Parasites in Liver & Biliary tree

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Parasites in Liver & Biliary Tree

Hepatic

- Protozoa
  - E. histolytica
  - Malaria
  - Babesiosis
  - African Trypanosomiasis
  - S. American Trypanosomiasis
  - Visceral Leishmaniasis
  - Toxoplasmosis
- Cestodes
  - Echynococcosis
- Trematodes
  - Schistosomiasis
- Nematodes
  - Toxocariasis
  - Hepatic Capillariasis
  - Strongyloidiasis
  - Filariasis

Biliary Tree

- Protozoa
  - Cryptosporidiasis
  - Microsporidiasis
  - Isosporidiasis
  - Protothecosis
- Trematodes
  - Fascioliasis
  - Clonorchiasis
  - Opistorchiasis
- Nematodes
  - Ascariasis

Parasites in the Liver

Entamoeba histolytica

- **Organism:** E. histolytica is a Protozoa Sarcodina that infects 1-5% of world population and causes 100000 deaths/y.
  - (E. dispar & E. moshkovskii are morphologically identical but only commensal; PCR or ELISA in stool needed to differentiate).
- **Distribution:** worldwide; more in tropics and areas with poor sanitation.
- **Location:** colonic lumen; may invade crypts and capillaries. More in cecum, ascending, and sigmoid.
- **Forms:** trophozoites (20 mcm) or cysts (10-20 mcm). Erytrophagocytosis is diagnostic for E. histolytica trophozoite.
- **Virulence:** may increase with immunosuppressant drugs, malnutrition, burns, pregnancy and puerperium.

Entamoeba histolytica

- **Clinical forms:**
  - I) asymptomatic;
  - II) symptomatic:
    - A. Intestinal:
      - a) Dysenteric,
      - b) Nondysenteric colitis.
    - B. Extraintestinal:
      - a) Hepatic: i) acute nonsuppurative hepatitis, ii) hepatic abscess,
      - b) Pulmonary,
      - c) Other extraintestinal foci.

Entamoeba histolytica

- **Transmission:**
  - fecal-oral, human to human, by contamination of food and water;
  - stool elimination of cysts up to 2 y;
  - up to 1.5 x 10^9 cyst/d;
  - 2000-4000 cyst inoculums cause disease.
- **Incubation:**
  - 2- 120 days (m= 21d)

Entamoeba histolytica

- **Clinical manifestations:**
  - **a) acute nonsuppurative hepatitis :**
    - is part of a severe amebic colitis;
    - Hepatomegaly without abscess, liver tenderness, and leukocytosis;
    - biopsy may show amebic granuloma.
  - **b) Amebic abscess:**
    - Amoeba arrives through portal v. or rarely through peritoneum.
    - Abscess size: from pin-point to > 15 cm.
    - Usually single (84%); 65% in Rt lobe, 35% in left.
    - More frequent in 20-40 y/o and in males.
    - Abrupt fever 38-40 ^{0}C., chills, afternoon & night sweats.
    - Rt abscess: intense & constant RUQ pain with Rt. scapular or shoulder radiation; worse with cough, deep breath or walking.
    - Lt abscess: epigastric pain radiating to Lt. shoulder. Nonproductive cough in 30%.
    - May have nausea, vomiting, diarrhea or weight loss.
    - Tender hepatomegaly exquisitely tender at percussion. Jaundice in 8%.

Entamoeba histolytica

- **Clinical manifestations:**
  - **Laboratory:**
    - Leukocytosis of >/= 15000 with mild anemia.
    - High alk. Phosph in 50%; mild bili elevation in 30%; may have mild elevation of ALT and hypoalbuminemia.
    - Indirect hemagglutination (+) in > 90%; may be (-) in 1st week; peak on 2nd- 3rd month; remain (+) for years.
    - Stool studies usually negative.
  - **Imaging:**
    - Ultrasound (+) in 75-95% with round/oval hypoechoic lesion with well defined margins and no prominent peripheral echoes.
    - CT with low density lesion with smooth margins and contrast enhancing peripheral ring.
    - MRI findings are similar to those of CT Scan.

Entamoeba histolytica

- **Complications:**
  - **Rupture in chest:**
    - most common with large lesions on right lobe, very close to diaphragm.
    - May give empyema, consolidation, abscess, or hepatobronchial fistula.
    - May cause pleuritic pain, cough, hemoptysis, dyspnea, and/or dark-chocolate sputum.
  - **Rupture in pericardium:**
    - most common with left lobe abscess. Ominous complication.
    - May cause pericarditis with effusion, CHF, or tamponade with shock.
    - May give chest pain, left shoulder pain and pericardial rub.
    - Liver abscess may be inconspicuous.
    - Tamponade is often fatal.

Entamoeba histolytica

- **Complications:**
  - **Rupture into peritoneum:**
    - may cause frank peritonitis, or walled-off intraperitonel abscess in case of slow leak.
  - **Other:**
    - Rupture into intestine (improves symptoms),
    - hemobilia due to arterial erosion,
    - biliary obstruction,
    - perinephric amoebic abscess,
    - brain abscess.

Entamoeba histolytica

- **Indications for Percutaneous Drainage:**
  - When bacterial superinfection is suspected.
  - Left lobe abscess with risk of pericardial rupture.
  - All pericardial or pleural fluid collections.
  - Large abscess (> 5 cm) close to liver surface (rupture risk).
  - Lack of response to therapy after 5-7 d
- **Medical Treatment:**
  - Metronidazole 750 TID po x 10 d
  - **Improvement expected in 3 days;** 95% cure rate.
  - Resolution in 2-23 months (m= 7-9 mo);
    - in 6 mo if < 5 cm;
    - in > 1 year if > 10 cm.
  - Luminal agent **to follow**: Diloxanide furoate 500 mg TID x 10 d or Paromomycin 30 mg/kg/d divided TID x 10 d

Echinococcosis (Hydatid & Alveolar)
(E. granulosus, E. multilocularis, E. vogeli)

- **Organism:** Platyhelminthe Cestode (tapeworm) 0.6 cm long.
  - E. granulosus:
    - definitive host (DH): dog, wolf, jackal, dingo, hyena, puma, fox, & cat.
    - Intermediate host (IH): sheep, cattle, goat, pig, moose, reindeer, & human.
  - E. multilocularis:
    - DH: foxes;
    - IH: mice, voles, lemmings, shrews.
  - E. vogeli:
    - DH: bush dog;
    - IH: pacas & spiny rats.
- **Distribution:**
  - E. granulosus: worldwide.
  - E. multilocularis: Alaska, Canada, North-central USA, Russia, Germany, Switzerland.
  - E. vogeli: Central & South America.

Echinococcosis (Hydatid & Alveolar)
(E. granulosus, E. multilocularis, E. vogeli)

- **Acquisition:**
  - Ingestion of contaminated food with DH stool containing eggs (or dog kiss).
  - Egg shell is digested and embryo penetrates small bowel wall and vessel;
  - Embryo is embolized to target organ capillaries (liver, lung, spleen, kidney, bone, or brain).
  - Cyst develops in 4-5d.; reaches 1 cm in 5 months;
    - grows 1 cm/y over many years.
  - Definitive Host is infected after eating the Intermediary Host.
  - Tapeworm lives in the intestine of Definitive Host.

Echinococcosis (Hydatid & Alveolar)

(E. granulosus, E. multilocularis, E. vogeli)

- **Clinical presentation in liver:**
  - **E. granulosus**
    - Asymptomatic, or symptoms due to mass effect (palpable mass);
    - May give jaundice if it compresses biliary tree, or
    - May give portal hypertension by compressing portal or hepatic veins.
    - Cyst may be pedunculated.
    - May perforate in chest, pericardium, peritoneum, bronchi, biliary tree, kidney, or intestine.
    - Rupture in cavity may cause massive seeding with formation of numerous new cysts.

Echinococcosis (Hydatid & Alveolar)
(E. granulosus, E. multilocularis, E. vogeli)

- **Clinical presentation in liver:**
  - **E. multilocularis**
    - does not form single cyst;
    - invades tissue with fibrous tissue mass with many cysts.
    - Behaves as slow growing malignancy, and cysts may metastasize.
    - Can not be surgically resected (other than transplant)
  - **E. vogeli**
    - causes a multiseptated cyst which produces also external cysts (polycystic mass).
  - The fluid of all hydatid cysts:
    - is very antigenic and leak or rupture may cause eosinophilia, asthma attack, or anaphylactic shock.
    - could become infected, forming an abscess.

Echinococcosis (Hydatid & Alveolar)
(E. granulosus, E. multilocularis, E. vogeli)

- **Laboratory:**
  - Mild leukocytosis with eosinophilia is rarely present (unless “leaking”).
  - May have elevation of Alk. Phosph, ALT and AST. Rare bili elevation.
  - In liver cyst the sensitivity of serology is:
    - Anti-Echinococcus IgG ELISA:
      - 80-90 percent for E. granulosus
      - 95-100% for E. multilocularis,
    - IgE ELISA: 82-92 percent,
    - Latex agglutination: 65-75 percent,
    - Hemagglutination: 80-90 percent,
    - Immunoblot (using antigen 5 and/or a B-rich fraction): 80-90 percent
    - Enzyme-linked immunotransfer blot: 80 percent.
    - False (+) with T. solium, T. saginata, neurocysticercosis, immune disorders.
    - False (-) more common in children and during pregnancy.
    - Sensitivity for cyst in other organs much is lower.

Echinococcosis (Hydatid & Alveolar)
(E. granulosus, E. multilocularis, E. vogeli)

- **Radiology:** MRI is better than CT scan at differentiating wall of hydatid cyst from that of ephitelial cyst.
- **Ultrasound** is the most common modality. There are 6 categories:
  - **CL**= cystic lesion of undetermined origin. Unilocular, uniformely anechoic, without hyperechoic rim; (if CE by other test, will be active but not fertile).
  - **CE1**= Echinococcal cyst-1 is unilocular, unechogenic, uniform, with visible wall. May have "snow flake" effect due to hydatid sand; round or oval; (usually active and fertile).
  - **CE2**= multivescicular, multiseptated, with vissible wall. Daughter cyst may partially or completely fill unilocular "mother cyst"; round or oval; (usually active and fertile).
  - **CE3**= anechogenic, with laminates membrane detachment from cyst wall (water-lily sign), or daughter cysts with echogenic and anechogenic areas, looking as complex mass. Cyst may be less rounded (transitional in degenerating process).
  - **CE4**= heterogeneous hypoechoic or dyshomogeneous. No daughter cysts; may have "ball of wool sign". (Inactive and usually infertile).
  - **CE5**= thick, arch shaped calcified wall with cone-shaped shadow; (inactive, usually infertile).

Echinococcosis (Hydatid & Alveolar)

(E. granulosus, E. multilocularis, E. vogeli)

- **Treatment:**
  - Chemotherapy followed by either surgery or Puncture + Aspiration + Injection + Reaspiration (PAIR).
  - **Chemotherapy:**
  - Albendazole 400 mg BID, PO (10-15 mg/kg/d divided BID) x 1 month followed by 2-week vacation x 3-6 cycles (continuos therapy may be more effective and with similar toxicity).
    - Levels should be check at 2 weeks and then every 3 months, with goal of 650-3000 nmol/mL.
    - Is given ideally x 1 month (at a minimum 4 days) before surgery or PAIR, and for 1 month after.
  - Addition of Praziquantel may improve efficacy and shorten therapy.

Echinococcosis (Hydatid & Alveolar)

(E. granulosus, E. multilocularis, E. vogeli)

- **Treatment:**
  - **Surgery** indicated with:
    - cyst > 10 cm with multiple daughter cysts,
    - superficial at risk of rupture,
    - causing compression or obstruction, or
    - infected cyst.
  - **PAIR** is done by puncturing and aspirating 30% of cyst volume, then injecting 95% alcohol or hypertonic saline, and 15 minutes later re-aspirating the cyst.
    - Should not be done if there is cyst communication with biliary tree;
    - MRCP or ERCP should be done before PAIR (risk of causing sclerosing cholangitis).
  - When surgery (including liver transplant) and PAIR are not possible, albendazole can be continue for > 10 years.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- A dozen or more other species of animal schistosomes can cause human infection, including schistosomes of birds and small mammals that cannot mature in the human host but die in the skin, where they cause a dermatitis.
- **Magnitude of the Problem:**
  - 200 million persons infected in 74 countries and territories.
  - 120 million have symptoms, 20 million have severe disease, and 100,000 die each year.
  - Control programs have been slow especially in sub-Saharan Africa, where more than 80% of cases occur.
  - Water resource development projects and population movements have spread the disease into regions where it was not previously endemic.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- **Organism:**
  - Is a Plathyhelminth Trematode (blood fluke);
    - Male 0.6-2.2 cm, round but partially flattened to hold female.
    - Female is round & slender 1.2-2.6 cm.
- **Geographic distribution:**
  - S. mansoni: Arabian peninsula, Africa, Caribbean, Central & South America.
  - S. japonicum: Japan, China, Philippines, Indonesia, Thailand
  - S. intercalatum: Central and West Africa.
  - S. mekongi: Cambodia, Laos

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- **Life cycle & Acquisition:**
  - Human is definitive host.
  - After entering contaminated fresh water, cercariae penetrates the skin (swimmer itch) and changes to schistosomulae;
  - schistosomulae migrate through lymphatics into circulation;
  - then travel to lungs and later to liver;
  - then go to portal vein branches and mature to adults;
    - S. mansoni is in IMV; S. japonicum in SMV.
  - After 30 d adult produces eggs. Female attaches to male, but migrates to intestine venules to deposit eggs.
  - Each worm produces 1000-3000 eggs/d.
  - Eggs migrate through intestinal wall and are eliminated in stool.
  - After 6 days, eggs mature and contaminate fresh water. Then enter snails and makes an sporocyst, which creates many cercariae that contaminate water and penetrate new swimmers.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Acute Schistosomiasis (Katayama Fever):***
  - Acquired from fresh water exposure (wading, swimming) in tropical regions worldwide.
  - Present 4 to 8 weeks after exposure with intermittent fever up to 39 ^{0}C, chills, sweats, headache, myalgias, pruritic maculopapular rash, malaise, asthenia, anorexia, nausea, vomiting and dysenteric diarrhea; lasts up to 2 months.
  - Physical exam shows :
    - mild hepatomegaly, soft splenomegaly, generalized lymphadenomegaly.
    - May have also bronchospasm and pneumonia.
    - Rarely causes acute abdomen and jaundice, specially in non-immune visitors.
    - Sigmoidoscopy shows mucosal edema, hyperemia, petechiae, and small ulcers. Later, biopsies and stool samples show schistosoma eggs.
    - Patients have peripheral blood eosinophilia.
  - May present initially with focal neurologic signs as a result of egg dissemination to the central nervous system.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Acute Schistosomiasis (Katayama Fever):***
  - Distinguished from malaria by generalized maculo-papular urticaria (immune reaction) and the findings of a pruritic rash at the site of cercarial penetration (usually on the legs), lymphadenopathy, and blood eosinophilia.
  - Best diagnostic test is rectal biopsy, followed by stool O&P (Kato-Katz concentration).
  - Serology with Falcon assay screening test–enzyme-linked immunosorbent assay (FAST-ELISA) is 99% specific for all species and has a sensitivity of 99% for *S. mansoni* infection, 95% for *S. haematobium,* but less than 50% for *S. japonicum.*
  - *Immunoblot can confirm ELISA test.*

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis:***
  - Symptoms may be absent or mild in patients who have light or moderate worm burdens but causes morbidity in persons with even light infections.
  - Chronic granulomatous inflammation and elevated levels of proinflamatory cytokines contribute to poor caloric intake, undernutrition, anemia of chronic inflammation, stunting, and impairment of work capacity and cognitive development.
  - Similar mechanisms, along with placental infection and inflammation, may be responsible for decreased birth weight and poor birth outcomes in infants born to mothers with chronic schistosomiasis.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis:***
  - Eosinophilia is often present.
  - Light infections caused by *S. mansoni, S. japonicum,* and *S. mekongi* may cause:
    - fatigue, intermittent abdominal pain, and diarrhea.
  - Heavy infections may cause:
    - blood loss from ulcerations or dysentery leading to a moderate degree of anemia.
  - Intestinal polyps have been observed (most commonly in Egypt).
  - Strictures or large inflammatory masses may cause obstruction or mimic carcinoma.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis & liver:***
  - Chronic S. mansoni, japonica, or mekongi causes hepatomegaly from granulomas around embolized eggs .
  - Infections with *S. intercalatum* tend to be lighter and produce less pathology.
  - Inflammatory hepatomegaly is common during childhood.
  - Hepatomegaly due to periportal, or Symmers “pipestem,” fibrosis may be seen after years of infection in up to 5% to 10% of infected young and middle-aged adults.
  - Granulomas and fibrosis cause a presinusoidal block to portal blood flow and eventually portal hypertension, splenomegaly, hypersplenism.
  - Usually liver cell perfusion is not reduced, hepatic function is preserved, and liver function tests remain normal.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis & liver:***
  - Natural progression of schistosomal disease occurs more rapidly in persons with S. japonica than with S. mansoni.
  - Coexisting alcoholic cirrhosis, chronic hepatitis B, or hepatitis C may cause jaundice and ascites.
  - Chronic coinfection with hepatitis B or C worsens the prognosis of persons with hepatosplenic schistosomiasis.
  - High rate of hepatitis C coinfection noted in Egypt reflects widespread transmission associated with parenteral antischistosomal treatment that was given until the 1980s, and impaired ability to clear the virus.
  - Persons with both schistosomiasis mansoni and chronic hepatitis B or C may be at higher risk for hepatoma than persons infected with hepatitis B alone.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis & luminal GI Tract:***
  - Repeated hematemesis from portal-hypertension related bleeding esophageal varices is associated with low mortality in persons with compensated disease but may lead to hepatic failure and death in persons with decompensated disease (due to coexistent liver disease).
  - Egg deposition occurs primarily in the colon;
    - may present with blood and mucus in the stool;
    - endoscopy shows polyps and inflamed rectal mucosa.
  - Patients may have protein loosing enteropathy.
  - Rectal/colon biopsy with direct microscopic exam of fresh tissue allows to differentiate treated disease from active disease, by finding an active “flame cell” in the egg.
  - Stool egg concentration >/= 400/gm indicate heavy infestation and high risk for complications.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis, lung, kidney & CNS:***
  - Lung:
    - S. mansoni and japonica, eggs may bypass the liver through portosystemic collateral vessels and cause pulmonary disease.
    - Can lead to cor pulmonale.
  - Kidney:
    - Subclinical glomerulonephritis is not uncommon in persons with chronic schistosomiasis; kidney biopsy shows deposits of immune complexes containing schistosomal antigens in the glomerular basement membrane.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis, lung, kidney & CNS:***
  - CNS:
    - Ectopic egg deposition in CNS occurs in 2-5% of S. japonicum infections and can cause serious cerebral and spinal cord disease.
    - May cause focal or generalized seizures, focal neurologic deficits, signs of increased intracranial pressure due to the mass effect, and diffuse encephalitis.
    - Computed tomography (CT) and magnetic resonance imaging (MRI) scans of the head show nodular and ring-enhancing lesions with surrounding edema.
  - Spinal Cord:
    - With *S. haematobium* and *S. mansoni* eggs reach the lower spinal cord through Batson's plexus and produce either granulomatous lesions of the conus medullaris and cauda equina or transverse myelitis with back pain and paraplegia.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis and infections:***
  - **Salmonella:** prolonged bacteremia with *Salmonella typhi* and other *Salmonella* species has been reported. Salmonella attaches to tegument and intestine of schistosoma and induces tolerance.
  - Unlike typhoid fever, the illness is indolent, with persistent fever, weight loss, and continuous bacteremia; and it can last months.
  - Treatment of the bacterial infection without treating the schistosomiasis may result in relapse of bacteremia and symptoms.
  - *Salmonella* bacteremia and bacteriuria have been associated with glomerulonephritis and nephrotic syndrome in persons with *S. haematobium* and *S. mansoni* infections.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Chronic Schistosomiasis and infections:***
  - **HIV:** coinfection has decreased egg excretion in persons with *S. mansoni* and *S. haematobium* infections because of impaired granuloma formation and increased trapping of eggs in tissue.
  - Treatment of schistosomiasis in persons with HIV coinfection has led to a decrease in HIV viral load, an increase in $CD4^+$ T-cell counts, a decrease in schistosomal fecundity and egg excretion, but poor killing of adult worms.
  - An immune reconstitution phenomenon with eosinophilic colitis and granulomas around dead and dying schistosome eggs followed antiretroviral treament of an HIV-infected man with untreated chronic schistosomiasis.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Treatment:***
  - **Chronic Schistosomiasis:**
    - Drug of choice: praziquantel (affects membrane permeability in the parasite).
    - Single treatment cure rates of 65% to 90%; if not cured, egg excretion is reduced by more than 90%.
    - Praziquantel does not affect developing schistosomula and may not abort an early infection.
    - Resistance to praziquantel may occur; may require multiple courses to clear infection.
    - Adverse effects usually mild and last < 24 hours; may be due to reactions to dying worms. Patients may report headache, dizziness, or abdominal discomfort and less commonly nausea, vomiting, diarrhea, bloody stools, fever, and urticaria.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Treatment (continuation):***
  - **Chronic Schistosomiasis:**
    - WHO now recommends that praziquantel be given to pregnant and lactating women with schistosomiasis.
    - Persons with known or suspected cysticercosis should remain under observation during therapy because of the risk for seizures or other neurologic consequences of dying cysticerci.
    - Persons with schistosomal disease of the CNS should also take corticosteroids to reduce the inflammation and edema around eggs.
    - More data are needed to determine whether combination therapy offers any advantages over monotherapy with praziquantel.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Treatment (continuation):***
  - **Acute Schistosomiasis:**
    - Katayama S. often require corticosteroids to suppress the inflammation, but there is no consensus about proper antihelmintic treatment.
    - Some administer praziquantel simultaneously with or shortly after administration of corticosteroids and treat *S. mansoni* and *S. haematobium* infections for up to 3 days and *S. japonicum* infections for up to 6 days . Other authors believe that praziquantel should not be used during the acute phase.
    - Antimalarial drugs artemether and artesunate, are active against all species of schistosomes, can kill schistosomula during the first 3 weeks of infection, and are synergistic with praziquantel in killing adult worms. They are effective as prophylactic agents against *S. japonicum* when given every 2 weeks for chemoprophylaxis.

Schistosomiasis

(S. mansoni, S. japonicum, S. intercalatum, S. mekongi)

- ***Treatment (continuation):***
  - **Acute Schistosomiasis (continue):**
    - In acute schistosomiasis, a second course of therapy is recommended 4 to 6 weeks after the onset of symptoms.
    - Stool should be examined for eggs 6 to 8 weeks after symptoms subside, and persons who remain infected should receive a single dose of praziquantel, 40 to 60 mg/kg.
  - **Follow-up Acute or Chronic Schistosomiasis Treatment:**
    - Because antischistosomal drugs may temporarily inhibit egg laying by adult worms, stool should be examined for up to 6 months after completion of therapy for both acute and chronic infections.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Organism & Magnitude of the problem:**
  - Plasmodium are Protozoa Apicomplexa (sexual & asexual generations)
  - in tropical developing countries causes > 500 million febrile illnesses and up to 2.5 million deaths annually.
  - up to 40% of the world's population is at risk for acquiring malaria.
  - most severe cases and deaths occur in children younger than 5 years old and in pregnant women.
- **Vector:** Anopheles mosquitoes (60 of the > 200 species).

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Life Cycle:**
  - life cycle and disease patterns are of recrudescence and relapse.
  - Anopheline mosquitoes transmit malaria by injecting sporozoites into the human host.
  - The sporozoites invade hepatocytes and then develop into schizonts.
  - Each infected hepatocyte ruptures to liberate 10,000 to 30,000 merozoites that invade circulating erythrocytes.
  - Growth and development of the parasites in red cells result in waves of merozoite invasion. This asexual blood cycle repeats every 48 (*P. falciparum*, *P. vivax*, *P. ovale*) or 72 (*P. malariae*) hours, leading to amplification of parasite density; paroxysms of chills, fevers, and sweats; and other manifestations of disease.
  - Some *P. vivax* and *P. ovale* parasites can postpone their development in the liver, persisting as latent forms called hypnozoites. Resumption of hypnozoite development months to years after initial infection can lead to malaria relapse that requires an additional round of drug therapy to treat recurrent symptoms and eradicate blood stages.
  - Hypnozoites are not eradicated by standard therapy (e.g., chloroquine) directed against blood stages.
  - Treating hypnozoites with primaquine can prevent relapses of malaria.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Signs & Symptoms:**
  - symptoms typically start 2 to 4 weeks after mosquito bite, depending on the immune status, strain and the species of *Plasmodium,* dose of sporozoites, and effects of partially effective chemoprophylaxis.
  - Malaria can be acutely malignant and painful, or more indolent and asymptomatic.
  - typically presents as an undifferentiated acute febrile illness with chills and rigors followed by fever up to 40^0 C in 100%; headache, 100%; weakness, 94%; profuse night sweats, 91%; insomnia, 69%; arthralgias, 59%; myalgias, 56%; diarrhea, 13%; and abdominal cramps, 8%.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Signs & Symptoms:**
  - Hepatomegaly occurs in up to 60% with P. vivax or P. falsiparum. Liver & spleen may be tender at palpation and percussion. Jaundice and renal failure may be seen in severe cases.
  - Paroxysms last several hours, can occur with a regular periodicity coinciding with the synchronous rupture of blood schizonts; may alternate with relatively asymptomatic periods.
  - It increases the morbidity and mortality associated with other diseases by stressing host systems and producing effects such as dehydration, anemia, and some degree of immune suppression.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- ***Severity of illness:***
  - *P. falciparum* malaria can be much more acute and severe than malaria caused by other *Plasmodium* species, although *P. vivax* can cause serious and fatal illness.
  - *P. knowlesi* produces acute illness and relatively high parasitemias.; hyperparasitemias are life-threatening.
  - largest fraction of deaths directly attributable to malaria are caused by severe complications of *P. falciparum* infection, including cerebral malaria, severe anemia, respiratory failure, renal failure, and severe malaria of pregnancy. Important contributory factors include metabolic acidosis, hypoglycemia, and superimposed bacterial infections. Fatal *P. falciparum* infections are often associated with multiple organ failure.
  - *P. vivax* is selective for reticulocytes and does not achieve high densities.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Cerebral malaria:**
  - histopathological finding is intense sequestration of parasitized erythrocytes in the cerebral microvasculature, often with ring hemorrhages, perivascular leukocyte infiltrates, thrombin deposition, activated platelets, and immunohistochemical evidence for endothelial cell activation.
  - Microvascular obstruction does not generally produce neurologic sequelae like in thrombotic stroke; with early successful treatment patients recover rapidly within 48 hours and without sequelae.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Hypoglycemia:**
  - causes coma and convulsions and contributes substantially to the morbidity and mortality.
  - depletion of liver glycogen stores after decreased food intake during the prodromal period may contribute to hypoglycemia.
  - Pathophysiology of hypoglycemia in children and adults are different.
  - In children: insulin levels are appropriate and hypoglycemia is associated with impaired hepatic gluconeogenesis and increased consumption of glucose by hypermetabolic peripheral tissues. Large amounts of glucose are also consumed by intraerythrocytic parasites.
  - In adults: hypoglycemia is associated with hyperinsulinemia, which may result from pancreatic islet cell stimulation by parasite-derived factors and/or parenteral quinine or quinidine therapy.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Anemia:** multifactorial and complex.
  - excess removal of noninfected erythrocytes may account for up to 90% of erythrocyte loss, mediated by processes (e.g., oxidative stress) that enhance the senescence and impair the deformability of erythrocytes.
  - intravascular lysis and phagocytic removal of infected erythrocytes.
  - impaired bone marrow responses is significant and probably involves general processes also found in other diseases.
- **Pulmonary edema:**
  - noncardiogenic pulmonary edema due to sequestration of infected erythrocytes in the lungs causing production of inflammatory cytokines that increase capillary permeability, leading sequentially to pulmonary edema, dyspnea, hypoxia, acute lung injury, and acute respiratory distress syndrome (ARDS).

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Metabolic acidosis:**
  - associated with significant lactic acidemia in up to 85% of cases.
  - caused by reduced delivery of oxygen to tissues, due to anemia (decreased oxygen-carrying capacity), sequestration (microvascular obstruction), and hypovolemia (reduced perfusion) as a result of fluid losses caused by fever, decreased intake, vomiting, and diarrhea.
- **Placental malaria:**
  - results in maternal morbidity and mortality, intrauterine growth retardation, premature delivery, low birth weight, and increased newborn mortality.
- **Splenic rupture:**
  - associated with acute and chronic infections; can occur spontaneously or with minor trauma, including manual examination of the spleen.
  - more commonly associated with vivax malaria, but has been associated with all four human malaria parasites.

Clinical Comparison of Malaria Types

	Vivax	Ovale	Malariea	Falciparum
Incubation	10-17 d	10-17 d	18-40 d	8-11 d
Prodrome Severity	++	+	++	+
Fever Periodicity	44-48 h	48-50 h	72 h	36-48 h
1st paroxysm severity	Mod - Severe	Mild	Mod - Severe	Severe
1st paroxysm duration	10 h	10 h	11 h	16-36 h
Untreated 1ry attack	3-8 wks	2-3 wks	3-24 wks	2-3 wks
Duration untreated	5-8 yr	1-1.5 yr	20-50 y	0.5-1.5 yr
Anemia	++	+	++	++++
CNS involvement	+/-	+/-	+/-	++++
Nephrotic S.	+/-	-	+++	+

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Diagnostic Considerations:**
  - because of the dangers of acute *P. falciparum* infection, all travelers who have visited a malaria-endemic area in the 3 months prior to onset of fever or other suggestive symptoms should be considered to have malaria until proven otherwise.
  - Even in patients beyond this time frame, it is wise to consider *P. falciparum* malaria
  - Cyclical paroxysms of chills and rigors, fever, and drenching sweats are characteristic although not necessarily specific for malaria.
  - A travel history that reveals risk of exposure months to years before in an endemic region is an alert for malaria and should always be sought in presentations of fever. Findings on physical examination may include pallor and hepatosplenomegaly.
  - Rarely, acute *Plasmodium* infections present with splenic rupture requiring surgery or conservative management.
  - Findings such as jaundice, diminished consciousness, or convulsions indicate severe malaria.
  - Rash, lymphadenopathy, and signs of pulmonary consolidation are distinctly uncommon.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Laboratory:**
  - Decreases in hemoglobin, hematocrit, and haptoglobin and increases in lactic dehydrogenase.
  - Microcytosis in patients from malaria-endemic areas often due to iron deficiency or thalassemia.
  - Leukocyte counts may be high, normal, or low.
  - Platelet counts may be normal or slightly low, but have been observed to be <70,000 in *P. falciparum* infection and occasionally in *P. vivax* infection.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- **Diagnosis:**
  - **Blood Smear:** Giemsa-stained blood smears is the standard for diagnosis. Thick and thin diagnostic blood smears should be *prepared and read immediately*
    - *P. malariae* often establishes parasitemias below levels of detection by microscopy. Patients can remain infected and asymptomatic for periods of many years before presenting with fevers, malaise, and splenomegaly decades after they have left an endemic area
    - *P. knowlesi* is indistinguishable from *P. malariae* on blood smear examination, showing both immature and mature forms in the circulation, however causes high parasitemia.
  - **Serology:** detection of *Plasmodium* histidine-rich protein 2 (HRP-2) has 96% sensitivity and 99% specificity for *Plasmodium* infection when compared with microscopy.

Malaria

(P. vivax, P. ovale, P. malariae, P. falciparum, P. knowlesi)

- ***Treatment Considerations:***
  - *P. falciparum* malaria can be fatal if not diagnosed and treated promptly. This is especially true of nonimmune travelers returning from visits to malaria-endemic areas.
  - Malaria has protean manifestations. Its diagnosis can be delayed by the nonspecificity of the clinical presentation and routine laboratory tests, especially if blood smears (and, if available, a rapid detection test) are not examined.
  - Life-threatening manifestations of malaria such as seizures, hypoglycemia, and pulmonary edema may develop rapidly in patients who appear relatively well at presentation or appear to respond initially to antimalarial drugs.
  - Although some patients with uncomplicated *P. falciparum* malaria can be treated successfully in an outpatient setting, patients with no immunity against the disease are at increased risk for sudden development of severe complications and should be hospitalized at least 48 hours to ensure adequate response to therapy, regardless of how well they appear at presentation.

Babesiosis

(B. microti, B. divergens, B. odocoilei, B. gibsoni)

- **Organism:**
  - Protozoa Apicomplexa.
- **Vector:**
  - ixodid tick (Ixodes dammini)
- **Geographic & Seasonal distribution in USA:**
  - late summer and early fall
  - Massachusetts, Connecticut, New York, New Jersey, Wisconsin, Missouri, Washington, Georgia, and North Carolina.

Babesiosis

(B. microti, B. divergens, B. odocoilei, B. gibsoni)

- **Clinical presentation:** Incubation 1-4 weeks.
  - Self limited except in s/p splenectomy.
  - Gradual onset of malaise, then fever, chills, sweating, headaches, arthralgia, myalgia, fatigue, and weakness.
  - Mild hepatosplenomegaly, mild to moderate hemolytic anemia.
  - Mild elevation of bili, AST, and ALT.
  - In splenectomized patients may be fulminant, with fever, anemia, jaundice and AKI.
  - Up to 10% of patients with Lyme disease may have Babesia co-infection.
- **Diagnosis:**
  - Thin & thick drop smear stained with Giemsa (Maltese cross).
  - Serology with Immunofluorescence, Immunoblot, or PCR.
- **Treatment:** Clindamycin + Quinine, or Azithromycin + Atovaquone for 7-10days.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Organism:**
  - flagellated protozoa parasites (mastigophora) that belong to the genus *Trypanosoma, subgenus Trypanozoon*.
  - Causes 100000 new infections/y, and 50000 deaths/y.
  - There are 3 subspecies: T. brucei brucei, T. brucei rhodesiense, and T. brucei gambiense; they are called T. brucei complex.
- **Vector:** Tsetse fly (palpalis & morsitans groups)
- ***Other forms of Transmission:***
  - *Congenital transmission and blood transfusion transmission are extremely rare.*

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African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Life Cycle:**
  - Transmitted by various species of bloodsucking tsetse flies that belong to the genus *Glossina*.
  - *Found only in Africa, they cover the rain forest and savanna. Parasite has development cycle in insects of both sexes.*
  - *The tsetse fly ingest infected human blood containing short stumpy trypomastigotes.*
  - *Once in the insect's midgut they transform in long, slender procyclic trypomastigotes.*
  - *After several multiplication cycles, they migrate to the salivary glands where they change to epimastygotes and multiply.*
  - *Finally they change to nondividing metacyclic trypomastigotes.*
  - *On the next tsetse fly bite, the infection is transmitted to another human, where the parasite changes to a bloodstream trypomastigote and multiplies.*

m1 marsano, 5/30/2011

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Stage I Disease:** Systemic African trypanosomiasis without CNS involvement.
  - The parasites first travel from the site of inoculation to regional lymph nodes, where they proliferate and cause an inflammatory lesion (trypanosomal chancre) 1 week after the bite and resolves over several weeks.
  - They then move through the lymphatics into the bloodstream, where multiplication continues, and finally into interstitial spaces, where multiplication also takes place; infection evolves over weeks or months.
  - The spleen may be enlarged, with generalized cellular proliferation, congestion, and focal necrosis. Later an endarteritis with perivascular infiltration of both parasites and lymphocytes may develop in lymph nodes and the spleen.
  - The heart is frequently involved in this stage of the disease, especially with *T. b. rhodesiense infections. A pancarditis may develop involving all layers of the heart, including the mural and valvular endocardia.* The conduction system may also be affected, and involvement of the autonomic innervation of the heart has also been reported

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Stage I Disease:** Systemic African trypanosomiasis without CNS involvement.
  - Normocytic anemia usually accompanied by a brisk reticulocytosis is common. Immune-mediated hemolysis may be important.
  - Platelet counts are often reduced, especially in infections with *T. b. rhodesiense. Disseminated intravascular coagulation before and during therapy has also been described.*
  - *A moderate leukocytosis is usually present, especially in the early months of the infection, and this is accompanied by polyclonal B-cell activation.*
  - *High titers of immunoglobulins are a striking and constant feature of the illness. They consist primarily of polyclonal IgM. A number of other factors, including heterophile antibodies, rheumatoid factor, and anti-DNA antibodies, are often detectable.*
  - *High levels of circulating antigen-antibody complexes are uniformly present.*
  - Erythrocyte sedimentation rates are elevated, and hypocomplementemia has also been noted.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Stage II Disease:** African trypanosomiasis with invasion of the CNS.
  - Parasites reach the brain and meninges via the bloodstream and cause meningoencephalitis or meningomyelitis, or both.
  - Found mainly in the frontal lobes, the pons, and the medulla, but other areas may be parasitized as well.
  - Edema and hemorrhages may be evident on gross examination of affected areas at autopsy. Trypanosomes are present in perivascular areas, and nests of organisms can be found without apparent relation to blood vessels.
  - The presence of parasites in the CNS is associated with infiltration of mononuclear cells that are predominantly lymphocytes, plasmacytes, and morular cells.
  - The CSF may be under increased pressure, and the total protein concentration is elevated, with mononuclear cells predominating in addition to small numbers of morular cells and eosinophils. Trypanosomes are frequently present in the CSF as well.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **West African Trypanosomiasis (T. gambiense):**
  - Indurated and painful chancre appears 1 to 2 weeks after the bite and resolves spontaneously over several weeks. The chancre may ulcerate and reach several centimeters; regional lymphadenopathy may also develop. Trypanosomal chancre is seldom seen in clinical practice. Most patients develop systemic trypanosomiasis without symptoms of localized disease.
  - The development of stage I (hemolymphatic) disease causes fever, which may appear weeks or months after the acquisition of the infection. The fever is with intermittent bouts of high temperatures lasting for several days, sometimes with extended periods being afebrile.
  - With chronicity, lymphadenopathy is a fairly constant feature of *gambiense trypanosomiasis. The nodes are typically discrete, movable, rubbery, and nontender. With time they frequently become indurated as fibrosis develops. Supraclavicular and cervical nodes are often visibly discernible, and enlargement of the nodes of the posterior cervical triangle, or Winterbottom's sign, is a classic finding in persons infected with T. b. gambiense. Hepatosplenomegaly may be present as well.*
  - Transient edema is frequent during the hemolymphatic phase of the illness and can occur in the face as well as in the hands, feet, and other periarticular areas.
  - Pruritus is common, and an irregular circinate rash is often present. The rash is typically located on the trunk, shoulders, buttocks, and thighs and consists of erythematous areas 5 to 10 cm in diameter with clear centers.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **West African Trypanosomiasis (T. gambiense):**
  - Other inconstant findings include malaise, headache, weakness, weight loss, arthralgias, and tachycardia.
  - Amenorrhea and infertility in women as well as a loss of libido and impotence in men are a consequence of neuroendocrine dysfunction.
  - CNS findings may develop months or even years after the initiation of the infection.
  - Irritability, personality change, and loss of the ability to concentrate may develop before changes in the CSF become evident. Progressive indifference develops, associated with daytime somnolence (sleeping sickness), sometimes alternating with restlessness and insomnia at night. Severe headache is common.
  - *A listless gaze reflects a loss of spontaneity, and speech may become indistinct.*
  - *Extrapyramidal signs often develop and may include choreiform movements of the trunk, neck, and extremities, tremors of the tongue and fingers, and fasciculations of a variety of muscle groups.*
  - *Ataxia is a frequent sign, and the patient may appear to have Parkinson's disease, as a shuffling gait, hypertonia, tremors, and slurred speech develop.*
  - *The final phase of the CNS disease is one of progressive neurologic impairment ending in coma and death.*

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **East African Trypanosomiasis (T. rhodesiense):**
  - Onset of symptoms occurs a few days after being bitten by an infected tsetse fly, but the incubation period may be as long as several weeks.
  - Typically in tourists, systemic signs of infection such as fever, malaise, and headache appear before the end of the trip or shortly after their return home.
  - As the illness progresses, the pattern of intermittent fever develops, and rash is a nearly constant feature of the early weeks of the illness.
  - Lymph node swelling is not prominent in *rhodesiense trypanosomiasis, and thus Winterbottom's sign is generally absent.*
  - *Persistent tachycardia unrelated to the fevers is frequently present early in the course of the illness, and in some patients death may result from arrhythmias and congestive heart failure due to pancarditis even before CNS disease develops.*
  - *Untreated rhodesiense trypanosomiasis usually leads to death in a matter of weeks to months, distinction between the hemolymphatic and CNS stages.*

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

	West African (*gambiense*)	*East African (rhodesiense)*
Organism	*Trypanosoma brucei gambiense*	*Trypanosoma brucei rhodesiense*
Vectors	Tsetse flies (*palpalis group*)	*Tsetse flies (morsitans group)*
Primary reservoir	Humans	Antelope and cattle
Human illness	Chronic (late CNS disease)	Acute (early CNS disease)
Duration of illness	Months to years	< 9 months
Lymphadenopathy	Prominent	Minimal
Parasitemia	Low	High
Diagnosis by rodent inoculation	No	Yes
Epidemiology	Rural populations.	Tourists in game parks; workers in wild areas; rural populations.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Diagnosis:**
  - If a chancre is present, fluid should be expressed and examined directly under light microscopy for the highly motile trypanosomes. Part of the specimen should be fixed and stained with Giemsa. This method is more effective in patients with West African trypanosomiasis because of the prominence of lymphadenopathy
  - Examination of wet preparations and Giemsa-stained thin and thick smears of peripheral blood is also a sensitive method for detection of infection with African trypanosomes. More likely to be successful in the hemolymphatic stage, and more useful in patients infected with *T. b. rhodesiense due to high parasitemias.*
  - *Because parasitemias may vary considerably from one day to the next, serial specimens should be examined.*
  - *If parasites are not seen in blood: concentrate the organisms by examining the buffy coat obtained by centrifuging 10 to 15 mL of anticoagulated blood and do a wet preparation with Giemsa staining.*
  - *Miniature anion exchange columns, which retain blood cells but not trypanosomes, also can be useful in detecting parasites* and PCR-based assays may be useful in some situations

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

- **Diagnosis:**
  - Examination of the CSF is mandatory in all patients suspected of having African trypanosomiasis
  - CSF: initially increased cell count. Later, increased opening pressure and elevated IgM level and total protein concentration.
  - Examination of CSF processed by single or double centrifugation methods often reveals trypanosomes in patients with CNS involvement
  - An additional approach is bone marrow aspiration. Trypanosomes may be found by careful examination of Giemsa-stained specimens.
  - Material aspirated from the bone marrow, blood, CNS, or lymph node can be inoculated into special liquid culture medium.
  - Several serologic assays are available to aid in the diagnosis of African trypanosomiasis, but the variable sensitivity and specificity of these tests mandate that treatment decisions still be based on demonstration of the parasite.

African Trypanosomiasis
(T. gambiense & T. rhodesiense)

TREATMENT

AGENT	STAGE I	STAGE II
T. brucei gambiense	Pentamidine	Eflornithine
	Alt: Suramin	Alt: Melarsoprol
T. brucei rhodesiense	Suramin	Melarsoprol

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Organism:** T. cruzi is a hemoflagellate protozoa (mastigophora)
- **Vector:** various *species of bloodsucking triatomine insects, or kissing bugs (Rhodnius prolixus and Triatoma infestans)*.
- **Magnitude of the Problem & Geographic Variability:**
  - Eighteen million people are infected with *T. cruzi; 50,000 persons die each year of Chagas' disease.*
  - In 2000 the total annual cost of the morbidity and death associated with Chagas' disease was thought to be more than 8 billion US dollars.
  - Only 10% to 30% of persons with chronic *infections will develop symptomatic Chagas' disease*
  - The prevalence of cardiac disease is lower in Venezuela, Colombia, Central America, and Mexico than in the rest of the endemic range (Argentina, Bolivia, Brazil, Chile, Paraguay, Peru, and Uruguay).
  - Megaesophagus and megacolon in association with *T. cruzi infection are virtually unknown in the northern endemic range, whereas they reach 15% to 20% in the southern endemic regions (Parasite strain or host features ?) In the USA,* only six autochthonous cases of Chagas' disease have been reported: three in Texas and one each in California, Tennessee, and Louisiana.
  - In blood donors in Los Angeles and Miami, the prevalence of *T. cruzi infection was 1 in 8800 in the general donor population and 1 in 710 among donors who had spent a month or more in an area in which Chagas' disease is endemic.*
  - Screening of U.S. blood donors for Chagas' disease began in January 2007

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- ***Life Cycle:*** Vectors are found in large numbers in the wild, where they transmit the parasite among many mammalian species that constitute the natural reservoir.
  - The insects become infected by sucking blood from humans or other mammals that have circulating trypomastigotes.
  - The ingested parasites multiply in the midgut of the insects as epimastigotes,
  - In the hindgut epimastigotes transform into infective metacyclic trypomastigotes that are discharged with the feces at the time of subsequent blood meals.
  - Transmission to a second vertebrate host occurs when mucous membranes, conjunctivae, or breaks in the skin are contaminated with bug feces containing the infective forms.
  - The parasites then enter a variety of host cell types and multiply in the cytoplasm after transformation into amastigotes.
  - When multiplying amastigotes fill the host cell, they differentiate into trypomastigotes, and the cell ruptures. The parasites released invade local tissues or spread hematogenously to distant sites, thus initiating further cycles of multiplication, primarily in muscle cells, and maintaining a parasitemia infective for vectors.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- ***Other forms of transmission:***
  - Transmission of *T. cruzi also occurs through blood transfusions* and typically takes place in cities when infected but asymptomatic migrants from endemic rural areas donate blood. Serologic screening of donated blood essentially has eliminated transmission by this route in most endemic areas.
  - *T. cruzi can also be transmitted by transplantation of organs obtained from chronically infected persons.* Roughly 5% of infants born to *T. cruzi–infected women have congenital Chagas' disease. Although some of these infants have severe problems as a result of the infection, most are completely asymptomatic.*
  - Interestingly, several outbreaks of acute Chagas' disease in humans in Brazil attributed to oral transmission through ingestion of food or drink contaminated with *T. cruzi–infected vectors or their excreta have been reported* In these incidents, many dozens of people became infected and some died of acute Chagas' disease.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- Skin:
  - In acute Chagas' disease, the inflammatory lesion caused by *T. cruzi at the site of entry is called a chagoma.*
- Heart: is the organ most commonly affected in chronic Chagas' disease.
  - Gross examination of the hearts of chronic chagasic patients who died of heart failure reveals marked bilateral ventricular enlargement, often involving the right side of the heart more than the left.
  - Thinning of the ventricular walls is common, as are apical aneurysms and mural thrombi.
  - Pathologic changes are also common in the conduction system of chronic chagasic hearts and often correlate with premortem rhythm disturbances.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- GI tract:
  - The striking features apparent on gross examination of the esophagus or colon of a patient with chronic Chagas' disease of the digestive tract (megadisease) are the enormous dilation and muscular hypertrophy of the affected organs.
  - On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen. A marked reduction in the number of neurons in the myenteric plexus is also apparent, and peri- and intraganglion fibrosis in the presence of Schwann cell proliferation and lymphocytosis is found.
  - In most patients, the clinical effects of this parasympathetic denervation are confined to the esophagus or the colon, or both, but similar lesions have been observed in the biliary tree, the ureters, and other hollow viscera.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Acute Chagas' disease:**
  - usually an illness of children, but it can occur at any age.
  - A small portion of acute infections *are recognized because of the mild and nonspecific symptoms and the lack of access to medical care.*
  - *The first signs of illness occur at least a week after invasion by the parasites.*
  - *When the parasite entered through the skin, a chagoma may appear (indurated area of erythema and swelling accompanied by local lymph node involvement).*
  - *Roma~na's sign is* the classic sign of acute Chagas' disease (painless edema of the palpebrae and periocular tissues when the conjunctiva is the portal of entry).
  - The initial local signs can be followed by fever, malaise, anorexia, and edema of the face and lower extremities.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Acute Chagas' disease:**
  - Generalized lymphadenopathy. Hepatomegaly is almost universal (due to heavy parasitism) and moderate splenomegaly also may appear. Anasarca may occur.
  - Overt CNS signs are not common; meningoencephalitis develops in some patients with a very poor prognosis.
  - Severe myocarditis develops in a small proportion of patients with acute disease, and most deaths are due to the resulting congestive heart failure. Nonspecific electrocardiographic changes are seen, but the life-threatening arrhythmias that are frequent in chronic Chagas' disease generally do not occur.
  - In untreated patients, symptoms resolve gradually over a period of weeks to months.
  - Areas of local reaction around the eye or other sites of parasite entry can persist for several weeks, as can the lymphadenopathy and splenomegaly.
  - After the spontaneous resolution of the acute illness, the patient enters what is called the indeterminate phase, which is characterized by asymptomatic and subpatent parasitemia and antibodies to a variety of *T. cruzi antigens.*

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Chronic symptomatic Chagas' disease:**
  - becomes apparent years or decades after the initial infection.
  - The heart is the organ most commonly involved, and symptoms reflect the rhythm disturbances, congestive heart failure, and thromboembolism that are characteristic of the chronic illness.
  - Dizziness, syncope, and, less commonly, seizures result from a wide variety of arrhythmias.
  - Cardiomyopathy develops insidiously; primarily affects the right ventricle, causing right-sided CHF.
  - As in patients with arrhythmias, the progression of cardiomyopathy symptoms may be gradual.
  - The clinical course is frequently complicated by emboli to the brain or other areas.
  - With megaesophagus, symptoms are similar to those of idiopathic achalasia and may include dysphagia, odynophagia, chest pain, cough, and regurgitation.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Chronic symptomatic Chagas' disease:**
  - Hypersalivation and salivary gland hypertrophy have been observed.
  - Aspiration can occur, especially during sleep, and in untreated patients repeated episodes of aspiration pneumonitis are common.
  - Weight loss and even cachexia in patients with megaesophagus can combine with pulmonary infection to result in death.
  - An increased incidence of cancer of the esophagus has been reported.
  - Patients with chagasic megacolon are plagued by chronic constipation and abdominal pain. Individuals with advanced disease can go for several weeks between bowel movements,
  - Acute obstruction, occasionally with volvulus, can lead to perforation, septicemia, and death.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Chagas & Immunosuppression:**
  - Immunosupression in chronic *T. cruzi may cause reactivation, with a severity that is greater than is typical of acute Chagas' disease in immunocompetent patients.*
  - The incidence of reactivation in *T. cruzi–infected patients who become immunosuppressed is not known.*
  - *Reactivations of chronic T. cruzi infections after renal transplantation have occur, and in two of these instances the central nervous system was involved.*
  - In infected patients who undergo solid organ transplantation, periodic monitoring for signs and symptoms of acute Chagas' disease should be carried out, and a specific search for *T. cruzi, including careful neurologic evaluation, should be performed when acute illnesses occur postoperatively.*
  - Immunosuppression caused by HIV can lead to recrudescence of chronic *T. cruzi infection.* Most of these patients developed *T. cruzi brain abscesses, which do not occur in immunocompetent T. cruzi–infected patients.*

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Chagas & Immunosuppression:**
  - *HIV viral loads increase in the context of reactivated acute Chagas' disease.*
  - Heart transplantation is an option in patients with end-stage Chagas' cardiac disease, and more than 100 *T. cruzi–infected patients have undergone the procedure in Brazil and the United States.*
  - Reactivated acute Chagas' disease has been less of a problem because reduced doses of cyclosporine have been used.
  - Patients who have had transplants for Chagas' heart disease occasionally develop cutaneous lesions containing large numbers of parasites.
  - Despite these problems, the long-term survival of Chagas' patients with heart transplants is greater than that of persons transplanted for other reasons, probably because the pathology of chronic *T. cruzi infection is often limited to the heart.*

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Diagnosis of acute Chagas' disease:**
  - Is made by detecting parasites in blood or tissue, or by PCR.
  - Circulating parasites are motile and can often be seen in wet preparations of anticoagulated blood or buffy coat viewed under a cover slip or in microhematocrit tubes. In many cases, the parasites can also be seen in Giemsa-stained smears. In acutely infected immunocompetent patients, examination of blood preparations is the cornerstone of detecting *T. cruzi.*
  - *In immunocompromised patients, other specimens such as lymph node and bone marrow aspirates, pericardial fluid, and cerebrospinal fluid should be examined microscopically. When these methods fail , culturing blood or other specimens in liquid media* or by xenodiagnosis (which is a method involving laboratory-reared insect vectors) may help. The sensitivity of these tests is only 50%.
  - In nine key human studies published in the 1990s, the sensitivities of the PCR assays ranged from 44.7% to 100%, with most results falling slightly over 90%. At the present time no PCR test for the detection of *T. cruzi is available commercially.*

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Diagnosis of Chronic *Chagas' disease:***
  - *Is usually diagnosed by detecting IgG antibodies that bind specifically to parasite antigens,*
  - *Currently more than 30 assays for serologic diagnosis of T. cruzi infection are available commercially. The majority are based on enzyme-linked immunosorbent assay, indirect hemagglutination, and indirect immunofluorescence formats, and they are used widely in Latin America for clinical testing and for screening donated blood.* Many of these conventional tests have sensitivities and specificities that are less than ideal, and false-positive reactions occur typically with specimens from patients having illnesses such as leishmaniasis, malaria, syphilis, and other parasitic and nonparasitic diseases.
  - The Pan American Health Organization has recommended that samples be tested in two assays based on different formats before diagnostic decisions are made.
  - The Ortho assay is currently being used to test almost the entire U.S. supply of donated blood.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Treatment:**
  - Current therapy for persons infected with *T. cruzi is unsatisfactory.*
  - *Two drugs are currently being used:* nifurtimox and benznidazole. Both have meaningful side effects, require prolonged therapy, and are at best only 70% effective.
  - Treatment must be given to *infants with congenital Chagas' disease, all persons with acute T. cruzi infection, and chronically infected children 17 years old or younger. This is supported by clinical trial results that indicate clearly that treatment of such patients is useful in terms of the likelihood of parasitologic cure.*
  - There is debate about treating persons in the indeterminate or chronic symptomatic phases. Currently there is no convincing evidence from properly controlled trials that treatment with either of the drugs is beneficial in such persons.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Megaesophagus associated with Chagas' disease:**
  - generally should be managed as is idiopathic achalasia.
  - The first approach is balloon dilation of the lower esophageal sphincter. Patients who fail to respond to repeated attempts at this approach are treated surgically.
  - Laparoscopic myotomy is being used with increasing frequency to treat idiopathic achalasia.

South American Trypanosomiasis
(Chagas Disease; T. cruzi)

- **Megacolon:**
  - Patients in the early stages of colonic dysfunction can be managed with a high-fiber diet and occasional laxatives and enemas.
  - Fecal impaction necessitating manual disimpaction may occur, as can toxic megacolon, which requires surgical treatment.
  - Volvulus usually occurs when the lengthened and enlarged sigmoid colon twists and folds on itself, causing a constellation of symptoms resulting from the obstruction. Endoscopic emptying can be performed initially in patients without radiographic, clinical, or endoscopic signs of ischemia in the affected area. Complicated cases should be treated with surgical decompression.
  - Surgical treatment of the megacolon is eventually necessary because of the high probability of recurrence of the volvulus. A number of surgical procedures have been used to treat advanced chagasic megacolon, and all include resection of the sigmoid colon as well as removal of part of the rectum. The latter is performed to avoid recurrence of megacolon in the segment of the colon that is anastomosed to the rectum.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Organism:**
  - L. donovani complex are Protozoa, Trypanosomatidae, hemoflagellate (mastigophora).
- **Vectors:**
  - for L. donovani are Phlebotomus argentipes and other anthropophilic Phlebotomus spp.
  - for L. infantum/L. chagasi, in Latin america, is Lutzomyia longipalpis.
- ***Reservoir:***
  - for L. donovani complex are dogs and rats. Persons with post–kala-azar dermal leishmaniasis (PKDL) may serve as the reservoir during interepidemic periods.
  - for L. infantum/L. chagasi, humans, dogs, and foxes may be the reservoir.

Visceral Leishmaniasis (Kala-Azar) (L. donovani complex)

- **Affected Populations:**
  - VL caused by L. infantum also occurs in Central Asia and historically in southern China.
  - In East Africa, VL occurs in Eritrea, Ethiopia, Kenya, Somalia, Sudan, and Uganda. L. donovani has been responsible for a very large epidemic among displaced persons in southern Sudan.
  - In the Mediterranean littoral and the Middle East, cases are typically encountered among infants, young children, and immunocompromised persons.
  - In Latin America L. infantum/L. chagasi is endemic and broadly distributed. Most areas have focal disease risk with a background of asymptomatic or subclinical infection with sporadic clinical cases in rural areas. Children are most frequently affected.
  - VL emerged as an important opportunistic disease among persons with AIDS in southern Europe in Spain, France, and Italy. Sharing of contaminated needles and syringes by intravenous drug users was implicated in artificial anthroponotic transmission of Leishmania in Spain.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Life cycle:**
  - promastigote, an elongate, motile form (1.5-3.5 mcm by 15-200 mcm) of the parasite found in the sandfly digestive tract and proboscis, is transmitted into the skin of a mammalian host by the bite of small, delicate female sand flies when they take a blood meal.
  - After inoculation by a sand fly, promastigotes are phagocytosed by macrophages in the dermis and transform into intracellular oval or round amastigotes (3-5 mcm in length) that lack an exteriorized flagellum.
  - Amastigotes are found inside phagolysosomes, where they multiply by simple binary division, eventually rupturing the cell and invading other reticuloendothelial (RE) cells.
  - Released amastigotes go on to infect other mononuclear phagocytes

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Pathogenesis:**
  - Skin lesions at the site where promastigotes are inoculated are usually not apparent in persons with VL.
  - Increasing numbers of amastigote-infected mononuclear phagocytes in the liver and spleen result in progressive hypertrophy of these organs, leading to clinically apparent hepatosplenomegaly.
  - The spleen often becomes massively enlarged as splenic lymphoid follicles are replaced by parasitized mononuclear cells.
  - In the liver there is a marked increase in the number and size of Kupffer cells, many of which contain amastigotes.
  - Infected mononuclear phagocytes are also found in the bone marrow, lymph nodes, skin, and other organs in this disseminated disease.
  - The outcome of infection and the manifestations of disease are associated with genetically determined human immune responses, host nutritional status and immunocompetence, and environmental factors.
  - Persons with self-resolving infection with *L. donovani or L. infantum/L. chagasi and those who have undergone successful chemotherapy develop protective immune responses, but*
  - *VL disease can develop years later if they become immunocompromised.*

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Clinical manifestations of VL:**
  - Incubation period is 2-8 months (range 10 days to more than a year).
  - Clinical disease may first become symptomatic years after exposure in persons who become immunocompromised (due to HIV /AIDS; immunosuppressive drugs such as corticosteroids, methotrexate, or the new class of TNF inhibitors; or use of immunosuppressive agents following solid organ transplantation). Anyone with a history of birth in, residence at, or travel to a *Leishmania-endemic area is at risk of late reactivation if he or she becomes immunocompromised.*

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Acute presentations in persons without immunity**
  - abrupt , with high fever and chills and sometimes with a periodicity that suggests malaria.
  - Chills, but seldom rigors, accompany the temperature spikes.
  - Later, the spleen can become massively enlarged. It is usually soft and nontender. The presence of a hard spleen suggests a hematologic disorder or another diagnosis such as schistosomiasis.
  - The liver also enlarges; it usually has a sharp edge, soft consistency, and a smooth surface.
  - Lymphadenopathy is common in patients in Sudan but uncommon in other geographic areas.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Subacute or chronic course**,
  - insidious onset of fever, weakness, loss of appetite, weight loss, failure to thrive, and abdominal enlargement caused by hepatosplenomegaly.
  - In endemic areas low-grade symptoms may persist for weeks to months before progressing to full-blown VL or resolving slowly. Because these symptoms may not be sufficiently severe to warrant medical attention in impoverished, endemic areas, patients may be called “subclinical” when they should be more appropriately called “oligosymptomatic.”
  - Fever may be intermittent, remittent with twice-daily temperature spikes (double quotidian), or, less commonly, continuous.
  - Fever is relatively well tolerated, and older clinical references routinely noted that the patients were not acutely ill or “toxic” in appearance.

Visceral Leishmaniasis (Kala-Azar) (L. donovani complex)

- **Other manifestations of VL:**
  - Elevated liver enzymes and bilirubin may be observed.
  - Peripheral edema may be seen late in the disease, particularly in malnourished children.
  - Hemorrhage can occur from one or more sites; epistaxis and gingival bleeding may be noted, as well as petechiae and ecchymoses on the extremities in late-stage disease.
  - Many patients with visceral leishmaniasis become cachectic. This appears to be mediated in part by TNF-α and other cytokines that are known to have catabolic and anorectic effects
  - Secondary bacterial infections are common in persons with advanced VL. Patients can present with coinfection or acquire secondary bacterial infections as nosocomial pathogens during hospitalizations. It is important to recognize and treat clinically significant bacterial coinfections Death may result from pneumonia, septicemia, tuberculosis, dysentery, or measles, or it may be the consequence of malnutrition, severe anemia, or hemorrhage.
  - Renal involvement in VL is common. Acute renal failure, nephrotic syndrome, and proteinuria have been reported.
  - Acute glomerulonephritis, proliferative glomerulonephritis, collapsing focal segmental glomerulosclerosis, acute interstitial nephritis, and tubular cell necrosis and tubulitis have also been described.

Visceral Leishmaniasis (Kala-Azar) (L. donovani complex)

- **Laboratory findings:**
  - Anemia, leukopenia, eosinopenia, thrombocytopenia, and hypergammaglobulinemia.
  - Anemia is almost always present and may be severe. It is usually normocytic and normochromic and appears to be due to a combination of factors including hemolysis, marrow replacement with leishmania-infected macrophages, hemorrhage, splenic sequestration of erythrocytes, hemodilution, and marrow-suppressive effects of cytokines such as TNF-α. Anemia and neutropenia have not been prominent in patients with VL who have undergone splenectomy.
  - Leukopenia is also prominent, with white blood cell counts occasionally as low as $1000/mm^3$. It is not known whether the observed neutropenia is due to increased margination, splenic sequestration, an autoimmune process, or a combination of those factors.
  - Eosinopenia (absence of eosinophils) is frequently observed.
  - Hypergammaglobulinemia, circulating immune complexes, and rheumatoid factors are present in the sera of most patients with visceral leishmaniasis The globulin level may be as high as 9 g/dL; the ratio of globulin to albumin is typically high.
  - The erythrocyte sedimentation rate is usually elevated.

Visceral Leishmaniasis (Kala-Azar) (L. donovani complex)

- ***VL and HIV:***
  - *When immunosuppression occurs in late-stage HIV infection, clinical VL can present as an opportunistic infection (OI).*
  - *VL may be the presenting syndrome of AIDS or another late-stage OI in the terminal stages of disease.*
  - *VL usually presents with typical combinations of fever, hepatomegaly, splenomegaly, weight loss, and pancytopenia when patients have CD4 counts of more than 50 cells/mm^3.*
  - *Atypical presentations and localization of parasites are more common when CD4 cells are fewer than 50 cells/mm^3.*
  - AIDS patients have extensive gastrointestinal tract involvement to include oral mucosa, esophagus, stomach, and small intestine and may present with chronic diarrhea.
  - Lung and pleural involvement presenting as pleural effusions
  - Bone marrow involvement presenting as aplastic anemia have been described.
  - The incidence of leishmanial OIs has decreased with the introduction of modern antiretroviral drug regimens but the number of cases of VL-HIV coinfection worldwide may increase dramatically as HIV infection continues to spread into *Leishmania-endemic regions.*
  - Although the incidence of VL as an OI decreased following the introduction of modern antiretroviral therapy, later relapse of VL remains problematic.

Visceral Leishmaniasis (Kala-Azar) (L. donovani complex)

- **Viscerotropic leihmaniasis:**
  - Unusual systemic syndrome associated with *L. tropica infection described in returning U.S. military personnel who served in the Persian Gulf War of 1990-1991.*
  - The symptoms included chronic low-grade fever, malaise, fatigue, and, in some cases, diarrhea. Mild splenomegaly was observed in some.
  - None of the troops developed classical kala-azar or progressive visceral leishmaniasis.
  - Subsequent studies failed to show an association between *L. tropica infection and chronic fatigue and other symptoms associated with the Gulf War syndrome.*

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- Post–kala-azar dermal leishmaniasis (PKDL):
  - Follows the treatment of VL due to *L. donovani in 5% to 10% of persons within 2 to 4 years following treatment in India and approximately 50% of persons within 6 months of treatment in the Sudan.*
  - The skin lesions of PKDL are chronic and may persist for as long as 20 years in India, whereas in the Sudan they persist for only a few months to a year.
  - The skin lesions consist of hyperpigmented or hypopigmented macules that progress to papules, nodules, and verrucous forms.
  - They are found on the face, trunk, extremities, oral mucous membranes, and, occasionally, the genitals.
  - They may be confused clinically and pathologically with leprosy.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- Post–kala-azar dermal leishmaniasis (PKDL):
  - Patients generally feel well.
  - The diagnosis is mainly clinical, but amastigotes can be detected in the skin in more than 80% of cases in the Sudan.
  - Antileishmanial treatment is generally indicated in Indian PKDL. In the Sudan, most cases cure spontaneously, but chronic or severe cases are treated.
  - In a few instances in India, VL has recurred in patients with PKDL.
  - Patients with PKDL are thought to be infectious and serve as reservoirs for continued anthroponotic infection.
  - Treatment of PKDL patients, at least to render them noninfectious to sand flies, is likely an important part of a future successful control strategy.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Diagnosis:**
  - In a patient with prolonged fever, progressive weight loss, weakness, pronounced splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia from a known endemic area the clinical diagnosis has very high PPV.
  - Clinical diagnosis without supporting parasitologic confirmation is unsatisfactory in patients with late-stage HIV infection or AIDS, returning travelers who may present with clinical symptoms months or years after exposure in low-transmission areas such as the Mediterranean, those with oligosymptomatic or viscerotropic syndromes, and those with atypical presentations.
  - The parasitologic diagnosis is done by demonstrating amastigotes in tissue, isolating promastigotes in culture, or with a positive PCR.
  - Aspirates from the spleen, bone marrow, liver, or lymph nodes should be cultured. Specimens can be inoculated into one of several media [Schneider's modified media, Novy-MacNeal-Nicolle (NNN) media, and others] and maintained at ambient temperatures, 22^0 C to 26^0 C. Results may take weeks to grow.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Diagnosis:**
  - Splenic aspiration, liver biopsy, lymph node aspirates, and bone marrow aspirates have all been used with success.
  - Splenic aspiration to obtain a few drops of fluid for Wright- and Giemsa-stained smears, culture, and PCR is the most sensitive method for parasite identification, with over 95% of samples being (+) compared with bone marrow aspirations. Quantitative splenic aspiration can be used to monitor response to treatment.
  - Bone marrow aspirate sensitivity approaches that of a splenic aspirate when microscopists spend more time reviewing the smear. Amastigotes are seen in 40% to 90% of patients when compared with a positive splenic aspirate. The wide range reflects the stage of disease and the rigor of microscopic review because of the lower parasite burden in the bone marrow.
  - Liver biopsy is inferior to splenic puncture or bone marrow biopsy but occasionally is positive when bone marrow is negative.

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Diagnosis:**
  - Lymph node aspiration or biopsy may be diagnostic when enlarged nodes are present, as is often the case in Sudan.
  - Amastigotes may also be seen within mononuclear cells in Wright- and Giemsa-stained smears of the buffy coat or in biopsy specimens of various organs.
  - In AIDS , amastigotes in macrophages have been identified in bronchoalveolar lavage fluid, pleural effusions, or biopsy specimens of the oropharynx, stomach, or intestine. When the diagnosis of VL is suspected, parasitologic confirmation may require one than one technique and repeated procedures.
  - High-titer antileishmanial antibodies are typically present in immunocompetent patients with VL.
  - Currently, enzyme-linked immunosorbent assay (ELISA) and dipstick tests using *L. infantum/L. chagasi recombinant k39 (rk39), a kinesin-like antigen* have demonstrated excellent sensitivity and specificity for the diagnosis of VL in immunocompetent persons in India and Brazil but less so for those in East Africa.
  - False-positive results may occur due to cross-reacting antibodies in patients with leprosy, Chagas' disease, cutaneous leishmaniasis

Visceral Leishmaniasis (Kala-Azar)
(L. donovani complex)

- **Treatment:**
  - Liposomal amphotericin B (AmBisome, Astellas Inc.) is the drug of choice for the treatment of VL in North America and any other setting where it can be safely administered and cost is not limiting. It is the only drug licensed for the treatment of VL in the United States
  - The FDA-approved regimen for immunocompetent patients is 3.0 mg/kg of body weight per day on days 1 to 5, 14, and 21. A higher dose of 4.0 mg/kg of body weight per day on days 1 to 5, 10, 17, 24, 31, and 38 is recommended for immunocompromised patients.
  - Cost and availability have limited its use in developing areas. Relapses can occur after liposomal amphotericin B and other forms of therapy in persons with AIDS, and an additional course(s) of liposomal amphotericin B may be necessary.
  - Chemotherapy of patients with PKDL is unsatisfactory. There are few controlled studies and only small case series. Also, clinical and parasitologic endpoints in PKDL are poorly defined. Severe PKDL in the Sudan is treated with Sodium Stibogluconate (SSG) at 20 mg/kg of body weight per day for 2 to 3 months and for up to 120 days in India with cure rates of 64% to 92% reported. The drug is toxic.

Toxoplasma Hepatitis
(T. gondii)

- **Organism:** Toxoplasma is a Protozoa Apicomplexa (coccidia). In USA infection rate is 2% per year of life.
- **Life Cycle:**
  - Cats shed oocysts after they ingest any of the three forms of the parasite, at which time an enteroepithelial cycle begins.
  - Sexual reproduction begins when the parasites penetrate the epithelial cells of the small intestine and initiate development of asexual and sexual (gametogony) forms of the parasite.
  - Oocyst wall formation begins around the fertilized gamete, and when still immature, oocysts are discharged into the intestinal lumen by rupture of intestinal epithelial cells. Unsporulated oocysts are subspherical to spherical and measure 10 to 12 mcm in diameter.
  - Oocysts are formed in the small intestine only in felids and are excreted in the feces for periods varying from 7 to 20 days. As many as 10 million oocysts may be shed in the feces in a single day.
  - Sporulation, required for oocysts to become infectious, occurs outside the cat within 1 to 5 days, depending on temperature and the availability of oxygen. Sporulated oocysts contain two sporocysts, each of which contains four sporozoites. Maturation is more rapid at warm temperatures (2 to 3 days at 24^{0}C compared with 14 to 21 days at 11^{0}C).
  - Oocysts may remain viable for as long as 18 months in moist soil; this results in an environmental reservoir from which incidental hosts may be infected.

Toxoplasma Hepatitis
(T. gondii)

- **Life Cycle: (continuation)**
  - Humans are infected by contact with cat feces, or by eating uncooked meat or milk from infected animals. Oocyst changes in the intestine into trophozoites. There are 2 types of trophozoites: bradyzoites that form cysts that will be eliminated in stool, and tachyzoites that invade tissue.
  - The tachyzoite form is oval to crescentic in shape and measures 2 to 3 mcm wide and 5 to 7 mcm long; it requires an intracellular habitat to multiply despite having all the usual eukaryotic machinery necessary for reproduction.
  - Tachyzoites are seen in both primary and reactivated infection; their presence is the hallmark of active infection.
  - They reside and multiply within vacuoles in their host's cells, can infect virtually all phagocytic and nonphagocytic cell types and multiply approximately every 6 to 8 hours to form rosettes. Continuous multiplication leads to cell disruption and release of organisms that go on to invade contiguous cells or are transported to other areas of the body by blood and lymph.
  - Tachyzoites appear to actively and rapidly migrate across epithelial cells and may travel to distant sites while extracellular.
  - Tachyzoites can be visualized in sections stained with hematoxylin and eosin but are better visualized with Wright-Giemsa and immunoperoxidase stains.

Toxoplasma Hepatitis
(T. gondii)

- **Clinical Presentation:**
  - Toxoplasma hepatitis is rare.
  - There are 3 different presentations: 1) Long prodrome of several months with lymphadenomegaly, with or without fever, followed by clinical hepatitis.; 2) Primary hepatitis without lymphadenomegaly; 3) Granulomatous hepatitis with generalized lymphadenomegaly.
  - Patients usually have fatigue, and may have anorexia and weight loss.
  - Symptoms usually disappear spontaneously, but weeks or months later the fatigue relapses is association with headache and nausea; vomiting is uncommon.
  - Then jaundice develops and the patient may develop a generalized, confluent, red-brown maculo-papular skin rash.
  - Physical findings usually are jaundice, hepatomegaly, splenomegaly, and lymphadenomegaly.

Toxoplasma Hepatitis
(T. gondii)

- **Liver Biopsy:**
  - acute generalized hepatitis, with hepatocyte necrosis and infiltration with lymphocytes, histiocytes, neutrophiles, and eosinophiles. Rarely granulomas are seen.
  - The immunoperoxidase technique, which uses antisera to *T. gondii, has proved both sensitive and specific.*

Toxoplasma Hepatitis
(T. gondii)

- **Diagnosis:**
  - Acute infection is diagnosed by the isolation of *T. gondii or amplification of its DNA in blood or body fluids; demonstration of tachyzoites in histologic sections of tissue or in cytologic preparations of body fluids, the demonstration of a characteristic lymph node histologic appearance or of characteristic serologic test results, or demonstration of T. gondii tissue cysts in the placenta, fetus, or neonate.*
  - Isolation of *T. gondii from the tissues of older children or adults may only reflect the presence of tissue cysts. Finding numerous tissue cysts in tissue sections especially associated with inflammation suggests but does not prove the presence of active infection.*
  - Isolation of *T. gondii from blood or body fluids establishes that the infection is acute.* Tissue cell culture has the advantage of widespread availability (e.g., virology laboratories) and yields results more rapidly (within 3 to 6 days) than does mouse inoculation. However, mouse inoculation is more sensitive.

Toxoplasma Hepatitis
(T. gondii)

- **Diagnosis:**
  - *PCR can be done in blood, CSF, or tissue. Sensitivity is variable.*
  - Serologic tests for the demonstration of specific antibody to *T. gondii is the primary method of diagnosis. A large number of tests have been described, some of which are available only in highly specialized laboratories. Different serologic tests often measure different antibodies that possess unique patterns of rise and fall with the time after infection.*
  - Initial serologic testing can be accomplished by simultaneously requesting IgG and IgM antibody tests. Commercial or nonreference laboratories can easily perform this task.
  - Only positive results in IgM antibody tests need to be sent for confirmatory testing to reference laboratories .
- **Treatment:** Pyrimethamine + Sulfadiazine or Clindamycin.

Toxocariasis
(T. canis, T. cati)

- **Organism:** Are tissue-dwelling nematodes.
- **Reservoir:** Dogs & cats; T. canis is more common than T. cati (dogs are indiscriminate defecators).
- **Life Cycle:** Parasite can only develop to adult in the GI tract of fetus & puppies < 5 wk old; in others they migrate to tissues an encyst. During pregnancy encysted parasites reactivate and infect the fetus through the placenta. Once they mature in the GI tract of the puppie, they persist for years, generating infective eggs that need to mature in the soil before infecting humans. Once ingested, they mature in the human gut to 2^{nd} stage larva, and penetrate the SB wall into the portal v circulation into the sinusoids; then penetrate the parenchyma, causing edema, hemorrhage, and eosinophilic infiltration; later encyst forming granulomas. Can also invade the heart, lymphatics, CNS, and eye.
- **Epidemiology:** More common in children 1-4. 50% of puppies and 20% of adult dogs are infected.Eggs are found in soil of 11% of backyards. Seroprevalence is from 5% in USA, to 62% in Trinidad/Tobago.

Toxocariasis
(T. canis, T. cati)

- **Clinical Presentation:** Most common in children.
- Small children:
  - Frequently have episodes of wheezing, cough, rhinorrhea, asthma-like attacks, or urticarial rash.
  - May have brief fever, GI upset, anorexia, failure to thrive and/or lymphadenomegaly.
  - Sometimes have only hepatomegaly and eosinophilia. Severe cases in toddlers may cause severe abdominal pain.
  - Unilateral visual difficulty may indicate chorioretinitis.
  - Epilepsy and myocarditis are rare.
- Older children and adults:
  - Insidious onset of fever of up to 39-40^0 C, night sweats, cough, nocturnal nausea and vomiting.
  - Tender hepatomegaly and lymphadenomegaly as well as splenomegaly are more common in older children.
  - Mild jaundice may be present.
- **Laboratory:** Eosinophilia in 75% of patients, as high as 90% of WBCs. May have mild elevation of bili, AST, ALT, or alk. phosph.

Toxocariasis
(T. canis, T. cati)

- **Diagnosis:**
  - Confirmed by finding larvae in the affected tissues by histologic examination or by digestion of tissue; however, larvae are frequently not found.
  - CT scans have demonstrated ill-defined hypodense round lesions in the liver
  - ELISA using extracts of excretory or secretory products of *T. canis* larvae appears specific and useful for confirming the clinical diagnosis.
- **Treatment:**
  - Most patients recover without specific therapy.
  - Anti-inflammatory or anthelmintic drugs may be considered for those with severe complications usually caused by involvement of the brain, lungs, or heart.
  - There is no proven effective therapy, although albendazole, thiabendazole, mebendazole, diethylcarbamazine, and other anthelmintics have been used.
  - Injury to the parasite may provoke an intense inflammatory response leading to worsening of the clinical picture.
  - Corticosteroids have been used with and without specific antilarval therapy, with some reports of improvement.

Hepatic Capillariasis
(C. hepatica)

- **Organism:** Is a nematode. Lives in livers of rats, mice, squirrels, muskrats hares, dogs, pigs, beavers and monkeys. Their stool contaminate the soil.
- **Acquisition:** Ingestion of dirt or food with embryonated eggs. The egg hatch in the cecum and the larvae penetrate the wall into a tributary of the portal v. Matures in the liver in 3 weeks. One week later the adult disintegrates, releasing massive amount of eggs that cause abscesses and granulomas.
- **Clinical presentation:** Acute illness with dehydration, malnutrition and lethargy. Fever up to 41^0 C, in the evening, with night sweats. Anorexia, nausea, vomiting, rarely hematemesis. May have diarrhea or constipation. The abdomen is distended and there is edema of hands and legs. Skin of hands and feet may be reddish and very tender. Massive hepatomegaly with some **splenomegaly.**
- **Laboratory:** leukemoid reaction of 30-80 K; eosinophilia of up to 85%; hypochromic anemia; hypergammaglobulinemia. May have elevated bili, AST, and ALT.
- **Diagnosis:** Liver Bx.
- **Treatment:** Thiabendazole. Poor prognosis.

Strongyloidiasis
(S. stercoralis)

- **Organism:** Is a nematode that can be free living in the soil (male & female), or a female hermaphrodite in the human duodenum/jejunum; adult is 2-3 mm long.
- **Magnitude:** 35 million infected worldwide.
- **Acquisition & Life Cycle:**
  - Free living adults copulate and produce rhabditiform larvae;
  - they mature to filariform larvae that can penetrate the skin of feet or hands of humans ("ground itch" or "larva currens", advancing 5-10 cm/h), and
  - then enter lymphatics and veins and are carried to the Rt hearth and then to the lungs.
  - then they migrate through the bronchial tree to the trachea and are finally swallowed.
  - Finally they colonize the duodenum and jejunum.
  - In the SB the female turns hermaphrodite and produces 40 eggs/d.
  - In the bowel the eggs mature to rhabditiform larvae that are excreted, and
  - sometimes the rhabditiform larvae matures in the bowel into filariform larvae and causes autoinfection, with persistent infection for many decades.

Strongyloidiasis
(S. stercoralis)

- **Clinical Presentation:**
  - Most patients are asymptomatic. Some have abdominal pain, weight loss, diarrhea, and even malabsorption.
  - HYPERINFECTION: Immunocompromised patients may develop massive hyperinfection syndrome that can be lethal.
  - They have fever, abdominal pain, diarrhea, hematochezia, vomiting, cough, dyspnea, wheezing, hemoptysis, and shock.
  - They may have bacteremia and meningitis.
  - Patients may have mild jaundice, altered mental status, abdominal tenderness, peritoneal signs, and hepatomegaly but no splenomegaly.
  - Sigmoid colon may show hemorrhagic colitis.
- **Laboratory:**
  - Eosinophilia is common, but may not be present.
  - Hypoalbuminemia with protein loosing enteropathy, mild elevation of bili, variable elevation of AST, ALT and alk phosph.
  - Blood cultures frequently (+) for gram(-) bacteria.

Strongyloidiasis
(S. stercoralis)

- **Diagnosis:**
  - duodenal aspirate is superior to stool study.
  - May show the parasite, larvae, or less commonly eggs.
  - Larvae may be found in sputum, ascites, urine, or lymph nodes.
  - Serologic tests using crude larval antigens, such as the enzyme-linked immunoassay offered by the Centers for Disease Control and Prevention, have 95% sensitivity but poor specificity to rule out *Strongyloides* infection when microscopic examinations are negative or not performed.
  - PCR in stool, or serum luciferase immunoprecipitation systems to detect IgG antibodies to a recombinant *Strongyloides* antigen (NIE) and *S. stercoralis* immunoreactive antigen (SsIR) has sensitivity and specificity of 100%
- **Treatment:**
  - Uncomplicated disease: Ivermectin 0.2 mg/kg POx 2 days.
  - Hyperinfection: Systemic antibiotics plus Ivermectin 0.2 mg/kg PO x >/= 7 days (until stool larva is negative)

Filariasis
(Wuchereria bancrofti)

- **Organism:**
  - Nematode (Lymphatic & blood dwelling).
  - Male 2.5-4 cm; female 5-10 cm.
  - Microfilaria are 245-300 mcm and circulate:
    - from 10 PM to 2 AM in India & Africa, and
    - from Noon to 8 PM in Pacific Islands and Vietnam.
- **Vector:**
  - Anopheles, Aedes, and Culex mosquitoes.
- **Magnitude:**
  - 106 million infected;
    - 45.5 million in India,
    - 40 million in Sub-Saharan Africa.

Filariasis

(Wuchereria bancrofti)

- **Clinical Manifestations:** May be asymptomatic.
  - May give fever + lymphadenitis +/- lymphangitis on limbs, breast or scrotum.
  - May cause hematuria +/- proteinuria or chyluria.
  - Preferential adult location is scrotal lymphatics.
- **Liver Disease:**
  - Pericaval Filariasis has been described to cause “Obliterative Hepatocavopathy” in Southern India and Nepal.
  - This leads to Budd-Chiari Syndrome.
- **Diagnosis:**
  - Larva in blood obtained at right time.
  - U/S of scrotal lymphatics may show “Filarial Dance Sign”.
  - Serology.
- **Treatment:** Diethylcarbamazine (DEC) + Ivermectin.

Parasites in the Biliary Tree

Ascariasis
(A. lumbricoides)

- **Organism:** Is a nematode. Male 15-30 cm; female 20-35 cm.
  - Each female produces 200000 eggs/d that mature in 2-3 wks.
  - Life expectancy 1 y.
- **Magnitude:** 1.3 Billion infected worldwide; 60000 deaths/y.
- **Acquisition & Life Cycle:**
  - Ingestion of eggs with contaminated food;
  - the larva hatch in the duodenum, penetrate intestine wall into blood and lymphatic vessels, then go through the liver, then the heart cavities, then into lung circulation.
  - they then penetrate into alveoli and migrate inside bronchial tree for 20 d;
  - finally enter esophagus and migrate to SB.
  - They mature in 2-3 months an produce new eggs. Infestation can be up to 1000 worms/person.

Ascariasis
(A. lumbricoides)

- **Clinical Manifestations:**
  - Initial infection with large number of larva may cause pneumonitis with asthma attacks, and severe eosinophilia.
  - Chronic infestation with large number of worms may cause intestinal obstruction.
  - Intestinal parasitosis causes mild or no eosinophilia.
  - Penetration into appendix may cause appendicitis.
  - Penetration into biliary tree is more common in children and young adults. May cause severe biliary cholic with fever, nausea, and vomiting.
    - Jaundice occurs in 10-20%.
    - Exquisitely tender hepatomegaly develops in 50%.
    - Ascaris can cause rupture of bile duct with bile peritonitis.
    - Rarely they penetrate portal or hepatic veins.
    - Worm embolism to pulmonary artery may occur.
  - Pancreatitis may occur when the pancreatic duct is penetrated.

Ascariasis
(A. lumbricoides)

- **Diagnosis:**
  - Stool or duodenal aspirate O&P.
  - Contrast X-Ray may show the parasite with contrast inside its own intestine. U/S may show bile duct worm.
  - ERCP may show the parasite in the bile duct. Endoscopy may show adult worms.
- **Treatment:**
  - Mechanical removal of biliary or hepatic worms + Albendazole 400 mg PO x 1
  - In intestinal obstruction, patient are first decompressed with NGT suction, and then one dose of Piperazine 150 mg/kg (max 3.5 gm) is given, followed by doses of 65 mg/kg given then q 12h x 6 doses.

Fascioliasis
(F. hepatica, F. gigantica)

- **Organism:** Is a Platyhelminth trematode;
  - F. hepatica = 3 cm x 1.5 cm.
  - F. gigantica = 7.4 cm.
  - **Intermediary host** is fresh water snail.
  - **Definitive host** are herbivores.
- **Magnitude:** 1 million infected worldwide.
- **Acquisition:**
  - ingestion of watercress and other aquatic vegetables.
  - Egg opens releasing metacercaria that burrows through the duodenum, into the peritoneum, then through Glisson's capsule into liver, and finally into biliary tree and GB.
  - Adult parasite form in 3-4 months, and releases eggs into bile and then intestine & feces.

Fascioliasis
(F. hepatica, F. gigantica)

- **Clinical presentation:**
- **Acute phase:**
  - dyspepsia followed by fever of 39-40^0 C and variable severity pain in RUQ and epigastrium, associated with prostration, anorexia, sweting, myalgia, arthralgia severe headache and nausea with vomiting.
  - May have severe diarrhea, jaundice, and/or urticaria.
  - Tender hepatomegaly is common, and splenomegaly or hemobilia may occur.
  - Patients have severe eosinophilia of 80-90% with leukocytosis of up to 35000.
  - Serum bili, alk phosph, AST and ALT are frequently elevated. Hypergamma IgG and IgM are common.
  - U/S is usually normal; CT scan may show small hypodense nodules and tortuous tracts.

Fascioliasis
(F. hepatica, F. gigantica)

- **Chronic phase:**
  - Often asymptomatic.
  - May cause symptoms of biliary obstruction or cholangitis.
  - Many patients will develop pigment biliary stones in GB and bile duct.
  - Patients may have diffuse RUQ and epigastric pain, nausea, vomiting, diarrhea and/or jaundice.
  - Hepatosplenomegaly may be present.
  - Up to 50% will have some eosinophilia.
  - Variable elevations of bili, alk phosph, AST, and ALT are present.
  - Fe deficiency anemia is common.

Fascioliasis
(F. hepatica, F. gigantica)

- **Diagnosis:**
  - Stool O&P, or even better duodenal aspirate O&P may show eggs.
  - ELISA serology can be diagnostic.
  - ERCP may show the parasite that can be extracted with a basket.
- **Treatment:**
  - Bithionol30-50 mg/kg every other day x 10-15 doses.
  - Triclabendazole is promising.

Clonorchiasis & Opisthorchiasis
(C. sinensis, O. viverrini, O. felineus)

- **Organisms:**
  - Are Platyhelminth trematodes.
  - Adult is 10-25 mm long x 3-5 mm wide.
- **Reservoir:** cats and dogs.
- **Intermediary hosts:** fresh water snail & fish.
- **Magnitude:**
  - 13.5 million infected worldwide.
  - Up to 26% of Asian immigrants in USA have liver flukes.
- **Acquisition:** ingestion of fresh-water fish, raw, pickled, smoked, or dried.

Clonorchiasis & Opisthorchiasis
(C. sinensis, O. viverrini, O. felineus)

- **Life Cycle:**
  - Water is contaminated with infected host feces with eggs.
  - Eggs operculate an release miracidia.
  - Miracidia is eaten by fresh-water snail and changes to sporocyst and then to rediae.
  - Rediae matures to cercaria and is released into the water and penetrates the skin of a fish transforming into a cyst that matures to metacercaria.
  - Human eats fresh water fish.
  - Metacercaria excyst in duodenum and migrate inside the lumen into biliary duct, GB, and pancreatic duct.
  - Then matures to adult and lays eggs after 4 weeks.

Clonorchiasis & Opisthorchiasis
(C. sinensis, O. viverrini, O. felineus)

- **Clinical Manifestations:**
- Acute phase:
  - Light infection are asymptomatic but may be repetitive and cause heavy parasite burden.
  - Heavy infections cause symptoms for less than 1 month, including fever, diarrhea, epigastric pain, anorexia, tender hepatomegaly, and sometimes jaundice.
  - Leukocytosis and eosinophilia are very common.
  - Eggs appear in stool 1 month after infection.

Clonorchiasis & Opisthorchiasis
(C. sinensis, O. viverrini, O. felineus)

- **Clinical Manifestations:**
- Chronic phase:
  - is due to the burden of adult worms in the biliary tree, pancreatic duct, and/or GB.
  - If < 100 flukes, usually asymptomatic.
  - Moderate infestations (< 1000) cause anorexia, nausea, abdominal fullness and distress.
  - Severe infestations (1000-20000)cause intrahepatic and extrahepatic biliary obstruction.
  - May have repetitive cholangitis.
  - Sometimes worms migrate into the liver.
  - Cholecystitis may occur.
  - Secondary biliary cirrhosis may develop.
  - Patient may have jaundice and hepatosplenomegaly.
  - Patients have higher risk (5-15 fold) for cholangiocarcinoma proportional to the parasite burden.
  - Patients may develop Oriental Cholangiohepatitis with formation of intraductal strictures and stones, and with recurrent cholangitis.

Clonorchiasis & Opisthorchiasis
(C. sinensis, O. viverrini, O. felineus)

- **Diagnosis:**
  - Stool or duodenal aspirate O&P. Need to use concentration techniques.
  - Serum Immunoblot for C sinensis has 92% sensitivity for active infection.
  - Monoclonal dot-ELISA for O. viverrini is close to 100% sensitive & specific. May not separate active from past infection.
- **Treatment:**
  - Praziquantel 75 mg/kg divided in 3 doses x 1 day. In very heavy clonorchiasis, 2 days of therapy may be needed.

Cryptosporidium, Microspora, Isospora, & Prototheca

Acalculous Cholecystitis, Papillary Stenosis & Sclerosing Cholangitis

- Organisms: All are protozoa.
  - cryptosporidium and isospora are Apicomplexa;
  - microspora is a Microsporidia; and
  - Prototheca wickerhamii is an Archaeplastida (algaemia)
- Clinical Considerations:
  - Diseases of GB and biliary tree that affect persons with HIV include:
    - non–HIV-associated conditions, such as cholelithiasis, and
    - AIDS-associated conditions, such as acalculous cholecystitis, cholangiopathy and papillary stenosis.
    - The incidence of AIDS acalculous cholecystitis and cholangiopathy is very low in settings where ART is widely used. At San Francisco Gen Hosp only 23 cases of AIDS cholangiopathy were reported between 1993 and 2003.
  - Noninfectious disorders (e.g., cholelithiasis) likely account for an increasing proportion of hepatobiliary disease in patients with HIV.

Cryptosporidium, Microspora, Isospora, & Prototheca

Acalculous Cholecystitis, Papillary Stenosis & Sclerosing Cholangitis

- **Papillary Stenosis:**
  - may be asymptomatic and present only with elevation of alkaline phosphatase, bilirrubin, and other liver enzymes;
  - often associated to extrahepatic biliary dilation,
  - may cause RUQ pain with nausea and vomiting; sometimes causes cholangitis,
  - if papillary stenosis is present, endoscopic sphincterotomy may produce relief of symptoms and biochemical resolution of cholestasis, although in some case series, the clinical effectiveness of this procedure has been disappointing.

Cryptosporidium, Microspora, Isospora, & Prototheca

Acalculous Cholecystitis, Papillary Stenosis & Sclerosing Cholangitis

- **Acalculous Cholecystitis:**
  - Symptoms: Postprandial pain, fever, right upper quadrant pain and tenderness, and an elevated serum alkaline phosphatase level.
  - U/S or CT scan in patients with advanced immunodeficiency, may suggest acalculous cholecystitis or AIDS-associated cholangitis.
  - In acute or chronic acalculous cholecystitis, the GB is thickened and edematous with obliteration of the gallbladder lumen without evidence of gallstones. Nonvisualization of the gallbladder with radionuclide hepatobiliary scintigraphy is also suggestive of cholecystitis.
  - If a cholecystectomy is performed, specimens should be sent for microbiologic and histopathologic evaluation. Before the advent of potent ART, opportunistic pathogens were identified in more than 50% of cases.
  - CMV, *Cryptosporidium*, and microsporidians are the pathogens most commonly associated with acalculous cholecystitis; however, multiple organisms or other pathogens, such as *Isospora belli or Prototheca wickerhamii*, may be recovered. Often no etiologic agent is identified after extensive microbiologic evaluation.

Cryptosporidium, Microspora, Isospora, & Prototheca

Acalculous Cholecystitis, Papillary Stenosis & Sclerosing Cholangitis

- **AIDS Cholangiopathy:**
  - ERCP patterns:
    - a) stenosis of the papilla of Vater with dilated extrahepatic biliary tract,
    - b) sclerosing cholangitis,
    - c) combination of sclerosing cholangitis and papillary stenosis, and
    - d) long choledocal stenosis or strictures.
  - ERCP with collection of bile from the common bile duct and duodenal or papillary biopsy may identify an opportunistic pathogen or malignancy.
  - Cholangitis is associated with opportunistic infections by CMV, *Cryptosporidium,* or microsporidians in more than one half of cases.
  - Among 82 patients with HIV in whom cryptosporidiosis developed during a waterborne outbreak, 24 (29%) had evidence of biliary involvement.
  - Biliary cryptosporidiosis is associated with CD4 cell counts less than 50 cells/mm3, and patients with HIV will likely have nausea, vomiting, and an elevated alkaline phosphatase.
  - Other infectious pathogens, such as *Cryptococcus neoformans*, *I. belli*, Prototheca wickerhamii, MAI, and *P. jirovecii*, and biliary tree malignant diseases, including lymphoma and Kaposi's sarcoma, have also been reported.
  - Bacterial superinfection may complicate any of these disease processes.