MID Test II Viruses and TB
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Herpesviruses and Smallpox

General Stuff

Common Features of Herpesviruses
•Morphology
• Basic mode of replication
• Primary infection followed by latency
• Ubiquitous
• Ability to cause recurrent infections
(reactivation of latent virus), **reinfections**
(with a new virus), **persistent infections**
(chronic low grade virus multiplication)
immortalizing infections (EBV only). The other form of infection is latent, and there is little viral gene expression, so the host cell survives.

8 Human Herpesviruses, 3 categories
• **Alpha: short reproductive cycle,variable host range, latent in sensory neurons**
– Herpes simplex virus (HSV 1, 2)
– Varicella- zoster virus (VZV)

• **Beta: long reproductive cycle, narrow host range, latent in lymphoid cells & others (salivary glands, kidney)**
– Cytomegalovirus (CMV)
– HHV6, HHV 7

• **Gamma: narrow host range; latent in lymphoid cells, associated with tumors**
– Epstein Barr Virus (EBV)
– Kaposi Sarcoma Virus (KSH, HHV8)

Replicative Cycle
1. Enveloped viral particle invades clss by utilizing receptors on the cell surface (HSV binds to members of Ig, TNF family and VSV to mannose-6 phosphate and heparan sulfate)
2. Glycoproteins (B, D, H, I) on virion – enable attachment of virus to cell (also used by the
3. Virus uncoats, DNA goes to nucleus and replicates

• **Transcription of viral genome and protein synthesis (cascade of gene expression), essential and luxury**
– 1. immediate early (IE): regulation of gene expression, DNA binding
– 2. early (E): more transcription factors, enzymes, DNA polymerase
– 3. late (L): structural proteins

4. Nuclecaspids are formed there, which extrude into the perinuclear space with an early envelope
5. Fuses with the RER → naked nuclecaspid goes into cytosol
6. **Nucleocaspid become enveloped** by tegument proteins and glycoprotiens in the **trans Golgi Network (TGN)**
7. Enveloped virion → incorporated into endosomes (HSV resists the acidic environment) → released extracellularly
8. virus in cell to cell spread). They are components of a new HSV2 vaccine.
9. Lytic infection → cell death
10. Latency occurs when the cascade is interrupted
11. Latent infection occurs in sensory neurons

– Latency associated transcripts (LATS)
– Minimal transcription of DNA, no translation

Because of cell → cell spread, CMI is crucial in host response; Ab's usually inefective (except for VSV infection.
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Herpesviruses can also spread as a free enveloped particle.

• **Encode targets for antiviral therapy**
– Thymidine kinase (TK), DNA polymerase

Clinical Presentation	Pathogenesis	Predisposing Factors/ Epidemiology	Likely Pathogens	Definitive Diagnosis	Complications	Treatment / Prevention
Genital Ulcers: ▪Multiple, bilateral grouped umbilicated vesicles which become postular and coalece into large PAINFUL ulcers ("shaggy") ▪severe painful vulvovaginits or balantis ▪with or without urthritis ▪pain, itching, dysuria with or without urethral discharge ▪tender inguinal lymphadenopathy In 1/3 of patients, symptomatic complaints: ▪headache, fever, malaise, and myalgia	▪Transmitted via sexual contact ▪Invades local cell → causes local inflammatory response ▪Spreads to other cells locally ▪Moves aliong sensory nervers (Schawn cells) to ganglia ▪Becomes latent, reactivates	Virus can be shed by symptomatic and asymptomatic individuals Most common STD in higher socioeconomic groups	**Herpes Simplex Virus 2 mostly, HSV-1 rarely (from oral → genital transmission)**	**Clinical:** ▪ulcerate leaving a shaggy ulcer ▪lymph node involvement **Microscopic:** ▪Wright-stained or Tzank stained: see multinucleated giant cell in Herpes (cytopathic involvement) **Serology:** ▪Rise in anitbody titers **Rule out syphilis, chancroid, LGV.**	Associated with primary disease: ▪Aseptic meningitis ▪Transverse myelitis ▪Sacral radiculopathy ▪Can be transmitted to newborn resulting in serious organ damage	**Acyclovir (ACV), famicylovirm, valacylovir**

Baby with: ▪**Ulcers in oral mucosa (gingivostomatatitis)** ▪Swollen friable gums ▪Secondary infection on the thumb from sucking on it (whitlow of the finger) ▪Baby may have fever or be irratable ▪Although infection looks severe, it's self limited	Saliva transmission	Usually transmitted by saliva Examiners should wear gloves, highly infectious at this point	**HSV-I**		May lead to poor nutrition and dehydration of a few days	No antiviral therapy
▪**Corneal ucers** ▪Lesions of the conjunctival epithelium (**karatitis** or keratoconjunctivitis)	Mouth → Hand → eye transmission				May lead to scarring or blindness	
▪**Severe infection of the skin**		**Person with underlying eczema**				
▪Headache ▪Fever ▪**Personality change**, ▪**Focal seizures**, ▪Skin lesions may be present (not helpful for diagnosis) **Test findings:** Abnormal EEG, CT, MR	**Focal Encephalitis**	Primary or recurrent HSV- 1 . Most common form of focal ncephalitis in USA - about 1000 cases of encephalitis annually		**Differential diagnosis:** TB meningitis, arbovirus, enterovirus, flavivirus, mycoplasma, tumor, toxoplasmosis, aneurysm **Diagnosis:** CSF culture is usually negative, but PCR is often positive for HSV		Treat with **ACV** if suspect disease; prognosis better in children than adults; early therapy is best
Newborn with: • **Skin, eye, mucous membrane (40%)** – **Skin vesicles** – Good prognosis with early treatment Untreated 75% develop disseminated infection **CNS Infection (35%)** – Fever, lethargy, seizures, abnormal CSF – 50% mortality; major sequelae if survive • **Disseminated disease (25%)** Hepatosplenomegaly, jaundice, hepatitis, pneumonia – 2/3 develop skin vesicles – 70% mortality	**Perinatal HSV** Perinatal HSV is usually due to Type 2 virus • 95% neonatal, 5% congenital	• Usually the mother is asymptomatic • Attack rate >10 times higher in maternal primary infection than recurrence; attack rate about 50% 1600 cases annually	**Usually HSV-2;** HSV-1 in very cases	▪Immunofluorescence ▪culture, ▪ PCR ▪Antibody titers are not useful	Skin, mucous membrane infection → untreated → disseminated infection	• Treat all newborn infants with possible HSV • Recurrent skin vesicles are associated with a poorer prognosis – may re- treat with ACV – May give 6 weeks of oral ACV
▪Fever and malaise (prodromal symptoms) ▪Papulovesicular rash **appears in crops on the trunk and then spreads to head and extremities (centripiltal)** ▪**Papules → vesicles → pustules** → crusts ▪Itching ▪Mild in chilren, severe in adults Years later.... ▪Painful vesicles along the course of a sensory nerve of the head or trunk ▪Pain can last for weeks ▪Postzoster neuralgia can be debilitating	**In the body VZV spreads from cell-to-cell** **Varicella (Chickepox)** • VZV → respiratory mucosa → blood (viremia) → T cells (long incubation period – 2 weeks from cell-cell spread) – Slow spread prevents host from being overwhelmed before the immune response develops **Zoster (Shingles)** • Latent infection in dorsal root ganglia (DRG) • 6 of 68 genes (also RNA and proteins) expressed during latency • Proteins of regulatory genes are expressed in	**• Varicella is likely to be severe in the Immunocompromised (lack of TH1 response)** – Prevent or modify with pre-formed antibodies just after exposure – Treat most patients immediately with acyclovir • The frequency of zoster is increased – Probably related to low CMI response – Likely to suffer post- herpetic neuralgia (PHN) (also elderly)	**Varicella Zoster Virus (VZV)**	• **Culture, DFA, PCR, cytology on skin rash** –Can distinguish the Oka virus from wild type virus • **Antibody titers, IgG** –Acute serum, early in illness –Convalescent serum, 10- 14 days after onset • **Antibody titers, IgM** –False positives and false negatives can be a problem Rule out smallpox	**After primary infection:** ▪bacterial superinfectio n, ▪encephalitis, ▪pneumonia, ▪congenital syndrome, ▪Reye's syndrome. **Post-herpetic nerualgia (elderly and immunocompromi sed)**	**Treatment** **ACV** (but not as useful as for HSV infections) **famicylovirm, valacylovir for elderly patients with zoster** **Prevention:** **Live, attenuated, infectious virus (Oka strain)** **Contraindications: pregnancy, immunocompromised, allergy to vaccine components** Major complaint afterwards: mild rash in 5% • This vaccine is extremely safe 80% completely protected; 20% partial immunity. Little evidence for waning immunity.

	cell cytoplasm, not nucleus • Suggests regulatory proteins are blocked from normal action, leading to inhibition of cascade of gene expression preventing lytic infection from occurring (latency) • Latency is established when cell- free VZV in skin vesicles invades neurons					
12-14 days afer exposure: **<u>Exanthema</u>** **Muculpapular rash (face mucosa → trunk → trunks and legs) → vesicles → pustules** (can become confluent on face) Severe looking rash gets progressively worse	Resp mucosa → LN → viremia (asymptomatic) → secondary viremia (rash)	**Bioterrorist Agent (currently eradicated around the world)** **<u>Transmission</u>** ▪Infectious via aerosol (droplet nuclei or aerosol) ▪Rapid person → person ▪Most at risk = household contacts ▪Secondary spread → 1-10 new cases ▪High rates of transmission in hospitals ▪less contagious than measles/varicella ▪Patients not contagious until rash begins **<u>Immunity</u>** ▪Worldwide immunity waned ▪30% mortality ▪**Vaccine after exposure still prevents illness**	**<u>Smallpox virus</u>**	**Rule out VCV (incubation similar, difference is prodome → where rash starts (smallpox = centrifugal), erythmema mutliforme** **Swab of vesicular fluid → PCR assay at CDC**		**<u>Tx</u>** No known treatment Strict quarantine **<u>Prev</u>** **<u>Live virus vaccine,</u>** **Admin:** poke with a needle (old school) → stab skin 3X for unvaccinated, 15X for previously vaccinated; draw blood See vacule → pustule → scab (if this doesn't happen, didn't work) Lasts for a while, best for three years afterwards, but steadily decline Can see normal extra reactions (extra lesions, LN swelling etc) **Contra: immunodeficiency, skin diseases (exema, or atopi dermatitis), preg women, cardiac problems** **Adverse event: infecting your eye by touching; generalized vaccinia** **Severe: someone with excema given vaccine, or progressive vaccinia in immunocompromised patient** Old vaccine can be diluted **Tx for complications → Ab for vaccinia** First responders ought to be pre-vaccinated So far complication rate has been low with pre-screening New complication → myopericarditis
Healthy Adult Host: • usually subclinical ▪Mononucleosis- like syndrome occurs but is rare Immunocompromised: ▪Fever ▪Pneumonia ▪Retinitis ▪Colitis ▪Lymphadenopathy ▪Rash ▪Encephalitis ▪Neutropenia, etc. • Fetal (congenital) infections: can be severe - 40,000 annual cases (1% of all infants) - 3,000 symptomatic at birth (jaundice, petechiae, microcephaly, prematurity) - 8,000 with sequelae (deafness,	– immune evasion • **Down regulation of MHC class I** expression to reduce effectiveness of cytotoxic T cells • Host defense: cellular not humoral immunity • Latency in bone marrow precursors of monocytic peripheral blood cells – Differentiation of monocytes into macrophages due to antigenic stimulation reactivates CMV • Adverse effects on ransplantation	**<u>Congenital</u>** **Most common congenital viral infection in US** • Risk to the infant is highest in first trimester (13 weeks) maternal infection - primary maternal infection poses greatest risk - the fetus is not always protected when an "immune" mother is re-infected with a different strain of CMV **<u>Transmission</u>** •Close personal contact – Sexual, day care, saliva, tears, urine – Virus is not usually airborne • Cell-associated virus, no skin lesions • Spread from secretions, on hands	**<u>Cytomegalovirus (CMV)</u>** • Largest of the herpesviruses	• Distinguish between congenital and perinatal – In congenital urine is culture +for CMV in first 3 weeks of life Diagnosis of CMV • Histology: has limitations (not specific) – Basophilic inclusion bodies – H&E, Pap staining • Cell culture – Cytopathic effect, immunofluorescence • Serology: acute and convalescent antibody titers are of limited value		Treatment of CMV • Ganciclovir – Phosphorylation by viral enzymes causes inhibition of viral DNA polymerase (related to acyclovir); toxicity: bone marrow suppression • Foscarnet – Inhibits viral DNA polymerase; renal, metabolic toxicity • Cidofovir – Inhibits viral DNA polymerase • Very toxic (renal, uric acid increase) Pre- emptive approach Identify infection before the illness Treatment used mostly for immunocompromised patients Control of CMV • Hand washing (eg, after diapering) • Condoms, abstinence • Beware of blood

retardation) • Perinatal infections: of little consequence		• intrauterine/ birth/breast milk •Transfusion •Transplantation		– False positive and false negative IgM titers • In situ hybridization • PCR		– Use seronegative, irradiated, filtered blood for high risk patients • Testing for CMV in transplantation (donor, recipeint) • Vaccine still not available
Young adults adult with: ▪Fever ▪Adenopathy ▪exudative pharyngitis ▪rash (ampicillin) ▪hepatosplenomegaly ▪fatigue	**Attachment** Major glycoprotein is gp 350 which binds to CD21 on B cells (C3d complement receptor) • Virus practices immune evasion – Genes that mimic IL 10 and decrease IF response, inhibit apoptosis **Latency** • B cells are latently infected in mononucleosis; T cells (atypical lymphocytes) are the host response • Latency persists in memory B cells • EBV is not related to chronic fatigue syndrome, but rarely severe chronic illness follows mononucleosis	– Patients with x- linked agammaglobuinemia can't be infected **Transmission:** • saliva (lytic)	**Epstein-Barr Virus (EBV)**	• Positive heterophile antobody (monospot) • EBV specific antibodies – Anti VCA (develops early, persists) – Anti EBNA (develops late persists)	▪Infectious mononucleosis, ▪nasopharyngeal ▪carcinoma, ▪lymphomas (including Burkitt's), ▪oral hairy leukoplakia (lytic infection), ▪X- linked proliferative disease (males only)	• In mononucleosis, give steroids if airway obstruction, hemolytic anemia, severe cardiac, neurologic disease (no specific antiviral therapy) • Experimental therapy forimmunocompromised patients with severe infections/tumors – Decrease immunosuppressive therapy if possible – Monoclonal antibodies (rituximab) – Infusion of leukocytes
Normal Hosts: Can cause non- specific fever and rash illness **Elderly, HIV- infected** • Causes Kaposi's Sarcoma • Causes primary-effusion lymphoma • Castleman's disease	• Encodes for human proteins (piracy) – IL- 6, Bcl- 2, cheomkines and receptor	• Infections are rare in children	**Herpesvirus 8 (KHSV)** • Closely related to EBV			No effective antiviral treatment.

Enteroviruses and GI Viruses

Clinical Presentation	Pathogenesis	Predisposing Factors/ Epidemiology	Likely Pathogens	Definitive Diagnosis	Treatment	Prevention
Asymptomatic infection most common (95%) **Abortive poliomyelitis** (4-8%) (Sx last a few days): ▪Fever ▪Headache ▪Sore throat ▪Listlessness ▪Anorexia ▪Vomiting ▪Abdominal pain ▪Normal neuro exam **Nonparlytic poliomyelitis** ▪Systemic symptoms more severe than above ▪See meningeal signs ▪Full recovery is norm **Spinal paralytic poliomyelitis** (0.1% of cases) – biphasic course w/ major, minor illnesses. Patient recovers after 1-3 days of mild illness, remains well for 2-5 days but then becomes abruptly ill with: ▪Headache ▪Fever ▪Vomiting ▪Neck stiffness This lasts for 1-2 days before: ▪Weakness ▪Flaccid paralysis ensue (on range of single muscle → quadriplegia) **Bulbar paralytic poliomyelitis** (paralysis of muscles innervated by CN): ▪Dsyphagia ▪Nasal speech ▪Dyspnea with (CN 9, 10 – most affected) ▪Vasomotor, respiratory centers may be involved **Polioencephalitis:** ▪Confusion ▪Changes in mental status ▪Uncommon and occurs primarily in infacnts	**Infection** ▪**Enters via gut** ▪Replicates in submucosal lyphoid tissue ▪Spreads to reticuloendothelial system ▪From there → blood → replicates in **gray matter** of motor neurons in brain, spinal cord → extensive necrosis **Immunity:** ▪IgA, IgG response ▪Infection provides life-long type specific immunity	▪**Used to be common childhood infection → but then later onset of disease as populations had better nutrition** ▪**Vaccine introduced in 1955 has helped eliminate polio in Westernized countries**	**Polioviruses** Picornavirus ▪Small ▪Non-enveloped ▪ssRNA (+) ▪icosohedral neucleocapsid	**Isolation of the virus:** ▪from throat secretions in first week of illness ▪from feces for several weeks ▪unlike other enteroviruses, rarely isolated from CSF ▪cuases cytopathic effect **Serologies** ▪rise in Ab titer	**Symptomatic relief and support.** **No antiviral therapy.**	2 vaccines: **Oral Polio Vaccine (OPV):** **Live attenuated vaccine** = mainstay of vaccination programs across world. Excreted in feces → allowed for futher spread to unvaccinated individuals (if ya can't beat em, join em). Rarely, vaccine led to paralytic disease. Therefore: **Inactivated Polio Vaccine (IPV)** – used, now just as immunogenic, and safer.
Do not usually cause symptomatic infections of the gastrointestinal system		**Distributed worldwide** **• More prevalent in summer and autumn in temperate climates (June-October)** **• Most infections occur in children < 1 year**	**"Other enteroviruses": Coxsackieviruses, echoviruses, newer enteroviruses** **DON"T NEED TO KNOW SPECIFIC VIRUSES**		Therapy is supportive	
Central Nervous System				PCR of spinal fluid usually reveals cause		
Aseptic meningitis Prodrome- fever, chills, malaise, URI Headache, fever, stiff neck, photophobia **– CSF: 10-500 WBC, lymphocytes, nl to slightly elevated protein, nl glucose**			90% of viral aseptic meningitis in the community due to group B coxsackieviruses and echoviruses			
Encephalitis CNS infection		Accounts for 11-22% of viral encephalitis when you include polioviruses	Unusual manifestation of echovirus and coxsackievirus			

		Prognosis, except in infants, is excellent				
Chronic meningoencephalitis		**Seen in patients with acquired or congenital defects in B cell function**	Echoviruses	Echoviruses can be recovered from CSF for months-years		Try to prevent with monthly IG
Paralytic Infections Usually less severe than poliomyelitis Paresis not permanent			Occasionally associated with coxsackie and echovirus infections Outbreaks of flaccid paralysis associated with coxsackievirus A7 and enterovirus 71			
Exanthems						
Morbilliform rashes **Fine, erythematous, maculopapular rashes** Rash appears simultaneously with fever and **starts on face**		**Common in summer months**	Associated with echovirus 9			
Roseoliform rashes **Discrete, nonpruritic, salmon-pink macules and papules on the face and upper chest** Prodrome of fever and pharyngitis Rash appears after defervescence and lasts1-5 days		**Contagious especially amongst young children**	Echovirus 16 most commonly associated			
Hand-foot-and-mouth disease **Distinctive vesicular eruption** **Fever and vesicles in the mouth and on the hands and feet** Can look like chickenpox but illness is generally milder		**Most common in children under age 10**	Coxsackie A16 or enterovirus 71			
Generalized vesicular eruptions Lesions look like those of hand-foot-and-mouth but occur in crops on the head, trunk and extremities Do not evolve into pustules or scabs (unlike chickenpox)			Most frequently caused by coxsackievirus A9 and echovirus 11			
Herpangina Vesicular rash involving pharynx and soft palate Fever, vomiting, myalgia and headache associated with prodrome		Summer outbreaks	Group A coxsackievirus			
Respiratory Disease **Upper respiratory infections** Fever with sore throat, cough and coryza		**Cause majority of summer colds in children**	Coxsackieviruses A21 and A24; echovirus 11			
Epidemic pleurodynia Acute disease with fever and sharp, spasmodic pain in chest/upper abdomen muscles Fever peaks one after onset of pain spasm Lasts 4-6 days usually but can persist for months						
Myopericarditis Inflammation of the myocardium and pericardium and Symptoms URI in 70% followed by Dyspnea, chest pain- precordial, dull	Virus appears to replicate in the myofibers leading to myofiber necrosis and local inflammation	**Special predilection for physically active adolescents and young adults** **Males outnumber females 2:1**	Enteroviruses, especially group B coxsackieviruses, group A types 4 and 16 Echoviruses 9 and 22 account for 50% of all cases of acute			

Fever, Malaise **EKGs usually abnormal,** cardiac enzymes elevated Complications: Can lead to chronic congestive heart failure			myopericarditis			
Enterovirus infection of the newborn Biphasic illness Mild non-specific symptoms between 3 and 7 days of life followed by 1-7 days of well-being Generalized disease follows Myocarditis with encephalitis-Fulminant hepatitis- hypotension, bleeding, multiple organ failure		**Neonates are especially susceptible to severe enterovirus infection** Most serious infections appear to occur perinatally and probably are acquired from the mother Lack of macrophage activity in the neonate is probably responsible for seriousness of infections	Echovirus 11 Group B Coxsackieviruses	Diagnosis by PCR of urine, feces, blood, CSF	Treatment is supportive; pleconaril disappointing	
Acute hemorrhagic conjunctivitis Epidemic outbreaks of eye pain, swelling and subconjunctival hemorrhage Usually bilateral Most cases resolve spontaneously		Highly contagious	Enterovirus 70 associated			
Range from asymptomatic to severe diarrhea • **First infection more severe than subsequent** • **Maximal disease incidence in infants 6-24 mos** • Up to 30% of adult cases are symptomatic – Symptoms include • Fever • Nausea/vomiting • Watery diarrhea without blood/mucous Dehydration/electrolyte imbalance lead to hospitalization and death	**Infection** Spread by **fecal-oral route** – Virus enters and replicates in mature villus cells of the small intestine – Infection kills cells and loss of absorptive area ensues **Disease** • Lactose intolerance common following infection • Enterotoxin may also contribute to diarrhea – Highly infectious and hardy • 1 pfu can cause disease • Not killed by many disinfectants	**Geography** – Worldwide distribution **Epidemiology** – Most common cause of diarrhea requiring hospitalization in the world • **Account for 10-20% of diarrhea-related deaths in children** • Up to 120,000 hospitalizations in US/year **Season** – Seasonal in temperate climates • **Occur in winter months in North America** • Outbreaks start in the south west and move up to the north east by spring **Host** **Everyone infected by age 3**	**Rotavirus** • Reovirus family – Wheel-like appearance – Large, non-enveloped RNA viruses – Eleven segments of double stranded RNA » Reassortment occurs » Require RNA polymerase to make mRNA • Seven antigenic groups named A-G – groups A-C cause disease in humans – group A viruses account for most human disease worldwide.	– **Clinical-** febrile infant with diarrhea in the winter – **ELISA**- detect rotavirus antigen in stool sample – **PCR** – Electron microscopy – Serology- epidemiological tool	– Replace **fluids and electrolytes** (oral or IV) – Early feeding- promote enterocyte regeneration – Do NOT give antidiarrheal agents	– Wash your hands – Chlorine containing disinfectants – **Vaccine** • Rotashield® – Live, oral vaccine – Rhesus-human recombinant – 15 cases of intussusception in first 10 months after licensure led to withdrawal
• Incubation period 24-48 hours followed by **abrupt onset of vomiting and diarrhea with fever** • **Lasts 24-72 hours** Diarrhea associated with transient malabsorption and decreased enzyme activity • Viral shedding highest in first 24-48 hours of illness	• Spread through **oral-fecal route** • Survive stomach acid and move to jejunum **Incredibly hardy** – Survives routine chlorination – Difficult to eradicate – Can persist for weeks • Secondary and tertiary cases common • Blunting of villi in jejunum seen on pathologic specimens	**Geography** • Widespread and common throughout the world **Season** • **No seasonal variation** • Affects **all age groups** • **Important causes of outbreaks of gastroenteritis**	**Caliciviruses** • Non-enveloped, single stranded, positive sense RNA viruses • RNA encodes 4 proteins – Helicase- unwinds double helical regions in RNA during replication – Protease- cleaves single polypeptide into proteins – RNA polymerase- replicates RNA – Capsid- covers RNA genome	• **Diagnosis clinical and epidemiologic** • Can't grow in tissue culture • EM of stool (in research settings)	• **Treatment is supportive- may require IV hydration**	

Viral Respiratory Infections, Anthrax, and TB

Clinical Presentation	Test Findings	Pathogenesis	Predisposing Factors/ Epidemiology	Likely Pathogens	Definitive Diagnosis	Complications	Treatment	Prevention
Classic presentation (nasty, self-limited): Required: ▪ **Fever** above 101 F ▪ **At least one systemic symptom** (myalgia, chills, malaise) ▪ And, **at least one respiratory symptom** (cough, nasal discharge) ▪ Incubation period = 1-2 days ▪ Sx can persist for 2 weeks ▪ Rarely: GI Sx ▪ **Complications** are quite common: (**pneumonia, myositis, neurological, Reyes syndrome**)	**Chest X-ray:** ▪ In severe cases (i.e. pandemic) see **bilateral, rapidly progressing** pneumonia (**primary viral**) ▪ Can also see **lobar infiltrate** (secondary bacterial**: S. pneumonia)** ▪ **Necrotizing pneumonia** (secondary bacterial: **S. areus**)	Infection is limited primarily to epithelium of the respiratory tract. **Key virulence factors:** **Neuraminidase protein (NA):** ▪ Surface protein (antigenic) ▪ Allows virus to **escape** the host cell and move through mucous **Hemagglutinin protein (HA):** ▪ Surface proteint (also antigenic) ▪ **Attachment** site ▪ Also, mediates fusion of viral envelope to endosome → allowing virus to get into cell **Immune evasion:** ▪ **Antigenic Drift:** ongoing **mutation** of RNA segments of NA,HA (this is why the **vaccine** needs to be changed every year) ▪ **Antigenic Shift: ressortment** of RNA segments (accounts for **pandemics** caused by type A virus). Influenza A virus of animals = new source of RNA → new HA or NA segments being introduced into human pop. No immunity → epidemics. **Other viral proteins:** ▪ **RNA polymerase** (PB1, PB2, PA) for replication ▪ NP = nucleocaspid. Covers the genome ▪ M1 protein: provides stability for type A, B viruses ▪ **M2:** acts as **ion channel** within endosome for type A (allows the DNA to get out; also a **drug target**) ▪ NS: nonstructural, function unknown	**Season:** ▪ Winter months **Transmission:** ▪ Respiratory droplets **Hosts:** ▪ **Healthy young adults:** deaths during pandemics most often caused by primary viral pneuomina ▪ **Older adults, chronically ill:** bacterial pneumonia = major cause of mortality ▪ **Children:** more susceptible to myositis, Reye's syndrome	**Influenza Virus** ▪ 3 types: A, B → disease; C = sublclinical ▪ enveloped ▪ ssRNA (-) ▪ C type – lacks Neuraminidase protein (key virulence factor) Nomenclature: A/Texas/1/77/H3N2 = ▪ Type A ▪ Isolated in Texas ▪ In 1977 ▪ 1 = strain designation ▪ H3N2 = subtype Review session: Binds to sialic acid residues, enters cell through receptor mediated endocytosis, mechanism of viral uncoating is well worked out.	**Clinical presentation:** ▪ Adequate for diagnosing most individuals **Rapid Ag test:** ▪ Nasopharyngeal swab ▪ Test of choice ▪ Highly sensitive, specific Others: ▪ Viral culture: used to monitor outbreaks ▪ PCR: not in widespread use	**Complications are very common:** **Pneumonia: (most common)** ▪ Primary viral, or ▪ Secondary bacterial (S. areus, S. pneumo, H. influenza, Group A strep). **Myositis:** ▪ Inflammation of the muscles (legs in children) **Neurologic:** ▪ Post-infectious encephalitis ▪ Guillain-Barre syndrome **Reyes syndrome:** ▪ Changes in mental status, liver function when given aspirin ▪ Mortality from increased ICP	**Rest and fluids:** ▪ Most people **Antivirals** (do not prevent complications, but may be used): **Amantadine, Rimantadine:** Interfere with M2 in Influenza A. **Limitations:** resistance, CNS side effects, elderly with renal insufficiency. **Neuraminidase inhibitors** (zanamivir and oselatamivir): decrease duration of Sx, prevent infections. Milder side effects.	**Vaccine** **Inactivated virus** (reduces hospitalization, death). Lower efficacy in immuno-suppressed. **For:** individuals > 50, cardiac, pulmonary, renal diseases, diabetes, immuno-suppressed, Hb disorders, nursing home residents, health care providers. Admin: 1/ yr. 5% → low grade fever (not the flu) **Antivirals:** Can be used for people who've been exposed.
2 – 7 days after exposure to someone who has been in Asia or Toronto recently with: ▪ **prodrome** of fever – Chills, headache, malaise, myalgia, diarrhea may also be present • **Next phase**: dry cough and/or shortness of breath • In **10-20% disease may be rapidly progressive** and require mechanical	**Chest X-ray** normal → focal interstitial infiltrates → more generalized infiltrates → consolidation→ ARDS **Labs** • Lymphopenia, thrombocytopenia, elevated CPK and hepatic enzymes may be seen	**SARS (not well characterized yet)** It is hypothesized that there is an Asian susceptibility based on HLA type, one type being very common in Hong Kong. There is also the hypothesized phenomenon of "super spreaders" that have a greater capacity to spread the virus. There have also been PCR studies that show that the virus' peak excretion occurs 10 days after infection, which differs greatly from other viruses that cause respiratory symptoms.	**Emerging Infection** **Evolving pathogen and new disease.** The outbreak of SARS has been traced from a single individual from Southern China. The patient traveled to Hotel Metropol in Hong Kong infecting other travelers there, who subsequently went back to their own countries and infected persons there. **Mortailty** To date there have been 8,427 cases in 29	**SARS - Coronaviruses** • Member of the Coronaviridae family • Pleomorphic 100-150 nm particle with characteristic surface projections – Single stranded, (+) sense RNA genome (27-32 kb) – Cytoplasmic replication – Viral assembly in Golgi apparatus and endoplasmic reticulum	• **Clinical suspicion – Particularly in a traveler from an endemic region or someone exposed to a possible/probable case** – Still investigational – **Sputum, blood and body fluids for viral cultures and PCR** • **May not be positive for up to 28 days**		Treatment is supportive	

ventilation			countries, and 813 deaths.	• Infect multiple species				
Young health person 14-17 days after exposure to rodents with: myalgia, malaise, and fever **(mild flu-like symptoms). General GI disturbances** (anorexia, nausea, vomiting, and abdominal pain) and **non-specific respiratory complaints** (cough, tachypnea, and tachycardia) may be observed. **Symptoms may rapidly progress to respiratory failure.**	**Chest X-ray:** Bilateral interstitial infiltrates (moderate to rapid progression), bilateral alveolar infiltrates, and pleural effusion **Labs:** a. elevated hemoconcentration (Hct) b. leukocytosis with left shift; atypical lymphocytes seen c. thrombocytopenia d. elevated liver enzymes, proteinuria, elevated creatinine may be seen	**Hantavirus Pulmonary Syndrome** Deposition in terminal respiratory bronchiole or alveolus • Local replication with viremia • Widespread infection of pulmonary endothelium – Cell invasion may be mediated by B3 integrins • Infiltration by CD4 and CD8 cells • Loss of vascular integrity in lungs • Capillary leak syndrome • Myocardial depression also seen	**Emerging infection** **New agent and disease** First described in 1993 in Four Corners area, New Mexico. **Epidemiology:** Basically localized to the western hemisphere all over the U.S. but less than 50 cases a year. However, when it does infect a patient, it is usually a young healthy person, and it is usually fatal. **Resevoirs:** **rodents (deer mice)** **Transmission** To humans **via inhalation of contaminated aerosolized excreta, especially urine.**	**Hantaviruses (Sin Nombre viruses)** Bunyaviridae family, segmented RNA, enveloped viruses.	**PCR of viral RNA in lung** **Serologically**	Hemorrhagic fever with renal syndrome (HFRS) b. Hantavirus pulmonary syndrome (HPS)—emerging infection.	Treatments is supportive	No vaccine
Infant presents with: ▪**Pneumonia** ▪**Bronchiolitis** **History:** Sx start with ▪Nasal congestion ▪Sore throat ▪Fever ▪Cough develops in first few days and becomes deeper and more prominent as infection proceeds **Physical:** ▪Increased RR, retraction of lower intercostals (indicates lower resp. tract involvement) **Adults:** ▪Common cold-like symptoms ▪May be worse depending on immune status	**Chest X-ray:** ▪"Peribronchial cuffing": infiltrate with edema of bronchial walls	**Infection involves primarily lower respiratory tract in infants** with without systemic spread (although may just be upper tract infection). Immune response probably contributes to pathogenesis. **Infection:** ▪Innoculation: through eyes and nose ▪Lyphocytic peribronchiolar infiltrate with edema of bronchial walls ▪Later proliferation and necrosis of bronchioles develops ▪Collections of sloughed epithelium → obstruction of small bronchioles → air trapping ▪Viral infection → may lead to pneumonia **Immune Response** ▪Most sever infections: when Ab titer high, CMI low (e.g. early infancy when maternal Ab present; vaccinated infants had worse outcomes) ▪CMI key for protecting against serious lower tract infections **Viral proteins:** ▪Attachment: F, G, SH ▪Nucleocaspid: N, L, P ▪RNA polymerase: NS1, NS2	**Host:** ▪**Virtually all children infected by age 2. Premature** infants (esp. w/ bronchopulmonary dysplasis, congenital heart disease, pulmonary disease) and those from **low SES** are at greater risk for serious disease ▪**Imunnocompromised:** (CMI esp.) **Season:** ▪**Winter bug**: outbreaks begin in Nov., peak in Jan, continue until April **Transmission:** ▪Respiratory droplets **Geography:** ▪everywhere	**Respiratory Syncytial Virus (RSV)** ▪Paramyxoviridae family ▪Enveloped ▪ssRNA (-)	**Cell culture:** ▪**multinucleated giant cells (syncytia cells)** ▪immuno-flourescence ▪serology not useful	**Pneumonia**	**Supportive care:** ▪mainstay for sick infants ▪Epinephrine, supple-mental 02 for hypoxic infants **Antiviral (Ribivirin):** ▪Aerosol for very sick infants ▪Interferes with RNA polymerase, and depletes intracellular nucleotide pools	**Passive Immunity:** ▪Monoclonal Ab (palivisum ab) ▪Immune globulin ▪Given 1X/month for at-risk infants ▪Doesn't benefit patients with congenital heart disease ▪No vaccine Hand washing
Bronchiolitis in infants **Croup in young**		Infection and death of respiratory epithelium without systemic spread of virus. Multinucleated giant cells caused by the giant cell fusion protein	**Transmission** Respiratory Droplets	**Parainfluenza Virus** ▪enveloped ▪helical nucleocapsid	**Isolation of virus in cell culture → immunoflourescence**		Supportive.	**No vaccine.**

<u>children</u> **Common cold in adults**		are a hallmark.		▪one piece of ssRNA (-) ▪RNA polymerase in virion **STABLE hemaglutinin and neuraminidase**	**Serology: four-flod rise in titer**			
Common-cold symptoms (for about a week): ▪Rhinorrhea ▪Congestion ▪Sneezing Also: ▪**Sore throat** (pharyngitis can be severe, can be exudative) ▪**Hoarseness, cough** (less common, but more persistent – lasting up to several weeks) ▪**Yellow-green sputum may be seen** ▪High fevers, myalgias, and chills **NOT** usually seen (should prompt other diagnoses)	Virus can be detected in nasal secretions as early as 10 hours after inoculation (but not usually done) Paranasal sinuses may be seen in CT scan	Infection is limited to **mucosa of upper respiratory tract** and conjunctiva. **<u>Infection:</u>** ▪**Innoculation:** nasal, ophthalmic mucosa ▪**Optimal growth at temp of nose** (33 degrees) → why doesn't infect lower resp. tract (37 degrees). Although, lower tract infection may happen in some infants. ▪**Replication:** in nonciliated lymphoepithelical cells of nasopharynx; primary infection in adenoidal tissues ▪**Attachment:** binds to **ICAM-1** receptor **<u>Immune response</u>:** ▪**Leads → Sx** ▪**Cytokines (esp. IL-8) elevated** and shown to cause Sx (release dependent on interaction of virus with ICAM and proportional to severity of symptoms)	**<u>High rate of community infection:</u>** ▪Due to multiple serotypes ▪Antigenic drift ▪reinfection **<u>Host:</u>** ▪Infants < 1 y.o. have highest rate of illness **<u>Season:</u>** ▪peaks in early fall and spring **<u>Geography:</u>** ▪Worldwide **<u>Transmission:</u>** ▪Respiratory droplets ▪Homes, schools ▪May survive on environmental surfaces for hours ▪Killed with lysol	**<u>Rhinoviruses:</u>** ▪Small, noneveloped ▪ssRNA (+) ▪picornaviridiae ▪100's of serotypes	**Clinical diagnosis**	▪**Paranasal sinuses** ▪**Exacerbation of chronic bronchitis** ▪**Asthma attacks** (mediator related)	**<u>Symptomatic Tx:</u>** ▪Decongestants ▪Antihistamines ▪Anticholinergics ▪NSAIDS Don't prescribe antibiotics for URI	**avoidance**
Upper and lower respiratory tract disease, especially phrayngitis and pneumonia		Virus primarily infects epithelium of respiratory tract and eyes. After acute infection, persisten, low-grade virus production without symptoms in the pharynx.	**<u>Transmission</u>** Respiratory droplets; iatrogenic in eye disease; fecal-oral with enteric strains	**<u>Adenovirus</u>** ▪Nonenveloped ▪Icosohedral neucleocapsid ▪Linear dsDNS ▪No virion polymerase ▪41 serotypes	Viral cell culture – see cytopathic effect Serology: Ab titer rise		**No antiviral therapy available.**	Live vaccine used in the military to prevent pneumonia (against types 3, 4,7)
Measles (serious disease) **Maculopapular rash**		Infects upper respiratory tract → LN → blood → other organs (including skin). **Giant cell pneumonia and encephalitis can occur.**	**<u>Transmission</u>** **Respiratory droplets** **Significant degree of mortality**	**<u>Measles Virus</u>** ▪enveloped ▪helical neucleocapsid ▪ssRNA (-) ▪RNA polymerase in virion		**Subacute sclerosing panencephalitis** is a rare complication	**No antiviral therapy available.**	**Live attenuated virus vaccine** (given with mumps, rubella)
Congenital malformations, cardiovascular, and CNS		Infects nasopharynx → LN → skin **If occurs during 1st trimester → congenital abnormalities**	**<u>Transmission:</u>** **Respiratory droplets, cross-placental**	**<u>Rubella Virus</u>** ▪Enveloped ▪Icosohedral nucleocapsid ▪One piece of ssRNA (+) ▪No viral polymerase ▪Single serotype	**To determine whether woman is immune – single serum specimen to detect IgG** **To see if infection has occurred, look for IgM**		**No antiviral therapy available.**	See above
<u>Inhalational Anthrax</u> **After 1-6 day incubation period** (closer to 1 day, but could be much longer): Flu-like symptoms →	**<u>Chest X-ray</u>** Non-specific clinical CXR – **widened mediastinum,** pleural effusions	Anthrax **<u>Inhalational (more lethal)</u>** Hemorrhagic mediastinitis → malignant edema with regional lymphadentis → toxic induced	**Bioterrorist Agent** Cutaneous → goal to get into the blood stream **Inhalational –> more dangerous**	**<u>Bacillus anthracis</u>** Non-motile, gram positive, rod, spore former, not contagious Does occur naturally	**<u>Inhalational Dx</u>** Non-specific clinical CXR – widened mediastinum, pleural effusions (key)		**Antibiotics** are effective against vegetative form, non spore form **Empiric – cipro or doxy**	Vaccine Attenuated form Good at preventing skin anthrax 6 doses –

Septic → untreated → necrotizing mediastinitis → death **Cutaneous** **1-7 days up to 14 after being exposed to white powdery substance:** Pruitic macule → vesicle → round ulcer → black eschar over 1-2 weeks Surrounding edema/erythema (pretty profound), but painless +/- painful regional lynphadenopathy untreated 5%-20% fatality rate If treated, do well		septicemia **Cutaneous** Necrotic lesion → malignant edema → w/ or w/o reional lymphadenitis → septicemia **Path** Alveolar mac → regional LN → Inf Dose = 1 or more spores		Spores are viable for years • Produces three exotoxins: – Edema factor – Lethal factor – Protective antigen	Gm stain.culture, PCR of blood CSF Large gram pos rods, rough, grayish colonize, non-nemolytic non-motile Usually penicillin susceptible Send culture to CDC NYCDOH **Cutaneous Dx** Vesicular fluid or border of skin lesion (gram stain, culture, sensitivity, PCR) Skin biopsy (culture, PCR, special CDC immuno test) Serologies – take wihile to develop		Plus one or two others: **clindamycin, rifampin imipenem** **After identification, 60 day course**	difficult to get limited supplies Prevention Primary-vaccination at risk (military) Secondar
History, commonly: ▪Fever ▪Fatigue ▪Night sweats ▪Weight loss ▪Anorexia ▪Chills **Pulmonary Sx (non-specific):** ▪Productive Cough ▪Hemoptysis ▪Pleuritic chest pain **Physical:** ▪Fever ▪Cachexia ▪Perhaps pulmonary consolidation **Extrapulmonary:** ▪Lymph ▪Bone/joint ▪Miliary ▪GU ▪CNS (meningeal)	**Lab findings:** ▪Mild anemia ▪Normal WBC, normal differential ▪Elevated ESR **Chest X-ray:** ▪Suggestive –apical infiltrates or cavities, hilar adenopathy. Different X-rays for HIV patients. If meningeal involvement → **lubar tap:** ▪Glucose: normal, or low ▪Protein: up ▪Lymphocytic predominance **Biopsies:** ▪LN: cervical node ▪Miliary: granulomas ▪Pleural: AFB staining often negative for some reason	▪Primary Infection: uimpeded replication and dissemination → secondary to lack of host immune response ▪Development of immune response: CD4 → cytokines → recruit Mac's → kill MTB, cause tissue damage (form Langhans giant cells, granulomas) ▪Clinical events – primary infection → mild viral like syndrome, PPD comes out positive. If not progressive, resolves into Ghon complex. ▪Progressive primary disease: (in immunocompromised, young children): military, CNS involvement, pleural disease (in absence of parenchymal involvement) = more common ▪Persistence of viable organisms: at secondary sites (lung apices, LNs, meninges, bones, kidneys). 85-90% of immunocompetent individuals do not progress further… ▪Reactivation (remaining 10-15%; weeks to decades later) often depends of weak host immune status → can't contain infection. 85% located in apical-posterior lungs, rest extrapulmonary. Get caseating necrosis of lungs ▪Exogenous reinfection: occurs in developing countries, homeless shelters. Postive PPD convers some protection.	Transmission: ▪Inhalation of respiratory droplets ▪GI (contaminated milk), skin exposure unsual Risk of infection: ▪Directly proportional to length of exposure to organisms Risk of disease: ▪Greatest in infants <6 mo ▪Time: highest after 1st year following primary infection ▪Decreased nutritional, immune status increase risk	**Mycobacterium Tuberculosis**	▪Clinical ▪PPD test ▪Interferon production by WBC's exposed to MTB Ag's ▪AFB culture ▪PCR, DNA probes		Exposure, no risk of infection: need to get repeated testing PPD (+), asymptomatic: monitor Sx, chest X-ray. Indications for Tx in this population: ▪Recent development of PPD (2 yrs) ▪Close contacts of known cases of infectious TB ▪Persons in hospitals, prisons, shelters, nursing homes ▪Children < 5 y.o. Those with increased risk for progression: ▪Fibrotic changes, apical scarring ▪Immunosupresseced ▪Underlying disease ▪Immigration within 5 years from area with high TB rate ▪Underweight persons ▪IDUs ▪People less than 35 y.o. Isoniazid Rifampin	

HIV Infection

<table>
<tr><th>Clinical Presentation</th><th>Test Findings</th><th>Pathogenesis</th><th>Predisposing Factors/
Epidemiology</th><th>HIV Structure / Replicative Cycle</th></tr>
<tr>
<td><u>Early, Acute Stage a.k.a. Acute retroviral syndrome (mononucleosis like picture):</u>
▪2-4 weeks after infection
▪fever
▪lethargy
▪sore throat
▪general lymphadenopathy
▪macular popular rash on the trunk, arms, and legs (but sparing palms and soles)

▪resolves spontaneously after 2 weeks

▪only 20% of patients seek care for illness at this stage

▪increased severity of this symptoms indicate more rapid progression of infection</td>
<td><u>Blood test:</u>
▪luekopenia
▪CD4 cells normal

<u>Serologies:</u>
▪Ab’s appear 3-4 weeks after infection (so prior testing results in false-negatives)
▪HIV can still be transmitted during this period</td>
<td rowspan="3">In acute infection:
▪Virus encounters DC’s on mucosal surface (DC-sign is a co-receptor on DC)
▪Virus is delivered to LN where active replication takes place
▪primary infection – R5 tropic (Mac’s)
▪high levels of viremia and viral dissemination occur
▪Down regulation of the virus by CMI occurs
▪Viral set point reached after about 6 months
▪Immune response, chemokine receptor status and HLA type are important co determinants of outcome

Once HIV infection is established:
▪acute viral response present throughout course of the disease
▪major reservoirs of infection exist outside of blood compartment: lymphoreticular tissues (most important), CNS, Genital tract
▪Virus exists as multiple quasispecies
▪Mixtures of viruses with differential phenotypic and genotypic characteristics may exist (drug resistance mutations vary across clones, compartments)
▪At least 10 * 10^9 virions produced and destroyed each day (even in asymptomatic individual), and combine this with:
▪High turnover rate: t1/2 of HIV in plasma is <6 hr and may be as short as 30 minutes (very dynamic infection even in asymptomatic individual)</td>
<td rowspan="3"><u>Emerging Infection</u>
New agent, new disease

<u>Determinants of Outcomes</u>

Viral Factors:
▪Escape from immune response: under immune selective pressure (CMI, humoral), mutations in gag, pol, env
▪Attenuation: nef deleted viruses associated with slow or long-term non progression in patients
▪Tropism: R5 → X4 virus conversions associated with increase in pathogenicity (there may be mix of these)
▪Subtypes: a bunch of them. Subtype B in US. Potential for varied subtypes to exhibit differential transmissibility and virulence. Potential for greater heterosexual.

Host Factors:
▪CMI:
▪CTL’s: eliminate virus infected cells, play prominent roles in control of viremia
▪T help: vital for CTLs
▪Humoral immunity: role unclear in prevention of transmission, progression
▪Chemokine receptors:
▪CCR5-delta32: homozygosity associated with decreased succeptibility to R5 virus infection; heterozygosity → delayed disease progression
▪Other genetic factors:
▪Class I alleles: B35, … → faster progression; …. → slow progression

<u>Transmission</u>
▪Sexual: hetero; male to male
▪Blood: transfusion; IV drug use; needle stick
▪Perinatal: intrapartum; breast feeding

▪Epidemic
▪Stable in US (NYC, DC, Puerto Rico most affected)
▪Not stable in subsaharran Africa, developing regions

<u>Risk Factors: Male</u>
▪Male → male (53%)
▪IDU (26%)

<u>Female</u>
▪Heterosexual contact (64%)</td>
<td rowspan="3"><u>Structure:</u>
▪Retrovirus family
▪ssRNA virus with an icosohedral nucleocapsid and lipid envelope
▪two identical copies of RNA and carries a reverse transcriptase

<u>Replication:</u>
▪binding and infection
▪reverse transcription and integration of viral DNA
▪transcription and translation
▪Modification and assembly
▪Budding and final assembly</td>
</tr>
<tr>
<td><u>Middle Stage (long latent period, measured in years, usually ensues):</u>
▪Patient is usually asymptomatic at this time and without complications

▪Rarely, patients may have have AIDS-related complex (ARC) with persistent fevers, fatigue, weight loss, and lymphadenopathy</td>
<td><u>Blood tests:</u>
▪Progressive CD4+ depletion (pt. loses 50-75 CD4+ cells per year if RNA is above 30,000)

<u>PCR:</u>
▪Average pt. has viral load set point of 30,000 copies of HIV RNA / ml</td>
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<tr>
<td><u>Late stage HIV infection (AIDS)</u>
▪most often manifested by Pneumocystis Pneumonia (PCP) or Kaposi’s sarcomas

Diseases or symptoms of other opportunistic infections include:
Lung:
▪Pneumonia
▪Tuberculosis
Mouth
▪Thrush
▪Hairy leukoplakia
▪Ulcerations
Esophagus
▪Thrush
▪Esophagitis
GI
▪Diarrhea
CNS
▪Meningitis
▪Brain abscess
▪Progressive multifocal leukoencephalopathy
Eye
▪Retinitis
Skin
▪Kaposi’s sarcoma
▪Zoster
▪Subcutaneous nodules
Reticularendothelial system
▪Lymphadenopathy or splenomegaly</td>
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HIV Infection (cont.)

Definitive Diagnosis / Prognosis	Complications	Treatment	Prevention
Diagnosis: **ELISA:** ▪HIV Ab detection (30 min – 1 hr) **Western blot:** ▪Detects serum Ab's to specific HIV proteins that are separated on a gel **PCR:** ▪RNA plasma levels (this would be positive in acute infection, when ELISA and Western blot would be false negatives – but would still do these together in acute infection to rule out established infection). **Prognosis:** ▪**Can develop prognosis based on CD4 and viral load** ▪**AIDS like impending train wreck: viral load = speed of train, CD4 count = distance from site of crash** ▪Independent predictors of outcomes ▪More viral load, less CD4 → AIDS ▪Absolute CD4 count: best established surrogate marker to predict time to AIDS, risk of specific OIs (near term), or death ▪Combine with viral load → can give very accurate prediction of time to AIDS in 5 years ▪RNA above 30,000 copies → 75 cell loss per year: higher RNA, faster CD4 count will decline ▪Gender specificity: after seroconversion – women have lower viral loads ▪Treatment decisions should be individualized **Non-progressors:** ▪May last for 10+ years, but will eventually get AIDS ▪Determined by host-factors primarily (chemokine receptor co-receptors key (CCR5) heterozygous individuals just as infectable → but not as progressive = lower viral load set point i.e. cells have less dense receptors for HIV) ▪Viral factors less so: nef deletion, non-clade B subtypes ▪Need to look at person with 351-500 CD4 count → if viral load over 100k → get ready to start treatment	**Opportunistic disease (often in a cascade pattern with dropping CD4+ levels)** ▪<300 – TB (any level of CD4 count) ▪Opportunistic infections occur at CD4 <200 ▪<200 – PCP ▪<100 – TE ▪<75 – CMV, dMAC – many people don't survive until this point	**Epitiope war: When do you start treatment?** ▪Patient's disease stage: any symptomatic individual; CD4 count; plasma HIV-1 RNA level ▪Patients commitment to therapy in light of side effects ▪Philosophy of treatment **Initiation of Retroviral Therapy** ▪Clinical outcome compromised if Tx begun when CD4 <200 → compromise outcome (worse than if you started above 200) ▪No virologic or immunologic advantage to starting at CD4 >350 vs. 200-350 ▪Usually start treating around 350 (would initiate earlier, but there are toxicities) **Antiretroviral therapy** ▪Markedly decreases rate of death from disease from protease inhibitors → most effective way to prevent OIs → restore host immune function ▪OI related events: ▪MAC adenitis (may suddenly appear as inflammatory illness after retroviral therapy due to immune system recovery) ▪Inflammatory flare of CMV retinitis ▪Previously stable hepatitis ▪Development of cavitary TB **Pathogenesis after administration of retroviral therapy (measured in log of viral load over time):** ▪1st phase: t1/2 = 1 day (productively infected CD4) ▪2nd phase: t1/2 = 2-4weeks (mac's, latenly infected CD4s, release of trapped virions from LN's) ▪3rd phase: t1/2 = 6-44 months (resting, memory CD4s): may not be a decline → irreducible reservoir. Can reemerge. **Therapeutic Implications for 1st and 2nd phase declines:** ▪Can assess antiviral potency in first 7-14 days (should see 1-2 log decline in first two weeks of therapy) ▪Trajectory over first 1-8 weeks can be predictive of subsequent response **3rd phase (Latent reservoir): Therapeutic implications** ▪Resting naïve CD4 cell activated by Ag → gets exposed to HIV → virus integrated into host cell → rapid production kills most of cells → some resting memory CD4 cells remain (only 1 million to 10 million cells total) ▪Viral eradication not possible with current drugs ▪Archive of replication competent history established ▪Despite presence of reservoir, minimal degree of drug resistance over 2-3 years **Drug Resistance** ▪Genetic variants are continuously produced as a result of high viral turnover and inherent error rate of RT ▪Viral replication 10^9-10^10 per day ▪RT error rate 10^-4 base/cycle ▪Emerge with drug selective pressure ▪Resistance emerges before exposure to drugs → quickly afterwards ▪Single mutation drugs most dangerous	Prophylaxis ▪PCP – TMX (<200) ▪Toxo – TMX or Dapsone + Pyrimethamine) (<100) ▪MAC – Clarithro/Azithromycin (<50) ▪TB – INH (9 months) (PPD+) – problems: high risk individuals have lost skin reactivity (therefore PPD reaction set at lower level); also other problem – in developing countries INH and PPD skin test not used in may areas ▪Proof immune restoration is actually occurring: ▪Recommendations PCP: primary prophylais withdrawn after CD4 > 200 for 3 months ▪Toxo: Primary >200 X 3 months; seconday, same for 6 months + asymptomatic ▪MAC: >100 X 3 months; same pattern, secondary, 100 X 6 months + asymptomatic

HIV Opportunistic Infections (Note: These are based on the information on the slides, see Lynn's Chart for more info)

Clinical Presentation	Test Findings	Pathogenesis	Predisposing Factors/ Epidemiology	HIV Structure / Replicative Cycle	Definitive Diagnosis / Prognosis	Treatment	Prevention
Pneumocystic pneumonia ▪Presents as subacute illness (fever, cough, dyspnea)	▪**Diffuse interstitial infiltrate on xray** ▪Predicted by CD4 count: by time reach **CD4 <200** → begin seeing PCP after 6 months		▪Most common life threatening infection of AIDS patients in US			**Addition of corticosteroids to antimicrobials cuts mortality of in sever disease of 50% (not intuitive: element of reaction to pathogen is not deficient, therefore reduce host response related disease)**	▪**Fully preventable with trimethoprim-sulfa (bactrin)**
CNS toxoplasmosis	▪Reactivation in AIDS assocatiated with **CD4 <100**		▪Transmission from cysts or uncooked meat (happens esp. in tropical regions: DR, etc.) ▪Most common CNS infections in AIDS	▪Protozoan parasite; cats shed oocysts,	Serum IgG = reliable markers (90% seroprevalence in tropics)		
Cryptococcal Disease ▪Initial asymptomatic pneumonia ▪Meningitis most common presentation, but wide dissemination frequent ▪May see ulcers in skin (most commonly recognized sites)	▪Spinal tap: good test for Ag ▪Reactivation **CD4 <100**			▪Ubiquitous soil fungus		**Amphotericin = drug of choice**	
CMV disease ▪Retinitis most common clinical form in AIDS population (pneumonia more common for transplant pop) ▪Other sites: colon, CNS	▪**Reactivation at CD4 <50** ▪Colonoscopy: colitis	▪Common viral infections (50% adult seroprevalence)					
MAC ▪Local lung disease known prior to AIDS ▪Non-specific features, liver, and spleen		▪Wide spread visceral dissemination in AIDS	▪Common in water		▪Diagnosis: blood culture (b/c mycobacteremia becomes so high) ▪Absence of inflammation in tissue sites (hallmark of the disease – see enormous densities of organism, no WBCs)		

Rabies/Prions

Clinical Presentation	Pathogenesis	Predisposing Factors/ Epidemiology	Likely Pathogens	Definitive Diagnosis	Treatment	Prevention
A week to a year after an animal bite: **Classical Rabies** ▪fever prodrome and spasm of laryngeal muscle ▪leads to hydrophobia because it hurts to swallow; ▪this also accounts for salivary retention and drooling, ▪and eventually leads to coma and paralysis. •**Nonspecific Symptoms & Signs:** These include itching, large pupils, stiffness, hypersensitivity to sounds, light, change in temperature. **Rarely presents as Gulliain Barre Syndrome (ascending paralysis).** • **Prodromal Phase, 2-4 days**. It's nonspecific so people have any kind of viral complaint. It depends on whether the virus is replicating in CNS or peripherally. • **Excitation Phase.** Here they develop weakness, weird ocular palsies, urinary retention and constipation. Basically you're just documenting their demise because you can't save them. • **Paralysis Phase.** You die of peripheral vascular collapse with flaccid paralysis if you don't drown in your own secretions first.	**Infection** ▪enters through break in skin ▪replicates in muscle cells → muscle spindles → nerve that innervates the spindle → spinal cord → moves throughout CNS, so every neuron is infected → **encephalitis** ▪**During axonal transport to CNS, virus is hidden from immune response** ▪High concentration of virus in saliva from shedding in sensory nerve endings in oral mucosa **High Mutation Rate** **No proofreading activity of the RNA polymerase.** This leads to a greater mutation rate of about 1 in 1000 that allows **opportunity for flexibility & enhanced fitness.** → results in a quasi-species (heterogeneous population of different RNA molecules that has certain predominant consensus genotypes)	**Epidemiology** Usually imported into US; high in other areas of world - India **Exposure:** **bites**, inhalation, transplants The distance from innoculation site to the brain determines latency to the disease. For example, a bite on foot will take longer to progress than a bite on the face. **Reservoirs in US** racoons- 44%, skunks- 28.5%, bats- 12.5, foxes- 5.5 **Mortality** 100% fatality rate if left untreated 60K estimatedhuman fatalities/y (30K in India)	**Rabies Viruses** ▪Rhabdovirus family ▪Bullet-shaped ▪Enveloped ▪Helical nuclueocapsid ▪One piece of ssRNA (-) ▪RNA-dependent, RNA polymerase ▪Codes for 5 proteins (L, P, N, N, G) ▪G: interacts with cellular receptor (Aceylcholine?) ▪L: RNA polymerase ▪M: interacts with cytomplasmic tail of G → assembly and budding from PM ▪Once in host, M and G not needed for spread in nervous system ▪Inverse correlation between G levels and pathogenicity	**Spinal tap** To determine which of the differential diagnoses of GBS, HIV, polio, and rabies your patient has. This comes up on boards. **Find and observe animal for ten days** **Diagnosis** RT-PCR saliva, CSF, urine, nerve tissue Fluorescent rabies antibody (FRA) test on brain tissue (more for animals than for people) **Animals, autopsies:** Presence of **Negri bodies.** Specific for rabies but present in only 50% of cases. (Cytoplasmic inclusions in pyramidal neurons in hippocampus and Purkinje cells in cerebellum)	**Once clinical symptoms arise, there is no effective treatment**	**Active Vaccination (Pre and Post Exposure)** ▪The best is the **human diploid cell vaccine** ▪**Pre: for high risk groups (vets, Peace Corps vol.)** ▪**Amdin:** It's painful, administered intradermally, and give on days 0,3,7,14,28 post-exposure. ▪**It is successful if given in time**, but once they're in the excitation stage, you give it to them but without expectation of any effect. **Passive Vaccination.** Infiltrates the wound site and vicinity with antibodies to prevent it from propagating and spreading centrifugally within CNS. You can use human rabies Ig and some people use horse rabies Ig though that can lead to serum sickness. **Admin: it's done just once.**
After long incubation period: **In New Guinea (Kuru):** ▪Prodromal: headaches, arthralgias ▪Neruologic: cerebellar ataxia, action tremor, involuntary movement → progressively worse dementia → death **Creutzfield-Jakob Disease:** Lack of coordination, dementia, motor weakness (Rule out Alzheimers in elderly) **Fatal familial insomnia** Autonomic dysfunction and sleep disturbances in middle → late life **Gertsman-Straussler-Schneiker** Midlife progressive spinocerebellar degeneration with associated dementia,	**Hardy proteins:** ▪Resistant to heat, formaldehyde, UV light • Role of **PrPc** may include synaptic plasticity since knockout mice developed subtle sleep defects. What is certain is that it's **essential to TSE pathogenesis.** **KO mice are resistant to TSE**. **The key determinant of disease is the cellular gene itself and its susceptibility of going through conformational change as result of coming into contact with prion protein in diet** (i.e. PrPc exposure to PrPsc changes it to PrPsc	**Kuru** ▪Exposure to brain and mucous membranes of infected individuals **CJD** ▪Sporadic: most common in elderly ▪Hereditary: rare autosomal dominant ▪Iatrogenic: exposure to growth hormone in pituitary, corneas, contaminated surgical instruments ▪**Variant: Ingestion of BSE infected meat or bone marrow (seen in younger populations)** Three phases: 1) first six months, little risk to humans; 2) prion concentrated in CNS and animal is asymptomatic and infectious; 3) animal symptomatic and infectious **BSE = endemic in UK ("mad cow")** **FFI and GSS** hereditary/genetic	**Prions** **Proteinacious infectious particles associated with transmissible spongiform encephalopathies (TSEs)** **PrPc (cellular) – protein product thought to be target of prion disease.** normal host protein encoded by single exon of a single copy gene in chromosome 20. It is attached to the neuronal surface by G proteins, are *__protease sensitive, and have a *α-helical secondary structure.__** • **PrPsc (prion scrapie) is *__protease insensitive so they accumulate in cytoplasmic vacuoles, eventually blocking normal physiological. They have a *β-sheet secondary structure.__**	Ususally, on basis of clinical syndrome and history. Definitive diagnosis is made by taking a **brain or lymphatic biopsy**, using **antibodies** to identify the proteins, then **digesting them with protease**. After digestion, only **the PrPsc signal has been preserved** because of its protease insensitivity whereas PrPc has been chewed up.	No reasonable treatments.	

Arboviral Infections / Encephalitides

Clinical Presentation	**Pathogenesis**	**Predisposing Factors/ Epidemiology**	**Likely Pathogens**	**Definitive Diagnosis**	**Complications**	**Treatment**	**Prevention**
4-10 day after insect bite (spectrum of severity): ▪mostly asymptomatic cases ▪mild "flu-like" illness to more sever cases: ▪fever, ▪ headache, ▪ mental status changes, ▪and possibly focal neurologic signs.	**Aboviral Encephalitis** **Asymptomatic Infections:** Arboviruses stay around by finding reservoirs of cells that are resistant to its cytopathic effects, such as mosquito cells, and muscle and neuronal cells in humans. **CNS Invasion → Encephalitis:** Arboviruses invade the CNS either through the vasculature from viremia or retrogradely through the olfactory nerves. Neuroinvasiveness and neurovirulence is primarily determined the age of the host. **Perivascular inflammation:** A histologic hallmark of arboviral encephalitis. The immune response can be damaging through excessive cytokine release. Arboviruses can also directly induce neuronal apoptotic death.	**Host** **Children** are at greatest risk for JBV (30% mortality), TBE, WEE, VEE, and LAC, **Elderly are at greatest risk for** SLE **and WNE.** EEE (60% mortality) affects all ages with equal risk. **Seasons** Infections occur seasonally with **peaks in late summer/early fall correlating with mosquito activity.** **Patterns of Infection** There are two epidemiologic patterns: a more infrequent, unpredictable epidemic like SLE and a more predictable annual caseload of infections in a given region like JBE.	Major US causes: (post 1999) **West Nile Encephalitis (WNE)**, **Eastern Equine Encephalitis (EEE). LaCrosse (LAC).** Others (don't need to know): St. Louis Encephalitis (SLE), Western Equine Encephalitis (WEE), and Powassan encephalitis (POW). (Don't need to know): Japanese B Encephalitis (JBE) predominates in South East Asia and Australia, Venezuelan Equine Encephalitis (VEE) in South America, WNE in Northern Africa and the Middle East, and Tick-Borne Encephalitis (TBE) in Eastern Europe and Russia.	**Serologically** (positive IgM or 4x increase in IgG titer), **CSF PCR test.**		**Treatment is supportive** with IFN-α, ribavirin, and other investigational trials not proving conclusive yet.	Aerial spraying, personal protective measures from bites. **Inactivated human vaccines** are available for JBE (also available for the amplifying hosts – pigs – to reduce reservoir) and TBE, and **live attenuated equine vaccines** are available for VEE, **EEE,** and WEE (not for humans!).
After mosquito bite: Most commonly an infection is asymptomatic. **an abrupt onset flu-like illness** with: ▪moderate to high fever, ▪headache, ▪sore throat, ▪backache, ▪myalgia, ▪arthralgia, ▪fatigue, ▪rash, ▪lymphadenopathy. **More serious cases:** ▪temperature above 38.0°C ▪and either focal neurologic signs, ▪ altered level of consciousness, ▪ or **diffuse profound motor weakness** ▪Negative for structural brain lesions.	May see motor weakness in encephalomyelitis **(West Nile documented to affect anterior spinal cord neurons).**	**Emerging Infection** Previously described agent, in a new location → now an established infection **Incidence** Largest recorded arboviral encephalitis epidemic in US history, with over 8,470 human cases in 45 states to date **Progression** 1 in 5 infections → West Nile Fever 1 in 150 → West Nile encephalomyelitis **Host** The more serious form of disease, West Nile encephalomyelitis, **strikies mainly those over 50 and/or the immunocompromised.**	**West Nile Virus** Flavivirus; reservoir = bird; vector = mosquito	1. **CSF**: Pleocytosis and positive **IgM** or 2. **Serum:** 4x rise in IgG titer. or: **PCR** for West Nile in serum or CSF are required for definitive diagnosis. **Rule out:** Bacteria, fungi, and structural lesions on brain imaging suggesting another diagnosis are also required.			
Arboviral Encephalitis (see above)		**Geography:** Eastern US **Season** Summer/fall **Outbreaks** Occasional in humans, frequent in	**Eastern Equine Encephalitis (EEE)** Alphavirus; vector = mosquito; reservoir = birds, horses		Permanent brain damage		

		horses **Mortality** 1/3 of cases are, fatal – regardless of age **Human Host** Anybody					
After mosquito bite: 1 in 5-20 infections have clinical disease with **jaundice.** 3 stages: **1) infection (viremia)** with fever, chills, headache, **back pain**, nausea, malaise, **minor gingival hemorrhages, epistaxis**, and **relative bradycardia** (Faget sign) **2) remission** **3) Intoxication** with **jaundice and black vomit**, delirium, stupor, acidosis, and shock. Also present are leuko/throbocytopenias, liver and kidney abnormalities, and coagulopathies.	▪Mosquito bite → replication in a regional lymph node ▪Viremia with infection of the Kupfer cells and hepatocytes. ▪The resulting liver degeneration causes release of inflammatory mediators and the sequelae of hemorrhagic diathesis, circulatory failure and shock.	**Geography** Ssub-Saharan Africa and South America (never Asia) Two epidemiologic patterns: **Endemic** **"Jungle yellow fever"**:non-human primate hosts and tree-hole breeding mosquito vector. **Epidemic** **"Urban yellow fever":** human hosts and urban mosquito vector (Aedes aegypti). **Mortality** High case-fatality rate of 20-50% in patients with jaundice.	**Yellow Fever** Flavivirus; vector = mosquito; reservoir = primates	**Serology, Viral isolation, PCR** but **NOT liver biopsy** because of bleeding diathesis.	Henorragic diathesis, circulatory failure, and shock	**Treatment is supportive.**	Preventable with mosquito controls, and improved sanitation/water systems, yet lapses in Africa has led to increasing epidemics. The live attenuated Yellow Fever 17D vaccine is effective and contraindicated in infants less than 6 months of age, in pregnant women, in the immunosuppressed, and in those with hypersensitivity reactions to eggs.
2-7 days after mosquito bite: Biphasic disease… **Early phase:** ▪major lumbosacral, joint, bone pain ▪fever, chills, headache, ▪transient maculopapular rash, and ▪Faget sign over the first two days and ▪Then anorexia, vomiting, and respiratory symptoms for days two to six. **Late phase following**: ▪defervescence results in fever, ▪limb/face rash, ▪lymphadenopathy, ▪ and minor hemorrhages. ▪Labs show leuko/ neutro/thrombocytopenia. There are no fatalities. **DHF** ▪Dengue fever ▪with thrombocytopenia ▪and hemoconcentration (from diffuse capillary leakage and major hemorrhages). ▪Can progress to DSS ▪Other clinical signs are respiratory distress and neurologic symptoms.	(Dengue fever is often called "breakbone fever"), **Immune enhancement phenomenon (in DHF)** With Dengue virus antibodies from a previous infection allow the **new cross-reactive virus greater access to macrophages** (antibody-dependent enhancement) and **cause increased T cell lysis of the infected macrophages, both of which cause greater release of inflammatory mediators.** **DSS** Due to increased vascular permiability	**Incidence** 100 million cases annually in all tropic and warm temperate zones. **Vector** **Aedes aegypti** and humans are the primary hosts. **Transmission** Air travel from viremic humans. Dengue Hemorrhagic Fever **(DHF),** a more serious disease which **occurs almost exclusively (>90%) in those with prior immunity to a heterotypic serotype, is on the rise because there is increasing endemicity** and co-circulation of the 4 Dengue serotypes. Incidence of DHF is only 1 in 14,000 with primary Dengue infections but 1 in 90 with secondary Dengue infections.	**Dengue Fever** Flavivirus; vector = mosquito; reservoir = primates		DHF can progress (30%) to **Dengue Shock Syndrome (DSS), defined as DHF with hypotension, circulatory failure and shock.**	Treatment with supportive measures can lower the case fatality rate of DHF from >10% to <1%.	