

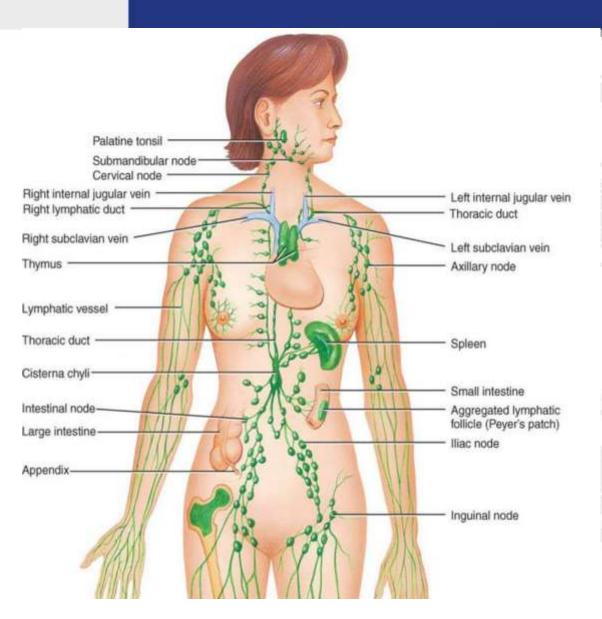
Differential diagnosis of diseases associated with lymphadenopathy

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- Lymphadenopathy is the enlargement of lymph nodes, infectious or noninfectious cause
- The antigen enters through
 a skin or mucosal lesion
 and is transported by
 lymphatic vessels to the
 nearest lymph node.
- Lymphatic vessels are distributed throughout the body except the brain and bones.



Etiology of diseases associated with lymphadenopathy

	<i>Non-i</i> nfectious etiology		
Viral diseases	Bacterial diseases	Parasitic and fungal diseases	a) Autoimmune diseases
Infectious mononucleosis CMV infection HIV infection HSV-1 and HSV-2, Varicella-zoster virus HHV-6, HHV-7, HHV-8 Rubella Measles Adenovirus HAV, HBV, HCV	Tularemia Plague Cat scratch disease Brucellosis Dyphtheria Tuberculosis Atypical mycobacterial infection Primary and secondary syphilis	Toxoplasmosis Leishmaniasis Trypanosomiasis Filariasis Rickettsioses Histoplasmosis Coccidiodomycosis	Rheumatoid arthritis Juvenile rheumatoid arthritis Connective tissue diseases Systemic lupus erythematosus Dermatomyositis Sjogren's syndrome b) Oncological diseases

Acute or chronic lymphocytic leukemia Hodgkin's, non-Hodgkin's lymphoma



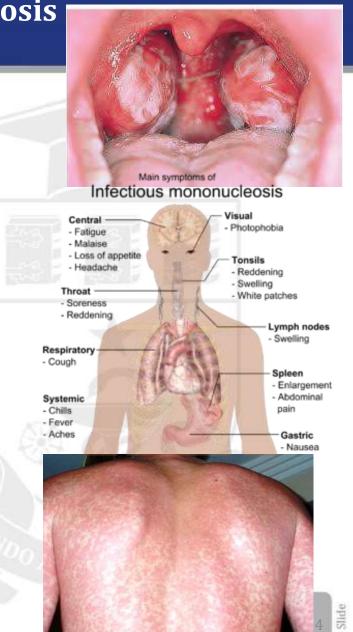
Infectious mononucleosis

Etiology and epidemiology

- The kissing diseaseis, is caused by the Epstein-Barr virus, also known as human Herpesvirus 4
- Causes some tumors: Burkitt's lymphoma, nasopharyngeal carcinoma, hairy leukoplakia of the tongue.
- Incubation period 2-7 weeks after exposure
- It is primarily spread through saliva
- The source is the sick person and the asymptomatic carrier

Clinical manifestations

- Intoxication syndrome irregular fever 38-40°C, usually lasting 1-3 weeks
- Symmetrical anterior, posterior, submandibular and occipital cervical **polyadenopathy**
- Follicular, pseudo-membranous tonsillitis, with edema of the uvula and pharynx
- Hepato-splenomegaly in 50-60% of cases
- Urticarial, erythematous, petechial rash in 5-10% of cases
- All people given <u>amoxicillin</u> or <u>ampicillin</u> develop a generalized, itchy maculopapular rash





Infectious mononucleosis

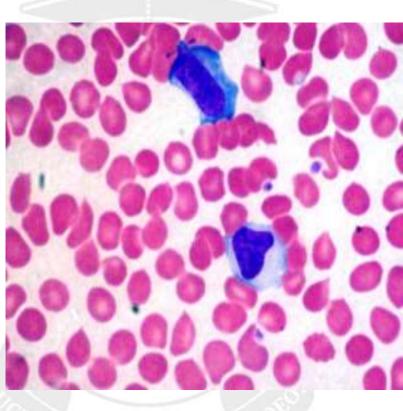
Laboratory data

- Leukocytosis with lymphomonocytosis about 70-80%,
- appearance of atypical lymphocytes,
- hyperbasophils in more than 10-15% of cases
- Thrombocytopenia in 50% of cases
- Moderate hepatic cytolysis in 80-90% of cases
- Rare hyperbilirubinemia in patients over 40 years of age

Serological confirmation of EBV

- Antibodies IgM EBV- VCA (*Viral Capsid Antigen*)

 in 90-100% acute cases and persists for 1-3
 months
- Antibodies IgG anti-EBNA (Epstein Barr Nuclear Antigen) – it is positive 3-4 weeks after the onset of the disease, it persists throughout life





Complications of infectious mononucleosis

Neurological complications :

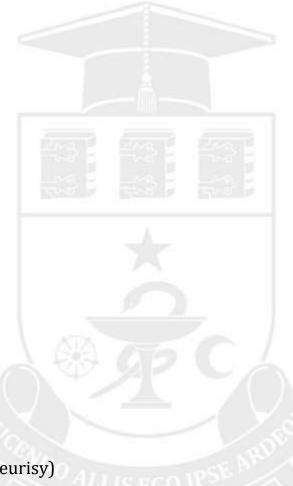
- Encephalitis (potentially fatal)
- Seizures
- Meningitis
- Cranial nerve palsies
- Transverse myelitis
- Ataxia
- CNS lymphoma

Hematological complications :

- Hemolytic anemia
- Thrombocytopenia
- Thrombocytopenic purpura
- Agranulocytosis

Other complications:

- Spleen rupture
- Respiratory complications (interstitial pneumonia and pleurisy)
- Hepatic complications acute liver failure



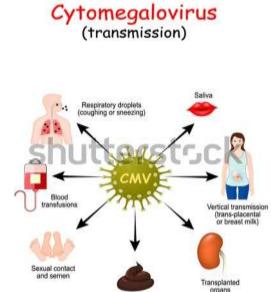


Cytomegalovirus infection

Etiological and epidemiological data:

- CMV is <u>human betaherpesvirus 5</u>
- Often causes perinatal and childhood infections
- Virus is present in milk, saliva, feces and urine
- CMV vertical transmission and through sexual contacts
- Latent CMV infection persists throughout life, reactivates in immunocompromised patients







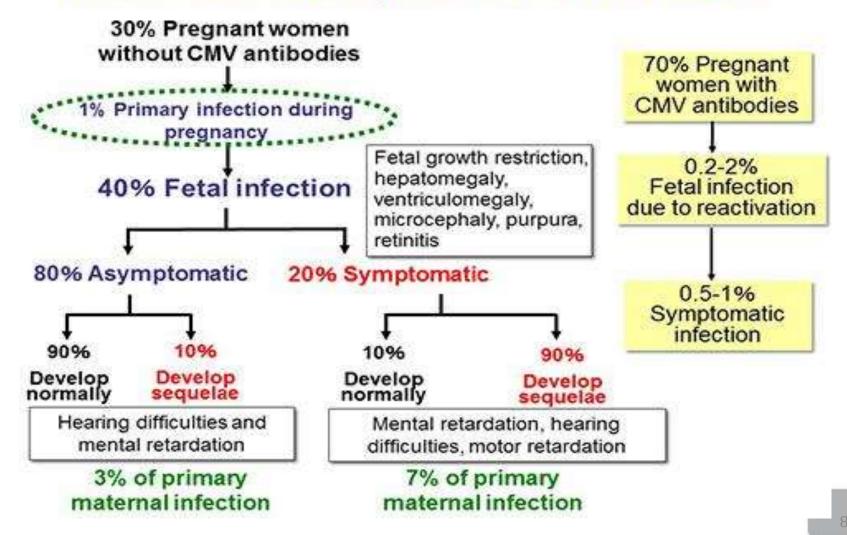
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Urine and feer



Congenital CMV infection

Potential infant disability from maternal CMV infection



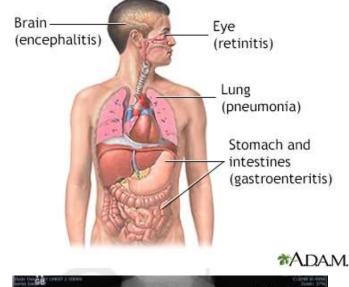
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Acute CMV infection

CMV mononucleosis syndrome

- incubation period 20-60 days,
- the acute phase 2-6 weeks
- in children often asymptomatic
- in adults febrile syndrome (2-4 weeks), chills, asthenia,
- Loss of appetite, weight loss, general malaise
- Muscular aches and fatigue, headaches
- Fever and sore throat
- Enlarged lymph nodes (in the neck region)
- Behavioral changes
- Epileptic seizures
- Diarrhea
- Pneumonia
- Specific organs may be affected:
 - Eye leading to blindness, light sensitivity
 - GI tract causing bleeding ulcers
 - Liver inflammation and hepatitis
 - Brain meningitis







Laboratory modification in CMV primary infection

CBC

- Leukocytosis with lymphomonocytosis
- Thrombocytopenia
- Hemolytic anemia

Biochemical tests

- Mild Cytolytic Syndrome in $\approx 90\%$ of cases
- In 10% ALAT >10 N

Confirmation of CMV infection

- Anti-CMV IgM positives persist 6-9 months after infection and can become positive during CMV reactivations
- In pregnant women with Anti-CMV IgM, the IgG antibody avidity test is recommended
- Investigation of pp65 antigen and CMV DNA by PCR in blood and urine are used to diagnose reactivations in immunocompromised patients
- Identification of DNA-CMV in the amniotic fluid of the pregnant woman, confirms CMV infection of the fetus in utero





HIV is transmitted

5%



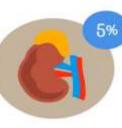
use of non-sterile syringes and tools



pregnancy breastfeeding



blood transfusion



organ transplant

80%

unprotected sex

HIV is not transmitted



food, drink, utensils



insect bites



kiss, touch



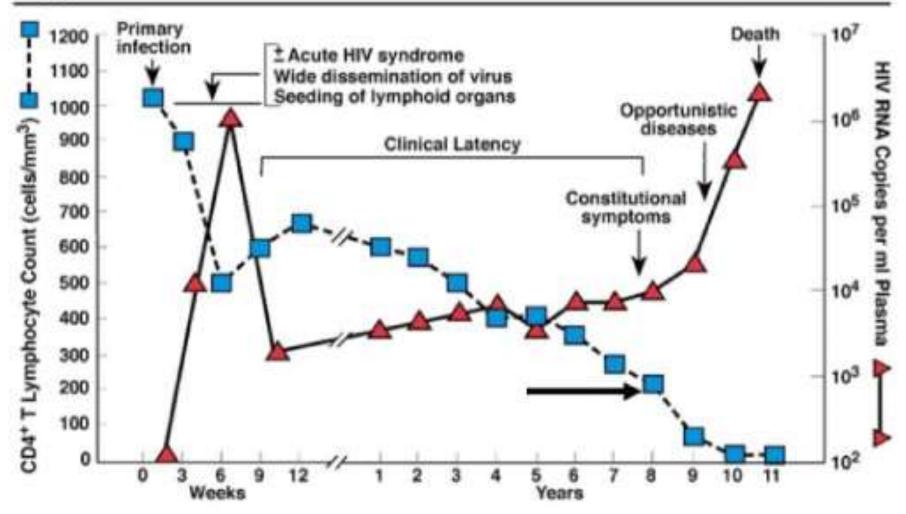
clothes, towels



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Typical Course of HIV Infection

T



Modified From: Fauci, A.S., et al, Ann. Intern. Med., 124:654, 1996



HIV/AIDS infection

HIV primary infection

- Symptomatic in 50-70% of cases
- Appears 3-6 weeks (maximum 6 months) after infection
- Polymorphic, non-specific, "Mononucleosis-like" or "Flu-like" simptoms
- Fever/asthenia in 80% of cases
- Symmetrical, painless polyadenopathy
- Erythematous tonsillitis
- Maculopapular or urticarial rash in 50-70% of cases
- Myalgias/arthralgias in 50% of cases
- Oral and/or genital ulcers in 40% of cases
- Weight loss > 2.5 kg in 30% of cases

Persistent generalized lymphadenopathy

- Present in 50-70% of patients
- Increase two or more groups of lymph nodes, except extrainguinal
- Size > 1 cm, painless, mobile
- Persists for > 3 months

Lymphadenitis in opportunistic diseases in stage AIDS

- Tuberculosis (cervical, axillary, mesenteric, mediastinal nodes)
- Hodgkin's lymphoma (cervical, axillary and inguinal nodes)
- L. non-Hodgkin (mediastinal, retroperitoneal, paraaortic or pelvic nodes)



Laboratory modification in HIV/AIDS infection

In acute retroviral syndrome (HIV)

- Leukocytosis with lymphomonocytosis
- atypical lymphocytes in blood smear Lymphopenia with ↓ CD4 lymphocytes, ↑ CD8 and ↓ CD4/CD8 ratio < 1
- Thrombocytopenia-in 25% of cases
- Mild cytolytic sindrom in 30% of cases

Confirmation of HIV infection

- In first 12 weeks after infection
- 2 Rapid IV generation tests (Anti-HIV+Ag p24) positive
- HIV-RNA (PCR) positive
- level of CD4 lymphocytes

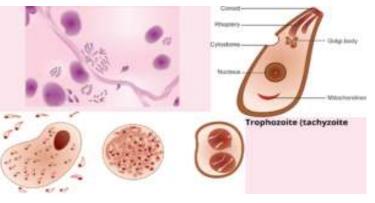
12 weeks after infection

- 2 Rapid III generation tests (Anti-HIV)- poz
- HIV RNA (PCR) poz
- CD4 lymphocyte level



Toxolplasmosis

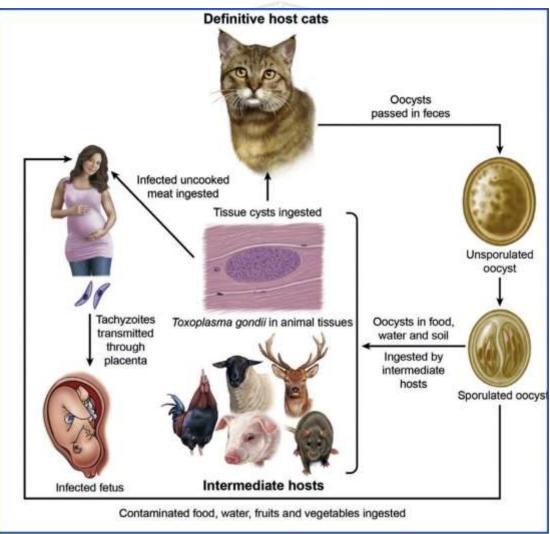
Toxoplasma gondii



Primary infection – at any age, more common in children and young adults Incubation between 5 days – 3 weeks

Clinical forms:

- Acute acquired toxoplasmosis in immunocompetent and immunocompromised patients
- Chronic acquired toxoplasmosis (reactivation)
- Congenital toxoplasmosis



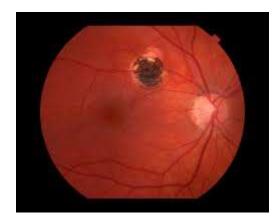
Clinical Features

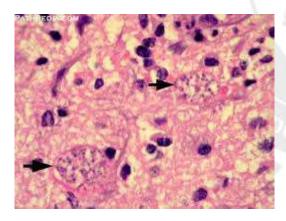
- Infection with *Toxoplasma* in immuno-competent persons is generally an asymptomatic infection.
- However, 10% to 20% of patients with acute infection may develop:
 - A flu-like illness.
 - Cervical lymphadenopathy.
 - Atypical pneumonia.
 - Acute encephalitis.
 - Chorioretinitis.
- Symptoms usually resolve within a few months to a year.

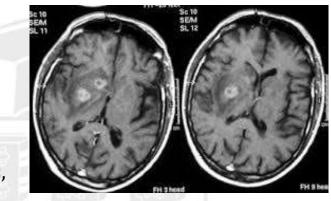


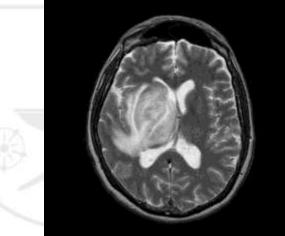
Toxoplasmosis in immunocompromised patients

- •HIV/AIDS (CD4< 100/mm3)
- Posttransplantation
- Oncohematological diseases with chemotherapy
- •AIDS associated toxoplasma encephalitis results from reactivation of chronic latent infection in more than 95%
- •The risk for cerebral toxoplasmosis approaches 30%.
- •In the CNS affected grey and white matter of brain, retina, lungs, heart and skeletal muscles.
- •Changes in mental status (75%)
- •Fever (10-72%)
- •Epileptic seizures (33%)
- •Headache (56%)
- •Focal neurological deficits(60%)





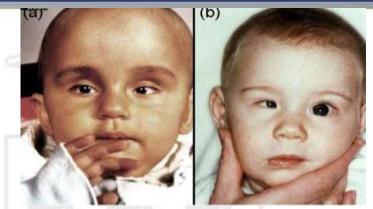






Congenital toxoplasmosis

- Hydrocephalus, microcephaly, ventriculitis
- Intracranial calcifications
- Cerebral palsy, deafness
- Epilepsy, psychomotor or mental retardation
- Maculopapular rash
- Generalized lymphadenopathy
- Hepatomegaly, splenomegaly, hyperbilirubinemia
- Petechiae associated with thrombocytopenia, anemia
- >80% of children present ocular sequelae : chorioretinitis, uveitis, optic nerve atrophy



a) bulging forehead b) microphthalmia







Toxoplasmosis. Diagnosis and treatment

Etiological diagnosis

✓ Anti-Toxo IgM (+), Anti-Toxo IgG (-) – acute infection

✓ Anti-Toxo IgM (+), Anti-Toxo IgG (+) - reactivation of chronic infection

✓ In pregnant women with Anti-Toxo IgM (+), Anti-Toxo IgG (-) – acute infection is suspected and repeated Anti-Toxo IgG in 2 weeks;

✓ Anti-Toxo IgM (+), Anti-Toxo IgG (+) – Ab avidity test (reactivation of chronic infection)

✓ DNA Toxo- by PCR from amniotic fluid, serum

Treatment

✓ Pirimetamina + Sulfadiazina

✓ Pirimetamina +Dapsona or

✓ Trimetoprim-sulfametaxozol 1 tab daily

Congenital infection

Pirimetamina (1mg/kg) + Sulfadiazina (100 mg/kg) + Acid folic, daily, 1 year

Ocular toxoplasmosis

Pirimetamina + Sulfadiazina or Clindamicina, 30 day





Herpetic viruses

Human viruses	Common name	Subfamily	The target cell	The transmission
Human herpes virus 1	Herpes simplex type 1	Alpha	Mucoepithelium	Close contact
Human herpes virus 2	Herpes simplex type 2	Alpha	Mucoepithelium	Close contact, the sexual way
Human herpes virus 3	Varicella-Zoster	Alpha	Mucoepithelium	Respiratory tract By contact
Human herpes virus 4	Epstein-Barr	Gamma	B-lymphocytes, epithelium	Saliva
Human herpes virus 5	Citomegalovirus	Beta	Epithelium, lymphocytes, monocytes	Transplacentar Blood transfusions Transplant
Human herpes virus 6	Measles/Roseola infantum	Beta	T-lymphocytes	Respiratory tract By contact
Human herpes virus 7	Exanthema Subitum	Beta	T-lymphocytes	Unknown
Human herpes virus 8	Kaposi's sarcoma	Gamma	Endothelial cells	Body fluids



HSV-1 infection

• The primary infection appears in the first 1-3 years, in 90% of cases - asymptomatic.

Clinical manifestations:

- herpes labialis gingivostomatitis (vesicular and ulcerative rash, *cervical adenopathy*, fever)
- **kerato-conjunctivitis** (presents the risk of corneal ulceration and blindness)
- eczema herpeticum (in patients with chronic eczema, as a generalized vesicular dermatitis)
- herpetic panaritium (in healthcare worker, in children – self-inoculation)
- **meningitis, meningo-encephalitis**, damage to the trigeminal or olfactory nerves (lethality 70%).





HSV-2 infection

- It mainly causes genital infections.
- Primary infection in people aged 15-25 (first sexual contact) or in newborns (congenital herpes, neonatal).
- In 75% of cases the primary infection is asymptomatic.

Clinical manifestations:

- *Genital herpes* (vesicular-ulcerative lesions of the penis, vulva, vagina, cervix, perineum, buttocks, herpetic proctitis). After the primary infection, the virus remains latent in the lumbar and sacral nodes, causing recurrences, with the same localization, less severe.
- *Neonatal herpes* Contracted by a newborn at birth or from healthcare worker with oral herpes or herpes panaritium. It is manifested by septicemia or conjunctivitis. Untreated, it progresses with visceral dissemination and death (65%). The infection can be asymptomatic.
- *Congenital infection* Transplacental transmission causes congenital malformations, heart defects.
- Cervical and vulvar cancer



displazie

de grad înalt





HSV-3 infection

Primary infection – chicken pox

- The source of the virus is man
- Transmission airborne, through nasopharyngeal secretions or through contact with vesicular fluid.
- It usually affects children aged 2-6 years, and non-immune adults in the winter-spring season.
- Maximum contagiousness 1-2 days before the rash and one week after the last eruptive pustule.
- Incubation period 14 days
- In the first 5 days damage to the respiratory system and local lymph nodes.
- After 5 days, fever and pruritic rash appear, then it spreads independently over the whole body, including the scalp (macule - papule - blisters with clear liquid, then crusts).



- The rash disappears without a scar after 2-3 weeks
- In immunocompromised persons hemorrhagic lesions, bacterial superinfection, encephalitis, pneumonia, disseminated chickenpox, lethal.
- In pregnant women in the first 20 weeks of pregnancy, chicken pox can cause an embryofetopathy



HSV-3 infection

Reactivation (Zona-Zoster)

- Characteristic for adults with compromised immunity
- During the primary infection, through sensitive or hematogenous nerves, VZV spreads to the spinal ganglia or cranial nerves, where it remains latent.
- In case of reactivation, the virus multiplies and moves via the centrifugal nerve to the corresponding skin sector, causing Zona-Zoster.
- The infection begins with severe neuralgia, hyperesthesia and vesicular, unilaterally rash, located in the dermatome of the affected nerve.
- It may be associated with meningitis or paralysis.
- Clinical forms: ophthalmic zoster, motor zoster, encephalomyelitis.
- The rash persist until the appearance of the immune response (humoral, cellular).





Measles Incubation period – 10 days Prodromal phase 4-5 days

- Fever 38-40^oC
- Fatigue, weakness, anorexia
- Cough, coryza, conjunctivitis

Specific symptomatic phase

- Erythematous, non-pruritic, maculopapular rash spreads for 3 days gradually head-trunk and abdomen -limbs, palms and soles, becoming confluent. On the 4th day it begins to disappear in the order in which it appeared
- Koplic spots on the oral mucosa

Complications of measles

- Pneumonia
- Otitis media
- Encephalitis

Acquired rubella Incubation period – 14 days Prodromal phase (1-5 days)

- General malaise
- Subfebrile temperature
- Upper respiratory tract simptoms

Specific symptomatic phase

- Generalized maculo-papular rash for ≤ 3 days
- Occipital and/or posterior auricular lymphadenopathy
- Arthralgias and arthritis common in adults

Congenital rubella – congenital malformations

- Eye (cataract)
- Hearing (deafness)
- Cardiac (pulmonary artery stenosis)



HSV7 and HSV8 infection

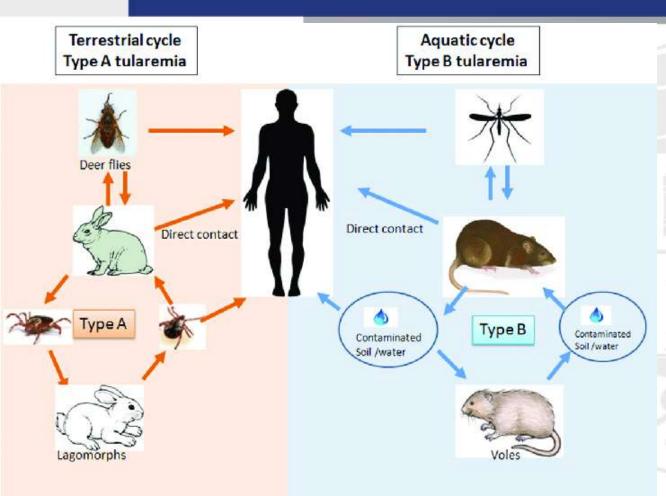
- **HSV7 -** Over 95% of adults have been infected and are immune to HHV-7
- Primary infection of HHV-7 among children between the ages of 2 and 5
- In adults develops with mononucleosis syndrome, in immunocompromised with pneumonia, encephalitis, retinitis, hepatitis
- It has been associated with cases of exanthem subitum, pityriasis rosea, neurological manifestations and transplant complications.
- **HSV 8 -** in 95% develops Kaposi's sarcoma, is transmitted sexually, through saliva, transplanted organs.
- **Cutaneous KS** nodules, 0.5-2 cm in size, violet, pink, brown, red-brown or purple-red on the face, neck, nose, oral cavity, lower extremities
- **KS with visceral localization** is frequently found in patients with HIV infection in any organ or system: lymph nodes, lungs, intestine, liver and spleen



Herpetic infection	Diagnosis of herpes infection	Treatment
HSV1 and HSV2	DNA-HSV1, HSV2 by PCR from vesicles, ulcerative lesions, CSFAnti- HSV1 and Anti-HSV2 IgM, IgG – in primary infections	Aciclovir, Valaciclovir, Famciclovir, Foscarnet, Penciclovir
HSV3 (Varicela-Zoster)	Clinically, to assess response of the host - Anti VZV IgG by ELISA or FAMA	Aciclovir, Valaciclovir, Famciclovir
HSV4 (EBV)	EBV-VCA IgM antibodiesIgG anti- EBNA antibodies EBV-DNA	-
HSV5 (CMV)	Anti-CMV IgM – acute phase/ CMV reactivationsAnti-CMV IgG - avidity testpp65 antigen and CMV DNA by PCR from blood and urine	Ganciclovir, Valganciclovir, Valaciclovir Cidofovir, Foscarnet
HSV6 (Measles, Roseola infantum)	-	-
HSV7 (Exantema subitum)	-	-
HSV8 (Kaposi's sarcoma)	BiopsyEndoscopy with biopsy	HAART therapy cryosurgery, intralesional vinblastine, excision, radiotherapy, systemic chemotherapy



Tularemia – rabbit fever

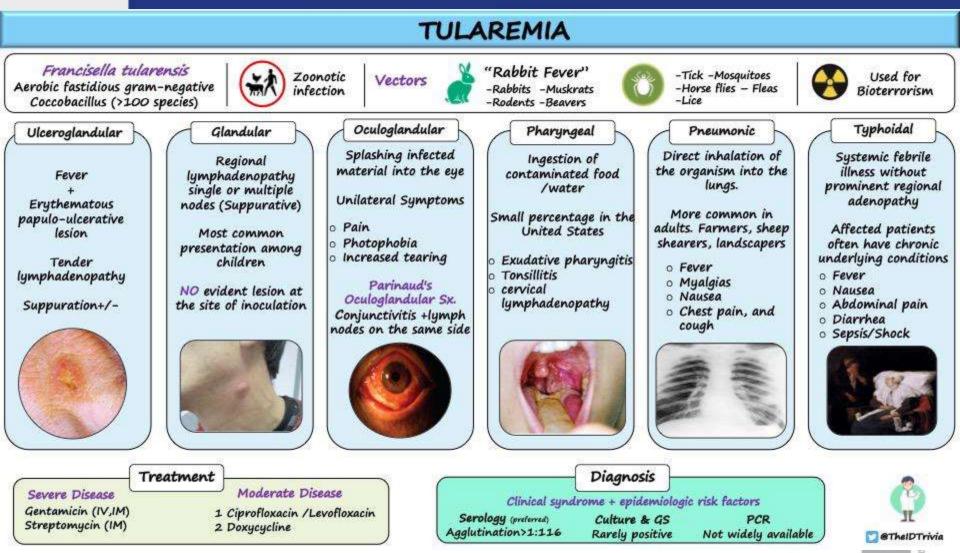


Infection caused by *Francisella tularensis* can occur from the bite of an infected tick, deer fly, other blood-feeding insects, or contact with an infected animal.

Infection can also occur after ingesting or inhaling the bacteria or after exposure to laboratory accidents. In nature, infections occur most frequently in hares, house rabbits and rodents

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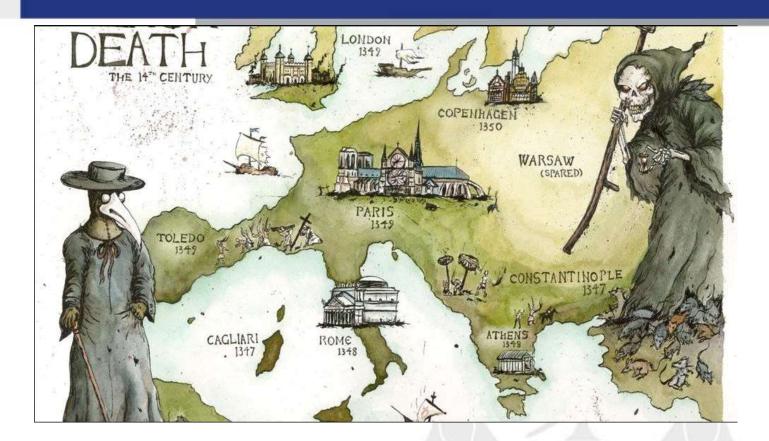


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Plague or Black Death

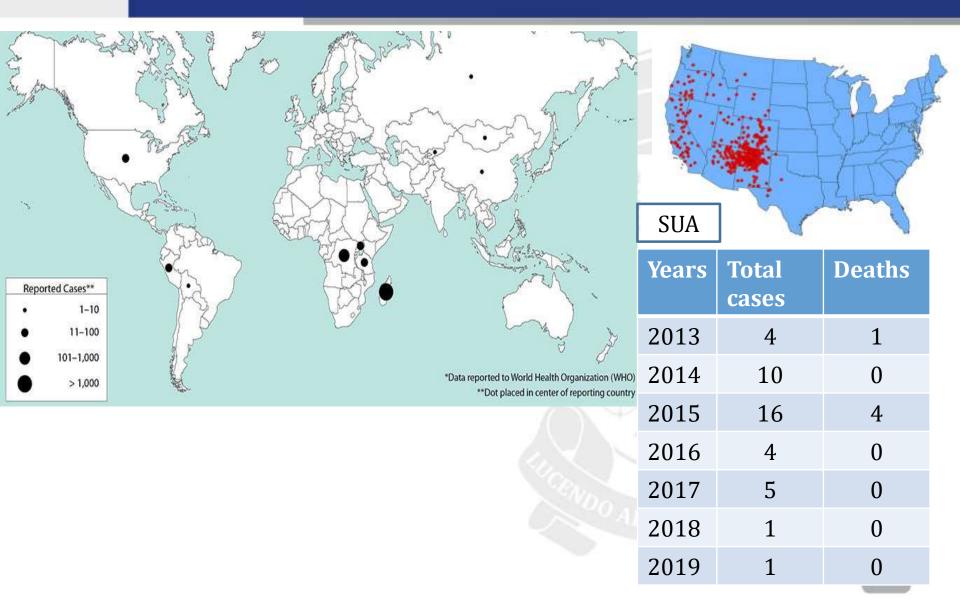


The "Black Death" was believed to be responsible for the disappearance of nearly 350-375 million people from the world's population. The "Black Death" started from Central Asia and reached Europe in 1347 where it killed approximately 30-60% of its population (between the years 1348-1350).

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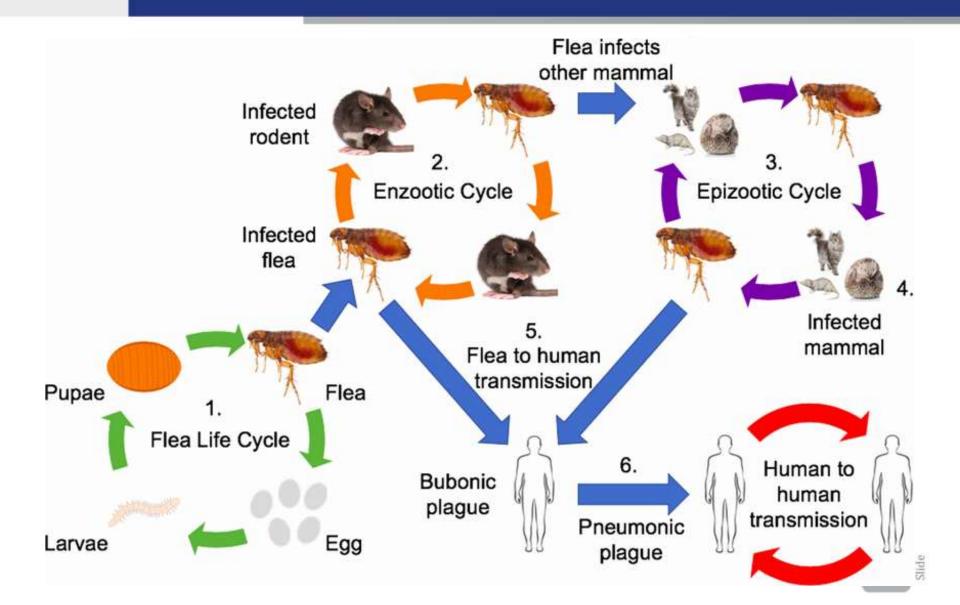


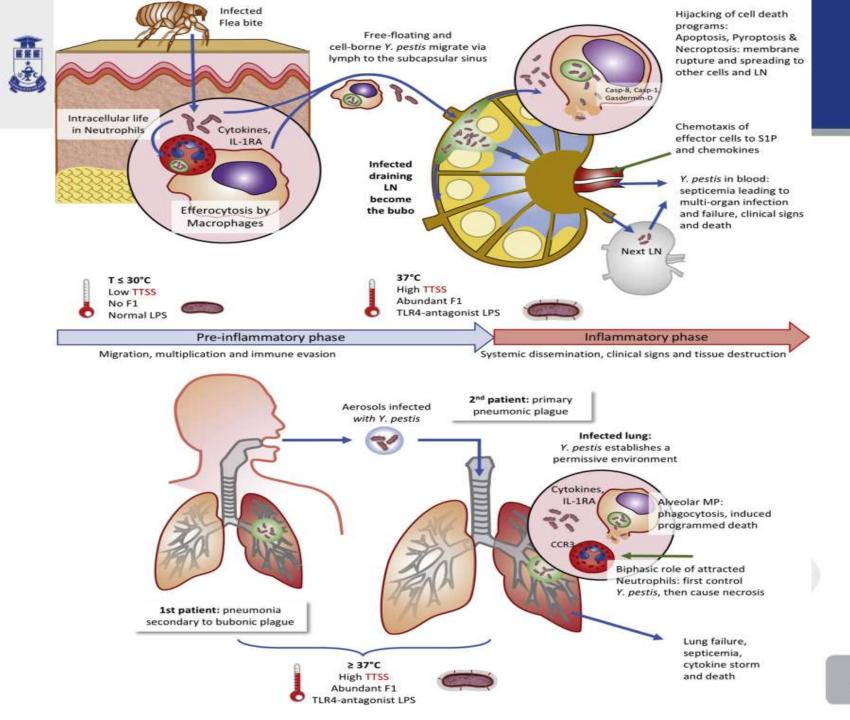
Plague cases reported in 2013-2019





Plague, epidemiology





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Plague, clinical forms

The bubonic form 80-95%

fever 38-39°C severe headache fatigue inguinal, axillary, cervical lymph nodes enlarged, painful, immobile, hyperemic,



Diagnosis: Cultures, RIF, PCR

The septicemic form 10-25%

fever 39-40°C chills headaches myalgia muscle weakness inflammation of the lymph nodes diarrhea, vomiting breathing difficulties difficulty swallowing delirium



Primary pulmonary form

Incubation period – 4-5 hours – 3 days sudden onset with fever, headache, myalgia, cough with hemoptysis chest pain, can be transmitted from person to person, mortality \approx 100%, with specific treatment \approx 50%



Slid

Treatment: Streptomycin, Gentamicin, Doxacycline



Cat Scratch Disease (Felinosis)

Primary inoculation papule

Bartonella henselae

1-3 weeks

Regional lymphadenitis

- 1. History of a cat scratch or lick 2 weeks prior.
- 2. Primary lesion: papule, vesicle or nodule
- 3. Sensitive regional lymphadenitis.
- 4. Fever, anorexia, malaise.
- 5. Extranodal manifestations prolonged fever, ocular and neurological manifestations, osteomyelitis

Treatment:

Azithromycin Rifampicin Trimethoprim-sulfamethoxazole Ciprofloxacin



Brucellosis - widespread zoonoses

Incubation period 2-3 weeks – 3-4 months

Brucella melitensis (goats, sheep, camels) Brucella abortus (cattle) Brucella suis (pigs)

Brucella canis (dogs)

Laboratory diagnosis Serological tests: RA Right IgM RA Heddelson PCR test

Treatment Streptomycin Gentamicin Doxycycline Rifampicin

Acute brucellosis

gradual onset
rolling fever
night sweats
anorexia, asthenia
headache, myalgia
lymphadenopathy,
hepatosplenomegaly
neurological disorders

Chronic brucellosis

prolonged low fever
arthritis, ankylosis
Spondylodiscitis
Orchoepididymitis
Hepatosplenomegal
meningitis
endocarditis



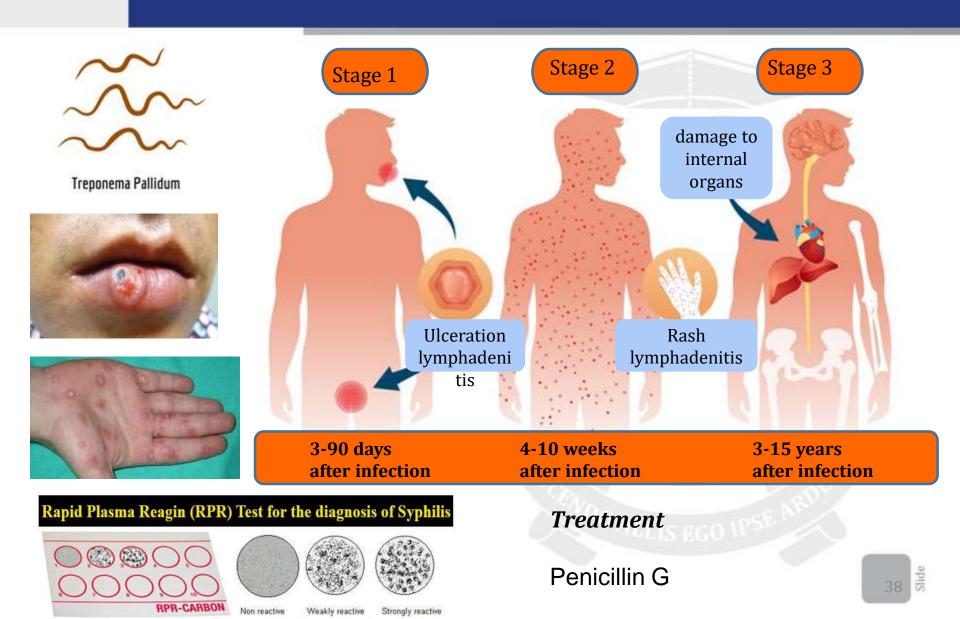




	Diphtheria	Tuberculosis	Atypical mycobacterial infection
Etiological agent	Corynebacterium diphtheriae	Mycobacterium tuberculosis	Mycobacterium avium Mycobacterium intracelulare
Incubation period	2-5 days	unknown	unknown
Transmission	Aerosol by close contact	Drops of saliva through coughing, sneezing or talking	Airborne Water drops from open tanks
Clinical manifestations	fever 38°C sore throat dysphagia fibrinous films breathing difficulties submandibular edema	Pulmonary TB 80% Fever 37-37.8°C Night sweats Productive cough > 3 weeks Hemoptysis Hilar/parahilar lymphadenopathy Weight loss CT-Cavity with caseous necrosis	COPD in adults Disseminated infection in the immunocompromised Chronic productive cough CT-Cystic lung cavity Weight loss Night sweats Dyspnea Abdominal pains
Lymphadenitis	local cervical lymphadenopathy	Posterior cervical, supraclavicular lymph nodes in 35% of extrapulmonary TB in HIV infected	Isolated cervical lymphadenopathy in children
Laboratory confirmation	Isolation of C.diphtheriae	Sputum microscopy at BAARX- pert MTB/RIF	Isolation of MAC from sputum, blood
Treatment	Anti diphtheria serum Penicillin,	Rifampicin Isoniazid	Azithromycin Clarithromycin



Sifilis





Tropical parasitic diseases

Trypanosomiasis - sleeping sickness

Leishmaniasis

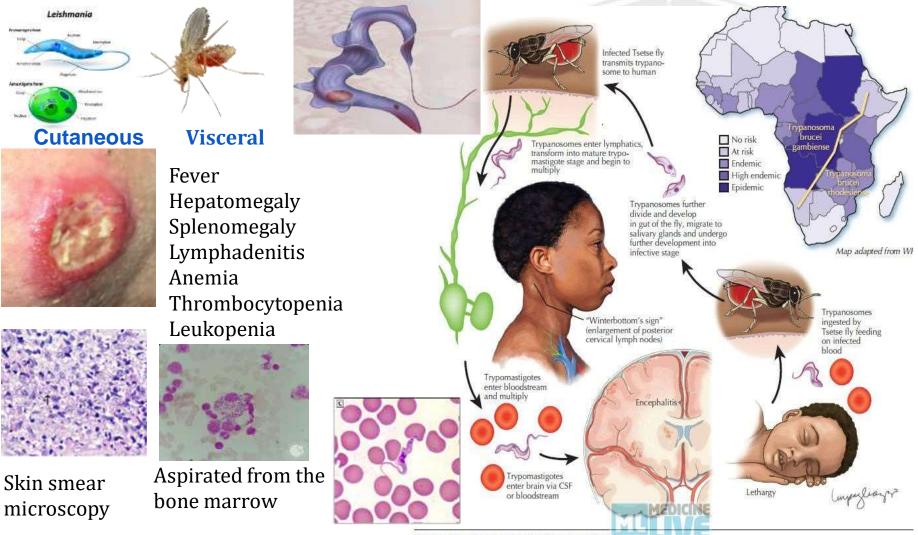
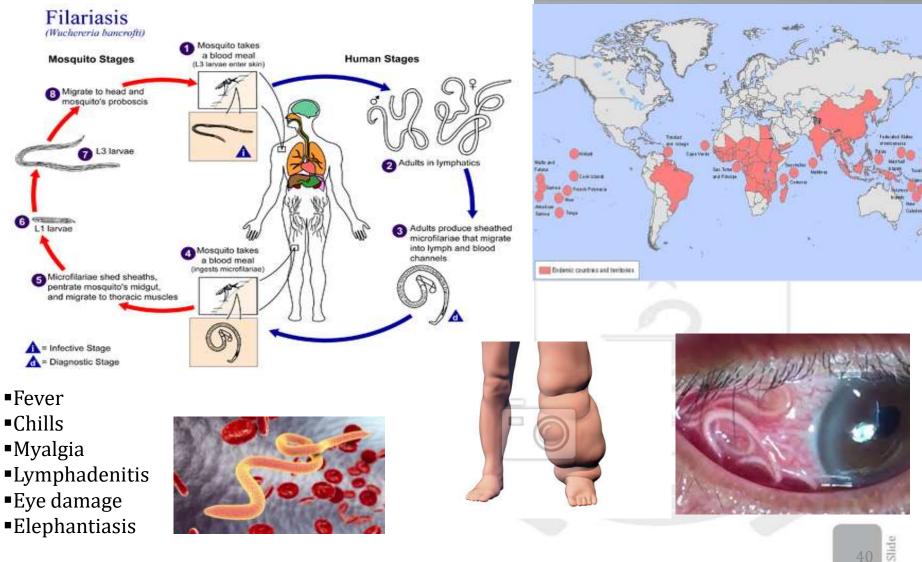


Figure 50-3 Trypanosomiasis (African Sleeping Sickness).



Filariasis





Thank You For Your Attention





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