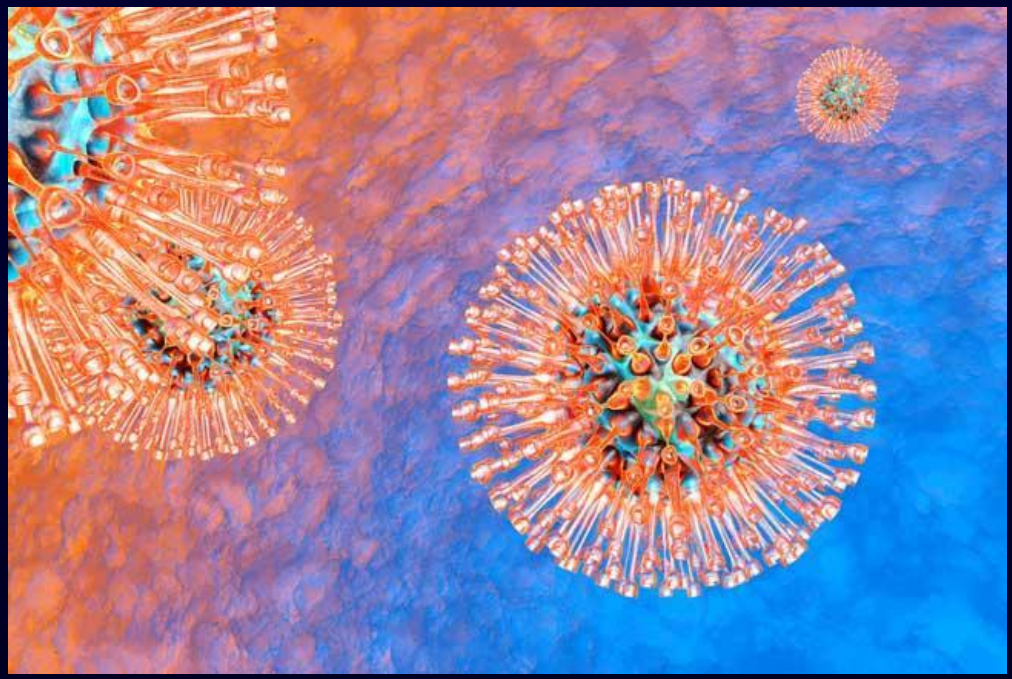
HERPESVIRUSES

Banner University Medical Center
Internal Medicine
2019



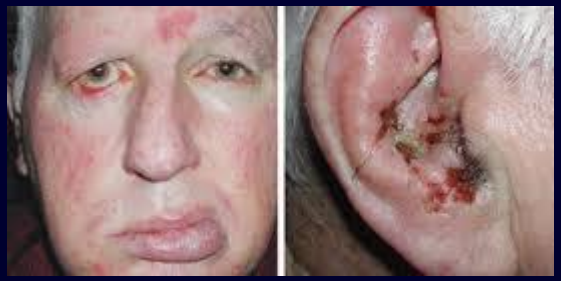
Nelson Nicolasora, MD
Infectious Disease

Objectives

- Learn about the 8 human herpesviruses and their clinical manifestations;
- Know when to use VZIG and the vaccines for varicella;
- Consider appropriate clinical situations when to test for a particular herpesvivirus;
- Know the different medications used against herpesviruses and;
- Recognize the neoplastic processes due to oncogenic herpesviruses.

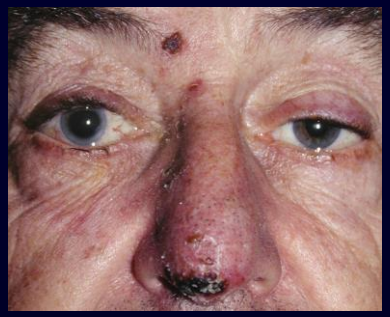
Case 1 : Quick recall. Eponyms and causative agent. Which is the incorrect match ?

A)



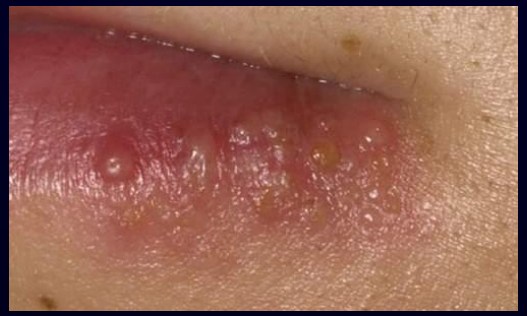
Ramsay-Hunt Syndrome = VZV

B)



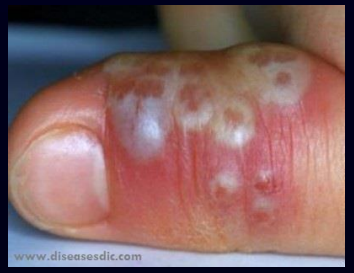
Hutchinson's sign = VZV

C)



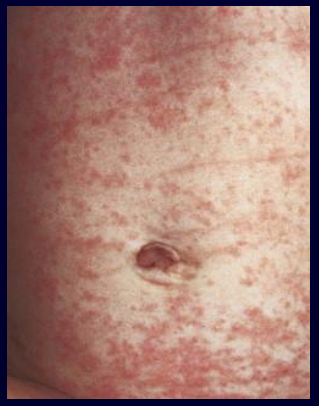
Herpes labialis= HSV1

D)



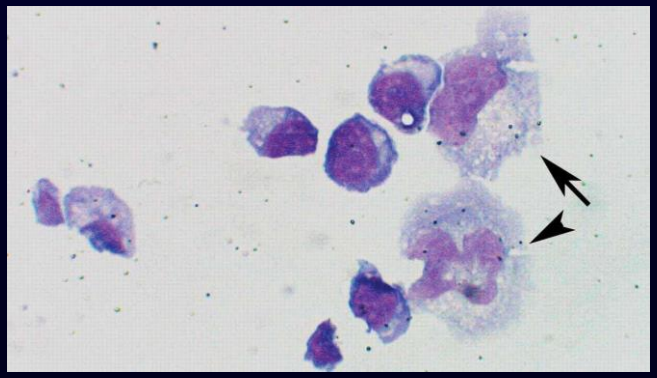
Herpetic whitlow= HSV1

E)



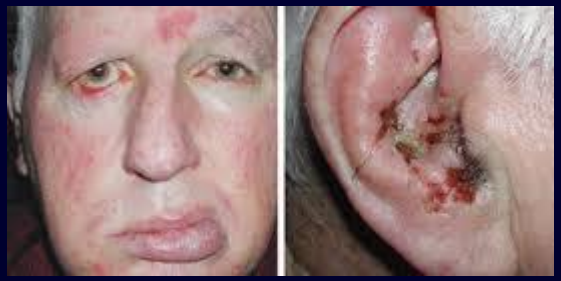
Exanthem subitum / Roseola after 4 days of fever = HHV-6

F)

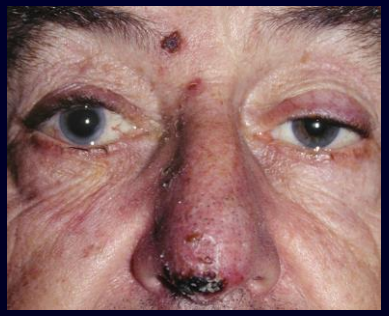


Mollaret's meningitis/recurrent meningitis= HSV-1 greater than HSV-2

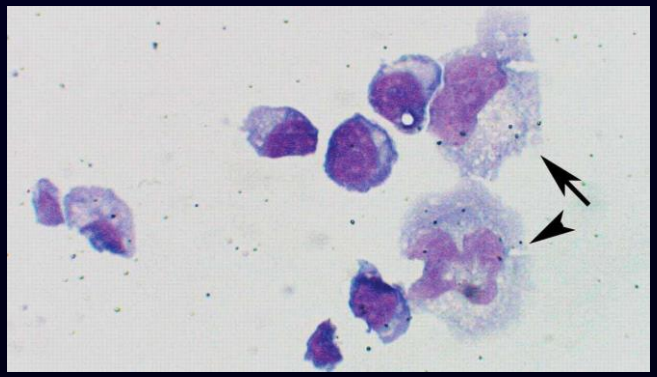
Case 1 : Quick recall. Eponyms and causative agent. Which is the incorrect match ?



Ramsay Hunt syndrome type 2 is the reactivation of herpes zoster in the geniculate ganglion. It is sometimes called herpes zoster oticus, and has variable presentation which may include a lower motor neuron lesion of the facial nerve, deafness, vertigo, and pain. A triad of ipsilateral facial paralysis, ear pain, and vesicles on the face, on the ear, or in the ear is the typical presentation..



Hutchinson's sign.
Vesicles on the tip of the nose, or vesicles on the side of the nose, precedes the development of ophthalmic herpes zoster. This occurs because the nasociliary branch of the trigeminal nerve innervates both the cornea and the lateral dorsum of the nose as well as the tip of the nose.



Mollaret's meningitis/recurrent meningitis= Classically and more commonly caused by HSV-2. HSV-1 causes Temporal lobe encephalitis.

Human Herpesvirus	Diseases
HHV-1 (HSV-1)	Oral herpes, herpetic whitlow, genital herpes, herpes encephalitis
HHV-2 (HSV-2)	Genital and oral herpes
HHV-3 (VZ)	Chickenpox and shingles
HHV-4 (EBV)	Infectious mononucleosis, lymphoproliferative disease to include Burkitt's lymphoma/Hodgkin's lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder (PTLD, HIV-associated hairy leukoplakia & CNS lymphoma)
HHV-5 (CMV)	Infectious mononucleosis like syndrome, retinitis
HHV-6 (HHV6A & HHV 6B)	Sixth disease (roseola infantum) exanthem subitem)
HHV-7	Undifferentiated febrile illness
HHV-8 (KSHV)	Kaposi's sarcoma, primary effusion lymphoma, some type of multicentric Castleman's disease

Human Herpesvirus	Diseases	Site of latency
HHV-1 (HSV-1)	Oral herpes, herpetic whitlow, genital herpes, herpes encephalitis	Neruon
HHV-2 (HSV-2)	Genital and oral herpes	Neuron
HHV-3 (VZ)	Chickenpox ang shingles	Neuron
HHV-4 (EBV)	Infectious mononucleosis, lymphoproliferative disease to include Burkitt's lymphoma, nasopharyngeal carcinoma, PTLD	B cells
HHV-5 (CMV)	CMV mononucleosis syndrome, ocular, colitis, hepatitis, pancytopenia, pneumonia	Mono-cytes & cells
HHV-6 (HHV6A & HHV 6B)	Sixth disease (roseola infantum) exanthem subitem)	T cells and?
HHV-7	Undifferentiated febrile illness	T cells and?
HHV-8 (KSHV)	Kaposi's sarcoma, primary effusion lymphoma, some type of multicentric Castleman's disease	B cells

Case#2 Recurrent HSV infection

RT a 48 M with HIV infection (CD4 count of 16 cells/uL, VL 2 M copies/mL) has a history of recurrent perianal HSV infection that had in the past responded to acyclovir or valacyclovir but recurred repeatedly. On this occasion, the painful ulcer has not responded to a 10-day course of acyclovir 400 mg 3x/day po followed by a 10-day course of valacyclovir 1g BID. The patient was adherent to his regimen. A swab of the vesicles was + for HSV.

If a virus DNA sequencing for resistance cannot be obtained, the best therapeutic option would be?

A) Intravenous acyclovir
B) Oral famciclovir
C) Oral valganciclovir
D) Intravenous ribavirin
E) Intravenous foscarnet

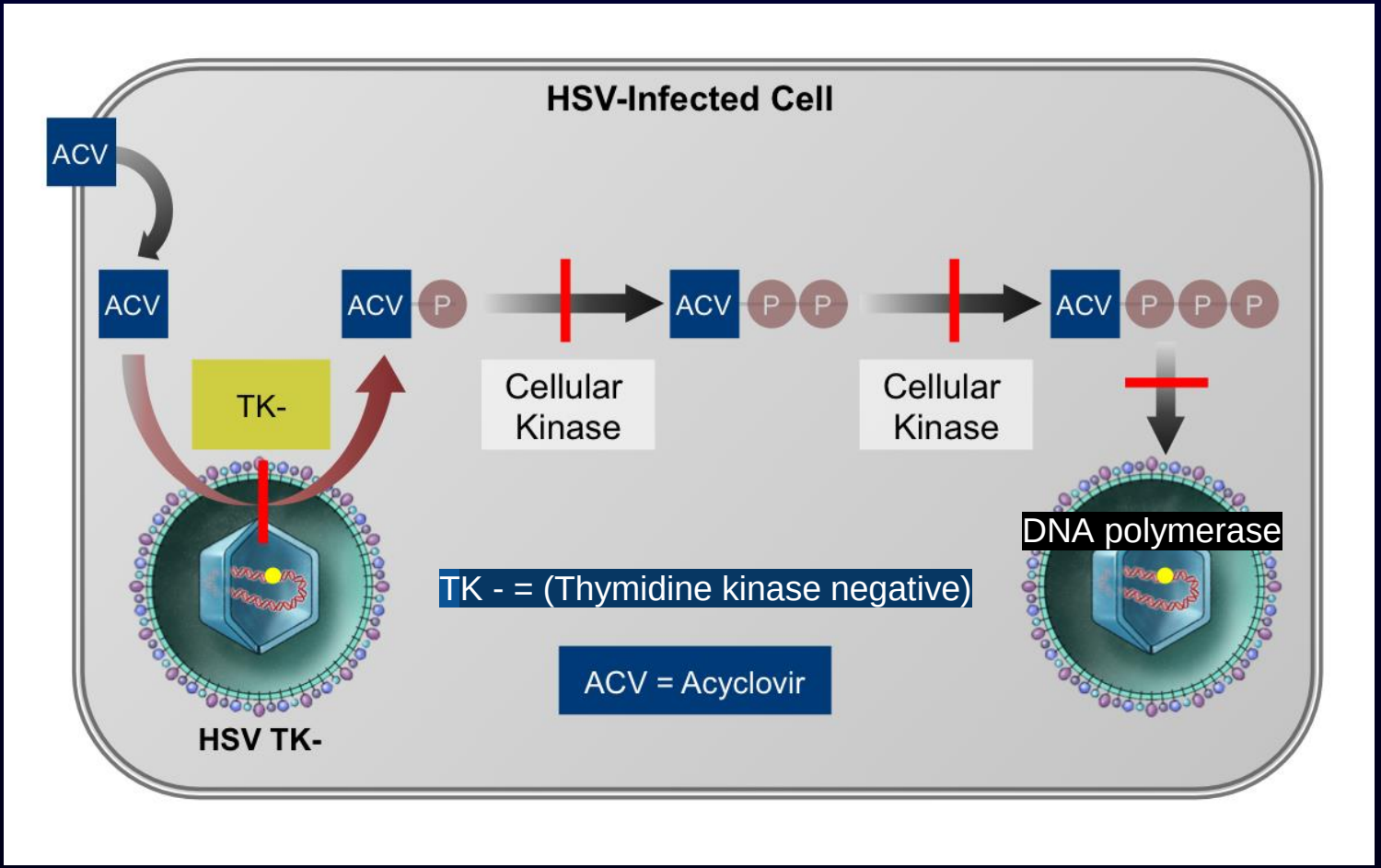
Antiviral Options for Human Herpesviruses

Human Herpesvirus				
HHV-1 (HSV-1)	Acyclovir (po/IV), Valacyclvoir Famciclovir Penciclovir	Ganciclovir (po/IV), Valganciclovir	Foscarnet	Cidofovir
HHV-2 (HSV-2)				
HHV-3 (VZ)				
HHV-4 (EBV)				
HHV-5 (CMV)		Ganciclovir (not HHV-A) Valganciclovir	Foscarnet	Cidofovir
HHV-6 (A & B				
HHV-7				
HHV-8 (KSHV)				

Case#3 Recurrent HSV infection

Mechanism of action and resistance to Acyclovir

P



Case# 3 Post-transplant infection

RF is a 46 F who was admitted to your service for abdominal pain, worsening diarrhea , and intermittent fever of 1-week duration. The rest of ROS is negative. She is S/P LRKT
due to ESRD 2 to autosomal dominant polycystic kidney disease 4 months ago. She is CMV + and she received an organ from a seronegative donor. She received valganciclovir for 3 months after transplantation. Medications are tacrolimus, prednisone, mycophenolate mofetil, and trimethoprim-sulfamethoxazole.

On PE, temp is 37.8 C, BP 144/90 mmHg, HR 104 bpm, RR 16 cpm. Mucous membranes are dry. The abdomen is soft with mild tenderness in the lower quadrants, BS are normal, without guarding or rebound tenderness, She has mild leukopenia, mildly elevated AST and ALT, normal abdominal x-ray, a stool culture positive for Candida albicans, and a negative C diff assay.

Which of the following is the most likely cause for the patients presentation?

A) Candida albicans
B) Clostridium difficile
C) Cytomegalovirus
D) Mycophenolate toxicity
E) Polyoma BK virus

Ans. C. Cytomegalovirus infection.

CMV is a common complication of transplantation especially in the first few months after transplantation when immunosuppression is typically the highest.

The patient recently finished the CMV prophylaxis (3 months) period and is at risk for CMV reactivation (status: CMV +/-)
She has typical symptoms of colitis, the colon and the esophagus are commons sites of reactivation after transplantation. Small bowel enteritis, hepatitis, and gastritis may also occur although less often. Quantitative PCR in serum can be suggestive, but colonoscopy with immunostains and the classic "owl's eye' finding on histopathology as well as a + tissue culture can establish a definitive diagnosis.

Candidal overgrowth can happen but patients are typically asymptomatic. The Clostridioides difficile assay is negative.

Mycophenolate can cause diarrhea, but the presence of fever is concerning for an infectious process.

Case# 4 Annual evaluation

JK is a 55 F with a medical history significant for hypothyroidism on levothyroxine, HTN, and well controlled DM2.

She had a history of VZV infection at the age of 36 in her right chest wall at the time that she was diagnosed with DM2. She has no PHN symptoms. She is asking if she is a candidate for the varicella vaccine. Which of the following is the right response based on the current ACIP guidelines?

A) a history of VZV means that she is immune from recurrent attacks of shingles
B) she needs to know her varicella antibody titers to see if she needs vaccination
C) the zoster vaccine live (ZVL) is the preferred agent for long lasting immunity
D) the recombinant zoster vaccine (RZV) is the preferred agent although the incidence of reactions is much higher than the ZVL

Ans D. Comparison between ZVL and RZV

	ZVL = Zoster Vaccine Live (Zostavax)	Recombinant Zoster Vaccine = RZV (Shingrix)
Type	**Live attenuated virus**	**Glycoprotein E + adjuvants (ASO1-B)**
Availabilty	**2006 (Froze)**	**2017 (Refrigerate)**
Shingles	**SPS-----51%**	**ZOE 50 --------97.2% ZOE 70 --------91.3%**
PHN	**SPS ------66.5%**	**ZOE 50 ---------91.3 % ZOE 70 ---------88.8%**
Reactogenic	**Less**	**84% reaction, 17% Grade 3 reaction**
Sustained efficacy	**1st yr drop 15-25% 6 yrs < 35% effective 10 yrs no protection**	**>4 years, 38 K patients**
Age	**>60**	**>50**
Dose	**1 SQ dose**	**2 IM doses, 0, 2-6 mos apart**

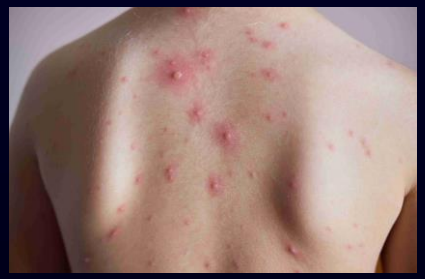
RZV Can be given after ZVL and after shingles, > 2 months.

Case#5 Post-exposure prophylaxis

PM a 49 year old year pro golfer comes in to the office for evaluation of recent exposure to chickenpox. He visited his sister's home last week. His nephew subsequently developed a rash (see image below) and was diagnosed with chickenpox a day after he left. He is asymptomatic . He never had chickenpox as a child and has not been immunized against varicella. Medical history is notable for severe psoriatic arthritis. His only medication is etanercept, a drug which he endorses in commercials.

His PE is unremarkable . The result of a serologic assay for antibodies against varicella zoster virus (VZV) is negative

He is asking if we can do anything for him since he is scheduled to be back on the PGA tour next week.



Which of the following is the most appropriate management?

A) Acyclovir therapy
B) Live attenuated vaccine (LAV)
C) Varicella zoster immunoglobulin (VZIG)
D) LAV and VZIG)

C. VZIG.

In general, the risk of transmission of VZV infection is higher with exposure to persons with primary varicella compared to herpes zoster. The period of contagiousness during primary varicella is estimated to begin approximately 1 to 2 days before the onset of rash. Persons with either illness are not infectious once the lesions have crusted over.

The usual incubation period of varicella in an adult or child is 14 to 16 days, but sometimes ranges from 10 to 21 days after exposure. The incubation may be prolonged for as long as 28 days after receipt of VariZIG or intravenous immunoglobulin and it may be shortened in immunocompromised patients.

The ACIP recommends that the following patient groups receive immunoprophylaxis :

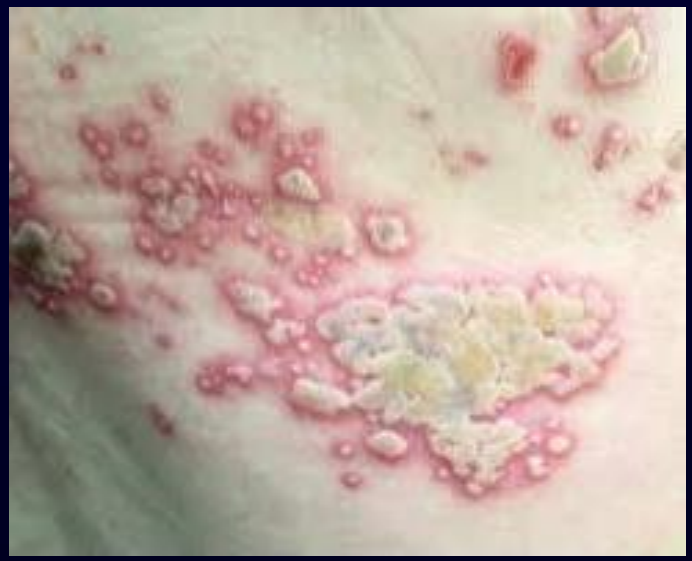
- Immunocompromised patients (including those with primary and acquired immunodeficiencies)
- Persons with neoplastic disease
- Persons taking immunosuppressive therapies
- Neonates

Pregnant women.

Passive immunoprophylaxis **is not indicated** in a patient with a history of two prior doses of varicella vaccine that preceded the onset of immunocompromised state.

Case#6 Isolation precautions

A 63 M is admitted to the hospital for management of varicella-zoster infection. He developed pain and tingling over the right posterior flank area 4 days ago, followed by lesions seen below. He reports fever without chills and no cough. He is undergoing immunosuppressive chemotherapy for stage III colon cancer and received his last dose 12 days ago. Medical history. His BP is under control on 5 mg of amlodipine.



Vital signs are unremarkable except for a T=38 C. PE : pale, the lesion as shown.
He is admitted for trasnfusion.

Which of the following is the most appropriate in-hospital precaution for preventing spread of infection?

A) Airborne
B) Airborne and contact
C) Contact
D) Contact and droplet
E) Droplet

Ans. B . Airborne and contact precaution.

Patients with VZV infection and the following findings should be placed in airborne (negative-pressure room) and contact precautions:

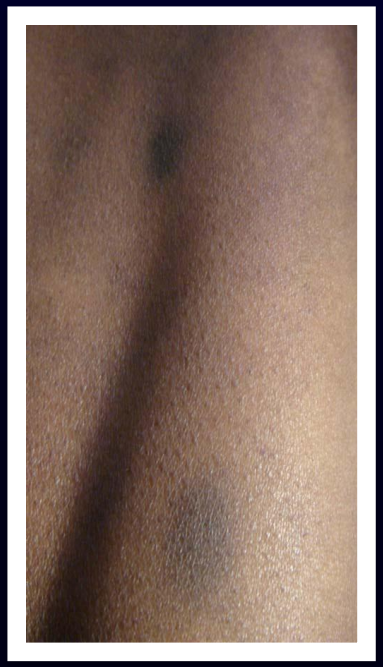
- **disseminated zoster; more widespread rash involving 3 (THREE) or more dermatomes and;**
- **immunocompromised host.**

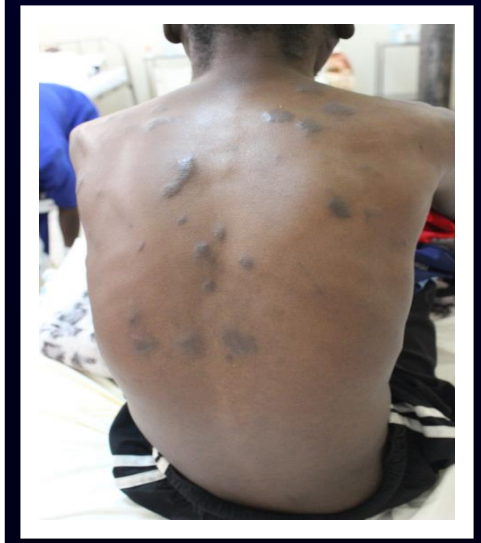
The VZ virus can be aerosolized in small respiratory droplet nuclei (<5 um) that can remain suspended for extended periods or travel long distances on air currents. (Other organisms requiring airborne precautions include: TB, measles, and chickenpox, latter with 90% household contact attack rate).

Case#3 : HIV patient with skin lesions

- 32yo homosexual male, S/P treatment for STDs to include Chlamydia, GC, HSV, and a couple of months ago a successful treatment with benzathine PCN for 2^0 syphilis with > 4-fold decline in titer. He has had HIV since 2004, and has been off cART for 2 years. His CD4 is 183 cells/uL and his viral load is 345,000 copies/mL. He presents on follow-up without any complaints and was noted to have skin lesion one exam.

- What is the next approach?
  A) treat again for syphilis
  B) consult Oncology
  for urgent chemotherapy
  C) initiate cART
  D) rule out AI
  E) initiate steroids for eczema





Case# 7 : Kaposi sarcoma in a patient with AIDS

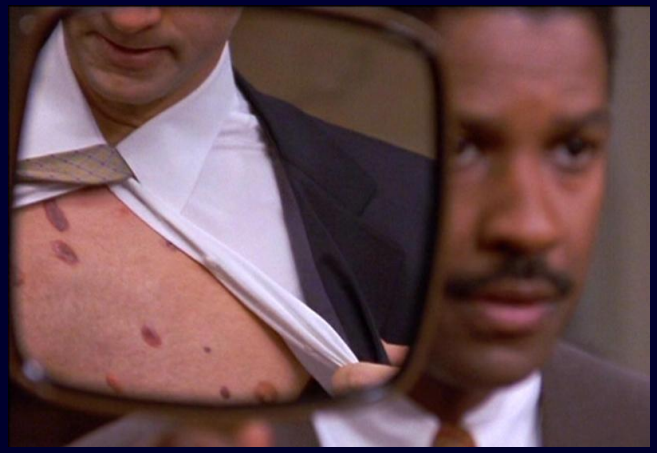
- Kaposi sarcoma herpesvirus KSHV/HHV-8 was discovered in 1994; common in MSM
- An oncogenic virus (like EBV, HBV, HCV, HTLV-1, & HPV)
- Causes PEL (primary effusion lymphoma) and Castleman's disease (multi-centric lymphoma)
- DDx: bacillary angiomatosis, syphilis, lymphoma, fungal infections, nevi etc. Confirm with a biopsy.
- 3 features of KS: angiogenesis, inflammation, and proliferation
- The lower the CD4, the higher the risk for KS; steroids can bring about the lesions
- Classic cutaneous lesions: oval, purplish, violaceous along skin realxed tension lines
- Rule out disseminated KS (mainly oral cavity, GI, and pulmonary)

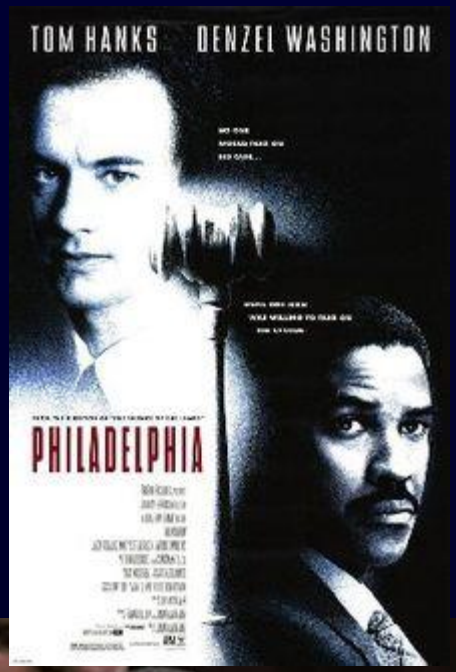
Case#3: Kaposi sarcoma in a patient with AIDS

	Epidemiologic forms of KS
AIDS-related KS	Most common tumor in HIV patients Standardized incidence ratio (SIR) for KS compared with the general population fell from 22.1K to 3.6K following widespread use of cART
Endemic or African KS	Primarily in sub-Saharan Africa before Hiv Dramatic increase since HIV epidemic
Classic KS	Indolent disease in Mediterraneean and Jewish orgin.
Organ transplant associated-KS	Primarily after SOT

Case#3: Kaposi sarcoma in a patient with AIDS

Treatment of KS	
ART	80% reduced risk of death on KS patients who received ART (Multicenter AIDS Cohort Study)
Localized therapy	Radiation therapy, intralesional vinbalstine
Chemotherapy	Paclitaxcel or liposomal anthracyclines (doxorubicin, daunorubicin). Other drugs: Vinca alkaloids (e.g. vincristine), gemcitabine, and bloemycin
	Primarily after SOT
Supportive	Reduce immunosuppression, manage pain Treat other infections Sirolimus and everolimus may help in transplant patients




TOM HANKS
DENZEL WASHINGTON
PHILADELPHIA


Andrew Beckett
Joe Miller

Thank you.

- **Spaceflight activates latent herpes viruses in astronauts, NASA study shows**