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ABBREVIATIONS

AE	–	Alveolar echinococcosis
AIDS	–	acquired immune deficiency syndrome
BUN	–	blood urea nitrogen
CE	–	Cystic echinococcosis
CBC		Count of blood cells
CLM	–	Cutaneous larva migrans
CSD	–	Catscratch disease
CSF	–	cerebrospinal fluid
EM	–	erythema migrans
GIT	–	Gastrointestinal tract
GWD	–	Guinea worm disease
HIV-1	–	human immunodeficiency virus type I
NCC	–	neurocysticercosis
PCR	–	polymerase chain reaction
RBCs	–	red blood cells
TMP-SMX	–	trimethoprim-sulfamethoxazole
URT	–	Upper respiratory tract
WBCs	–	white blood cells
WHO	–	World Health Organization

INTRODUCTION. GENERAL ASPECTS OF TROPICAL PATHOLOGY

Tropical diseases are diseases that are prevalent in or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation. Insects such as mosquitoes and flies are by far the most common disease carrier (,) or vector. These insects may carry a parasite, bacterium or virus that is infectious to humans and animals. Most often the disease is transmitted by an insect "bite", which causes transmission of the infectious agent through subcutaneous blood exchange. Vaccines are not available for most of the tropical diseases, and many do not have cures.

Human exploration of tropical rainforests, deforestation, rising immigration, and increased international air travel and other tourism to tropical regions has led to an increased incidence of such diseases. The term “neglected” highlights that diseases affect mainly poor and marginalized populations in low-resource settings. The people who are most affected by these diseases are often the poorest populations, living in remote, rural areas, urban slums or conflict zones. Neglected tropical diseases persist under conditions of poverty and are concentrated almost exclusively in impoverished populations in the developing world. Lacking a strong political voice, people affected by these tropical diseases have a low profile and status in public health priorities. Lack of reliable statistics and unpronounceable names of diseases have all hampered efforts to bring them out of the shadows. Neglected tropical diseases include 17 diseases: dengue, rabies, blinding trachoma, Buruli ulcer, endemic treponematoses (yaws), leprosy (Hansen disease), Chagas disease, human African trypanosomiasis (sleeping sickness), leishmaniasis, cysticercosis, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematode infections, lymphatic filariasis, onchocerciasis (river blindness), schistosomiasis (bilharziasis), soil-transmitted helminthiases (intestinal worms).

Neglected tropical diseases affect more than 1 billion people, primarily poor populations living in tropical and subtropical climates. They are frequently clustered together geographically and individuals

are often afflicted with more than one parasite or infection. More than 70% of countries and territories that report the presence of neglected tropical diseases are low-income or lower-middle-income economies.

Infections are caused by unsafe water, poor housing conditions, and poor sanitation. Children are the most vulnerable to these diseases, which kill, impair or permanently disable millions of people every year, often resulting in life-long physical pain and social stigmatization.

There is a reason to be optimistic, however. Many neglected tropical diseases can be prevented, eliminated or even eradicated with improved access to existing safe and cost-effective tools. Control relies on simple interventions that can be carried out by non-specialists – for example schoolteachers, village heads and local volunteers – in community-based preventive action.

The World Health Organization (WHO) has produced overwhelming evidence to show that the burden caused by many of the 17 NTD diseases that affect more than 1 billion people worldwide can be effectively controlled and, in many cases, eliminated or even eradicated.

Preventive Chemotherapy and Transmission Control (PCT) of NTD focuses on diseases for which a strategy exists as well as on tools and the availability of safe and effective drugs that make it feasible to implement large-scale preventive chemotherapy. The diseases include cysticercosis, dracunculiasis (guinea-worm disease), foodborne trematode infections, lymphatic filariasis, onchocerciasis, schistosomiasis, and soil-transmitted helminthiasis. Blinding trachoma control through the SAFE strategy – combining drug treatment with hygiene and environmental management – can be linked to helminth control interventions to improve the overall health of affected communities.

To provide national programmes with technical guidelines that emphasize a coordinated, cost-effective approach to the implementation of national elimination and control activities where preventive chemotherapy is the main tool of WHO, i.e. regular anthelminthic drug administration to all people at risk of morbidity due to helminthic diseases, starting early in life.

To coordinate preventive chemotherapy and transmission control global strategies in consultation with WHO country and regional offices, collaborating centres and partners from academic and research

institutions, the private sector, nongovernmental development organizations, international agencies, and other United Nations organizations.

Innovative and Intensified Disease Management (IDM) of NTD focuses on diseases for which cost-effective control tools do not exist and where the large-scale use of existing tools is limited. The diseases include Buruli ulcer, Chagas disease, human African trypanosomiasis, and leishmaniasis and share the following characteristics: difficult and costly to manage – diagnosis, treatment and follow up, burden is poorly understood, lack of appropriate control tools relatively lower investment in research and development; people affected often live in remote rural areas with limited access to diagnosis and treatment. The goal is to encourage the rapid development and implementation of better control tools and to ensure the full involvement of national control programmes; to advocate for health service development in affected areas.

Vector-borne diseases (VBDs) account for 16% of the estimated global burden of communicable diseases. ***Vector control*** is an important component in the prevention and control of VBDs, especially for transmission control. Wector ecology and management (VEM), as a cross-cutting activity, develops and promotes strategies, guidelines, and standards for vector control, including sound management of pesticides. VEM promotes integrated vector management to improve efficacy, cost-effectiveness, ecological soundness and sustainability of vector control interventions for VBD control.

Neglected zoonotic diseases are a subset of the neglected tropical diseases. Zoonoses are diseases that are naturally transmitted from vertebrate animals to humans and vice-versa. Their management needs integrated approaches and application of veterinary science, which are part of the NTD strategic approach to transmission control. Acknowledging that several zoonotic diseases merit attention, the NTD that are being targeted that are also zoonotic diseases are rabies, echinococcosis, taeniasis/cysticercosis, foodborne trematodiases, human African trypanosomiasis, leishmaniasis, and schistosomiasis.

There is growing evidence of the importance of zoonotic causes of non-malarial febrile illness and diseases such as anthrax, brucellosis, and leptospirosis.

This group of diseases requires collaborative, cross-sectoral

efforts of human and animal health systems and a multidisciplinary approach that considers the complexities of the ecosystems where humans and animals coexist. Preventing and mitigating their occurrence in humans requires control and, where feasible, elimination of the diseases in their animal reservoirs.

VIRAL HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "viral hemorrhagic fever" is used to describe a severe multisystem syndrome (multisystem in that multiple organ system (systems) in the body are affected). Characteristically, the overall vascular system is damaged, and the body's ability to regulate itself is impaired. These symptoms are often accompanied by hemorrhage (bleeding); however, the bleeding is itself rarely life-threatening. While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease.

Arenaviridae. Arenaviridae are spread to humans by rodent contact and include Lassa virus in Africa and several rare South American hemorrhagic fevers such as Machupo, Junin, Guanarito, and Sabia. Lassa virus is the most clinically significant of the Arenaviridae, accounting for serious morbidity and mortality in West Africa.

Lassa fever first appeared in Lassa, Nigeria, in 1969. It has been found in all countries of West Africa and is a significant public health problem in endemic areas. In populations studied, Lassa fever accounts for 5-14% of hospitalized febrile illnesses. Its natural reservoir is a small rodent whose virus-containing excreta, is the source of transmission.

Lassa fever is responsible for an estimated 100,000-300,000 infection per year, with 5,000 deaths. Cases have been reported throughout West Africa, particularly in Nigeria, Sierra Leone, Guinea, and Liberia.

Bunyaviridae. This group includes Rift Valley fever (RVF) virus, Crimean-Congo hemorrhagic fever (CCHF) virus, and several hantaviruses. The RVF and CCHF viruses are both arthropod-borne

viruses. RVF virus, an important African pathogen, is transmitted to humans and livestock by mosquitos and by the slaughter of infected livestock. CCHF virus is carried by ticks and causes a fulminant, highly pathogenic form of VHF notable for aerosol transmission of infective particles. Outbreaks of CCHF have occurred in Africa, Asia, and Europe.

Rift Valley fever (RVF) virus and Crimean-Congo hemorrhagic fever (CCHF) are responsible for intermittent epidemics in Africa (for RVF) and in areas of Africa, Asia, and Europe (for CCHF). VHFs due to Hantavirus infection continues to be an ongoing health concern, particularly in Asia, affecting up to 200,000 patients annually.

Filoviridae. The most notorious of the VHF viruses, including Ebola and Marburg viruses, belongs to the Filoviridae family. Ebola virus first was described in 1976 after outbreaks of a febrile, rapidly fatal hemorrhagic illness were reported along the Ebola River in Zaire (now the Democratic Republic of the Congo) and Sudan. Sporadic outbreaks have continued since that time, usually in isolated areas of central Africa.

Marburg virus, named after the German town where it first was reported in 1967, is another highly pathogenic member of the Filoviridae family that is traced to central Africa. As in Ebola, the natural host for the virus is unknown.

Ebola virus appears sporadically in endemic areas of the former Zaire and Sudan. Ebola virus also has been reported in Gabon, the Ivory Coast, and Uganda. Outbreaks appear to propagate in hospital settings, often involving health care providers.

Flaviviridae. Yellow fever and dengue fever are the most well-known diseases caused by flaviviruses. Both are mosquito-borne; yellow fever is found in tropical Africa and South America, and dengue fever is found in Asia, Africa, and the Americas.

Due to a resurgence in the last 3 decades, dengue fever is now considered second only to malaria in terms of importance as a tropical disease. Multiple recent large outbreaks have occurred throughout the tropics, with the most severe outbreaks occurring in Southeast Asia and the western Pacific regions. Transmission is via the bite of the infected female *Aedes* mosquito, although dengue can also be transmitted via transfusion.

Yellow fever continues to be a serious problem in tropical areas of South America and Africa, where vaccination is not widespread.

The World Health Organization estimates that approximately 200,000 cases per year occur in Africa.

Dengue HF is endemic in Southeast Asia, Africa, Central America, and South America, and the WHO estimates that 50-100 million cases occur annually. In the first 3 months of 2011, Rio de Janeiro had already recorded more than 10,000 cases of dengue infection.

Transmission. Viruses causing hemorrhagic fever are initially transmitted to humans when the activities of infected reservoir hosts or vectors and humans overlap. The viruses carried in rodent reservoirs are transmitted when humans have contact with urine, fecal matter, saliva, or other body excretions from infected rodents. The viruses associated with arthropod vectors are spread most often when the vector mosquito or tick bites a human, or when a human crushes a tick.

However, some of these vectors may spread the virus to animals, livestock, for example. Humans then become infected when they care for or slaughter the animals.

Some viruses that cause hemorrhagic fever can spread from one person to another, once an initial person has become infected. Ebola, Marburg, Lassa, and Crimean-Congo hemorrhagic fever viruses are examples. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids. For example, contaminated syringes and needles have played an important role in spreading infection in outbreaks of Ebola hemorrhagic fever and Lassa fever.

Mortality/Morbidity. Case-fatality rates of patients with VHF vary from less than 10% (eg, in dengue HF) to approximately 90%, as has been reported in patients with Ebola-Zaire and the recent Angola Marburg outbreak. The outbreak of Ebola-Sudan in Uganda had a 50% case-fatality rate.

Complications from VHF infection include retinitis, orchitis, hepatitis, transverse myelitis, and uveitis. In patients who recover from Lassa fever infection, deafness is the most common complication. Spontaneous abortion also is common. Renal insufficiency is associated with HFRS infection.

Seven families of viruses contain pathogens that cause encephalitis in humans. Four of those families contain the bulk of

these pathogens: the Flaviviridae, Togaviridae, Bunyaviridae, and Herpesviridae. Viruses of the family Flaviridae that cause encephalitis include West Nile, St. Louis encephalitis, Japanese encephalitis (JE), Murray Valley encephalitis (MVE), tick-borne encephalitis (including Central European and Russian spring-summer encephalitis), and Powassan. Viruses of the genus Alphavirus of the family Togaviridae that cause encephalitis include eastern equine encephalitis (EEE), western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE). Encephalitogenic members of the Bunyaviridae family include California, La Crosse, Jamestown Canyon, and Rift Valley fever viruses.

YELLOW FEVER

Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. The "yellow" in the name refers to (the) jaundice that affects some patients. Symptoms of yellow fever include fever, headache, jaundice, muscle pain, nausea, vomiting, and fatigue. A small proportion of patients who contract the virus develop severe symptoms and approximately half of those die within 7 to 10 days.

Yellow fever virus is RNA virus (e) in the family Flaviviridae. Virions are enveloped and spherical, with a diameter of about 40 nm. The lipid bilayer envelope contains a matrix (M) protein and the envelope (E) protein, which is variably glycosylated. The genome, a single segment of positive-sense RNA, is bound into a nucleocapsid with a basic capsid (C) protein. Virions enter host cells by receptor-mediated endocytosis. Viral RNA synthesis occurs in the cytoplasm, and protein synthesis proceeds in the endoplasmic reticulum, from which mature virions are released through the plasma membrane by exocytotic fusion.

Epidemiology. Yellow fever occurs in tropical America and in Africa in endemic zones bounded by about 15 degrees north latitude and 15 degrees south latitude. Epidemic (urban) yellow fever is transmitted in an interhuman cycle by A. aegypti mosquitoes, which after feeding on viremic humans can transmit infections to other hosts for 1 to 2 weeks. Although Asia is a receptive area for the virus because of the widespread abundance of A. aegypti vector mosquitoes, the disease has never been reported from the region.

Sylvatic yellow fever, in which the virus is transmitted between forest mosquitoes and monkeys, and incidentally infects persons who work in or who visit forested areas, predominates in South America. Sporadic cases and outbreaks occur principally during the late rainy season (January to May), when vector Haemagogus species mosquitoes are most abundant. In Africa, recurrent viral activity during the rainy season leads to a high level of enzootic and endemic transmission among monkeys and humans and periodically to outbreaks in the forest and moist savanna regions. Cases originating in these emergence zones may spread to villages in the dry savanna and to urban areas where there is a risk for interhuman A. aegypti borne epidemic transmission. In many instances, only fatal cases are recognized, and the several hundred officially reported cases from South America and several thousand from Africa may represent only 1% of true morbidity.

Resistance to acquiring yellow fever may be associated with cross-immunity to dengue fever virus and other flaviviruses. This cross-reactive immunity may provide a barrier to the introduction of yellow fever to Asia.

Countries regarded as yellow fever infected. Africa: Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo (Zaire), Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast (Cote D'Ivoire), Kenya, Liberia, Mali, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, Sudan (South of 15° N), Togo, Uganda, Tanzania, Zambia. ***America:*** Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, Trinidad and Tobago, Venezuela, Panama.

Pathology and pathophysiology: The initial replicative sites are reticuloendothelial cells of local lymph nodes, bone marrow, spleen, and Kupffer cells, from which virions disseminate hematogenously to multiple sites during the early period of infection. The principal pathologic finding is a patchy, primarily midzonal eosinophilic degeneration of hepatocytes with minimal inflammatory or proliferative responses, reflecting apoptotic cell death. Hepatocytes surrounding the central vein and portal areas are spared to a greater degree, and the reticular architecture is largely preserved. Hepatocytes undergo an acidophilic degeneration progressing from a cloudy appearance to progressive shrinkage of the cytoplasm and formation

of Councilman's bodies. Accumulation of ceroid pigment and microvesicular fat is prominent. Torres bodies, intranuclear inclusions, are found occasionally. Viral antigen can be identified in hepatocytes and within Councilman's bodies. Transient nonspecific changes of hepatitis are found after the acute stages of illness, and healing proceeds without fibrosis; anecdotal cases of chronic active hepatitis have been reported. The kidneys are enlarged and edematous. Glomeruli may show mesangial proliferation and capillary endothelial swelling, whereas the interstitium is edematous with swollen tubular epithelial cells that may contain viral antigen. Degeneration and necrosis of the myocardium and lesions in the conduction system may be present. Viral antigen can be detected in occasional myocardial fibers. The absence of an inflammatory response and the cellular morphology of degenerating kidney and cardiac cells suggest an apoptotic mechanism of all deaths in the organs as well. Depletion of lymphocytes in B-cell areas of lymph nodes and spleen may compromise the immune response.

Viral clearance results from a combination of humoral and cellular responses. Viremia disappears within about 5 days after the acute onset of illness with the elaboration of neutralizing antibodies and non-neutralizing antibodies to NS1. Cytokines released in the course of cellular responses to infected parenchymal and monocytic cells may account for the vascular instability shock and other elements of a systemic inflammatory response-like syndrome.

The immunoglobulin M antibody titer remains elevated for years in some patients and in vaccinees, suggesting the possibility of viral persistence.

Clinical presentation. Classic yellow fever is a biphasic illness progressing through three stages: infection, remission, and intoxication. Infection may result in subclinical infection, a self-limited influenza-like syndrome, or in 15% to 25% of cases, fulminating illness that leads to death within days. After an incubation period of 3 to 6 days, an abrupt onset of fever and chills is followed rapidly by headache, backache, generalized myalgias, nausea, and vomiting. Few physical signs are present other than flushing of the face and conjunctivae and Faget's sign, a relative bradycardia. After 3 to 4 days, symptoms and fever remit for a period of hours to 1 or 2 days, only to recur and intensify in patients who progress to the fulminant stage of intoxication. The illness evolves into a secure

multisystem hemorrhagic fever characterized notably by jaundice, the clinical sign for which the disease is named, renal dysfunction, and clinical manifestations of a hemorrhagic diathesis and ultimately hypotension and potentially fatal shock. Mucosal bleeding petechiae and ecchymoses, bleeding from venipuncture sites and gastrointestinal hemorrhage, the black vomit mentioned in early descriptions of the disease, may be severe and reflect a reduced hepatic synthesis of clotting factors, platelet dysfunction, and disseminated intravascular coagulation. Transaminases are elevated, reflecting principally hepatocellular damage, which can lead to the hepatorenal syndrome in severe cases. Oliguria and azotemia may represent prerenal volume depletion, due to vomiting, and extravasation, but albuminuria is a key feature of the disease, and in severe cases, oligoanuria and elevated creatinine develop, possibly due to primary glomerular and interstitial nephritis. Acute tubular necrosis may follow as a late event associated with hypotension. Myocarditis may be detected in electrographic abnormalities and less frequently may be manifested clinically by cardiac dysfunction and arrhythmias after occurring late in the illness. Signs and symptoms of encephalopathy associated with hepatic and renal failure reflect cerebral edema. Secondary bacterial infections, including pneumonia and bacteremia, frequently complicate the course of illness and can contribute to death. The overall case-fatality rate is 5% to 10%, but 20% to 50% of patients entering the stage of intoxication may die.

Physical examination. Physical examination findings for yellow fever include fever, relative bradycardia for the degree of fever (Faget sign), conjunctival injection, and skin flushing.

Other physical findings, such as scleral icterus, jaundice, epigastric tenderness, and hepatomegaly, develop as disease progresses. Early appearance of jaundice indicates a poor prognosis.

Disseminated intravascular coagulation (DIC), induced by liver dysfunction, leads to consumption of platelets and clotting factors. This process clinically presents as a combination of a bleeding diathesis and organ ischemia secondary to fibrin deposition throughout the microcirculation. Petechiae, purpura, mucosal bleeding, and gastrointestinal bleeding (gross or hemoccult) will often be apparent.

Diagnosis. Clinical laboratory abnormalities include leukopenia, albuminuria, prolonged prothrombin time, and elevations in serum

transaminase and indirect and direct bilirubin values and in serum urea nitrogen and creatinine. Early and marked transaminase and bilirubin elevations signal a poor outcome. Mild chemical disturbances in liver function may be present in anicteric cases. Thrombocytopenia and other signs of consumptive coagulopathy are present in some cases. Hepatic damage may lead to hypoglycemia. The cerebrospinal fluid may be under pressure and exhibits a pattern of elevated protein without pleocytosis, most consistent with encephalopathy and cerebral edema.

The diagnosis of yellow fever frequently is confirmed serologically by demonstrating fourfold or greater increases in complement-fixing or neutralizing antibodies or by detecting specific immunoglobulin M in a single serum sample by immunoglobulin M capture enzyme immunoassay. Patients with previous flavivirus infections or immunization develop heterologous antibodies that limit the interpretation of serologic reactions to yellow fever virus, especially in broadly reactive assays such as hemagglutination inhibition. In patients who have had numerous flavivirus infections, serologic assays may be uninterpretable.

Isolation of virus from the blood of viremic cases (during the initial acute phase of illness and before the virus is cleared in the period of transmission) is possible. Detection of yellow fever virus genomic sequences in blood or organs is performed by PCR.

In fatal cases, viral antigen and genome should be sought in liver tissue by immunohistochemical staining or in situ hybridization, respectively.

Ordinary histopathologic examination of viscerotomy samples is a widely used approach to surveillance, but it is contraindicated for critically ill patients; moreover, histopathologic diagnosis is nonspecific because other toxic and infectious agents, especially other hemorrhagic fever viruses, can produce similar pathologic patterns.

The differential diagnosis of mild cases includes malaria, dengue, and other self-limited diseases. Severe cases must be differentiated from leptospirosis, louse-borne relapsing fever, typhoid fever, acute viral hepatitis, and other viral hemorrhagic fevers produced by Lassa, Ebola, Marburg, Congo-Crimean hemorrhagic fever, dengue, and Rift Valley fever viruses. Intoxications, sometimes associated with traditional medicines, also should be considered.

Treatment. Treatment is symptomatic and supportive only. No specific treatment is available for yellow fever.

In the toxic phase, supportive treatment includes therapies for treating dehydration and fever.

In severe cases, death can occur between the 7-10 days after onset of the first symptoms.

Prevention and treatment of hypoglycemia with intravenous drips and of gastrointestinal bleeding with H2 antagonists or proton pump inhibitors have been recommended as well as surveillance and treatment of secondary bacterial infection. The pathogenesis of the bleeding diathesis in yellow fever is not clear, but in one small study, administration of heparin led to the improvement of patients shown to have disseminated intravascular coagulation. Vitamin K and fresh-frozen plasma are recommended to replenish liver-dependent clotting factors. Dialysis may be needed to treat renal failure. Liver transplantation was considered as an option in a case imported to Europe. Nosocomial infection from direct contact with patient blood or fluids is not considered a risk; however, mosquito-borne transmission is possible for about the first 5 days of acute illness, when patients should be isolated by bed nets and other means.

Prevention. The live attenuated virus (17D) vaccine was created by serial passages of yellow fever virus through chick and mouse embryo cells. Dr. Max Theiler of the Rockefeller Institute developed this vaccine in 1937. Since 1945, more than 200,000,000 doses have been administered.

The WHO, United Nations Children's Fund (UNICEF), and the World Bank have recommended that yellow fever vaccine be added to the routine Expanded Program on Immunization in developing nations. However, poor financing remains a problem and a major reason for low vaccination rates among residents of endemic areas. In the United States, the yellow fever vaccine is available at designated state health departments and selected travel clinics.

This vaccine should be administered to residents of and travelers to endemic areas. The seroconversion rate for adults and children receiving the vaccine is 99%. Protective antibodies form within 7-10 days, and protection lasts for at least 10 years. The vaccine is safe and effective in asymptomatic adult patients with HIV and CD4 counts of greater than 200/µL. The vaccine appeared ineffective when administered to 1-year-old infants who were HIV positive (CD4 count >200/µL).

The yellow fever vaccine has a long record of safety, but clinicians should be aware of two severe complications from the vaccine:

1. Yellow fever-associated neurotropic disease (previously known as post vaccine encephalitis), occurs 7-21 days after vaccination. Of the 1/8 000 000 people who contract this disease, full recovery is typical.

2. Yellow fever-associated viscerotropic disease occurs 2-5 days after vaccination. It is characterized by fever, myalgia, arthralgia, increased liver enzymes and bilirubin, lymphopenia, thrombocytopenia, disseminated intravascular coagulation, hypotension, oliguria, and rhabdomyolysis. There have been 13 cases reported out of over 100 million doses administered worldwide.

Strategies for yellow fever control include control of Ae. aegypti in urban centres, infant immunization, vaccination campaigns, outbreak prevention, epidemic detection, and control.

RIFT VALLEY FEVER

Rift Valley fever (RVF) is an illness caused by a virus that is spread through mosquito bites. It is also spread by direct contact with blood, fluids, or tissues of infected animals such as cattle, buffalo, sheep, goats, and camels.

Rift Valley fever (RVF) is a viral disease that can cause mild to severe symptoms. The mild symptoms may include: fever, muscle pains, and headaches which often last for up to a week. The severe symptoms may include: loss of the ability to see beginning three weeks after the infection, infections of the brain causes severe headaches and confusion, and bleeding together with liver problems which may occur within the first few days. Those who have bleeding have a chance of death as high as 50%.

Epidemiology. Outbreaks of the disease have only occurred in Africa and Arabia. Outbreaks usually occur during periods of increased rain which increase the number of mosquitoes.

Transmission. The vast majority of human infections result from direct or indirect contact with the blood or organs of infected animals. The virus can be transmitted to humans through the handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or from the disposal of carcasses or fetuses. Certain occupational groups such as herders, farmers, slaughterhouse workers, and veterinarians are therefore at

higher risk of infection. The virus infects humans through inoculation, for example via a wound from an infected knife or through contact with broken skin, or through inhalation of aerosols produced during the slaughter of infected animals. The aerosol mode of transmission has also led to infection in laboratory workers.

There is some evidence that humans may also become infected with RVF by ingesting the unpasteurized or uncooked milk of infected animals.

Human infections have also resulted from the bites of infected mosquitoes, most commonly the Aedes mosquito.

Transmission of RVF virus by hematophagous (blood-feeding) flies is also possible.

To date, no human-to-human transmission of RVF has been documented, and no transmission of RVF to health care workers has been reported when standard infection control precautions have been put in place.

There has been no evidence of outbreaks of RVF in urban areas.

Clinical presentations. The incubation period (interval from infection to onset of symptoms) for RVF varies from two to six days.

In humans, the virus can cause several syndromes. Usually, patients have either no symptoms or only a mild illness with fever, headache, myalgia and liver abnormalities. In a small percentage of cases (<2%), the illness can progress to hemorrhagic fever syndrome, meningoencephalitis (inflammation of the brain), or affect the eye. Patients who become ill usually experience fever, generalised weakness, back pain, dizziness, and weight loss at the onset of the illness. Typically, people recover within two to seven days after onset.

About 1% of people with the disease die of it.

Those infected either experience no detectable symptoms or develop a mild form of the disease characterized by a feverish syndrome with sudden onset of flu-like fever, muscle pain, joint pain, and headache.

Some patients develop neck stiffness, sensitivity to light, loss of appetite and vomiting; in these patients the disease, in its early st ages, may be mistaken for meningitis.

The symptoms of RVF usually last from four to seven days, after which time the immune response becomes detectable with the appearance of antibodies and the virus gradually disappears from the blood.

Severe form of RVF. While most human cases are relatively mild, a small percentage of patients develop a much more severe form of the disease. This usually appears as one or more of three distinct syndromes: ocular (eye) disease (0,5-2% of patients), meningoencephalitis (less than 1%) or haemorrhagic fever (less than 1%).

Ocular form: In this form of the disease, the usual symptoms associated with the mild form of the disease are accompanied by retinal lesions. The onset of the lesions in the eyes is usually one to three weeks after the appearance of the first symptoms. Patients usually report blurred or decreased vision. The disease may resolve itself with no lasting effects within 10 to 12 weeks. However, when the lesions occur in the macula, 50% of patients will experience a permanent loss of vision. Death in patients with only the ocular form of the disease is uncommon.

Meningoencephalitis form: The onset of the meningoencephalitis form of the disease usually occurs one to four weeks after the first symptoms of RVF appear. Clinical features include an intense headache, loss of memory, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma. Neurological complications can appear later (>60 days). The death rate in patients who experience only this form of the disease is low, although residual neurological deficit, which may be severe, is common.

Haemorrhagic form: The symptoms of this form of the disease appear two to four days after the onset of illness, and begin with evidence of severe liver impairment, such as jaundice. Subsequently, signs of haemorrhage then appear such as vomiting blood, passing blood in the faeces, a purpuric rash or ecchymoses (caused by bleeding in the skin), bleeding from the nose or gums, menorrhagia and bleeding from venepuncture sites. The case-fatality ratio for patients developing the haemorrhagic form of the disease is high at approximately 50%. Death usually occurs three to six days after the onset of symptoms. The virus may be detectable in the blood for up to 10 days, in patients with the hemorrhagic icterus form of RVF.

The total case fatality rate has varied widely between different epidemics but, overall, has been less than 1% in those documented. Most fatalities occur in patients who develop the haemorrhagic form.

In livestock, the fatality level is significantly higher. Pregnant livestock infected with RVF abort virtually 100% of foetuses. An

epizootic (animal disease epidemic) of RVF is usually first indicated by a wave of unexplained abortions.

Other signs in livestock include vomiting and diarrhoea, respiratory disease, fever, lethargy, anorexia and sudden death in young animals.

Diagnosis. Acute RVF can be diagnosed by using several different methods. Serological tests such as enzyme-linked immunoassay (the "ELISA" or "EIA" methods) may confirm the presence of specific IgM antibodies to the virus. The virus itself may be detected in blood during the early phase of illness or in post-mortem tissue using a variety of techniques including virus propagation (in cell cultures or inoculated animals), antigen detection tests and RT-PCR.

Treatment and vaccines. As most human cases of RVF are relatively mild and of short duration, no specific treatment is required for these patients. For the more severe cases, the predominant treatment is general supportive therapy.

An inactivated vaccine has been developed for human use. However, this vaccine is not licensed and is not commercially available. It has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure to RVF. Other candidate vaccines are under investigation.

Prevention of the disease in humans is by vaccinating animals against the disease. This must be done before an outbreak occurs as if it is done during an outbreak it may worsen the situation. Stopping the movement of animals during an outbreak may also be useful. As may decreasing mosquito numbers and avoiding their bites. There is a human vaccine; however, as of 2010, it is not widely available. Once infected there is no specific treatment.

CONTAGIOUS VIRAL HEMORRHAGIC FEVERS

Ebola, Marburg, Lassa, and Crimean-Congo hemorrhagic fever viruses can spread from one person to another, once an initial person has become infected. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids. For example, contaminated

syringes and needles have played an important role in spreading infection in outbreaks of Ebola hemorrhagic fever and Lassa fever.

LASSA FEVER

This severe acute viral infection has the potential to produce epidemics, and as such surveillance, mechanisms to detect outbreaks and to monitor control measures are critical in affected countries.

Epidemiology. Lassa fever occurs exclusively in West Africa. Although the clinical disease has been documented in Sierra Leone, Liberia, Guinea, and Nigeria, serologic evidence of infection has been reported from virtually all other countries in the region. Lassa fever is an extremely common infection in endemic areas; estimates range from thousands to tens of thousands of cases annually, with no predilection for age or sex. Multimammate rats of the genus Mastomys are reservoirs for Lassa virus; at least two species (Mastomys huberti and Mastomys erythroleucus) are infected. M. huberti is highly commensal with humans and regularly contaminates houses and peridomestic areas with infectious urine and respiratory secretions. Humans apparently become infected through contact with these infectious excreta as aerosols or fomites. Strongest associations occur for households with high rodent populations, indiscriminate food storage, and direct rodent contact.

Lassa virus is transmitted from rodents to humans and from human to humans, although the relative importance of each mode of spread remains poorly defined. Clustering of cases and seropositive subjects have been seen, but the presumed common source for exposure is usually unrecognized. Person-to-person transmission of Lassa virus is well described. Infections have followed direct contact with febrile patients and have occurred by sexual transmission during incubation and convalescence. The virus has been recovered from breast milk, and transmission from nursing mothers to infants probably occurs. Nosocomial infections are well recognized, and explosive outbreaks, possibly due to airborne spread, although uncommon, have occurred in Nigeria and Liberia. Experience in endemic areas indicates that application of barrier nursing and isolation practices can significantly reduce the risk for nosocomial spread. The laboratory-acquired infection has been described as well.

Pathogenesis. The principal targets for arenaviruses appear to be macrophages and, to a lesser extent, vascular endothelium. Clinicopathologic manifestations stem from endogenous mediator release, extravasation of fluid into extravascular spaces, and activation of hematologic and immunologic cascades. Infection with Lassa virus results in widespread dissemination of virus, but the damage is limited to focal hepatic necrosis without significant inflammatory response, some evidence of interstitial pneumonitis, and occasional focal adrenal cortical necrosis. Liver damage is variable, with concomitant cellular injury, necrosis, and regeneration. Histopathologic changes are insufficient by themselves to account for death, however.

The outcome in Lassa fever correlates with the degree of virus replication. Increases of serum aspartate aminotransferase levels to greater than 150 IU/L, but not of other hepatic enzymes, are also associated with a poor prognosis. Levels of interleukin-8 and interferon-inducible protein-10, typically high in patients with acute nonfatal Lassa fever, are low or undetectable in those with a fatal disease. Cardiac involvement has been limited to hemorrhage and lymphocytic infiltrates in the pericardium and with occasional interstitial myocarditis. The severe retrosternal or epigastric pain present in many patients may be due to pleural or pericardial involvement. Increased vascular permeability is significant. Important clinical events in fatal disease are a consequence of endothelial and platelet dysfunction (despite adequate numbers of circulating platelets). An inhibitor of platelet function has been identified in the serum of nonhuman primates and of patients with severe Lassa fever, specifically inhibiting platelet-dense granule and adenosine triphosphate release and also suppressing superoxide generation in neutrophils. Platelet and fibrinogen turnover is normal, and there is no increase in fibrinogen breakdown products; therefore, disseminated intravascular coagulation is not significant.

Clinical presentation. After an incubation period of 8 to 14 days (3 weeks at most), patients note the gradual onset of fever, malaise, and headache. During a period of several days, sore throat, myalgia, arthralgia, epigastric or retrosternal pain, severe frontal headache, and dry cough develop. By the end of the first week, patients are highly febrile and in a toxic condition. Conjunctivitis, lymphadenopathy, abdominal and muscle tenderness, hypotension, and relative bradycardia may be found at physical examination. A painful purulent

pharyngitis is found in about 40% of cases and is sometimes associated with vesicles or ulcers. There is no characteristic rash, and neither cutaneous hemorrhages nor jaundice is seen early in the disease. With disease progression, edema of the face and neck and evidence of fluid buildup in the lungs occur. Hemorrhage is associated with fatal outcome but occurs in only 15% to 20% of patients; most often bleeding is from the gums and nose, less frequently from the gastrointestinal tract or vagina. About one-fifth of patients has pleural or pericardial rubs.

Neurologic signs are infrequent; stupor, coma, and convulsions, as well as hemorrhage and severe hypotension, portend a poor prognosis. The duration of illness is typically about 1 month in survivors. Recovery is slow, and convalescence may be complicated by pericarditis, orchitis, uveitis, pleural effusion, or ascites. Acute-onset eighth cranial nerve deafness develops in up to 25% of patients and may be permanent.

Lassa fever is particularly hazardous for pregnant women. The risk for death during the third trimester is nearly six times that during the first two. Spontaneous or therapeutic abortion improves outcome, but fetal and perinatal wastage is high. Lassa fever in infants and extremely young children may present as swollen baby syndrome due to diffuse edema and abdominal distention. In older children, cough and gastrointestinal symptoms may dominate the clinical picture.

Lassa fever is an important cause of morbidity and mortality among adults in parts of West Africa. In Sierra Leone, 10% to 16% of all adult medical hospitalizations, 39% to 47% of adult febrile admissions, and 30% of adult medical deaths were due to Lassa fever. The case fatality among hospitalized patients is 16% to 17%. The case fatality among pregnant women is higher, reaching 30% or more during the third trimester. In children, Lassa fever is similarly important. Studies suggest that more than 20% of febrile pediatric admissions in endemic areas are due to this disease; the case fatality in children younger than 15 years is estimated at 12% to 14%.

Physical examination. Pharyngitis, often exudative, occurs early. Conjunctivitis also may be seen. Later, in severe disease, CNS signs can be seen, including tremors, confusion, encephalopathy, and seizures. Focal CNS signs usually are absent, and CSF is normal. Bleeding is seen in only 15-20% of patients, it usually is limited to mucosal surfaces, and it is limited in severity.

Diagnosis. Most clinical laboratory studies in Lassa fever are not diagnostically useful. Leukopenia may be present early, but normal or elevated white cell counts are more typical as the disease progresses. Platelet counts are normal or elevated, although platelets themselves are dysfunctional. Proteinuria occurs in severe cases of the disease. High serum viremia and aspartate aminotransferase values higher than 150 IU/L are associated with poor outcomes (50% and 73% mortality rates, respectively; 80% if both factors coexist).

Laboratory criteria for diagnosis:

• Isolation of virus (only in laboratory of biosafety level 4) from blood, urine or throat washings or

• Positive IgM serology or seroconversion (IgG antibody) in paired serum specimens or

• Demonstration of Lassa virus antigen in autopsy tissues by immunohistochemistry or in serum by ELISA

• Positive PCR from serum or autopsy tissues.

Differentiating Lassa fever from arbovirus diseases, malaria, typhoid fever, and other febrile illnesses common to West Africa is difficult on clinical grounds. Triads of pharyngitis, retrosternal pain, and proteinuria, or pharyngitis, retrosternal pain, and vomiting, yielded the best combinations of sensitivity, specificity, and positive predictive value in a single published case-control study from Sierra Leone. Lymphopenia, thrombocytopenia, and defects of qualitative platelet function are found during this stage.

Treatment. Specific and careful symptomatic care is needed in more severe infections associated with those agents linked to hemorrhagic fever. The antiviral drug ribavirin is effective in treating Lassa fever. It is administrated by intravenous infusions a 2 g dose followed by 1g every 6 h for 4 days than 0,5 g every 8 h for 6 more days. Although dosing by both oral and intravenous routes reduces mortality, the parenterally administered drug is more effective. The optimal benefit is derived within the first 6 days of illness.

Prevention. A vaccinia-vectored Lassa fever virus vaccine has been developed and tested in animal models but has not yet been evaluated in humans.

In the event of significant exposure (e.g., needlestick or intimate personal contact) to Lassa virus (or any other pathogenic arenavirus), it has been recommended that oral ribavirin, 500 mg four times daily for 7 days, be administered. The efficacy of this prophylactic regimen

is unproved, however, and close monitoring of disease contacts for at least one normal incubation period, with the initiation of therapy at the first sign of illness, represents an acceptable alternative.

EBOLA AND MARBURG HEMORRHAGIC FEVERS

Ebola haemorrhagic fever is a rare but severe disease occurring primarily in areas of African rain forest. The disease is characterized by person-to-person transmission through close contact with patients, dead bodies or infected body fluids. Epidemics of the disease can be dramatically amplified in health care centres with poor hygiene standards; the attendant potential for explosive nosocomial infection constitutes the main threat to public health posed by the disease. Surveillance is aimed at early detection of cases in order to avoid epidemics and possible international spread of the disease. Marburg virus infections are extremely rare. They appear to be similar to Ebola haemorrhagic fever and recommendations for both viral infections are the same.

The Filoviridae are a family of RNA viruses capable of inducing severe and highly lethal hemorrhagic fevers in primates, including humans. Five viruses have been described: Marburg virus and four Ebola viruses subtypes. Only four group of viruses within the genus Ebola virus (Ebola, Sudan, Taï Forest, and Bundibugyo viruses) are known to cause disease in people. Reston virus is known to cause disease in nonhuman primates and pigs, but not in people. It is unknown if the Bombali virus, which was recently identified in bats, causes disease in either animals or people. Ebola virus diseases are clinically indistinguishable from Marburg virus disease.

Epidemiology. Filoviruses were unknown to science until 1967, when simultaneous outbreaks of hemorrhagic fever occurred in Marburg and Frankfurt, Germany, and Belgrade, Yugoslavia. Thirty-two cases (25 primary and 7 secondary) of what came to be known as Marburg virus disease was (were) recognized, 7 of which were fatal. Primary infections were linked to contact with African green monkeys shipped from a primate export facility in Uganda. The virus then disappeared from view until 1975 when a young Australian tourist who had traveled in Zimbabwe contracted Marburg virus infection and died in a Johannesburg, South Africa, hospital. His female

traveling companion became ill a week after onset in her partner, and a nurse in Johannesburg subsequently became infected, but both survived. In 1980, an expatriate engineer contracted the disease in northwestern Kenya and died; his physician became ill but survived. In 1987, a Danish teenager contracted the disease in Kenya and died. An extensive outbreak of Marburg fever occurred at Durba in the Democratic Republic of Congo from 1998 to 2000 (with the retrospective identification of disease in 1997). A total of 103 cases were diagnosed with 69 deaths in 1998 and 1999, and at least 16 additional cases were diagnosed in 2000 until flooding denied access to a local mine that was the presumptive source of the infection.

Two simultaneous explosives, but unrelated, outbreaks of hemorrhagic fever in 1976 in northern Zaire and southern Sudan proved to be the sentinel cases of Ebola virus disease in humans. These epidemics lasted for months and affected more than 500 persons. Mortality was quite high (nearly 90% in Zaire and 50% in Sudan), and secondary cases associated with exposure to blood or other body fluids (e.g., reuse of needles and syringes, sexual contacts) were common. Isolated Ebola virus cases in 1972 (one putative nonfatal case retrospectively identified by serology, along with one probable fatal case), 1976 (one nonfatal laboratory infection) and 1977 (a single fatal case in Tandala, Zaire), together with a second outbreak in southern Sudan involving 34 persons (22 fatalities) in 1979, round out the confirmed experience with these viruses in Africa before the 1990 s. Despite extensive investigation, no reservoir, vector, or naturally occurring source for any Marburg virus infection has ever been identified. The natural history of filoviruses remains enigmatic. That these are zoonotic viruses is strongly suggested by the patterns of human infection, the biologic properties of the agents, and some intriguing epidemiologic associations with exposure to bats (supported by laboratory evidence of virus replication and circulation).

Despite the extensive ecologic study, however, no natural source for any filovirus has been identified. Person-to-person transmission of filoviruses has been documented in association with parenteral or mucous membrane exposure to contaminated body fluids by direct contact, large-particle droplets, or fomites. The role of small-particle aerosol transmission is less clear, however. Experimental aerosol transmission of Marburg and Ebola viruses has been demonstrated, and aerosol spread of Ebola Reston virus may have occurred among

quarantined cynomolgus monkeys.

Pathogenesis. Hematogenous spread of Ebola and Marburg viruses to multiple organs follows mucous membrane exposure or direct inoculation of virus. Extensive virus replication is associated with focal necrotic changes in the liver, spleen, lymph nodes, kidney, lung, and gonads. The most prominent pathologic changes are observed in the liver, where foci of parenchymal necrosis containing Councilman-like bodies are seen. The presence of virus is strongly correlated with visible necrosis. Few inflammatory cells accompany the hepatic lesions, however, and blood biochemical changes suggest that liver damage is not central to disease outcome. There is also nearly complete obliteration of lymphoid cells in the spleen.

The major manifestation of this usually severe disease is vascular failure. Pathologic features of fatal Marburg and Ebola virus infection typically include hemorrhages in skin, mucous membranes, alimentary luminal surfaces, and viscera. These abnormalities are temporally associated with increased vascular permeability. Extravasation of fluid into abdominal viscera, lungs, and kidneys precipitates organ dysfunction. Endothelial cell dysfunction and subsequent loss of vascular integrity appear to be due both to direct (cytopathology) and indirect (mediator-induced) virus effects. Ebola virus particles are capable of adhering to a variety of cell types, including vascular endothelium, through a specialized glycoprotein. Folate receptor has been implicated as a cofactor for cellular entry of both Marburg and Ebola, but other cell surface molecules are almost certainly involved as well. Disseminated intravascular coagulation has been observed in primate models of Marburg virus infection, but its role in human pathogenesis is uncertain.

Humans and other primates fatally infected with filoviruses die with high viremias and little or no evidence of an effective humoral immune response. In animal models, both cellular and humoral components of the immune system appear important in protection from lethal infection.

Clinical presentation. Ebola haemorrhagic fever begins with acute fever, diarrhoea that can be bloody (referred to as “diarrhée rouge” in francophone Africa), and vomiting.

The incubation period for African filoviruses in humans typically ranges from 2 to 21 days. The onset of illness is sudden, with severe frontal headache, fever, chills, myalgias, extreme malaise, and

anorexia. Nausea, vomiting, diarrhea, and abdominal pain are common early in the disease. Conjunctivitis, hiccups, retrosternal pain, pharyngitis, and oral ulcerations are frequently described as well. Patients appear prostrate and apathetic and may be disoriented. A maculopapular rash that ultimately desquamates in survivors appears on the trunk and back around the 5th day of illness. Gross bleeding is frequent and is most often seen from mucous membranes (including the gastrointestinal tract), nasopharynx, and vagina; petechiae and oozing from venipuncture sites are also commonly observed. Dehydration and significant wasting occur as the disease progresses. At a later stage, there is frequent involvement of the central nervous system, manifested by somnolence, delirium, or coma. The central nervous system is affected as judged by the development of severe headaches, agitation, confusion, fatigue, depression, seizures, and sometimes coma. The circulatory system is also frequently involved, with the most prominent signs being edema and conjunctivitis. Hemorrhagic symptoms are infrequent (,) and include hematemesis, hemoptysis, melena, and bleeding from mucous membranes (gastrointestinal tract, nose, vagina, and gingiva).

The cutaneous presentation may include: maculopapular rash, petechiae, purpura, ecchymoses, and hematomas (especially around needle injection sites). Development of hemorrhagic symptoms is generally indicative of a negative prognosis. Instead, death occurs due to multiple organ dysfunction syndrome (MODS) due to fluid redistribution, hypotension, disseminated intravascular coagulation, and focal tissue necrosis.

Thrombocytopenia and leukopenia with a left shift are present early in disease. After a few days, significant neutrophilia appears. Serum biochemical studies show elevated enzyme values (aspartate aminotransferase higher than alanine aminotransferase), with normal or only slightly elevated bilirubin values. Viremia is present during acute disease and can persist for weeks in visceral organs and other sites (e.g., semen, anterior chamber of the eye) after apparently normal recovery.

Death due to progressive shock occurs on days 6 to 16 of illness. Infections in pregnancy produce many maternal deaths, and abortion or fetal demise is virtually universal. Convalescence is prolonged for survivors, requiring many weeks for recovery from the severe wasting that typically occurs. The case-fatality rate ranges from 50% to 90%.

Physical examination. Findings are similar for both Ebola and Marburg virus diseases. The findings upon physical examination depend on the stage of disease in which patients present. Early in the disease, patients may present with fever, pharyngitis, and severe constitutional signs and symptoms. A maculopapular rash, more easily seen on white skin than on dark skin, may be present around day 5 of infection and is most evident on the trunk. Bilateral conjunctival injection is also common. Late in the disease, patients often develop an expressionless faces. At this point in the disease, bleeding from intravenous puncture sites and mucous membranes is common.

Myocarditis and pulmonary edema also are seen in the later stages of the disease. Terminally ill patients often die tachypneic, hypotensive, anuric, and in a coma.

Diagnosis.

Laboratory criteria for diagnosis:

- Positive serology (ELISA for IgG and/or IgM), or
- Positive virus isolation (only in a laboratory of biosafety level 4) or
- Positive skin biopsy (immunohistochemistry) or
- Positive PCR.

CBC: the early phase of infection is characterized by thrombocytopenia, leukopenia, and a pronounced lymphopenia. Neutrophilia develops after several days.

Elevations in aspartate aminotransferase and alanine aminotransferase. Bilirubin may be normal or slightly elevated.

Treatment. There is currently no effective virus-specific therapy for Filoviruses. Treatment is primarily supportive in nature and includes minimizing invasive procedures, balancing fluids and electrolytes to counter dehydration, administration of anticoagulants early in infection to prevent or control disseminated intravascular coagulation, administration of procoagulants late in infection to control hemorrhaging, maintaining oxygen levels, pain management, and administration of antibiotics or antimycotics to treat secondary infections. Human interferon, in conjunction with convalescent plasma, was used in a patient who survived, although experimental studies have shown no in vitro sensitivity of filoviruses for interferon. The use of immune serum in animal studies and blood from survivors in two anecdotal reports of Ebola hemorrhagic fever in humans have shown promise, but the efficacy of these treatments has not been

clearly shown. In the absence of more definitive therapy, infusion of human convalescent plasma containing strain-specific antibodies or whole blood (containing inflammatory mediators) would seem justified (assuming the infusate is free of other infectious agents).

Prevention. Licensing of a recombinant EBOV and possibly MARV vaccine is to be expected in the United States of America within 5 years. Experience in epidemic settings supports the central role of interruption of person-to-person transmission through early identification of cases and intervention in limiting the spread of disease among close personal contacts. Prevention of nosocomial spread can be accomplished through the use of sterile equipment, adequate decontamination procedures, and application of barrier nursing practices. The absence of identified reservoirs or vectors precludes the use of ecologic controls to limit the acquisition of disease from natural sources. Recognition of risks to individuals involved in work with wild-caught monkeys or their tissues has resulted in the institution of controls pertaining to importation and quarantine of animals.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral disease with a wide geographic distribution. Human infections have been recognized in Eastern Europe, the Middle East, across Asia as the Far East as China, and throughout Africa. The etiologic agent of what had been known since the 1930 s as Crimean hemorrhagic fever was identified as a virus in 1947. Clinical disease is rare in infected mammals, but commonly severe in infected humans, with a 30% mortality rate. Outbreaks of illness are usually attributable to handling infected animals or people.

Epidemiology. The epidemiology of CCHF is tied to complex relationships that exist between the virus's arthropod vectors and their nonhuman vertebrate hosts. The virus is a parasite of at least 24 species of ixodid (hard) ticks, particularly Hyalomma species. Transovarial and transstadial transmission of CCHF virus have been documented in several of these tick species, which presumably serve as both reservoir and vector of the agent. In addition, the ticks feed on (and infect) a wide variety of wild and domestic animals, including

birds; specific vertebrate hosts are parasitized (and possibly infected) in both a tick species and a life cycle stage-specific pattern. In general, wild hares and large herbivores represent the major vertebrate amplifier reservoirs. Human infections occur secondary to bites from infected ticks; exposure to viremic animal blood, tissues, and excreta; and nosocomially. The last route is particularly significant inasmuch as several serious outbreaks of CCHF have occurred among hospital personnel after exposure to infectious materials from unsuspected cases. Mammals, including hares, hedgehogs, rodents, and birds have been implicated as reservoirs of CCHFV; however, it is believed that they are more likely to be amplifying hosts rather than true reservoirs. Ticks of the Hyalomma spp. also, act as a reservoir.

CCHFV can be transmitted to humans via exposure to infected tissues/secretions during the slaughtering of infected animal and via exposure to small-particle aerosols from infected rodent excreta. Zoonosis is also possible indirectly via infected tick bites.

Like all lipids enveloped viruses, CCHFV is readily inactivated by common fixatives such as glutaraldehyde, formalin, and paraformaldehyde; chlorine-based disinfectants, such as 1% sodium hypochlorite; and by 70% alcohol, hydrogen peroxide, peracetic acid, and iodophor compounds. Typically, areas and or objects that have come into contact with viral haemorrhagic fever viruses can be disinfected with a 1:100 dilution of sodium hypochlorite.

The virus is susceptible to high temperature (56°C for 30 minutes, or 60°C for 15 minutes), UV light (1,200 to 3,000 $\mu W/cm^2$), and low pH (less than 6). The virus does not survive in matured meat. The virus is also inactivated in 40% ethanol within 2 minutes.

The virus is stable under wet conditions for 7 hours at 37°C, 11 days at 20°C, and 15 days at 4°C (20). Under dry conditions, the virus is stable for at least 90 minutes, but less than 24 hours.

Seasonality of CCHF depends on local climatic conditions, and peaks correspond to periods of maximal tick infestation. CCHF is a rural disease, and many of the endemic areas are remote; information on incidence and prevalence is consequently variable in quality. Important exceptions are infections among butchers, tanners, and animal handlers in urban centers in the Middle East from either imported animals or acute infection of naïve animals or their shed ticks. A relatively high range of illness-to-infection ratios have been

reported from some countries (from 20% to 50%), but human infections have not been recognized in some areas where infected ticks or seropositive animals and humans have been found [reviewed in Watts and colleagues and Peters and LeDuc. This variability is unexplained but may relate to geographic differences in virulence among CCHF virus strains, the predominant mode of disease acquisition, or density of infection in the reservoir or vector populations. Case fatality among hospitalized patients in Eurasia has ranged from 13% to 50%; in southern Africa, the mortality rate is about 30%, despite the availability of relatively advanced medical care.

Crimean-Congo hemorrhagic fever occurs most frequently among agricultural workers following the bite of an infected tick, and to a lesser extent among slaughterhouse workers exposed to the blood and tissues of infected livestock and medical personnel through contact with the body fluids of infected patients.

During the summers of 1944 and 1945 over 200 cases of an acute, hemorrhagic, febrile illness occurred in Soviet troops rescuing the harvest following the ethnic cleansing of the Crimean Tatars.

In July 2013, in Kariyana village in Babra Taluka, Amreli district, India the virology report of four persons who died last week tested positive for CCHF.

On August 16, 2013, a farmer from Agago, Uganda was treated at Kalongo Hospital for a confirmed CCHF infection. Additionally, the deaths of three other people in the northern region were suspected to have been caused by the virus. Six people who had come in contact with the Agago man were placed under observation and released after showing no symptoms in two weeks. Another unrelated suspected CCHF patient as admitted to Mulago Hospital on the same day.

Pathogenesis. CCHF is a multisystem disease. Generalized vascular damage, endothelial lesions, and scattered focal hemorrhages with edema are typically seen in multiple organs. Immunohistochemical studies have demonstrated the presence of viral antigen concentrated in mononuclear phagocytes, endothelial cells, and hepatocytes. Histologically, focal to massive necrosis of the liver is seen, but the degree of hepatic involvement is generally disproportionate to the amount of antigen present. Although the association of parenchymal necrosis in the liver with the presence of viral antigen suggests that cell damage may be mediated by direct

viral cytopathic effect, it is unclear whether circulating inflammatory mediators play a role in cell damage. Disseminated intravascular coagulation is well documented as an early and prominent feature of CCHF, and the resultant microthrombus formation with subsequent infarction is undoubtedly critical in pathogenesis. In contrast to other viral hemorrhagic fevers, gross bleeding in CCHF is quite common, and the volume of blood loss may be significant. Anemia or circulatory collapse may contribute to death in fatal cases.

Clinical presentation. The incubation period ranges from 1 to 12 days depending on the mode of transmission. Typically, after a 1-3 day incubation period following a tick bite (5-6 days after exposure to infected blood or tissues), flu-like symptoms appear, which may resolve after one week. After 3 to 5 days, a brief remission of several hours duration may be seen in one third to two-thirds of patients, followed by a second, overtly hemorrhagic, phase of illness. During this latter period, bradycardia, pulmonary edema, and hypovolemic shock occur. Petechiae appear on most patients, distributed over the chest and abdomen. Epistaxis is common, and in more severe cases, uncontrolled bleeding at other mucosal surfaces, as well as venipuncture sites, may occur. In such cases, large pressure-associated ecchymoses frequently are seen. This stage may last 3 to 10 days and is associated with changes in mood and affect. The liver becomes swollen and painful. Disseminated intravascular coagulation may occur as well as acute kidney failure and shock, and sometimes acute respiratory distress syndrome. Patients usually begin to show signs of recovery after 9-10 days from when the symptoms appear, however, 30% of the cases result in death on the second week of the illness.

Diagnosis. Leukopenia, thrombocytopenia, and elevated serum transaminase values are generally present at the time of initial clinical consultation. Studies of South African patients showed that leukocytosis (white cell count of 10,000 cells/mm^3 or higher), severe thrombocytopenia (platelet count of 20,000 cells/mm^3 or lower), or marked abnormalities of serum transaminase levels (aspartate aminotransferase level of at least 200 IU/L, alanine aminotransferase level of at least 150 IU/L) or coagulation (activated partial thromboplastin time of 60 seconds or more, or fibrinogen levels of at least 110 mg/dL) were 90% predictive of a fatal outcome is seen during the first 5 days of illness.

CCHF virus is readily recovered from blood after its inoculation

into newborn mice or cell cultures. Viral antigen can be demonstrated in many organs of fatal cases by immunohistochemistry and nucleic acid detection. In most patients, virus-specific IgM and IgG antibodies can be detected by indirect IF or EIA on days 7 to 9 of illness, with IgM falling to low or undetectable levels by 3 to 5 months. However, virus-specific IgM and IgG may be absent in early or fatal cases; antigen should be sought by EIA for acute diagnosis. Neutralizing antibody appears toward the end of the first week of illness but reaches only modest titer (1:16 to 1:256) and persists only 4 to 5 months in survivors.

Treatment. Intensive supportive therapy. For patients without haemorrhagic complications, treatment with analgesics and antipyretics is effective (4). Patients with haemorrhagic manifestations are given therapy aimed at maintaining fluid and electrolyte balance, circulatory volume, and blood pressure (2, 4). In severe cases, fresh platelets, fresh frozen plasma, albumin, or coagulation factors are administered. Administration of ribavirin, or convalescent plasma with a high neutralising antibody titre are regarded as useful treatments. Treatment of CCHF with immune plasma has been generally unsuccessful. The virus is sensitive in vitro to ribavirin, and this drug has been reported to be useful in management of South African and Pakistani CCHF cases.

Immunization. None is available. Vaccines based on the inactivated virus have been investigated since the 1970s, and more recently, possible DNA vaccines have been studies, although the safety and efficacy of these vaccines have not been demonstrated for humans.

Prophylaxis. Control of tick populations with insecticides, and application of insect repellent to limit tick bites in endemic areas. Post-exposure prophylaxis with oral ribavirin for those considered to have been in contact with highly viraemic patients (200 mg twice daily, for 5 days).

DENGUE FEVER

Dengue fever, including Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS), is the most significant arthropod-borne viral disease worldwide. It occurs in over 100 countries and territories and threatens the health of over 2 500 million people in tropical and subtropical regions. Dengue fever is a severe disease with

high epidemic potential. An estimated 500 000 patients, 90% of them below the age of 15, are hospitalized with DHF / DSS every year. WHO aims to accelerate the final development of an attenuated dengue vaccine.

The dengue syndrome is an acute febrile viral exanthem accompanied by a headache, myalgia, anorexia, gastrointestinal disturbances, and prostration caused by viruses transmitted by mosquitoes.

Characteristics of the pathogen. The four dengue viruses are single-stranded, enveloped, positive-sense RNA viruses of the family of Flaviviridae. The family is composed of 54 serologically related viruses. Dengue viruses are spherical, 50-nm virions consisting of a nucleocapsid core about 30 nm in diameter surrounded by a lipoprotein envelope. Virions contain three structural proteins. The capsid protein surrounds the genome. The envelope (E) contains replicates of the E and matrix (M) proteins embedded in a lipid bilayer. The lipid is derived from host cell membranes. When assembled into a virion, the E protein bears epitopes that are specific for the virus serotype. Presumably, these serve as sites for viral attachment to plasma membranes and entry into host cells. Other epitopes are shared between dengue viruses (dengue subgroup antigens) or nondengue flaviviruses (flavivirus group antigens). Neutralization can be achieved only when antibody attaches conformationally to the virion surface at several discontinuous segments of the E protein.

Epidemiology. Dengue viruses are transmitted by mosquitoes of the daytime-biting Stegomyia family, principally A. aegypti. In most tropical areas, A. aegypti is highly urbanized, breeding in water stored for drinking or bathing or in rainwater collected in manufactured or natural containers. In Africa and tropical Asia, a jungle cycle exists with high rates of dengue virus transmission among several species of monkeys. In Malaysia, dengue viruses may be maintained in a cycle involving Aedes niveus, which feed on both monkeys and humans. Viruses from the urban and jungle cycles are genetically distinct, suggesting that discrete transmission cycles.

Currently, A. aegypti is almost universally distributed in the tropics between 30 degrees north and 20 degrees south latitude, an area in which nearly half of the world’s populations live. Dengue viruses have spread throughout this range. Most transmission occurs at

altitudes below 2,000 feet and during the rainy season. Frosts or sustained cold weather destroys adult mosquitoes and interrupts transmission. A. aegypti has a short flight range, and the dispersal of dengue viruses is almost entirely due to the movement of viremic humans. Under epidemic conditions, dengue usually spreads along major transportation arteries. Typically, it exhibits the epidemiologic features of a respiratory tract disease. An infected index case introduces the virus into a household infested with A. aegypti, and after the combined extrinsic (mosquito) and intrinsic (host) incubation periods, secondary cases occur. As a result, dengue transmission is intense in crowded, urban areas. In some countries, middle- and upper-income housing provides more mosquito-breeding sites than does that of the urban poor.

Nonimmune populations support outbreaks of classic dengue fever. In certain areas where multiple dengue types are endemic, outbreaks of DHF-DSS are common. The case-fatality rate is 1% to 5%. Countries principally involved are China (Hainan), the Philippines, Vietnam, Laos, Cambodia, Thailand, Malaysia, Indonesia, Myanmar, Bangladesh, India, and Sri Lanka. Small outbreaks have been reported from Pakistan. In the American hemisphere, DHF-DSS first occurred in 1981, when Cuba experienced a sharp outbreak.

Disease factors: Dengue-2 serotype is most virulent; increased severity with secondary infections is observed; increased risk in children <15 years and elderly is observed; the greatest risk of DHF is in infants; its course is more severe in females; increased mortality with comorbid conditions is observed; it is less common in malnourished children.

Replication and Transmission of Dengue Virus. Virus transmitted to a human in mosquito saliva. The virus replicates in target organs. The virus infects white blood cells and lymphatic tissues. The virus is released and circulates in the blood. The second mosquito ingests virus with blood. The virus replicates in mosquito midgut and other organs, infects salivary glands. The virus replicates in salivary glands.

Clinical presentation. Host factors, such as age, ethnicity, and sex, influence the severity of dengue illness. For example, primary dengue infections are milder in children than in adults. The severity of secondary dengue infections, however, is inversely related to age; the

youngest children are at highest risk for developing acute vascular permeability and the DHF (Dengue hemorrhagic fever) – DSS syndrome (Dengue shock syndrome). Females are at higher risk for severe disease and death than males. Blacks are intrinsically less susceptible to severe and fatal disease accompanying second dengue infections.

Dengue Clinical Syndromes may be divided in 4 categories:

- Undifferentiated fever
- Classic dengue fever
- Dengue hemorrhagic fever
- Dengue shock syndrome.

Undifferentiated Fever. This may be the most common manifestation of dengue. Prospective study found that 87% of students infected were either asymptomatic or only mildly symptomatic. Other prospective studies including all age- groups also demonstrate silent transmission. Many patients experience a prodrome of chills, erythematous mottling of the skin, and facial flushing (a sensitive and specific indicator of dengue fever). The prodrome may last for 2-3 days. Children younger than 15 years usually have a nonspecific febrile syndrome, which may be accompanied by a maculopapular rash.

Classic dengue fever begins with sudden onset of fever, chills, and severe (termed breakbone) aching of the head, back, and extremities, as well as other symptoms. The fever lasts 2-7 days and may reach 41°C. Fever that lasts longer than 10 days is probably not due to dengue. Pain and other accompanying symptoms may include any of the following; headache, retro-orbital pain, general body pain (arthralgias, myalgias), nausea and vomiting, rash, weakness, altered taste sensation, anorexia, sore throat, mild hemorrhagic manifestations (eg, petechiae, bleeding gums, epistaxis, menorrhagia, hematuria), lymphadenopathy.

Hemorrhagic Manifestations of Dengue.

- Skin hemorrhages: petechiae, purpura, ecchymoses
- Gingival bleeding
- Nasal bleeding
- Gastro-intestinal bleeding: hematemesis, melena
- Hematuria
- Increased menstrual flow.

Clinical case definition for Dengue Hemorrhagic Fever need to present 4 necessary criteria:

1. Fever, or recent history of acute fever.
2. Hemorrhagic manifestations.
3. Low platelet count (100,000/mm3 or less).
4. Objective evidence of "leaky capillaries:"elevated hematocrit (20% or more over baseline); low albumin; pleural or other effusions.

Clinical Case Definition for Dengue Shock Syndrome.

1. Presence of 4 criteria for DHF;
2. Evidence of circulatory failure manifested indirectly by all of the following:

- Rapid and weak pulse;
- Narrow pulse pressure (less than 20 mm Hg) OR hypotension for age;
- Cold, clammy skin and altered mental status.

3. Frank shock is direct evidence of circulatory failure.

The severity of DHF can be established according to four grades of DHF

- Grade 1
- Fever and nonspecific constitutional symptoms
- Positive tourniquet test is an only hemorrhagic manifestation
- Grade 2
  - Grade 1 manifestations + spontaneous bleeding
- Grade 3
  - Signs of circulatory failure (rapid/weak pulse, narrow pulse pressure, hypotension, cold/clammy skin)
- Grade 4
  - Profound shock (undetectable pulse and BP).

Danger Signs in Dengue Hemorrhagic Fever

- Abdominal pain – intense and sustained;
- Persistent vomiting;
- Abrupt change from fever to hypothermia, with sweating and prostration
- Restlessness or somnolence
- Encephalopathy
- Hepatic damage
- Cardiomyopathy
- Severe gastrointestinal hemorrhage
- Encephalitis/Encephalopathy (decreased level of consciousness:

lethargy, confusion, coma, seizures, nuchal rigidity, paresis)

- Hepatic damage
- Cardiomyopathy
- Severe gastrointestinal hemorrhage.

***Physical examination*:**

Up to half of patients with dengue fever develop a characteristic rash. The rash is variable and may be maculopapular or macular. Petechiae and purpura may develop as hemorrhagic manifestations. Hemorrhagic manifestations most commonly include petechiae and bleeding at venipuncture sites.

A tourniquet test is often positive. This test is performed by inflating a blood pressure cuff on the upper arm to midway between diastolic and systolic blood pressures for 5 minutes. The results are considered to be positive if more than 20 petechiae per square inch are observed on the skin in the area that was under pressure. Other hemorrhagic manifestations include nasal or gingival bleeding, melena, hematemesis, and menorrhagia.

Neurologic manifestations such as seizures and encephalitis/encephalopathy have been reported in rare cases of dengue infection

Diagnosis:

- Leukopenia
- Thrombocytopenia (<100,000)
- Modest liver enzyme elevation (2-5x nml)
- Laboratory criteria for diagnosis
- One or more of the following
- Isolation of the dengue virus from serum, plasma, leukocytes, or autopsy samples
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titres to one or more dengue virus antigens in paired serum samples. Hemagglutination inhibition assay (HI) is gold standard. Paired acute and convalescent HI assay, positive if >4 fold titer rise;
- Demonstration of dengue virus antigen in autopsy tissue by immunohistochemistry or immunofluorescence or in serum samples by EIA
- Detection of viral genomic sequences in autopsy tissue, serum or CSF samples by polymerase chain reaction (PCR).

Differential Diagnosis: hepatitis, tick-borne diseases, rocky mountain spotted fever, malaria, yellow fever, meningitis, pediatrics bacteremia and sepsis, pediatrics meningitis and encephalitis.

Treatment. Treated DHF/DSS is associated with a 3% mortality rate. Untreated DHF/DSS is associated with a 50% mortality rate.

No specific antiviral medication is currently available to treat dengue. The treatment of dengue fever is symptomatic and supportive in nature. Bed rest and mild analgesic-antipyretic therapy are often helpful in relieving lethargy, malaise, and fever associated with the disease. Acetaminophen (paracetamol) is recommended for treatment of pain and fever. Aspirin, other salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided.

Patients with dengue hemorrhagic fever or dengue shock syndrome may require intravenous volume replacement. Plasma volume expanders can be used in patients who do not respond to isotonic fluids. Cases of DHF should be observed every hour. Serial platelet and haematocrit determinations, drop in plaelets and rise in haematocrits are essential for early diagnosis of DHF. Timely intravenous therapy – isotonic crystalloid solution – can prevent shock and/or lessen its severity. If the patient's condition becomes worse despite giving 20ml/kg/hr for one hour, replace crystalloid solution with colloid solution such as Dextran or plasma. As soon as improvement occurs replace with crystalloid. In case of shock, give oxygen. For correction of acidosis (sign: deep breathing), use sodium bicarbonate.

Treatment with corticosteroids is shown not to reduce mortality with severe dengue shock. 2 studies of 63 and 92 pediatric DHF shock pts treated with hydrocortisone 50mg/kg or methylprednisolone 30mg/kg in 1 dose vs placebo. Avoid giving steroids and antibiotics. They do not show any benefit. Insertion of nasogastric tube to determine concealed bleeding or to stop bleeding (by cold lavage) is not recommended since it is hazardous.

Prevention. Biological: Target larval stage of Aedes in large water storage containers; Larvivorous fish (Gambusia), endotoxin producing bacteria (Bacillus), copepod crustaceans (mesocyclops). Chemical: Insecticide treatment of water containers; Space spraying (thermal fogs).

HANTAVIRAL DISEASES

All hantaviruses are associated with a predominant (murid) rodent host in which they establish a chronic inapparent infection. These agents are presently divided into New World and Old World complexes, a scheme that also neatly segregates their rodent reservoirs and clinical presentations. Old World hantaviruses are etiologic agents linked to hemorrhagic fever with renal syndrome (HFRS), whereas New World hantaviruses cause a severe acute febrile illness characterized by noncardiogenic pulmonary edema and shock; this syndrome is referred to as hantavirus pulmonary syndrome (HPS). At least 23 hantaviruses are currently recognized, 20 of which have been linked to human disease. HFRS gained widespread attention as a serious and frequently fatal affliction of United Nations forces during the Korean War. However, syndromes of fever, hematologic abnormality, and renal dysfunction had actually been recognized as distinct clinical entities throughout the Far East, Scandinavia, and central Europe for many decades previously. In 1953, Gadjusek noted clinical and epidemiologic similarities among these geographically diverse disorders and proposed a common cause. The causative agent of HFRS in Korea, Hantaan virus, was identified by Lee and Lee in 1976 through demonstration of antigen in the lungs of infected reservoir rodents, the striped field mouse (Apodemus agrarius). In November 1993, a new hantavirus, associated with what is now known as HPS, was identified in deer mice (Peromyscus maniculatus) captured in the Four Corners area of the Southwest. This agent, Sin Nombre virus, was the first in a series of New World hantaviruses now known to be well established in various rat and mouse species throughout the Americas.

Epidemiology. The epidemiology of hantavirus infections is tightly linked to the ecology, population dynamics, and distribution of the various rodent reservoirs. Within endemic areas, circumscribed foci or microfoci of rodent infection and human disease are seen. Chronically infected animals shed large amounts of virus in saliva, urine, and feces. It is thought that humans become infected through contact with these contaminated secreta and excreta by inhalation of small-particle aerosols or contact of mucous membrane or nonintact skin with infectious materials. Human HFRS cases number in the tens

to thousands annually, depending on the infecting virus and the geographic setting. The burden of HPS has yet to be defined, although cases will likely number in the dozens to hundreds annually during most years throughout the Americas. With the exception of Seoul virus infections, HFRS is a rural disease. Hantaan virus circulates across eastern Russia, China, and the Korean peninsula, carried by the striped field mouse.

Pathogenesis. The portal of viral entry is the respiratory tract (by inhalation) or mucous membranes and nonintact skin (by direct contact or inoculation). Serum antibodies are generally present at clinical presentation, and the virus can be detected for up to 7 to 10 days after onset of illness from peripheral blood mononuclear cells (and possibly plasma). The renal, hematologic, and cardiovascular systems are most severely affected in HFRS. Pathologic changes in fatal cases of classic HFRS involve multiple organ systems, but a triad of lesions consisting of hemorrhagic necrosis of the renal medulla, anterior pituitary, and cardiac right atrium is characteristic. Hantaviruses display an in vivo predilection for endothelial cells and macrophages, and it is presumed that inflammatory mediators play a significant role in the vascular damage that underlies the pathologic changes observed clinically in HFRS and HPS. With endothelial compromise, capillaries and small blood vessels become grossly dilated; this leads to extravasation of fluid and, to a lesser extent, cellular elements, into surrounding tissues. Vascular dysregulation and release of soluble factors acting on hematologic and immunologic systems occur as well. The clinical features of classic HFRS, including flushing, facial edema, conjunctival effusion and injection, pulmonary edema, and petechiae, are manifestations of this generalized capillary and small vessel damage. The peculiar distribution of the triad lesions is poorly understood but probably reflects susceptibility of these organ sites to the volume shifts, pressure necrosis, and anoxia resulting from multisystem vascular insults. In HPS, cardiac function is depressed without obvious viral invasion of the myocardium, suggesting action by some soluble mediators. The perfusion deficit leading to hypotension appears to be localized because a multiorgan dysfunction syndrome is conspicuously absent. Such localized perfusion deficits may be based on viral target organ specificity and serve to explain, at least in part, the different hantaviral tropisms for HFRS (renal endothelium) and

HPS (pulmonary endothelium).

Clinical presentation. The clinical features in hemorrhagic fever with renal failure syndrome (HFRS) consist of a triad of fever, hemorrhage, and renal insufficiency. Other common symptoms during the initial phase of the illness include a headache, myalgia, abdominal and back pain, nausea, vomiting, and diarrhea. The disease may range from mild to severe. Subclinical infections are especially common in children.

The disease has 5 progressive stages: febrile, hypotensive, oliguric, diuretic, and convalescent. Physicians should be aware of the various presentations during each stage. Individual patients can completely skip stages.

Physical examination. Physical examination of the patient is based on the stage of the illness. The febrile stage occurs in all patients and lasts about 4-6 days. The disease is characterized by an abrupt onset of fever with a temperature in the range of 40°C. Patients may complain of a headache, chills, abdominal pain, and malaise. Flushing of the face, neck, and chest due to probable vascular dysregulation may be observed. Petechia may occur in the axilla and soft palate. Subconjunctival hemorrhage is noted in one-third of patients. Absolute bradycardia may be noted.

The hypotensive stage lasts approximately a few hours to 2 days. It occurs in 11% of patients and coincides with defervescence. Patients may have tachycardia, which may indicate impending shock. Patients may have acute abdomen caused by a paralytic ileus. Patients may have convulsions or purposeless movements.

The oliguric stage occurs in 65% of the patients and lasts about 3-6 days. Oliguria, hypertension, bleeding tendency (caused by uremia), and edema are characteristic of this stage. Patients may develop pulmonary edema. Thrombocytopenia usually resolves in the oliguric stage.

The diuretic stage lasts 2-3 weeks. Diuresis in the range of 3-6 L/d occurs after symptoms from the previous stage disappear. Responsiveness of the collecting duct to vasopressin is reduced. Rapid signs of dehydration and severe shock can occur during this stage if fluid replacement is inadequate. The patient's volume status should be closely monitored.

The convalescent stage may last for as long as 3-6 months. Clinical recovery usually begins in the middle of the second week, with a gradual resolution of symptoms and azotemia. The

concentrating capacity of the renal tubules recovers over many months.

Diagnosis.

- Enzyme-linked immunosorbent assay (ELISA) is useful in detecting antihantaviral-specific immunoglobulin M (IgM) early in the course of the illness.
- Antihantaviral immunoglobulin G (IgG) titers may be elevated for prolonged periods (as long as 10 y).
- Blood findings usually reveals clinically significant leukocytosis, an elevated or normal hematocrit level, and thrombocytopenia.
- Elevated levels of liver enzymes, and serum creatinine can be observed.
- Hyponatremia, hyperphosphatemia, and hyperkalemia may occur during the oliguric phase.
- Complement (C3) levels may be decreased; therefore, hemorrhagic fever with renal failure syndrome should be included in the differential diagnosis of hypocomplementemic acute nephritic syndrome.
- The coagulation profile can be altered with a prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), or bleeding time. levels of fibrin-degradation products may also be elevated.
- Urinalysis consistently shows hematuria and proteinuria. Proteinuria may last for few years after the attack.
- Increased levels of nitric oxide (NO) during the acute phase of the hemorrhagic fever with renal failure syndrome illness are correlated with disease activity.

Treatment. Treatment depends on the stage of the disease and on the patient's hydration status and hemodynamic condition. The most essential step in managing hemorrhagic fever with renal failure syndrome (HFRS) is maintaining the patient's circulatory and hemodynamic status.

During active illness, maintaining fluid and electrolyte balance is mandatory. Consider the use of diuretics, such as furosemide, when the patient has volume overload and oliguria. Dialysis is indicated if the patient has prolonged oliguria with no response to medical treatment and if renal failure is rapid deteriorating with worsening fluid and electrolyte abnormalities.

Prevention. The prevalence and ubiquity of reservoirs make rodent population control impractical in the field. However, measures to minimize infestations in domestic and peridomestic settings, coupled with general guidelines for avoidance of rodents and their excreta, should reduce exposure risk. Insecticides should be used simultaneously with rodent extermination techniques to control fleas, which may serve as vectors for other human pathogens (e.g., Yersinia pestis).

No vaccine has yet proved effective in preventing hantavirus infections in controlled clinical trials.

SANDFLAY FEVER (PHLEBOTOMUS FEBRIS)

Sandfly fever, also known as ‘three-day fever’ or ‘pappataci fever’ or ‘Phlebotomus fever’ is a viral infection that causes self-limited influenza-like symptoms and characterized by a rapid onset. The disease occurs commonly in endemic areas in summer months and especially in August during which sandflies are active.

Historical information. Disease was first described in 1799 by about U.Barnetgom. Malta ("Mediterranean fever"). In 1886 A. Peak disease was identified in independent nosological form and its relationship with the mosquitoes was proved in 1909 by R.Derrom, Christof Franzen, S.Taussigom who suggested the name Febris papatasii and established viral nature of the disease. In Russia, the first cases were described by V.D.Shreder (1913), E.I.Martsinovskiy (1917), N.I.Latyshev (1923), etc. The pathogen was isolated in 1944 by A.Seybin (Sicilian and Neapolitan viruses). Sh.D.Moshkovsky (1936), P.A.Petrischeva and A.Ya.Alymov (1939) discovered transovarial transmission of the virus in mosquitoes.

Etiology. Pathogens are viruses of kind phlebovirus, family Bunyaviridae related to environmental group Arboviruses, having helical symmetry type, size 90-110 nm. The virus contains single-stranded RNA.

Sicilian (typical), Naples and other viruses cause dog disease. The viruses are killed at a temperature of 56°C, at -70°C and stored up to 1 year. At a dry state they can exist for many years. Cultured in medium VERO this virus causes lethal infection in newborn mice.

Epidemiology. Dog disease is endemic transmissible virus prone

to epidemic spread. Sources of pathogens are sick people in the period of viremia and infected female mosquitoes Ph. papatassii, capable of transovarial transmission. Mosquitoes become infectious after 6-8 days after the blood-sucking on a sick person. The mechanism of infection is transmissible, but parenteral infection through poorly treated tools is possible.

Dog disease epidemic season coincides with the summer mosquitoes, lasting from May to October. In subtropical and tropical regions it often has a two-wave character.

Incidence is usually endemic, but among non-immune individuals outbreaks are possible. Susceptibility is general, the local population is usually infected in childhood which leads to development of homologous immunity, recurrent disease are rare.

Habitat disease coincides with the area of mosquitoes and includes countries located within 20-45 ° N. In our country, foci of infection were eliminated in the 40s, but sporadic cases of the disease rarely recorded.

Pathogenesis and post-mortem picture. On-site mosquito bite is often a painful inflammatory reaction of the skin in the form of itchy papules surrounded by a zone of hyperemia.

After inoculated virus replication in macrophage viremia developes, which determines the initial manifestation of the disease. Sandfly fever virus is fixed in CNS cells, autonomic sympathetic ganglia, causing cerebral dysfunction and hypertension. Fixation of the virus in the bone marrow results in leukopenia relative limfomonocytosis. Changes of internal organs have not been studied.

Clinical manifestation. The incubation period lasts 3-7 days. The disease develops suddenly: there is a fever, during the first-day body temperature reaches 39-40°C and remains elevated from 2 to 5 days. Patients complain of severe headache, arthralgia, myalgia is common, especially in the calf and lumbar muscles. The condition is characterized by pain in the eyeballs and superciliary region. Repeated vomiting in children and seizures can be observed.

On examination, the following symptoms are determined in patients: puffiness and redness of face, neck and upper chest, resembling sunburn. The disease is characterized by conjunctivitis, photophobia. Taussig syndrome (sharp pain when pressing the moving eyeballs or when trying to lift the eyelids) and Pick syndrome (limited injection of vessels on the sclera in the outer or inner corner

of the eye rarely a triangle top to the pupil) are considered to be pathognomonic.

Often hyperemia of throat, swollen uvula with punctate hemorrhages, herpes labialis are observed. On the exposed skin there can be papules at the site of the mosquito bite which disappear in 4-5 days. A number of patients on the 2-3rd day of the illness may appear macula popular or morbilliform rash, which disappear after normalization of body temperature.

During the first day of illness tachycardia, alternating with further bradycardia can be observed. Blood pressure is usually reduced. Tongue can be dry and covered with white cover. Size of the liver and spleen is not changed.

The disease is characterized by following neurological symptoms: severe headache, insomnia, dizziness, hypersensitivity, autonomic lability, sometimes, meningeal syndrome; in severe cases delirium, loss of consciousness may develop.

In haemogram there is marked leukopenia with relative lymphomonocytosis, aneozinofiliya, neutropenia with a predominance of young forms. ESR is not changed. Urinalysis reveals albuminuria.

Lumbar puncture reveals increased intracranial pressure, a slight increase in protein content and positive Pandey and Nonne-Apelt samples.

On the 3-4 th day of the disease temperature usually critically decreases. The state is accompanied by excessive sweating, improving the condition of patients, reduction of myalgia and headache.

Convalescence period lasts for 2-3 weeks and is characterized by severe fatigue, often mental depression, neuralgia and sweating. Sometimes temperature increase is possible and transient cerebral preservation hypertension and autonomic lability occurs.

Complications are extremely rare, they occur usually due to related infections. The lethal outcomes are extremely rare.

Diagnostics. It is based on an analysis of the complex epidemiological, clinical and laboratory data. Verification is achieved by isolation of the virus from the blood in the febrile period and by use of serological tests (HAI, DNC, RN) on the 5-6th day of illness.

Differential diagnosis is conducted with acute respiratory infections, malaria, tick-borne Lyme disease, typhus, leptospirosis.

Treatment. Patients are hospitalized. They undergo detoxication and symptomatic therapy. In cases of cerebral hypertension diuretics

are used.

Convalescents are dischared after 14-21 days on the 7-10th day of apyrexia.

Prevention is carried out by killing mosquitoes and protection from their attacks, the creation of active immunity via vaccination (according to epidemiological indications).

CHIKUNGUNYA

Chikungunya (in the Makonde language "that which bends up") virus (CHIKV) is an arthropod-borne virus, of the genus Alphavirus, that is transmitted to humans by virus-carrying Aedes mosquitoes. There have been recent breakouts of CHIKV associated with severe illness.

CHIKV infection causes an illness with a similar mode of transmission as dengue fever, with an acute febrile phase lasting two to five days, followed by a longer period of joint pains in the extremities. The pain associated with CHIKV infection of the joints may persist for weeks or months, or in some cases years. Prevention is via mosquito control and preventing bite by infected mosquitoes. There is no specific treatment with medications used to help with symptoms.

Epidemiology. Chikungunya virus is an alphavirus closely related to the o'nyong'nyong virus, the Ross River virus in Australia, and the viruses that cause eastern equine encephalitis and western equine encephalitis.

Three genotypes of this virus have been described: West African, East/Central/South African and Asian genotypes.

Chikungunya is generally spread through bites from Aedes aegypti mosquitoes, but recent research by the Pasteur Institute in Paris has suggested chikungunya virus strains in the 2005-2006 Reunion Island outbreak incurred a mutation that facilitated transmission by Asian tiger mosquito (Aedes albopictus). Concurrent studies by arbovirologists at the University of Texas Medical Branch in Galveston, Texas, confirmed definitively that enhanced chikungunya virus infection of A. albopictus was caused by a point mutation in one of the viral envelope genes (E1). Enhanced transmission of chikungunya virus by A. albopictus could mean an

increased risk for chikungunya outbreaks in other areas where the Asian tiger mosquito is present. A recent epidemic in Italy was likely perpetuated by A. albopictus. In Africa, chikungunya is spread via a sylvatic cycle in which the virus largely resides in other primates in between human 0outbreaks.

Chikungunya has been identified in nearly 40 countries in Asia, Africa, Europe and also in the Americas.

Transmission.The virus is transmitted from human to human by the bites of infected female mosquitoes. Most commonly, the mosquitoes involved are Aedes aegypti and Aedes albopictus, two species which can also transmit other mosquito-borne viruses, including dengue. These mosquitoes can be found biting throughout daylight hours, though there may be peaks of activity in the early morning and late afternoon. Both species are found biting outdoors, but Aedes aegypti will also readily feed indoors.

After the bite of an infected mosquito, onset of illness occurs usually between four and eight days but can range from two to 12 days.

Symptoms. Chikungunya is characterized by an abrupt onset of fever frequently accompanied by joint pain. Other common signs and symptoms include muscle pain, headache, nausea, fatigue and rash. The joint pain is often very debilitating, but usually lasts for a few days or may be prolonged to weeks.

Most patients recover fully, but in some cases joint pain may persist for several months, or even years. Occasional cases of eye, neurological and heart complications have been reported, as well as gastrointestinal complaints. Serious complications are not common, but in older people, the disease can contribute to the cause of death. Often symptoms in infected individuals are mild and the infection may go unrecognized, or be misdiagnosed in areas where dengue occurs.

Diagnosis. Several methods can be used for diagnosis. Serological tests, such as enzyme-linked immunosorbent assays (ELISA), may confirm the presence of IgM and IgG anti-chikungunya antibodies. IgM antibody levels are highest three to five weeks after the onset of illness and persist for about two months. Samples collected during the first week after the onset of symptoms should be tested by both serological and virological methods (RT-PCR).

The virus may be isolated from the blood during the first few days of infection. Various reverse transcriptase–polymerase chain reaction (RT-PCR) methods are available but are of variable

sensitivity. Some are suited to clinical diagnosis. RT-PCR products from clinical samples may also be used for genotyping of the virus, allowing comparisons with virus samples from various geographical sources.

Treatment. There is no specific antiviral drug treatment for Chikungunya. Treatment is directed primarily at relieving the symptoms, including the joint pain using anti-pyretics, optimal analgesics and fluids. There is no commercial chikungunya vaccine.

Prevention and control. The proximity of mosquito vector breeding sites to human habitation is a significant risk factor for chikungunya as well as for other diseases that these species transmit. Prevention and control relies heavily on reducing the number of natural and artificial water-filled container habitats that support breeding of the mosquitoes. This requires mobilization of affected communities. During outbreaks, insecticides may be sprayed to kill flying mosquitoes, applied to surfaces in and around containers where the mosquitoes land, and used to treat water in containers to kill the immature larvae.

For protection during outbreaks of chikungunya, clothing which minimizes skin exposure to the day-biting vectors is advised. Repellents can be applied to exposed skin or to clothing in strict accordance with product label instructions. Repellents should contain DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). For those who sleep during the daytime, particularly young children, or sick or older people, insecticide treated mosquito nets afford good protection. Mosquito coils or other insecticide vaporizers may also reduce indoor biting.

Basic precautions should be taken by people traveling to risk areas and these include use of repellents, wearing long sleeves and pants and ensuring rooms are fitted with screens to prevent mosquitoes from entering.

KYASANUR FOREST DISEASE

In 1957 T.H. Work and his colleagues isolated the causative agent of the disease from monkeys and sick people. Subsequent experimental studies have shown that the virus is fairly well

cultivated. It has been proven by their pathogenicity for mice and monkeys.

Synonyms: Kyasanur Forest disease in India; Fievre hemorragique de la foret de Kyasanur; Maladie de la foret de Kyasanur.

Kyasanur Forest Disease (BCL) is acute natural focal arboviral disease characterized by severe course with severe hemorrhagic syndrome.

First as an independent unit of clinical disease Kyasanur Forest has been found in the tropical forests of the western area of Mysore in southern India in 1957.

Etiology. Pathogen refers to the environmental group of arboviruses family togaviruses flavivirus genus (group B). Unlike other viruses of this group it is not associated with encephalitis and haemorrhagic fever. Virus is close to the agents of Omsk hemorrhagic fever, yellow fever and dengue. Virus genome is presented by RNA. Currently, the virus genome is being scrutinized. The major virion proteins of the genome are sequenced which results in recombinant vaccine development.

Epidemiology. Haemaphysalis spinigera ticks transmit infection to humans. At the moment it is assumed that the main role in the circulation of viruses in nature is played by mites H. spinigera, which do not attack humans, but feed on small mammals.

Haemaphysalis spinigera ticks in turn become infected in the larval and nymphal stages when feeding on small mammals, and the transition to the imaginal stage of development occurs mainly after attack of large mammals (cows, monkeys) and birds.

It should be noted that the discovery in 1957 set dead monkeys, was the first signal the emergence of previously unknown disease. Epizootic observed in monkeys Macaca radiata and Presbytis entellus, abundant living in this area. Among large animals these primate species play an important role in maintaining the circulation of the virus.

Pathogenesis. The pathogenesis is characterized by specific intoxication, vascular damage, leading to massive hemorrhage in the stomach, intestines, kidneys; hyperplasia of the reticuloendothelial system and degenerative changes in the liver and heart muscle. Pathophysiology of the main features is associated with impaired hematopoiesis and damage to capillaries. The disease is determined by

the specific localization of the pathological process. It is possible that the hemorrhagic syndrome is caused by disseminated intravascular coagulation of varying severity. Death usually occurs on the 2nd week of the disease, when the antibody titer increases and decreases the temperature of the patients. Death is usually preceded by coma, which is a consequence not of encephalitis and encephalopathy. Morphological changes occur due to necrosis of the central zone of the liver lobes and appear like acidophilic cytoplasmic inclusions resembling Kaunsilmena body with yellow fever.

Symptoms and flow. The incubation period is not more than 8 days. The disease begins suddenly with shaking chills. Body temperature rises to 39-40°C. Patients complain of a severe headache, expressed general weakness, muscle pain (especially in the lumbar region and shin muscles). Retroorbital pain, cough, and abdominal pain is observed. In addition, photophobia and polyarthralgia develop. The initial phase of the disease is characterized by a generalized hypersensitivity of the skin. At the same time apathy and prostration may be present.

On the 3-4 th day of illness the condition of patients worsens. Nausea, vomiting, diarrhea, visible redness of the mucous membranes, the injection of the conjunctival vessels and sclera are observed. On the mucosa of the soft palate there are papules vesicular elements of great diagnostic value. In the same period of the disease bleeding from the nose, gums, gastrointestinal tract (some patients can be observed bloody vomit) is recorded. Often there is hemoptysis. Hemorrhagic rash on the skin (purpura) is possible. Cervical and axillary lymph nodes are increased, generalized lymphadenopathy may develop.

On the 7-11 th day of illness the body temperature in the morning is somewhat reduced, sometimes it becomes normal, but increases again in the evening. In this phase of the disease bradycardia is marked. Slight and rough dry rales can be heard. In hemoptysis sonorous bubbling rales can be auscultated. The abdomen is soft, with deep palpation determining soreness. Sometimes hepatosplenomegaly is observed.

Laboratory studies show that during the first phase of the illness leukopenia with the decrease in total leukocyte count to 3h109/l on 4-6 th day is observed. Leukopenia can be combined with neutropenia, thrombocytopenia. In the urine there is a moderate amount of white blood cells, the cells of the renal epithelium. Cerebrospinal fluid is

normal. Afebrile after a period of 7-9th to 15 to 21 days 50% of patients developing the second phase of fever, persisting for 2-12 days. Besides returning fever, this phase is characterized by severe headaches, stiff neck, disorders of consciousness, coarse tremor, dizziness, abnormal reflexes, as well as the appearance of the symptoms typical of the first phase of the illness. For very severe forms of the disease body temperature rises to 40-41°C, the expressed hemorrhagic syndrome, dehydration and death can occur. Convalescence may be delayed up to 30-45 th day of illness.

Diagnosis and differential diagnosis. Diagnosis of the disease is based on data epidemiological anamnesis, clinical manifestations and laboratory findings (acute onset, severe headache, chills, pain in the lumbar region and in the extremities, mucous congestion, vascular injection of the sclera and conjunctiva, hemorrhagic syndrome, leukopenia, thrombocytopenia, etc.). Apply complement fixation and hemagglutination inhibition with paired sera. Virus isolation from blood should be applied, because viremia is stored for a long time.

The differential diagnosis should be performed with other hemorrhagic fevers, and, above all, with the closest on the etiology and clinical manifestations – Omsk hemorrhagic fever. At last haemorrhagic manifestations are often observed on the skin (20-25% of patients) and the mucous membranes of the oropharynx as petechial elements.

Treatment. No effective causal treatment. Apply pathogenetic and symptomatic treatment, similar treatment of other Central Asian hemorrhagic fevers.

Mortality is from 1 to 10%. In prolonged convalescence asthenia is marked. Persistent residual phenomena are usually not observed.

Prevention. Due to the fact that the main route of infection is a tick-transmissibility of great importance in the prevention of disease is the timely application of repellents (dimetilftolat, dibutilftolat, diethyl toluamide, etc.). To kill ticks acaricidal agents are used. Speculation about the possibility of alimentary tract and aspiration spread of the disease necessitate isolation of the patient and of the current and final disinfection. In the 90s developed highly effective vaccine against the disease, which has been successfully used in endemic areas of India.

JAPANESE ENCEPHALITIS

Japanese encephalitis (JE) virus is the leading cause of vaccine-preventable encephalitis in Asia and the western Pacific. For most travelers to Asia, the risk for JE is very low but varies based on destination, duration of travel, season, and activities. Humans can be infected when bitten by an infected mosquito. Most human infections are asymptomatic or result in only mild symptoms. However, a small percentage of infected persons develop inflammation of the brain (encephalitis), with symptoms including sudden onset of headache, high fever, disorientation, coma, tremors and convulsions. About 1 in 4 cases are fatal. There is no specific treatment for JE. Patient management focuses on supportive care and management of complications. Steps to prevent JE include using personal protective measures to prevent mosquito bites and vaccination.

Etiology. Japanese encephalitis (JE) virus, a flavivirus, is closely related to West Nile and St. Louis encephalitis viruses. JE virus is transmitted to humans through the bite of infected Culex species mosquitoes, particularly Culex tritaeniorhynchus.

Epidemiology. The virus is maintained in a cycle between mosquitoes and vertebrate hosts, primarily pigs and wading birds. Humans are incidental or dead-end hosts, because they usually do not develop high enough concentrations of JE virus in their bloodstreams to infect feeding mosquitoes.

JE virus transmission occurs primarily in rural agricultural areas, often associated with rice production and flooding irrigation. In some areas of Asia, these conditions can occur near urban centers.

In temperate areas of Asia, JE virus transmission is seasonal. Human disease usually peaks in the summer and fall. In the subtropics and tropics, transmission can occur year-round, often with a peak during the rainy season.

Symptoms. Less than 1% of people infected with Japanese encephalitis (JE) virus develop clinical illness.

In persons who develop symptoms, the incubation period (time from infection until illness) is typically 5-15 days.

Initial symptoms often include fever, headache, and vomiting.

Mental status changes, neurologic symptoms, weakness, and movement disorders might develop over the next few days.

Seizures are common, especially among children.

Treatment. No specific treatments have been found to benefit patients with JE, but hospitalization for supportive care and close observation is generally required.

Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve some symptoms.

Prevention. Inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (manufactured as IXIARO) is the only JE vaccine licensed and available in the United States. This vaccine was approved in March 2009 for use in people aged 17 years and older and in May 2013 for use in children 2 months through 16 years of age. Other JE vaccines are manufactured and used in other countries but are not licensed for use in the United States.

IXIARO is given as a two-dose series, with the doses spaced 28 days apart. The last dose should be given at least 1 week before travel. For persons aged 17 years and older, a booster dose may be given if a person has received the two-dose primary vaccination series one year or more previously and there is a continued risk for JE virus infection or potential for reexposure. Although studies are being conducted on the need for a booster dose for children, data are not yet available.

All travelers to Japanese encephalitis (JE) endemic areas should take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne infectious dis-eases. For some travelers who will be in a high-risk setting based on season, location, duration, and activities, JE vaccine can further reduce the risk for infection.

Avoid Mosquito Bites. Use Insect Repellent, use an EPA-registered insect repellent such as those containing DEET, IR3535, picaridin or oil of lemon eucalyptus. Even a short time outdoors can be long enough to get a mosquito bite. For more information about insect repellents, see Protection against Mosquitoes, Ticks, & Other Insects & Arthropods.

Wear Proper Clothing to Reduce Mosquito Bites. When weather permits, wear long-sleeves, long pants and socks when outdoors. Mosquitoes may bite through thin clothing, so treating clothes with repellent containing permethrin or another EPA-registered repellent will give extra protection. Don't apply repellents containing permethrin directly to skin.

Reduce Exposure to Mosquitoes During Peak Biting Hours. The mosquitoes that transmit JE virus feed mainly outside during the

cooler hours from dusk to dawn. Travelers to high risk areas should consider minimizing outdoor activities at these times if possible. To reduce the risk of JE and other vector-borne diseases, travelers should stay in air-conditioned or well-screened rooms, or use a bed net and aerosol room insecticides.

Obtain Vaccine if Recommended.

JE vaccine is recommended for travelers who plan to spend 1 month or more in endemic areas during the JE virus transmission season. This includes long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JE virus transmission.

Vaccine should also be considered for the following:

– Short-term (less than 1 month) travelers to endemic areas during the transmission season, if they plan to travel outside an urban area and their activities will increase the risk of JE virus exposure. Examples of higher-risk activities or itineraries include: 1) spending substantial time outdoors in rural or agricultural areas, especially during the evening or night; 2) participating in extensive outdoor activities (such as camping, hiking, trekking, biking, fishing, hunting, or farming); and 3) staying in accommodations without air conditioning, screens, or bed nets.

– Travelers to an area with an ongoing JE outbreak.

– Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel.

MONKEYPOX

Monkeypox is an exotic infectious disease caused by the monkeypox virus. The disease was first identified in laboratory monkeys, hence its name, but in its natural state it seems to infect rodents more often than primates. The disease is indigenous to Central and West Africa. An outbreak that occurred in the United States in 2003 was traced to a pet store where imported Gambian pouched rats were sold.

Etiology and epidemiology. Monkeypox virus is a zoonotic viral disease that occurs primarily in remote villages of Central and West Africa in proximity to tropical rainforests where there is more frequent

contact with infected animals. Monkeypox is usually transmitted to humans from rodents, pets, and primates through contact with the animal's blood or through a bite. Human monkeypox can be difficult to distinguish clinically from smallpox (to which it is closely related) and chickenpox (to which it is not).

Monkeypox virus causes the disease in both humans and animals. It was first identified in 1958 as a pathogen of crab-eating macaque monkeys (Macaca fascicularis) being used as laboratory animals. The crab-eating macaque is often used for neurological experiments. Monkeypox virus is an Orthopoxvirus, a genus of the family Poxviridae that contains other viral species that target mammals. The virus is mainly found in tropical rainforest regions of central and West Africa.

The virus was first discovered in monkeys (hence the name) in 1958, and in humans in 1970. Between 1970 and 1986, over 400 cases in humans were reported. Small viral outbreaks with a death rate in the range of 10% and a secondary human to human infection rate of about the same amount occur routinely in equatorial Central and West Africa. The primary route of infection is thought to be contact with the infected animals or their bodily fluids. The first reported outbreak in the United States occurred in 2003 in the midwestern states of Illinois, Indiana, and Wisconsin, with one occurrence in New Jersey. The outbreak was traced to a prairie dogs infected from an imported Gambian pouch rat. No deaths occurred.

The virus can spread both from animal to human and from human to human. Infection from animal to human can occur via an animal bite or by direct contact with an infected animal’s bodily fluids. The virus can spread from human to human by both respiratory (airborne) contact and contact with infected person's bodily fluids. Incubation period is 10-14 days. Prodromal symptoms include swelling of lymph nodes, muscle pain, headache, fever, prior to the emergence of the rash.

In addition to monkeys, reservoirs for the virus are found in Gambian pouched rats (Cricetomys gambianus), dormice (Graphiurus sp.) and African squirrels (Heliosciurus, and Funisciurus). The use of these animals as food may be an important source of transmission to humans.

Monkeypox as a disease in humans was first associated with an illness in the Democratic Republic of the Congo (formerly Zaire), in

the town of Basankusu, Équateur Province, in 1970. A second outbreak of human illness was identified in DRC/Zaire in 1996-1997. In 2003, a small outbreak of human monkeypox in the United States occurred among owners of pet prairie dogs. The outbreak originated from Villa Park, Illinois, outside of Chicago, when an exotic animal dealer kept young prairie dogs in close proximity to an infected Gambian pouched rat (Cricetomys gambianus) recently imported from Accra, Ghana. Seventy-one people were reportedly infected, of which there were no fatalities.

A second African focus of infection has been discovered in Sudan. No infected patients died.

Symptoms. In humans, monkeypox is similar to smallpox, although it is often milder. Vaccination against smallpox is assumed to provide protection against human monkeypox infection considering they are closely related viruses and the vaccine protects animals from experimental lethal monkeypox challenge. This has not been conclusively demonstrated in humans because routine smallpox vaccination was discontinued following the apparent eradication of smallpox and due to safety concerns with the vaccine. Limited person-to-person spread of infection has been reported in disease-endemic areas in Africa. Case-fatality ratios in Africa have ranged from 1% to 10%.

Prevention and treatment. Currently, there is no proven, safe treatment for monkeypox. Smallpox vaccine has been reported to reduce the risk of monkeypox among previously vaccinated persons in Africa. The United States Centers for Disease Control and Prevention (CDC) recommends that persons investigating monkeypox outbreaks and involved in caring for infected individuals or animals should receive a smallpox vaccination to protect against monkeypox. Persons who have had close or intimate contact with individuals or animals confirmed to have monkeypox should also be vaccinated. The people who have been infected can be vaccinated up to 14 days after exposure. CDC does not recommend preexposure vaccination for unexposed veterinarians, veterinary staff, or animal control officers, unless such persons are involved in field investigations.

HIV-INFECTION

The first reports of homosexual patients suffering from previously rare diseases such as pneumocystis pneumonia and Kaposi.s sarcoma were published in May 1981 (Centers for Disease Control 1981). However, it took almost two years until, in 1983, the human immunodeficiency virus type I (HIV-1) was defined as the primary cause of the acquired immunodeficiency syndrome (Barre-Sinoussi 1983, Broder 1984, Gallo 1984).

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and partners launched the 90–90–90 targets; the aim was to diagnose 90% of all HIV-positive persons, provide antiretroviral therapy (ART) for 90% of those diagnosed, and achieve viral suppression for 90% of those treated by 2020. This is estimated to result in 73% of people with HIV achieving viral suppression, a crucial step in ending the AIDS epidemic by 2030.2 However, 36.9 million people are living with HIV today and about 2.1 million new infections were recorded in 2015. This high rate of new infections continues to fuel the epidemic. Reports from national HIV programmes suggest that the 90–90–90 targets agenda for 2020 risks are unrealistic.

Viral Structure and Cycle of replication. HIV-1 and HIV-2 may be distinguishable from each other by the degree of condensation of the nucleocapsid, particularly as it separates from the envelope. There are 3 HIV-1 genotypes; M (Main), O (Outlayer), and N (New). M group comprises a large number of subtypes and recombinant forms. Subtypes are A, A2, B, C, D, F1, F2, G, H, J and K, recombinant forms are AE, AG, AB, DF, BC, CD. O and N group subtype are not clearly defined, especially since there are so few N group isolates. However, certain subgroups may be difficult to detect by certain commercial assays.

The HIVs are spherical viruses of approximately 100 nm in diameter. The core or nucleocapsid is condensed into a cylindrical, trapezoidal, or triangular shape instead of the spherical shape as for the HTLVs. Gag proteins compile the conical core of the mature HIV virion. MA protein lies underneath the lipid membrane and makes contact with it via the amino-terminal myristylated and positively charged segment. CA protein forms the capsid, the outer layer of the core. The complex of NC protein and viral RNA is in the center of the

core. RT and IN molecules are associated with this complex by binding to the nucleic acid. Some host-cell proteins, such as MHC class I proteins, may be incorporated in the viral membrane.

The HIV has a sophisticated replication cycle, involving at least nine functional genes with identified products. The rate of replication may vary in different cell types.

The HIV envelope glycoprotein, Env, binds to CD4 and a coreceptor, which is a member of the chemokine receptor family (attachment of viral particle).

Fusion of the viral and cell membrane results in the entry of a viral core carrying the HIV genome into the cytoplasm (entry or penetration).

Reverse transcription follows the entry, and the resulting proviral DNA is transported to the nucleus, where it integrates into the host genome.

Transcription and splicing of the various messages occur in the nucleus, using the integrated chromosomal provirus as template.

Both genomic and nongenomic forms of RNA are transported to the cytoplasm, where translation occurs.

Viral genomes and newly produced structural proteins are transported to assembly sites at the cytoplasmic membrane, where morphogenesis and budding of progeny virus occur.

HIV coreceptors. CD4 attaches to the T cell receptor complex (TCR) on CD4+ T-cells and binds to HLA class II molecules on antigen-presenting cells. Despite this broad spectrum of potentially available coreceptors, CCR5 and CXCR4 seem to represent the most relevant coreceptors for HIV-1 in vivo (fig. 1).

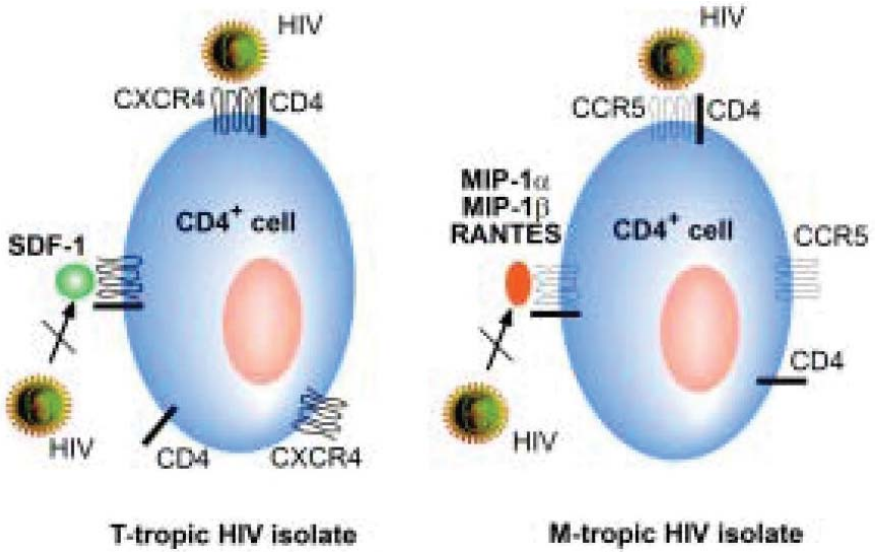

Fig. 1. – HIV co-reseptors

The importance of CCR5 as the predominant coreceptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (Liu 1996). In vitro experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically have a 32 base pair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5.

Epidemiology. This is not the place for a detailed description of the epidemiological situation of the HIV pandemic. The prevalence and incidence of HIV/AIDS vary considerably from continent to continent, from country to country, from region to region. Several countries in sub-Saharan Africa report infection rates of 30%, especially in urban areas. In other countries, HIV prevalence still remains low. However, low national prevalence rates can be misleading. They often disguise serious epidemics that are initially concentrated in certain localities or among specific population groups and that threaten to spill over into the wider population. The joint United Nations program on HIV/AIDS (UNAIDS) provides by far the best and most comprehensive overview. The annual AIDS epidemic update of UNAIDS reports on the latest developments in the global HIV/AIDS epidemic. With maps and regional summaries, it provides the most recent estimates of the epidemic.s scope and explores new trends in the epidemic.s evolution. It can be found at the Website.

Transmission routes. There are several ways in which someone can become infected with HIV. These transmission routes are well defined. HIV infection can be transmitted through:

• unprotected sexual intercourse with an infected partner;

• injection or transfusion of contaminated blood or blood products (infection through artificial insemination, skin grafts and organ transplants is also possible);

• sharing unsterilized injection equipment that has been previously used by someone who is infected;

• maternofetal transmission (during pregnancy, at birth, and through breastfeeding).

Natural history. The natural history described in the following refers to HIV infection in the absence of HAART.

The acute viral syndrome of primary HIV infection (which is defined as the time period from initial infection with HIV to the development of an antibody response) shows symptoms that often resemble those of mononucleosis. These appear within days to weeks following exposure to HIV (see Chapter .Acute HIV-1 Infection.).

However, clinical signs and symptoms may not occur in all patients. During acute HIV infection, there is usually a high plasma viremia and frequently a marked decrease in CD4+ T-cells. The CD4+ T-cell count later increases again, normally to levels inferior to the pre-infection values (see Fig. 2).

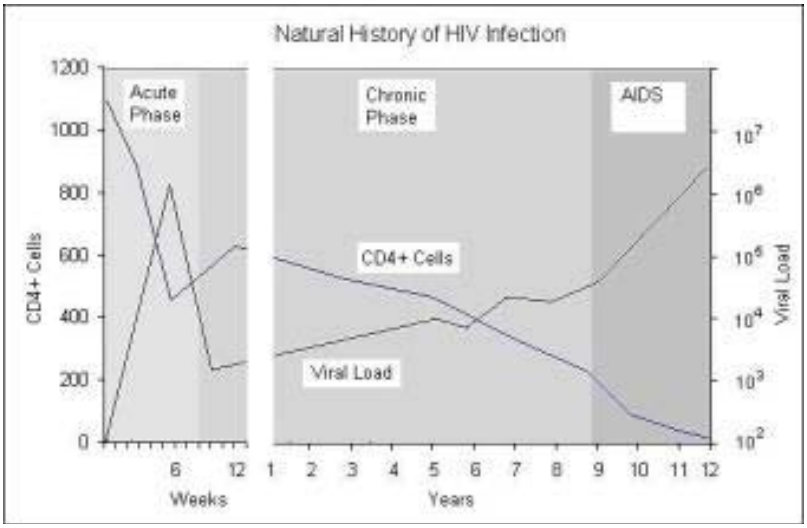

Fig. 2. – CD4+ T-cell count and viral load during HIV infection

After the acute infection, equilibrium between viral replication and the host immune response is usually reached, and many infected individuals may have no clinical manifestations of HIV infection for years. Even in the absence of antiretroviral treatment, this period of clinical latency may last 8-10 years or more. However, the term “latency period” may be misleading, given the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T-cells.

At the end of the .latency period, a number of symptoms or illnesses may appear which do not fulfill the definition of AIDS. These include slight immunological,dermatological, hematological and neurological signs. Many of them are listed in the Category B of the CDC classification system. Constitutional symptoms, such as fever, weight loss, night sweats, and diarrhea may also develop. In this situation, the level of 200 CD4+ T-cells/µl is an important cut-off,

below which the risk of many AIDS-defining illnesses increases, among them several opportunistic infections (OI) and certain neoplasms. Above 200 CD4+ Tcells/µl, most AIDS-defining illnesses are rare events.

However, the course of infection may vary dramatically, and in some cases, the progression to AIDS occurs rapidly. Host factors mainly determine whether or not an HIV-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5% of all infected patients (for details, see. Pathogenesis of HIV-1 Infection.).

Examples of OI: protozoal – pneumocystis carinii (now thought to be a fungi), toxoplasmosis, crytosporidosis. Fungal – candidiasis, crytococcosis, histoplasmosis, coccidiodomycosis. Bacterial – Mycobacterium avium complex, MTB, atypical mycobacterial disease; salmonella septicaemia, multiple or recurrent pyogenic bacterial infection. Viral – CMV, HSV, VZV, JCV.

Examples of AIDS-defining neoplasms: the most frequent opportunistic tumour, Kaposi's sarcoma, is observed in 20% of patients with AIDS. KS is observed mostly in homosexuals and its relative incidence is declining. It is now associated with a human herpes virus 8 (HHV-8). Malignant lymphomas are also frequently seen in AIDS patients.

CDC classification system. The most widely accepted classification system of HIV infection, initially published by the U.S. Centers for Disease Control and Prevention (CDC) in 1986, is based on certain conditions associated with HIV infection. This classification system was intended for use in conducting public health surveillance and it has been a useful epidemiological tool for many years. In 1993, the CDC classification was revised (CDC 1993). Since then, the clinical definition of AIDS has been expanded in the USA (not in Europe) to include HIV-infected patients with a CD4+ T-cell count of less than 200 cells/µl or less than 14% of all lymphocytes, even in the absence of the listed conditions.

Thus, the current CDC classification categorizes persons on the basis of clinical conditions and CD4+ T-lymphocyte counts. There are three clinical categories (A, B, C. see Table 10) and three CD4+ T-lymphocyte categories (1, 2, 3, see Table 10). For example, a patient with oropharyngeal candidiasis and a CD4+ T-cell count of

250/µl would be classified as B2; someone with asymptomatic infection and a CD4+ T-cell count of 550/µl would be in category A1. Categorization of the CD4+ T-cells should be based on the lowest accurate CD4+ T-cell count (CD4 nadir.) and not on the most recent one. For children less than 13 years of age, there is a modified and revised classification system for HIV infection. It should also be noted that, besides the CDC classification, the World Health Organization

(WHO) has also published a staging system for HIV infection. The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

Table 1. – CDC classification system

CD4 cell category	***Clinical categories***		
	A	***B***	***C***
>500/mm^3	A1	B1	C1
200-499/mm^3	A2	B2	C2
<200/mm^3	A3	B3	C3

Clinical categories of the CDC classification system in HIV-infected persons

Category A

Asymptomatic HIV infection; acute (primary) HIV infection with accompanying illness or history of acute HIV infection; persistent generalized lymphadenopathy.

Category B

Symptomatic conditions* that are not included among conditions listed in clinical. Examples include, but are not limited to:

bacillary angiomatosis; candidiasis, oropharyngeal (thrush), candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy; cervical dysplasia (moderate or severe)/cervical carcinoma in situ; constitutional symptoms, such as fever (38,5°C) or diarrhea lasting longer than 1 month; hairy leukoplakia, oral Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome; idiopathic thrombocytopenic purpura; listeriosis; pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess; peripheral neuropathy.

Category C - AIDS-defining illnesses

Candidiasis of bronchi, trachea, or lungs; candidiasis,

esophageal; cervical cancer, invasive; coccidioidomycosis, disseminated or extrapulmonary; cryptococcosis, extrapulmonary; cryptosporidiosis, chronic intestinal (greater than 1 month's duration); cytomegalovirus disease (other than liver, spleen, or nodes); cytomegalovirus retinitis (with loss of vision); encephalopathy, HIV-related; Herpes simplex: chronic ulcer(s) (greater than 1 month's duration) or bronchitis, pneumonitis, or esophagitis; histoplasmosis, disseminated or extrapulmonary; isosporiasis, chronic intestinal (greater than 1 month's duration); Kaposi's sarcoma; lymphoma, Burkitt's (or equivalent term); lymphoma, immunoblastic (or equivalent); lymphoma, primary, of brain; mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary; mycobacterium tuberculosis, any site (pulmonary or extrapulmonary); mycobacterium, other species or unidentified species, disseminated or extrapulmonary; pneumocystis pneumonia; pneumonia, recurrent; progressive multifocal leukoencephalopathy; salmonella septicemia, recurrent; toxoplasmosis of brain; wasting syndrome due to HIV.

Once a Category C condition has occurred, the person will remain in Category C.

WHO Disease Staging System for HIV Infection and Disease

In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1. An update took place in 2005, 2012. Most of these conditions are opportunistic infections that are easily treatable in healthy people.

Stage I: HIV infection is asymptomatic and not categorized as AIDS

Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections

Stage III: includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis

Stage IV: includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma; these diseases are indicators of AIDS.

Table 2. – Comparison Between AIDS and HIV

Parameter	***HIV***	***AIDS***
Definition	HIV is a virus, harming the body's immune system by attacking helper T cells or CD4 cells	Most advance stage of HIV disease. A CD4 count of fewer than 200 cells/mm^3 is one of the qualifications for a diagnosis of AIDS. It occurs when weakened immune system of the patient, due to Human Immunodeficiency Virus , developes one or more opportunistic infections
Spread of infection	HIV can be spread through various ways; most notable being sexual intercourse, the exchange of certain body fluids (blood, pre-ejaculate, semen, vaginal secretions, and breast milk)	Only patients with HIV can develop AIDS
Treatment	ART can slow the progression from HIV to AIDS, and increase survival. Some researches have claimed to cure the disease, while others have a different opinion	ART has only proved to be palliative rather being curative

HIV virus can cause AIDS. However not everyone who is infected with HIV develops AIDS. HIV infected patients can live for years without developing AIDS symptoms.

HIV diagnosis. The diagnosis of an HIV infection is normally made indirectly, i.e. through the demonstration of virus-specific antibodies (Gurtler 1996). These are found in virtually 100% of those infected with HIV and constitute a marker of a humoral immune response against the agent. A direct diagnosis of HIV infection is also possible: either through the demonstration of infectious virus (using cell culture, this is only possible in laboratories of at least biological safety level 3), of viral antigens (p24 antigen ELISA) or of viral nucleic acid (i.e. viral genome); the latter is also termed nucleic acid testing (NAT). Viral genome detection is nowadays most often used, as it does not require a high security laboratory, is more sensitive than antigen detection and allows quantification. Quantitative viral genome assays have gained great importance: The determination of the so-called "viral load", i.e. the concentration of viral RNA in plasma, has become an indispensable tool for guiding antiretroviral therapy.

HIV antibody diagnosis.

Testing for HIV antibodies invariably necessitates the availability of at least two different assays:

1. A screening test (ELISA)
2. At least one confirmatory test (Western Blot).

It is important to note that two different specimens from the same patient should be tested before the diagnosis is confirmed.

If the result of such a screening test is positive, this has to be confirmed by at least one confirmatory assay.

Rapid/simple test devices

Nowadays, a number of rapid HIV tests are available; these are also referred to as "point-of-care", "bedside" tests or "rapid/simple test devices". These tests are based on one of four immunodiagnostic principles: particle agglutination, immunodot (dipstick), immunofiltration or immune chromatography (Giles 1999, Branson 2000). Currently six rapid tests are available in the US: OraQuick® Rapid HIV-1/2 Antibody Test; Reveal™ Rapid HIV-1 Antibody Test; Uni-Gold Recombigen® HIV Test; Multispot HIV-1/HIV-2 Rapid Test; HIV 1/2 Stat Pak; Sure Check HIV 1/2 Assay. All are interpreted visually.

Any HIV test which can be performed by laypersons always carries the potential of misuse (such as compulsory testing of prisoners, etc.).

When to test?

After an infection, it normally takes between three to twelve weeks before the antibodies produced through the immune response of the infected individual become detectable. An HIV test should therefore not be performed too early after a potential risk contact, even though, understandably, concerned patients may be anxious and press for it. It is important, however, after an occupational exposure, e.g. a needlestick injury, to test immediately in order to confirm initial seronegativity in the person exposed to HIV! In around 5% of newly infected individuals it will take more than two months until antibodies are formed. Another test may therefore be indicated later on.

Problem: The "diagnostic window".One important problem of HIV antibody testing is the so-called "diagnostic window". This is the time period that elapses between the time of acquisition of HIV infection until detectable levels of antibodies are present (Busch 1997). The switch from antibody-negative to antibody-positive is called "seroconversion". The screening tests currently used are able to recognize an HIV infection six weeks after primary infection in about 80% and after the 12th week in almost 100% of cases; only in very rare cases is an infection recognized after just three or even six months.

Fourth generation screening assays attempt to shorten the duration of the "diagnostic window" by detecting HIV antibodies and HIV p24 antigen simultaneously.

Special case: Babies born to HIV-infected mothers

Fortunately, the risk of mother-to-child transmission of HIV (MTCT) has been extremely reduced in industrialized countries and may be as low as 1%. Nevertheless, HIV diagnosis is essential in all exposed newborns!

In babies born to HIV-infected mothers, HIV antibodies are normally detectable up to around 12 to 15 months of age, and rarely beyond 18 months. These are passively acquired maternal antibodies transferred transplacentally into the unborn child from around the 30th week of pregnancy onwards. These maternal IgG antibodies confer some physiological immune protection against many infections but in the case of HIV are without protective efficacy. This means, however, that most children of HIV-positive mothers, including those not themselves infected (the majority in any setting), will initially have positive HIV antibody test results, albeit with decreasing reactivities over time, until they become negative after complete elimination of maternal antibodies. The laboratory may be able to indicate that the degree of reactivity is decreasing, but confirmation should still take place at a later date, as this is NOT diagnostic.

If HIV antibodies persist in a vertically exposed child beyond the age of 15 months, the child is usually HIV-infected.

Today, PCR allows a more rapid diagnosis. HIV infection of the child should be diagnosed or, hopefully, excluded directly through detection of the virus. So far it is unclear whether the detection of proviral (intracellular) HIV cDNA (from leucocytes) or of (extracellular) HIV RNA (from blood plasma) is more sensitive.

Tests for monitoring disease progression and response to therapy.

CD4+ T lymphocyte count. The CD4+ T lymphocyte count should be tested after diagnosis of HIV infection. If HAART is not yet indicated, the CD4+ T lymphocyte count should be repeated every 3-6 months. Once on treatment, the CD4+ T lymphocyte count should be monitored every 6 months.

A patient requiring HAART should be managed by a medical practitioner with experience in the care of patients with HIV.

The HIV-1 viral load.

- This test serves a number of purposes:

• It determines the viral setpoint and acts as a long-term predictor of prognosis.

• It acts as a guide for deciding when to initiate HAART. Certain guidelines recommend starting treatment if the viral load is greater than 100 000 copies/ml, unless the patient has been recently infected and has not yet reached a viral setpoint.

• It is a measure of viral response to therapy. An acceptable response to therapy is considered to be:

• It is an indicator of the development of viral resistance to therapy:

- Primary failure of therapy is indicated by a viral load that does not decrease as expected after initiation of HAART.
- Secondary failure of therapy refers to an increase in the viral load of 1 log or greater on two separate specimens at least two weeks apart after an initial adequate response to HAART.

It must be noted that the HIV-1 viral load should not be used for the diagnosis of HIV-1 infection.

Anti-Retroviral Susceptibility Testing. It is now generally accepted that anti-viral susceptibility testing should be a routine part of the management of HIV-infected patients. It is reported that the outcome would be better if the results are interpreted by an expert in this area.

There are two types of antiviral susceptibility assays:

Phenotypic – very difficult and expensive to carry out. Thought to give a better idea of the actual situation in vivo.

Genotypic – the RT and Protease genes are sequenced. This can be done in-house and the results interpreted automatically by the HIV sequence database in the US.

Antiretroviral therapy in people Living with HIV

Antiretroviral therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection.

ART is also recommended for individuals with HIV to prevent HIV transmission.

When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible. Thus, once initiated, ART should be continued, with the following key treatment goals:

• Maximally and durably suppress plasma HIV RNA;

• Restore and preserve immunologic function;

• Reduce HIV-associated morbidity and prolong the duration and quality of survival; and

• Prevent HIV transmission.

Sixe classes of drugs are currently available:

• ***Nucleoside and nucleotide analogs (NRTIs or .nukes.):*** Zidovudine (AZT, ZDV, Retrovir), Didanosine (ddI, Videx, Videx EC), Stavudine (d4T, Zerit), Lamivudine (3TC, Epivir), Abacavir (ABC, Ziagen), Combivir (AZT/3TC), Trizivir (AZT/3TC/ABC), Tenofovir (TDF, Viread), Emtricitabine (FTC, Emtriva), Epzicom (ABC/3TC), Truvada (FTC/TDF)

• ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs)***: Nevirapine (NVP, Viramune), Delavirdine (DLV, Rescriptor), Efavirenz (EFV, Sustiva)

• ***Protease inhibitors (PIs)***: Amprenavir (APV, Agenerase), Lopinavir/ritonavir (KAL, Kaletra®), Atazanavir (ATV, Reyataz®), Fosamprenavir (fos-APV, Lexiva®), Tipranavir (TPV, Aptivus®), Darunavir (DRV, Prezista®)

• ***Fusion inhibitor:*** Enfuvirtide (Fuzeon®)

• ***Integrase inhibitor*** – Raltegravir

• ***CCR5 inhibitors*** – Maraviroc (SelzentryTM).

Mechanism of action and efficacy. Nucleoside analogs (nukes.) are also referred to as nucleoside reverse transcriptase inhibitors. Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates, they compete with physiological nucleosides, differing from them only by a minor modification in the ribose molecule. The incorporation of nucleoside analogs induces the abortion of DNA synthesis, as phosphodiester bridges can no longer be built to stabilize the double strand.

NNRTIs bind directly and noncompetitively to the enzyme at a position in close proximity to the substrate binding site for nucleosides. The resulting complex blocks the catalyst activated binding site of the reverse transcriptase. This, in turn, can bind fewer nucleosides, slowing polymerization down significantly.

Protease inhibitors (PIs). If the protease is inhibited and proteolytic splicing prevented, non-infectious virus particles will result. Since 1995, protease inhibitors have revolutionized the treatment of HIV infection.

Although PIs have been criticized at times due to their frequently high pill burden and side effects, they remain an essential component of HAAR.

Fusion inhibitor inhibits entry of HIV into the CD4 cell. T-20 binds to glycoprotein gp41 (a protein on the viral membrane). This binding prevents a change in the shape of the membrane protein and prevents fusion of the virus and the CD4 cell membrane.

Maraviroc binds to the CCR5 receptor on the membrane of human cells such as CD4 cells. This binding prevents the interaction of HIV-1 gp120 and human CCR5 which is necessary for entry into the cell. Maraviroc does not prevent HIV-1 entry into CXCR4-tropic or dual-tropic cells.

Adherence as a goal of therapy

Adherence is the Achilles heel of antiretroviral therapy. There is no question that HAART has to be taken regularly. All or nothing: with regard to resistance, it is still better not to take any drugs at all. Taking more than 90% or less than 69% of drugs were both associated with a lower risk for resistance (Sethi 2003). Compliance is defined as consent and acceptance of a treatment regimen by the patient. In the mid-90s a newer, more politically correct term was adopted – adherence. This term describes both clinician and patient working together to achieve a treatment concept acceptable for both, and emphasizes, that not only the patient may be responsible for treatment failure. Adherence includes all factors that influence staying on a regimen, in terms of .acceptability

Whichever term is used, three facts remain:

1. If only 5% of pills are not taken, treatment success is put at risk.
2. Clinicians usually overestimate the compliance of their patients.
3. The more complex the therapy, the worse the compliance.

Risk patients for noncompliance include individuals with substance or alcohol abuse or those experiencing side effects. Many studies have, however, also identified patients with depression, living alone, or of a younger age, as being particularly at risk (Murri 2001, Frank 2002, Glass 2006). Positive factors are physician experience, confidence of the patient in the positive effects of HAART, and social support. Race, sex or stage of disease does not seem to be relevant.

Prevention. Contracting HIV increases with the number of sexual partners. A change in the lifestyle would obviously reduce the risk.

The spread of HIV through blood transfusion and blood products had virtually been eliminated since the introduction of blood donor screening in many countries.

AZT had been shown to be effective in preventing transmission of HIV from the mother to the fetus. The incidence of HIV infection in the baby was reduced by two-thirds. The management of health care workers exposed to HIV through inoculation accidents is controversial. Anti-viral prophylaxis had been shown to be of some benefit but it is uncertain what is the optimal regimen.

Vaccines are being developed at present but progress is hampered by the high variability of HIV. Since 1987, more than 30 HIV candidate vaccines have been tested in approximately 60 Phase I/II trails, involving more than 10,000 healthy volunteers. A phase III trial involving a recombinant gp120 of HIV subtype B was reported in Feb 2005 to be ineffective in preventing HIV infection.

THE DAMAGE OF THE VARIOUS ORGANS AND SYSTEMS IN HIV-INFECTED PATIENTS

Diseases of the heart and lungs

Dilated cardiomyopathy:Caused by side effect of AZT, HIV infection infarction, lack of L-carnitine, and selenium; effects of cytokines, an autoimmune origin.before the era of HAART – in 6-7% of patients after the introduction of HAART has decreased frequency of 7 times.

Pulmonary hypertension: may be – a genetic predisposition.The frequency of 0,5%, HAART does not affect the decrease in frequency.
Infective endocarditis of tricuspid valve: Endocarditis should be excluded from the IDU at a fever that occurred for no apparent reason. IDU in HIV-positive rate is 4 times higher.

Diseases of the skin

Bacillary angiomatosis: caused by Bartonella quintana or B.Henselae. When the number of CD4 lymphocytes <50 mkl-1.

Cryptococcosis: caused by Cryptococcus neoformans. When the number of CD4 lymphocytes <100 ml-1. All patients with clinical symptoms of cryptococcal infection should include an analysis of CSF.

Athlete (dermatomycosis): tinea feet, smooth skin, groin, onychomycosis: caused by Tinea rubrum, T. mentagrophytes, M. canis,

E. floccosum, T. tonsurans, T.verrucosum, T. soudanense, M. Furtur.

Drug rash: caused by antimicrobial drugs: sulfonamides, beta-lactam antibiotics, anticonvulsants, NNRTIs, and darunavir fosamprenovira composed of molecules that include sulfocomponent.

Folliculitis: caused by bacterial folliculitis (Staphylococcus aureus), yeasts and mites, parasites in the follicles. It occurs in 18% of cases of skin diseases in HIV-infected patients.

Abrasions: caused by Staphylococcus aureus. In the IDU may be associated with the introduction of drugs.

Infection with HSV: caused by HSV. Antibodies to HSV-1 or HSV-2 are found in 95% of HIV-infected patients.

Shingles: caused by Herpes Zoster. Pozhiloy age, late-stage HIV infection. The risk of HZ in HIV-infected lymphocytes with any number of CD 4 in 15-25 times higher compared to the risk for the population as a whole. HAART has minimal effect on morbidity.

Nodular prurigo: caused by insect bites. When the number of CD4 lymphocytes <200 ml-1. It occurs in 6% of cases of skin diseases in HIV-infected patients.

Scabies: caused by scabies (cortical or Norwegian scabies) – a severe form of scabies occurs in immunosuppressed individuals, including AIDS.

Seborrheic: caused by yeast fungus. It occurs in 11% of cases.

Dermatitis: caused by Pityrosporum. Seborrhea in HIV-infected, he may not play a major role. Skin diseases in HIV-infected patients.The flow is improved by HAART.

Diseases of the digestive tract

Candidiosal stomatitis and phyrangitis is caused by immunodeficiency, antibiotics, chronic administration of corticosteroids. When the number of CD4 lymphocytes <250 ml-1.

Aphthous stomatitis: etiology unknown. On HAART for greatly improving.

Esophagitis: caused by Candida 50-70%, 10-20% of CMV, HSV 2-5%, 10-20% of aphthous ulcers. When the number of CD4 lymphocytes <100 ml-1. Prior to the era of HAART, symptoms of the esophagus developed in one third of AIDS patients.

Acute diarrhea: caused by C. difficile 54%, Shigella 14%, C. jejuni 14%, Salmonella 7%, S.aureus 4%, M. avium 2%. ATM: nelfinovir, lopinavir / ritonavir, saquinavir, didanosine (dosage form containing buffering agents). 15-30% of the viruses (noroviruses,

adenoviruses, astroviruses, picornavirus, kalitsivirusy). In 25-40% of cases of idiopathic diarrhea. The diagnosis is made if the patient is unformed or watery stools >3 times a day for 3-10 days.

Chronic diarrhea: caused by Criptosporidium parvum, Entamoeba histolitica, Giardia lamblia, Isospora delli, CMV. In 20-30% of cases of idiopathic diarrhea. Most often when CD4 lymphocyte count <100 ml-1. Diagnosis is made when more than two episodes of unformed or liquid stools per day for a month or more.

Diseases of the liver and pancreas

Cholangiopathy is caused by Criptosporidium, Micosporidium, Ciclospora, CMV.

In 20-40% of cases of idiopathic holangiopatiya. When the number of CD4 lymphocytes <100 ml-1 on HAART for a significantly improved.

Hepatitis is caused by viral hepatitis A, B, C, D, alcohol or other drugs, autoimmune mechanisms, steatosis, hemochromatosis, sarcoidosis, MAC infection, CMV infection, side effects of medications (acetaminophen, izoniozid, statins, etc.), HAART-associated hepatitis.

Pancreatitis is caused by CMV infection, MAC infection, tuberculosis, cryptosporidiosis, toxoplasmosis, cryptococcosis, alcoholism, cholelithiasis, the side effects of drugs. For HIV-positive disease is 5 times higher.After the advent of HAART to reduce the incidence did not happen.

Diseases of the blood

Anemia: high viral load, female gender, low body mass index, belonging to the Negroid race, tumor (lymphoma, SC), MAC infection, tuberculosis, CMV infection, histoplasmosis, parvovirus B19, inadequate supply of nutrients, vitamins and minerals (vit. B12 and folic acid, in violation of their absorption, iron deficiency), inhibition of bone marrow hematopoietic drugs (AZT, ganciclovir, valganciclovir, sulfonamides, dapsone, amphotericin anticancer drugs, ribavirin, pyrimethamine, interferon, TMP-QMS, phenytoin) directly with HIV, hemolytic anemia drug (dapsone, primaquine, ribavirin). Develops in 12% of patients with CD4 lymphocyte counts <200 ml-1 and in 37% of patients with OI. Anemia is a poor prognostic sign, regardless of the number of CD4 lymphocytes and viral load.

Idiopathic thrombocytopenic purpura (ITP) is caused by HIV infection pluripotent hematopoietic progenitor cells in bone marrow, a side effect of medications (rifampin, amphotericin B, vancomycin,

ethambutol, sulfizoksazol, heparin, quinidine, preparations of gold, TMP-QMS, lithium salt). HAART: the restoration of immunity leads to an increase in platelet count after 3 months.

Thrombotic thrombocytopenic purpura (TTP) is caused by thrombus formation in various organs. The incidence has not been established. It can be observed both at early and late stages of HIV infection.

Neutropenia: caused by direct effects of HIV, a side effect of drugs (AZT, ganciclovir, valganciclovir, flucytosine, amphotericin B, sulfonamides, pyrimethamine, pentamidine, anticancer drugs, interferon). HAART: the total number of neutrophils increased in the recovery of immunity.

Malignant neoplasm

Cancer of the rectum is caused by Human Papilloma Virus. Among HIV-infected women the incidence increased.

Cervical cancer is caused by Human Papilloma Virus. Increasing incidence of HIV was not detected.

Kaposi's sarcoma is caused by human HSV type 8. It occurs in HIV-infected people in 20 thousand times more. In the era of HAART, the incidence has decreased by about a factor of 100. ON HAART regression of the tumor elements and longer life of the patient is observed.

Non-Hodgkin's lymphoma is caused by (NHL) virus E-B (50-80% of cases), immunosuppression. When the number of lymphocytes CD4 <100 mkl-1. The prevalence of the disease in AIDS patients is 3%.

In burkitt's lymphoma risk in AIDS patients is 15 times higher.

Hodgkin's disease (Hodgkin's disease): in the HAART era the incidence of HIV-infected people has increased.

Primary CNS lymphoma is caused by B-E virus. When the number of lymphocytes CD4 <50 ul-1. Do frequency of use of HAART among HIV-infected persons was 2-6%.After the introduction of HAART, the incidence decreased slightly.

Initial exudative lymphoma (PEL): caused by human HSV type 8, E-B virus is rare. It develops in 0,004-0,14% of AIDS patients. Against the background of HAART may come complete regression of PEL.

Diseases of the Nervous System

The peripheral nervous system

The syndrome of neuromuscular weakness in HIV disease is caused by Violation of mitochondrial function due to the toxic action

of a group of dideoxynucleosides NRTIs, particularly d4T.

Inflammatory demyelinating polyneuropathy is caused by Immunopathogenetic mechanisms. Is rare.

Sensory neuropathy is a direct effect of HIV, a side effect of NRTIs (didezoxinucleosides) – ddl and d4T. When the number of CD4 lymphocytes <200 ml-1.Vozmozhno improvement after beginning HAART.

Central nervous system

Cytomegalovirus encephalitis is caused by CMV. When the number of CD4 lymphocytes <50 ml-1. The frequency of <0,5% of AIDS patients.

Dementia (HIV dementia, HIV encephalopathy) is caused by CNS HIV, older age, hepatitis C and drug use. When the number of lymphocytes CD 4 <200 ml-1 to the era of HAART developed in 7% of AIDS patients. Currently, 2-3% of patients become ill with AIDS.

Progressive multifocal leucoencephalopathy is caused by JC virus activation (which refers to persistent) in immunocompromised patients. It occurs in 1-2% of AIDS patients.

The number of CD4 lymphocytes in the range 35-100 ml-1, but 7-25% of patients CD4 lymphocyte counts >200-1. Against the background of HAART can be observed and improvement and stabilization, and progression of the disease.

Toxoplasma encephalitis is caused by Toxoplasma gondii, reactivation of latent infection.When the number of CD4 lymphocytes <100 ml-1.

Diseases of the Eye

CMV retinitis is caused by CMV. When the number of CD4 lymphocytes <50 ml-1. It develops in about one-third of HIV-infected patients not receiving HAART. HAART improves prognosis.

Microangiopathy, at low amounts of CD4 lymphocytes. In the HAART severity of the disease may be reduced.

Microsporidiose keratoconjunctivitis is caused by Encephalitozoon hellem. HAART improves the course of the disease.

Choriopathy is caused by Pneumocistis jiroveci.

Toxoplasmosis retinitis is caused by Toxoplasma gondii, reactivation of latent infection.When the number of CD4 lymphocytes is <100 ml-1.

Syphilitic eye disease: uveitis, optic neuritis, chorioretinitis; caused by Treponema pallidum.

Eye involvement with shingles is caused by HZ. When the number of CD4 lymphocytes <100 ml-1.

Diseases of the oral mucosa

Gingivitis is caused by Anaerobic bacteria.

Hairy leucoplakia of mouth (VLPR) is caused by intensive replication of the virus E-B. It is found exclusively in HIV-infected at a low number of CD4 lymphocytes. In the HAART the disease disappears.

The increase in the salivary glands due to diffuse infiltrative lymphocytosis syndrome (SDIL) associated with HIV, mycobacteria, CMV. In the era of HAART, the frequency of this complication has declined substantially.

Mental disorders

Bipolar disorder (manic-depressive psychosis, TIR) is diagnosed in 9% of AIDS patients to consult a psychiatrist.

Delirium, frequency of occurrence in HIV-positive is 12-29%.

Psychasthenia, is diagnosed in 20% of AIDS patients to consult a psychiatrist.

Major depressive disorder, occurs in 20% of AIDS patients to consult a psychiatrist.

Mental disorders associated with substance use disorders, opioid dependence, dependence on cocaine, methamphetamine, benzodiazepines.

Diseases of the respiratory system

Pneumonia is caused by S. pneumoniae, M. tuberculosis, S. aureus (IDUs), influenza virus, non-Hodgkin's lymphoma. When the number of lymphocytes CD4>200 ml-1.

The above + P. Jiroveci, cryptococcosis, histoplasmosis, coccidioidomycosis, Nokardia, M. kansasii, Kaposi's sarcoma. When the number of CD4 lymphocytes 50-200 ml-1. The above + P. aeruginosa, Aspergillus, MAC infection, CMV. When the number of CD4 lymphocytes <50 ml-1 Before the era of HAART, the risk of bacterial pneumonia in HIV-infected persons was 7.8 times higher in comparison with the general population.

Diseases of the Kidney

Acute renal failure (ARF) is caused by HIV-AN, TTP, cryoglobulinemia as a complication of hepatitis C and nephrotoxic effects of drugs (aminoglycosides, amphotericin. B, cidofovir, foscarnet, pentamidine, trimethoprim-QMS, acyclovir (w/high doses)NSAIDs, indinavir, tenofovir), diabetes, chronic kidney disease

and liver. The risk is much higher in the CD4 lymphocyte count <100 ml-1.

Receiving HAART>3 months reduces the risk of more than 10 times.

Chronic renal failure (CRF) is caused by reduced glomerular filtration rate to <60 ml/min/ 1,7 m^2. The risk of progression to end-stage is much higher in afrikanoamerikantsev relatively rare terminal stage in patients Caucasians.

Heroin nephropathy, caused by toxic effects on the glomerular epithelial cells. The frequency is higher among African Americans.

HIV – associated nephropathy, caused by HIV defeat endothelial and glomerular mesangial cells.Risk factors: the stage of AIDS and viral load >100,000 copies/mL, male sex, renal disease in close relatives. It occurs almost exclusively in patients of African descent.

HAART reduces the risk of HIV-AN.

HIV – associated immune-mediated glomerulonephritis; develop in 15-80% of HIV – infected.

Co-infection with hepatitis C virus, hepatitis C virus, the severity of nephrotic syndrome, reducing the compliment, the presence of immune complexes containing HCV antigens, circulating cryoglobulins in the blood.

Genitals

The rate of transmission of genital infections depends on the level of viral load of HIV in an infected partner

Anogenital warts is caused by HPV Man papilomavirus type 6, 11, 16, 18, secondary syphilis, carcinoma.

Cervical intraepithelial neoplasia is caused by human papilomavirus HPV type 16, 18, 32-80%. The frequency is reduced in patients receiving HAART.

Genital herpes is usually due to HSV type 2,5% – Herpes simplex virus type 1. The frequency of isolation of the virus culture is associated with a decrease in CD4 +, HIV viral load increase.

Genital ulcers, etiology depends on the geographic region. HSV – 52-31%, Hemophilus ducreyi – 23-39%, Treponema pallidum – 10-19%, lymphogranuloma venerium – 6%, mixed infection – 5%, idiopathic aphthae.

Urethritis, cervicitis occurs due to gonorrhea (50% more infected S.trachomatis) S.trachomatis, Ureaplasma urealyticum. Women – HSV, candidiasis, trichomoniasis. At present, the frequency decreased due to the use of condoms.

Hormonal contraception increases the risk of infection S.trachomatis.

Inflammation of the appendages, due to gonorrhea, chlamydia, anaerobic flora, Enterobacteriaceae, Streptococcus spp. Runs hard, often requiring hospitalization, complicated by peritonitis, tubo-ovarian abscess is often required laparoscopy for diagnosis.

TYPHOID FEVER

Typhoid fever is an acute, life-threatening febrile disease caused by the bacterium Salmonella enterica serotype Typhi. Paratyphoid fever is a similar illness caused by S. Paratyphi A, B, or C.

Etiology. Humans are the only source of these bacteria; no animal or environmental reservoirs have been identified. Typhoid and paratyphoid fever are most often acquired via consumption of water or food that has been contaminated by feces of an acutely infected or convalescent person or a chronic, asymptomatic carrier.

According to estimates 22 million cases of typhoid fever and 200,000 related deaths occur worldwide every year; an additional 6 million cases of paratyphoid fever are estimated to occur annually. Approximately 300 cases of typhoid fever and 150 cases of paratyphoid fever are reported every year in the United States, most of which are in recent travelers. The risk of typhoid fever is the highest for travelers to southern Asia (6–30 times higher than for all other destinations). Other areas of risk include East and Southeast Asia, Africa, the Caribbean, and Central and South America. The risk of paratyphoid fever is also increasing among travelers to southern and Southeast Asia.

Travelers to southern Asia are at the highest risk for infections that are nalidixic acid–resistant or multidrug-resistant (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole). Travelers who are visiting friends and relatives (VFRs) are at increased risk. Although the risk of acquiring typhoid or paratyphoid fever increases with the duration of stay, travelers acquire typhoid fever even during visits <1 week to countries where the disease is endemic.

Fig. 3. – Areas of risk from Typhoid fever

The most notorious carrier of typhoid fever–but by no means the most destructive–was Mary Mallon, also known as Typhoid Mary. In 1907, she became the first American carrier to be identified and traced. She was a cook in New York. She is closely associated with fifty-three cases and three deaths. Public health authorities told Mary to give up working as a cook or have her gall bladder removed. Mary quit her job but returned later under a false name. She was detained and quarantined after another typhoid outbreak. She died of pneumonia after 26 years in quarantine.

Pathophysiology of typhoid fever is a complex process which proceeds through several stages). The disease begins with an asymptomatic incubation period of 7-14 days, (inversely related to the size of the infecting dose), during which bacteria invade macrophages and spread throughout the reticuloendothelial system. The first week of symptomatic disease is characterized by progressive elevation of the temperature followed by bacteremia. The second week begins with the development of rose spots, abdominal pain and splenomegaly. The third week is marked by a more intense intestinal inflammatory response particularly in the Peyer's patches with associated necrosis which can result in perforation and hemorrhage. These clinical stages are associated with complex cellular events just now being understood.

First, ingested bacteria must survive the acidic environment of the stomach. The known increased risk of typhoid fever with concomitant Helicobacter pylori infection may express itself via the hypochlorhydria associated with chronic H.pylori infection. Invading organisms pass through the intestinal epithelial cells and come into

contact with phagocytic cells in the Peyer's patches of the intestinal wall. However the macrophages do not kill the bacteria. Thence, bacterial replication is primarily intracellular. Salmonella avoids encapsulation in lysosomes by diverting normal cellular mechanisms. Bacteria inject effector proteins into the cells of the innate immune system (macrophages and natural killer cells) though a type III protein secretion system (TTSS) which stimulate both pro and anti-inflammatory responses.

Clinical picture. Over the asymptomatic incubation period of 7-14 days the bacteria proliferate and spread through the blood stream to other cells in the reticuloendothelial system in the liver, spleen, bone marrow and gall bladder. As replication inside phagocytic cells continues, bacteria are shed into the blood stream in sustained but low concentrations and the clinical syndrome of fever, headache and abdominal pain begins. The gallbladder is felt to be a significant site for ongoing exposure of intestinal epithelial cells to the pathogen. The inflammatory response to this process of repeated exposure is felt to give rise to the necrosis which is a prominent feature of the disease. This occurs in areas of greatest macrophage concentration such as the Peyer's patches and explains why intestinal bleeding and perforation are the most frequent complications. Elsewhere typhoid nodules, foci of macrophages and lymphocytes proliferate. As the infection progresses the typical changes of sepsis accumulate in the heart, brain and kidneys. If not interrupted this process may lead to circulatory failure and death from overwhelming sepsis.

Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week. In the first week, the temperature rises slowly and fever fluctuations are seen with relative bradycardia, malaise, headache, and cough. A bloody nose (epistaxis) is seen in a quarter of cases and abdominal pain is also possible. There is leukopenia, a decrease in the number of circulating white blood cells, with eosinopenia and relative lymphocytosis, a positive reaction and blood cultures are positive for Salmonella typhi or paratyphi. The classic Widal test is negative in the first week.

In the second week of the infection, the patient lies prostrate with high fever in plateau about 40°C (104°F) and bradycardia (sphygmothermic dissociation), classically with a dicrotic pulse wave. Delirium is frequent, frequently calm, but sometimes agitated. This

delirium gives to typhoid the nickname of "nervous fever". Rose spots appear on the lower chest and abdomen in about a third of patients. There are rhonchi in lung bases.

The abdomen is distended and painful in the right lower quadrant. Diarrhea can occur in this stage: six to eight stools in a day, green with a characteristic smell, comparable to pea soup. However, constipation is also frequent. The spleen and liver are enlarged (hepatosplenomegaly) and tender, and there is elevation of liver transaminases. The Widal reaction is strongly positive with antiO and antiH antibodies. Blood cultures are sometimes still positive at this stage. (The major symptom of this fever is that the fever usually rises in the afternoon up to the first and second week.)

In the third week of typhoid fever, a number of complications can occur:

- Intestinal hemorrhage due to bleeding in congested Peyer's patches; this can be very serious but is usually not fatal.
- Intestinal perforation in the distal ileum: this is a very serious complication and is frequently fatal. It may occur without alarming symptoms until septicemia or diffuse peritonitis sets in.
- Encephalitis
- Neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects.
- Metastatic abscesses, cholecystitis, endocarditis and osteitis

The fever is still very high and oscillates very little over 24 hours. Dehydration ensues and the patient is delirious (typhoid state). By the end of the third week the fever starts subsiding (defervescence). This carries on into the fourth and final week.

Diagnosis. Infection with typhoid or paratyphoid fever results in a very low-grade septicemia. A single blood culture is positive in only half the cases. Stool culture is not usually positive during the acute phase of the disease. Bone marrow culture increases the diagnostic yield to about 80% of cases.

The Widal test is an old serologic assay for detecting IgM and IgG to the O and H antigens of salmonella. The test is unreliable but is widely used in developing countries because of its low cost. Newer serologic assays are somewhat more sensitive and specific than the Widal test but are infrequently available.

Olso used RPGA test.

As there is no definitive serologic test for typhoid or paratyphoid fever, the diagnosis often has to be made clinically. The combination of a history of risk for infection and a gradual onset of fever that increases in severity over several days should raise suspicion of typhoid or paratyphoid fever.

Treatment. Where resistance is uncommon, the treatment of choice is a fluoroquinolone such as ciprofloxacin 500 mg 2/day 7-14 days or a third-generation cephalosporin such as ceftriaxone (1-2 g. 2/day) or cefotaxime (2 g. 3-4/day) 14 days. Cefixime is a suitable oral alternative.

Typhoid fever in most cases is not fatal. Antibiotics, such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, amoxicillin and ciprofloxacin, have been commonly used to treat typhoid fever in microbiology. Treatment of the disease with antibiotics reduces the case-fatality rate to approximately 1%.

When untreated, typhoid fever persists for three weeks to a month. Death occurs in between 10% and 30% of untreated cases. In some communities, however, case-fatality rates may reach as high as 47%.

Prevention. Centre for Disease Control and Prevention (CDC), the USA, recommends typhoid vaccine for travelers to areas where there is an increased risk of exposure to S.Typhi. The typhoid vaccines do not protect against S. Paratyphi infection. Both typhoid vaccines protect 50–80% of recipients; travelers should be reminded that typhoid immunization is not 100% effective, and typhoid fever could still occur. Two typhoid vaccines are available in the United States:

Table 3. – Typhoid vaccines available in USA

VACCINATION	*AGE (y)*	*DOSE, MODE OF ADMINISTRA-TION*	*NUMBER OF DOSES*	*DOSING INTERVAL*	*BOOSTING INTERVAL*
Oral, Live, Attenuated Ty21a Vaccine (Vivotif)[1]					
Primary series	≥6	1 capsule,[2] oral	4	48 hours	Not applicable
Booster	≥6	1 capsule,[2] oral	4	48 hours	Every 5 years
Vi Capsular Polysaccharide Vaccine (Typhim Vi)					
Primary series	≥2	0.50 mL, intramuscular	1	Not applicable	Not applicable
Booster	≥2	0.50 mL, intramuscular	1	Not applicable	Every 2 years

[1]The vaccine must be kept refrigerated (35.6°F–46.4°F, 2° C–8°C).
[2]Administer with cool liquid no warmer than 98.6°F (37°C).

RICKETTSIASIS

Rickettsial diseases are a group of infections caused by Gram negative bacteria of the genus Rickettsia species. They are zoonotic infections that cause typhus and spotted fevers.

Rickettsia named after **Howard Taylor Ricketts** died of Typhus fever contracted during his studies discovered spotted fever rickettsia (1906).

Rickettsiae replicate within the cytoplasm of endothelial cells and smooth muscle cells of capillaries, arterioles and small arteries causing necrotizing vasculitis. Most are febrile infections with a characteristic rash. Despite the similar name, Rickettsia bacteria do not cause rickets, which is a result of vitamin D deficiency.

Rickettsial diseases may be grouped on the basis of Clinical features and Epidemiological aspects as follows (table 4).

Table 4. – Rickettsial agent

Diseases	***Rickettsial agent***	***Insect vector***	***Mammalian reservoir***
Typhus group			
Epidemic typhus	R. *prowazekii*	Louse	Human
Murine typhus (Endemic typhus)	R. *typhi*	Flea	Rodents
Scrub typhus	R. *tsutsugamushi*	Mite	Rodents
Spotted fever group			
Mediterranean spotted fever	R. conorii	Tick	Rodent, Dog
Rocky mountain spotted fever	R. rickettsia	Tick	Rodents, Dogs
Rickettsial pox	R. akari	Mite	Mice

Morphology. In smears from infected tissues, rickettsiae appear as pleomorphic gram negative coccobacilli Non motile non capsulated, they stain bluish purple with Giemsa and Castaneda stains. It can not grow in cell free media. Growth generally occurs in the cytoplasm of infected cells.

Cultivation. They are readily cultivated in the yolk sac of developing chick embryo. They also grow on mouse fibroblast, HeLa, Hep2, Detroit-6 and other continuous cell lines but tissue cultures are not satisfactory for primary isolation. Guinea pigs and mice are useful

for the isolation of rickettsiae from patients.

Resistance. Rickettsiae are readily inactivated by physical and chemical agents. They are rapidly destroyed at 560 C and at RT when separated from host components. They can be preserved in skimmed milk or a suspending medium containing sucrose, potassium phosphate and glutamate (SPG medium).

All spotted fever group rickettsiae contain these cross-reactive antigens identified by the indirect fluorescent antibody serologic test, so that routine species differentiation within the serologic group can be difficult or impossible. R. rickettsii contains species-specific epitopes that can be identified by monoclonal antibodies.

Vaccination. Currently no commercial vaccine is available for any rickettsial disease. Infection with R. rickettsiiand R. conoriiis believed to confer long lasting immunity against re-infection. Thus, it is feasible to develop a vaccine against rickettsial diseases. In theory, a subunit vaccine targeting a conserved rickettsial protein suchas OmpB may be developed to prevent all rickettsial diseases. An attenuated organism that can multiply, but does not cause disease in the host, has been proved to be effective in protection against rickettsial infections in humans and laboratory animals. Attenuated Rickettsiahas been selected by passage inchicken egg yolk sacs in the past and was recently achieved by gene knockout technology.

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

RMSF originated as an emerging infectious disease on the western frontier in the Rocky Mountains. Now the disease is found all over the United States, and over half of the cases occur in the southeastern and south-central regions of the United States and in South America (Center for Disease Control and prevention (CDC, 2010).

Virulent rickettsiae such as R. rickettsiineed an animal host to amplify the organisms for establishing new lines of transovarian rickettsial maintenance (e.g., D. variabilis ticks acquire R. rickettsii while feeding on rickettsemic cotton rats) (Niebylski etal., 1999). Each species of pathogenic SFG rickettsiae may have one or multiple tick vector species. The vectors of Rocky Mountain spotted fever are D. variabilis (American dog tick) in the eastern two-thirds of the US and regions of the Pacific coast states, D. andersoni (wood tick) in the Rocky Mountain states, Rhipicephalus sanguineus (brown dog tick)

in the southwestern US, northern Mexico, and South America and Amblyomma cajennenseand A. aureolatumin South America. The seasonal and geographic distribution of each rickettsiosis reflects the months of activity of the vector and its contact with humans. Over 90% of cases with Rocky Mountain spotted fever occur during April through September. Approximately 250-2000 cases of Rocky Mountain spotted fever have been reported annually in the United States (CDC, 2010).

Clinical presentation. Rocky Mountain spotted fever caused by R. rickettsii is a very severe disease, and fatal cases occur in association with delayed or ineffective antibiotic treatment in as many as 4% of cases. RMSF occurs 1-2 weeks after feeding by an infected tick. The disease is characterized by acute onset of fever with chills that may be accompanied by headache, malaise, myalgia, gastrointestinal symptoms (nausea, vomiting, anorexia, abdominal pain, diarrhea, abdominal tenderness); cough; conjunctival injection±photophobia neurologic signs (altered mental status, focal neurologic deficits, including cranial or peripheral motor nerve paralysis or sudden transient deafness).

A macular or maculopapular rash appears 3-5 days following onset in most (~90%) patients, and the rash has a centripetal pattern of spread, meaning that it begins on the extremities and spreads towards the trunk. In severe disease, petechiae appear in the center of the maculopapules. Red to purple spots (petechiae) are usually not seen until day 6 or later after onset of symptoms. Petechial rash is considered a sign of progression to severe disease. Every attempt should be made to begin treatment before petechiae develop. However, 10% to 15% of persons with RMSF never develop a rash, a condition referred to as "Rocky Mountain spotless fever"(Sexton & Corey, 1992). The target of Rickettsia is endothelium of blood vessels.

Inflammation and damage of endothelia of capillary blood vessels by Rickettsiaresults in increased vacular permeability, which causes rash, hypovolemic hypotension, pulmonary and cerebral edema and organ failure. Other spotted fevers may have similar clinical symptoms as RMSF, but are less severe. Rash is less frequent in less severe rickettsioses such as African tick bite fever and R. parkeri infection. Focal skin necrosis with a dark scab (an eschar) at the site of tick feeding is a common feature of boutonneuse fever, African tick bite fever, North Asian tick typhus, Queensland tick typhus, Japanese spotted fever, Flinders Island spotted fever, rickettsialpox, tick-borne

lymphadenopathy, and the recently described infections in the US caused by R. parkeriand a novel strain 364 D, but is rarein Rocky Mountain spotted fever.

Diagnosis. General laboratory findings: thrombocytopenia, mildly elevated hepatic transaminase levels, hyponatremia.

Laboratory confirmation: Antibodies to R. rickettsiiare detectable 7-10 days after illness onset. The gold-standard serologic test looks for a four-fold change in antibody titers using immunofluorescence assay (IFA) on paired samples. The first sample should be taken within the first week of illness and the second should be taken 2 to 4 weeks later. Demonstration of a four-fold change in IgG-specific antibody titer by immunofluorescence assay (IFA) test in paired serum samples; or Detection of DNA in a skin biopsy of rash by polymerase chain reaction (PCR) assay (generally unreliable for acute blood samples). Immunohistochemical (IHC) staining of organism.

IgM antibodies are less specific than IgG antibodies and are more likely to generate false positives. IgM results alone should not be used for laboratory diagnosis. Antibody titers are frequently negative in the first 7-10 days of illness, thus serologic tests may be falsely negative during this time period.

Anaplasmosis, ehrlichiosis and Rocky Mountain spotted fever are treated in the same manner with doxycycline. Clinical suspicion of any of these diseases is sufficient to begin treatment. Delay in treatment may result in severe illness and even death. Doxycycline must be use as the first-line treatment for suspected RMSF in patients of all ages (table 8). The use of doxycycline to treat suspected RMSF in children is recommended by both the CDC and the American Academy of Pediatrics Committee on Infectious Diseases. Use of antibiotics other than doxycycline increases the risk of patient death.

Table 5. – Doxycycline for treatment of RMSF

Age category	***Drug***	***Dosage***	***Maximum***	***Duration (days)***
Adults	Doxycycline	100 mg twice per day, orally or IV 100 mg/dose	100 mg/dose	Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5-7 days.
Children weighing <100 lbs. (45,4 kg)	Doxycycline	2,2 mg/kg per dose twice per day, orally or IV	100 mg/dose	

Chloramphenicol is a second line, less effective treatment that can be used inthe rare instance of contraindication to use of doxycycline. Ciprofloxacin, other fluoroquinolones are effective but are not recommended for the severe rickettsioses.

EPIDEMIC TYPHUS

Epidemic typhus is also called "camp fever", "jail fever", "hospital fever", "ship fever", "famine fever", "putrid fever", "petechial fever", "louse-borne typhus". It has been distributed worldwide and was one of the man's major scourges. It frequently played a decisive role in wars in Europe from the 15th through 20th centuries, thus affecting the course of European history (Conlon JM, 2007). It killed millions of people through this period. For example, typhus killed hundreds of thousands of prisoners in Nazi concentration camps during World War II. Henrique da Rocha Lima in 1916 proved that the bacterium Rickettsia prowazekii was the agent responsible for typhus; he named it after H. T. Ricketts and Stanislaus von Prowazek, two zoologists who had died from typhus while investigating epidemics. Once these crucial facts were recognized, Rudolf Weigl in 1930 was able to fashion a practical and effective vaccine production method by grinding up the insides of infected lice that had been drinking blood. It was, however, very dangerous to produce, and carried a high likelihood of infection to those who were working on it. Although worldwide epidemics of typhus may not occur again, the threat of louse-borne typhus is still real as small scale epidemics or large scale epidemics in settings of extreme poverty and natural and manmade disasters. Louse-borne typhus occurs in epidemics when social, economic, or political systems are disrupted exposing a large population such as refugees to louse infestation due to lack of hygiene. This situation has been observed in recent outbreaks of typhus in Burundi, Algeria, Peru, and Russia. In 1997, it was estimated that as many as 100,000 cases of typhus occurred in the refugee camps of Burundi during a civil war (Raoult et al., 2004).

The causative organism is Rickettsia prowazekii, transmitted by the human body louse (Pediculus humanus corporis).

T*ransmission.* Epidemic typhus is transmitted primarily by the human body louse, Pediculus humanus corporis. However, the louse is

only a vector and not a reservoir because infected lice die 5-7 days after they become infected with R. prowazekii. Rickettsia prowazekii multiplies in louse gut epithelium, which detaches, ruptures and releases rickettsiae into the feces. The louse feces containing rickettsiae are scratched intothe skin, rubbed into mucous membranes suchas the conjunctiva, or inhaled. Humans can develop latent infection after acute louse-borne typhus and serve as reservoirs of R. prowazekii. R. prowazekiican be reactivated causing recrudescent typhus fever (Brill-Zinsser disease) when latently infected persons' immunity wanes.

Signs and symptoms

Symptoms include severe headache, a sustained high fever, cough, rash, severe muscle pain, chills, falling blood pressure, stupor, sensitivity to light, and delirium. A rash begins on the chest about five days after the fever appears, and spreads to the trunk and extremities. A symptom common to all forms of typhus is a fever which may reach 39°C (102°F) Starts with fever and chills.

Rash occurs on the 4^{th} or 5^{th} day, trunk and limbs are usually affected (sparing palms and soles). Patients become stuporous and delirious during the second week.

Case fatality rate (if untreated) is 40%, it increases with age.

In those who recover from disease, Rickettsia remains dorment for years in the lymphoid tissue or organs.

Reactivation – recrudescent typhus (Brill Zinsser disease).

Diagnosis. The diagnosis of epidemic typhus fever is based on signs and symptoms of illness, as well as laboratory blood tests.

A complete blood count (CBC) may show anemia and low platelets. Other blood tests for typhus may show: high level of typhus antibodies; low level of albumin; low sodium level; mild kidney failure; mildly high liver enzymes.

Historically murine typhus and epidemic typhus were difficult to differentiate due to similar clinical symptoms, but epidemic typhus is more severe than murine typhus. Murine typhus occurs predominantly in summer and fall, and epidemic typhus usually occurs in winter.

Treatment. The infection is treated with antibiotics. Tetracyclines are first-line treatment, and doxycycline may be used to avoid tooth staining in children. Tetracyclines are rickettsiostatic, not rickettsicidal. Chloramphenicol is a second line, less effective treatment that can be used inthe rare instance of contraindication to

use of doxycycline. Ciprofloxacin, other fluoroquinolones, azithromycin, and clarinthromycin are effective against certain rickettsiae but are not recommended for the severe rickettsioses. Because diagnostic tests can take time and may be insensitive, antibiotics are usually begun presumptively to prevent significant deterioration, complications, death, sequelae, and prolonged recovery.

Intravenous fluids and oxygen may be needed to stabilize the patient. The mortality rate is 10% to 60%, but is vastly lower (close to zero) if intracellular antibiotics such as tetracycline are used before 8 days. Infection can also be prevented by vaccination.

SCRUB TYPHUS

Scrub typhus (Mite-borne typhus, Tsutsugamushi disease) or Bush typhus is a form of typhus caused by the intracellular parasite Orientia tsutsugamushi, a gram-negative α-proteobacterium of familyRickettsiaceae first isolated and identified in 1930 in Japan. Scrub typhus is an acuteinfectious disease that is emerging and re-emerging in South-East Asia and thesouth-western Pacific region. It can have a case-fatality rate of up to 30% ifuntreated. Epidemics occur when susceptible individuals are brought intoendemic areas (e.g., during military operations). In some countries (e.g., Japan) it is a notifiable disease. Multi-drug resistance has been documented inThailand.

Epidemiology. The distribution of O. tsutsugamushi extends north to Japan, Russia, and the Primorske Karai region in the Russian Far East, south to northern Australiaand the western Pacific islands, and west to Afghanistan, Pakistan, and areasbordering the Central Asian Republics. Human O. tsutsugamushi occurs widely in these regions, but not everywhere. Scrub typhus is probably one of the most underdiagnosed andunderreported febrile illnesses requiring hospitalization in the region. The absence of definitive signs and symptoms combined with a general dependence upon serological tests make the differentiation of scrub typhus from othercommon febrile diseases such as murine typhus, typhoid fever and leptospirosisquite difficult.

Causative agent. Orientia tsutsugamushi Formerly-R.tsutsugamushi – R.orientalis (Tsutsugam=dangerous, Mushi=insect/mite). ***Vector*** is

trombiculid mites. The mite inhabits sharply demarcated areas in the soil where the micro ecosystem is favourable. Humans are infected while passing through these Mite islands by mite larvae (Chiggers) bites. The mite larvae feed on the serum of warm blooded animals only once during its cycle of development. Adult mites feed only on plants. Resrviors – rodents and birds. Scrub typhus originally is found in scrub jungles sandy beaches, mountains, deserts, equatorialrain forests.

Zoonotic tetrad for establishment of scrub typhus needs 4 essential factors: orienta tsutsugamushi; chiggers; rats; transitional forms of vegetation/Incubation period: 1-3 weeks.

Clinical presentation. A disease with a primary "punched out" skin ulcer (eschar) where the bite(s) occurred, followed by acute onset fever after several days, along withheadache, profuse sweating, conjunctival injection and lymphadenopathy. Withina week, a dull maculo-papular rash appears on the trunk, extends to the extremities and disappears in few days. Cough is also common. Defervescence within 48 hours following tetracycline therapy strongly suggests a rickettsial etiology.Eschar may be absent in some geographic areas and in highly endemic areas wherereinfection is frequent. Rash may be overlooked in patients with dark or sunburned skin.

Complications. Pneumonitis, encephalitis, and myocarditis occur in the late phase of illness.

Diagnosis. Laboratory findings: leukopenia and abnormal liver function tests are commonly seen in the early phase of the illness.

Laboratory criteria for diagnosis. Isolation of Orientia tsutsugamushi by inoculation of patient blood in white mice (preferably treated with cyclophosphamide at 0,2 mg/g intraperitoneally orintramuscularly on days 1,2 and 4 after inoculation).

Serology: detection of specific IgMat 1:100 or higher by Enzyme Immunoassay (EIA) or 1:32 dilution or higher by Immunoperoxidase (IP) or 1:10 dilution or higher by Indirect Immunofluorescence (IF). Other methods include culture and PCR.

Case classification. Suspected: a case that is compatible with the clinical description. Confirmed: a suspected case with laboratory confirmation.

Treatment. Without treatment, the disease is often fatal. Since the use of antibiotics, case fatalities have decreased from 4-40% to less than 2%. The drug most commonly used is doxycycline.

Rifampinand azithromycin are alternatives. Azithromycin is an alternative in children and pregnant women with scrub typhus and when doxycycline-resistance is suspected. Ciprofloxacin cannot be used safely in pregnancy and is associated with stillbirths and miscarriage. Combination therapy with doxycycline and rifampicin is not recommended due to possible antagonism.

Other drugs that may be effective are clarithromycin, roxithromycin, and the fluoroquinolones, but there is no clinical evidence on which to recommend their use. Azithromycin or chloramphenicol is useful for infection in children or pregnant women.

MARSEILLES FEVER

Marseilles fever (Mediterranean spotted fever or Boutonneuse fever) an infectious disease that is caused by Rickettsia conorii which is transmitted by the brown dog tick (Rhipicephalus sanguineus). The disease occurs predominantly in Mediterranean areas such as India and Africa.

R. conorii broadly grouped under the heading "Spotted Fever group Rickettsia (SFGR)" have been shown to cause human infections. Tick-borne SFGR are transmitted to humans by the bite of an infected tick, and may cause similar signs and symptoms to those observed for RMSF. These pathogens include several species of Rickettsia found in the United States, including R. parkeri and Rickettsia species 364D. In addition, numerous tick-borne SFGR pathogenic to humans have been described internationally, including but not limited to R. conorii and R. africae.

Clinical presentation. The onset of symptoms is usually sudden and the incubation period is usually between 6 and 10 days. The initial symptoms generally include fever, headache, fatigue, and muscle aches. A maculopapular or petechial rash may be present, and frequently a distinctive eschar (blackened or crusted skin) may develop at the site of a tick bite. Multiple eschars may be present if more than one tick bite occurred. The observance of an eschar at the site of tick bite may provide the clinician with a diagnostic clue that can help differentiate the infection from RMSF, although eschars may also be rarely reported with R. rickettsii infection. R. conorii and some

other SFGR infections may be more severe.

The list of signs and symptoms mentioned in various sources for Marseilles fever includes the 11 symptoms listed below: fever – may last 1-2 weeks; chills; black crusted ulceration at site of tick bite; rash – starts 3-5 days after fever starts and lasts 10-20 days after other symptoms disappear; muscle pain; joint pain; severe headache; malaise; slowed heart rate; enlarged liver – in a third of patients; increased alkaline phosphatase level – in a third of patients with primary cause of marseilles fever.

Complications list for Marseilles fever: pericarditis, heart failure, acute kidney failure, myocarditis, nephritis, adult respiratory distress syndrome, pleuritis, pneumonitis, phlebitis, vasculitis, encephalopathy, death.

Venous thrombosis is more common in pregnant patients.

Diagnosis. Physicians seeking confirmation of infection with a SFGR pathogen may elect to use commercially available serologic assays that diagnose RMSF, and should report it as a case of "Spotted Fever Rickettsiosis" to their state health department. Additional methods that may be used to help identify the causative agent include polymerase chain reaction (PCR) assay, immunohistochemistry (IHC), and culture isolation of a swab or biopsy from an eschar or rash site.

Treatment. All suspect patients should be treated as if they have R. rickettsii infection. Tick-borne SFGR infections respond well to treatment with doxycycline, and this is considered the antibiotic of choice for patients of all ages. Doxycycline is the first line treatment for adults and children of all ages: Adults: 100 mg every 12 hours; Children under 45 kg (100 lbs): 2.2 mg/kg body weight given twice a day. Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Standard duration of treatment is 7 to 14 days.

Chloramphenicol or ciprofloxacin are also used.

Prognosis The infection is rarely fatal. Patients have a natural immunity to the infection.

Prevention. The best prevention is to prevent tick bites. Information on preventing tick bites includes use of personal insect repellents, choosing clothing that limits tick attachment, and avoiding areas where ticks may be present.

LYME DISEASE

Definition. Lyme disease, or Lyme borreliosis, is an emerging infectious disease caused by at least three species of bacteria belonging to the genus Borrelia. Borreliaburgdorferisensustricto is the main cause of Lyme disease in the United States, whereas Borreliaafzelii and Borreliagarinii cause most European cases. The disease is named after the town of Lyme, Connecticut, USA, where a number of cases were identified in 1975. Although Allen Steere realized that Lyme disease was a tick-borne disease in 1978, the cause of the disease remained a mystery until 1981, when B. burgdorferi was identified by Willy Burgdorfer.

Lyme disease is the most common tick-borne disease in the Northern Hemisphere. Borrelia is transmitted to humans by the bite of infected ticks belonging to a few species of the genus Ixodes ("hard ticks").

Epidemiology. Endemic areas are northeastern coastal states: Wisconsin and Minnesota, coast of Oregon and Northern California. Rising frequency attributed to enlarging deer population and concurrent suburbanization. High risk areas are wooded or brushy, unkempt grassy areas & fringe of these areas. Lower risk is on lawns that are mowed. Life cycle (fig. 4).

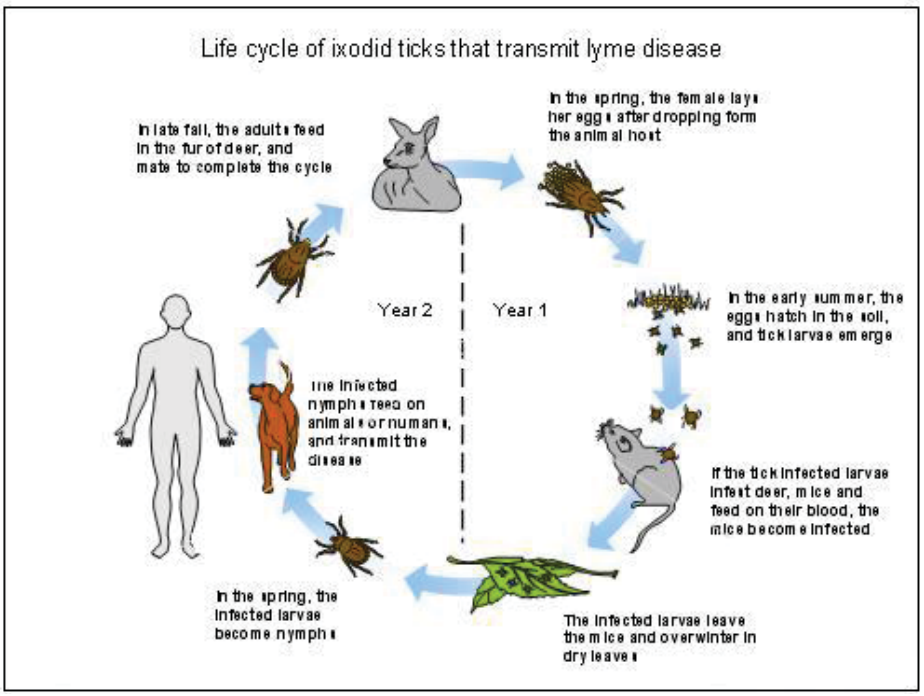

Fig. 4. – Life cycle of ixodid ticks

Lyme disease may develop into a chronic persistent infection in a fashion somewhat similar to syphilis. For this reason, Lyme disease has been divided into stages. Clinical stages:

- Stage 1 – Acute, localized disease
- Stage 2 – Subacute, disseminated disease
- Stage 3 – Chronic or late persistent infection.

Common name of the stage 2 and stage 3 is late Lyme disease.

Acute infection. Tick must have been feeding for at least 24-48 hrs. Stage I is characterized by a rash – erythema migrans (EM) which is an erythematous ring that develops around the tick bite site about 8 to 9 days (range, 3 to 32 days) after exposure. EM rashes expand slowly over a few days after which they may develop a "bull's-eye" appearance consisting of a red ring with central clearing. However, EM may take alternate forms – solid lesions, blue-purple hues, and crusted or blistering lesions have all been documented. The rash is not painful or pruritic, but it may be warm to the touch. Smaller secondary (migratory) rings may occur later. Neurologic manifestations may occur in stage I concurrently with EM, but they are more frequent in stage II. Erythema migrans develops 1 to 4 weeks after bite. Without treatment rash clears within 3 to 4 weeks. About 50% of patients will also complain of flu-like illness - fever, chills, myalgia.

In the acute stage I, a systemic flu-like syndrome with fever, chills, and malaise may occur. Neurologic manifestations include headache and neck stiffness but normal cerebrospinal fluid (CSF) parameters.

Disseminated disease. Stage II, the subacute stage, is characterized by prominent cardiac and neurologic manifestations. This stage usually begins several months after the bite and the onset of ECM. Symptoms usually involve skin, CNS, musculoskeletal and cardiac system. Dermatological manifestations new skin lesions, smaller and less migratory than initial erythema and urticaria have been noted. Stage II is also referred to as the "early neurologic stage" because dissemination of the organism to the central nervous system begins. During this stage, aseptic meningitis with complications of cranial nerve palsies, especially facial (Bell's palsy), and radiculoneuritis are most prominent. The facial or Bell's palsy is usually bilateral. The radiculoneuritis may take the form of a Guillain-Barré-like syndrome, but the CSF shows pleocytosis; sometimes the

radiculoneuritis is focal. Occasionally, mild meningoencephalitis along with irritability, emotional lability, decreased concentration and memory, and sleep abnormalities may occur.

Neurologic complications occur weeks to months later in about 15% to 20% of untreated patients. Symptoms:

- unilateral or bilateral Bell's palsy
- Lyme meningitis
- motor and sensory radiculoneuropathy
- mononeuritis multiplex
- subtle cognitive difficulties
- encephalitis, encephalomyelitis, subtle encephalopathy, pseudotumor cerebri (all rare).

Musculoskeletal symptoms evolve into frank arthritis in up to 60% of untreated patients. Onset averages 6 months from initial infection. Symptoms are following: migratory pain in tendons, bursae, muscle, and bones; transient, migratory arthritis and effusion in one or multiple joints; knee is most common site, not more than 3 joints are involved. The course of disease lasts from several days to few weeks then joints return to normal. Baker's cyst is observed; if untreated, arthritis may recur in the same or different joints.

Cardiac involvement is noted in about 5% to 10% beginning several weeks after infection. Transient heart block may be consequence. Range from asymptomatic to first-degree heart block to complete. Cardiac phase lasts from 3 to 6 weeks.

Chronic – late persistent. Stage III, the chronic stage, is characterized by chronic arthritis. Neurologic manifestations also occur in stage III but they are less prominent than those of stage II. Stage III usually begins about 1 year after onset. Then the latent period from several months to years follows. After initial infection 60% to 80% will have musculoskeletal complaints. Most common is arthritis of knee – may also occur in ankle, elbow, hip, shoulder. Neurologic impairment distalparesthesias, radicular pain, memory loss, fatigue.

Stage III or the chronic stage is also referred to as the "late neurologic stage." This stage is characterized by chronic or late persistent infection of the nervous system. Syndromes included in this stage are encephalopathy, encephalomyelopathy, and polyneuropathy. The encephalopathy is characterized by memory and other cognitive dysfunction. The encephalomyelopathic signs are combined with

progressive long tract signs and optic nerve involvement. White matter lesions may be visible on magnetic resonance imaging of the brain. The late polyneuropathy is primarily sensory.

Additional manifestations of chronic stage are: conjunctivitis, keratitis, uveitis; mild hepatitis; splenomegaly.

Post-Lyme Disease Syndromes. There is no well-accepted definition of post-Lyme disease syn-drome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. Whatever definition is even-tually adopted, having once had objective evidence ofB. burg-dorferiinfection must be a condition sine qua non. There is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (more than 6 months) sub-jective symptoms after recommended treatment regimens for Lyme disease.

Differential diagnosis. Human babesiosis (fever, chills, sweats, arthralgias, headache, lassitude, pts with both appear to have more severe Lyme disease), Ehrlichiosis described as “rashless Lyme disease”, high fever & chills & may become prostrate in day or two.

Differential diagnosis in acute and early disseminated stages is Rocky Mountain spotted fever, humanbabiosis, summertime viral illnesses, viral encephalitis, bacterial meningitis.

Differential diagnosis in late disseminated and chronic stages is gout, pseudogout, Reiter’s syndrome, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, depression, fibromyalgia, chronic fatigue syndrome.

Diagnosis. General laboratory findings: elevated erythrocyte sedimentation rate, mildly elevated hepatic transaminases, microscopic hematuria or proteinuria, in Lyme meningitis, CSF typically shows lymphocytic pleocytosis, slightly elevated protein, and normal glucose.

Laboratory diagnosis: demonstration of diagnostic IgM or IgG antibodies in serum. A two-tiertesting protocol is recommended-EIA or IFA should be performed first; if positive or equivocal it is followed by a Western blot. Isolation of organism from a clinical specimen should be performed. In suspected Lyme meningitis, testing for intrathecal IgM or IgG antibodies may be helpful.

Serologic tests are insensitive during the first few weeks of infection. During this stage, patients with an EM rash may be diagnosed clinically. While not necessary, acute and convalescent titers may be helpful in some cases. In persons with illness >1 month, only IgG testing should be performed (not IgM). A positive IgM test alone is not sufficient to diagnose current disease. Due to antibody persistence, single positive serologic test results cannot distinguish between active and past infection. Serologic tests cannot be used to measure treatment response. Enzyme immunoassay (EIA) and immunofluorescence assay (IFA) tests have low specificity and may yield false-positive results. They may cross-react with antibodies to commensal or pathogenic spirochetes, some viral infections (e.g., varicella, Epstein-Barr virus), or certain autoimmune diseases (e.g., lupus).

Treatment. Treatment regimens listed in the following table are for Lyme disease (table 6).

Table 6. – Table of recommended antibiotics and dosages for treatment of Lyme Disease

Symptom	***Drug (oral/intravenous)***	***Adult Dosage***	***Pediatric Dosage***[2]
Tick Bite	Doxycycline[3,4] or observation only	200mg PO single dose	Age < 8 y: not recommended; Age ≥ 8 y: 4 mg/kg (max. 200 mg/dose)
ERYTHEMA MIGRANS & OTHER SYMPTOMS OF EARLY DISSEMINATION	Doxycycline[3,5,6,7] OR	100mg POb.i.d.	Age < 8 y: not recommended; Age ≥ 8 y: 4 mg/kg div. b.i.d. (max. 100 mg/dose)
	Amoxicillin[6,8]	500mg POt.i.d.	50 mg/kg/day div. t.i.d. (max. 500 mg/dose)
	Cefuroximeaxetil[6,8]	500mg POb.i.d.	30 mg/kg/day div. b.i.d. (max. 500 mg/dose)
NEUROLOGIC DISEASE Facial nerve palsy	Doxycycline[3,5] OR	100mg POb.i.d.	Age < 8 y: not recommended; Age ≥ 8 y: 4 mg/kg div. b.i.d. (max. 100 mg/dose)
	Amoxicillin8	500mg POt.i.d.	50 mg/kg/day div. t.i.d. (max. 500 mg/dose)
	Ceftriaxone OR	2 g/day IV	50-75 mg/kg/day IV (max. 2 g/dose)
	Cefotaxime OR	2 g IV given q8h	150-200 mg/kg/day IV div.t.i.d. or div. q.i.d. (max. 6 g/day; max. 2 g/dose)
More serious CNS disease[9]	Penicillin G[10]	18-24 million units/day IV div. doses given q4h	200,000 – 400,000 units/kg/day IV div. doses given q4h (max. 18-24 million units/day)
CARDIAC DISEASE Mild	Doxycycline[3,5] OR	100mg POb.i.d.	Age < 8 y: not recommended; Age ≥ 8 y: 4 mg/kg b.i.d.

Symptom	*Drug (oral/intravenous)*	*Adult Dosage*	*Pediatric Dosage*[2]
			(max. 100 mg/dose)
More serious[9,11]	Amoxicillin[8]	500mg POt.i.d.	50 mg/kg/day div. t.i.d. (max. 500 mg/dose)
	Ceftriaxone OR	2 g/day IV	50-75 mg/kg/day IV (max. 2 g/dose)
	Cefotaxime OR	2 g IV given q8h	150-200 mg/kg/day IV div. t.i.d. or div. q.i.d. (max. 6 g/day; max. 2 g/dose)
	Penicillin G[10]	18-24 million units/day IV div. doses given q4h	200,000 – 400,000 units/kg/day IV div. doses given q4h (max. 18-24 million units/day)
ARTHRITIS Mild	Doxycycline[3,5] OR	100mg POb.i.d.	Age < 8 y: not recommended; Age ≥ 8 y: 4 mg/kg b.i.d. (max. 100 mg/dose)
	Amoxicillin[8]	500mg POt.i.d.	50 mg/kg/day div. t.i.d. (max. 500 mg/dose)
More serious[9]	Ceftriaxone OR	2 g/day IV	50-75 mg/kg/day IV (max. 2 g/dose)
	Penicillin G[10]	18-24 million units/day IV div. doses given q4h	200,000 – 400,000 units/kg/day IV div. doses given q4h (max. 18-24 million units/day)

NOTES:

1. Clinicians generally recommend 14-21 days for oral drugs and 14-28 days for intravenous treatment.

2. Should not exceed adult dosage.

3. Or use tetracycline HCI (acromycin, and others), 250-500 mg q.i.d.; Doxycycline (and any other tetracyclines) are relatively contraindicated for pregnant and lactating women.

4. A single preventative dose of doxycycline can be used within 72 hours after tick removal for patients age ≥ 8 if the attached tick is identified as an adult or nymphal Ixodes scapularis tick estimated to have been attached for at least 36 hours (on the basis of degree of engorgement with blood or certainty about the time of exposure) and if the local rate of Borrelia burgdorferi infection among ticks is at least 20 percent. If any one of these criteria is not met, then observation is recommended instead. The efficacy of this single preventative dose of doxycycline is unknown for human granulocytic anaplasmosis (HGA) and babesiosis.

5. Doses should be taken with 8 oz. of fluid and with food to reduce risk of esophageal irritation and gastrointestinal intolerance. Effective for HGA.

6. Adult patients who cannot tolerate doxycycline, amoxicillin, or cefuroxime axetil may use the following alternatives (however, these treatments are less effective): azithromycin (500 mg PO daily for 7 to 10 days),clarithromycin (500 mg PO twice daily for 14 to 21 days if patient is not pregnant), or erythromycin (500 mg orally four times per day for 14 to 21 days). Children should use the following recommended dosages:azithromycin, 10 mg / kg daily (max. 500 mg / day); clarithromycin, 7.5 mg / kg twice daily (max. 500 mg per dose); and erythromycin, 12.5 mg / kg four times daily (max. 500 mg / dose). Patients treated with macrolidesshould be followed closely to ensure resolution of clinical symptoms.

7. Duration of doxycycline treatment for patients presenting erythema migrans (in absence of cardiac or neurological symptoms) is 14 (range: 10-21) days.

8. Not effective for HGA.

9. In late disease, the response to treatment may be delayed for several weeks or months.

10. Patients with impaired renal function should receive a reduced penicillin dosage.

11. A temporary pacemaker may be necessary.

For patients intolerant of amoxicillin, doxycycline, and cefuroximeaxetil, the macrolides azithromycin, clarithromycin, or erythromycin may be used, although they have a lower efficacy. Patients treated with macrolides should be closely observed to ensure resolution of clinical manifestations.

In chronic diseases a longer course of antibiotics should be given (30 days). IV cefotaxim is preffered for neurological diseases.

Prevention. Wearing the light-colored clothes makes it easier to spot ticks. It is recommended to wear long pants and long sleeves. The use of tick repellent, such as permethrin, on clothes and DEET on skin is effective. Check yourself for ticks after being outside. Remove tick head immediately.

EHRLICHIOSIS

Ehrlichiosis is a tickborne bacterial infection, caused by bacteria of the family Anaplasmataceae, genera Ehrlichia and Anaplasma. Ehrlichiosis is obligate intracellular bacteria wich infect and kill white blood cells.

Etiology. Ehrlichiosis is a nationally notifiable disease in the United States. There have been cases reported in every month of the year, but most cases are reported during April–September. These months are also the peak months for tick activity.

Six species have been shown to cause human infection:

Anaplasma phagocytophilum (is endemic to New England, north central and Pacific regions of the United States). *Ehrlichia ewingii* and *Ehrlichia chaffeensis* (south central and southeastern states of the United States). *Ehrlichia canis* and *Neorickettsia sennetsu, Ehrlichia muris* (Eastern Europe and Japan).

Ehrlichia are transported between cells through the host cell filopodia during initial stages of infection, whereas, in the final stages of infection the pathogen ruptures the host cell membrane.

Ehrlichiae are obligate intracellular bacteria which attack white blood cells, a feature even more specialized at the species level:

E. canis infects canine monocytes and lymphocytes but only rarely infects neutrophils;

E. ewingii infects canine granulocytes;

E. chaffeensis infects predominantly monocytes and macrophages;

A. phagocytophilum infects granulocytes.

Pathogenesis. The elementary body is the infective stage and enters the monocyte or other leucocyte types by phagocytosis. Elementary bodies are individual ehrlichiae about 1 μm in diameter and usually coccoid or ellipsoid in shape. Once they are captured inside the phagosomes, the pathogens replicate by binary fission, forming clusters of tightly packed elementary bodies termed initial bodies. Additional growth and replication leads to the formation of the morula, the configuration that typifies the genus. Rupture of the host cell releases the elementary bodies to infect new cells.

Clinical picture. Clinical features of ehrlichiosis and anaplasmosis are similar. The onset of symptoms usually occurs about three weeks after an individual has been bitten by a tick. Symptoms may initially include fever, chills, headaches, muscle pain (myalgia), and a general feeling of weakness and fatigue (malaise). Rash may appear on the skin (can look like red splotches or pinpoint dots).

In 2008, the ehrlichiosis case definition was split into four categories:

- Ehrlichia chaffeensis infection
- Ehrlichia ewingii infection
- Anaplasma phagocytophilum infection
- Undetermined ehrlichiosis/anaplasmosis

Symptoms may then progress to include nausea, vomiting, loss of appetite (anorexia), and/or weight loss. Some affected individuals may also experience coughing, diarrhea, sore throat (pharyngitis), and pain in the abdominal area.

In most cases of ehrlichiosis, there is also an abnormal decrease in white blood cells (leukopenia), a low number of circulating blood platelets (thrombocytopenia), and/or an abnormal increase in the level of certain liver enzymes (hepatic transaminases). Some affected individuals may also experience inflammation of the liver (hepatitis).

In some severe cases of ehrlichiosis, if appropriate treatment is not received, symptoms may include shortness of breath (dyspnea); abnormalities in the blood's ability to clot properly (coagulopathy), potentially resulting in gastrointestinal bleeding; and/or neurologic

abnormalities due to involvement of the brain and the spinal cord (central nervous system).

Affected individuals with CNS involvement may develop abnormal tissue changes (lesions) in the brain, experience inflammation of the protective membranes covering the brain and spinal cord (meningitis), and/or have abnormalities in the fluid surrounding the brain and spinal cord (cerebrospinal fluid).

Neurologic symptoms and findings may include confusion, abnormal sensitivity to light (photophobia), stiffness of the neck, episodes of uncontrolled electrical disturbances in the brain (seizures), and/or coma. Additional neurologic abnormalities may include exaggerated reflex responses (hyperreflexia), impaired coordination of voluntary movements (ataxia), and/or loss of some motor function in the facial area due to impairment of one or more of the 12 nerve pairs arising from the brain (cranial nerve palsy).

In severe cases, if ehrlichiosis is left untreated, life-threatening complications may result, such as kidney (renal) and/or respiratory failure.

Diagnosis. Ehrlichiosis may be diagnosed based upon a thorough clinical evaluation, characteristic findings, and specialized laboratory tests.

Blood tests may reveal findings often associated with the ehrlichioses such as abnormally low levels of blood platelets (thrombocytopenia), low levels of certain white blood cells (leukopenia), and/or elevated levels of certain liver enzymes (such as aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).

In some cases, laboratory tests may reveal abnormalities of the cerebrospinal fluid. In addition, chest X-rays may reveal abnormalities in the lungs (e.g., pulmonary infiltrates, increased fluid in the lungs).

Specialized laboratory tests may include Indirect Immunofluorescence Assays (IFA) conducted on the fluid portion of an affected individual's blood (serum). IFA testing has been used in confirming a diagnosis of all known types of Human Ehrlichiosis.

Measurable diagnostic rises in antibody response to the Ehrlichia bacteria may not occur until approximately three weeks. As a result, initial IFA blood serum results may be negative in some cases. Therefore, more sensitive testing techniques that can help establish early diagnosis may be used in some cases.

One such is Polymerase Chain Reaction (PCR). PCR conducted on certain bacterial DNA sequences obtained from patients' blood samples may confirm Ehrlichiosis due to a particular strain of Ehrlichia. PCR has been used to establish an early diagnosis of Ehrlichiosis.

Treatment. Treatment of ehrlichiosis and anaplasmosis is best started before laboratory results return. When treatment is started early, patients generally respond rapidly and well.

The treatment of Ehrlichiosis usually entails standard doses of tetracycline antibiotics. Doxycycline is the medications of choice. For people allergic to antibiotics of the tetracycline class, rifampin is an alternative. Early clinical experience suggested that chloramphenicol may also be effective.

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves and has been afebrile for 24 to 48 h but is continued for at least 7 days. Chloramphenicol is no longer effective.

Some patients continue to experience headache, weakness, and malaise for weeks after adequate treatment.

Prevention. No human vaccine is available for ehrlichiosis. Tick control is the main preventive measure against the disease.

Preventing tick access to skin includes:

1. Staying on paths and trails.
2. Tucking trousers into boots or socks.
3. Wearing long-sleeved shirts.
4. Applying repellents with diethyltoluamide (DEET) to skin surfaces.

After tick bite the patient can also use doxycycline 200 mg po once.

Q FEVER

Etiology. Q fever is most often related to inhalation of aerosolized organisms during animal exposure, occupational exposure, and tick bites (usually to domesticated household and farm animals). C burnetii – a strict, intracellular, pleomorphic, gram-negative coccobacillus classified as a Legionellae species – is the causative organism; it localizes in the mammary glands, uterus, and feces of domestic and small mammals. However, because of the persistence of Coxiella organisms in nature as a sporelike structure (making it highly

resistant to inactivation; it can survive for months in dust and feces particles), C burnetii can infect people with no known contact with animals. For example, an outbreak of Q fever was reported in people living along a road on which farm vehicles contaminated with straw and manure traveled. Laboratory outbreaks have also occurred. Only 1 case of documented human-to-human transmission exists.

Why chronic Q fever develops in certain patients is unknown. Current understanding of chronic Q fever indicates activation of a previously asymptomatic infection.

Epidemiology. First described in Australia in 1937, multiple international reports of Q fever clusters have been described over the years. The frequency ranges from 5% in urban areas to 30% in rural areas. Because Q fever infection can frequently be asymptomatic or present as a flulike illness in its milder forms, this results in an underrepresentation of the actual incidence. Epidemiological serological testing of specimens from blood donors has discovered a higher incidence throughout Africa, ranging from 18% to 37%, whereas "at-risk" farmers in the United Kingdom demonstrated 29% seropositivity. The United Kingdom reports approximately 100 cases annually.

In southern France and Spain, Q fever is highly prevalent; this disease is the second most common cause of community-acquired pneumonia and causing 5-8% of endocarditis cases. More recently, a few clusters of Q fever were reported in the province of Nova Scotia, Canada, and were related to exposure to parturient cats.

Q fever is endemic in the Middle East. Transmission may be influenced by hot, dusty conditions and livestock farming practices that may facilitate windborne spread.

In addition, a large number of Q fever cases have been reported in The Netherlands since 2007, with over 3700 human cases reported through March 2010. Infected dairy goat farms are believed to be the source of the outbreak, and most human cases have been reported in the southern region of the country.

Moreover, acute disease seems to have regional variations. An influenzalike illness is the most common presentation of Q fever in Australia. Hepatitis has been reported in France, southern Spain, and Ontario, Canada. Pneumonia is more common in Crete; Switzerland; Nova Scotia, Canada; and the Basque region of Spain. The reason for these variations is unknown, but animal studies suggest important strain differences could be a factor.

As noted earlier, Q fever is a ubiquitous zoonotic disease caused by C burnetii, with protean clinical manifestations that are not yet fully understood. C burnetii has a worldwide distribution from its reservoirs (including mammals, birds, and ticks), and the development of Q fever is strongly related to exposure to farm animals (primarily cattle, sheep, and goats) and particularly parturient animals (including cats and rabbits) because the organism is reactivated in pregnant animals. In one reported case, an obstetrician developed symptoms of Q fever 1 week after delivering a child to a woman who had Q fever. A characteristic of infection with C burnetii is that only humans regularly express the disease.

Initially classified as a species of the genus Rickettsia because of its obligatory intracellular growth requirements, C burnetii is now recognized as a bacterium within the gamma group of Proteobacteria. Genome and 16SrRNA sequencing have identified substantial homology with Legionella pneumophila, also a member of that taxonomic group.

C burnetii is a strict, intracellular, pleomorphic, gram-negative coccobacillus with an incubation period of 9-40 days; the average incubation period is 20 days (range, 18-21 d). Q fever is primarily transmitted by: (1) aerosolization from newborn animals, their placentas, and contaminated hides and fur; (2) ingestion of raw milk and goat cheese; (3) transfusions of blood products; (4) mother to offspring (ie, vertical) transmission; and (5) tick bites. Even wind patterns may make a difference by spreading aerosolized organisms downwind. Outbreaks of Q fever have occurred in an industrial setting from straw board that had been drilled open during part of the construction process. Although the respiratory system is the main organ system affected, the gastrointestinal (GI) and cardiac systems can also be affected.

Clinic. Q fever is a protean disease that lacks a distinct clinical presentation. Almost 50% of patients are asymptomatic. Common presentations vary geographically. For example, in the Basque region of northern Spain, pneumonia is a common finding, whereas in southern Spain, hepatitis predominates.

The primary factor leading to the identification of Q fever is the epidemiologic circumstance: a history of exposure, particularly occupational exposure, exposure to parturient animals or their newborn, or tick bites.

Most common symptoms include fever:

Acute Q fever. Sixty percent of patients with Q fever are asymptomatic. The incubation period varies from 2 to 6 weeks (range, 14-39 d; average, 20 d). The 3 main clinical presentations are as follows:

A self-limited, influenzalike febrile illness (up to 40°C) (88-100%) of abrupt onset, which is often accompanied by headache (68-98%) (typically retrobulbar), myalgia (47-69%) (arthralgia is uncommon), chills (68-88%), fatigue (97-100%), and sweats (31-98%); the temperature returns to normal within 5-14 days.

Pneumonia (predominant in North America), usually mild in nature (crackles auscultated in 50% of cases) or as an incidental radiographic finding; when there is respiratory involvement, patients have a dry, nonproductive cough (24-90%), dyspnea, and pleuritic chest pain; this condition is rarely fulminant but occasionally progresses to acute respiratory distress syndrome (ARDS).

Hepatitis (predominant in Europe), usually with mild elevation of transaminases (2-3 times the reference range) and may be associated with antismooth muscle, antiphospholipid, or antinuclear antibodies; jaundice and acute gastrointestinal (GI) symptoms (nausea and vomiting, diarrhea [rare], right upper quadrant abdominal pain) are rare; manifestations resolve within 2-3 weeks.

Cardiovascular and neurologic manifestations develop in approximately 1% of patients and include pericarditis, myocarditis, and meningoencephalitis. A dissociation between heart rate and temperature occurs in one third of cases, some patients with acute Q fever pericarditis report chest pain, patients with myocarditis may experience palpitations, chest pain, or dyspnea. The 3 major neurologic syndromes of Q fever are meningoencephalitis or encephalitis, meningitis, and myelitis and peripheral neuropathy. Other neurologic symptoms may include headache, confusion, and neck stiffness.

Dermatologic manifestations in the form of erythema nodosum or other nonspecific exanthemas, maculopapular rash, or diffuse punctiform pruritic rash may also be associated with acute disease. Rash is not a typical feature of Q fever, but skin manifestations have been reported in up to 20% of French patients.

Obstetric manifestations include spontaneous abortion. Rare presentations have included thyroiditis, mediastinal lymphadenopathy,

pancreatitis, mesenteric panniculitis, epididymitis, orchitis, priapism, inappropriate secretion of antidiuretic hormone (SIADH), optic neuritis, Guillain-Barré syndrome, and extrapyramidal neurologic disease.

Chronic Q fever. Among patients with acute infection, 0,2-1,4% may develop chronic infection, but few data are available regarding this. Chronic infection (defined as infection lasting longer than 6 months) may not manifest until months or even years after acute infection.

Endocarditis with negative culture findings and seropositivity (culture positivity and seropositivity or culture negativity and seronegativity are relatively uncommon) is the main clinical presentation of chronic Q fever, usually occurring in patients with preexisting cardiac disease including valve defects, rheumatic heart disease, and prosthetic valves. Patients in immunocompromised states (eg, due to acquired immunodeficiency syndrome [AIDS], renal failure, hematologic cancer [including lymphoma], and long-term corticosteroid use) are also susceptible. Patients may present with heart failure or nonspecific symptoms, including low-grade fever, fatigue, chills, arthralgia, dyspnea, rash from septic thromboembolism, and night sweats.

Other systemic manifestations include the following:

Vascular (infections of aneurysms, grafts, prostheses); osteoarticular (osteomyelitis, coxitis, spondylodiskitis, arthritis, septic arthritis, no associated host factors in children, immunocompromise or prosthetic joints in adults); obstetric (spontaneous abortion, premature labor (likely due to placentitis)); hepatic (chronic hepatitis (usually associated with endocarditis), neurologic (mononeuritis, optic neuritis), pulmonary (interstitial fibrosis, pseudotumor), renal (glomerulonephritis).

Chronic fatigue syndrome has also been described in approximately 10% of patients, more than 6 months following acute Q fever. In addition, C burnetii could be added to the organisms involved in TORCH syndrome (toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex).

Diagnosis. The diagnosis of Q fever relies on a high index of suspicion as suggested by the epidemiologic features and is proven by serologic analysis. The organism is very infectious, and isolation ought to be done in biosafety level 3 laboratories. If a clinician thinks

Q fever is a likely diagnosis, the laboratory should be notified so that they can take appropriate precautions.

Electrocardiography (ECG) may show T-wave abnormalities if myocarditis and pericarditis are present.

Acute Q fever may present with the following laboratory results:

A complete blood cell (CBC) count usually shows a normal white blood cell (WBC) count (70-90%) (elevated WBC in as many as 30%.), mild thrombocytopenia (25%) (followed by a reactive thrombocytosis during the convalescent period), and, in rare cases, hemolytic anemia.

Liver function tests usually show mild elevation of transaminases (2-3 times the reference range in 70-85% of patient) and alkaline phosphatase (2-3 times the reference range) without hyperbilirubinemia.

The erythrocyte sedimentation rate (ESR) is usually elevated (55 mm/h ± 30 mm/h)

Several positive autoimmune antibodies, including antismooth muscle and antiphospholipid, may be seen.

Blood cultures are typically negative (Note that, although possible, attempting to isolate the organism from blood is a dangerous practice; cases of Q fever have developed in laboratory technicians).

C burnetii can be seen on smears or frozen tissue prepared with a routine Giemsa stain. Histopathologic changes consistent with doughnut granulomata the liver and bone marrow may be observed, but these are not specific for C burnetii. They can also occur in Hodgkin lymphoma, typhoid fever, cytomegalovirus infection, infectious mononucleosis, and allopurinol hypersensitivity.

In chronic Q fever, the following laboratory results may be observed:

- Anemia of chronic disease
- Elevated ESR
- Elevated gamma globulins (polyclonal)
- Elevated rheumatoid factor (RF)
- Increased creatinine levels.

Most cases of Q fever are diagnosed based on detection of phase I and II antibodies (between acute and convalescent paired sera); a 4-fold rise in complement-fixing antibody titer against phase II antigen occurs and yields the highest specificity. This requires a baseline sample and another sample in 3-4 weeks. Thus, serologic tests are not helpful acutely but may later confirm the diagnosis: Seroconversion

generally occurs between days 7 and 15 and is almost always present by 21 days.

The 3 serologic techniques used for diagnosis include indirect immunofluorescence (IIF) (method of choice), complement fixation, and enzyme-linked immunosorbent assay (ELISA) (comparable to IIF). As noted above, significant titers may take 2-4 weeks to appear. Laboratory values vary considerably, so clinicians must interpret results according to their local standards.

Raoult et al recommended serologic testing 2 years following treatment in patients with valvulopathy after acute infection, whereas Healy et al recommended serial testing every 4 months for 2 years, with additional investigation in those with elevated phase 1 immunoglobulin G (IgG) titers greater than 800.

Serologic follow-up to detect a rise in phase I IgG titers of 1:800 or more can be performed twice every 3 months. If detected, transesophageal echocardiography and serum real-time polymerase chain reaction (PCR) techniques can be performed in an attempt to diagnose endocarditis. Sensitivities may be as low as 18% in early disease.

Interpretation of Q fever serology is challenging in regard to discordance of the serologic results from different reference laboratories. None of these results should be used in isolation, and their interpretation should always be applied in the appropriate clinical context. False-positive serologic results may occur in legionellosis and leptospirosis.

Treatment. As with any patient with a febrile illness, the physician should maintain a sufficient level of suspicion about any patient with fever to exclude other potentially life-threatening diseases, which, in the case of tick-borne disease, involves presumptive antibiotic therapy.

Although specific antimicrobial therapy is indicated, most patients improve spontaneously. However, when Q fever is diagnosed, the administration of antibiotics is appropriate to prevent progression to chronic disease, which is far more resistant to treatment. In addition, supportive care with fluids, antitussives, and antipyretics may improve patient comfort. Patients should avoid ingestion of unpasteurized dairy products as well.

Surgical intervention may be necessary in some cases; for example, surgical treatment can affect survival in endovascular complications such as mycotic aneurysm or vascular graft infections.

Valvular replacement is indicated for intractable heart failure. C burnetii can persist on endocardial tissue even after valve replacement; therefore, antibiotics should be continued following surgery. Surgical debridement is also recommended for osteoarticular infections.

CHOLERA

Definition. Cholera is an infection of the small intestine caused by the bacterium Vibrio cholerae. It is an acute diarrhoeal disease that can kill within hours if left untreated.

Epidemiology. Cholera affects an estimated 3-5 million people worldwide, and causes 100,000-130,000 deaths a year as of 2010. This occurs mainly in the developing world. Cholera remains both epidemic and endemic in many areas of the world. From 1987 until 1995, Angola, particularly Luanda and the coastal areas, was affected by recurrent seasonal epidemics of cholera, which resulted in an estimated 90,000 cases and more than 4,500 deaths. Since 1995, there have been no major cholera epidemics in Angola and only occasional reports of unconfirmed cases within Luanda. Approximately 45% of the cases were reported from Luanda, 17% from Benguela, and 8% from Malange. The outbreak appeared to be waning in September and October, but the number of cases began to rise again in early November with the arrival of the rains.

Vibrios in Nature. Vibrios are among the most common bacteria in surface water worldwide. They appear curved aerobic rods and are motile, possesing a polar flagellum. V.cholerae serogroups O1 and O139 casue cholera in humans, while other vibrios may cause sepsis or enteritis Epidemiology and spread of Cholera closely parallels the recognition of V.cholerae transmission in water and the development of sanitary system.

Morphology and Identification

- V.cholerae is a comma shaped curved rod 2-4 μm long'
- It is actively motile by means of polar flagellum
- On prolonged cultivation, vibrios may become straight rods that resemble the gram-negative enteric bacteria.

Enrichment Medium. Enrichment of the fecal specimens are done on Alkaline peptone water. Venktraman Ramakrishan Meidum is

simple medium can be used as transport medium.

Culture. V.cholerae produces convex, smooth, round colonies that are opaque and granular in transmitted light. Grow well at 37°C on many defined media. Vibrios grow at a very high pH (8-5 – 9-5) and are rapidly killed by acid. In resource poor laboratories MacConkey's agar can be used.

Selective Medium – TCBS. V.cholerae grows well on Thiosulphate citrate bile sucrose (TCBS) agar, on which it produces yellow colonies that are readily visible against the dark green background of the agar.

Growth Characteristics. V.cholerae ferments sucrose and mannose but not arabinose. A positve Oxidase test is key step in preliminary identification of V.cholerae and other Vibrios. Vibrio species are susceptible to compound 0/129 and differentiates from Aeromonas. Vibrios usually grow on medium containing 6% NaCl. Halophilic vibrios need and grow in the presence of >6% NaCl. On Blood agar Vibrios show hemodigesion.

Antigenic Structure and Biological Classification. Many Vibrios share a single heatlaible H antigen. Antibodies to H antigen are probably not involved in the protection of susceptible hosts. V.cholerae has O lipopolysachhrade that confer serologic specificity. There are at least 139 O antigen groups. V.cholerae strains of O group 1 and O group 139 cause classic cholera. Occasionally non 01/non 0139 V.cholerae cause Cholera like disease.

V.cholerae – typing. V.cholerae 01 has determinants that make possible futher typing. Serotypes are: Ogawa, Inaba and Hikojima.

Epidemic V.cholerae is biotyped into Classic and El Tor Vibrios.

The El Tor vibrios produce a Hemolysin and positive results with Voges-Proskauer test. It is resistant to Polymyxin B. Molecular techniques can also be used to type V.chlorae. Tests can be done reference laboratories and technically demanding.

New Epidemic of V.cholrae 0139.

The epidemic of cholera caused by V cholerae 0139 has affected at least 11 countries in southern Asia. V cholerae 0139 produces severe watery diarrhea and dehydration that is indistinguishable from the illness caused by V cholerae 01, and appears to be closely related to V cholerae 01 biotype El Tor strains. Specific totals for numbers of V cholerae 0139 cases are unknown because affected countries do not report infections caused by 01 and 0139 separately; however,

>100,000 cases of cholera caused by V cholerae 0139 may have occurred.

V.cholerae – 0-139. V.cholerae 0139 is very similar to V.cholerae 01 El Tor biotype. V.cholerae 0139 donot produce 01 type lipopolysachhrade and does not have all the genes necessary to make this antigen. V.cholerae 0139 make a polysachhrdie capsule like other non 01 V.cholerae strains while V.cholerae 01 does not make a capsule.

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Vibrio cholerae – Enterotoxin. V.cholerae produce heat labile enterotxoin with a Mol wt of about 84,000 consisting of sub units A (MW 28,000) and B. Ganglioside GM_1 serves as a mucosal receptor for subunit B, which promotes entry of subunit A into the cell. Activation of subunit A_1 yields increased levels of intracellular $_cAMP$ and results in prolonged hyper secretion of water and electrolytes. There is increased sodium dependent chloride secretion, and absorption of sodium and chloride is inhibited. The genes for V.cholerae Enterotoxin are on the bacterial chromosome. Cholerae Enterotoxin is antigenically related to LT of Escherichia.

Cause. About one hundred million bacteria must typically be ingested to cause cholera in a normal healthy adult. This dose, however, is less in those with lower gastric acidity. Children are also more susceptible, with two- to four-year-olds having the highest rates of infection. Individuals' susceptibility to cholera is also affected by their blood type, with those with type O blood being the most susceptible. Persons with lower immunity, such as persons with AIDS or children who are malnourished, are more likely to experience a severe case if they become infected. The cystic fibrosis genetic mutation in humans has been said to maintain a selective advantage: heterozygous carriers of the mutation (who are thus not affected by cystic fibrosis) are more resistant to V. cholerae infections. In this model, the genetic deficiency in the cystic fibrosis transmembrane conductance regulator channel proteins interferes with bacteria binding to the gastrointestinal epithelium, thus reducing the effects of an infection.

Transmission. Cholera is typically transmitted by either contaminated food or water. In the developed world, seafood is the

usual cause, while in the developing world it is more often water. Cholera has been found in only two other animal populations: shellfish and plankton.

People infected with cholera often have diarrhea, and if this highly liquid stool, colloquially referred to as "rice-water" or "faucet butt", contaminates water used by others, disease transmission may occur. The source of the contamination is typically other cholera sufferers when their untreated diarrheal discharge is allowed to get into waterways, groundwater or drinking water supplies. Drinking any infected water and eating any foods washed in the water, as well as shellfish living in the affected waterway, can cause a person to contract an infection. Cholera is rarely spread directly from person to person. Both toxic and nontoxic strains exist. Nontoxic strains can acquire toxicity through a temperate bacteriophage. Coastal cholera outbreaks typically follow zooplankton blooms, thus making cholera a zoonotic disease.

Pathology and pathogenesis. Most bacteria, when consumed, do not survive the acidic conditions of the human stomach.The few surviving bacteria conserve their energy and stored nutrients during the passage through the stomach by shutting down much protein production. When the surviving bacteria exit the stomach and reach the small intestine, they need to propel themselves through the thick mucus that lines the small intestine to get to the intestinal walls, where they can thrive. V. cholerae bacteria start up production of the hollow cylindrical protein flagellin to make flagella, the cork-screw helical fibers they rotate to propel themselves through the mucus of the small intestine.

Once the cholera bacteria reach the intestinal wall, they no longer need the flagella to move. The bacteria stop producing the protein flagellin, thus again conserving energy and nutrients by changing the mix of proteins which they manufacture in response to the changed chemical surroundings. On reaching the intestinal wall, V. cholerae start producing the toxic proteins that give the infected person a watery diarrhea. This carries the multiplying new generations of V. cholerae bacteria out into the drinking water of the next host if proper sanitation measures are not in place. V.cholerae is pathogenic to humans. When bacteria are consumed with food few organism as much as 10^2–10^4 organisms are adequate to cause an attack because of the buffering capacity of the food. Any medication or conditions that

decrease stomach acidity makes a person more susceptible to infection with V.cholrae. But a person with normal gastric acidity has to consume 10^{10} or more V.cholerae are when ingested with water.

Cholera is not an invasive infection. Organisms do not reach blood, only act locally. Virulent V.cholerae organism attach to the microvillus of the brush border of epithelial cells. They multiply and liberate cholera toxin and perhaps Mucinase and Endotoxin.

Clinical features. The incubation period is 1-4 days for person who develop symptoms, depends on the size of the inoculums ingested Manifest with Nausea , vomiting, profuse diarrhea, and abdominal cramps, Rice water stool characteristic of cholera loss of fluid leads to profound dehydration & Circulatory collapse and anuria.

Diarrhea leads to loss 20-30 liters of fluids per day. It results in dehydration, shock, acidosis and can lead to death. About 60% of infections are caused by classic V.cholerae and are asymptomatic, about 75% of infections are caused by El Tor biotype.

The diarrhea is frequently described as "rice water" in nature and may have a fishy odor. An untreated person with cholera may produce 10-20 litres of diarrhea a day with fatal results. For every symptomatic person, three to 100 people get the infection but remain asymptomatic. Cholera has been nicknamed the "blue death" due to a patient's skin turning a bluish-gray hue from extreme loss of fluids.

If the severe diarrhea and vomiting are not aggressively treated, they can, within hours, result in life-threatening dehydration and electrolyte imbalances. The typical symptoms of dehydration include low blood pressure, poor skin turgor (wrinkled hands), sunken eyes, and a rapid pulse.

Diagnosis. A rapid dip-stick test is available to determine the presence of V. cholerae. In those samples that test positive, further testing should be done to determine antibiotic resistance. In epidemic situations, a clinical diagnosis may be made by taking a patient history and doing a brief examination. Treatment is usually started without or before confirmation by laboratory analysis.

Stool and swab samples collected in the acute stage of the disease, before antibiotics have been administered, are the most useful specimens for laboratory diagnosis. If an epidemic of cholera is suspected, the most common causative agent is V. cholerae.

Direct microscopy of stool is not recommended, as it is

unreliable. Microscopy is preferred only after enrichment, as this process reveals the characteristic motility of Vibrio and its inhibition by appropriate antisera. Diagnosis can be confirmed, as well, as serotyping done by agglutination with specific sera.

Stool Examination. Stool specimens appear as Rice water. Microscopy of the stool reveals mucus, epithelial cells and large number of vibrios. Milder cases are difficult to differentiate from other diarrheal diseases. El Tor vibrios cause milder disease than classic biotypes.

Specimen Collections. Stool specimens are collected in acute stage of the disease before the antibiotics are administered. Simple collection of stool in a wide Mouthed container is safe and hygienic. Specimens should not be collected from bed pans. Vomitus is not advised to collect.

Laboratory Diagnosis. Mucus flecks from stool are cultured. Smears are not useful for diagnosis. Dark field microscopy shows rapidly motile vibrios.

Laboratory Diagnosis Culture:

- Growth is rapid on Blood agar,
- On TCBS medium typical colonies can be picked in 18 hours.
- The stool specimens can be transported in Venkatraman Ramakrishnan medium
- Alkaline peptone water is ideal enrichment medium

Confirmatory Tests for V.cholerae

- V.chlorae organisms are further identified by slide agglutination tests using anti – 0 group 1 or group 139 Antisera and by Biochemical reactions

Immunity in Cholerae. Gastric acid produces some protection against cholera vibrios. An attack of cholera if followed by immunity to reinfection but the duration and degree of immunity are not known. In experimental animals specific IgA antibodies occur in the lumen of intestine. Vibriocidal antibodies in the serum titer >1:20 have been associated with protection against colonization and disease. The presence of antitoxin antibodies have not been asociated with protection.

When you suspect Cholera. The diagnosis of cholera should be considered in patients with watery diarrhea who have recently (i.e., within 7 days) returned from cholera-affected countries. Patients with

suspected cholera should be reported immediately to local and state health departments.

Treatment.

- The most important part of therapy consists of correction water and electrolyte imbalance to correct severe dehydration and salt depletion.
- Oral Tetracycline tends to reduce stool output in cholera and shortens the period of excretion of vibrios
- In some endemic areas tetracycline resistance has emerged the genes are carried by transmissible plasmids

Continued eating speeds the recovery of normal intestinal function. A CDC training manual specifically for cholera states: «Continue to breastfeed your baby if the baby has watery diarrhea, even when traveling to get treatment. Adults and older children should continue to eat frequently».

Fluids. In most cases, cholera can be successfully treated with oral rehydration therapy (ORT), which is highly effective, safe, and simple to administer. Rice-based solutions are preferred to glucose-based ones due to greater efficiency. In severe cases with significant dehydration, intravenous rehydration may be necessary. Ringer's lactate is the preferred solution, often with added potassium. Large volumes and continued replacement until diarrhea has subsided may be needed.

If commercially produced oral rehydration solutions are too expensive or difficult to obtain, solutions can be made. One such recipe calls for 1 litre of boiled water, 1/2 teaspoon of salt, 6 teaspoons of sugar, and added mashed banana for potassium and to improve taste.

Electrolytes. As there frequently is initially acidosis, the potassium level may be normal, even though large losses have occurred. As the dehydration is corrected, potassium levels may decrease rapidly, and thus need to be replaced.

Antibiotics. Antibiotic treatments for one to three days shorten the course of the disease and reduce the severity of the symptoms. Doxycycline is typically used first line, although some strains of V. cholerae have shown resistance. Other antibiotics proven to be effective include cotrimoxazole, erythromycin, tetracycline, chloramphenicol, and furazolidone. Fluoroquinolones, such as

norfloxacin, also may be used, but resistance has been reported.

Sari filtration. An effective and relatively cheap method to prevent transmission of V. cholera is the practice of folding a sari (a long fabric garment) multiple times to create a simple filter for drinking water. Folding saris four to eight times may create a simple filter to reduce the amount of active V. cholera in the filtered water. The education of proper sari filter use is imperative, as there is a positive correlation between sari misuse and the incidence of childhood diarrhea; soiled saris worn by women are vectors of transmission of enteric pathogens to young children. Educating at-risk populations about the proper use of the sari filter method may decrease V. cholera-associated disease.

Prevention. Sterilization: Proper disposal and treatment of infected fecal waste water produced by cholera victims and all contaminated materials (e.g. clothing, bedding, etc.) are essential. All materials that come in contact with cholera patients should be sanitized by washing in hot water, using chlorine bleach if possible. Hands that touch cholera patients or their clothing, bedding, etc., should be thoroughly cleaned and disinfected with chlorinated water or other effective antimicrobial agents.

Sewage: antibacterial treatment of general sewage by chlorine, ozone, ultraviolet light or other effective treatment before it enters the waterways or underground water supplies helps prevent undiagnosed patients from inadvertently spreading the disease.

Sources: Warnings about possible cholera contamination should be posted around contaminated water sources with directions on how to decontaminate the water (boiling, chlorination etc.) for possible use.

Water purification: All water used for drinking, washing, or cooking should be sterilized by either boiling, chlorination, ozone water treatment, ultraviolet light sterilization (e.g. by solar water disinfection), or antimicrobial filtration in any area where cholera may be present.

Control of Cholerae

• Needs improvement of Sanitation associated with water treatment and food.

- Patients infected preferably isolated
- Excreta disinfected
- All contacts to be followed up

Use of Vaccine and Chemoprophylaxis

- Chemoprophylaxis with antibiotics is effective.

• Repated injection of vaccine containing either Lipopolysaccharides extracted from Vibrios or dense Vibrios suspension can offer limited prevention to heavely exposed persons.

• Vaccines not useful in Epidemic controls

• Prevention of Cholera

• Although cholera can be life-threatening, it is easily prevented and treated. In the United States, because of advanced water and sanitation systems, cholera is not a major threat; however, everyone, especially travelers, should be aware of how the disease is transmitted and what can be done to prevent it.

• Several regions in the Devloping countries continue to be endemic locations.

Prognosis. If people with cholera are treated quickly and properly, the mortality rate is less than 1%; however, with untreated cholera, the mortality rate rises to 50-60%. For certain genetic strains of cholera, such as the one present during the 2010 epidemic in Haiti and the 2004 outbreak in India, death can occur within two hours of the first sign of symptoms.

LEPTOSPIROSIS

Leptospirosis is an acute anthropo-zoonotic infection. It occurs in tropical, subtropical and temperate zones. Weil Disease, Hemorrhagic Jaundice, Mud Fever, Swineherd Disease,Canicola Fever, seven-day fever found commonly in Japan, Cane cutter's disease in Australia, Rice field Leptospirosis in Indonesia, Fort Bragg fever in U.S.Andamanhaemorrhagic fever (AHF).

The genera Leptospira contain three species, namely L interrogans, L biflexa and L parva. The first includes 23 serogroups and more than 250 serovars and is the principal cause of leptospirosis in humans and animals, most common being L. canicola, L. hardjo and L. hebdomadis.

Two types of leptospirosis are:

1. Anicteric leptospirosis or self-limited illness (85% to 90% of the cases).

2. Icteric leptospirosisorweil's syndrome (5% to 10%).

The etiologic agent of leptospirosis is Leptospira interrogans. It is a thin spiral organism 0,1 mm x 6-20mm, with tightly set coils. It is

characterized by very active motility, by rotating ("spinning") and bending. Usually one or both ends of this single-cell organism are bent or hooked. Because of their narrow diameter, the leptospires are best visualized by dark-field illumination or phase contrast microscopy and they do not stain readily with aniline dyes.

Epidemiology. Cases are seen sporadically throughout the year. But an outbreak occurs during the rainy season because of widespread contamination by infected rodent urine in flood water. Rodents are displaced from their burrows and drains by the water. High humidity and heavy rainfall intensify the outbreak. Rats and bandicoots distribute more virulent leptospires through their urine into the environment than other animals.

Locations where the infection is commonplace, caused by high rainfall, close human contact with livestock or wild animals, poor sanitation or workplace exposure (rice farming, etc). Example countries in class L2 are India, Central America and certain areas of the Pacific Rim. L1 – General. Locations where the infection is at the international average of 0,05 cases per 100,000, and infection is usually the result of accidental exposure through wild rats, livestock or direct contact with water through leisure or occupation. Example countries in class L1 are North America, Europe, Australia and the former Soviet territories.

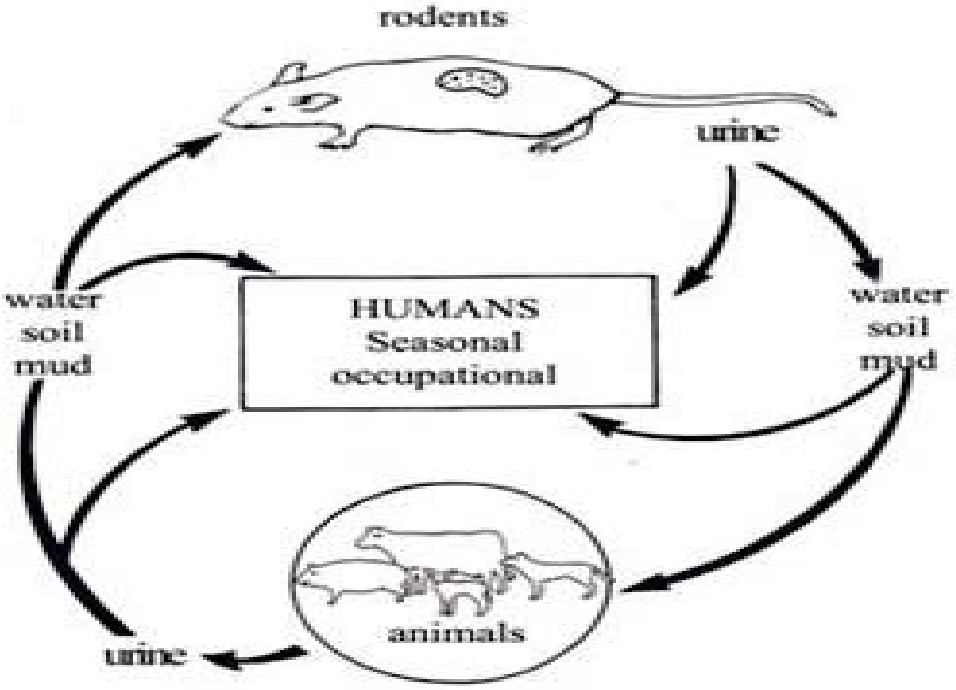

Fig. 5. – Life cycle of Leptospiras

Reservoirs. Wild and domestic animals rodents, livestock (cattle, horses, sheep, goats, swine), canines, and wild mammals are the reservoir for leptospirosis. Many animals have prolonged leptospiruria without suffering from the disease themselves (fig. 14). The incubation period (time of exposure to first symptoms) in animals is anywhere from 2 to 20 days. In dogs the liver and kidney are most commonly damaged by leptospirosis. In addition, there are recent reports of a pulmonary form of canine leptospirosis associated with severe hemorrhage in the lungs similar to the human pulmonary hemorrhagic syndrome. Vasculitis may occur, causing edema and potentially disseminated intravascular coagulation (DIC). Myocarditis, pericarditis, meningitis, and uveitis are also possible sequelae. One should strongly suspect leptospirosis and include it as part of a differential diagnosis if the sclerae of the dog's eyes appear jaundiced (even slightly yellow). The absence of jaundice does not eliminate the possibility of leptospirosis, and its presence could indicate hepatitis or other liver pathology rather than leptospirosis. Vomiting, fever, failure to eat, reduced urine output, unusually dark or brown urine, and lethargy are also indications of the disease.

Modes of Transmission: by direct or indirect contact of nasal, oral, or eye mucosal membranes or abraded or traumatized skin with urine or carcasses of infected animals. Urine: Indirect exposure through water, soil, or foods contaminated by urine from infected animals is the most common route. After a short period of circulating high levels of the spirochete in their blood, animals shed the spirochete in their urine, contaminating the environment. Inhalation of droplet aerosols of contaminated fluids can occasionally occur.

Clinical features. The incubation period lasts from 2 to 26 days, but usually it is 7-12 days. Humans with leptospirosis usually excrete the organism in the urine for 4-6 weeks and occasionally for as long as 18 weeks. Person-to-person transmission is considered extremely rare.

Leptospiral infection in humans causes a range of symptoms, and some infected persons may have no symptoms at all. Leptospirosis is a biphasic disease that begins with flu-like symptoms (fever, chills, myalgias, intense headache). The first phase resolves, and the patient is briefly asymptomatic until the second phase begins. This is characterized by meningitis, liver damage (causing jaundice), and renal failure. The infection is often wrongly diagnosed due to the wide range of symptoms. This leads to a lower registered number of

cases than exists. Symptoms of leptospirosis include high fever, severe headache, chills, muscle aches, and vomiting, and may include jaundice, red eyes, abdominal pain, diarrhea, and rash. Initial presentation may resemble pneumonia. The symptoms in humans appear after a 4–14 day incubation period.

Complications: azotemia, oliguria, hemorrhage, purpura, hemolysis, gastrointestinal bleeding, hypoprothrombinemia and thrombocytopenia.

Diagnosis. Direct Evidence (demonstration of leptospires or their products): microscopy, dark-field microscopy, phase contrast microscopy. ***Indirect Evidence*** (detection of antibodies to leptospira): macroscopic agglutination test (MSAT), Indirect fluorescent antibody test (IFAT), indirect haemagglutination test (IHA), counter immuno electrophoresis (CIEP), Complement fixation test (CFT).

Other techniques: ELISA, microcapsule agglutination test (MCAT), lepto-dipstick, serogroup/serovar specific tests, microscopic agglutination test (MAT), serovar specific ELISA.

Treatment. Six million units of penicillin daily I.V (10-14 days) should be taken. Amoxycillin, Erythromycin, & Doxycycline are used too. Patients with MOF (Multi organ failure) should be observed and treated in intensive care unit.

Prevention. To prevent illness, prevent contamination of living, working and recreational areas by urine of infected animals.

• Control rodent populations in areas of human habitation.

• Domestic animal owners should take necessary precautions to minimize their animal's potential contact with wildlife (e.g., do not feed pets outside or allow animals to roam unsupervised).

• Do not allow animals to urinate in or near ponds or pools.

• Keep animals away from gardens, playgrounds, sandboxes, and other places children may play.

• Among domesticated animals, vaccination of swine, cattle, and dogs should be carried out.

Chlorination is seldom useful, as virulent leptospires withstand up to 4 ppm in potable water. Filtered water is not safe. Using boiled or ultraviolet irradiated water is advisable. Water tanks must be sealed if possible. Food articles must be stored in properly fitting containers. Bathroom and kitchen waste pipes must be blocked at night. Try avoiding walking in flood water. If you have to, wear gum boots. Heavy drinking and smoking predispose damage to the liver and the

kidneys which in turn become vulnerable to leptospiral infection. Protected water supply to all should be provided. Proper collection, transport, treatment and secured disposal of garbage. Drinking boiled water. Disinfection of contaminated work areas should be performed.

Providing proper protective clothing, shoes, gloves, etc. to high-risk occupional groups.

BRUCELLOSIS

Brucellosis (sin.: Maltese, Mediterranean fever, Bruce disease, Bang disease) is infectious-allergic disease, which has a tendency to chronicity. It is characterized by prolonged fever, lesions of the musculoskeletal, nervous, cardiovascular, genitourinary, and other body systems.

Etiology. The presence of an epizootic outbreaks among animals (live-stock, domestic), human contact with these animals, livestock development, migration of people from southern countries contribute to the maintenance of disease in neighboring countries with Belarus. On the other hand, the high frequency of chronicity and disability is associated with late diagnosis of the disease.

There are six basic kinds of pathogens of brucellosis currently known: B. melitensis, B. abortus bovis, B. abortus suis, B. neotomae, B. canis, B. ovis. The main carriers of Br. melitensis, pathogenic to humans are sheep and goats. Morphologically Brucella species do not differ from each other. Microbes are spherical or ovoid, 0.3-0.6 microns in size, Gram-negative, can grow on nutrient media. In the first generation at culturing Brucella grow slowly (2-4 weeks), with passages their growth accelerates. Influenced by antibiotics, bacteria can be transformed into L- shape. Endotoxin is released at their destruction. Brucella are thermolabile: at 60°C they are killed within 30 min; boiling instantly destroys bacteria. At low temperatures, they can be stored for a long time. Brucella die quickly when exposed to sunlight and conventional disinfectants in the working concentrations.

The main manifestations of the epidemic process. Sources of brucellosis infection for humans are small ruminants and cattle, pigs, and reindeers in some areas. Most epidemiological significance belongs to small ruminants due to high pathogenicity of Br. melitensis for humans. Sporadic cases of brucellosis occur when people are infected from sick horses, camels, mules, yaks, dogs, cats. A sick

person is not a source of infection. Animal brucellosis during pregnancy entails an abortion in most cases. Pathogen is found in large quantities in aborted fetuses, membranes, amniotic fluid, placenta.

Great epidemiological significance in the transmission of infection from animals to humans belongs to a raw meat and dairy products: cheese, milk and meat. In raw milk products Brucella exist for 15-60 days, in the meat - up to 20 days. Aerosol mechanism of infection is possible. It is caused by penetration of microbes via the upper respiratory tract with dust particles of wool, manure, litter, the ground. In intense outbreaks, especially sheep and swine brucellosis, the main route of infection is contact.

Connection of brucellosis cases with sick animals and animal products causes obvious professional nature of this infection. The main contingent of patients – workers of the livestock industry (assistance at lambing, abortions) and plants processing animal products. Immunity in brucellosis is low-level and short, on average, it lasts 6-9 months. Immunity is not strictly specific. This makes it possible to vaccinate people with novirulent bovine-type strain (Br. bovis), creating immunity to ovine type too (Br. melitensis).

Pathogenesis. The entry of the pathogen to regional lymph nodes via the lymphatic system is the first phase of pathogenesis that corresponds to the incubation period. Brucella may remain for a long time in the lymph nodes, causing immunological reorganization of an organism without any clinical symptoms (primary latency). With a significant accumulation of the pathogen, Brucella can enter the bloodstream and spread throughout the body – phase of hematogenous drift, primary generalization. Clinically, this corresponds to the acute period of the disease, characterized by fever, chills, sweats, micropolyadenitis and other symptoms. Pathogen is captured from blood by cells of the mononuclear phagocyte system of various organs (liver, spleen, bone marrow, etc.) with the formation of metastatic foci of infection in them – phase of polyfocal localizations. Since the beginning of generalization of infection and formation of metastatic lesions, immunoallergic changes occur in the body and define features of pathogenesis and pathologic course of the disease. Brucella remain in metastatic foci for a long period, being the source of multiple generalization of the pathogen with the development of allergic reactivity changes - phase of exofocus colonization and allergic

reactivity changes. Chronic course of the disease, accompanied by repeated and multiple generalization of the pathogen from the metastatic foci, characterizes the disease as chronic sepsis. The next phase is a phase of residual metamorphosis – corresponds to outcomes of brucellosis, ending with either complete resorption of inflammation, or formation of persistent irreversible scarring of the affected organs and tissues.

Classification. The most appropriate is classification by G.P. Rudnev (1955). According to this classification, there are acute (up to 3 months), subacute (up to 6 months), chronic (more than 6 months) and residual (clinical effects) forms of brucellosis. This classification takes into account not only the duration of the disease, but the severity (mild, moderate, severe), and phases of compensation, decompensation, and subcompensation of the process in each case of the disease.

Clinical picture. The incubation period of brucellosis lasts from 7 to 30 days. Symptomatic forms of brucellosis manifest as prolonged fever, chills, increased sweating, hepatosplenomegaly, disorders of musculoskeletal, nervous, cardiovascular, urogenital, and other body systems.

Acute and subacute forms of brucellosis. The beginning of the disease is often characterized by prodromal period lasting for 3-5 days, which is presented by malaise, weakness, depressed mood, rapid mental and physical fatigue, mild headache, loss of appetite. By the end of the prodromal period, signs of intoxication aggravate. Major clinical symptoms of the disease develop. The cardinal are: pyrexia, chills accompanied by heavy sweats, and hepatosplenomegaly. Fever is prolonged, temperature is remitting in the height of the disease with the elevation in the afternoon or in the evening. It can be undulate (wavy) and intermittent, or prolonged low-grade. Despite the high fever, the condition of patients is slightly disturbed, euphoria and talkativeness are often marked.

The acute form. Multiple-chilling, sometimes stunning chills are observed in patients in the acute form of brucellosis within the same day. At the beginning of the chill body temperature sometimes drops below the norm, then there are fever, dry mouth, gradually increasing temperature. Every time chills and fever lead to profuse sweating. Lymph nodes, especially cervical and axillary, are enlarged to the size of beans, painless and not glomerated to the surrounding tissue.

Sometimes, the mesenteric lymph nodes are involved in the process. Dense, painful nodules - fibrositis and cellulitis, are formed in the subcutaneous tissue in the tendons and muscles.

There are moderate expansion of the boundaries of the heart, muted tones, systolic murmur at the apex found in the majority of patients. In severe cases may develop myocarditis, endocarditis, pericarditis. In the acute form of the disease, with the development of toxicoseptic process, changes in the respiratory organs are revealed: upper respiratory tract catarrh, bronchitis, pneumonia, bronhoadenitis. The liver and spleen are enlarged, soft, painful on palpation. Aching pain in the right upper quadrant, rarely - slight jaundice are often marked in case of liver involvement.

The nervous system involvement in the hight of an acute form of the disease is manifested by headaches, irritability, emotional instability, excessive fatigue, sleep disturbance. Mental disorders, meningism and meningitis are present in severe cases of brucellosis infection. Meningitis course is usually sluggish, without clearly defined general cerebral and meningeal symptoms. Only in some cases meningitis occurs with bright symptoms. Brucellous meningitis is usually serous.

Musculoskeletal system is affected only in a subset of patients in acute brucellosis. Short-term joint pain disappears with decreasing signs of intoxication.

Subacute form. It must be remembered that a significant portion of patients have a tendency to disease lingering with its transition in subacute and chronic forms. This also contributes to delayed diagnosis and late initiation of treatment. In this case, Brucella may persist even in the absence of clinical symptoms after causal treatment of patients. They are located intracellularly in the mononuclear phagocyte system of internal organs.

Relapses can occur in 1-2 months after recovery and later. Relapses of brucellosis usually present with chills, fever, sweating. Focal disease of individual organs and systems (most often the musculoskeletal system is affected) develops at the earliest days of recurrence.

Chronic form of brucellosis develops most often as a result of past acute and subacute forms of the infection and its recurrence. However, its development is possible immediately after the initial latency period (primary chronic brucellosis).

Based on the polymorphism of the clinical picture, Rudnev (1966) suggested clinical classification of chronic brucellosis:

• Visceral form: cardiovascular, pulmonary, Banti disease

• Osteo-articular or locomotor form: joint, bone damage, soft skeleton involvement; combined form.

• Nervous form: the peripheral nervous system, CNS involvement.

• Urogenital form

• Clinically combined form

• Chronic brucellosis-mixed: brucellosis associated with malaria; brucellosis associated with tuberculosis; brucellosis associated with syphilis and other sexually transmitted infections.

Chronic brucellosis is most often characterized by disorders of the musculoskeletal system: arthritis, bursitis, tenosynovitis, periostitis, perichondritis. Polyarthritis with involvement of large joints in the pathological process is specific for the disease.

The peripheral nervous system involvement in chronic brucellosis is manifested by radiculitis, plexitis, intercostal and other types of neuralgia, numbness, paresis, neuritis of the auditory and visual nerves with a significant hearing and vision loss. Meningitis and meningoencephalitis in chronic brucellosis are distinguished by slow course and mild clinical symptoms. Chronic intoxication of the CNS, especially the cerebral cortex, in cases of prolonged course of infection results in profound neuroses, reactive states, hypochondria, psychoses. Short-term psychosensory disorders, optic-vestibular and receptor disorders are observed. More persistent are mental disorders with asthenic, hypochondriacal syndromes, memory loss, decrease or increase of emotional excitability.

Urogenital system is often affected in chronic brucellosis: orchitis, epididymitis, oophoritis, salpingitis, endometriosis, menstrual disorder and abortion.

Blood picture is changed: leukopenia, lymphocytosis, monocytosis, eosinopenia, thrombocytopenia.

Individuals who have suffered from brucellosis (residual phase brucellosis), often have some residual effects, mostly functional, caused by immunoallergic changes in the body and disorders of the autonomic nervous system. These patients present with excessive sweating, irritability, neuro-psychiatric changes, arthralgia are often present. Joint pain is permanent, visible changes in the joints are not

detected. These pain is worse when performing physical activity and in connection with the change of weather. The body temperature of the patient is usually normal, at least low-grade. Sometimes organic changes of musculoskeletal system with joints deformation due to proliferation of periarticular tissues, revealed by clinical observation and X-ray examination, are revealed in patients with past brucellosis.

The prognosis is usually favorable. Mortality is extremely low. The prognosis for disability and health is not always satisfactory.

Diagnosis. Clinical data, epidemiological history and laboratory studies results are taken into account in the diagnosis of brucellosis. Epidemiological history, indicating the possibility of a professional or domestic infestation is very important in the diagnosis of brucellosis. Each case that is suspicious for brucellosis, must be laboratory-confirmed. Bacteriological, biological, serological and allergy research methods are usually used.

The agent may be isolated using a specific medium from blood, bone marrow, bile, urine, lymph nodes, cerebrospinal fluid, synovial fluid (arthritis), vaginal fluid, spleen aspirate. Brucella growth occurs slowly over a month. Bacteriological methods are carried out in specialized laboratories because of their complexity and the need of precautions. In recent years, it is often possible to isolate L-shaped Brucella.

Immunofluorescence method is used in the laboratory diagnosis of brucellosis, as it allows to identify Brucella in various test materials, even seeded by associated microflora.

Wright agglutination test plays a major part among the serological methods of diagnosis of brucellosis infection. It is often positive since the early days of the disease. Agglutinin titer in the test serum not less than 1:200 is considered diagnostically significant. For rapid serodiagnosis of brucellosis is used Heddlson reaction with whole serum and concentrated antigen. Complement-fixation test, indirect hemagglutination test and Coombs' test also have a diagnostic value in brucellosis infection. They have a higher sensitivity than the other serological tests. Sensitivity of complement-fixation test can be increased by long complement fixation (within 18 hours) - prolonged reaction of complement fixation and formulation with L-forms of Brucella.

Allergological methods of brucellosis diagnosis include the Burne reaction by intradermal brucellin injection - Brucella broth

culture filtrate. This reaction is based on the ability of the organism, sensitized by brucella antigen, specifically respond by development of a local process in the form of skin redness and swelling. Reaction is considered according to size of edema: edema in diameter up to 1 cm is considered suspicious, from 1 to 3 cm – weakly positive, from 3 to 6 cm – positive, more than 6 cm – strongly positive.

Treatment. Brucellosis therapy depends on the phase of the disease, the degree of compensation of the pathological process and immunoallergic adjustment of the organism.

Treatment of acute and subacute forms of brucellosis begins with antibiotics that have an antibacterial effect, result in a decrease in temperature, decrease of toxicity and sweating. Chloramphenicol is administered 0.5 g every 4 hours (3 g per day) until a normal temperature, followed by 0.5 g every 6 hours. Highly effective in brucellosis are Doxycycline 200 mg/day up to 6 weeks together with Riphampicin 600-900 mg/day per os, or Doxycycline 200 mg/day to 6 weeks, together with Gentamicin 4 mg/kg 2-3 times/day IM. Duration of treatment is 14 days or more. Second and subsequent courses of treatment are carried out in 10-14 days.

In chronic brucellosis antibiotics are used only in case of aggravation of symptomatic signs of disease. In chronic brucellosis pronounced therapeutic effect has the use of brucellosis curative (killed) vaccine in a dose of microbial cells in 1 ml. The vaccine is often administered intravenously by a two-step. It is advisable to introduce it intradermally for debilitated persons or those giving a strong reaction to the intravenous administration of the vaccine. When injected intradermally, vaccine is given repeatedly with increasing doses at each subsequent time. 0.1 ml (25 million microbial bodies) of vaccine can be injected in one site. If a dose is increased, vaccine is injected at several sites simultaneously (0.1 ml – 1 site, 0.2 ml – 2 sites, etc.), up to 10 sites in the last day of vaccine therapy. Intervals between doses of vaccine are 2-3 days. To prevent relapses of brucellosis, antibrucellar gamma globulin was proposed.

Corticosteroids are used in severe acute brucellosis, and sometimes in subacute and chronic forms of the disease.

Periarticular and intraarticular administration of Hydrocortisone is effective for arthritis and periarthritis. Prescribed drugs in subacute and chronic brucellosis, mainly affecting the musculoskeletal system and the peripheral nervous system, include nonsteroidal anti-

inflammatory drugs with analgesic action. Stimulating and desensitizing therapy is widely used for the treatment of patients with brucellosis. A positive effect on patients with disorders of the musculoskeletal system has physiotherapy (diathermy, UHF therapy, etc.), therapeutic excercises and massage. Patients with chronic brucellosis at a stage of compensation or with residual phenomena are recommended spa treatment. Particularly favorable results are obtained by treatment with radon or sulfur-radon waters. Treatment by mud is effective in joints lesions.

Prevention. Basic disease prevention measures are to eliminate brucellosis of farm animals, which is determined by strict compliance with veterinary and sanitary rules. In order to prevent brucellosis in humans, disinfection of milk is produced by boiling and pasteurization. Products made of the raw milk are kept before use the required time. Measures should be undertaken to prevent the spread of the pathogen from meat and meat products. Skins and animal dander should be subjected to decontamination. To work with infected animals or to work on enterprises that process their raw products, are allowed persons that respond positively to brucellin or are vaccinated against this infection, while using protective clothing and disinfectants. Live Brucella vaccine is used for specific prophylaxis. Immunity lasts for 1-2 years. Specific prophylaxis of brucellosis in humans is carried out in areas where there is animal morbidity. Persons serving farm animals, and employees of enterprises processing animal products shall be vaccinated.

TROPICAL NON-VENEREAL TREPONEMATOSIS

Treponematosis, also known as treponemiasis, traditionally refers to the group of nonvenereal diseases (including endemic syphilis [nonvenereal syphilis]) caused by treponema species that are morphologically and serologically identical to each other and to treponema pallidum subspecies pallidum, the cause of venereal syphilis. They differ only in their clinical manifestations. Treponema species typically associated with nonvenereal disease are transmitted among children living in tropical, subtropical, or warm arid climates, chiefly by direct contact. In humans, the pathogenic treponemes include t. pallidum pallidum, treponema pertenue (yaws), treponema endemicum (bejel or endemic syphilis), and treponema carateum (pinta).

Treponemes usually invade traumatized cutaneous or mucosal surfaces that come in contact with a draining open sore of the index case. A primary cutaneous lesion appears at the site of inoculation following an incubation period of a few weeks. Treponema may be spread from this site either topically (by scratching) or hematogenously. These lesions often heal spontaneously. Treponematosis can remain latent or it may recur.

The secondary stage of any of these diseases follows the dissemination of the treponemes. It may begin while the primary lesion is still present or after a variable latent period. It may also resolve spontaneously, recur, or persist. The long-term effects of these infections include multiple cutaneous lesions and destruction of bones or cartilage.

In 1997, the world health organization (who) estimated that 460,000 new cases of endemic treponematosis occurred worldwide. Currently, more than 2.5 million people may be infected.

Endemic syphilis (bejel) (t. pallidum endemicum) is typically spread among children, most commonly in the Middle East and the southern regions of the Sahara desert. In Europe, cases have been diagnosed in children who have moved from endemic areas. In one study, 12% of children younger than 5 years in niger were seropositive. High rates of seropositivity are also observed in Mali, Burkina Faso, and Senegal. Pinta (t. carateum), which occurs in the Caribbean and in Central and South America, is more common in young adults.

Yaws (t. pallidum pertenue) occurs mainly in equatorial regions and can be found in South America, Central America, the Caribbean, Africa, and Southeast Asia. It is associated with high humidity and rainfall. Fifty years ago, the who recognized that endemic treponematoses-yaws in particular-were a major cause of disfigurement and disability and a significant economic burden in poor countries.

In Haiti and the Dominican republic, a pilot project was initiated to eradicate the disease with mass applications of penicillin. This project was so successful that it was extended to 46 other countries. Overall, the incidence of yaws was reduced to isolated foci of endemicity. As public health priorities changed and support for the eradication programs lapsed, the disease saw a resurgence in the 1970s and 1980s. The introduction of mass treatment has been

necessary in some areas. In a who survey in 2012, the status of yaws was unknown in many of the countries where it had previously been known to be endemic.

Now that an oral treatment has been recommended for first-line therapy, a new eradication campaign is being planned by the who.

Mortality/morbidity. Untreated treponematosis may cause disfiguring cutaneous lesions and deformities of bone, cartilage (particularly the nose), and skin, potentially leading to significant disfigurement, pain, and disability. Affected children can become socially ostracized and often miss school. Thickening and cracking of the soles may make walking difficult. Treponematosis can extract a significant economic toll on already-disadvantaged populations. Fortunately, with penicillin or azithromycin therapy, cure rates of 95-97% are possible.

YAWS

Epidemiology. Yaws (also known as frambesia tropica, thymosis, polypapilloma tropicum, parangi, bouba, frambösie, and pian) is a tropical infection of the skin, bones and joints caused by the spirochete bacterium Treponema pallidum pertenue.

The term yaws is thought to be of Caribbean origin. In the language of the Carib Indian people, yaya is the word for "a sore."

Alternatively, the disease term yaws may have come from Africa where the word yaw may have meant "a berry." Because the lesions of yaws look like berries, the disease is also called frambesia (or frambesia tropica) from the French framboise, meaning "raspberry." Other older names for yaws include granuloma tropicum, polypapilloma tropicum, and thymiosis.

Yaws is spread by direct contact with the fluid from a lesion of an infected person. The contact is usually of a non-sexual nature. The disease is most common among children, who spread it by playing together. Yaws is often diagnosed by the appearance of the lesions. Blood antibody tests may be useful but cannot separate previous from current infections. Polymerase chain reaction (PCR) is the most accurate method of diagnosis.

Prevention is, in part, by curing those who have the disease thereby decreasing the risk of transmission. Where the disease is

common, treating the entire community is effective. Improving cleanliness and sanitation will also decrease spread. Treatment is typically with antibiotics including: azithromycin by mouth or benzathine penicillin by injection. Without treatment, physical deformities occur in 10% of cases.

Yaws is common in at least 14 tropical countries as of 2012. The disease infects only humans. In the 1950s and 1960s the World Health Organization (WHO) nearly eradicated yaws. Since then the number of cases has increased and WHO is again trying to eradicate the disease by 2020. The last estimate of the number of people infected was more than 500,000 in 1995. Although one of the first descriptions of the disease was made in 1679 by Willem Piso, archaeological evidence suggests that yaws may have been present among humans as far back as 1.6 million years ago.

About three quarters of people affected are children under 15 years of age, with the greatest incidence in children 6-10 years old. Therefore, children are the main reservoir of infection. Because T. pallidum pertenue is temperature- and humidity-dependent, yaws is found in humid tropical regions in South America, Africa, Asia and Oceania.

Mass treatment campaigns in the 1950s reduced the worldwide prevalence from 50-150 million to fewer than 2.5 million; however during the 1970s there were outbreaks in South-East Asia and there have been continued sporadic cases in South America. It is unclear how many people worldwide are infected at present.

The global prevalence of this disease and the other endemic treponematoses, bejel and pinta, was reduced by the Global Control of Treponematoses (TCP) programme between 1952 and 1964 from about 50 to 150 million cases to about 2.5 million (a 95 percent reduction). Following the cessation of this program yaws surveillance and treatment became a part of primary health systems of the affected countries. However incomplete eradication led to a resurgence of yaws in 1970s with the largest number of case found in the Western Africa region.

Cause. The disease is transmitted by skin-to-skin contact with an infective lesion, with the bacterium entering through a pre-existing cut, bite or scratch.

T. pallidum pertenue has been identified in non-human primates (baboons, chimpanzees, and gorillas) and studies show that

experimental inoculation of human beings with a simian isolate causes yaws-like disease. However, no evidence exists of crosstransmission between human beings and primates, but more research is needed to discount the possibility of a yaws animal reservoir in non-human primates.

Clinic. The disease begins with a round, hard swelling of the skin, 2 to 5 centimeters in diameter. The center may break open and form an ulcer. This initial skin lesion typically heals after three to six months. After weeks to years, joints and bones may become painful, fatigue may develop, and new skin lesions may appear. The skin of the palms of the hands and the soles of the feet may become thick and break open. The bones (especially those of the nose) may become misshapen. After five years or more large areas of skin death with subsequent scarring may occur.

Within 90 days (but usually less than a month) of infection a painless but distinctive "mother yaw" nodule appears, which enlarges and becomes warty in appearance. Nearby "daughter yaws" may also appear simultaneously. This primary stage resolves completely within six months.

The secondary stage occurs months to years later, with typically widespread skin lesions that vary in appearance, including "crab yaws" on the palms of the hands and soles of the feet with desquamation. These secondary lesions frequently ulcerate and are then highly infectious, but heal after six months or more. About 10% of people then go on to develop tertiary disease within five to ten years (during which further secondary lesions may come and go), with widespread bone, joint and soft tissue destruction, which may include extensive destruction of the bone and cartilage of the nose (rhinopharyngitis mutilans or "gangosa").

BEJEL

Bejel, or endemic syphilis, is a chronic skin and tissue disease caused by infection by a subspecies of the spirochete Treponema pallidum.

Bejel is also known by a variety of other names, including belesh, dichuchwa, endemic syphilis, nonvenereal syphilis, frenga, njovera, skerljevo, siti, or treponematosis-bejel type.

Although the organism that causes bejel, Treponema pallidum endemicum, is morphologically and serologically indistinguishable from Treponema pallidum pallidum, which causes venereal syphilis, transmission of bejel is not venereal in nature, generally resulting from mouth-to-mouth contact or sharing of domestic utensils, and the courses of the two diseases are somewhat different.

The primary lesions are painless, white, mucinous ulcers within the oral cavity, where they may be overlooked.

Secondary lesions may be in the mouth or widely disseminated. The secondary lesions may be papules, macules, or various other rashes.

The organism may infect the periosteal space, which leads to bone deformities.

Late in the disease course, a condition known as gangosa (destruction of nasopharyngeal cartilage) may occur.

Ocular manifestations include uveitis, optic atrophy, and chorioretinitis.

PINTA

Pinta is a human skin disease endemic to Mexico, Central America, and South America caused by infection with a spirochete, Treponema pallidum carateum, which is morphologically and serologically indistinguishable from the organism that causes syphilis.

The primary lesions appear 1-3 weeks after inoculation as slowly enlarging copper-colored papules, which may become hyperkeratotic and blue. Smaller satellite lesions may be observed and may coalesce with the larger ones. The lymph draining this area may be swollen. Lesions may persist for years and may heal, leaving hypopigmentation.

Secondary lesions may develop within 3-12 months as small papules, which are often located at the site of primary lesions. The lesions may be numerous and are called pintids. They are initially red but can become pigmented and appear blue over time. Lesions may later become depigmented to varying degrees, leading to a mottled appearance. Later manifestations are limited to cutaneous involvement. The deeper tissues or viscera are not involved.

Diagnosis of treponematosis should be suspected in persons with appropriate clinical findings (eg, chronic skin or bone lesions) who live in or are from endemic areas. As with other treponeme

diseases, confirmation of the diagnosis depends on dark-field examination, if available, or serologic testing. The epidemiologic setting is vital because the nonvenereal treponemes cannot be distinguished from T pallidum pallidum (the cause of venereal syphilis) with laboratory studies.

Tests for endemic treponematosis are the same as for syphilis. Because treponemes cannot be easily and readily cultured, use other laboratory methods of identifying infection. The current tests for syphilis fall into the following 3 categories: direct microscopic identification when lesions are present, nontreponemal tests used for screening, and treponemal tests used for confirmation.

Direct microscopy. Direct microscopic identification of treponemes from lesion fluids by either dark-field microscopy or direct fluorescent antibody should be the initial step in diagnosing a treponemal infection. This is most helpful during the primary stage of infection because treponemal antibodies do not usually appear until 1-4 weeks after the lesion has formed.

A negative dark-field finding does not exclude the diagnosis of treponematosis because the organisms may be too few if the lesion is in the healing stage or if the infection has been altered by treatment.

Nontreponemal tests. These include the nontreponemal rapid plasma reagin (RPR) test and the Venereal Disease Research Laboratory (VDRL) test. These tests usually become positive within 2-4 weeks of the appearance of the primary lesion. They can be used as tests of cure because they usually become negative after treatment.

RPR is inexpensive and rapid and is convenient for screening large numbers of sera specimens.

The standard nontreponemal test is the VDRL slide test, in which serum is tested for its ability to flocculate a suspension of cardiolipin-cholesterol-lecithin antigen. This test is based on the observation that antibodies elicited against treponemal surface antigens cross-react with cardiolipin.

Treponemal tests. The confirmatory treponemal tests are the fluorescent treponemal antibody absorption (FTA-ABS) test, T pallidum hemagglutination assay (TPHA), and T pallidum particle agglutination assay (TPPA). These tests use T pallidum organisms as the antigen. The patient's serum is first absorbed to remove any naturally occurring cross-reacting antibody; it is then reacted with the organism.

Because of the nonstandardized, qualitative, and subjective nature of this test, its principal use is to confirm any positive VDRL or RPR test result.

New rapid point-of-care tests are currently being evaluated.

Treatment. Treatment of treponematosis is based on single-dose antibiotic therapy with benzathine penicillin or azithromycin. Treponemes are highly sensitive to azithromycin and penicillin, which are the drugs of choice.

The WHO revised policies for treating yaws in 2012. One oral dose of azithromycin (30 mg/kg, not to exceed 2 g) is now recommended as equivalent to benzathine benzylpenicillin. Because of the ease of administration and low cost, it is now considered the drug of first choice.

Yaws, pinta, and endemic syphilis may also be treated with benzathine penicillin G. Children younger than 10 years should receive 600,000 U intramuscularly, and children older than 10 years should receive 1.2 million U intramuscularly.

Alternatives are appropriate only if azithromycin or benzathine penicillins cannot be used. Tetracycline (25 mg/kg/d for 10-14 d) and chloramphenicol (25 mg/kg/d for 10-14 d) have been used successfully, as has a 10-day course of doxycycline. Other penicillins, cephalosporins, and macrolides are probably active against the treponemes; however, quinolones, aminoglycosides, and sulfa antibiotics are ineffective.

Treatment failures with penicillin have been reported, but reinfection could not be ruled out.

Other important measures from the perspective of the individual patient and for public health include avoiding contact with others with cutaneous lesions and careful follow-up care to identify and to re-treat initial treatment failures.

Follow up. Conscientious follow-up care to detect treatment failures and reinfection is recommended. Treatment failures or reinfections should be treated again. If penicillin was initially used, one of the alternative antibiotics listed might be considered.

Prevention. Yaws is a relatively easy disease to eradicate. Humans are likely the only reservoir of infection. A single injection of long-acting penicillin or other beta lactam antibiotic cures the disease and is widely available; and the disease is highly localised making case tracing relatively easy.

In April 2012, WHO initiated a new global campaign for the eradication of yaws, which has been on the WHO eradication list since 2011. According to the official roadmap, elimination should be achieved by 2020. So far, this appears to have met with some success, since no cases have been seen in India since 2004.

Certification for disease free status requires an absence of the disease for at least five years. In India this happened on 19 September 2011. In 1996 there were 3,571 yaws cases in India; in 1997 after a serious elimination effort began the number of cases fell to 735. By 2003 the number of cases was 46. The last clinical case in India was reported in 2003 and the last latent case in 2006. India is a country where yaws has been fully eradicated and no case has been reported after 2003.

In March 2013, WHO convened a new meeting of yaws experts in Geneva to further discuss the strategy of the new eradication campaign. The meeting was significant, and representatives of most countries where yaws is endemic attended and described the epidemiological situation at the national level. The disease is currently known to be present in Indonesia and Timor-Leste in South-East Asia; Papua New Guinea, the Solomon Islands and Vanuatu in the Pacific region; and Benin, Cameroon, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana and Togo in Africa. As reported at the meeting, in several such countries, mapping of the disease is still patchy and will need to be completed before any serious eradication effort could be enforced.

CHLAMYDIOSIS

Chlamydiosis refers to any disease or infection caused by members of the family *Chlamydiaceae;* takes many forms including: psittacosis and ornithosis in birds, placentopathy manifested by abortion in enzootic abortion of ewes, sporadic bovine encephalomyelitis, pneumonitis in all species except pig, conjunctivitis in sheep, cats and laboratory rodents, polyarthritis in sheep, cattle, horse, enteritis in cattle and lagomorphs, and septicemia in epizootic chlamydiosis in lagomorphs.

CHLAMYDOPHILA PNEUMONIA INFECTION

C. pneumoniae was first isolated from the conjunctiva of a child in Taiwan.

It was initially considered a psittacosis strain because the morphology of the inclusions produced in cell culture was similar.

However, it was subsequently shown that the Taiwan isolate (TW-183) was related serologically to a pharyngeal isolate, designated AR-39, and was unrelated to psittacosis strains.

This new organism was initially called TWAR, then classified as *Chlamydia pneumoniae,* and, finally, placed in the new genus *Chlamydophila.*

Only a single serotype (TWAR) has been identified. Respiratory secretions transmit infection; no animal reservoir has been identified.

It is suspected to be a significant cause of acute exacerabations of asthama.

The organism is chronic, often insiduous, respiratory pathogen to which there appears to be little immunity.

Clinical reactivation of existing infection and reinfection are probably common, although the two are difficult to distinguish.

Seroepidemiological studies indicate that some 60 to 80% of people worldwide become infected with *Ch. pneumoniae* during their life, atan incidence of 1 to 2% per year.

Ch. pneumoniae is a human pathogen.

It is an important cause of bronchitis, pneumonia, and sinusitis, infections being transmitted person to person by respiratory secretions.

Infection is believed to be common (an estimated 200,000 to 300,000 cases of *C. pneumoniae* pneumonia occur annually), and most common in adults.

Clinics. This organism causes pneumonia, phayngitis, bronchitis, otitis, and sinusitis with an incubation period of about 21 days.

More than 50% of people have serologic evidence of past infections. Most C. pneumoniae infections are asymptomatic or mild, causing a persistent cough and malaise; most patients do not require hospitalization.

More severe respiratory tract infections typically involve a single lobe of the lungs. These infections cannot be differentiated from other

atypical pneumonias, such as those caused by Mycoplasma pneumoniae, Legionella pneumophila, and respiratory viruses. The role of C. pneumoniae in the pathogenesis of atherosclerosis remains to be defined.

It is known that C. pneumoniae can infect and grow in smooth muscle cells, endothelial cells of the coronary artery, and macrophages. The organism has also been demonstrated in biopsy specimens of atherosclerotic lesions by means of culture, PCR amplification, immunohistologic staining, electron microscopy, and in situ hybridization. Thus the association of C. pneumoniae with atherosclerotic lesions is clear. What is not clear is the role of the organism in the development of atherosclerosis. The disease is believed to result from an inflammatory response to chronic infection; however, this remains to be proven.

Diagnosis of C. pneumoniae infections is difficult.

Ch. peumoniae is one of the commonest causes of community acquired pneumonia, seldom identified as the causal agent because laboratory tests for its diagnosis are not widely used.

The organisms do not grow in the cell lines used for the isolation of C. trachomatis, and although C. pneumoniae will grow in the HEp-2 cell line, this cell line is not used in most clinical laboratories.

Detection of C. pneumoniae by NAATs has been successful, and these tests appear to be the most sensitive diagnostic methods available.

However, NAATs are not used in most laboratories at this time. CF or MIF tests can be used to make a serologic diagnosis.

Because the CF test reacts with Chlamydia and Chlamydophila, it is not specific for C. pneumoniae infection.

The MIF test uses C. pneumoniae EBs as antigen, so it is specific.

Treatment. Macrolides (erythromycin, azithromycin, clarithromycin), tetracyclines (tetracycline, doxycycline), or levofloxacin administered for 10 to 14 days has been used to treat infections.

Control of exposure to C. pneumoniae is likely to be difficult because the bacterium is ubiquitous.

PSITTACOSIS

Psittacosis is the term used to describe human infection with *Chlamydophilapsittaci* (formerly known as *Chlamydia psittaci*) a member of the family Chlamydiaceae. When avian are infected with *Chlamydophilapsittaci,* the term avian chlamydiosis is used. The disease in avians is also known as parrot Fever and ornithosis.

Etiology. *Chlamydophila psittaci* is an obligate intercellular organism. The developmental cycle includes two forms: the elementary and the reticulate bodies. The elementary body is thought to survive for prolonged periods in the environment, but cannot replicate. After attaching to a susceptible host cell, the elementary body enters the cytoplasm and transforms into a larger flexible-walled form called the reticulate body. The reticulate body is noninfectious and incapable of extracellular survival. After infection, the reticulate bodies reorganize to form infectious elementary bodies that leave the cells in 48-72 hrs.

Under the new taxonomic classification *Chlamydiaceae*, has two genera: *Chlamydia* and *Chlamydophila*. *Chlamydia* genera includes *C. trachomatis, C. muridarum,* and *C. suis*. *Chlamydophila*includes the newly renamed strains of *C. abortus, C. felis, C. pecorum, C. pneumoniae, C. caviae, and C. psittaci. Chlamydophilapsittaci* has eight known serovars; six have been primarily isolated in birds and two strains have been isolated in mammals. Identification of serovar may help to determine the source of infection

The Chlamydial organism is very resistant to drying. Infectivity of *C. psittaci* has been documented in canary feed for 2 months, in poultry litter for up to 8 months, straw and hard surfaces for 2-3 weeks, and in diseased turkey carcasses for less than 1 year.

Epidemiology. Psittacosis occurs worldwide as a sporadic disease. In the United State, psittacosis is reportable in humans, but true incidence is unknown due to poor reporting compliance and frequent misdiagnosis. There are 50-100 confirmed cases per year (1-2 deaths per year), but some estimate as many as 100-200 cases per year is more likely. Pet store employees, owners of pet birds, and poultry processing plant workers account for the majority of the reported cases.

From 1988 through 2002, the CDC received reports of 923 cases of Psittacosis, which is likely an under representation of the actual

number of cases because psittacosis is difficult to diagnose and cases often go unreported. Bird fanciers and pet bird owners accounted for 43% of cases of psittacosis and pet shop employees for 10%. In the 1980s, about 70% of cases in which the source of infection was known was a result of exposure to caged birds.

There are many specific occupational and recreational activities that could increase the risk of acquiring Psittacosis:

- Lab workers
- Veterinarians
- Avian quarantine workers
- Zoo workers
- Farmers
- Pregnant women
- Bird fanciers (pigeon fanciers too)
- Bird owners
- Pet shop employees
- Poultry slaughter and processing workers
- Wildlife rehab workers

Transmission to Humans

- Inhalation
  - Dried infective droppings
  - Secretions or dust from feathers
- Mouth-to-beak
- Direct contact
  - Handling plumage or tissues of infected birds
- Person-to-person transmission
  - Not proven
  - Venereal transmission reported.

Psittaci is excreted in the feces and nasal discharges of infected birds. The organism is environmentally labile but can remain infectious for several months if protected by organic debris. Man is an incidental, dead-end host. Because human infection can result from transient exposure to infected birds or their droppings, the average person may be at risk without recalling or reporting having contact with birds. Infection may occur via inhalation of aerosols of dried infective avian excreta. Other means of exposure include mouth-to-beak contact and handling of infected birds' plumage and tissues.

While feral pigeons in towns worldwide are commonly infected, zoonotic spread of infection from asymptomatic pigeons appears low. Person to person transmission has suggested but not proven. Venereal transmission has also been reported. Food borne transmission has not been documented.

Human Disease: Psittacosis. Incubation period in humans ranges 1 to 4 weeks; most patients develop symptoms after 10 days. Severity of clinical signs ranges from inapparent to systemic illness with severe pneumonia. Pneumonia occurs most commonly in adults 30-60 years old. Other signs include abrupt onset of fever, chills, headache, malaise, myalgia, nonproductive cough, breathing difficulty, chest tightness, splenomegaly (present in 1-10% of patients), and rash (truncal lesions resembling those of typhoid fever, pink macules 2-4 mm diameter).

Clinical Signs. After several days of untreated illness, lethargy and sluggish speech may be seen with coma or stupor. Other organ systems can be involved causing endocarditis, placentitis, myocarditis, hepatitis, arthritis, keratoconjunctivitis, and encephalitis. Respiratory failure, thrombocytopenia, and fetal death have been reported. Epistaxis and mucocutaneous manifestations frequently occur. Arthralgia is rare.

Diagnosis. Cases are confirmed on the basis of clinical signs of illness and laboratory results. The organism can be cultured from respiratory secretions, but it is only performed in a few labs due to technical difficulty and safety concerns. Analysis of paired titers with a 4-fold rise in titer being confirmatory can be performed using complement fixation tests (CF is the test most routinely used in laboratories for human cases) or microimmunofluorescence (MIF). A reciprocal titer of 16 of IgM using MIF also confirms infection. A probable case is one that is epidemiologically linked to a confirmed case of psittacosis, or if a single titer of 1:32 is found.

Differential Diagnosis

- Coxiella burnetii (Q fever)
- Legionella
- Chlamydia pneumoniae
- Mycoplasma pneumoniae
- Influenza
- Tularemia

Treatment and Prognosis. With proper treatment, case fatality rates are 1-5%. Tetracycline is the drug of choice for treatment. Remission of symptoms usually is evident within 48-72 hours, but relapse may develop. Without treatment symptoms may resolve in a few weeks to months. Without treatment the case fatality rate is 10-40%.

Gestational Psittacosis. There have been 14 reports of gestational psittacosis. These cases were reported prior to the reclassification of chlamydial organisms, thus serovar confirmation is not reported. It appears that two cases involved bird association most likely due to *C. psittaci* and 12 cases involved sheep and goat exposure to *C. abortus.*

Prevention and Control. To prevent transmission of *C. psittaci* to persons and birds, the following control measures are recommended: Protect and educate those at risk. Persons in contact with birds need to know about the zoonotic nature of the disease. People at risk should wear protective clothing, gloves, surgical cap, HEPA filter mask when cleaning cages or handling birds. Disinfect the cages daily (easily killed) with 1:1,000 quaternary ammonium compounds, 1% Lysol, 70% isopropyl alcohol, or 1:100 bleach. It is important to wet the carcass with water and detergent prior to performing necropsies and work under a hood with an exhaust fan.

Always maintain records of bird transactions (date buy or sell, transport, band id, etc) for not less than one year to aid in identifying sources of infected birds and potentially exposed persons. Never purchase or sell birds with clinical signs of illness. Isolate newly acquired, ill or exposed birds at least 30 days. Isolate birds coming back from bird shows. Test birds before sale or boarding. Discard wood, litter, and nest materials to reduce contamination from dust. Protect birds from undue stresses like chilling, shipping, poor husbandry, or malnutrition. A vaccine is not available for *C. psittaci*. *C. psittaci* has previously been part of several country's bioweapons research programs. Some characteristics that may make it a good potential bioweapon include its stability in the environment, ease for aerosolization and ease to obtain (worldwide occurrence).

LEGIONELLOSIS

Legionellosis is a potentially fatal infectious disease caused by Gram negative, aerobic bacteria belonging to the genus Legionella. Over 90% of legionellosis cases are caused by Legionella pneumophila, a ubiquitous aquatic organism that thrives in temperatures between 25 and 45°C (77 and 113°F), with an optimum around 35°C (95°F).

Legionnaires' disease acquired its name in July 1976 when an outbreak of pneumonia occurred among people attending a convention of the American Legion in Philadelphia. On January 18, 1977 the causative agent was identified as a previously unknown bacterium, subsequently named Legionella. Some people can be infected with the Legionella bacterium and have only mild symptoms or no illness at all.

The dose of legionella necessary for infection is unknown, but the infective dose for susceptible humans can be assumed to be low, as patients have been known to be infected after exposure of only a few minutes to the sources of some outbreaks, and at up to 3,2 km from the source of others. Infection depends on the water contamination level by bacteria, the effectiveness of formation and dissemination of bacteria through air, host factors and the virulence of the particular strain of Legionella.

Etiology. The causative agents, legionellae, are freshwater bacteria that are found in aquatic environments worldwide but artificial water systems sometimes provide environments conducive to the growth of Legionella bacteria. These bacteria survive within or between the cells as parasites of free-living protozoa and within biofilms which develop in water systems where bacteria survive. They can cause human infections by infecting other human cells utilizing a similar mechanism to that used to infect protozoa. L. pneumophila is the species most frequently isolated from patients with either community, travel-associated or hospital-acquired legionellosis.

L. pneumophila is specifically considered as a pathogen of the respiratory tract. Other infections have also been reported, including haemodialysis fistulae, pericarditis, and wound and skin infections. Bacteraemia is often associated with Legionnaires' disease. Intestinal infections may only occur as part of respiratory infections, and where gastrointestinal symptoms have on occasion been described.

No animal infections have been specifically recorded.

Infections of protozoa such as Hartmannellavermiformis and related protozoa have been shown to be able to support the growth of L. pneumophila in tap water. Also Acanthamoeba, Naegleria and Tetrahymena can be infected by L. pneumophila pathway may be how these organisms survive in the environment.

Epidemiology. Legionnaires' disease is believed to occur worldwide. It is estimated that in the United States there are between 10,000 and 50,000 cases of Legionnaires' disease each year, according to OSHA from the U.S.

The incidence of community-acquired Legionnaires' disease varies widely according to the setting investigated and the diagnostic methodology applied. Since many countries lack appropriate methods of diagnosing the infection or surveillance systems capable of monitoring the situation, the real magnitude of the problem is unknown. In 2003, 34 countries (population: 467,76 million) out of the 36 in the European Working Group for Legionella Infections reported a total of 4578 cases, meaning an average rate across Europe of 9.8 per million population. Based on findings from Denmark where a high level of testing for legionella in patients with pneumonia is developed, a more realistic incidence would be closer to 10 000 cases a year for the same 36 countries.

Risk factors for community-acquired and travel-associated Legionellosis include: male, over 50 years, smoker, a history of heavy drinking, pulmonary related deaths, immuno-suppression, and chronic debilitating illnesses.

Risk factors for hospital-acquired pneumonia in the host are: recent surgery, intubation, which is the process of placing a tube in the trachaea, mechanical ventilation, aspiration, presence of nasogastric tubes, and the use of respiratory therapy equipment. The most susceptible hosts are immuno-compromised patients, including organ transplant recipients and those, receiving corticosteroid treatment.

Improvements in diagnosis and surveillance in developing countries would be expected to reveal far higher levels of morbidity and mortality than are currently recognised. Similarly, improved diagnosis of human illness related to legionella species and serogroups other than legionella pneumophila would improve knowledge about their incidence and spread.

Transmission. Legionella organisms can be spread by aerosols

such as wind. Infection results from inhalation of contaminated water sprays or mists. Infection can also occur by inhalation, particularly during outbreaks in hospital. The bacteria live in water and colonize hot and cold water systems at temperatures of 20 to 50 degrees Celsius (optimal 35 degrees Celsius). They contaminate air conditioning cooling towers, hot and cold water systems, humidifiers, whirlpool spas and other water-containing devices. There is no direct human-to-human transmission.

Signs and symptoms. Legionellosis takes two distinct forms: Legionnaires' disease, also known as "Legion Fever" is the more severe form of the infection and produces pneumonia. Pontiac fever is caused by the same bacterium but produces a milder respiratory illness without pneumonia that resembles acute influenza.

Legionnaires' disease has an incubation period of two to ten days (but up to 16 days has been recorded in some recent well-documented outbreaks), for Pontiac fever, it is shorter, generally a few hours to 2 days.

Initially, symptoms are fever, loss of appetite, headache, malaise and lethargy. Some patients may also have muscle pain, diarrhoea and confusion. There is also usually an initial mild cough, but as many as 50% of patients can present phlegm. Blood-streaked phlegm or hemoptysis occurs in about one-third of the patients. The severity of disease ranges from a mild cough to a rapidly fatal pneumonia. Death occurs through progressive pneumonia with respiratory failure and/or shock and multi-organ failure.

Untreated Legionnaires' disease usually worsens during the first week. In common with other risk factors causing severe pneumonia, the most frequent complications of legionellosis are respiratory failure, shock and acute kidney and multi-organ failure. Recovery always requires antibiotic treatment, and is usually complete, after several weeks or months. In rare occasions, severe progressive pneumonia or ineffective treatment for pneumonia can result brain in sequelae.The death rate as a result of legionnella is dependent on: the severity of the disease, the appropriateness of initial anti-microbial treatment, the setting where legionella was acquired, and host factors (i.e. the disease is usually more serious in patients with immuno-suppression). The case fatality rate may be as high as 40-80 per 100 in untreated immuno-suppressed patients and can be reduced to 5-30 per 100 through appropriate case management and depending on the

severity of the clinical signs and symptoms. For persons able to develop an immune response the death rate is usually within the range of 10-15%.

Patients with Legionnaires' disease usually have fever, chills, and a cough, which may be dry or may produce sputum. Some patients also have muscle aches, headache, tiredness, loss of appetite, loss of coordination (ataxia), and occasionally diarrhea and vomiting. Laboratory tests may show that patients' renal functions, liver functions and electrolytes are deranged, including hyponatremia. Chest X-rays often show pneumonia with bi-basal consolidation. It is difficult to distinguish Legionnaires' disease from other types of pneumonia by symptoms or radiologic findings alone; other tests are required for diagnosis.

Persons with Pontiac fever experience fever and muscle aches without pneumonia. They generally recover in 2 to 5 days without treatment.

Diagnosis. Delay in diagnosis and administration of appropriate antibiotic treatment, increasing age and presence of co-existing diseases are predictors of death from Legionnaires' disease.

People of any age may suffer from Legionnaires' disease, but the illness most often affects middle-age and older persons, particularly those who smoke cigarettes or have chronic lung disease. Immunocompromised patients are also at elevated risk. Pontiac fever most commonly occurs in persons who are otherwise healthy.

The most useful diagnostic tests detect the bacteria in sputum, find Legionella antigens in urine samples (Due to renal fibrosis) , or the comparison of Legionella antibody levels to in two blood samples taken 3 to 6 weeks apart. A urine antigen test which is simple, quick, and very reliable will only detect Legionella pneumophilaserogroup 1. In addition the urine antigen test will not identify the specific subtypes so it cannot be used to match the patient with the environmental source of infection.

Treatment. Current treatments of choice are the respiratory tract quinolones (levofloxacin, moxifloxacin, gemifloxacin) or newer macrolides (azithromycin, clarithromycin, roxithromycin). The antibiotics used most frequently have been levofloxacin and azithromycin. Macrolides are used in all age groups while tetracyclines are prescribed for children above the age of 12 and quinolones above the age of 18. Rifampicin can be used in

combination with a quinolone or macrolide. Tetracyclines and erythromycin led to improved outcomes compared to other antibiotics in the original American Legion outbreak. These antibiotics are effective because they have excellent intracellular penetration and Legionella infects cells.

The mortality at the original American Legion convention in 1976 was high (34 deaths in 180 infected individuals) because the antibiotics used (including penicillins, cephalosporins, and aminoglycosides) had poor intracellular penetration. Mortality has plunged to less than 5% if therapy is started quickly. Delay in giving the appropriate antibiotic leads to higher mortality.

***Prevention*.** There is no vaccine currently available for Legionnaires' disease.

Various studies have shown that some 40% to 60% of cooling towers tested contained Legionella. A recent research study provided evidence that Legionella pneumophila, the causative agent of Legionnaires' disease, can travel airborne at least 6 km from its source. It was previously believed that transmission of the bacterium was restricted to much shorter distances. A team of French scientists reviewed the details of an epidemic of Legionnaires' disease that took place in Pas-de-Calais in northern France in 2003-2004. There were 86 confirmed cases during the outbreak, of whom 18 died. The source of infection was identified as a cooling tower in a petrochemical plant, and an analysis of those affected in the outbreak revealed that some infected people lived as far as 6-7 km from the plant.

Patients with the non-pneumonic form of infection do not require any antibiotic treatment and the symptomatic approach is sufficient. Patients with Legionnaires' disease always require antibiotic treatment, following laboratory confirmation of diagnosis.

A study of Legionnaires' disease cases in May 2005 in Sarpsborg, Norway concluded that: "The high velocity, large drift, and high humidity in the air scrubber may have contributed to the wide spread of Legionella species, probably for >10 km."

In 2010 a study by the UK Health Protection Agency reported that 20% of cases may be caused by infected windscreen wiper water. The finding came after researchers spotted that professional drivers are five times more likely to be infected.

Temperature affects the survival of Legionella as follows:

- 70 to 80°C (158 to 176°F): Disinfection range
- At 66°C (151°F): Legionellae die within 2 minutes
- At 60°C (140°F): Legionellae die within 32 minutes
- At 55°C (131°F): Legionellae die within 5 to 6 hours
- Above 50°C (122°F): They can survive but do not multiply
- 35 to 46°C (95 to 115°F): Ideal growth range
- 20 to 50°C (68 to 122°F): Legionellae growth range
- Below 20°C (68°F): Legionellae can survive but are dormant

Removing slime may be an effective control process. The public health threat posed by legionellosis can be addressed via preventive measures. Although it is impossible to eradicate the source of infection, it is possible to reduce the risks substantially. Prevention of Legionnaires' disease depends on good maintenance of possible sources, including regular cleaning and disinfection and the application of other physical (temperature) or chemical measures (biocide) to minimise growth. Some examples are: the regular cleaning and disinfection of cooling towers together with frequent or continuous addition of biocides; maintaining an adequate level of a biocide such as chlorine in a spa pool along with a complete drain and clean of the whole system at least weekly; keeping hot and cold water systems clean and either keeping the hot water at 60°C and the cold below 20°C or alternatively treating them with a suitable biocide to limit growth. Applying such controls particularly in hospitals, industrial sites, hotels, leisure centres, etc will greatly reduce the risk of legionella contamination and prevent the occurrence of sporadic cases.

Such control and prevention measures must be accompanied by proper vigilance on the part of general practitioners and community health services for the detection of cases.

Limiting growth. Legionella bacteria itself can be inactivated by UVC light. However, Legionella bacteria that grow and reproduce in amoebae or that are sheltered in corrosion particles cannot be killed by UV light alone. An innovative way is the combination of ultrasonics and UVC light. This uses a two-stage process, where ultrasonic cavitation disrupts the amoebae or corrosion particles and leaves the Legionella bacteria exposed for UV radiation. Such combined systems are used for example in hot water systems in sensitive areas, such as hospitals, where the inhabitants are more vulnerable than in normal environments.

Legionella longbeachae, an organism in the Legionella family, is found in soils and compost. Thus, the dust from purchased bags of soil, compost, or potting mix is a potential source of Legionella.

Prognosis. According to the journal Infection Control and Hospital Epidemiology, hospital-acquired Legionella pneumonia has a fatality rate of 28%, and the principal source of infection in such cases is the drinking-water distribution system. If is untreated mortality can hit 80%.

BARTONELLOSIS

Bartonellosis is an infectious disease produced by bacteria of the genus Bartonella. Bartonella cause diseases such as Carrión´s disease, trench fever, cat-scratch disease, bacillary angiomatosis, peliosis hepatis, chronic bacteremia, endocarditis, chronic lymphadenopathy, and neurological disorders.

Members of the genus Bartonella are facultative intracellular bacteria, alpha 2 subgroup Proteobacteria. The genus comprises:

Table 7. – Members of the genus Bartonella

Bartonella species	***Reservoir***	***Disease***
Bartonella bacilliformis	Human	Carrion´s disease/Verruga peruana
Bartonella Quintana	Human	Trench fever, bacteremia, bacillary angiomatosis, endocarditis
Bartonella henselae	Cats	Cat scratch disease, bacillary angiomatosis, bacteremia, endocarditis
Bartonella elizabethae	Rats	Endocarditis
Bartonella grahamii		Retinitis
Bartonella vinsoni	Dogs	Endocarditis, bacteremia
Bartonella washonsis	Rodents	Myocarditis
Bartonella clarridgiae	Cats	Bacteremia
Bartonella rochalimae	Human	Carrion´s disease like syndrome

CATSCRATCH DISEASE

Etiology. Catscratch disease is usually caused by B henselae, formerly known as Rochalimaea henselae. B henselae is a small, fastidious, slow-growing, gram-negative, aerobic, nonmotile, pleomorphic bacillus. In the genus Bartonella, B bacilliformis,

B quintana, B elizabethae, B vinsonii, and B koehlerae are also responsible for human disease. B clarridgeiae, has rarely been associated with cases of CSD.

Studies have demonstrated B henselae seropositivity rates ranging from 3,1-61,6% in the general population, depending on the country in which the study was performed. In all instances, few patients ever experienced symptoms, suggesting that only a minority of exposures to B henselae result in CSD.

Domestic cats are the natural reservoir and vectors of B henselae. In cats, B henselae infection is asymptomatic. Fleas are believed to transmit the bacteria between cats, and seroprevalence in cats is highest in warm or humid climates, where prevalence of flea infestation among cats is higher.

The transmission of B henselae from cats to humans occurs via a scratch or bite when the bacterium is present on the cat's claws or oral cavity. More than 90% of patients with CSD have a recent history of contact with a cat, usually a kitten, and about 75% of these patients give a history of cat scratch or bite. Dogs have been implicated in 5% of cases. Occasional cases of infection associated with monkey bites have also been reported.

Kittens younger than 12 months are 15 times more likely to transmit the disease than adult cats. Kittens are more likely to be bacteremic with B henselae and are more likely to scratch. Individuals who have been scratched or bitten by a kitten are 27 times more likely to become infected, and people who have at least one kitten with fleas are 29 times more likely to become infected than people whose animals were free of fleas.

In approximately 1% of diagnosed cases, no animal scratch is implicated. Person-to-person transmission has not been documented. No evidence exists to suggest transmission from cat fleas to humans. Ticks and biting flies have also recently been recognized as potential vectors. Cases occurring after scratches from thorns, wood splinters, and crab claws have occurred. However, in each of these cases, the patient recalled that a cat licked the abrasion.

Familial outbreaks have been documented and have usually involved siblings, or in rare instances parents. Symptoms among siblings often appear within 3 weeks of the index case.

A rare report describes veterinarian who developed fever of unknown origin and persistent backache a month after an accidental

needle puncture. Serology and molecular identification confirmed it to be B henselae infection.

Epidemiology. CSD disease has been reported worldwide; however, the international incidence is unknown. Seroprevalence rates vary greatly throughout the world, ranging from 0,6-37% and reflecting cat populations in each country. The disease is more prevalent in areas with warm humid climates.

In temperate climates, catscratch disease predominantly occurs in autumn and winter; in the tropics, seasonal changes in frequency of the disease are not observed. Sanguinetti-Morelli et al (2011) found that in France, most cases of CSD occurred from September to April, with a peak in April.

At least 2 genotypes of B henselae have been isolated from cats in Europe. B henselae is endemic in Europe, Africa, Australia, and Japan. In Germany, B henselae was the causative agent of head and neck lymphadenopathy in 61 (13,4%) of 454 patients and the most common cause of lymphadenopathy in adults and children.

Pathogenesis. Most cases of CSD are caused by Bartonella henselae. Bartonella species are small pleomorphic, fastidious, facultative, gram-negative, and intracellular bacilli. Infection appears to confer lifelong immunity, as reports of recurrences of clinical catscratch disease are rare.

The hallmark of CSD is regional adenopathy proximal to the site of inoculation. In immunocompetent patients, Bartonella infection causes a granulomatous and suppurative response. In immunocompromised patients, the response to Bartonella infection can be vasculoproliferative with neovascularization. Bartonella is able to promote angioproliferation through adhesin A, which is observed in bacillary angiomatosis, peliosis, and verruga peruana.

Nine outer membrane proteins (OMP) of B henselae have been identified. The 43-kD OMP is a major protein capable of binding endothelial cells; further investigation is needed to clarify its role in the pathogenesis of CSD.

Feline infection with B henselae is common and asymptomatic. In the United States, 28% of surveyed cats had antibodies against the organism. In California, blood cultures were positive in 56% of domestic cats younger than 1 year and in 34% of cats older than 1 year. More than three fourths of all cats in California had antibodies to B henselae as evidence of prior infection; however, only 21% of pet

cats were bacteremic, compared with 61% of stray cats.

A similar survey of cats in the Baltimore area found seropositivity in 12-14% of domestic cats versus 44% of feral animals. Cats can be asymptomatically bacteremic for months, even while antibody titers are developing.

The organism has been isolated from fleas residing on infected cats. Studies have shown that flea-vectored transmission of infection among cats occurs with high efficiency and that in the absence of fleas, infected cats do not transmit the infection to uninfected cats.

Although flea-vectored transmission to humans has not been documented, it could explain some cases in which the patient has no history of exposure to cats. Treatment of cats with doxycycline is associated with a reduction of bacteremia, but whether such treatment prevents relapse or reinfection is unknown.

Familial and household clustering of cases of CSD have been reported. However, only one member of a family in contact with an infected cat usually is affected.

Zangwill et al found an 18% prevalence rate of seropositivity to B henselae among family members of patients with CSD. Upon further questioning, 43% of these individuals reported symptoms consistent with CSD during the previous 2 months. In the same study, matched control subjects not exposed to cats exhibited a 3,6% seropositivity rate. Carithers found similar results in a series of 1200 patients; 18,5% of asymptomatic family members had positive CSD antigen skin test results.

Many organ systems are affected by CSD, including the lymph nodes, CNS, eyes (neuroretinitis), skin (bacillary angiomatosis, erythema nodosum, erythema multiforme), lungs, and bones (arthritis and osteomyelitis).

Lymph nodes. In general, lymph nodes become enlarged in 1-2 weeks after exposure. They are often tender and occasionally become fluctuant.

Lymphoid hyperplasia with arteriolar proliferation and reticular cell hyperplasia is seen early in the disease. As the disease progresses, granulomas appear, with central necrosis surrounded by lymphocytes. Histiocytes and multinucleated giant cells are often present. Finally, stellate microabscesses form, and nodes can become fluctuant.

Central nervous system. Encephalopathy is the most common neurologic manifestation, occurring in 2-3% of patients. This

complication may be more common in adults than in children. The onset is usually abrupt and occurs 1-6 weeks after the lymphadenopathy becomes apparent.

Patients can become confused and disoriented, and their condition can deteriorate to coma. About 50% of patients have a fever. Focal findings of hemiparesis and reflex abnormalities may be noted. Seizures, which occur in as many as 80% of patients with neurologic sequelae, are often prolonged and recurrent.

The pathogenesis of encephalopathy is unknown, but it is not likely due to direct infection, because CSF is usually normal and recovery is rapid, often without antibiotic therapy. CT scans are often normal, and CSF examination shows mononuclear pleocytosis in 20-30% of patients. Electroencephalographs (EEGs) show nonspecific slowing. Recovery is usually complete in a 1 week or longer, but persistent neurologic deficits have been reported.

Neuroretinitis. Patients with neuroretinitis generally present with painless, unilateral visual loss. Examination reveals decreased visual acuity, decreased color vision, and centrocecal scotoma. The optic disc appears edematous, and exudates frequently surround the macula.

Neuroretinitis is possibly due to a subretinal angiomatous nodule similar to that seen in bacillary angiomatosis.

Bacillary angiomatosis almost exclusively occurs in patients who are immunocompromised. Skin lesions consisting of numerous brown to violaceous or colorless vascular tumors of the skin and the subcutaneous tissue are the most common manifestation. Disseminated disease may involve bone, liver, spleen, lymph nodes, the gastrointestinal and respiratory tracts, and bone marrow.

B henselae and Bartonella quintana have been isolated from samples of cutaneous and osseous bacillary angiomatosis lesions. Histologic examination with Warthin-Starry staining reveals vascular proliferation with numerous bacillary organisms.

Pulmonary. Six cases of CSD with pneumonia and 8 cases with pleural thickening and/or effusion have been reported. In these cases, pulmonary features developed 1-5 weeks after lymphadenopathy occurred. Systemic signs of infection, including fever, were present in 85%. One case in which a massive abscess involved the chest wall has been reported.

Vertebral osteomyelitis and splenic abscess. Rolain et al have described vertebral osteomyelitis with splenic abscess in a patient with

CSD. B henselae was specifically identified as the etiological agent using several direct and indirect methods, including histologic and serologic assays, as well as immunofluorescent detection on slide appositions using a monoclonal antibody. This represents the second case of osteomyelitis associated with CSD.

***Clinic*.** Patients with catscratch disease (CSD) most often seek medical care because of tender regional lymphadenopathy, typically involving axillary, cervical, submandibular, or preauricular nodes.

Most patients with CSD report a history of exposure to cats, and especially kittens. When questioned, patients may recall being scratched, licked, or bitten by a cat in the previous 2-8 weeks. Transmission can occur by petting alone with subsequent self-inoculation via a mucous membrane, skin break, or conjunctiva. However, infection with B henselae can be transmitted by arthropod vectors, and a history of an animal scratch or bite is not necessary for disease transmission.

More than 90% of patients with CSD develop one or more 3- to 5-mm red-brown nontender papules at the site of inoculation 3-10 days after the bacteria are introduced. These primary lesions last for 1-3 weeks then recede as lymphadenopathy appears.

Within 1-3 weeks, lymphadenopathy develops in a single node or group of regional nodes draining the inoculation site. Single node involvement occurs in more than one half of patients. More than 65% of cases involve the nodes in the axillae or anterior or posterior triangles of the neck. Inguinal lymphadenopathy has been reported in 17% of cases.

Lymphadenopathy can be moderately tender, with erythema and increased warmth of the overlying skin. Lymphadenopathy remains regional and typically resolves within 2-4 months but may last up to 6-12 months. Rarely, it may persist for a year or more. Approximately 10-30% of nodes may suppurate, requiring needle aspiration.

Approximately 50% of patients also experience systemic symptoms. These might include the following: malaise/fatigue (29,4%), fever (28%), anorexia (14,5%), headache (13%), sore throat (7%), arthralgia (2,5%), CNS findings are present in 5% of patients with CSD. In addition to headaches, these may include mental status changes, seizures, myelitis, transient peripheral neuropathy, and retinitis. The presence of abdominal pain with a history consistent with CSD suggests CSD hepatitis/splenitis, a self-limited

granulomatous condition.

Diagnosis Consider all causes of subacute and chronic lymphadenopathy. However, infection with cytomegalovirus, human immunodeficiency virus type 1, or Epstein-Barr virus usually is associated with lymphadenitis at more than one site. In patients with persistent skin papules and regional lymphadenopathy, consider leishmaniasis, Nocardiosis, and fungal infections.

Because the clinical manifestations of infection with Bartonella henselae are different in patients who are immunocompromised, an entirely different differential diagnosis is appropriate. Bartonella infection leads to vasculoproliferative lesions, namely bacillary angiomatosis (B henselae, Bartonella quintana) and peliosis (B henselae only). The differential diagnosis includes malignant neoplasms (eg, Kaposi sarcoma, angiosarcoma) and benign reactive conditions (eg, pyogenic granuloma, angiolymphoid hyperplasia with eosinophilia).

Indirect fluorescence assay (IFA) testing and Enzyme-linked immunoassay (ELISA) are used to detect serum antibody to B henselae. An antibody titer that exceeds 1:64 suggests recent Bartonella infection. Paired acute and convalescent sera (drawn 6 wk apart) showing a 4-fold or greater increase is confirmatory. With IFA and ELISA tests, some cross-reactivity may occur between Bartonella species (especially B henselae and B quintana) and other bacteria such as Chlamydia psittaci.

IFA testing for Bartonella is quite variable, as many different tests are available; test sensitivity may be as low as 53% but is up to 100% in some series, with a specificity of 98%. About 84% of patients have positive titers within 1-2 weeks of clinical CSD, and 16% develop positive titers 4-8 weeks later.

Accuracy of IFA can be improved by concurrent use of both immunoglobulin G (IgG) and immunoglobulin M (IgM) testing. Specificity of IgM and IgG testing ranges from 88-98% and 50-62%, respectively. Most populations have low (2-6%) background seropositivity rates, limiting false-positive test results. The IFA shows cross-reactivity between Bartonella species, Epstein-Barr virus, cytomegalovirus, Toxoplasma gondii, and Streptococcus pyogenes.

ELISA testing for IgM has a sensitivity of 95% and a specificity of 77%. ELISA for IgG has a sensitivity of only 18%. Genotypic and phenotypic differences between B henselae strains are widely

encountered and lead to antigenic variation and difficulty in interpreting the results of serologic tests.

A standard pattern of anti-B henselae IgG and IgM production does not seem to exist. Some patients with CSD have high levels of both IgG and IgM, some have high levels of only IgM, and others have low levels of both. The timing of IgG and IgM response is variable, and cross-reactivity between different Bartonella species may occur. In one study, 25% of patients remained IgG seropositive for longer than 1 year. Antibody kinetics do not reliably predict severity or duration of disease.

The prevalence of seropositivity in cats living in the same house as a human with CSD is 81%, versus 14-44% in unselected households.

Treatment. Antibiotics are not indicated in most cases of CSD, but they may be considered for severe or systemic disease. Reduction of lymph node size has been demonstrated with a 5-day course of azithromycin and may be considered in patients with severe, painful lymphadenopathy; however, no reduction in the duration of symptoms has been shown. Immunocompromised patients should be treated with antibiotics because they are particularly susceptible to systemic disease and bacteremia.

Margileth et al reported the results of therapy for catscratch antigen–proven CSD with 18 different antimicrobials in 268 adult and pediatric patients. They concluded that the following 4 antibiotics were the most effective for patients with severe CSD:

Rifampin – Efficacy of 87%

Ciprofloxacin – Efficacy of 84%

Gentamicin intramuscularly – Efficacy of 73%

Trimethoprim/sulfamethoxazole (TMP-SMZ) – Efficacy of 58%

Preventation. Pet quarantine, disposal, or euthanasia is unnecessary. The ability of the animal to transmit the organism is transient.

Although doxycycline treatment of cats is associated with decreased B henselae bacteremia, this treatment has not been shown to reduce the risk of cat-to-human transmission.

The natural history of feline infection and infectivity remains unknown. Feline B henselae bacteremia has been reported to last from weeks to months, with 100-fold fluctuations in bacteremic levels and intermittent negative cultures.

Given the established link between flea infection and B henselae transmission, common sense measures seem prudent (eg, avoiding stray cats, keeping pets free of fleas).

Children should be taught how to handle pets gently. Any scratch or bite, especially from a kitten, should be brought to the attention of parents and carefully followed up.

LEPROSY

Leprosy is a chronic infection caused by the acid-fast, rod-shaped bacillus Mycobacterium leprae. Leprosy can be considered 2 connected diseases that primarily affect superficial tissues, especially the skin and peripheral nerves. Initially, a mycobacterial infection causes a wide array of cellular immune responses. These immunologic events then elicit the second part of the disease, a peripheral neuropathy with potentially long-term consequences.

Etiology. M leprae is the causative agent associated with leprosy, which has been recognized as an infectious disease for the last 2 millennia. M leprae was discovered as the causative agent in 1873. The acid fast, gram-positive bacillus is an obligate intracellular organism with a predilection for Schwann cells and macrophages. M leprae has not been successfully grown using artificial media.

In 2009, the discovery of a new cause of leprosy, Mycobacterium lepromatosis, was announced. Genetically, M leprae and M lepromatosis are very similar, but M lepromatosis causes the diffuse form lepromatous leprosy found in Mexico and the Caribbean

Epidemiology. According to WHO figures, the number of new cases of leprosy detected worldwide and the prevalence during 2010 as reported by 130 countries; globally, 228 474 new cases were detected. The worldwide registered prevalence at the beginning of 2010 was 192 246 cases. Six major countries in Asia, Africa, and South America have not achieved the goal of elimination (<1 case per 10,000 populations). Approximately 86% of reported cases are found in 11 countries: Bangladesh, Brazil, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nepal, Nigeria, Philippines, and the United Republic of Tanzania. Overall, the prevalence of leprosy has decreased since the introduction of short-course MDT in 1982. The global annual detection rate for leprosy has also been declining since 2001.

Transmission. Humans are the primary reservoir of M leprae. Animal reservoirs of leprosy have been found in 3 species: 9-banded armadillos, chimpanzees, and mangabey monkeys.

The route of transmission has not been definitively established, although human-to-human aerosol spread of nasal secretions is thought to be the most likely mode of transmission in most cases. Leprosy is not spread by touch, since the mycobacteria are incapable of crossing intact skin. Living near people with leprosy is associated with increased transmission. Among household contacts, the relative risk for leprosy is increased 8- to 10-fold in multibacillary and 2- to 4-fold in paucibacillary forms.

The incubation period of leprosy is long, ranging from a few months to 20-50 years. The mean incubation time is estimated to be 10 years for lepromatous leprosy and 4 years for tuberculoid leprosy. The organism's slow dividing time (once every 2 wk) contributes to the challenge of epidemiologically linking exposures to the development of disease.

Leprosy is generally more common in males than in females, with a male-to-female ratio of 2:1. In some areas in Africa, the prevalence of leprosy among females is equal to or greater than that in males.

Leprosy has a bimodal age distribution, with peaks at ages 10-14 years and 35-44 years. Leprosy is rare in infants. Children appear to be most susceptible to leprosy and tend to have the tuberculoid form.

Pathophysiology. Leprosy is not a highly infectious disease. The principal means of transmission is by aerosol spread from infected nasal secretions to exposed nasal and oral mucosa. The areas most commonly affected by leprosy are the superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, and the testes. These areas tend to be cool parts of the body. Tissue damage depends on the degree to which cell-mediated immunity is expressed, the type and extent of bacillary spread and multiplication, the appearance of tissue-damaging immunologic complications (ie, lepra reactions), and the development of nerve damage and its sequelae.

M leprae has a high affinity for macrophages and Schwann cells. For Schwann cells in particular, the mycobacteria bind to the G domain of the alpha-chain of laminin 2 (found only in peripheral nerves) in the basal lamina. Their slow replication within the Schwann

cells eventually stimulates a cell-mediated immune response, which creates a chronic inflammatory reaction. As a result, swelling occurs in the perineurium, leading to ischemia, fibrosis, and axonal death.

The genomic sequence of M leprae was only completed within the last few years. One important discovery is that although it depends on its host for metabolism, the microorganism retains genes for the formation of a mycobacterial cell wall. Components of the cell wall stimulate a host immunoglobulin M antibody and cell-mediated immune response, while also moderating the bactericidal abilities of macrophages.

The strength of the host's immune system influences the clinical form of the disease. Strong cell-mediated immunity (interferon-gamma, interleukin [IL]-2) and a weak humoral response results in mild forms of disease, with a few well-defined nerves involved and lower bacterial loads. A strong humoral response (IL-4, IL-10) but relatively absent cell-mediated immunity results in lepromatous leprosy, with widespread lesions, extensive skin and nerve involvement, and high bacterial loads. Therefore, a spectrum of disease exists such that cell-mediated immunity dominates in mild forms of leprosy and decreases with increasing clinical severity. Meanwhile, humoral immunity is relatively absent in mild disease and increases with the severity of disease.

Toll-like receptors (TLRs) may also play a role in the pathogenesis of leprosy. M leprae activates TLR2 and TLR1, which are found on the surface of Schwann cells, especially with tuberculoid leprosy. Although this cell-mediated immune defense is most active in mild forms of leprosy, it is also likely responsible for the activation of apoptosis genes and, consequently, the hastened onset of nerve damage found in persons with mild disease. Alpha-2 laminin receptors found in the basal lamina of Schwann cells are also a target of entry for M leprae into these cells, while activation of the ErbB2 receptor tyrosine kinase signaling pathway has been identified as a mediator of demyelination in leprosy.

The activation of macrophages and dendritic cells, both antigen-presenting cells, is involved in the host immune response to M leprae. IL-1beta produced by antigen-presenting cells infected by mycobacteria has been shown to impair the maturation and function of dendritic cells .Because bacilli have been found in the endothelium of skin, nervous tissue, and nasal mucosa, endothelial cells are also

thought to contribute to the pathogenesis of leprosy. Another pathway exploited by M leprae is the ubiquitin-proteasome pathway, by causing immune cell apoptosis and tumor necrosis factor (TNF)–alpha/IL-10 secretion.

Classification of leprosy:

Leprosy has 2 classification schemas: the 5-category Ridley-Jopling system and the simpler and more commonly used WHO standard.

Ridley-Jopling system:

Depending on the host response to the organism, leprosy can manifest clinically along a spectrum bounded by the tuberculoid and lepromatous forms of the disease. Most patients fall into the intermediate classifications, which include borderline tuberculoid leprosy, midborderline leprosy, and borderline lepromatous leprosy. The classification of the disease typically changes as it evolves during its progression or management. The Ridley-Jopling system is used globally and forms the basis of clinical studies of leprosy. It may also be more useful in guiding treatment regimens and assessing risk of acute complications.

WHO system:

The WHO recommends classifying leprosy according to the number of lesions and the presence of bacilli on a skin smear. This method is useful in countries where biopsy analysis in unavailable.

Paucibacillary leprosy is characterized by 5 or fewer lesions with absence of organisms on smear. Paucibacillary leprosy generally includes the tuberculoid and borderline lepromatous categories from the Ridley-Jopling system.

Multibacillary leprosy is marked by 6 or more lesions with possible visualization of bacilli on smear. Lepromatous leprosy, borderline lepromatous leprosy, and midborderline leprosy on the Ridley-Jopling scale are included in the multibacillary leprosy category.

Symptoms. Painless skin patch accompanied by loss of sensation but not itchiness (Loss of sensation is a feature of tuberculoid leprosy, unlike lepromatous leprosy, in which sensation is preserved).

Loss of sensation or paresthesias where the affected peripheral nerves are distributed. Wasting and muscle weakness. Foot drop or clawed hands (may result from neuritic pain and rapid peripheral nerve damage). Ulcerations on hands or feet. Lagophthalmos,

iridocyclitis, corneal ulceration, and/or secondary cataract due to nerve damage and direct bacillary skin or eye invasion.

Symptoms in reactions.

Type 1 (reversal) – Sudden onset of skin redness and new lesions.

Type 2 (erythema nodosum leprosum [ENL) – Many skin nodules, fever, redness of eyes, muscle pain, and joint pain.

The cardinal signs of leprosy include hypoesthesia, skin lesions, and peripheral neuropathy. The first physical signs of leprosy are usually cutaneous. The subtype of leprosy often determines the degree of skin involvement.

Tuberculoid leprosy. The initial lesion is often a sharply demarcated hypopigmented macule that is ovoid, circular, or serpiginous. The lesions may be somewhat elevated with a dry scaly center and erythematous borders.

Common lesion sites include the buttocks, face, and extensor surfaces of limbs. The perineum, scalp, and axilla are not normally involved because of the temperature differential in these zones, as predilection is toward cooler zones.

As the disease progresses, lesions tend to destroy the normal skin organs such as sweat glands and hair follicles.

Superficial nerves that lead from the lesions tend to enlarge and are sometimes palpable. The patient may experience severe neuropathic pain. Nerve involvement can also lead to trauma and muscle atrophy.

Lepromatous leprosy. This form is characterized by extensive bilaterally symmetric cutaneous involvement, which can include macules, nodules, plaques, or papules. Multiple flat hypopigmented lesions are observed.

Unlike lesions in tuberculoid leprosy, those in lepromatous leprosy have poorly defined borders and raised and indurated centers. As in all forms of leprosy, lepromatous lesions are worst on cooler parts of the body. Common areas of involvement include the face, ears, wrists, elbows, buttocks, and knees.

Hoarseness, loss of eyebrows and eyelashes, and nasal collapse secondary to septa perforation may occur in advanced cases of disease. Involvement of the eye may include keratitis, glaucoma, or iridocyclitis as seen in the image below.

The leonine facies associated with leprosy develop as the disease progresses, and the facial skin becomes thickened and corrugated.

Axillary and inguinal adenopathy may develop, in addition to

scarring of the testes and subsequent gynecomastia and sterility.

Nerve involvement in lepromatous leprosy is not as severe as in tuberculoid leprosy, since nerves, although visibly thickened and highly infected, still function reasonably well in early stages of the disease.

Borderline tuberculoid leprosy. The lesions are few or moderate and asymmetric with almost complete anesthesia. Peripheral nerves are often involved and thickened asymmetrically, and cutaneous nerves are sometimes enlarged.

Midborderline leprosy. The number of skin lesions is moderate, and they are asymmetrical and somewhat anesthetic. Peripheral nerves may be somewhat symmetrically enlarged, but cutaneous nerves are not.

Borderline lepromatous leprosy. Moderate to numerous slightly asymmetrical skin lesions appear with minor or no anesthesia. Peripheral nerves are often enlarged symmetrically, but cutaneous nerves are not.

Indeterminate leprosy. Skin lesions are typically either hypopigmented or hyperpigmented macules or plaques. Patients may note that these lesions are anesthetic or paresthetic.

Laboratory Studies. The WHO case definition of leprosy is M leprae infection in an individual who has not completed a course of treatment and has one or more of the following:

- Hypopigmented or reddish skin lesions with loss of sensation
- Involvement of the peripheral nerves as demonstrated by their thickening and associated loss of sensation
- Skin smear positive for acid-fast bacilli.

Laboratory studies include the following:

Skin biopsy, nasal smears, or both are used to assess for acid-fast bacilli using Fite stain. Biopsies should be full dermal thickness taken from an edge of the lesion that appears most active.

Serologic assays can be used to detect phenolic glycolipid-1 (specific for M leprae) and lipoarabinomannan (commonly seen in mycobacteria).

Immunologic tests include the following:

Lepromin skin test (not available in the United States): Although not diagnostic of exposure to or infection with M leprae, this test assesses a patient's ability to mount a granulomatous response against a skin injection of killed M leprae. Patients with tuberculoid leprosy or borderline lepromatous leprosy typically have a positive response (>5

mm). Patients with lepromatous leprosy typically have no response.

Phenolic glycolipid-1: This is a specific serologic test based on the detection of antibodies to phenolic glycolipid-1. This test yields a sensitivity of 95% for the detection of lepromatous leprosy but only 30% for tuberculoid leprosy.

Polymerase chain reaction (PCR): PCR and recombinant DNA technology have allowed for the development of gene probes with M leprae – specific sequences. This technology can be used to identify the mycobacterium in biopsy samples, skin and nasal smears, and blood and tissue sections.

Lymphocyte migration inhibition test (LMIT): As determined by a lymphocyte transformation and LMIT, cell-mediated immunity to M leprae is absent in patients with lepromatous leprosy but present in those with tuberculoid leprosy.

Medical Care. In response to the increased incidence of dapsone resistance, the WHO introduced a multidrug regimen in 1981 that includes rifampicin, dapsone, and clofazimine (tab. 8). Some clinical studies have also shown that certain quinolones, minocycline, and azithromycin have activity against M leprae. The WHO recently recommended single-dose treatment with rifampin, minocycline, or ofloxacin in patients with paucibacillary leprosy who have a single skin lesion. However, the WHO still recommends the use of the long-term multidrug regimens whenever possible because they have been found to be more efficacious.

Table 8. – Leprocy multidrug regimens treatment

Types of leprosy	*Daily, Self-Administered*	*Monthly Supervised*	*Months of Treatment*
Paucibacillary	Dapsone 100 mg	Rifampicin 600 mg	6-12
Multibacillary	Dapsone 100 mg, Clofazimine 50 mg	Rifampicin 600 mg, Clofazimine 300 mg	24
Pediatric	Dapsone 2 mg/kg, Clofazimine 1 mg/kg	Rifampicin10 mg/kg, Clofazimine 6 mg/kg	Same as adults

Paucibacillary leprosy should be treated for 6-12 months with dapsone 100 mg/day unsupervised plus rifampin 600 mg/month supervised. This regimen should be followed by treatment with dapsone as monotherapy for 3 years in patients with tuberculoid leprosy or 5 years in patients with borderline lepromatous leprosy.

Multibacillary leprosy should be treated for 24 months with dapsone 100 mg/day unsupervised, clofazimine 50 mg/day unsupervised, and rifampin 600 mg plus clofazimine 300 mg/month supervised. Corticosteroids have been used to treat nerve damage associated with leprosy, but a recent review of 3 randomized controlled trials shows no significant long-term effect. Prednisolone is believed to minimize pain and acute inflammation. The recommended initial dose is prednisolone 40 mg daily.

Surgical Care. The goals of surgical treatment in patients with leprosy are to prevent further deterioration, to improve motor function, and, in some cases, to improve sensation.

Amputation is a last resort and is reserved for cases of extremely diseased tissue. Eye procedures: Loss of eyelid function may be treated with passing a strip from the temporalis muscle through the eyelid and connecting it to the inner canthus. Tarsorrhaphy may help narrow the opening of the eyelid, and canthoplasty reduces sagging of the eyelids.

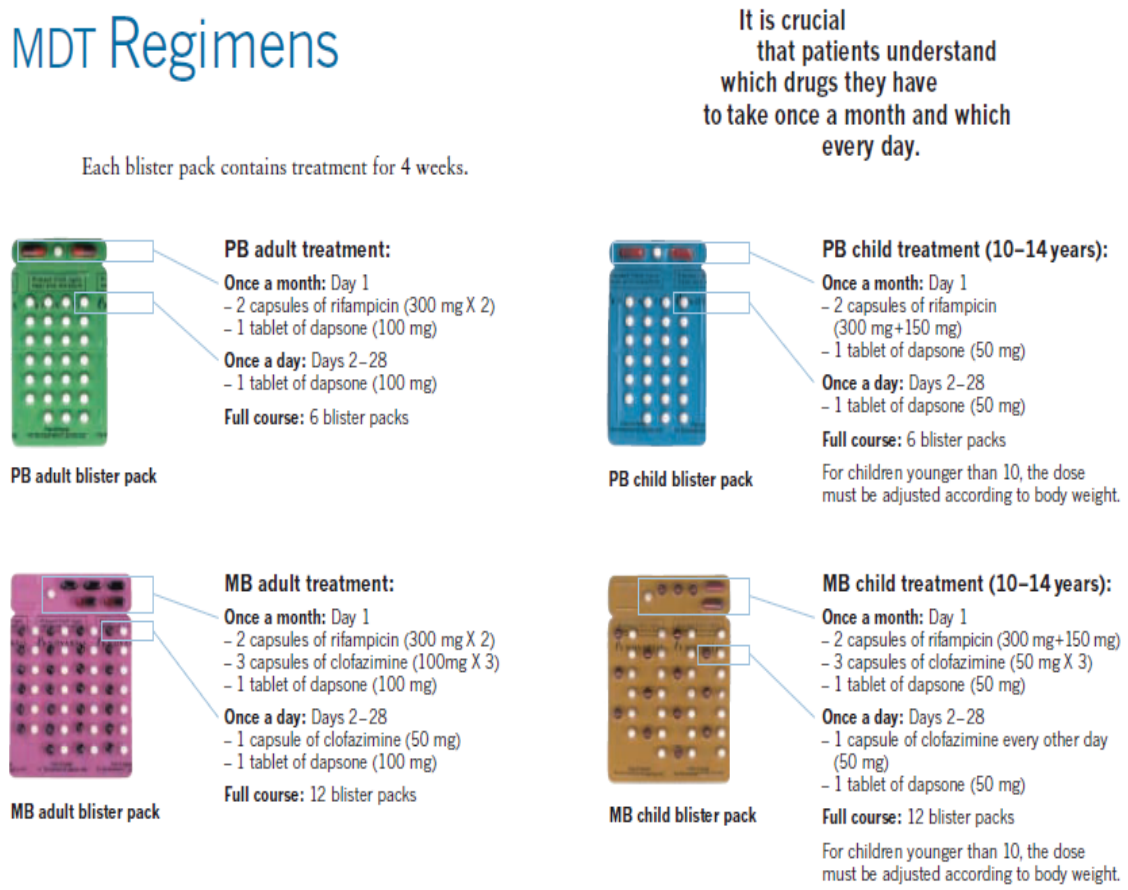

Fig. 6. – Leprocy multidrug regimens treatment

Cosmetic surgery. After the disease is controlled medically, the following cosmetic procedures may also be considered: nasal reconstruction, removal of excess skin, replacement of eyebrows using transplants of scalp hair, removal of breast tissue formation due to gynecomastia.

Prognosis. Recovery from neurologic impairment is limited, but skin lesions generally clear within the first year of therapy. Discoloration and skin damage typically persist.

Physical therapy, reconstructive surgery, nerve and tendon transplants, and surgical release of contractures have all contributed to increasing the functional ability in patients with leprosy. A common residual deformity is insensitive feet, as seen in persons with diabetes.

Prevention. Patients with leprosy should be advised about the importance of continuing long-term therapy until the course of antibiotics is completed. The WHO recommends that the monthly administration of rifampin should be directly observed. In patients with leprosy who have advanced nerve damage, self-care techniques are of utmost importance in maintaining function and preventing further disability. The use of visual input to regulate activity, self-inspection, hygiene, and proper footwear can help to prevent ulcer formation and tissue damage.

The WHO recommends examination of all household contacts of patients with leprosy, with careful instructions to seek medical care if signs and symptoms of leprosy appear.

BURULI ULCER

Etiology. Buruli ulcer is caused by a germ that mainly affects the skin but which can also affect the bone. The causative organism is called Mycobacterium ulcerans, which although different, belongs to the same family of organisms that cause leprosy and tuberculosis.

Epidemiology. Buruli ulcer has been reported in over 30 countries with tropical and subtropical climates but it may also occur in some countries where it has not yet been recognized. Limited knowledge of the disease, its focal distribution and the fact that it affects mainly poor rural communities contribute to low reporting of cases. Progress is being made now to develop tools for early diagnosis, to understand exactly how infection is transmitted and to improve treatment.

The infection occurs in well defined areas throughout the world, mostly tropical areas – in several areas in Australia, in Uganda, in

several countries in West Africa, in Central and South America, in southeast Asia and New Guinea. It is steadily rising as a serious disease, especially in West Africa and underdeveloped countries, where it is the third leading cause of mycobacterial infection in healthy people, after tuberculosis and leprosy. In East Africa, thousands of cases occur annually and in these areas the disease has displaced leprosy to become the second most important mycobacterial disease of man (after tuberculosis).

The disease is more likely to occur where there have been environmental changes such as the development of water storages, sand mining and irrigation.

Buruli ulcer is currently endemic in the Benin, Côte d'Ivoire, Ghana, Guinea, Liberia, Nigeria, Sierra Leone and Togo. In Ghana, 1999 data indicated that the prevalence rate of the disease in the Ga West District was 87,7 per 100,000, higher than the estimated national prevalence rate at 20,7 per 100,000 generally, and 150,8 per 100,000 in the most disease-endemic districts.

Buruli ulcer has been reported from at least 32 countries around the world, mostly in tropical areas:

West Africa: Benin, Burkina Faso, Côte d'Ivoire, Ghana, Liberia, Nigeria, Togo, Guinea, Sierra Leone.

Other African Countries: Angola, Cameroon, Congo, Democratic Republic of Congo, Equatorial Guinea, Gabon, Sudan, Uganda.

Western Pacific: Australia, Papua New Guinea, Kiribati; Americas: French Guyana, Mexico, Peru, Surinam.

Asia: China, Malaysia, Japan.

In several of these countries, the disease is not considered to be a public healthproblem, hence the current distribution and the number of cases are not known. Possible reasons include: the distribution of the disease is often localized in certain parts of endemic countries; Buruli ulcer is not a notifiable disease.

In most places where the disease occurs, patients receive care from private sources such as voluntary mission hospitals and traditional healers. Hence the existence of the disease may not come to the attention of the ministries of health.

It most commonly occurs in Africa: Congo and Cameroon in Central Africa, Côte d'Ivoire, Ghana and Benin in West Africa. Some Southeast Asian countries (Papua New Guinea) and Australia have

major foci, and there have been a few patients reported from South America (French Guyana and Surinam) and Mexico. Focal outbreaks have followed flooding, human migrations, and man-made topographic modifications such as dams and resorts. Deforestation and increased basic agricultural activities may significantly contribute to the recent marked increases in incidences of M. ulceransinfections, especially in West Africa, where the disease is rapidly emerging.

Pathogenesis. The disease is primarily an infection of subcutaneous fat, resulting in a focus of necrotic (dead) fat containing myriads of the mycobacteria in characteristic spherules formed within the dead fat cells. Skin ulceration is a secondary event.

M. ulcerans releases a lipid toxin, mycolactone, which functions as an immune suppressant, necrotising agent and activator of cellulardeath.

Healing may occur spontaneously but more often the disease is slowly progressive with further ulceration, granulation, scarring, and contractures. Secondary infection may occur with other nodules developing and infection may occur into bone. Although seldom fatal, the disease results in considerable morbidity and deformity.

Th1-mediated immune responses are protective against M. ulcerans infection, whereas Th2-mediated responses are not.

Symptoms. Buruli ulcer often starts as a painless, mobile swelling in the skin called nodule. Infection often leads to extensive destruction of skin and soft tissue with the formation of large ulcers usually on the legs or arms. If patients seek treatment at the early stage, antibiotics can prove to be successful. Delayed treatment may cause irreversible deformity, long-term functional disability such as restriction of joint movement, extensive skin lesions and sometimes life-threatening secondary infections.

Early diagnosis and treatment are vital.

Prevention and Treatment.Research for a vaccine to treat Buruli ulcer is continuing, although the current Bacille Calmette-Guérin (BCG) vaccine appears to offer some short-term protection. A safe and effective vaccine may be the most effective way to combat Buruli ulcer in the long term.

Current WHO recommendations for treatment are as follows:

A combination of rifampicin and streptomycin/amikacin for eight weeks as a first-line treatment for all forms of the active disease. Nodules or uncomplicated cases can be treated without hospitalization.

Surgery mainly to remove necrotic tissue, cover skin defects and correct deformities. Interventions to minimize or prevent disabilities.

MELIOIDOSIS

Melioidosis is an infectious disease caused by a Gram-negative bacterium, Burkholderia pseudomallei, found in soil and water. It is of public health importance in endemic areas, particularly in Thailand and northern Australia. It exists in acute and chronic forms. Symptoms may include pain in chest, bones, or joints; cough; skin infections, lung nodules and pneumonia.

B. pseudomallei was previously classed as part of the Pseudomonas genus and until 1992, it was known as Pseudomonas pseudomallei. It is phylogenetically related closely to Burkholderia mallei which causes glanders, an infection primarily of horses, donkeys and mules. The name Melioidosis is derived from the Greek melis meaning "a distemper of asses" with the suffixes -oid meaning "similar to" and -osis meaning "a condition", that is, a condition similar to glanders.

Epidemiology. Melioidosis is endemic in parts of southeast Asia (including Thailand, Laos and southern China, Singapore, Malaysia, Burma and Vietnam), Taiwan and northern Australia. Multiple cases have also been described in Hong Kong and Brunei India, and sporadic cases in Central and South America, the Middle East, the Pacific and several African countries. Although only one case of melioidosis has ever been reported in Bangladesh, at least five cases have been imported to the UK from that country. There are recent news reports that B. pseudomallei has been isolated from soil in Bangladesh, but this remains to be verified scientifically. This suggests that melioidosis is endemic to Bangladesh and that there is a problem of underdiagnosis or under-reporting there most likely due to a lack of adequate laboratory facilities in affected rural areas.

Northeast Thailand has the highest incidence of melioidosis recorded in the world (21,3 cases of melioidosis per 100,000 people per year). In Northeast Thailand, 80% of children are positive for antibodies against B. pseudomallei by the age of 4; the figures are lower in other parts of the world.

Melioidosis is a recognised disease in animals, including cats, goats, sheep, and horses. Cattle, water buffalo, and crocodiles are

considered to be relatively resistant to melioidosis despite their constant exposure to mud. [31] An outbreak at the Paris Zoo in the 1970s ("L'affaire du jardin des plantes") was thought to have originated from an imported panda.

Burkholderia pseudomallei is normally found in soil and surface water; a history of contact with soil or surface water is therefore almost invariable in patients with melioidosis; that said, the majority of patients who do have contact with infected soil suffer no ill effects. Even within an area, the distribution of B. pseudomallei within the soil can be extremely patchy, and competition with other Burkholderia species has been suggested as a possible reason. Contaminated ground water was implicated in one outbreak in northern Australia. Also implicated are severe weather events such as flooding tsunamis and typhoons. It has been suggested, on the basis of whole genome sequencing, that humans may play a role in moving B. pseudomallei from place to place.

The single most important risk factor for developing severe melioidosis is diabetes mellitus. Other risk factors include thalassaemia, kidney disease, occupation (rice paddy farmers), and cystic fibrosis. The mode of infection is believed to be either through a break in the skin, or through the inhalation of aerosolized B. pseudomallei. Person-to-person spread has been described but is extremely unusual. HIV infection does not predispose to melioidosis.

There is a clear association with increased rainfall: with the number (and severity) of cases increasing following increased precipitation.

Clinic. Acute melioidosis. In the subgroup of patients where an inoculating event was noted, the mean incubation period of acute melioidosis was 9 days (range 1–21 days). Patients with latent melioidosis may be symptom free for decades; the longest period between presumed exposure and clinical presentation is 62 years. The potential for prolonged incubation was recognized in US servicemen involved in the Vietnam War, and was referred to as the "Vietnam time-bomb". There is a wide spectrum of severity; in chronic presentations, symptoms may last months, but fulminant infection, particularly associated with near-drowning, may present with severe symptoms over hours.

A patient with active melioidosis usually presents with fever. Pain or other symptoms may be suggestive of a clinical focus, which is

found in around 75% of patients. Such symptoms include cough or pleuritic chest pain suggestive of pneumonia, bone or joint pain suggestive of osteomyelitis or septic arthritis, or cellulitis. Intra-abdominal infection (including liver and/or splenic abscesses, or prostatic abscesses) do not usually present with focal pain, and imaging of these organs using ultrasound or CT should be performed routinely. In one series of 214 patients, 27,6% had abscesses in the liver or spleen (95% confidence interval, 22,0% to 33,9%). It has been suggested that B. pseudomallei abscesses have a characteristic "honeycomb" or "swiss cheese" architecture (hypoechoic, multi-septate, multiloculate) on CT.

There are regional variations in disease presentation: parotid abscesses characteristically occur in Thai children but this presentation has only been described once in Australia. Conversely, prostatic abscesses are found in up to 20% of Australian males but are rarely described elsewhere. An encephalomyelitis syndrome is recognised in northern Australia.

Patients with melioidosis usually have risk factors for disease, such as diabetes, thalassemia, hazardous alcohol use or renal disease, and frequently give a history of occupational or recreational exposure to mud or pooled surface water. However, otherwise healthy patients, including children, may also get melioidosis.

In up to 25% of patients, no focus of infection is found and the diagnosis is usually made on blood cultures or throat swab. Melioidosis is said to be able to affect any organ in the body except the heart valves (endocarditis). Although meningitis has been described secondary to ruptured brain abscesses, primary meningitis has not been described. Less common manifestations include intravascular infection, lymph node abscesses (1,2-2,2%), pyopericardium and myocarditis, mediastinal infection, and thyroid and scrotal abscesses and ocular infection.

Chronic melioidosis. Chronic melioidosis is usually defined by a duration of symptoms greater than 2 months and occurs in approximately 10% of patients. The clinical presentation of chronic melioidosis is protean and includes such presentations as chronic skin infections, chronic lung nodule and pneumonia. In particular, chronic melioidosis closely mimics tuberculosis, and has sometimes been called "Vietnamese tuberculosis".

Diagnosis. A definitive diagnosis is made by culturing the organism from any clinical sample, because the organism is never part

of the normal human flora.

A definite history of contact with soil may not be elicited as melioidosis can be dormant for many years before manifesting. Attention should be paid to a history of travel to endemic areas in returned travellers. Some authors recommend considering possibility of melioidosis in every febrile patient with a history of traveling to and/or staying at endemic areas.

A complete screen (blood culture, sputum culture, urine culture, throat swab and culture of any aspirated pus) should be performed on all patients with suspected melioidosis (culture on blood agar as well as Ashdown's medium). A definitive diagnosis is made by growing B. pseudomallei from any site. A throat swab is not sensitive but is 100% specific if positive, and compares favourably with sputum culture. The sensitivity of urine culture is increased if a centrifuged specimen is cultured, and any bacterial growth should be reported (not just growth above 104 organisms/ml which is the usual cut off). Very occasionally, bone marrow culture may be positive in patients who have negative blood cultures for B. pseudomallei, but these are not usually recommended. A common error made by clinicians unfamiliar with melioidosis is to only send a specimen from the affected site (which is the usual procedure for most other infections) instead of sending a full screen.

Ashdown's medium, a selective medium containing gentamicin, may be required for cultures taken from non-sterile sites. Burkholderia cepacia medium may be a useful alternative selective medium in non-endemic areas, where Ashdown's is not available. A new medium derived from Ashdown known as Francis medium may help differentiate B. pseudomallei from B. cepacia and may help in the early diagnosis of melioidosis, but has not yet been extensively clinically validated.

Many commercial kits for identifying bacteria may misidentify B. pseudomallei (see Burkholderia pseudomallei for a more detailed discussion of these issues).

There is also a serological test for melioidosis (indirect haemagglutination), but this is not commercially available in most countries. A high background titre may reduce the positive predictive value of serological tests in endemic countries. A specific direct immunofluorescent test and latex agglutination, based on monoclonal antibodies, are used widely in Thailand but are not available

elsewhere. There is almost complete cross-reactivity with B. thailandensis. There exists a commercial ELISA kit for melioidosis which appears to perform well, but no ELISA test has yet been clinically validated as a diagnostic tool.

It is not possible to make the diagnosis on imaging studies alone (X-rays and scans), but imaging is routinely performed to assess the full extent of disease. Imaging of the abdomen using CT scans or ultrasound is recommended routinely, as abscesses may not be clinically apparent and may coexist with disease elsewhere. Australian authorities suggest imaging of the prostate specifically due to the high incidence of prostatic abscesses in northern Australian patients. A chest x-ray is also considered routine, with other investigations as clinically indicated. The presence of honeycomb abscesses in the liver are considered characteristic, but are not diagnostic.

The differential diagnosis is extensive; melioidosis may mimic many other infections, including tuberculosis.

Treatment. Current treatment. The treatment of melioidosis is divided into two stages, an intravenous high intensity phase and an eradication phase to prevent recurrence.

Intravenous intensive phase. Intravenous ceftazidime is the current drug of choice for treatment of acute melioidosis. Meropenem, imipenem and the cefoperazone-sulbactam combination (Sulperazone) are also active. Intravenous amoxicillin-clavulanate (co-amoxiclav) may be used if none of the above four drugs are available, but it produces inferior outcomes. Intravenous antibiotics are given for a minimum of 10 to 14 days, and are not usually stopped until the patient's temperature has returned to normal for more than 48 hours. Even with appropriate antibiotic therapy, fevers often persist for weeks or months, and patients may continue to develop new lesions even while on appropriate treatment. The median fever clearance time in melioidosis is 10 days: and failure of the fever to clear is not a reason to alter treatment. It is not uncommon for patients to require parenteral treatment continuously for a month or more.

Intravenous meropenem is routinely used in Australia: outcomes appear to be good and meropenem is currently being tested with ceftazidime in a Thai clinical trial (ATOM).

There are theoretical reasons for believing that mortality might be lower in patients treated with imipenem: first, there is less endotoxin released by dying bacteria during imimipenem treatment,

and the minimum inhibitory concentration for imipenem is lower than for ceftazidime. However, no clinically relevant difference was found in mortality between imipenem and ceftazidime treatment. The MIC of meropenem is higher for B. pseudomallei than for many other organisms, and patients being haemofiltered will need more frequent or higher doses.

Moxifloxacin, cefepime, tigecycline and ertapenem do not appear to be effective in vitro. Piperacillin-sulbactam, doripenem and biapenem appear to be effective in vitro, but there is no clinical experience on which to recommend their use.

Adjunctive treatment with GCSF or co-trimoxazole were not associated with decreased fatality rates in trials in Thailand.

Eradication phase. Following the treatment of the acute disease, it is recommended that eradication (or maintenance) treatment with co-trimoxazole and doxycycline be used for 12 to 20 weeks to reduce the rate of recurrence. Chloramphenicol is no longer routinely recommended for this purpose. Co-amoxiclav is an alternative for those patients who are unable to take co-trimoxazole and doxycycline (e.g., pregnant women and children under the age of 12), but is not as effective. Single agent treatment with a fluoroquinolone (e.g., ciprofloxacin) or doxycycline for the oral maintenance phase is ineffective.

In Australia, co-trimoxazole is used on its own for eradication therapy, with relapse rates that are lower than those seen in Thailand; there is also in vitro evidence to suggest that co-trimoxazole and doxycycline are antagonistic, and that co-trimoxazole on its own may be preferable. A randomised controlled trial (MERTH) to compare this with the current standard of co-trimoxazole and doxycycline started in 2006 and is due for completion in 2008. Studies reinforce the need for adequate follow up and good adherence to the eradication phase of therapy. Dosing for co-trimoxazole is based on weight: (<40 kg: 160/800 mg every 12 hours; 40-60 kg: 240/1200 mg every 12 hours, >60 kg: 320/1600 mg every 12 hours).

Surgical treatment. Surgical drainage is usually indicated for prostatic abscesses and septic arthritis, may be indicated for parotid abscesses and not usually indicated for hepatosplenic abscesses. In bacteraemic melioidosis unresponsive to intravenous antibiotic therapy, splenectomy has been attempted, but there is only anecdotal evidence to support this practice.

Historical treatment. Prior to 1989, the standard treatment for acute melioidosis was a three-drug combination of chloramphenicol, co-trimoxazole and doxycycline; this regimen is associated with a mortality rate of 80% and is no longer be used unless no other alternatives are available. All four drugs are bacteriostatic (they stop the bacterium from growing but do not kill it) and the action of co-trimoxazole antagonizes both chloramphenicol and doxycycline.

PROTOZOAL INFECTIONS. MALARIA

Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquitoes. The most important of the parasitic diseases of humans, it is transmitted in 108 countries containing 3 billion people and causes nearly 1 million deaths each year. Malaria is the most highly prevalent tropical disease, with high morbidity and mortality and high economic and social impact.

Epidemiology. Malaria has been eliminated from the United States, Canada, Europe, and Russia; in the late twentieth and early twenty-first centuries, however, its prevalence rose in many parts of the tropics. Despite enormous control efforts, increases in the drug resistance of the parasite, the insecticide resistance of its vectors, and human travel and migration have contributed to this resurgence. Occasional local transmission after importation of malaria has occurred in several southern and eastern areas of the United States and in Europe, indicating the continual danger to nonmalarious countries. Although there are many promising new control and research initiatives, malaria remains today, as it has been for centuries, a heavy burden on tropical communities, a threat to nonendemic countries, and a danger to travelers. In 2010 an estimated 219 million cases of malaria occurred worldwide and 660,000 people died, most (91%) in the African Region and 86% in children aged less than 5 years.

Etiology and Pathogenesis. **Six species** of the genus *Plasmodium* cause nearly all malarial infections in humans. These are

P. falciparum
P. vivax
P. ovale: two sub species P.O curtisi, P.O wallikeri
P. malariae

***P. Knowlesi (monkey malaria*).**

In Southeast Asia the monkey malaria parasite which can be reliably identified only by molecular methods. Almost all deaths are caused by P.falciparum malaria.

Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from its salivary gland during a blood meal. These microscopic motile forms of the malarial parasite are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction.

By this amplification process (known as *intrahepatic* or *pre erythrocytic schizogony* or *merogony*), a single sporozoite eventually may produce from 10,000 to >30,000 daughter merozoites. The swollen infected liver cell eventually bursts, discharging motile *merozoites* into the bloodstream. These merozoites then invade the red blood cells (RBCs) and multiply six- to twentyfold every 48-72 h. When the parasites reach densities of 50/L of blood (100 million parasites in the blood of an adult), the symptomatic stage of the infection begins. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain dormant for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or *hypnozoites*, are the cause of the relapses that characterize infection with these two species. After entry into the bloodstream, merozoites rapidly invade erythrocytes and become *trophozoites*. Attachment is mediated via a specific erythrocyte surface receptor. In the case of *P. vivax*, this receptor is related to the Duffy blood-group antigen. Most West Africans and people with origins in that region carry the Duffy-negative FyFy phenotype and are therefore resistant to *P. vivax* malaria. During the early stage of intraerythrocytic development, the small "ring forms" of the different parasitic species appear similar under light microscopy. As the trophozoites enlarge, species-specific characteristics become evident, pigment becomes visible, and the parasite assumes an irregular or ameboid shape.

By the end of the 48-h intraerythrocytic life cycle (24 h for *P. knowlesi*, 72 h for *P. malariae*), the parasite has consumed two-thirds of the RBC's hemoglobin and has grown to occupy most of the cell. It is now called a *schizont*. Multiple nuclear divisions have taken place (*schizogony* or *merogony*), and the RBC then ruptures to release 6–30 daughter merozoites, each potentially capable of invading a new

RBC and repeating the cycle. The disease in human beings is caused by the direct effects of RBC invasion and destruction by the asexual parasite and the host's reaction. After a series of asexual cycles (*P. falciparum*) or immediately after release from the liver (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*), some of the parasites develop into morphologically distinct, longer-lived sexual forms (*gametocytes*) that can transmit malaria.

After being ingested in the blood meal of a biting female anopheline mosquito, the male and female gametocytes form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feeding.

Malarial ***pathogenesis*** done by three main mechanisms:

Cytoadherence. Plasmodium falciparum-infected erythrocytes adhere specifically to venular endothelium and thereby evade spleen-dependent immune mechanisms.

Erythrocyte resetting – spontaneous binding of uninfected erythrocytes to Plasmodium falciparum-infected erythrocytes (rosetting) has been suggested to have a critical role in the induction of cerebral malaria.

Sequestration is caused by the adherence of infected erythrocytes to capillary endothelial cells by means of a specific interaction between a parasite-derived molecule present at the surface of the malaria-infected red cell and specific host cell receptors.

Table 9. – Characteristics of Plasmodium Species Infecting Humans

	Finding for Indicated Species			
Characteristic	***P. falciparum***	***P. vivax***	***P. ovale***	***P. malariae***
Duration of intrahepatic phase (days)	5,5	8	9	15
Number of merozoites released per infected hepatocyte	30,000	10,000	15,000	15,000
Duration of erythrocytic cycle (hours)	48	48	50	72
Red cell preference	Younger cells (but can invade cells of all ages)	Reticulocytes and cells up to 2 weeks old	Reticulocytes	Older cells
Morphology	Usually only	Irregularly	Infected	Band or

Finding for Indicated Species				
Characteristic	***P. falciparum***	***P. vivax***	***P. ovale***	***P. malariae***
	ring forms; banana-shaped gametocytes	shaped large rings and trophozoites; enlarged erythrocytes; Schüffner's dots	erythrocytes, enlarged and oval with tufted ends; Schüffner's dots	rectangular forms of trophozoites common
Pigment color	Black	Yellow-brown	Dark brown	Brown-black
Ability to cause relapses	No	Yes	Yes	No

Life cycle of P. falciparum. Sporozoites injected by anopheline mosquitoes travel through the dermis and enter the blood stream to invade hepatocytes. ***Diagnostic stage*:** Each infected hepatocyte generates tens of thousands of merozoites, which then break out and reenter the bloodstream to invade erythrocytes. Numerous rounds of asexual reproduction follow, with repeated invasion of erythrocytes every 48 hours. ***Infective stage:*** Some parasites in the erythrocytes develop into sexual stage gametocytes, which circulate in the bloodstream and are taken up by female mosquitoes during a blood meal. In the mosquito midgut, gametes emerge from the gametocytes and cross-fertilize. The resulting zygote develops into an ookinete that crosses the midgut wall and grows into an oocyst. Mitotic division within the oocyst produces thousands of sporozoites that break out and travel through the hemolymph to the mosquito salivary glands, from which they are injected into a human host.

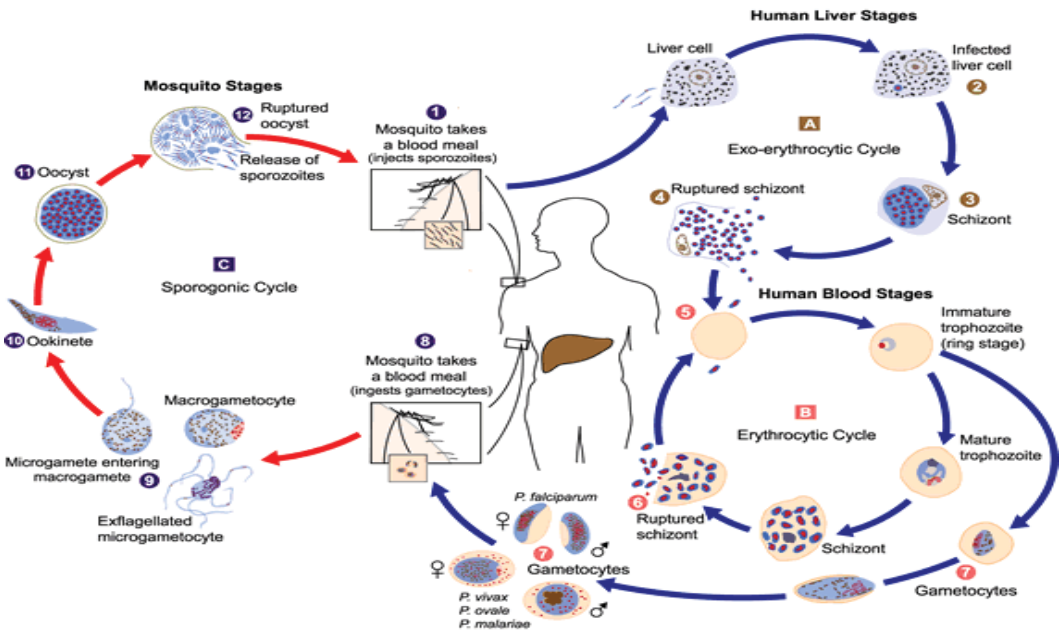

Fig. 7. - Life cycle of P. falciparum

Incubation Period. The incubation period in most cases varies from 7 to 30 days. The shorter periods are observed most frequently with P. falciparum and the longer ones with P. malariae.

Antimalarial drugs taken for prophylaxis by travelers can delay the appearance of malaria symptoms by weeks or months, long after the traveler has left the malaria-endemic area. (This can happen particularly with P. vivax and P. ovale, both of which can produce dormant liver stage parasites; the liver stages may reactivate and cause disease months after the infective mosquito bite).

Such long delays between exposure and development of symptoms can result in misdiagnosis or delayed diagnosis because of reduced clinical suspicion by the health-care provider. Returned travelers should always remind their health-care providers of any travel in malaria-risk areas during the past 12 months.

Clinical Features. Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death. Malaria disease can be categorized as uncomplicated or severe (complicated).

Malaria is a very common cause of acute febrile illness in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, there is not neck stiffness or photophobia as occurs in meningitis. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. Early or prodrome 2-3 day before paroxysm: headache, fatigue, abdominal discomfort, muscle aches, fever, diarrhea, nausea, vomiting (same like URT infection or GIT infection).

The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection with *P. vivax* or *P. ovale*.

Malarial paroxysms: chill (last 1h longer) or rigors: in hot climate with apprehensive, mild shivering turn in to violent shaking with teeth chattering. Peripheral vasoconstriction and goose flesh in some patients cause vomiting, and children may have convulsion;

fever: chill followed by severe hotness/ fever with throbbing headache palpitation, tachycardia, prostration, postural syncope, vomiting, meanwhile the fever reach its high peak; ***sweat:*** fever is subsided and patient usually feel sleepy. The fever is irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40°C in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of encephalopathy (cerebral malaria). Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anemia, and (in some cases) a palpable spleen. Anemia is common among young children living in areas with stable transmission, particularly where resistance has compromised the efficacy of antimalarial drugs.

In nonimmune individuals with acute malaria, the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise healthy individuals in malaria-endemic areas and reflects repeated infections.

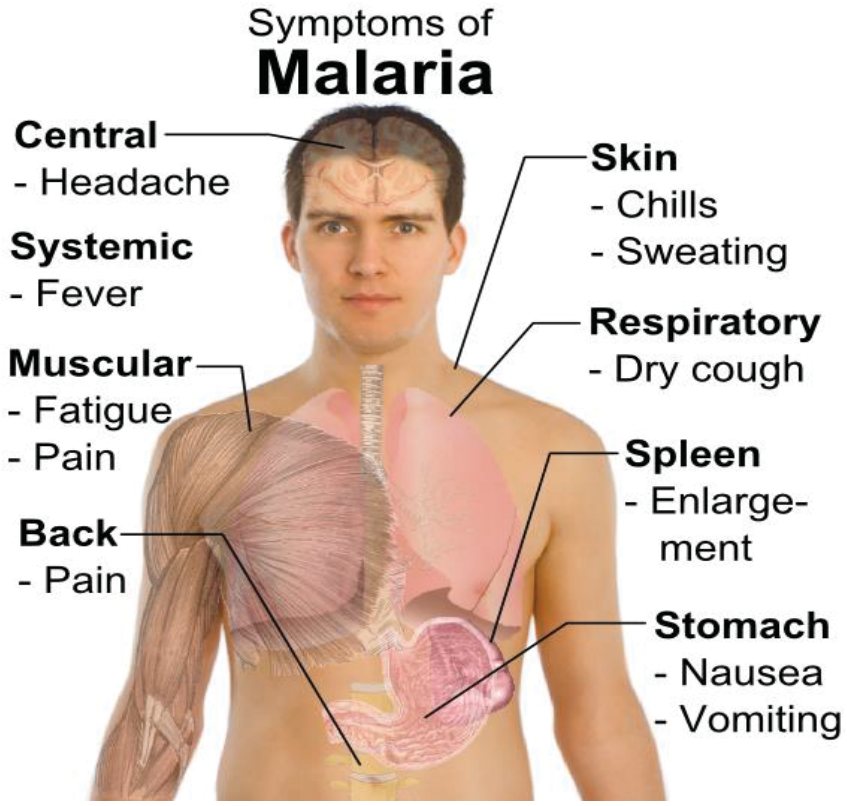

Fig. 8. – Clinical symptoms of malaria

Slighten largement of the liver is also common, particularly among young children. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated malaria and usually resolves over 1–3 weeks. Malaria is not associated with a rash like those seen in meningococcal septicemia, typhus, enteric fever, viral exanthems, and drug reactions. Petechial hemorrhages in the skin or mucous membranes-features of viral hemorrhagic fevers and leptospirosis-develop only rarely in severe falciparum malaria.

Criteria of severe malaria (WHO, 2000):

- Prostration
- Impaired consciousness
- Respiratory disstress (ARDS)
- Multiply convulsion
- Pulmonary edema (in Xray)
- Jaundice
- Hemoglobinuria

Lab.tests of severe malaria:

- Anemia: Hb <5d/dl or Hct<15%
- Hypoglycemia <2,2mmol/l or 40mg/dl
- Acidosis HCO3 <15mmol/l or atrial pH <7,35
- Renal creatinine increased or urine out >12ml/kg/h
- Hyperlactaemia >5mmol/l

Complications.

Cerebral Malaria. Coma is a characteristic and ominous feature of falciparum malaria and, despite treatment, is associated with death rates of 20% among adults and 15% among children. Any obtundation, delirium, or abnormal behavior should be taken very seriously. The onset may be gradual or sudden following a convulsion.

Cerebral malaria manifests as diffuse symmetric encephalopathy; focal neurologic signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are absent. The eyes may be divergent and a pout reflex is common, but other primitive reflexes are usually absent. The corneal reflexes are preserved, except in deep coma. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be seen. On routine funduscopy, 15% of patients have retinal

hemorrhages; with pupillary dilatation and indirect ophthalmoscopy, this figure increases to 30-40%. Other funduscopic abnormalities include discrete spots of retinal opacification (30-60%), papilledema (8% among children, rare among adults), cotton wool spots (<5%), and decolorization of a retinal vessel or segment of vessel (occasional cases). Convulsions, usually generalized and often repeated, occur in 10% of adults and up to 50% of children with cerebral malaria. More covert seizure activity is also common, particularly among children, and may manifest as repetitive tonic-clonic eye movements or even hypersalivation. Whereas adults rarely (i.e., in <3% of cases) suffer from neurologic sequelae, 5% of children survive cerebral malaria – especially those with hypoglycemia, severe anemia, repeated seizures, and deep coma – have residual neurologic deficit when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition and learning (all of varying duration) have been reported. The majority of these deficits improves markedly or resolve completely within 6 months. Approximately 10% of children surviving cerebral malaria have a persistent language deficit. The incidence of epilepsy is increased and the life expectancy decreased among these children.

Typical Malarial retinopathy: macular and peripheral whitening and vessels changing.

Outcames of cerebral malaria: Hemeplgia, Cortical blindness, Epilepsy, Ataxia, Cognitive learning disability.

Hypoglycemia, an important and common complication of severe malaria, is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both host and, to a much lesser extent, the malaria parasites. To compound the situation, quinine (and quinidine), which is still widely used for the treatment of both severe and uncomplicated falciparum malaria, is a powerful stimulant of pancreatic insulin secretion. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycemia is difficult: the usual physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria. More severe clinical presentation occurs in pregnancy and children.

Acidosis, an important cause of death from severe malaria, results from accumulation of organic acids. Hyperlactatemia commonly coexists with hypoglycemia. In adults, coexisting renal impairment often compounds the acidosis; in children, ketoacidosis may also contribute. Other still-unidentified organic acids are major contributors to acidosis. Acidotic breathing, sometimes called respiratory distress, is a sign of poor prognosis. It is often followed by circulatory failure refractory to volume expansion or inotropic drug treatment and ultimately by respiratory arrest. The plasma concentrations of bicarbonate or lactate are the best biochemical prognosticators in severe malaria. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, hypovolemia, lactate production by the parasites, and a failure of hepatic and renal lactate clearance. The prognosis of severe acidosis is poor.

Noncardiogenic pulmonary edema. Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. The pathogenesis of this variant of the adult respiratory distress syndrome is unclear. The mortality rate is >80%. This condition can be aggravated by overly vigorous administration of IV fluid. Noncardiogenic pulmonary edema can also develop in otherwise uncomplicated vivax malaria, where recovery is usual.

Renal impairment. Renal impairment is common among adults with severe falciparum malaria but rare among children. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration and agglutination interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis. Renal cortical necrosis never develops. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days. Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure.

Hematologic abnormalities. Anemia results from accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. In severe malaria, both

infected and uninfected RBCs show reduced deformability, which correlates with prognosis and development of anemia. Splenic clearance of all RBCs is increased. In nonimmune individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. As a consequence of repeated malarial infections, children in many areas of Africa may develop severe anemia resulting from both shortened survival of uninfected RBCs and marked dyserythropoiesis. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual. Of patients with severe malaria, <5% have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis from stress ulceration or acute gastric erosions may also occur rarely.

Liver dysfunction. Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections; is more common among adults than among children; and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism. Occasional patients with falciparum malaria may develop deep jaundice (with hemolytic, hepatic, and cholestatic components) without evidence of other vital-organ dysfunction.

Other complications. Patients who develop spontaneous bleeding should be given fresh blood and IV vitamin K. Convulsions should be treated with IV or rectal benzodiazepines and, if necessary, respiratory support. Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation; IV antimicrobial agents and oxygen should be administered, and pulmonary toilet should be undertaken. Hypoglycemia or gram-negative septicemia should be suspected when the condition of any patient suddenly deteriorates for no obvious reason during antimalarial treatment. In malaria-endemic areas where a high proportion of children are parasitemic, it is usually impossible to distinguish severe malaria from bacterial sepsis with confidence. It is increasingly accepted that these children should be treated with both antimalarials and broad-spectrum antibiotics from the outset. Because nontyphoidal *Salmonella* infections are particularly common,

empirical antibiotics should be selected to cover these organisms. Antibiotics should be considered for severely ill patients of any age who are not responding to antimalarial treatment.

Other manifestations of malaria.

Neurologic defects may occasionally persist following cerebral malaria, especially in children. Such defects include troubles with movements (ataxia), palsies, speech difficulties, deafness, and blindness.

Recurrent infections with P. falciparum may result in severe anemia. This occurs especially in young children in tropical Africa with frequent infections that are inadequately treated.

Malaria during pregnancy (especially P. falciparum) may cause severe disease in the mother, and may lead to premature delivery or delivery of a low-birth-weight baby.

On rare occasions, P. vivax malaria can cause rupture of the spleen or acute respiratory distress syndrome (ARDS).

Nephrotic syndrome (a chronic, severe kidney disease) can result from chronic or repeated infections with P. malariae.

Hyperreactive malarial splenomegaly (also called "tropical splenomegaly syndrome") occurs infrequently and is attributed to an abnormal immune response to repeated malarial infections. The disease is marked by a considerably enlarged spleen and liver, abnormal immunologic findings, anemia, and a susceptibility to other infections (such as skin or respiratory infections).

Malaria Relapses. A 'relapse' is a renewed manifestation of clinical symptoms (caused by parasitaemia, which means parasites in the blood) of a malarial infection, and comprises of two types: «recrudescence» and «recurrence», the latter of which is considered a true relapse.

A recrudescence is a renewed manifestation of symptoms due to an increase in the surviving population of erythrocytic forms; in other words, infection in the blood persists. In P. malariae a small number of parasites in the blood stream can cause a recrudescence after up to 50 years. In P. falciparum the parasites persist in the blood for a much shorter period and recrudescences cause renewed bouts of fever for up to one or two years in persons in whom the infection is not completely eradicated.

A recurrence/true relapse is a renewed manifestation due to multiplication of the parasites in the blood from an exo-erythrocytic (which means outside the blood cells) source, and most commonly

from the liver cells. Dormant forms of the parasite, called hypnozoites, can become activated by some kind of trigger to resume growth and burst into circulation, invade red blood cells and cause a relapse. This 'latency' is only existent in P. vivax. It is absent in P. falciparum. Thus, although P. falciparum is much more dangerous than P. vivax, it is more easily cured by drugs, except where drug resistance has appeared.

Diagnosis. The more reliable methods for the diagnosis of malaria is demonstration of the parasite (table 10).

The diagnosis of malaria rests on the demonstration of asexual forms of the parasite in stained peripheral-blood smears. After a negative blood smear, repeat smears should be made if there is a high degree of suspicion. Of the Romanowsky stains, Giemsa at pH 7.2 is preferred; Field's, Wright's, or Leishman's stain can also be used. Both thin and thick blood smears should be examined. The thin blood smear should be rapidly air-dried, fixed in anhydrous methanol, and stained; the RBCs in the tail of the film should then be examined under oil immersion (x1000 magnification). The level of parasitemia is expressed as the number of parasitized erythrocytes per 1000 RBCs. The thick blood film should be of uneven thickness. The smear should be dried thoroughly and stained without fixing. As many layers of erythrocytes overlie one another and are lysed during the staining procedure, the thick film has the advantage of concentrating the parasites (by 40- to 100-fold compared with a thin blood film) and thus increasing diagnostic sensitivity.

Both parasites and white blood cells (WBCs) are counted, and the number of parasites per unit volume is calculated from the total leukocyte count. Alternatively, a WBC count of 8000/L is assumed. This figure is converted to the number of parasitized erythrocytes per microliter. A minimum of 200 WBCs should be counted under oil immersion. Interpretation of blood smear films requires some experience because artifacts are common. Before a thick smear is judged to be negative, 100-200 fields should be examined under oil immersion. In high-transmission areas, the presence of up to 10,000 parasites/L of blood may be tolerated without symptoms or signs in partially immune individuals. Thus in these areas the detection of malaria parasites is sensitive but has low specificity in identifying malaria as the cause of illness. Low-density parasitemia is common in other conditions causing fever.

Table 10. – Methods for the Diagnosis of Malaria

Method	***Procedure***	***Advantages***	***Disad antages***
Thik blood film	Blood should be uneven in thickness but sufficiently thin to read the hands of a watch through part of the spot. Stain dried, unfixed blood spot with Giemsa, Field's, or another Romanowsky stain. Count number of asexual parasites per 200 WBC (or per 500 at low densities). Count gametocytes separately.	Sensitive (0.001% parasitemia); species specific; inexpensive	Requires experience (artifacts may be misinterpreted as low-level parasitemia); underestimates true count
Thin blood film	Stain fixed smear with Giemsa, Field's, or another Romanowsky stain. Count number of RBCs containing asexual parasites per 1000 RBCs. In severe malaria, assess stage of parasite development and count neutrophils containing malaria pigment. Count gametocytes separately.	Rapid; species specific; inexpensive; in severe malaria, provides prognostic information	Insensitive (<0.05% parasitemia); uneven distribution of *P. vivax*, as enlarged infected red cells concentrate at leading edge
Plasmodium LDH dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibodies capture the parasite antigens and read out as colored bands. One band is genus specific (all malarias), and the other is specific for *P. falciparum*	Rapid; sensitivity similar to or slightly lower than that of thick films for *P. falciparum* (0.001% parasitemia)	Slightly more difficult preparation than PfHRP2 tests; may miss low-level parasitemia with *P. vivax, P. ovale*, and *P. malariae* and does not speciate these organisms; does not quantitate *P. falciparum* parasitemia
Microtube concentration methods with acridine orange staining	Blood is collected in a specialized tube containing acridine orange, anticoagulant, and a float. After centrifugation, which concentrates the parasitized cells around the float, fluorescence microscopy is performed	Sensitivity similar or superior to that of thick films (0.001% parasitemia); ideal for processing large numbers of samples rapidly	Does not speciate or quantitate; requires fluorescence microscopy

Malaria cannot be diagnosed clinically with accuracy, but treatment should be started on clinical grounds if laboratory confirmation is likely to be delayed. In areas of the world where malaria is endemic and transmission is high, low-level asymptomatic parasitemia is common in otherwise healthy people. Thus malaria may not be the cause of a fever, although in this context the presence of >10,000 parasites/L (0.2% parasitemia) does indicate that malaria is the cause. Antibody and polymerase chain reaction tests have no role in the diagnosis of malaria except that PCR is increasingly used for genotyping and speciation in mixed infections.

Laboratory Findings. Normochromic, normocytic anemia is usual. The leukocyte count is generally normal, although it may be raised in very severe infections. There is slight monocytosis, lymphopenia, and eosinopenia, with reactive lymphocytosis and eosinophilia in the weeks after the acute infection. The erythrocyte sedimentation rate, plasma viscosity, and levels of C-reactive protein and other acute-phase proteins are high. The platelet count is usually reduced to 10^5/L. Severe infections may be accompanied by prolonged prothrombin and partial thromboplastin times and by more severe thrombocytopenia. Levels of antithrombin III are reduced even in mild infection. In uncomplicated malaria, plasma concentrations of electrolytes, blood urea nitrogen (BUN), and creatinine are usually normal. Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, calcium, phosphate, and albumin together with elevations in lactate, BUN, creatinine, urate, muscle and liver enzymes, and conjugated and unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects. Urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean opening pressure at lumbar puncture is 160 mm of cerebrospinal fluid (CSF); usually the CSF is normal or has a slightly elevated total protein level (<1.0 g/L (<100 mg/dL)) and cell count (<20/L).

Treatment. When a patient in or from a malarious area presents with fever, thick and thin blood smears should be prepared and *examined immediately* to confirm the diagnosis and identify the species of infecting parasite. Repeat blood smears should be performed at least every 12–24 h for 2 days if the first smears are negative and malaria is strongly suspected. Alternatively, a rapid antigen detection card or stick test should be performed. Patients with

severe malaria or those unable to take oral drugs should receive parenteral antimalarial therapy. If there is any doubt about the resistance status of the infecting organism, it should be considered resistant.

Antimalarial drug susceptibility testing can be performed but is rarely available, has poor predictive value in an individual case, and yields results too slowly to influence the choice of treatment. Several drugs are available for oral treatment. The choice of drug depends on the likely sensitivity of the infecting parasites. Despite increasing evidence of chloroquine resistance in *P. vivax* (from parts of Indonesia, Oceania, eastern and southern Asia, and Central and South America), chloroquine remains the treatment of choice for the non-falciparum malarias (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*) except in Indonesia and Papua New Guinea, where high levels of resistance in *P. vivax* are prevalent.

Presently several classes of antimalarial drugs exist:

- Arylominoalcohols – quinoline methanols (quinine and quinidine), mefloquine, lumefantrine;
- 4-Aminoquinolines – chloroquine and amodiaquine;
- Bisquinolines – piperaquine
- Folate-synthesis inhibitors – type 1 antifolate drugs (sulphones and sulphonamides); type 2 antifolate drugs (the biguanides proguanil and chlorproguanil and the diaminopyrimidine pyremethamine)
- 8-Aminoquinolines – primaquine and tafenoquine
- Antibiotics – tetracycline, doxycycline, clindamycin, azithromycin, fluoroqunolones
- Peroxides – artemesin, derivate and semisynthetic analogues (artemether, arteether, artesunate, artelinic acid)
- Naphthoquinones – atovaquine.

Characteristics of the more common using antimalarial drugs are shown in Table 11.

Table 11. – Antimalarial drugs

Drug(s)	***Pharmacokinetic Properties***	***Antimalarial Activity***	***Minor Toxicity***	***Major Toxicity***
Quinine, quinidine	Good oral and IM absorption (quinine); *Cl* and *V* reduced, but plasma protein binding (principally to 1 acid glycoprotein) increased (90%) in malaria; quinine $t_1/_2$: 16 h in malaria, 11 h in healthy persons; quinidine $t_1/_2$: 13 h in malaria, 8 h in healthy persons	Acts mainly on trophozoite blood stage; kills gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* (but not *P. falciparum*); no action on liver stages	*Common:* "Cinchonism": tinnitus, high-tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG QT interval prolongation (quinine usually by <10% but quinidine by up to 25%) *Rare:* Diarrhea, visual disturbance, rashes	*Common:* Hypoglycemia *Rare:* Hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopenia, hemolysis, hemolytic-uremic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis *Note:* Quinidine more cardiotoxic
Chloroquine	Good oral absorption, very rapid IM and SC absorption; complex pharmacokinetics; enormous *Cl* and *V* (unaffected by malaria); blood concentration profile determined by distribution processes in malaria; $t_1/_2$: 1-2 months	As for quinine but acts slightly earlier in asexual cycle	*Common:* Nausea, dysphoria, pruritus in dark-skinned patients, postural hypotension *Rare:* Accommodation difficulties, keratopathy, rash *Note:* Bitter taste, well tolerated	*Acute:* Hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions *Chronic:* Retinopathy (cumulative dose, >100 g), skeletal and cardiac myopathy
Piperaquine	Adequate oral absorption, enhanced by fats; similar pharmacokinetics to chloroquine; $t_1/_2$: 21–28 days	As for chloroquine, but retains activity against multidrug-resistant *P. falciparum*	Epigastric pain, diarrhea, slight ECG QT_C prolongation	None identified
Amodiaquine	Good oral absorption; largely converted to active metabolite desethylamodiaquine	As for chloroquine	Nausea (tastes better than chloroquine)	Agranulocytosis; hepatitis, mainly with prophylactic use; should not be used with efavirenz
Primaquine	Complete oral absorption; active metabolite not known; $t_1/_2$: 7 h	Radical cure; eradicates hepatic forms of *P. vivax* and *P. ovale;* kills all stages of gametocyte development of *P. falciparum*	Nausea, vomiting, diarrhea, abdominal pain, hemolysis, methemoglobinemia	Massive hemolysis in subjects with severe G6PD deficiency
Mefloquine	Adequate oral absorption; no parenteral preparation; $t_1/_2$: 14–20 days (shorter	As for quinine	Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness,	Neuropsychiatric reactions, convulsions, encephalopathy

Drug(s)	*Pharmacokinetic Properties*	*Antimalarial Activity*	*Minor Toxicity*	*Major Toxicity*
	in malaria)		nightmares, sense of dissociation	
Halofantrine	Highly variable absorption related to fat intake; $t_1/_2$: 1–3 days (active desbutyl metabolite $t_1/_2$: 3–7 days)	As for quinine	Diarrhea	Cardiac conduction disturbances; atrioventricular block; ECG QT_c interval prolongation; potentially lethal ventricular tachyarrhythmias
Lumefantrine	Highly variable absorption related to fat intake; $t_1/_2$: 3–4 days	As for quinine	None identified	None identified
Artemisinin and derivatives (artemether, artesunate)	Good oral absorption, slow and variable absorption of IM artemether; artesunate and artemether biotransformed to active metabolite dihydroartemisinin; all drugs eliminated very rapidly; $t_1/_2$: <1 h	Broader stage specificity and more rapid than other drugs; no action on liver stages; kills all but fully mature gametocytes of *P. falciparum*	Reduction in reticulocyte count (but not anemia); neutropenia at high doses	Anaphylaxis, urticaria, fever
Pyrimetha-mine	Good oral absorption, variable IM absorption; $t_1/_2$: 4 days	For blood stages, acts mainly on mature forms; causal prophylactic	Well tolerated	Megaloblastic anemia, pancytopenia, pulmonary infiltration
Proguanil (chloroguani-de)	Good oral absorption; biotransformed to active metabolite cycloguanil; $t_1/_2$: 16 h; biotransformation reduced by oral contraceptive use and in pregnancy	Causal prophylactic; not used alone for treatment	Well tolerated; mouth ulcers and rare alopecia	Megaloblastic anemia in renal failure
Atovaquone	Highly variable absorption related to fat intake; $t_{1/2}$: 30–70 h	Acts mainly on trophozoite blood stage	None identified	None identified
Tetracycline, doxycycline	Excellent absorption; $t_{1/2}$: 8 h for tetracycline, 18 h for doxycycline	Weak antimalarial activity; should not be used alone for treatment	Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, moniliasis, benign intracranial hypertension	Renal failure in patients with impaired renal function tetracycline)

Treatment of Malaria. If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used

as a part of treatment regimen. Other options should be used. CDC adopted the following schemes of Malaria treatment.

Uncomplicated malaria/ P. falciparum or Species not identified

1. Chloroquine-resistant or of unknown resistance

A. Atovaquone-proguanil (Malarone™); Adult tab = 250 mg atovaquone/ 100 mg proguanil; 4 adult tabs po qd x 3 days.

B. Artemether-lumefantrine (Coartem™); 1 tablet = 20mg artemether and 120 mg lumefantrine; 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following 2 days (5 - <15 kg: 1 tablet per dose; 15 - <25 kg: 2 tablets per dose; 25 - <35 kg: 3 tablets per dose; ≥35 kg: 4 tablets per dose).

C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin; Quinine sulfate: 542 mg base (=650 mg salt) po tid x 3 or 7 days; Doxycycline: 100 mg po bid x 7 days; Tetracycline: 250 mg po qid x 7 days; Clindamycin: 20 mg base/kg/day po divided tid x 7 days.

D. Mefloquine (Lariam™ and generics); 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose. Total dose= 1,250 mg salt.

2. Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)

Chloroquine phosphate (Aralen™ and generics; 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours). Total dose: 1,500 mg base (=2,500 mg salt) OR

Hydroxychloroquine (Plaquenil TM and generics) 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours. Total dose: 1,550 mg base (=2,000 mg salt)

Uncomplicated malaria/P. malariae or P. knowlesi in all regions of World

Chloroquine phosphate:Treatment as above OR Hydroxychloroquine: Treatment as above

Uncomplicated malaria/P. vivax or P. ovale in all regions of World

Chloroquine phosphate plus Primaquine phosphate

Chloroquine phosphate: Treatment as above

Primaquine phosphate: 30 mg base po qd x 14 days OR Hydroxychloroquine plus Primaquine phosphate (Hydroxychloroquine: Treatment as above; Primaquine phosphate: 30 mg base po qd x 14 days).

Uncomplicated malaria/P. vivax Chloroquine-resistant (Papua New Guinea and Indonesia)

A. Quinine sulfate plus either Doxycyclineor Tetracycline plus Primaquine phosphate (Quinine sulfate: Treatment as above Doxycycline or Tetracycline: Treatment as above; Primaquine phosphate: Treatment as above).

B. Atovaquone-proguanil plus Primaquine phosphate (Atovaquone-proguanil: Treatment as above; Primaquine phosphate: Treatment as above)

C. Mefloquine plus Primaquine phosphate (Mefloquine: Treatment as above; Primaquine phosphate: Treatment as above).

Uncomplicated malaria: alternatives for pregnant women

Chloroquine-sensitive: Chloroquine phosphate: Treatment as above OR Hydroxychloroquine: Treatment as above;

Chloroquine-resistant: Quinine sulfate plus Clindamycin (Quinine sulfate: Treatment as above; Clindamycin: Treatment as above) OR Mefloquine: Treatment as above.

Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant P. falciparum infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

For P. vivax and P. ovale infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with P. vivax and P. ovale infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy.

Treatment of severe malaria. Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome,

circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by P. falciparum.

Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically.

Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion. Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

Drugs for severe malaria. Quinidine gluconate plus one of the following: Doxycycline, Tetracycline, or Clindamycin. Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24hours. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America.

Doxycycline: Treatment as above.

If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.

Tetracycline: Treatment as above

Clindamycin: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.

Investigational new drug:

Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), Doxycycline (Clindamycin in pregnant women), or Mefloquine

3. Prevention

- Vector control using insecticides and larvicides
- No vaccine has been convincingly shown to be protective but trails are in progress
- Protection from biting is essential by use of knock down insect sprays, mosquito bed nets, insect repellents, mosquito coil sensible clothing covering limbs and avoiding exposure at night
- Drug prophylaxis protects against developing diseases, the choice depends upon the likelihood and type of malaria countries (and areas within) being visited. the duration of intended stay the prevalence of chloroquine resistant p.falciparum and host factors(age pregnancy medical contraindications to certain drugs)the following are the most commonly used regimens in the major malarious areas
- Chloroquine /paludrine (south Asia central America)
- Mefloquine or dexycycline or malarone (Africa south east Asia south America Bangladesh)
- Chemoprophylaxis should start 1 week before departing and continue for 4 weeks after returning(1 week for malarone)
- Standby therapy is appropriate for travelers with symptoms suggestive of malaria in remote malarious regions without easy access to medical facilities especially in Southeast Asia fansidar, malaron and artemisinin are the most important drug in this category treatment for malaria should not be considered until at least 10 days have elapsed after entering a malarious area.

Recommendations for prophylaxis depend on knowledge of local patterns of *Plasmodium* species drug sensitivity and the likelihood of acquiring malarial infection. When there is uncertainty, drugs effective against resistant *P. falciparum* should be used (atovaquone-proguanil (Malarone), doxycycline, or mefloquine).

Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs.

Prognosis. Mortality is exceptionally rare in p.vivax p.ovale, and p. malariae infection. For patients with complicated p. falciparum infection mortality approaches 10-20%. In those who survive cerebral malaria about 5% of adults and 10% of children have neurological sequelae.

Malaria in Pregnancy. In areas of high malaria transmission, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, 170 g) and consequently increased infant and childhood mortality rates. In general, infected mothers in areas of stable transmission remain asymptomatic despite intense accumulation of parasitized erythrocytes in the placental microcirculation. Maternal HIV infection predisposes pregnant women to malaria, predisposes their newborns to congenital malarial infection, and exacerbates the reduction in birth weight associated with malaria.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections and are particularly vulnerable to high-level parasitemia with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. Fetal death is usual in severe malaria. Congenital malaria occurs in <5% of newborns whose mothers are infected; its frequency and the level of parasitemia are related directly to the parasite density in maternal blood and in the placenta. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 110 g), but, in contrast to the situation in falciparum malaria, this effect is more pronounced in multigravid than in primigravid women. About 150,000 women die in childbirth yearly, with most deaths occurring in low-income countries; maternal death from hemorrhage at childbirth is correlated with malaria-induced anemia.

Malaria in children. Most of the nearly 1 million persons who die of falciparum malaria each year are young African children. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, acute renal failure, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past were attributed incorrectly

to "anemic congestive cardiac failure" but in fact is usually caused by metabolic acidosis, often compounded by hypovolemia. In general, children tolerate antimalarial drugs well and respond rapidly to treatment.

Malaria and HIV/AIDS are a horrible mix of infections that encourage each other to the total detriment of the patient. Human immunodeficiency virus, (HIV) is a virus that attacks the immune system, making the patient more suceptable to diseases and infections. Malaria which is a parasite attacks the red blood cells with little or no resistance from the immune system which is under attack from HIV. This places the patient living with HIV at very serious risk.

For this reason it is generally accepted that a patient who is living with HIV who is infected with malaria will experience a more severe infection as their immune system is not working properly. Malaria in turn will worsen the HIV infection by increasing the patient's viral load.

People living with HIV who travel into or who live in malaria endemic areas are at risk from severe malaria. Studies have shown that the worse a person's HIV infection the worse their malaria. In Africa it has ben shown that HIV infected local residents living in high risk areas get more severe infections more often.

Recently it has been noted that people living with HIV have poorer responses to some antimalarial medications. This is particularly true for the Artemesinins and sulphadoxine / pyrimethamine (SP). Also, some antimalarial drugs clash with the antiretroviral medications used in treatment of HIV/AIDS.

Malaria and HIV/AIDS in Pregnancy. Because HIV/AIDS weakens the immune system which in the pregnant mother is already suppressed any resistance the body might have to the parasite infection is drastically reduced. HIV positive mothers who are infected with malaria have a harder time recovering from the disease because of the presence of HIV in their system.

HIV positive mothers are more likely to have increased infections, and adverse birth outcomes. They are also more likely to develop clinical malaria. Some reseach indicates the co-infectionwith placental malaria and HIV during pregnancy significantly increases the risk if HIV transmission from mother to newborn.

Travel Advice. No one should ever put themselves at risk from malaria; especially those living with HIV. Medical experts strongly

suggest that people living with HIV should not expose themselves to the risk of malaria and should, if at all possible, avoid travelling into malaria endemic areas.

If the exposure to malaria is unavoidable they should speak to their HIV care giver and travel clinic about the best preventative strategy. If malaria is contracted then disclosure of their HIV status to the attending physician would be essential for planning their treatment regime.

LEISHMANIASIS

Leishmaniasis is a protozoal disease of mammals capable of causing a spectrum of clinical syndromes ranging from cutaneous ulcerations to systemic infections. It is largely zoonotic. It can beaused by more than 23 pathogenic species. It is transmitted in many tropical and sub-tropical countries and affects as many as 12 million people worldwide, with 1,5–2 million new cases each year.

***Etiology*.** Caused by a protozoa Phylum Sarcomastigophora Order Kinetoplastida Family Trypanosomatidae, Genus Leishmania.

Epidemiology. Visceral leishmaniasis (VL) also known as kala-azar. It is highly endemic in the Indian subcontinent and in East Africa. An estimated 200 000 to 400 000 new cases of VL occur worldwide each year. Over 90% of new cases occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan.

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis and causes ulcers on exposed parts of the body, leaving life-long scars and serious disability. About 95% of CL cases occur in the Americas, the Mediterranean basin, and the Middle East and Central Asia. Over two-third of CL new cases occur in six countries: Afghanistan, Algeria, Brazil, Colombia, Iran (Islamic Republic of) and the Syrian Arab Republic. An estimated 0,7 million to 1,3 million new cases occur worldwide annually.

Mucocutaneous leishmaniasis leads to partial or total destruction of mucous membranes of the nose, mouth and throat. Almost 90% of mucocutaneous leishmaniasis cases occurs in the Plurinational State of Bolivia, Brazil and Peru.

Leishmaniasis is found in some parts of 88 countries within Central America, South America, Africa, India, the Middle East, Asia, southern Europe, and the Mediterranean.

Animal reservoir. For most species of Leishmania, an animal reservoir is required for endemic conditions to persist. Infections in wild animals are usually not pathogenic, with the exception of dogs, which may be severely affected.

Common Old World hosts: domestic and feral dogs, rodents, foxes, jackals, wolves, raccoon-dogs, and hyraxes.

Common New World hosts: sloths, anteaters, opossums, and rodents.

Transmission. Indirect Transmission is more common. It occurs through the bite of the female sandfly of genus Phlebotomus in the Old World and Lutzomyia in the New World.

Direct transmission is also possible although it is rare. It can be through contact way (from ulcer and sexually), through blood transfusions, needle sharing, or during pregnancy through the placenta.

Species causing different forms of leishmaniasis:

Localized cutaneous leishmaniasis:

Old World

- L donovani - China, India, Bangladesh, Sudan
- L tropica - Middle East, China, India, Mediterranean
- L major - Middle East, Africa, India, Asia
- L aethiopica - Ethiopia, Kenya, Namibia
- Leishmania infantum - Asia, Africa, Europe

New World

- Leishmania leishmania mexicana - Central and South America, North America
- L leishmania amazonensis - Dominican Republic, Central America, South America
- L leishmania venezuelensis - Venezuela
- L viannia braziliensis - Central America, South America
- L viannia guyanensis - Guyana, French Guyana, Surinam, Brazil
- L viannia panamensis - Costa Rica, Panama, Colombia, Ecuador
- L viannia peruviana - Peru, Argentina
- Leishmania donovani chagasi - Texas, Caribbean, Central America, South America

Diffuse cutaneous leishmaniasis:

Old World

- L aethiopica - Ethiopia, Kenya, Namibia

New World

- L leishmania mexicana - Central, South America, North America
- L leishmania amazonensis - Dominican Republic, Central America, South America

Leishmaniasis recidivans:

Old World

- L tropica - Middle East, China, India, Mediterranean

New World

- L viannia braziliensis - Central America, South America

Post-kala-azar leishmaniasis:

Old World

- L. donovani - China, India, Bangladesh
- L. infantum - Asia, Africa, Europe

New World

- L donovani chagasi - Central America, South America

Visceral leishmaniasis:

Old World

- L. donovani - India and East Africa
- L. infantum - Mediterranean

Visceral leishmaniasis:

New World

- L donovani chagasi – Central America, South America.

Life cycle. Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals. Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages and transform into amastigotes. Amastigotes multiply in infected cells and affect different tissues, depending in part on which Leishmania species is involved. These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes. In the sandfly's midgut, the parasites differentiate into promastigotes, which multiply, differentiate into metacyclic promastigotes and migrate to the proboscis (fig. 7).

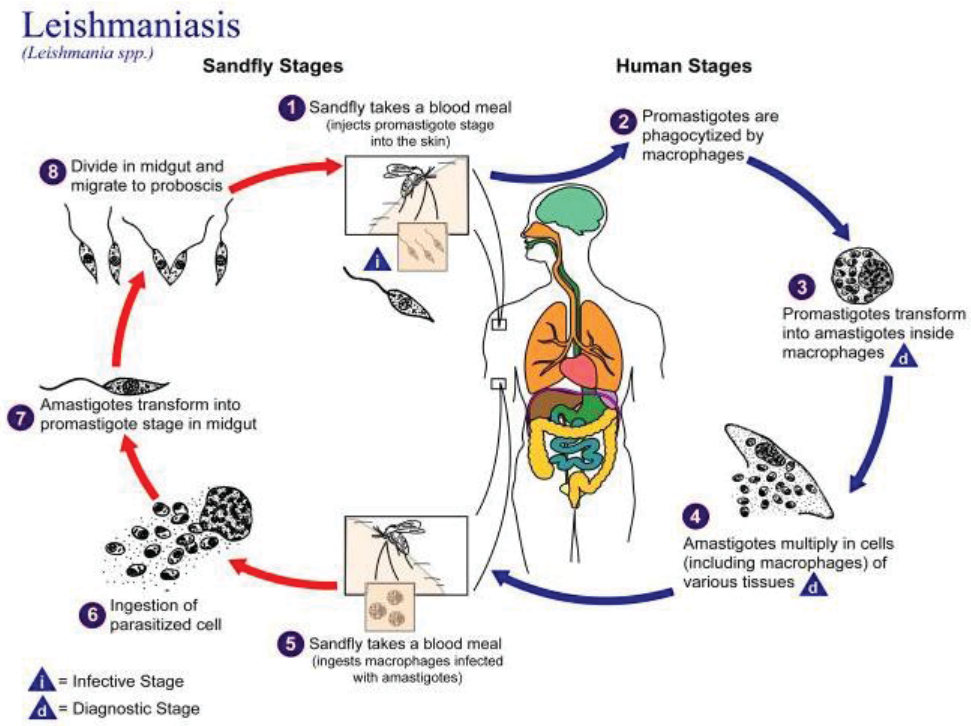

Fig. 9. – Life cycle of leishmania

Classification. Leishmaniasis may be divided into the following types:

Cutaneous:

- Localized
- Diffuse
- Leishmaniasis recidivans
- Post-kala-azar dermal leishmaniasis

Mucocutaneous

Visceral

- viscerotropic

Clinical presentation. In cutaneous leishmaniasis, the hallmark of the disease is skin lesions, which can spontaneously heal in 2-10 months. In mucocutaneous leishmaniasis, mucosal ulcerations usually develop by metastasis from disseminated protozoa rather than by local spread. Secondary infection plays a prominent role in the size and persistence of ulcers. Ulcer progression is slow and steady.

Typically, visceral leishmaniasis incubates for weeks to months before becoming clinically apparent. The disease can be subacute, acute, or chronic, and can manifest in patients who are immunocompromised years after they have left endemic regions.

Cutaneous leishmaniasis. This is the most common form of

leishmaniasis, both in general and in U.S. travelers. After the bite of an infected sandfly, the incubation period is usually several weeks after inoculation, but this incubation period is variable. Initial lesions can appear immediately after a bite, or the incubation period may last for several months. These lesions are usually painless. Skin trauma can result in activation of seemingly latent cutaneous infection long after the initial bite. Over a period of weeks to years, some lesions may resolve spontaneously without pharmacotherapy. Unless otherwise specified, cutaneous leishmaniasis refers to localized cutaneous leishmaniasis, rather than to much less common forms, such as diffuse cutaneous leishmaniasis and disseminated cutaneous leishmaniasis.The broad spectrum of clinical manifestations of cutaneous leishmaniasis is often compared with that of leprosy. Cutaneous leishmaniasis can be simple or diffuse. Different species, as well as host factors, can also affect the clinical picture, where some species cause "wet" ulcers and others "dry" ulcers.

In general, cutaneous leishmaniasis causes skin lesions, which can persist for months, sometimes years. Systemic signs usually are absent. Initially, the lesion is a small, red papule up to 2 cm in diameter. Over several weeks, the papule becomes darker and will crust in the center, eventually ulcerating to present a typical appearance of an ulcer with raised edges and surrounding dusky red skin. The ulcers can be moist or open with seropurulent exudate or dry with a crusted scab. After about 3-6 months, the ulcers heal, leaving a raised border. Regional adenopathy, satellite lesions, and subcutaneous nodules can be present. Untreated sores can leave depigmented retracted scars.The skin lesions usually develop within several weeks or months after the exposure but occasionally first appear years later (for example, in the context of trauma or immunosuppression). The lesions typically evolve from papules to nodular plaques to ulcerative lesions, with a raised border and central depression, which can be covered by scab or crust; some lesions persist as nodules. The lesions usually are painless but can be painful, especially if ulcerative lesions become infected with bacteria or if the lesions are near a joint. The healing process typically results in atrophic scarring.

Even patients with localized cutaneous leishmaniasis quite commonly develop more than one primary lesion (on the same or different parts of the body), satellite lesions, regional

lymphadenopathy (occasionally bubonic), and/or nodular lymphangitis (sporotrichoid-like subcutaneous nodules). Sometimes lymphadenopathy is noticed first, before skin lesions develop.

Patients with any of the following findings should be referred early to avoid long term complications:

- Big lesions (greater than an inch in size)
- Many lesions (3 or more)
- Sores on the face
- Sores on the hands and feet
- Sores over joints leishmaniasis

Mucocutaneous leishmaniasis. The incubation period is from 1-3 months. Mucocutaneous leishmaniasis can be the primary manifestation of the disease, but the primary lesions may also be limited to cutaneous manifestations, with mucosal lesions appearing only later in the course of disease when untreated cutaneous lesions progress to involve the oral and nasal surfaces. Cutaneous lesions can be single or multiple. Secondary mucosal lesions often develop after the primary lesion has healed. Mucosal lesions can progress to involve the entire nasal mucosa and the hard and soft palates. Cases in which the time between the primary lesion and the appearance of mucosal involvement is up to 2 decades have been reported.

Initial symptoms related to mucosal lesions may include nasal obstruction and bleeding. Mucosal lesions become painful gradually and can become sites of infection, sometimes leading to sepsis.

Without treatment, the entire nasal mucosa and palates become deformed with ulceration and erosion of the nasal septum, lips, and palate. The disease attacks cartilaginous areas (as depicted below) but usually spares bony structures, and it can leave extreme disfigurement. Signs include gingival edema, periodontitis, and adenopathy.

Visceral leishmaniasis. Visceral leishmaniasis is endemic in over 60 countries. The incidence is estimated at 500 000 cases each year. It is the most severe form of leishmaniasis and it can be fatal in the absence of treatment. Deadly epidemics frequently occur in the anthroponotic foci of Bangladesh, India, Nepal and Sudan, where humans are believed to be the sole reservoir. Kala azar is the Indian name for visceral leishmaniasis. The term means "black disease," which is a reference to the characteristic darkening of the skin that is seen in patients with the disease. The term kala-azar – which means

black (kala) fever (azar) in Hindi – often is reserved for severe (advanced) cases of visceral leishmaniasis, although the terms kala-azar and visceral leishmaniasis sometimes are used interchangeably. If untreated, severe cases of visceral leishmaniasis typically are fatal, either directly from the disease or indirectly from complications, such as secondary (myco)bacterial infection or hemorrhage. Many subclinical cases occur and go unrecognized for each clinically recognized case. Malnutrition has been shown to contribute to the development of clinical disease.

Like cutaneous leishmaniasis, visceral leishmaniasis can take different forms ranging from asymptomatic or self-resolving disease to fulminant disease. The onset can be chronic, subacute, or acute. Although the incubation period generally ranges from weeks to months, asymptomatic infection can become clinically manifested years to decades after the exposure in people who become immunocompromised for other medical reasons (such as HIV/AIDS). Visceral leishmaniasis usually is caused by the species L. donovani and L. infantum (L. chagasi generally is considered synonymous with L. infantum) and affects internal organs (particularly, spleen, liver, and bone marrow).

The stereotypical manifestations of clinically manifested visceral infection include:

- fever
- weight loss (cachexia; wasting)
- hepatosplenomegaly (usually, the spleen is more prominent than the liver)
- pancytopenia - i.e., anemia, leukopenia, and thrombocytopenia
- a high total protein level and a low albumin level, with hypergammaglobulinemia

Lymphadenopathy may be noted, particularly in some geographic regions, such as Sudan.

Bouts of fever occur. Hepatosplenomegaly occurs secondary to compensatory production of phagocytic blood cells. Wasting and weakness are observed. Darkening of the skin is characteristic (thus, the name kala azar or black fever). Diarrhea may occur. Lymphadenopathy is often present. In visceral leishmaniasis, patients may die of hemorrhage (secondary to infiltration of the hematopoietic system), severe anemia, secondary bacterial infections of mucous

membranes, bacterial pneumonia, septicemia, tuberculosis, dysentery, or measles.

Complications: intercurrent infections, internal hemorrhage, renal amyloidosis, post kala-azar dermal leishmaniasis.

Some patients develop ***post kala-azar dermal leishmaniasis*** (PKDL), a syndrome characterized by skin lesions (such as erythematous or hypopigmented macules, papules, nodules, and patches), typically first noticed and most prominent on the face, that develop at variable intervals after (or during) therapy for visceral leishmaniasis. PKDL is best described in cases of L. donovani infection in South Asia and East Africa. In general, PKDL is more common, develops earlier, and is less chronic in patients in East Africa. For example, in Sudan, PKDL is noted in up to 60% of patients, typically from 0 to 6 months after therapy for visceral leishmaniasis, and often heals spontaneously. In contrast, in South Asia, PKDL is noted in ~5-15% of patients, on average several years after initial therapy, and usually requires additional treatment. Persons with chronic PKDL can serve as important reservoir hosts of infection.

Diagnosis depends on:

- Epidemiological anamnesis and patient's origin;
- Clinical aspect;
- Laboratory investigations.

Heightened awareness of individuals, small unit leaders, and medical personnel is critical. Sores that will not heal have to be referred for evaluation – even if not “typical” for leishmaniasis. Individuals with fevers, weight loss, gastrointestinal complaints, anemia, abnormal liver tests should be referred for evaluation.

Leishmaniasis is diagnosed by detecting Leishmania parasites (or DNA) in tissue specimens – such as from skin lesions, for cutaneous leishmaniasis, or from bone marrow, for visceral leishmaniasis – via light-microscopic examination of stained slides, specialized culture techniques, or molecular methods.

The species can be identified by various approaches, such as molecular methods and biochemical techniques (isoenzyme analysis of cultured parasites).

Diagnosis of cutaneous leishmaniasis. Appearance of one or more lesions, typically on uncovered parts of the body. The face, neck, arms and legs are the most common sites. At the site of

inoculation a nodule appears, and may enlarge to become an indolent ulcer. The sore remains in this stage for a variable time before healing, and typically leaves a depressed scar. Other atypical forms may occur. In some individuals, certain strains can disseminate and cause mucosal lesions. These sequelae involve nasopharyngeal tissues and can be very disfiguring.

Differential diagnosis of the ulcerated form includes an infected mosquito bite, tropical ulcer, cutaneous diphtheria, Mycobacterium ulcerans, sporotrichosis and amoebic ulcer.

Differential diagnosis of the papular form includes tuberculosis, lepromotous leprosy, sarcoidosis.

Microscopy of the parasite in Giemsa stains or histological section can reveal the parasite (fig. 10).

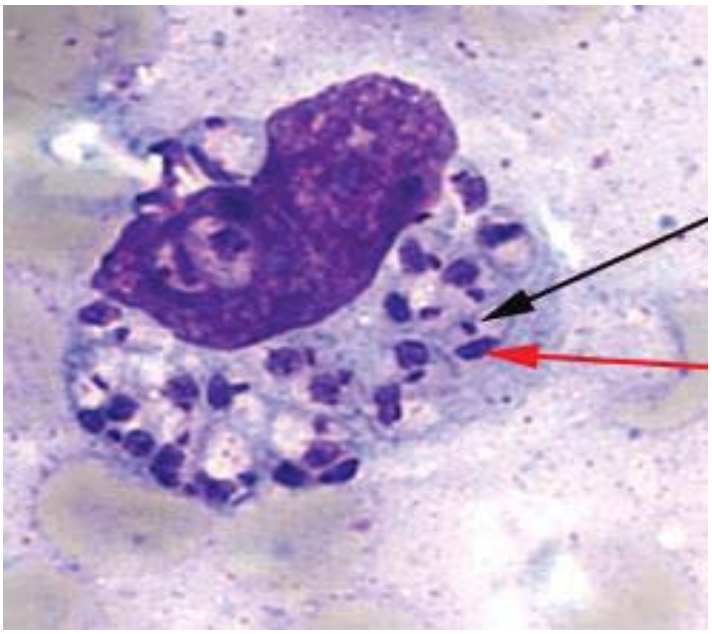

Fig. 10. – Light-microscopic examination of a stained bone marrow specimen from a patient with visceral leishmaniasis-showing a macrophage (a special type of white blood cell) containing multiple *Leishmania* **amastigotes** (the tissue stage of the parasite). Note that each amastigote has a **nucleus** (red arrow) and a rod-shaped **kinetoplast** (black arrow). Visualization of the kinetoplast is important for diagnostic purposes, to be confident the patient has leishmaniasis. (www.CDC.gov.)

Culture of the organisms is unreliable because organisms are difficult to isolate from the lesion.

The leishmaniasis skin test (Montenegro test) produces positive results 3 months after the appearance of lesions. The Montenegro test

is performed by injecting killed promastigotes intradermally and examining the skin 48 hours later to see if a delayed-type hypersensitivity response has formed. A positive result is defined as induration of 5 mm or more. No leishmanin skin-test preparation has been approved for use in the United States.

Serologic tests such as isoenzyme or monoclonal antibody analysis are not well established. PCR is being used more frequently and is more accurate

Diagnosis of mucocutaneous leishmaniasis.

Diagnosis preferably is made by culture of the organism, but organisms are often scant. On biopsy, a nonspecific granulomatous reaction often is observed. Giemsa stain may show the organisms. Results from the leishmania skin test are positive after 2-3 months of infection.

Diagnosis of visceral leishmaniasis:

Differential diagnosis is wide and includes typhoid, brucellosis, lymphoma, disseminated tuberculosis, tropical splenomegaly syndrome, hepatic schistosomiasis, lepromotous leprosy.

An illness with prolonged irregular fever, splenomegaly and weight loss as

its main symptoms.

Laboratory criteria for diagnosis:

• positive parasitology (stained smears from bone marrow, spleen, liver, lymph nodes, blood or culture of the organism from a biopsy or aspirated material);

• positive serology (IFA, ELISA).

Serologic testing can provide supportive evidence for the diagnosis. The performance of various serologic assays may vary by geographic region and by host factors (for example, the sensitivity of serologic testing generally is lower in HIV-coinfected patients, particularly if the HIV infection predated the Leishmania infection). Most serologic assays do not reliably distinguish between active and quiescent infection. Definitive diagnosis is made by observing the parasite (amastigotes) on stained Giemsa smears or by observing the culture of bone marrow, splenic, hepatic, or lymph node aspirates. For visceral leishmaniasis, although the diagnostic sensitivity is highest for splenic aspirates (>95% vs. <90% for other organs/tissues), the procedure can be associated with life-threatening hemorrhage, even if conducted under radiologic guidance. Bone marrow aspiration is

much safer. Examples of other potential sources of specimens for diagnostic testing include liver, lymph node, and whole blood or buffy coat. Among HIV-infected patients, the parasite also may be found in atypical sites (such as the gastrointestinal tract).

Cultures are grown on NNN medium. Culture grows for 1-3 weeks.

Complete blood count: normocytic normochromic anemia, leukopenia with decreased neutrophils, and thrombocytopenia may occur due to parasitic bone-marrow infiltration. The severity of pancytopenia may vary with only 1 or 2 cell lines decreased. Bone marrow infiltration may cause anemia, thrombocytopenia, and leukopenia with a relative monocytosis and lymphocytosis.

Treatment and medication.

The treatment approach depends in part on host and parasite factors. Some approaches/regimens are effective only against certain Leishmania species/strains and only in particular geographic regions. Even data from well-conducted clinical trials are not necessarily generalizable to other settings. Of particular note, data from the many clinical trials of therapy for visceral leishmaniasis in parts of India are not necessarily directly applicable to visceral leishmaniasis caused by L. donovani in other areas, to visceral leishmaniasis caused by other species, or to treatment of cutaneous and mucosal leishmaniasis.

Treatment of cutaneous leishmaniasis. Decisions about whether and how to treat should be individualized. The treatment approach depends in part on the Leishmania species/strain and the geographic area in which infection was acquired; the natural history of infection, the risk for mucosal dissemination/disease, and the drug susceptibilities in the pertinent setting; and the number, size, location, evolution, and other clinical characteristics of the patient's skin lesions.

Therapy of cutaneous leishmaniasis may be indicated to:

• decrease the risk for mucosal dissemination/disease (particularly for New World species in the Viannia subgenus; see Disease)

• accelerate healing of the skin lesions

• decrease the risk for relapse (clinical reactivation) of the skin lesions

• decrease the local morbidity caused by large or persistent skin lesions, particularly those on the face or ears or near joints

• decrease the reservoir of infection in geographic areas where

infected persons (vs. non-human animals) serve as reservoir hosts (such as in Kabul, Afghanistan, and other Leishmania tropica-endemic areas, where transmission is anthroponotic).

In general, the first sign of a therapeutic response to adequate treatment is decreasing induration (lesion flattening). The healing process for large, ulcerative lesions often continues after the end of therapy. Relapse (clinical reactivation) typically is noticed first at the margin of the lesion.

Systemic therapy (parenteral)

For pentavalent antimonial (SbV) therapy. The standard daily dose is 20 mg of SbV per kg, administered IV or IM. The traditional duration of therapy is 20 days for cutaneous leishmaniasis (10 days may suffice in some settings) and 28 days for mucosal (and visceral) leishmaniasis. For some patients, adjustment of the daily dose or the duration of therapy may be indicated.

Conventional amphotericin B deoxycholate traditionally has been used as rescue therapy for cutaneous (and mucosal) leishmaniasis. Lipid formulations of amphotericin B typically are better tolerated than conventional amphotericin B. However, the data supporting their use for treatment of cutaneous (and mucosal) leishmaniasis are anecdotal; standard dosage regimens have not been established. When lipid formulations (e.g., liposomal amphotericin B) have been used for treatment of cutaneous leishmaniasis, patients typically have received 3 mg per kg daily, by IV infusion, for a total of 6 to 10 or more doses.

In the United States, pentamidine isethionate is uncommonly used for treatment of cutaneous leishmaniasis. Its limitations include the potential for irreversible toxicity and variable effectiveness.

Systemic therapy (oral)

In March 2014, FDA approved the oral agent miltefosine for treatment of cutaneous leishmaniasis in adults and adolescents who are not pregnant or breastfeeding. The FDA-approved indications are limited to infection caused by three particular species, all three of which are New World species in the Viannia subgenus – namely, Leishmania (V.) braziliensis, L. (V.) panamensis, and L. (V.) guyanensis. Even for these species, the effectiveness of miltefosine has been variable in different geographic regions. Use of miltefosine for treatment of infection caused by other Leishmania species in the New World or by any species in the Old World would constitute off-

label use, as would treatment of children less than 12 years of age. See above for additional perspective and considerations regarding miltefosine.

The "azoles" ketoconazole, itraconazole, and fluconazole – administered orally-have been used with mixed results, in various settings. For example:

• Ketoconazole (adult regimen: 600 mg daily for 28 days) showed modest activity against L. mexicana and L. (V.) panamensis infection in small studies in Guatemala and Panama, respectively. However, itraconazole (adult regimen: 200 mg twice daily for 28 days) was ineffective against L. (V.) panamensis infection in a clinical trial in Colombia.

• Use of fluconazole (adult regimen: 200 mg daily for 6 weeks) for treatment of L. major infection in various countries in the Old World has been associated with mixed results. Preliminary data from Iran suggest that a higher daily dose (400 vs. 200 mg) might be more effective against L. major infection. Preliminary, uncontrolled data from northeastern Brazil suggest that a regimen of 8 mg per kg daily for 4 to 6 weeks might be effective against L. (V.) braziliensis infection in that region.

Local therapy

Some cases of cutaneous leishmaniasis without risk for mucosal dissemination/disease might be candidates for local therapy, in part depending on the number, location, and characteristics of the skin lesions. Examples of local therapies that might have utility in some settings include cryotherapy (with liquid nitrogen), thermotherapy (use of localized current field radiofrequency heat), intralesional administration of SbV, and topical application of paromomycin (such as an ointment containing 15% paromomycin/12% methylbenzethonium chloride in soft white paraffin).

Visceral Leishmaniasis

The use of highly effective systemic therapy for leishmaniasis is important, as is supportive care – for example, therapy for malnutrition, anemia/bleeding, and intercurrent infections.

Liposomal amphotericin B is FDA-approved for treatment of visceral leishmaniasis. The FDA-approved regimen for immunocompetent patients consists of 3 mg per kg daily, by IV infusion, on days 1–5, 14, and 21 (total dose of 21 mg/kg).

Conventional amphotericin B deoxycholate is highly effective

therapy for visceral leishmaniasis but generally is more toxic than liposomal amphotericin B. Immunocompetent patients typically receive 0,5 to 1,0 mg per kg – either daily or every other day – by IV infusion – for a total dose of approximately 15 to 20 mg per kg. Longer courses of therapy may be indicated for some patients.

Pentavalent antimonial (SbV) therapy generally remains highly effective in most regions, with the notable exception of parts of South Asia. See above about CDC's IND protocol for sodium stibogluconate (Pentostam®). The standard dosage regimen for immunocompetent patients consists of 20 mg of SbV per kg daily, IV or IM, for 28 days. For some patients, adjustment of the daily dose or the duration of therapy may be indicated.

Other parenteral agents that have merit in some settings include paromomycin sulfate (the chemical equivalent of aminosidine), which is not available for parenteral administration in the United States – and – pentamidine isethionate, a second-line agent whose limitations include suboptimal effectiveness (most notably, in parts of South Asia) and the potential for irreversible toxicity.

Miltefosine is considered the first highly active oral agent for visceral leishmaniasis. In March 2014, FDA approved miltefosine for treatment of visceral leishmaniasis caused by Leishmania donovani, in adults and adolescents who are not pregnant or breastfeeding. Use of miltefosine for visceral leishmaniasis caused by other species (e.g., L. infantum) would constitute off-label use, as would treatment of children less than 12 years of age. See above for additional perspective and considerations regarding miltefosine.

Coinfection with HIV. The most common clinical presentation of leishmaniasis in persons with AIDS is a disseminated visceral disease syndrome, but the distribution varies geographically, refecting diferences in the predominant parasite species. In Europe, visceral disease has beenreported in 95% of cases (87% typical visceral, 8% atypical visceral). In contrast, in Brazil, mucocutaneous (43%) and cutaneous (20%) are common. Among persons with visceral disease, the most common clinical and laboratory finings are fever (65-100%), systemic malaise (70-90%), splenomegaly (usuallymoderate) (60-90%), hepatomegaly without splenomegaly (34-85%), hepatosplenomegaly (68-73%), lymphadnopathy (12-57%), andpancytopenia (50-80%). Anemia is usually marked with <10g hemoglobin/dL (49-100%), leucopenia moderate with 2,400

leukocytes/μL (56-95%), and thrombocytopenia is usually present (52-93%). Splenomegaly is somewhat less common in HIV-coinfected patients than in immunocompetent patients with VL. Among those with more profound immunosuppression, atypical manifestations have been described, including involvement of the upper and lower gastrointestinal tract, lung, pleural and peritoneal cavities, and skin. Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis. Nonulcerative cutaneous lesions that mimic KS, nodular difuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described. However, the presence of Leishmania amastigotes in skin might occur in the absence of lesions or in combination with other pathology, such as KS, and might not indicate that the parasite is the cause of the lesions. Disfiguring mucosal lesions associated with anergy to Leishmania antigens have been observed among European persons with AIDS, in contrast to mucocutaneous disease in immunocompetent persons that is associated with strong leishmanin skin-test responses.

Treatment of Disease. Liposomal amphotericin B is the only agent approved by the FDA for the treatment of visceral leishmaniasis. The FDA-approved regimen for immunosuppressed patients consists of 4 mg per kg daily on days 1–5, 10, 17, 24, 31, and 38 (total dose of 40 mg/kg). Some immunosuppressed patients may need even higher total doses and/or secondary prophylaxis (chronic maintenance therapy), in particular, HIV-coinfected patients with CD4 counts <200 cells/mm3. However, standard approaches to antileishmanial treatment and secondary prophylaxis have not been established – for example, the optimal agent, dose, and dosing interval for maintenance therapy.

Pentavalent antimony is the most widely used treatment for leishmaniasis in many parts of the world and remains the ART should be initiated or optimized following standard practice for HIV-infected patients. Appropriate use of ART has substantially improved the survival of coinfected patients in Europe and decreases the likelihood of relapse after antileishmanial therapy.

Prognosis. Generally, the prognosis is excellent with appropriate therapy. Mortality in patients with visceral disease is reduced to approximately 5% with early therapy. Without therapy, most patients with visceral disease die within 2 years.

In some endemic regions, pentavalent antimonial resistance is causing increased mortality rates. After successful treatment, patients generally acquire immunity from the L. sp they were infected.

Prevention and Control

No vaccines or drugs to prevent infection are available.

The best way for travelers to prevent infection is to protect themselves from sand fly bites. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin.

In general, prevention and control measures must be tailored to the local setting and typically are difficult to sustain. Control measures against sand fly vectors or animal reservoir hosts might be effective in some settings.

In many geographic areas where leishmaniasis is found in people, infected people are not needed to maintain the transmission cycle of the parasite in nature; animal reservoir hosts (such as rodents or dogs), along with sand flies, maintain the cycle. For example, in L. infantum/L. chagasi-endemic regions, dogs serve as the main reservoir hosts; control strategies for such areas are being evaluated.

In some parts of the world, infected people are needed to maintain the cycle; this type of transmission (human-sand fly-human) is called anthroponotic. For example, in the Indian Subcontinent (South Asia), the transmission of L. donovani is anthroponotic. In such areas, early detection and effective treatment of patients can serve as a control measure; suboptimal treatment can lead to development and spread of drug resistance. Because the transmission is intra- and peridomiciliary (rather than sylvatic), spraying dwellings with residual-action insecticides and using bed nets treated with long-lasting insecticides may be protective.

TRYPANOSOMIASIS

Trypanosomiasis refers to three types of protozoan infections and spread to humans through insect bites. 2 kinds of African trypanosomiasis: East African and West African which are both known as sleeping sickness. The disease can affect people living on the African continent south of the Sahara Desert. American trypanosomiasis also is called Chagas disease which occurs only on the American continents, from Mexico to Argentina.

HUMAN AFRICAN TRYPANOSOMIASIS

Human African trypanosomiasis (HAT), also called sleeping sickness, is endemic to sub-Saharan Africa. It is caused by the flagellate protozoan Trypanosoma brucei, which exists in 2 morphologically identical subspecies:

- Trypanosoma brucei rhodesiense (East African or Rhodesian African trypanosomiasis)
- Trypanosoma brucei gambiense (West African or Gambian African trypanosomiasis).

The trypanosome is transmitted to humans through the bite of a tsetse fly of the genus Glossina (fig. 11).

Fig. 11. – Tsetse fly

Epidemiology. Humans are the main reservoir for Trypanosoma brucei gambiense (West HAT), but this species can also be found in pigs and other animals. West HAT is likely in rural communites with river water contact. T. b. gambiense (West African sleeping sickness) is found predominantly in central Africa and in limited areas of West Africa. Most of the sleeping sickness in Africa is caused by this form of the parasite. Epidemics of sleeping sickness have been a significant public health problem in the past, but the disease is reasonably well-controlled at present, with 7,000-10,000 cases reported annually in recent years. Over 95% of the cases of human infection are found in Democratic Republic of Congo, Angola, Sudan, Central African Republic, Chad, and northern Uganda. Humans are the important

reservoir of infection, although the parasite can sometimes be found in domestic animals (e.g., pigs, dogs, goats). Imported infection in the U.S. is extremely rare, and most cases have occurred in African nationals who have immigrated rather than in returning U.S. travelers.

Wild game animals and cattle are the main reservoir of T. b. rhodesiense (East HAT). East HAT is a sporadic deseases of persons in contact with animal reservoir (safari park visitors). Each year a few hundred cases are reported to the World Health Organization. Over 95% of the cases of human infection occur in Tanzania, Uganda, Malawi, and Zambia. Animals are the primary reservoir of infection. Cattle have been implicated in the spread of the disease to new areas and in local outbreaks. A wild animal reservoir is thought to be responsible for sporadic transmission to hunters and visitors to game parks. Infection of international travelers is rare, but it occasionally occurs. In the U.S., one case per year, on average, is diagnosed. Most cases of sleeping sickness imported into the U.S. have been in travelers who were on safari in East Africa.

Both forms of sleeping sickness are transmitted by the bite of the tsetse fly (Glossina species). Tsetse flies inhabit rural areas, living in the woodlands and thickets that dot the East African savannah. In central and West Africa, they live in the forests and vegetation along streams. Tsetse flies bite during daylight hours. Both male and female flies can transmit the infection, but even in areas where the disease is endemic, only a very small percentage of flies are infected. Although the vast majority of infections are transmitted by the tsetse fly, other modes of transmission are possible. Occasionally, a pregnant woman can pass the infection to her unborn baby. In theory, the infection can also be transmitted by blood transfusion or sexual contact, but such cases have rarely been documented.

T. b. gambiense is found in Central and Western Africa and causes a chronic condition that can remain in a passive phase for months or years before symptoms emerge.

T. b. rhodesiense is the acute form of the disease, but has a much more limited geographic range. It is found in Southern and Eastern Africa and symptoms of infection emerges in a few weeks and is more virulent and faster. According to recent estimates, the disability adjusted life years (9 to 10 years) lost due to sleeping sickness are 2.0 million.

Recent estimates indicate that over 60 million people living in

some 250 locations are at risk of contracting the disease, and there are about 300,000 new cases each year. The disease has been recorded as occurring in 36 countries, all in sub-Saharan Africa. It is endemic in southeast Uganda and western Kenya, and kills more than 40,000 Africans a year. Life cycle (Fig. 12).

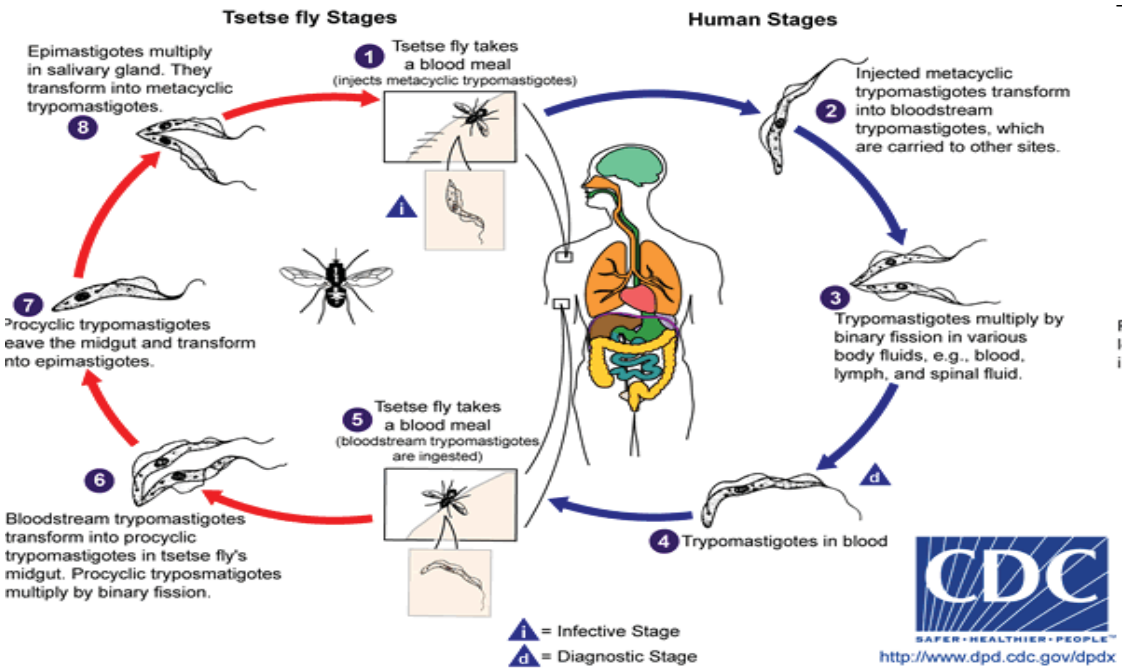

Fig. 12. – Life cycle of trypanosoma brucei

During a blood meal on the mammalian host, an infected tsetse fly (genus Glossina) injects metacyclic trypomastigotes into skin tissue. The parasites enter the lymphatic system and pass into the bloodstream The number 1. Inside the host, they transform into bloodstream trypomastigotes The number 2, are carried to other sites throughout the body, reach other blood fluids (e.g., lymph, spinal fluid), and continue the replication by binary fission The number 3. The entire life cycle of African Trypanosomes is represented by extracellular stages. The tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host (The number 4, The number 5). In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission The number 6, leave the midgut, and transform into epimastigotes The number 7. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission (the number 8). The cycle in the fly takes approximately 3 weeks. Humans are the main reservoir

for Trypanosoma brucei gambiense, but these species can also be found in animals. Wild game animals are the main reservoir of T. b. rhodesiense.

Signs and symptoms.

The natural course of HAT can be divided into different and distinct stages. Their recognition and differentiation is important for the clinical menagment of the patients.

Tripanosomal chancre. A trypanosomal chancre may appear around 48 hours after the tsetse bite. This is an itchy, painful, inflammatory reaction at the site of the bite. The chancre is an indurated (hardened) red or purple nodule, 2 to 5 cm in diameter, which is accompanied by enlarged lymph nodes. A central necrotic eschar (dark-coloured crust) may form before the chancre desquamates (peels off in scales) within 2 to 3 weeks, leaving no trace.They heal without treatment after 2 to 4 weeks, leaving a permanent, hyperpigmented spot.

Tripanosomal chancre occurs in about half the cases of T. b. rhodesiense. In T. b. gambiense, they are much less common and often go undetected in endemic populations.

The skin signs of trypanosomiasis exept chancre include trypanids, itching and petechiae. Trypanids are transient rashes that occur 6 to 8 weeks after the onset of illness in approximately 50% of light-skinned patients. Trypanids are found on the trunk and may have the following characteristics: red patches, urticarial or macular, targetoid, haemorrhagic.

Mild or intense itch with scratch-marks, acroparaesthesias (pins and needles), erythema nodosum, ichthyosis, jaundice, and purpura have been reported.

Petechiae are small red, purple, or brown spots due to bleeding into the skin. They are a rare complication that may be accompanied by generalised flushing.

African trypanosomiasis symptoms occur in two stages:

The 1st stage is the haemolymphatic phase;

The 2nd stage is the meningoencephalitic stage.

Tryp brucei gambiense – slow to enter CNS, but Tryp brucei rhodesiense – invade CNS early.

The 1st stage of HAT is characterized by fever, headaches, joint pains, and itching, severe swelling of lymph nodes, Winterbottom's sign (swollen lymph nodes along the back of the neck). If left

untreated, it can lead to anaemia, endocrine, cardiac, and kidney disfunctions.

The 2nd stage of HAT, called **the neurological phase**, begins when the parasite invades the central nervous system by passing through the blood-brain barrier. The term "sleeping sickness" comes from the symptoms of the neurological phase. The symptoms include confusion, reduced coordination, and disruption of the sleep cycle, with bouts of fatigue punctuated with manic periods leading to daytime slumber and night-time insomnia. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma and death. Damage caused in the neurological phase can be irreversible.

***Diagnosis*.** In the early stages, a painful chancre, which originates as a papule and evolves into a nodule may be found at the primary site of tsetse fly bite. There may be fever, intense headache, insomnia, painless lymphadenopathy, anaemia, local oedema and rash. In the later stage, there is cachexia, somnolence and signs of central nervous system involvement. The disease may run a protracted course of several years in the case of Trypanosoma brucei gambiense. In case of T. b. rhodesiense, the disease has a rapid and acute evolution. Both diseases are always fatal without treatment.

Laboratory criteria for diagnosis. Presumptive: serological: card agglutination trypanosomiasis test (CATT) for T. b. gambiense only or immunofluorescent assay (IFA) for T. b. rhodesiense mainly and possibly for T. b. gambiense. Confirmative: parasitological: detection(microscopy) of trypanosomes in blood, lymph nodes aspirates or CSF.

In T. b. rhodesiense infection, the identification of suspected cases relies on the clinical presentation and a history of exposure. The level of parasitemia is relatively high, particularly in the first stage of disease, and trypanosomes can be found in blood. In centrifuged blood, the parasite sediments just above the white cells, and examination of buffy coat will increase sensitivity. Slides stained with Giemsa can be used, but it is easiest to find the parasite by microscopic examination of fresh wet preparations, because the trypanosomes are motile and attract the eye. Delay between sampling and microscopy should be minimized, because trypanosomes will lose motility within a few hours. Parasites can also be found in fluid expressed in trypanosomal chancres and in lymph node aspirates. Serologic testing is not used for the diagnosis of T. b. rhodesiense infection.

Detecting trypanosomes in T. b. gambiense infection is more difficult. The card agglutination test for trypanosomiasis/T. b. gambiense is a serologic screening test used for mass population screening in endemic areas of Africa. The test is not specific enough for confirmation of infection, but it is helpful in identifying suspect cases. For parasitologic confirmation, a posterior cervical lymph node (if present) is punctured and the fluid examined. The yield in lymph node examination varies from about 40% to 80%. Trypanosomes can also be found in blood, however, the yield is low, and concentration techniques (e.g. buffy coat examination, miniature anion-exchange centrifugation technique) are helpful. Serial examinations on consecutive days may be needed. All patients should have a lumbar puncture before and after treatment to determine whether there is central nervous system involvement. An elevated level of IgM in the cerebrospinal fluid is the most sensitive indicator of the meningoencephalitic phase.

Treatment. Antitrypanosomal treatment is indicated for all persons diagnosed with African trypanosomiasis. Choice of therapy depends on the infecting subspecies of the parasite and on the disease stage. The first line drugs for both first and second stage disease are highly effective. *Pentamidine*, given by intravenous infusion over 2 hours or by intramuscular injection, is used to treat first stage T. b. gambiense infection. It is generally well tolerated, but adverse reactions of hypoglycemia, injection site pain, diarrhea, nausea and vomiting occur. *Suramin* is used to treat first stage T. b. rhodesiense. Suramin is also effective against T. b. gambiense, but it is not often used because severe reactions occur in persons who are co-infected with Onchocerca volvulus. Adverse reactions to suramin are frequent, but usually mild and reversible. These include drug rash, nephrotoxicity, and peripheral neuropathy. In rare instances, suramin administration results in a hypersensitivity reaction, and, for this reason, a small test dose is usually given prior to the full first dose.

Second stage T. b. gambiense is treated with *eflornithine*, which is given in 4 intravenous infusions daily for 14 days. Adverse effects of eflornithine include bone marrow suppression, gastrointestinal symptoms, and seizures. Eflornithine is highly effective, but the difficulty in administering 4 infusions daily in rural African facilities has led to the use of eflornithine (dosed less frequently) in combination with nifurtimox. The efficacy of the combination

regimen appears to be at least as high as eflornithine monotherapy. Eflornithine is not effective against T. b. rhodesiense and it is not recommended for treating the East African form of the disease. *Melarsoprol*, an organoarsenic compound, is the only drug available for treating second stage T. b. rhodesiense. Adverse reactions to melarsoprol can be severe and life-threatening. An encephalopathic reaction occurs in 5-10% of patients with a case-fatality rate of approximately 50% when it occurs. *Prednisolone* is often given to patients who are being treated with melarsoprol to reduce the risk of encephalopathy. Other adverse reactions observed with melarsoprol include skin reactions, gastrointestinal upset, and peripheral neuropathy. Intravenous injections of melarsoprol are painful and can cause phlebitis. The drug is administered by use of lengthy and complicated dosing schedules, however, an abbreviated 10-day regimen appears promising (table 12).

Table 12. – The drugs for treatment HAT

Species	***Drug of choice***	***Adult Dosage***	***Pediatric Dosage***
T. b. rhodesiense, hemolymphatic stage	Suramin	1 gm IV on days 1,3,5,14, and 21	20 mg/kg IV on days 1, 3, 5, 14, and 21
T. b. rhodesiense, CNS involvement	Melarsoprol	2-3.6 mg/kg/day IV x 3 days. After 7 days, 3.6 mg/kg/day x 3 days. Give a 3rd series of 3.6 mg/kg/d after 7 days.	2-3.6 mg/kg/day IV x 3 days. After 7 days, 3.6 mg/kg/day x 3 days. Give a 3rd series of 3.6 mg/kg/d after 7 days.
T. b. gambiense, Hemolymphatic stage	Pentamidine	4 mg/kg/day IM or IV x 7-10 days	4 mg/kg/day IM or IV x 7-10 days
T. b. gambiense, CNS involvement	Eflornithine	400 mg/kg/day in 4 doses x 14 days	400 mg/kg/day in 4 doses x 14 days

Prevention. The leading principle for sleeping sickness control is the reduction of human reservoir through treatment of infected individuals and the reduction of man-fly contact through adapted vector control. The only sure means of preventing infection is by avoiding areas infested by tsetse flies. Tsetse flies are attracted to bright and contrasting colors and can bite through light clothing. Use of repellents, although only partially protective, and wearing heavy, light-colored trousers and long-sleeved shirts reduces the risk of tsetse bites. Pentamidine is no longer recommended as a prophylactic drug because the dose used is not curative, may mask infection until CNS

invasion occurs, and promotes the emergence of drug-resistant strains of the parasite.

Strategies for controlling sleeping sickness in West and Central Africa involve systematic surveillance of populations at risk and early detection and treatment of infected persons to reduce the human reservoir of disease. In these regions and in East Africa, vector control efforts are directed at reducing contact between humans and flies by using simple, inexpensive, and nonpolluting technologies such as tsetse traps and screens.

CHAGAS DISEASE

Chagas disease or American trypanosomiasis is caused by the parasite Trypanosoma cruzi. Chagas disease is named after the Brazilian physician Carlos Chagas, who discovered the disease in 1909. In the United States, Chagas disease is considered one of the neglected parasitic infections (NPI).

It is transmitted by reduviid or kissing bugs, which live in cracks and holes of substandard housing primarily found in South and Central America. These insects become infected after biting an animal or person who already has Chagas disease. Infection is spread to humans when an infected bug deposits feces on a person's skin, usually while the person is sleeping at night. The person often accidently rubs the feces into the bite wound, an open cut, the eyes, or mouth. Infected mothers can pass infection to their baby during pregnancy, at delivery, or while breastfeeding (vertical).

Epidemiology. Risk Factors

American trypanosomiasis affects 17 countries with 16-18 million infected and over 100 million individuals at risk of infection. The disease is prevalent in the northern part of South America (the Andean Region) and in Central America; almost 25 million people are at risk and there are 5 to 6 million infected. The disease is potentially fatal and non-treatable; one third of those infected become incapacitated due to cardiac damage. Infection can also be acquired through blood transfusion.The triatomine bug thrives under poor housing conditions (for example, mud walls, thatched roofs), so in endemic countries, people living in rural areas are at greatest risk for acquiring infection. Public health efforts aimed at preventing

transmission have decreased the number of newly infected people and completely halted vectorborne transmission in some areas. Infection acquired from blood products, organ transplantation, or congenital transmission continues to pose a threat.

Life Cycle of Trypanosoma cruzi (fig. 12). An infected triatomine insect vector (or "kissing" bug) takes a blood meal and releases trypomastigotes in its feces near the site of the bite wound. Trypomastigotes enter the host through the wound or through intact mucosal membranes, such as the conjunctiva (the number 1). Common triatomine vector species for trypanosomiasis belong to the genera Triatoma, Rhodnius, and Panstrongylus.

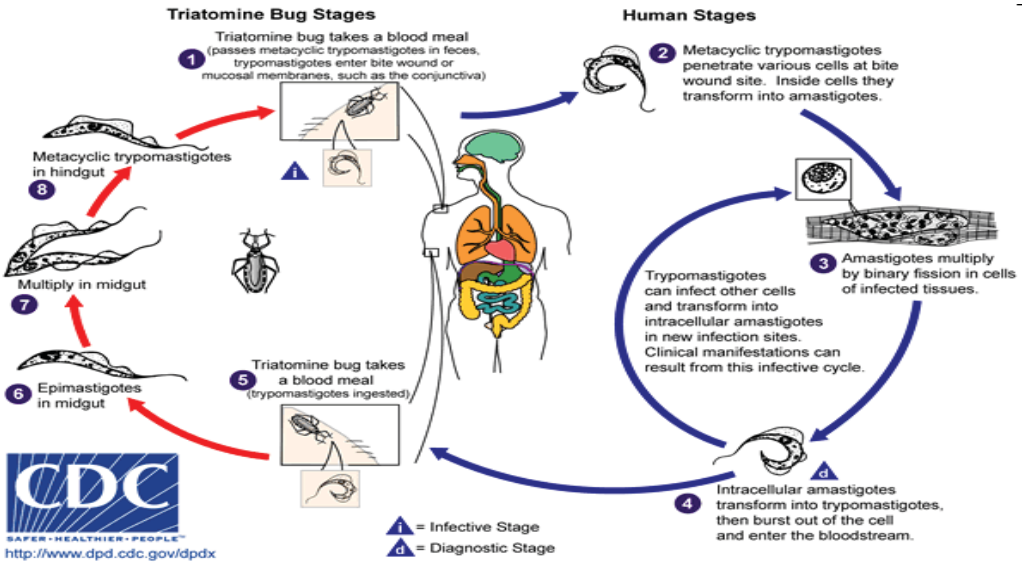

Fig 12. – Life Cycle of Trypanosoma cruzi

Inside the host, the trypomastigotes invade cells near the site of inoculation, where they differentiate into intracellular amastigotes (the number 2). The amastigotes multiply by binary fission (the number 3) and differentiate into trypomastigotes, and then are released into the circulation as bloodstream trypomastigotes (the number 4). Trypomastigotes infect cells from a variety of tissues and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle. The bloodstream trypomastigotes do not replicate (different from the African trypanosomes). Replication resumes only when the parasites enter another cell or are ingested by another vector. The “kissing” bug becomes infected by feeding on human or animal blood that contains

circulating parasites (the number 5). The ingested trypomastigotes transform into epimastigotes in the vector's midgut (the number 6). The parasites multiply and differentiate in the midgut (the number 7) and differentiate into infective metacyclic trypomastigotes in the hindgut (the number 8).

Signs and symptoms. Acute stage. Acute symptoms only occur in about 1% of cases. Most people infected do not seek medical attention. The most recognized symptom of acute Chagas infection is the Roma's sign, or swelling of the eye on one side of the face, usually at the bite wound or where feces were rubbed into the eye. Other symptoms are usually not specific for Chagas infection. These symptoms may include fatigue, fever, enlarged liver or spleen, and swollen lymph glands. Sometimes, a rash, loss of appetite, diarrhea, and vomiting occur. In infants and in very young children with acute Chagas disease, swelling of the brain can develop in acute Chagas disease, and this can cause death. In general, symptoms last for 4-8 weeks and then they go away, even without treatment.

Indeterminate stage: Eight to 10 weeks after infection, the indeterminate stage begins. During this stage, people do not have symptoms.

Chronic stage: Ten to 20 years after infection, people may develop the most serious symptoms of Chagas disease. Cardiac problems, including an enlarged heart, altered heart rate or rhythm, heart failure, or cardiac arrest are symptoms of chronic disease. Chagas disease can also lead to enlargement of parts of the digestive tract, which result in severe constipation or problems with swallowing. In persons who are immune compromised, including persons with HIV/AIDS, Chagas disease can be severe. Not everyone develops the chronic symptoms of Chagas disease.

Diagnosis. The diagnosis of Chagas disease can be made by observing the parasite in a blood smear by microscopic examination. A thick and thin blood smear are made and stained for visualization of parasites. Parasitologic methods, including identification of trypomastigotes in blood by microscopy, are most effective during acute infections. Circulating parasite levels decrease rapidly within a few months and are undetectable by most methods during the chronic phase.

Diagnosis of chronic Chagas disease is made after consideration of the patient's clinical findings, as well as by the likelihood of being

infected, such as having lived in an endemic country. Diagnosis is generally made by testing with at least two different serologic tests. Two commonly used techniques are enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody test (IFA). To increase accuracy of diagnosis, careful consideration of the patient's history to identify possible risks for infection may be helpful.

Laboratory Diagnosis:

Microscopic examination:

• of fresh anticoagulated blood, or its buffy coat, for motile parasites

• of thin and thick blood smears stained with Giemsa, for visualization of parasites.

Isolation of the agent:

• inoculation in culture with specialized media (e.g. NNN, LIT)

• inoculation into mice

• xenodiagnosis, where uninfected triatomine bugs are fed on the patient's blood, and their gut contents examined for parasites 4 weeks later.

Medication. Antiparasitic treatment is indicated for all cases of acute or reactivated Chagas disease and for chronic Trypanosoma cruzi infection in children up to age 18. Congenital infections are considered acute disease. Treatment is strongly recommended for adults up to 50 years old with chronic infection who do not already have advanced Chagas cardiomyopathy. For adults older than 50 years with chronic T. cruzi infection, the decision to treat with antiparasitic drugs should be individualized, weighing the potential benefits and risks for the patient. Physicians should consider factors such as the patient's age, clinical status, preference, and overall health.

The two drugs used to treat infection with Trypanosoma cruzi are nifurtimox and benznidazole. In the United States, these drugs are not FDA approved and are available only from CDC under investigational protocols. For both drugs, side effects are fairly common, and tend to be more frequent and more severe with increasing age.

Common side effects of benznidazole treatment include: allergic dermatitis, peripheral neuropathy, anorexia and weight loss, insomnia. The most common side effects of nifurtimox are: anorexia and weight loss, polyneuropathy, nausea, vomiting, headache, dizziness or vertigo.

Contraindications for treatment include severe hepatic and/or

renal disease. As safety for infants exposed through breastfeeding has not been documented, withholding treatment while breastfeeding is also recommended. The following table outlines recommended dosage regimens by age group (table 13).

Table 13. – Drugs for treatment of Chagas diseases

Drug	*Age group*	*Dosage and duration*
Benznidazole	< 12 years	5-7.5 mg/kg per day orally in 2 divided doses for 60 days
	12 years or older	5-7 mg/kg per day orally in 2 divided doses for 60 days
Nifurtimox	≤ 10 years	15-20 mg/kg per day orally in 3 or 4 divided doses for 90 days
	11-16 years	12.5-15 mg/kg per day orally in 3 or 4 divided doses for 90 days
	17 years or older	8-10 mg/kg per day orally in 3 or 4 divided doses for 90 days

Prevention. No vaccine or chemoprophylactic agent prevents T. cruzi infection. Travelers should avoid sleeping in houses or outdoor areas that may be infested with triatomine bugs. Transfusion-induced Chagas disease can be prevented by careful serologic screening of blood donors or by treating donor blood with gentian violet for at least 24 hours before transfusion. Efforts to prevent transmission of T. cruzi by triatomine vectors in endemic areas focus on application of insecticides in houses by sprays, fumigant canisters, and impregnated paints; and improvement of housing to discourage colonization by triatomine bugs; and by education and community-based surveillance for reinfestation of houses. Vector control and screening of blood donors have reduced the incidence of new cases to nearly zero in Chile and Uruguay and much of Argentina, Brazil, and Venezuela.

Both agents are limited in their capacity to effect parasitologic cure (a complete elimination of T. cruzi from the body), especially in chronically infected patients, and resistance to these drugs has been reported. Studies suggest that antiparasitic treatment leads to parasitological cure in about 60-85% of adults and more than 90% of infants treated in the first year of acute phase Chagas disease.

Treatment of complication in chronic stage. In the chronic stage, treatment involves managing the clinical manifestations of the disease. For example, pacemakers and medications for irregular

heartbeats, such as the anti-arrhythmia drug amiodarone, may be life saving for some patients with chronic cardiac disease,while surgery may be required for megaintestine. The disease cannot be cured in this phase, however. Chronic heart disease caused by Chagas disease is now a common reason for heart transplantation surgery.

Until recently, however, Chagas disease was considered a contraindication for the procedure, since the heart damage could recur as the parasite was expected to seize the opportunity provided by the immunosuppression that follows surgery. It was noted that survival rates in Chagas patients could be significantly improved by using lower dosages of the immunosuppressant drug ciclosporin. Recently, direct stem cell therapy of the heart muscle using bone marrow cell transplantation has been shown to dramatically reduce risks of heart failure in Chagas patients.

Prevention and Control. The infection can be effectively eliminated through interruption of vector transmission and systematic screening of blood donors. Elimination has been successful in some countries of the Southern Cone of South America (Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay).

In endemic areas of Mexico, Central America, and South America improved housing and spraying insecticide inside housing to eliminate triatomine bugs has significantly decreased the spread of Chagas disease. Further, screening of blood donations for Chagas is another important public health tool in helping to prevent transfusion-acquired disease. Early detection and treatment of new cases, including mother-to-baby (congenital) cases, will also help reduce the burden of disease.

In the United States and in other regions where Chagas disease is now found but is not endemic, control strategies are focused on preventing transmission from blood transfusion, organ transplantation, and mother-to-baby.

Chagas diseases co-exist with HIV. Recently new aspects of the immunopathology of Chagas disease have been described in patients infected with HIV and unusual clinical manifestations such as cutaneous lesions, involvement of central nervous system and/or serious cardiac lesions related to the reactivation of the parasite have been reported.

Among patients with HIV infection, symptomatic reactivation of chronic, latent T. cruzi infection can be triggered by profound immunosuppression.

Persons with chronic Chagas disease who are HIV infected usually have higher levels of T. cruzi parasitemias than their counterparts who are HIV negative. Clinical reactivation occurs in HIV-infected patients, as it does with patients who are immunosuppressed by other processes. One prospective study found reactivation in 11 (21%) of 53 patients during a median follow-up interval of 58 months. The majority of cases occur in patients with CD4+ counts <200 cells/μL or prior OIs.

The clinical features of reactivated Chagas disease among patients with HIV infection differ from those observed in persons who are immunosuppressed from other causes. Approximately 75% of HIV-infected patients with reactivation experience an acute meningoencephalitis that is indistinguishable clinically from toxoplasmosis. About 25-50% of patients also have myocarditis at autopsy, but it is not usually the primary manifestation of reactivation.

T. cruzi infection should be considered in the differential diagnosis of CNS mass lesions and cardiac disease (arrhythmias or heart failure) among patients with HIV infection who have epidemiologic risk factors for Chagas disease. The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than Toxoplasma lesions. CT and MRI show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of T. cruzi amastigotes in glial cells and, less often, in neurons. CSF shows a mild pleocytosis (lymphocyte predominance), increased protein, and T. cruzi trypomastigotes.

Serologic tests to detect the antibody responses to T. cruzi infection are useful for diagnosis of disease in chronically infected patients, to screen blood donors, and for seroepidemiologic studies. The techniques used include indirect hemagglutination, direct agglutination, complement fixation, indirect immunofluorescence, ELISA, and radioimmunoprecipitation assays. In the United States, multiple serologic tests are licensed for diagnosis. In late 2006, an ELISA assay for screening blood donors was licensed. As of December 2008, approximately 700 confirmed-positive donations have been reported. Detection of IgM antibodies is not sensitive, even during the acute stage of infection. Diagnosis based on serologic tests requires two positive tests performed with different techniques.

Treatment of Disease. Chemotherapy of Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations for patients with acute, early chronic, and reactivated disease. Benznidazole, 5–8 mg/kg body weight/day for 30–60 days, is the initial treatment most commonly recommended. Nifurtimox, 8–10 mg/kg body weight/day, administered for 90–120 days is an alternative. However, the duration of therapy with either of these agents has not been studied for persons coinfected with HIV. Mortality is high, even in patients who receive chemotherapy. Limited data suggest that early recognition and treatment of reactivation might improve prognosis. ART is likely to reduce or prevent initial reactivtion of T. cruzi or its recurrence. ART should be initiated or optimized once a patient with acute disease is clinically stable.

AMEBIASIS

Amebiasis is a disease caused by the parasite Entamoeba histolytica. It can affect anyone, although it is more common in people who live in tropical areas with poor sanitary conditions. E. histolytica belongs to thegenus Entamoeba, along with 5 other parasites: E. coli, E. hartamanni, E. dispar, E. gingivalis, and E. polecki. However, only E. histolytica causes Amebiasis. Several protozoan species in the genus Entamoeba colonize humans, but not all of them are associated with the disease. Entamoeba histolytica is well recognized as a pathogenic ameba, associated with intestinal and extraintestinal infections. The other species are important because they may be confused with E. histolytica in diagnostic investigations.

Epidemiology. Entamoeba species infect approximately 10% of the world's population. The prevalence of Entamoeba infection is as high as 50% in areas of Central and South America, Africa, and Asia. In Egypt, 38% of individuals presenting with acute diarrhea to an outpatient clinic were found to have amebic colitis. E histolytica seroprevalence studies in Mexico revealed that more than 8% of the population was positive. Asymptomatic E histolytica infections seem to be region-dependent, as high as 11% in Brazil. Since the introduction of molecular techniques, it is estimated that 500 million individuals with Entamoeba infection are colonized by E dispar.

Transmission occurs in several ways:

- By ingesting cysts in fecally contaminated food/drinks.
- By directly inoculating trophozoites in the colon or other sites (ex. Anal sex).
- By fecal-oral self-inoculation (hand to mouth).

Mortality/Morbidity. Amebiasis is second only to malaria in terms of protozoa-associated mortality. The combined prevalence of amebic colitis and amebic liver abscess is estimated at 40-50 million cases annually worldwide, resulting in 40,000-100,000 deaths.

Asymptomatic intestinal amebiasis occurs in 90% of infected individuals. However, only 4%-10% of individuals with asymptomatic amebiasis who were monitored for one year eventually developed colitis or extraintestinal disease.

Case fatality rates associated with amebic colitis range from 1,9-9,1%. Amebic colitis evolves to fulminant necrotizing colitis or rupture in approximately 0,5% of cases; in such cases, the mortality rate jumps to greater than 40%.

The mortality rate due to amebic liver abscess has fallen to 1-3% in the last century following the introduction of effective medical treatment. Nevertheless, amebic liver abscess is complicated by sudden intraperitoneal rupture in 2-7% of patients, leading to a higher mortality rate.

Life Cycle (fig. 13). Cysts and trophozoites are passed in feces. Cysts are typically found in formed stool, whereas trophozoites are typically found in diarrheal stool. Infection by Entamoeba histolytica occurs by ingestion of mature cysts in fecally contaminated food, water, or hands. Excystation occurs in the small intestine and trophozoites are released, which migrate to the large intestine. The trophozoites multiply by binary fission and produce cysts, and both stages are passed in the feces. Because of the protection conferred by their walls, the cysts can survive days to weeks in the external environment and are responsible for transmission. Trophozoites passed in the stool are rapidly destroyed once outside the body, and if ingested would not survive exposure to the gastric environment. In many cases, the trophozoites remain confined to the intestinal lumen (noninvasive infection) of individuals who are asymptomatic carriers, passing cysts in their stool. In some patients the trophozoites invade the intestinal mucosa intestinal disease), or, through the bloodstream,

extraintestinal sites such as the liver, brain, and lungs (extraintestinal disease), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively E. histolytica and E. dispar. These two species are morphologically indistinguishable unless E. histolytica is observed with ingested red blood cells (erythrophagocystosis). Transmission can also occur through exposure to fecal matter during sexual contact (in which case not only cysts, but also trophozoites could prove infective).

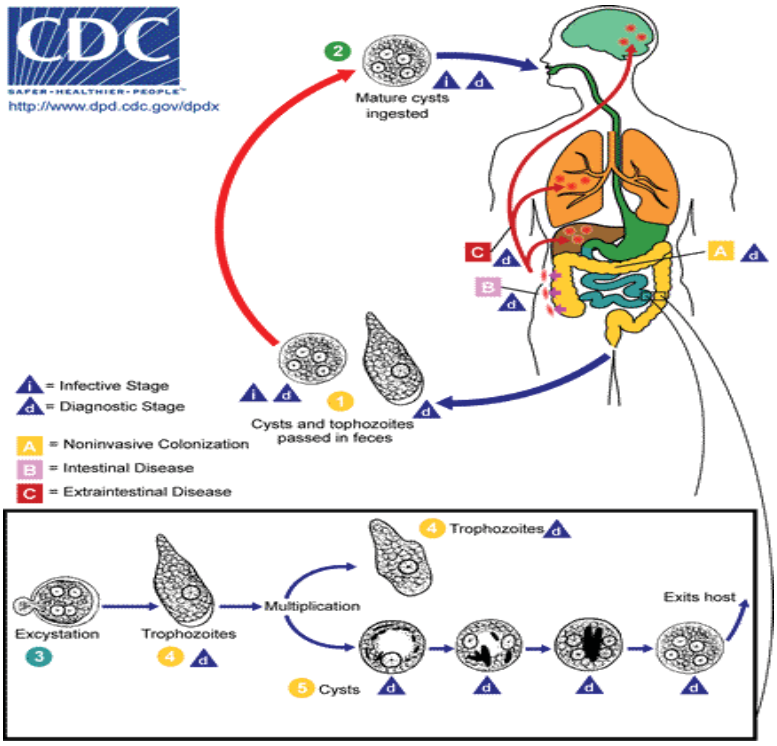

Fig. 13. - Life Cycle of Entamoeba histolytica

Pathogenesis. E. histolytica is a pseudopod-forming, nonflagellated protozoal parasite that causes proteolysis and tissue lysis (hence its name) and can induce host-cell apoptosis. Humans and perhaps nonhuman primates are the only natural hosts. Ingestion of E histolytica cysts from the environment is followed by excystation in the terminal ileum or colon to form highly motile trophozoites. Upon colonization of the colonic mucosa, the trophozoite may encyst and is then excreted in the feces or may invade the intestinal mucosal barrier and gain access to the blood stream and disseminate to the liver, lung, and other sites. Excreted cysts reach the environment to complete the cycle.

Disease may be caused by only a small number of cysts, but the processes of encystation and excystation are poorly understood. The adherence of trophozoites to colonic epithelial cells seems to be mediated by a galactose/N–acetylgalactosamine (GAL/GalNAc)-specific lectin. A mucosal immunoglobulin A (IgA) response against this lectin can result in fewer recurrent infections. Both lytic and apoptotic pathways have been described. Cytolysis can be undertaken by amoebapores, a family of peptides capable of forming pores in lipid bilayers. Furthermore, in animal models of liver abscess, trophozoites induced apoptosis via a non-Fas and non–tumor necrosis factor-α1 receptor pathway. The amoebapores, at sublytic concentrations, can also induce apoptosis.

Clinical Presentation. Non-pathogenic infections occur in 90% of infected individuals, pathogenic Infections in 10% of infected individuals. Many carriers of Amebiasis have no symptoms, and eventually clear the infection without disease. However, 4-10% of asymptomatic carriers develop symptomatic infections within 1 year. For this reason, it is strongly suggested these asymptomatic individuals obtain treatment.

Invasive intestinal amoebiasis (9%).

Intestinal amebiasis may involve any part of the bowel. It usually involves caecum and ascending colon followed by sigmoid colon, rectum, and appendix. In severe cases the entire colon is involved. There may be extension into the terminal ileum. Symptoms occur 1-4 weeks after ingestion. These include vague and nonspecific abdominal symptoms, such as watery and bloody diarrhea, abdominal pain, cramping, flatulence, weight loss, and chronic fatigue. Fever occurs occasionally, and megacolon is present very rarely (0.5% patients). The clinical features show a wide spectrum from minimal changes in bowel habit to severe dysentery. A relapsing course is common.

Mild symptoms: abdominal cramps, diarrhea, passage of 3-8 semiformed stools per day, passage of soft stools with mucus and occasional blood, fatigue, excessive gas, rectal pain while having a bowel movement (tenesmus), unintentional weight loss.

Severe symptoms: abdominal tenderness, bloody stools, passage of liquid stools with streaks of blood, passage of 10 - 20 stools per day, fever, vomiting.

Acute necrotizing colitis with perforation. Development of such

fulminant course is found to be associated with various factors including male gender, age over 60 years, associated liver abscess, progressive abdominal pain, and signs of peritonitis, leukocytosis, hyponatremia, hypokalemia, and hypoalbuminemia. FAC, in majority of cases has characteristic symptoms and signs such as severe abdominal distention and pain with peritoneal signs, sepsis with high fever, watery or bloody mucoid diarrhea and dehydration. Peritonitis develops either because of frank perforation or a slow leak through an extensively diseased bowel.

Apart from its rarity, clinical significance of fulminant amoebiasis lies in the fact that the condition is difficult to diagnose and treat, and associated with a very high mortality rate. Diagnosis is often confused with idiopathic inflammatory bowel disease resulting in erroneous administration of steroids. Colonoscopic appearance and colonic tissue biopsy are helpful in differentiating amoebiasis from other forms of colitis. Clinical symptoms, laboratory studies and X-ray findings are insufficient to make an accurate diagnosis. Conventional method of microscopic examination of stool is less sensitive (25% to 60%). Antigen detection both in the patient's stool and serum is more sensitive and specific method. Pathology of the invaded colonic tissue shows transmural inflammation widespread necrosis along with large numbers of amoebic trophozoites within the inflammatory exudates.

For acute amoebic colitis, once suspected, early diagnosis and aggressive supportive and antiamoebic treatment should be instituted. If fulminant colitis develops, the outcome is poor with mortality ranging from 55% to 87,5%, peritonitis being the commonest cause of death. Early diagnosis and surgical treatment significantly decrease mortality. It has been stated that conservative surgery has no place in the management of acute amoebic colitis, and primary total resection is the treatment of choice. Because there is a high risk of suture breakdown in tissue containing amoebae; a staged operation in the form of exteriorization of the proximal and distal transected ends, and bowel reconstruction 3-6 months later, is highly recommended for amoebic colitis. Also, in endemic areas, patients with severe and undiagnosed colitis should be treated presumptively with specific antiamoebic therapy until a diagnosis of amoebic colitis can be excluded (Shilpi Singh Gupta et al, 2009).

Differential diagnosis: Diarrhea with blood in the stool –

Infection due to Shigella, salmonella, campylobacter, enteroinvasive and enterohemorrhagic Escherichia coli. Noninfectious conditions include inflammatory bowel disease, ischemic colitis, diverticulitis and.

Amebic lesions begin as small foci of necrosis that progress to ulcers.

In the early stages the colonic ulcers have a narrow neck and thus appear as small nodules with a minute surface opening (5 mm in diameter).

As the ulcers enlarge they always retain their undermined base but the ulcerated area of the mucosa becomes larger. (Muscle coat of the large intestine form a barrier to the penetrating trophozoites which fan out latarally producing a flask-shaped ulcer with narrow neck and broad base).

Large irregular geographic patterns are formed on the bowel mucosa.

The base of the ulcer is covered by grey – white exudate.

There is always undenuded mucosa between the ulcers.

Typical endoscopic appearance of amebic colitis-Small discrete areas of ulceration (red arrow) with normal intervening mucosa (black arrow).

Occasionally (5-10% cases) the trophozoites penetrate the muscle and serous layers to produce intestinal perforation.

Ameboma- Napkin-like constrictive lesion of the colon. This is an inflammatory thickening of the bowel wall in response to the parasites. It resembles carcinoma of colon in location, symptoms, gross and radiographic appearance.

Microscopic features. The ulcer is typically 'flask-shaped' and the broad base is composed of fibrin and cellular debris.

A sharp line divides the necrotic and viable mucosa (this feature demonstrates the lytic action of the trophozoites).

Trophozoites are found on the surface of the ulcers, in the exudate and in the crater. They are frequently found in the submucosa, muscularis propria, serosa and small veins of the submucosa. There is little inflammatory response in the early ulcers. However, as the ulcer widens there is accumulation of neutrophils, lymphocytes, histiocytes, plasma cells and sometimes eosinophils. Histologic sections of an ameboma reveal granulation tissue, fibrosis, chronic inflammatory cells and clusters of trophozoites usually concentrated in the

submucosa near small points of ulceration. Amebic trophozoites are spherical or oval-shaped (15-20 micrometer in diameter) with a thin cell membrane and single nucleus with prominent nuclear border and central karyosome. The cytoplasm is vacuolated (may be confused with macrophages). The PAS procedure stains the cytoplasm of the trophozoites (red) and makes them stand out in tissue section. The organisms will appear black when stained by the Heidenhain's iron hematoxylin method. Presence of trophozoites containing red blood cells is indicative of tissue invasion by virulent E.histolytica parasites. Organisms are also demonstrated by immunoperoxidase stains.

Extraintestinal Amebiasis:

A. Liver: Liver abscess (can present months to years after travel) is ten times more common in men than women, and rare in children. Parasites penetrate portal vessels and embolize the liver. Patients may have single or multiple liver abscesses. The abscess cavity is sometimes filled with chocolate coloured pasty material (anchovy sauce-like). The wall contains abundant fibrin and trophozoites are clustered in the fibrin at the junction of viable and necrotic tissue. Symptoms include: fever, cough, dull abdominal pain, nausea, diarrhea, ulcers, constipation, gas, hepatomegaly, cough, and weight loss. Symptoms can last for less than 10 days, although others may be chronic (e.g. weight loss).

B. Respiratory tract. Liver abscess penetrate the diaphragm to involve pleura and lung. Involvement of pericardium results in pericardial effusion, amebic pericarditis, cardiac tamponade and cardiac failure. Symptoms include cough and chest pain.

C. Brain. Rarely liver abscess or a lesion in the colon may spread amebae to the brain by hematogenous route. Cerebral lesions localize in any part of the brain. Initially there are minute areas of softening which expand to larger necrotic lesions. This is very rare. Symptoms are headache, vomiting, and seizures. 50% of patients with cerebral abscesses die.

D. Other: This can include areas such as urinary tract problems, genital disease, perianal disease, and cutaneous lesions.

Peritonitis and intra-abdominal abscesses Caused by intestinal perforation or by rupture of liver abscess.

Cutaneous amebiasis results from extension of rectal amebiasis (to the anus, perianal skin and vulva) or extension of an amebic liver abscess (to the skin of the abdominal wall or flank). Macroscopically there is marked epithelial hyperplasia (with a cauliflower -like surface

resembling carcinoma) punctuated by small circumscribed ulcers. Histologically there is papillary acanthosis of the epithelium and chronic inflammatory response. Trophozoites are concentrated over points of ulceration in adjacent epidermis and in the superficial layers of the ulcer.

Diagnosis. Microscopy. Microscopic stool examination for trophozoites from a single stool sample in amebic colitis is only 33-50% sensitive. Examination of 3 stool samples over no more than 10 days can improve the detection rate to 85-95%.

Stool leukocytes may be found, but in fewer numbers than in shigellosis. Identification of the parasite in a liver abscess aspirate is only 20% sensitive. The presence of intracytoplasmic red blood cells in trophozoites is diagnostic of E histolytica infection, although recent studies demonstrated the same phenomenon with E dispar.

Cultures can be performed using fecal or rectal biopsy specimens and liver abscess aspirates. The success rate is between 50% and 70%, but the technique is technically difficult. Overall, it is less sensitive than microscopy.

Serology Antigen detection. Enzyme-linked immunosorbent assay (ELISA) is used to detect antigens from E histolytica in stool samples. Several kits are commercially available.

Antigen-based ELISA kits using monoclonal antibodies against the GAL/GalNAc–specific lectin of E histolytica (E histolytica II, TechLab, Blacksburg, VA) yield an overall sensitivity of 71-100% and specificity of 93-100%. One study showed a much lower sensitivity (14,2%).

Multiple serologic assays are available for the diagnosis of amebiasis. ELISA is the most used assay throughout the world and is used to measure the presence of serum antilectin antibodies (IgG). The sensitivity for detection of antibodies to E histolytica in patients with amebic liver abscess is 97,9%, whereas the specificity is 94,8%. False-negative results can occur within the first 7-10 days following infection.

Immunofluorescent assay (IFA) is also rapid, reliable, and reproducible. In the setting of amebic liver abscess, the sensitivity and specificity of IFA was shown to be 93,6% and 96,7%, respectively. Polymerase chain reaction

Nonspecific laboratory tests. In case of amebic liver abscess:

leukocytosis without eosinophilia (80%), elevated alkaline phosphatase (80%), mildly elevated transaminases, mild anemia, elevated erythrocyte sedimentation rate.

Imaging Studies. Both ultrasonography and CT scanning are sensitive but nonspecific for amebic liver abscess. Lesions are usually solitary and located in the right hepatic lobe (70-80%), although multiple abscesses are possible.

On sonograms, amebic liver abscesses usually appear as a homogenous hypoechoic round lesion.

On CT scans with intravenous contrast, amebic liver abscess can appear as a rounded, low-attenuation lesion with an enhancing rim. Furthermore, the abscess may be homogenous or septated, with or without observable fluid levels.

Treatment. Drugs for treatment of amebiasis are presented in table 14.

Table 14. – Drugs for treatment of amebiasis

Drug	*Adult dosage*	*Pediatric dosage*
Asymptomatic 1. Iodoquinol or 2. Paromomycin or 3. Diloxanide furoate	 650 mg PO tid x 20d 25-35 mg/kg/d PO in 3dos.x7d 500 mg PO tid x 10d	 30-40 mg/kg/d (max.2g) PO in3 dose x 20d 25-35 mg/kg/d PO in 3 doses x7d 20 mg/kg/d PO in 3 doses x 10d
Mild to moderate intestinal disease 4. Metronidazole or 5. Tinidazole	 500-750 mg PO tid x 7-10d 2 g once PO daily x 3d	 35-50 mg/kg/d PO in 3 doses x7-10d >3yrs: 50 mg/kg/d (max. 2g) PO in 1 dose x 3d
Either followed by 1. Iodoquinol or 2. Paromomycin	 650 mg PO tid x 20d 25-35 mg/kg/d PO in 3 dos.x7d	 30-40 mg/kg/d (max. 2g) PO in3 doses x 20d 25-35 mg/kg/d PO in 3 doses x7d
Severe intestinal and extraintestinal disease 4. Metronidazole or 5. Tinidazole **either followed by** 1. Iodoquinol or 2. Paromomycin	 750 mg PO tid x 7-10d 2g once PO daily x 5d 650 mg PO tid x 20d 25-35 mg/kg/d PO in 3 dos.x7d	 35-50 mg/kg/d PO in 3 doses x7-10d >3yrs: 50 mg/kg/d (max. 2g) PO in 1 dose x 3d 30-40 mg/kg/d (max. 2g) PO in 3 doses x 20d 25-35 mg/kg/d PO in 3 doses x7d

For asymptomatic infections, iodoquinol, paromomycin, or diloxanide furoate (not commercially available in the U.S.) are the drugs of choice. For symptomatic intestinal disease, or extraintestinal,

infections (e.g., hepatic abscess), the drugs of choice are metronidazole or tinidazole, immediately followed by treatment with iodoquinol, paromomycin, or diloxanide furoate.

BALAN TIDIASIS

Balantidiasis (also known as balantidiosis) is defined as large-intestinal infection with Balantidium coli, which is a ciliated protozoan (and the largest protozoan that infects humans). B coli is known to parasitize the colon, and pigs may be its primary reservoir. These parasites can be transmitted through the fecal-oral route by contaminated food and water. Balantidium coli infection is mostly asymptomatic, but people with other serious illnesses can experience persistent diarrhea, abdominal pain, and sometimes a perforated colon.

Epidemiology. Balantidiasis tends to be more common among persons who handle pigs. The disease is reported most commonly in Latin America; Southeast Asia; and Papua, New Guinea. In 1971, a balantidiasis outbreak involving 100 people occurred in Truk following a typhoon [1]. In France, a pork butcher with immunosuppression due to alcohol use developed occupational balantidiasis.

Humans can become infected by eating and drinking contaminated food and water that has come into contact with infective animal or human fecal matter. Infection can occur in several ways, including the following examples:

- eating meat, fruits, and vegetables that have been contaminated by an infected person or contaminated by fecal matter from an infected animal
- drinking and washing food with contaminated water, or
- having poor hygiene habits.

Risk factors for balantidiasis include contact with pigs, handling fertilizer contaminated with pig excrement, and living in areas where the water supply may be contaminated by the excrement of infected animals. Poor nutrition, achlorhydria, alcoholism, and immunosuppression may also be contributing factors.

Life cycle (fig. 13). Cysts are the parasite stage responsible for transmission of balantidiasis. The host most often acquires the cyst through ingestion of contaminated food or water. Following ingestion,

excystation occurs in the small intestine, and the trophozoites colonize the large intestine. The trophozoites reside in the lumen of the large intestine of humans and animals, where they replicate by binary fission, during which conjugation may occur. Trophozoites undergo encystation to produce infective cysts. Some trophozoites invade the wall of the colon and multiply. Some return to the lumen and disintegrate. Mature cysts are passed with feces.

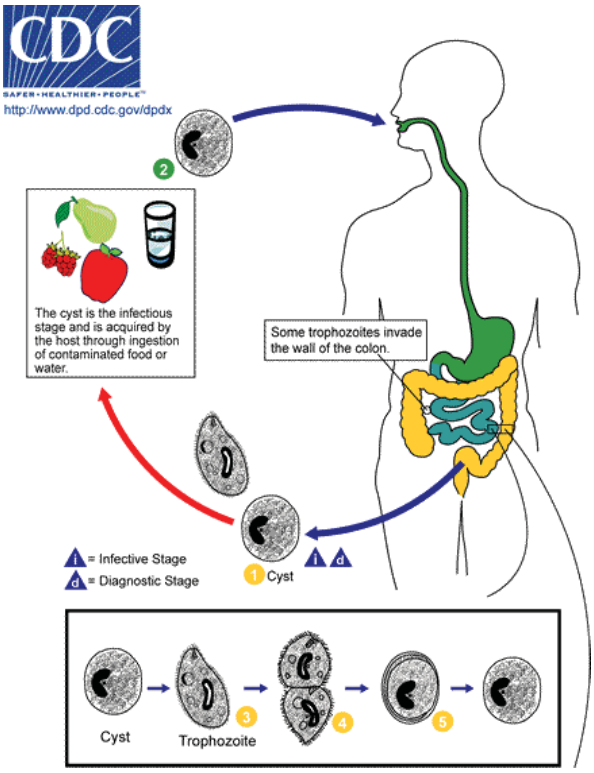

Fig. 14. – Life cycle of Balantidium coli

Pathogenesis. B coli exists as a trophozoite and a cyst and usually affects the large intestine, from the caecum to the rectum. The trophozoites replicate by binary fission and conjugation, and they subsist on bacteria. Humans ingest infective cysts, which then migrate to the large intestine, cecum, and terminal ileum. The organisms primarily dwell in the lumen but can also penetrate the mucosa and cause ulcers. B coli produces hyaluronidase, potentially enhancing its ability to invade the mucosa.

Clinical Features. Most people infected with Balantidium coli experience no symptoms. Balantidium coli infects the large intestine in humans and produces infective microscopic cysts that are passed in the feces, potentially leading to re-infection or infection of others. Potential symptoms of balantidiasis include the following: diarrhea

(watery, bloody, mucoid), nausea, vomiting, abdominal pain, anorexia, weight loss, headache, mild colitis, fever, severe and marked fluid loss (resembling amebic dysentery).

People who are immune-compromised are the most likely to experience more severe signs and symptoms. These include persistent diarrhea, dysentery, abdominal pain, weight loss, nausea, and vomiting. If left untreated, perforation of the colon can occur.

Diagnosis and lab studies. Wet smear stool specimens.

B coli does not stain well on permanent stained smears, complicating diagnosis of balantidiasis; however, the diagnosis can be made by examining wet smears of stool specimens or scrapings from the periphery of ulcers during an endoscopic examination.

On unstained specimens, the trophozoite is recognized by its large size (approximately 50-100 μm in length and 40-70 μm in width), a short ciliary covering, and its spiraling motility. It is frequently observed under low power. On stained preparations, the trophozoite characteristically shows 2 nuclei: the macronucleus, which is kidney-shaped, and the micronucleus, which is spherical and lies close to the macronucleus. Cysts may be spherical or ellipsoid and are approximately 50-70 μm long. Newly encysted organisms observed on unstained specimens may still have cilia, but cilia disappear after a longer period of encystment. Observation of a macronucleus and a micronucleus is diagnostic if observed in a cyst on a stained specimen.

Treatment. Three medications are used most often to treat Balantidium coli: tetracycline, metronidazole, and iodoquinol.

Tetracycline: adults, 500 mg orally four times daily for 10 days; children ≥ 8 years old, 40 mg/kg/day (max. 2 grams) orally in four doses for 10 days. (Note: Tetracyclines are contraindicated in pregnancy and in children < 8 years old. Tetracycline should be taken 1 hour before or 2 hours after meals or ingestion of dairy products.). Alternatives: Metronidazole: adults, 500-750 mg orally three times daily for 5 days; children, 35-50 mg/kg/day orally in three doses for 5 days. Or Iodoquinol: adults, 650 mg orally three times daily for 20 days; children, 30-40 mg/kg/day (max 2 g) orally in three doses for 20 days. (Note: iodoquinol should be taken after meals.).

Nitazoxanide: has been tried in small studies, which suggest some therapeutic benefit (adults, 500 mg orally twice daily for 3 days; children age 4-11 years old 200 mg orally twice daily for 3 days; children 1-3 years old 100 mg orally twice daily for 3 days).

GIARDIASIS

Giardiasis (popularly known as beaver fever) is a zoonotic parasitic disease caused by the flagellate protozoan Giardia lamblia (also sometimes called Giardia intestinalis and Giardia duodenalis). The giardia organism inhabits the digestive tract of a wide variety of domestic and wild animal species, as well as humans. It is the most common pathogenic parasitic infection in humans worldwide; in 2013, there were about 280 million people worldwide with symptomatic giardiasis.

Infection is transmitted through ingestion of infectious G lamblia cysts. The organism is known to have multiple strains with varying abilities to cause disease, and several different strains may be found in one host during infection. The infective dose is low in humans; 10-25 cysts are capable of causing clinical disease in 8 of 25 subjects. Ingestion of more than 25 cysts results in a 100% infection rate.

Person-to-person transmission, often associated with poor hygiene and sanitation, is a primary means of infection. Diaper changing and inadequate hand washing are risk factors for transmission from infected children. Children attending day care centers, as well as day-care workers, have a higher risk of infection secondary to fecal-oral transmission.

Water-borne transmission is responsible for a significant number of epidemics in the United States, generally following ingestion of unfiltered surface water. Giardia cysts retain viability in cold water for as long as 2-3 months. Giardia was implicated in 90 waterborne outbreaks in the United States from 1964-1984, affecting 23,500 persons.

Venereal transmission occurs through fecal-oral contamination. Food-borne epidemics have been reported, most commonly secondary to contamination by infected food-handlers. Pets frequently harbor Giardia in their GI tracts, but they are not thought to be a significant cause of outbreaks in humans.

Epidemiology. Giardia has a worldwide distribution, occurring in both temperate and tropical regions. It continues to be the most frequently identified human protozoal enteropathogen. Prevalence rates vary from 4-42%. In the industrialized world, overall prevalence rates are 2-5%. In the developing world, G intestinalis infects infants

early in life and is a major cause of epidemic childhood diarrhea. Prevalence rates of 15-20% in children younger than 10 years are common.

Giardia is the most common gut parasite in the United Kingdom, and infection rates are especially high in Eastern Europe. Prevalence rates of 0,94-4,66% and 2,41-10,99% have been reported in Italy.

A 2005 study demonstrated a Giardia infection rate of 19,6 per 100,000 population per year in Canada. While the yearly incidence of the disease was stable, a significant seasonal variation was observed, with a peak in late summer to early fall, which correlates with the pattern found in the United States. New Zealand reports more than 30 cases of giardiasis per 100,000 population every year, which is one of the highest among the industrialized countries.

Giardiasis accounts for a relatively small percentage of traveler's diarrhea. It is more likely to be found as the cause of diarrhea that occurs or persists after returning home from travel to developing regions of the world due to its relatively long incubation period and persistent symptoms. Giardia has been identified as the causative agent in a large percentage of cases among travelers to the region of St. Petersburg, Russia, where tap water is the primary source.

The highest prevalence of G intestinalis reached 73,4% in Western Nepal. In Bangladesh, a disparity between health prevention and health spending is observed. The Dhaka study performed within the urban areas had identified G intestinalis in 11% of diarrheal stool specimens.

In Ethiopia, the prevalence has been reported to range from 2,0% to 11,4%. Prevalence of G intestinalis has been reported 13,9% in Côte d'Ivoire.

Life cycle (fig. 15). Cysts are resistant forms and are responsible for transmission of giardiasis. Both cysts and trophozoites can be found in the feces (diagnostic stages). The cysts are hardy and can survive several months in cold water. Infection occurs by the ingestion of cysts in contaminated water, food, or by the fecal-oral route (hands or fomites). In the small intestine, excystation releases trophozoites (each cyst produces two trophozoites). Trophozoites multiply by longitudinal binary fission, remaining in the lumen of the proximal small bowel where they can be free or attached to the mucosa by a ventral sucking disk. Encystation occurs as the parasites transit toward the colon. The cyst is the stage found most commonly in nondiarrheal

feces . Because the cysts are infectious when passed in the stool or shortly afterward, person-to-person transmission is possible. While animals are infected with Giardia, their importance as a reservoir is unclear.

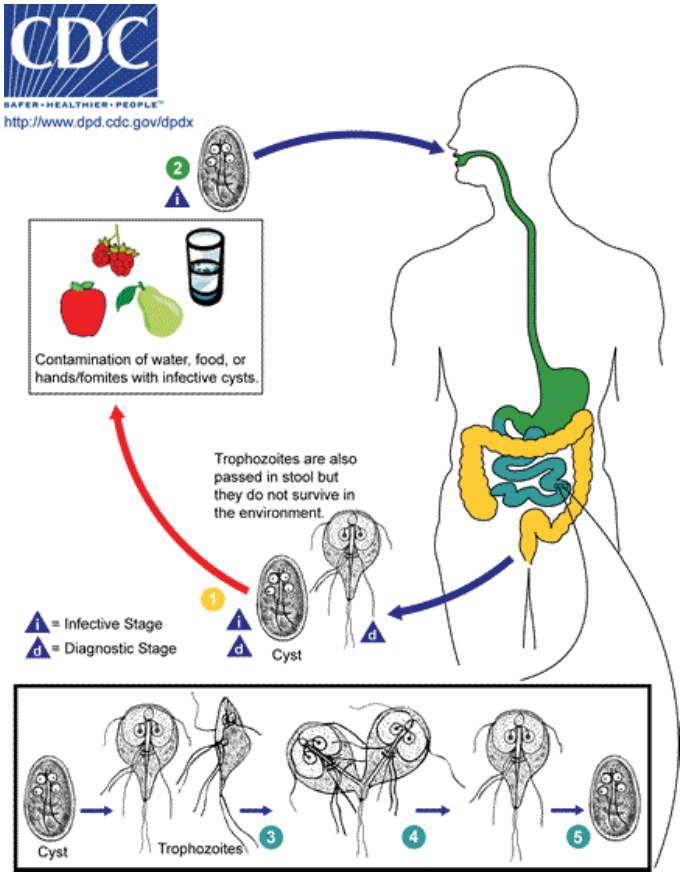

Fig. 15. – Life cycle of Giardia

Pathogenesis. Giardia are flagellated protozoans that cause decreased expression of brush border enzymes, morphological changes to the microvillus, and programmed cell death of small intestinal epithelial cells. There is no invasion of giardia trophozoites, and small intestinal morphology may appear normal in light microscopy.

The attachment of trophozoites causes villus flattening and inhibition of enzymes that break down dissacharide sugars in the intestines. Ultimately, the community of microorganisms that lives in the intestine may overgrow and may be the cause of further symptoms, though this idea has not been fully investigated. The alteration of the villi leads to an inability of nutrient and water absorption from the intestine, resulting in diarrhea, one of the

predominant symptoms. In the case of asymptomatic giardiasis, there can be malabsorption with or without histological changes to the small intestine. The degree to which malabsorption occurs in symptomatic and asymptomatic cases is highly varied.

The species Giardia intestinalis uses enzymes that break down proteins to attack the villi of the brush border and appears to increase crypt cell proliferation and crypt length of crypt cells existing on the sides of the villi. On an immunological level, activated host T lymphocytes attack endothelial cells that have been injured in order to remove the cell. This occurs after the disruption of proteins that connect brush border endothelial cells to one another. The result is heavily increased intestinal permeability.

There appears to be a further increase in programmed cell death by Giardia intestinalis, which further damages the intestinal barrier and increases permeability. There is significant upregulation of the programmed cell death cascade by the parasite, and, furthermore, substantial downregulation of the anti-apoptotic protein Bcl-2 and upregulation of the proapoptotic protein Bax. These connections suggest a role of caspase-dependent apoptosis in the pathogenesis of giardiasis.

Giardia protects its own growth by reducing the formation of the gas nitric oxide by consuming all local arginine, which is the amino acid necessary to make nitric oxide. Arginine starvation is known to be a cause of programmed cell death, and local removal is a strong apoptotic agent.

Clinical presentation. Some people with giardia infection never develop signs or symptoms but still carry the parasite and can spread it to others through their stool. For those who do get sick, signs and symptoms usually appear one to two weeks after exposure and may include:

- Watery, sometimes foul-smelling diarrhea that may alternate with soft, greasy stools
- Fatigue or malaise
- Abdominal cramps and bloating
- Belching gas with a bad taste
- Nausea
- Weight loss.

Signs and symptoms of giardia infection usually last two to four

weeks, but in some people they last longer or recur.

Complications. Giardia infection is almost never fatal in industrialized countries, but it can cause lingering symptoms and serious complications, especially in infants and children. The most common complications include:

Dehydration. Often a result of severe diarrhea, dehydration occurs when the body doesn't have enough water to carry out its normal functions.

Failure to thrive. Chronic diarrhea from giardia infection can lead to malnutrition and harm children's physical and mental development.

Lactose intolerance. Many people with giardia infection develop lactose intolerance – the inability to properly digest milk sugar. The problem may persist long after the infection has cleared.

Diagnosis. The mainstay of diagnosis of giardiasis is microscopic examination of the stool. This can be for motile trophozoites or for the distinctive oval G.lamblia cysts.

The entero-test uses a gelatin capsule with an attached thread. One end is attached to the inner aspect of the patient's cheek, and the capsule is swallowed. Later, the thread is withdrawn and shaken in saline to release trophozoites which can be detected with a microscope.

Immunologic enzyme-linked immunosorbent assay (ELISA) testing is now available. These tests are capable of a 90% detection rate or more.

Because Giardia lamblia is difficult to detect, this often leads to a delay in diagnosis or misdiagnosis; several tests should be conducted over a one-week period.

Treatment. Children and adults who have giardia infection without symptoms usually don't need treatment unless they're likely to spread the parasites. Many people who do have problems often get better on their own in a few weeks.

When signs and symptoms are severe or the infection persists, doctors usually treat giardiasis with medications such as:

Metronidazole (Flagyl). Metronidazole is the most commonly used antibiotic for giardia infection. Side effects may include nausea and a metallic taste in the mouth. Don't drink alcohol while taking this medication. Tinidazole (Tindamax). Tinidazole works as well as metronidazole and has many of the same side effects, but it can be

given in a single dose.

Nitazoxanide (Alinia). Because it comes in a liquid form, nitazoxanide may be easier for children to swallow. Side effects may include nausea, flatulence, yellow eyes and brightly colored yellow urine.

Prevention. No drug can prevent giardia infection. But common-sense precautions can go a long way toward reducing the chances that you'll become infected or spread the infection to others.

Wash your hands. This is the simplest and best way to prevent most kinds of infection. Wash your hands after using the toilet or changing diapers and before eating or preparing food. When soap and water aren't available, alcohol-based sanitizers are an excellent alternative.

Purify wilderness water. Avoid drinking untreated water from shallow wells, lakes, rivers, springs, ponds and streams unless you filter it or boil it for at least 10 minutes at 158 F (70 C) first.

Keep your mouth closed. Try not to swallow water when swimming in pools, lakes or streams.

Use bottled water. When traveling to parts of the world where the water supply is likely to be unsafe, drink and brush your teeth with bottled water that you open yourself. Don't use ice, and avoid raw fruits and vegetables, even those you peel yourself.

Practice safer sex. If you engage in anal sex, use a condom every time. Avoid oral-anal sex unless you're fully protected.

TOXOPLASMOSIS

Toxoplasmosis is caused by the protozoan parasite Toxoplasma gondii. In the United States it is estimated that 22,5% of the population 12 years and older have been infected with Toxoplasma. In various places throughout the world, it has been shown that up to 95% of some populations have been infected with Toxoplasma. Infection is often highest in areas of the world that have hot, humid climates and lower altitudes. Toxoplasmosis is not passed from person-to-person, except in instances of mother-to-child (congenital) transmission and blood transfusion or organ transplantation.

Epidemiology. People typically become infected by three principal routes of transmission: foodborne, animal-to-human (zoonotic), mother-to-child (congenital). Always cook meat

thoroughly and use clean knives, utensils and cutting boards on all foods. The tissue form of the parasite (a microscopic cyst consisting of bradyzoites) can be transmitted to humans by food. People become infected by: Eating undercooked, contaminated meat (especially pork, lamb, and venison). Accidental ingestion of undercooked, contaminated meat after handling it and not washing hands thoroughly (Toxoplasma cannot be absorbed through intact skin). Eating food that was contaminated by knives, utensils, cutting boards, or other foods that had contact with raw, contaminated meat.

Cats play an important role in the spread of toxoplasmosis. They become infected by eating infected rodents, birds, or other small animals. The parasite is then passed in the cat's feces in an oocyst form, which is microscopic. Kittens and cats can shed millions of oocysts in their feces for as long as 3 weeks after infection. Mature cats are less likely to shed Toxoplasma if they have been previously infected. A Toxoplasma-infected cat that is shedding the parasite in its feces contaminates the litter box. If the cat is allowed outside, it can contaminate the soil or water in the environment as well. People can accidentally swallow the oocyst form of the parasite. People can be infected by: Accidental ingestion of oocysts after cleaning a cat's litter box when the cat has shed Toxoplasma in its feces. Accidental ingestion of oocysts after touching or ingesting anything that has come into contact with a cat's feces that contain Toxoplasma. Accidental ingestion of oocysts in contaminated soil (e.g., not washing hands after gardening or eating unwashed fruits or vegetables from a garden). Drinking water contaminated with the Toxoplasma parasite.

Mother-to-child (congenital) transmission. A woman who is newly infected with Toxoplasma during pregnancy can pass the infection to her unborn child (congenital infection). The woman may not have symptoms, but there can be severe consequences for the unborn child, such as diseases of the nervous system and eyes.

Rare instances of transmission. Organ transplant recipients can become infected by receiving an organ from a Toxoplasma-positive donor. Rarely, people can also become infected by receiving infected blood via transfusion. Laboratory workers who handle infected blood can also acquire infection through accidental inoculation.

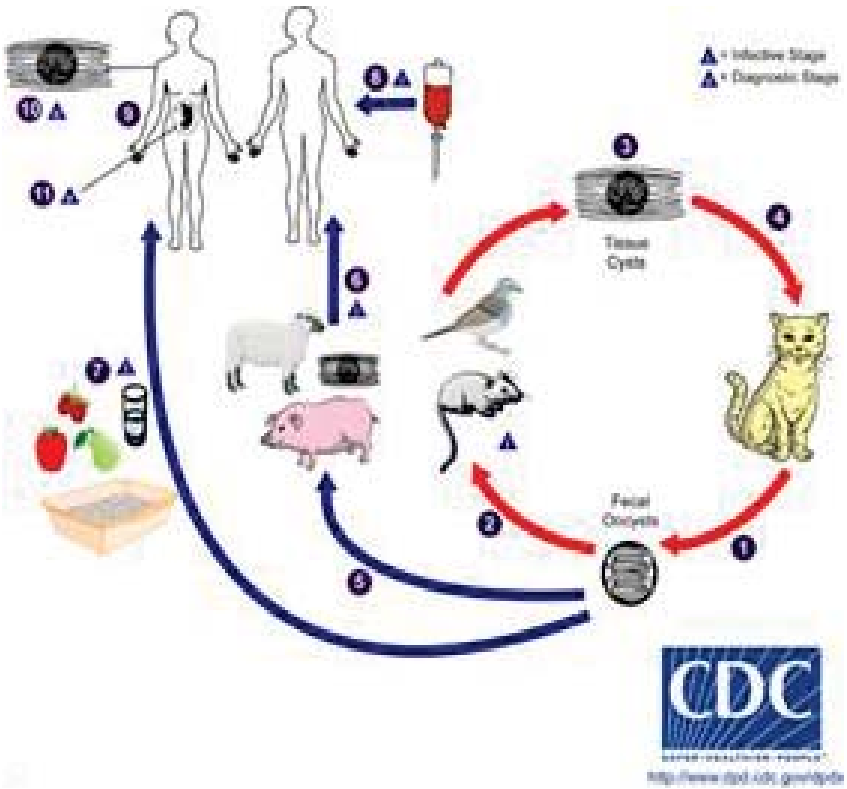

Fig. 16. – *Life Cycle of* Toxoplasma gondii

Causal Agent. Toxoplasma gondii is a protozoan parasite that infects most species of warm blooded animals, including humans, and can cause the disease toxoplasmosis.

The only known definitive hosts for Toxoplasma gondii are members of family Felidae (domestic cats and their relatives). Unsporulated oocysts are shed in the cat's feces. Although oocysts are usually only shed for 1-2 weeks, large numbers may be shed. Oocysts take 1-5 days to sporulate in the environment and become infective. Intermediate hosts in nature (including birds and rodents) become infected after ingesting soil, water or plant material contaminated with oocysts. Oocysts transform into tachyzoites shortly after ingestion. These tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. Cats become infected after consuming intermediate hosts harboring tissue cysts. Cats may also become infected directly by ingestion of sporulated oocysts. Animals bred for human consumption and wild game may also become infected with tissue cysts after ingestion of sporulated oocysts in the environment. Humans can become infected by any of several routes: eating undercooked meat of animals harboring tissue cysts; onsuming food or water contaminated with cat feces or by contaminated environmental

samples (such as fecal-contaminated soil or changing the litter box of a pet cat); blood transfusion or organ transplantation; transplacentally from mother to fetus.

In the human host, the parasites form tissue cysts, most commonly in skeletal muscle, myocardium, brain, and eyes; these cysts may remain throughout the life of the host. Diagnosis is usually achieved by serology, although tissue cysts may be observed in stained biopsy specimens. Diagnosis of congenital infections can be achieved by detecting T. gondii DNA in amniotic fluid using molecular methods such as PCR.

Clinical presentation.

Healthy people who become infected with Toxoplasma gondii often do not have symptoms because their immune system usually keeps the parasite from causing illness. Only 10-20% of toxoplasmosis cases in adults and children are symptomatic. Toxoplasmosis is a serious and often life-threatening disease in immunodeficient patients. When illness occurs, it is usually mild with "flu-like" symptoms (e.g., tender lymph nodes, muscle aches, etc.) that last for several weeks and then go away. However, the parasite remains in their body in an inactive state. It can become reactivated if the person becomes immunosuppressed.

Acute toxoplasmosis in immunocompetent persons

• Approximately 80-90% of patients are asymptomatic. Symptomatic disease may be characterized as follows:

• Patients may have cervical lymphadenopathy with discrete, usually nontender, nodes smaller than 3cm in diameter

• Fever, malaise, night sweats, and myalgias have been reported

• Patients may have a sore throat

• Retroperitoneal and mesenteric lymphadenopathy with abdominal pain may occur

• Retinochoroiditis is reported.

Congenital toxoplasmosis may manifest as a mild or severe neonatal disease, with onset during the first month of life or with sequelae or relapse of a previously undiagnosed infection at any time during infancy or later in life. Congenital toxoplasmosis has a wide variety of manifestations during the perinatal period. This is most severe when maternal infection occurs early in pregnancy. Approximately 15-55% of congenitally infected children do not have detectable T gondii – specific IgM antibodies at birth or early infancy.

Approximately 67% of patients have no signs or symptoms of infection.

Retinochoroiditis occurs in about 15% of patients, and intracranial calcifications develop in about 10%. Cerebrospinal fluid (CSF) pleocytosis and elevated protein values are present in 20% of patients.

Infected newborns have anemia, thrombocytopenia, and jaundice at birth. Microcephaly has been reported. Affected survivors may have mental retardation, seizures, visual defects, spasticity, hearing loss or other severe neurologic sequelae.

The prevalence of sensorineural hearing loss is as high as 28% in children who do not receive treatment. Generally if a woman has been infected before becoming pregnant, the unborn child will be protected because the mother has developed immunity. If a woman is pregnant and becomes newly infected with Toxoplasma during or just before pregnancy, she can pass the infection to her unborn baby (congenital transmission). The damage to the unborn child is often more severe the earlier in pregnancy the transmission occurs. Potential results can be a miscarriage, a stillborn child, a child born with signs of toxoplasmosis (e.g., abnormal enlargement or smallness of the head).

Infants infected before birth often show no symptoms at birth but may develop them later in life with potential vision loss, mental disability, and seizures.

Persons with ocular disease. Eye disease (most frequently retinochoroiditis) from Toxoplasma infection can result from congenital infection or infection after birth by any of the modes of transmission discussed on the epidemiology and risk factors page. Eye lesions from congenital infection are often not identified at birth but occur in 20-80% of infected persons by adulthood. However, in the U.S. <2% of persons infected after birth develop eye lesions. Eye infection leads to an acute inflammatory lesion of the retina, which resolves leaving retinochoroidal scarring. Symptoms of acute disease include eye pain, sensitivity to light (photophobia), earing of the eyes, blurred vision. The eye disease can reactivate months or years later, each time causing more damage to the retina. If the central structures of the retina are involved there will be a progressive loss of vision that can lead to blindness.

Persons with compromised immune systems. Persons with compromised immune systems may experience severe symptoms if

they are infected with Toxoplasma while immune suppressed. For example, a person who is HIV-infected and who has reactivated Toxoplasma infection can have symptoms that include fever, confusion, headache, seizures, nausea, and poor coordination. Persons who acquire HIV infection and were not infected previously with Toxoplasma are more likely to develop a severe primary infection.

Diagnosis. A Toxoplasma-positive reaction, stained by immunofluroescence (IFA). The diagnosis of toxoplasmosis is typically made by serologic testing. A test that measures immunoglobulin G (IgG) is used to determine if a person has been infected. If it is necessary to try to estimate the time of infection, which is of particular importance for pregnant women, a test which measures immunoglobulin M (IgM) is also used along with other tests such as an avidity test.

Diagnosis can be made by direct observation of the parasite in stained tissue sections, cerebrospinal fluid (CSF), or other biopsy material. These techniques are used less frequently because of the difficulty of obtaining these specimens.

Parasites can also be isolated from blood or other body fluids (for example, CSF) but this process can be difficult and requires considerable time.

Molecular techniques that can detect the parasite's DNA in the amniotic fluid can be useful in cases of possible mother-to-child (congenital) transmission.

Ocular disease is diagnosed based on the appearance of the lesions in the eye, symptoms, course of disease, and often serologic testing.

Treatment of immunocompetent adults with lymphadenopathic toxoplasmosis is rarely indicated; this form of the disease is usually self-limited. If visceral disease is clinically evident or symptoms are severe or persistent, treatment may be indicated for 2 to 4 weeks. Treatment for ocular diseases should be based on a complete ophthalmologic evaluation. The decision to treat ocular disease is dependent on numerous parameters including acuteness of the lesion, degree if inflamation, visual acuity, and lesion size, location, and persistance (for example, "classic therapy" for ocular toxoplasmosis, adults: pyrimethamine 100 mg for 1 day as a loading dose, then 25 to 50 mg per day, plus sulfadiazine 1 gram four times per day, plus folinic acid (leucovorin) 5-25 mg with each dose of pyrimethamine; pediatric dose: pyrimethamine 2 mg/kg first day then 1 mg/kg each

day, plus sulfadiazine 50 mg/kg two times per day, plus folinic acid (leucovorin) 7,5 mg per day) for 4 to 6 weeks followed by reevaluation of the patient's condition. Leucovorin protects the bone marrow from the toxic effects of pyrimethamine. If the patient has a hypersensitivity reaction to sulfa drugs, pyrimethamine plus clindamycin can be used instead. The fixed combination of trimethoprim with sulfamethoxazole has been used as an alternative, as well as other drugs such as atovaquone and pyrimethamine plus azithromycin, which have not been extensively studied .

Therapy for ocular toxoplasmosis. Ocul Immunol Inflamm. Corticosteroids are sometimes prescribed in addition to antiparasitic agents.

Management of maternal and fetal infection varies depending on the treatment center. In general, spiramycin is recommended (for the first and early second trimesters) or pyrimethamine/sulfadiazine and leucovorin (for late second and third trimesters) for women with acute T. gondii infection diagnosed at a reference laboratory during gestation. PCR is often performed on the amniotic fluid at 18 gestation weeks to determine if the infant is infected. If the infant is likely to be infected, then treatment with drugs such as pyrimethamine, sulfadiazine, and leucovorin is typical. Congenitally infected newborns are generally treated with pyrimethamine, a sulfonamide, and leucovorin for 1 year.

Persons with AIDS who develop active toxoplasmosis (usually toxoplasmic enchephalitis) need treatment that must be taken until a significant immunologic improvement is achieved as a result of antiretroviral therapy (see Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents). Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.

Toxoplasma gondii Encephalitis in HIV-infected persons. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts. Primary infection occasionally is associated with acute cerebral or disseminated disease.

Epidemiology. Seroprevalence varies substantially among different communities (e.g., approximately 15% in the United States and 50-75% in certain European countries). In the pre-ART era, for patients with advanced immunosuppression who were seropositive for

T. gondii and not receiving prophylaxis with drugs active against T. gondii, the 12-month incidence of TE was approximately 33%. The incidence of toxoplasmosis in patients who are seronegative for T. gondii is low. If well-documented cases did occur among seronegative patients, they would presumably represent either primary infection, reactivation of latent disease in patients unable to produce detectable antibody, or patients who were tested with insensitive assays. The incidence and associated mortality in Europe and the United States have decreased substantially with the initiation of ART and the broad use of prophylaxis regimens active against T. gondii.

Clinical disease is rare among patients with CD4+ counts >200 cells/µL. The greatest risk occurs among patients with a CD4+ count <50 cells/µL. Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and have sporulated in the environment (sporulation requires at least 24 hours). No transmission of the organism occurs by person-to-person contact.

Clinical Manifestations. Brain involvement (ie, toxoplasmic encephalitis), with or without focal CNS lesions, is the most common manifestation of toxoplasmosis in individuals with AIDS. Clinical findings include the following: altered mental state, seizures, weakness, cranial nerve disturbances, sensory abnormalities, cerebellar signs, meningismus, movement disorders, neuropsychiatricmanifestations.

The characteristic presentation is usually a subacute onset, with focal neurologic abnormalities in 58-89% of cases. However, in 15-25% of cases, the clinical presentation is more abrupt, with seizures or cerebral hemorrhage. Most commonly, hemiparesis and/or speech abnormality is the major initial manifestation.

Brainstem involvement often produces cranial nerve lesions, and many patients exhibit cerebral dysfunction with disorientation, altered mental state, lethargy, and coma.

Less commonly, parkinsonism, focal dystonia, rubral tremor, hemichorea-hemiballismus, panhypopituitarism, diabetes insipidus, or syndrome of inappropriate antidiuretic hormone secretion may dominate the clinical picture.

In some patients, neuropsychiatric symptoms such as paranoid psychosis, dementia, anxiety, and agitation may be the major manifestations.

Diffuse toxoplasmic encephalitis may develop acutely and can be rapidly fatal; generalized cerebral dysfunction without focal signs is the most common manifestation, and CT scan findings are normal or reveal cerebral atrophy.

Spinal cord involvement manifests as motor or sensory disturbances of single or multiple limbs, bladder or bowel dysfunctions, or both and local pain. Patients may present with clinical findings similar to those of a spinal cord tumor. Cervical myelopathy, thoracic myelopathy, and conus medullaris syndrome have been reported.

Pulmonary toxoplasmosis (pneumonitis) due to toxoplasmosis is increasingly recognized in patients with AIDS who are not receiving appropriate anti-HIV drugs or primary prophylaxis for toxoplasmosis. The diagnosis may be confirmed by demonstrating T gondii in bronchoalveolar lavage fluid.

Pulmonary toxoplasmosis occurs mainly in patients with advanced AIDS (mean CD4+ count of 40 cells/µL ±75 standard deviation) and primarily manifests as a prolonged febrile illness with cough and dyspnea. Pulmonary toxoplasmosis may be clinically indistinguishable from P (carinii) jiroveci pneumonia, and the mortality rate, even when treated appropriately, may be as high as 35%.

Extrapulmonary toxoplasmosis develops in approximately 54% of persons with toxoplasmic pneumonitis.

Ocular toxoplasmosis, ie, toxoplasmic retinochoroiditis, is relatively uncommon in patients with AIDS; it commonly manifests as ocular pain and loss of visual acuity. Funduscopic examination usually demonstrates necrotizing lesions, which may be multifocal or bilateral. Overlying vitreal inflammation is often present and may be extensive. The optic nerve is involved in as many as 10% of cases.

Other, uncommon manifestations of toxoplasmosis in patients with AIDS include the following:

- Panhypopituitarism and diabetes insipidus
- Multiple organ involvement, with the disease manifesting as acute respiratory failure and hemodynamic abnormalities similar to septic shock
- Syndrome of inappropriate antidiuretic hormone secretion and possibly orchitis
- Gastrointestinal system invasion of T gondii may result in

abdominal pain, diarrhea, and/or ascites (due to involvement of the stomach, peritoneum, or pancreas)

- Acute hepatic failure
- Musculoskeletal involvement
- Parkinsonism
- Focal dystonia
- Rubral tremor
- Hemichorea-hemiballismus. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can be observed after dissemination of infection but are rare manifestations in this patient population. CT scan or MRI of the brain will typically show multiple contrast-enhancing lesions, often with associated edema. However, toxoplasmosis also can manifest as single lesions in the brain.

Diagnosis. HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies. The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent. Quantitative antibody titers are not diagnostically useful. Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. For TE, this requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Organisms are demonstrable with hematoxylin and eosin stains, although immunoperoxidase staining by experienced laboratories might increase sensitivity. Detection of T. gondii by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) has produced disappointing results; although specificity is high (96-100%), sensitivity is low (50%) and the results usually are negative once specific anti-toxoplasma therapy has been started.

The differential diagnosis of focal neurological disease in patients with AIDS includes central nervous system (CNS) lymphoma; mycobacterial infection (especially TB); fungal infection (e.g., cryptococcosis); Chagas disease; bacterial abscess; and rarely PML, which can be distinguished on the basis of imaging studies (PML lesions typically involve white matter rather than gray matter, are noncontrast enhancing, and produce no mass effect).

The majority of clinicians rely initially on an empiric diagnosis,

which can be established as an objective response, on the basis of clinical and radiographic improvement, to specific anti-T. gondii therapy in the absence of a likely alternative diagnosis. Brain biopsy is reserved for patients who fail to respond to specific therapy. In patients with contrast-enhancing mass lesions, detection of Epstein-Barr virus (EBV) by PCR in CSF is highly suggestive of CNS lymphoma. Positron emission tomography (PET) (192) or single-photon emission computed tomography (SPECT) scanning (193) might be helpful for distinguishing between TE and primary CNS lymphoma, but no imaging technique is completely specific.

Preventing Exposure. HIV-infected persons should be tested for IgG antibody to Toxoplasma soon after the diagnosis of HIV infection to detect latent infection with T. gondii. HIV-infected persons, including those who lack IgG antibody to Toxoplasma, should be counseled regarding sources of Toxoplasma infection.

Preventing Disease. Toxoplasma-seropositive patients who have a CD4+ count of <100 cells/μL should be administered prophylaxis against TE. The double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for PCP prophylaxis also is effective against TE and is therefore recommended. TMP-SMX, one double-strength tablet three times weekly, is an alternative. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP. Atovaquone with or without pyrimethamine/leucovorin also can be considered. Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against TE and is not recommended.

Toxoplasma-seronegative persons who are not taking a PCP prophylactic regimen known to be active against TE (e.g., aerosolized pentamidine) should be retested for IgG antibody to Toxoplasma when their CD4+ counts decline to <100 cells/μL to determine whether they have seroconverted and are therefore at risk for TE. Patients who have seroconverted should be administered prophylaxis for TE as described previously.

CRYPTOSPORIDIOSIS

Cryptosporidium is a microscopic parasite that causes the diarrheal disease cryptosporidiosis. Both the parasite and the disease are commonly known as "Crypto." There are many species of Cryptosporidium that infect humans and animals. The parasite is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it very tolerant to chlorine disinfection.

The parasite is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it very resistant to chlorine-based disinfectants. During the past 2 decades, Crypto has become recognized as one of the most common causes of waterborne disease (recreational water and drinking water) in humans in the United States. The parasite is found in every region of the United States and throughout the world.

Epidemiology. Cryptosporidium lives in the intestine of infected humans or animals. An infected person or animal sheds Crypto parasites in the stool. Millions of Crypto germs can be released in a bowel movement from an infected human or animal. Cryptosporidium may be found in soil, food, water, or surfaces that have been contaminated with the feces from infected humans or animals. Transmission of Cryptosporidium parvum and C. hominis occurs mainly through contact with contaminated water (e.g., drinking or recreational water). Occasionally food sources, such as chicken salad, may serve as vehicles for transmission. Many outbreaks in the United States have occurred in waterparks, community swimming pools, and day care centers. Zoonotic and anthroponotic transmission of C. parvum and anthroponotic transmission of C. hominis occur through exposure to infected animals or exposure to water contaminated by feces of infected animals. Crypto can be spread:

Life cycle (fig. 16). Sporulated oocysts, containing 4 sporozoites, are excreted by the infected host through feces and possibly other routes such as respiratory secretions. Following ingestion (and possibly inhalation) by a suitable host, excystation occurs. The sporozoites are released and parasitize epithelial cells of the gastrointestinal tract or other tissues such as the respiratory tract. In these cells, the parasites undergo asexual multiplication (schizogony or merogony) and then sexual multiplication (gametogony) producing

microgamonts (male) and macrogamonts (female).

Upon fertilization of the macrogamonts by the microgametes, oocysts develop that sporulate in the infected host. Two different types of oocysts are produced, the thick-walled, which is commonly excreted from the host, and the thin-walled oocyst, which is primarily involved in autoinfection. Oocysts are infective upon excretion, thus permitting direct and immediate fecal-oral transmission.

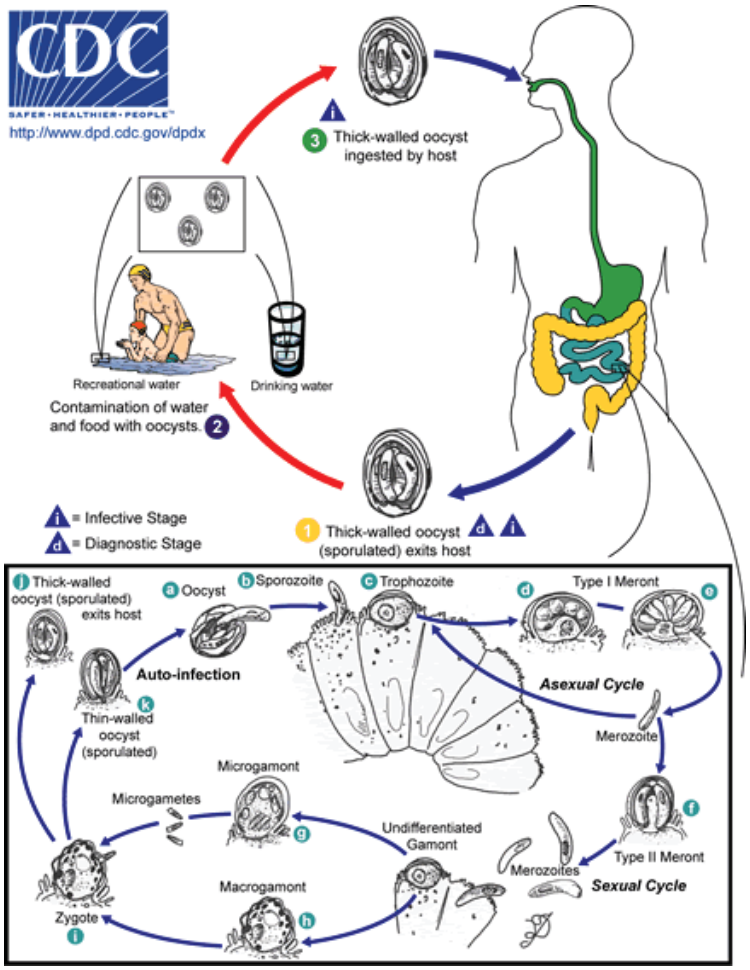

Fig. 17. – ***Life cycle of Crypto***

Note that oocysts of Cyclospora cayetanensis, another important coccidian parasite, are unsporulated at the time of excretion and do not become infective until sporulation is completed.

People who are in poor health or who have weakened immune systems are at higher risk for more severe and more prolonged illness.

Clinical manifestation. Symptoms of cryptosporidiosis generally begin 2 to 10 days (average 7 days) after becoming infected with the parasite. The most common symptom of cryptosporidiosis is

watery diarrhea. Other symptoms include: stomach cramps or pain, dehydration, nausea, vomiting, fever, weight loss. Some people with Crypto will have no symptoms at all.

Symptoms usually last about 1 to 2 weeks (with a range of a few days to 4 or more weeks) in persons with healthy immune systems. Occasionally, people may experience a recurrence of symptoms after a brief period of recovery before the illness ends. Symptoms can come and go for up to 30 days.

While the small intestine is the site most commonly affected, Cryptosporidium infections could possibly affect other areas of the digestive tract or the respiratory tract.

People with weakened immune systems may develop serious, chronic, and sometimes fatal illness. Examples of people with weakened immune systems include: people with AIDS; those with inherited diseases that affect the immune system; and cancer and transplant patients who are taking certain immunosuppressive drugs. The risk of developing severe disease may differ depending on each person's degree of immune suppression.

Cryptosporidiosis in HIV-infected persons. Persons at greatest risk for disease have advanced immunosuppression, typically CD4+ counts of <100 cells/μL. The three most common species infecting humans are C. hominis, C. parvum, and C. meleagridis. Infections are usually caused by one species but might be mixed.

In developed countries with low rates of environmental contamination where potent ART is widely available, cryptosporidiosis occurs at an incidence of <1 per 100 person-years among persons with AIDS. Infection occurs through ingestion of Cryptosporidium oocysts. Viable oocysts in feces can be transmitted directly through contact with infected humans or animals, particularly those with diarrhea. Oocysts can contaminate recreational water sources (e.g., swimming pools, lakes) and public water supplies and might persist despite standard chlorination (see Appendix: Food and Water-Related Exposures). Person-to-person transmission is common, especially among sexually active men who have sex with men (MSM). Young children with cryptosporidial diarrhea might infect adults during diapering and cleaning after defecation.

Clinical Manifestations. Patients with cryptosporidiosis most commonly have acute or subacute onset of profuse, nonbloody, watery diarrhea, accompanied often by nausea, vomiting, and lower

abdominal cramping. Fever is present in approximately one third of patients and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with Cryptosporidium, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4+ counts. Pulmonary infections also have been reported.

Diagnosi. Cryptosporidium species can be cultivated in vitro, but not as a routine diagnostic procedure. Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue. Acid-fast staining methods, with or without stool concentration, are most frequently used in clinical laboratories. Oocysts stain varying intensities of red with a modified acid-fast technique, permitting their differentiation from yeasts, which are of similar size and shape but are not acid fast. Cryptosporidium oocysts also can be detected by direct immunofluorescence, which offers the greatest sensitivity and specificity, or by enzyme-linked immunosorbent assays (ELISAs). Molecular methods such as PCR are predicted to enhance sensitivity further. Cryptosporidial enteritis also can be diagnosed from small intestinal biopsy sections. The organism, which appears basophilic with hematoxylin and eosin staining, occurs alone or in clusters in various developmental stages on the brush border of the mucosal epithelial surfaces.

Among persons with profuse diarrheal illness, a single stool specimen is usually adequate for diagnosis. Among persons with milder disease, repeat stool sampling is recommended, although no controlled studies have demonstrated the utility of three consecutive stool samples as is the case in Giardia duodenalis infection.

Preventing Exposure. HIV-infected persons should be educated and counseled concerning the different ways that Cryptosporidium can be transmitted.

HIV-infected persons (particularly those with CD4+ counts < 200 cells/μL), should avoid direct contact with diarrhea or stool from pets, particularly any stray pets, or dogs and cats aged <6 months. HIV-infected persons should not drink water directly from lakes or rivers. HIV-infected persons should be aware that lakes, rivers, and salt water beaches and some swimming pools, recreational water parks, and ornamental water fountains might be contaminated with human or animal waste that contains Cryptosporidium. They should avoid swimming in water that is likely contaminated and should avoid

swallowing water while swimming or playing in recreational water.

HIV-infected persons should avoid eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters taken from certain commercial oyster beds. In a hospital, standard precautions (i.e., use of gloves and handwashing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person. However, because of the potential for fomite transmission, some specialists recommend that HIV-infected persons, specifically persons who are severely immunocompromised, should not share a room with a patient with cryptosporidiosis.

If HIV-infected persons travel in developing countries, they should be warned to avoid drinking tap water or using tap water to brush their teeth.

Preventing Disease. Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, appropriate initiation of ART before the patient becomes severely immunosuppressed should prevent this disease. Rifabutin or clarithromycin, when taken for MAC prophylaxis, have been found to protect against cryptosporidiosis.

Treatment of Disease. In the setting of severe immunosuppression, ART with immune restoration to a CD4+ count >100 cells/μL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection. Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or IV route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions.

No pharmacologic or immunologic therapy directed specifically against C. parvum has been shown to be consistently effective when used without ART.

Nitazoxanide is an orally administered nitrothiazole benzamide with in vivo activity against a broad range of helminths, bacteria, and protozoa. When administered for 3 days at 500 mg twice daily to HIV-uninfected adults with cryptosporidiosis, nitazoxanide resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.

HIV-infected adults with cryptosporidiosis with CD4+ >50 cells/μL treated with 500--1,000 mg twice daily of nitazoxanide for 14 days experienced substantially higher rates of parasitological cure and resolution of diarrhea than persons receiving placebo treatment . Data from a compassionate use program before the advent of combination ART, which included primarily white male adults with a median CD4+ count <50 cells/μL, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment. Adverse events associated with nitazoxanide are limited and typically mild, and no important drug-drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, a trial of nitazoxanide in conjunction with ART, but never instead of ART, may be considered.

Treatment with antimotility agents (e.g., loperamide, tincture of opium) can palliate symptoms by reducing diarrheal frequency and volume, but these agents are not consistently effective. Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved for the treatment of secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents and is usually not recommended.

NEMATODE INFECTION

GENERAL CHARACTERISTICS OF NEMATODE INFECTION

The phylum Nematoda includes both free-living and parasitic species, which are widely distributed in nature. The diseases they cause rank among the most prevalent communicable infections, with more than one billion people worldwide infected. The geographic distribution of roundworms in many tropical and subtropical regions closely parallels socioeconomic and sanitary conditions. In certain locales, coinfection with Ascaris lumbricoides, Trichuris trichiura, and hookworms is common. Although many subjects are asymptomatic, those with a high worm burden, especially children, may suffer significant morbidity including anemia, malnutrition, and impaired physical and cognitive development. Constant reinfection is common in most endemic areas; thus, periodic treatment regimens that result in

reductions in parasitic burden may be more practical than attempts to completely eliminate infection.

The roundworms are true geohelminths, which have no intermediate host but have eggs, or in the case of Strongyloides, larva and adults which may survive in soil for days to years.

FILARIASIS

Filarial parasites infect approximately 200 million humans worldwide although mansonellosis is thought to cause insignificant clinical disease. Chronic filariasis, although not responsible for significant mortality, is associated with tremendous suffering and long-term debility in diverse populations, with a resultant adverse socioeconomic impact on afflicted individuals and their communities.

Non-human Brugia, Dirofilaria, Mansonella species are most commonly implicated. Pathologic identification requires expert consultation. Filarial parasites may be classified according to the habitat of the adult worms in the vertebral host:

The cutaneous group: includes Loa loa, Onchocerca volvulus, and Mansonella streptocerca.

The lymphatic group: includes Wuchereria bancrofti, Brugia malayi, and Brugia timori.

The body-cavity group: includes Mansonella perstans and Mansonella ozzardi.

All human infections are caused by filariae of the family Onchocercidae. The long, thin adult worms reside in the subcutaneous tissues, lymphatics, or peritoneum. Female adults are usually much larger than males because of the large number of larvae contained in the uteri. Sexual reproduction yields microfilariae, the usual diagnostic stage, which migrates in the blood or skin. These microfilariae are ingested by an obligate, bloodsucking arthropod that serves as an intermediate host within which the microfilariae develop into third-stage larvae. These infective larvae escape from the insect at the time of feeding and then migrate within the human host to the tissues or lymphatics, where they develop into adult worms. Generally, repeated and prolonged exposure to infective larvae is required for establishment of human infection. Incubation periods range from 3 to 12 months so a history of remote exposure must be

elicited in travelers. Adult worms live for 5 to 15 years but because an individual adult worm cannot multiply within the same host, an increased parasite burden requires ongoing re-infection (table 14).

Clinical disease varies between species and results from the host's immune response to either the migrating microfilariae or dying adult parasites. In advanced lymphatic filariasis, bacterial superinfection of compromised vessels plays an important role.

Table 15. – Characteristics of Human Filarial Infections

Organism	***Geographic distribution***	***Habitat of adult worms***	***Vector***	***Location of microfilariae***	***Periodicity of microfilariae***
Wuchereria bancrofti	Worldwide, tropics and subtropics	Lymphatic system	Mosquitoes: *Culex, Anopheles, Aedes* sp.	Blood	Nocturnal; South Pacific form is subperiodic
Brugia malayi	Southeast Asia, India, western Pacific	Lymphatic system	Mosquitoes: *Anopheles, Mansonia* sp.	Blood	Nocturnal
Brugia timori	Islands of Timor and Flores	Lymphatic system	Mosquitoes: *Anopheles* sp.	Blood	Nocturnal
Onchocerca volvulus	Africa, Latin America	Subcutaneous tissues	*Simulium* sp. (black flies)	Skin	None
Loa loa	West and Central Africa	Subcutaneous tissues	*Chrysops* sp. (deer flies)	Blood	Diurnal
Mansonella perstans	Africa, Central and South America	Body cavities, mesenteric and retroperitoneal tissues	*Culicoides* sp. (biting midges)	Blood	None
Mansonella streptocerca	West and Central Africa	Subcutaneous tissues	*Culicoides* sp.	Skin	None
Mansonella ozzardi	Caribbean, Central and South America	Subcutaneous tissues	*Culicoides* and *simulium* sp.	Blood	None

Lymphatic filariasis (LF). Lymphatic filariasis remains a major cause of overt or hidden clinical disease in much of Asia, Africa, the Western Pacific and certain parts of the Americas. It is the second leading cause of permanent long-term disability. The prevalence is increasing world-wide, with at least 120 million people affected at different stages of the disease. W. bancrofti, which has no animal reservoir, is endemic in 76 countries in Africa, South America, the Caribbean, the Indian subcontinent, Southeast Asia, and the western Pacific. B. malayi is endemic in India, Southeast Asia, and the western Pacific; B. timori is localized to the islands of Timor and Flores in the Indonesian archipelago. Newer, more sensitive diagnostic techniques

suggest that the number of people with lymphatic filariasis is considerably underestimated. Filarial infections are usually first detected in asymptomatic 5- to 10-year-old children in endemic regions.

More than 100 filarial species of animals are described. When these parasites accidentally enter humans the larvae quickly die in tissues and on occasion cause an inflammatory response, which comes to clinical attention.

Wuchereria bancrofti and Brugia malayi are the main causes of lymphatic filariasis in humans, although other minor members of the genus Brugia, such as Brugia timori, can cause human disease. These threadlike nematodes infect approximately 120 million people worldwide and are responsible for a spectrum of disease ranging from asymptomatic infections with microfilaremia to disfiguring lymphatic obstructive disease including elephantiasis.

W. bancrofti usually shows nocturnal periodicity; microfilariae appear in the peripheral circulation late at night. Culex and Anopheles mosquitoes transmit this form of W. bancrofti, which is mainly present in Africa, India, Southeast Asia, and Latin America. A diurnal form of infection caused by W. bancrofti exists in the South Pacific; this is transmitted by day-biting Aedes mosquitoes. B. malayi infections with nocturnal periodicity, transmitted by Anopheles and Mansonia mosquito species, are found in areas of India, Sulawesi, Vietnam, and China. A less common subperiodic form characterized by less exaggerated fluctuations in microfilarial blood density is found in areas of Southeast Asia where it is associated with numerous animal reservoirs. B. timori demonstrates nocturnal periodicity and is transmitted by anopheline mosquitoes.

Life cycle of the worm.

The adult worms live in the lumen of lymphatic vessels. The females measure 4 to 10 cm in length; the W. bancrofti females are longer than those of B. malayi, whereas the males are about 4 and 1,5 cm long, respectively. The adult parasites are thin; the females measure approximately 250 and 150 Bμm in diameter, respectively. The adult worms reproduce sexually to yield large numbers of microfilariae or first-stage larvae, which migrate into the bloodstream. When mosquitoes take a blood meal from infected humans, they ingest the microfilariae, which then undergo two molts to become infective third-stage larvae during a 10- to 20-day period.

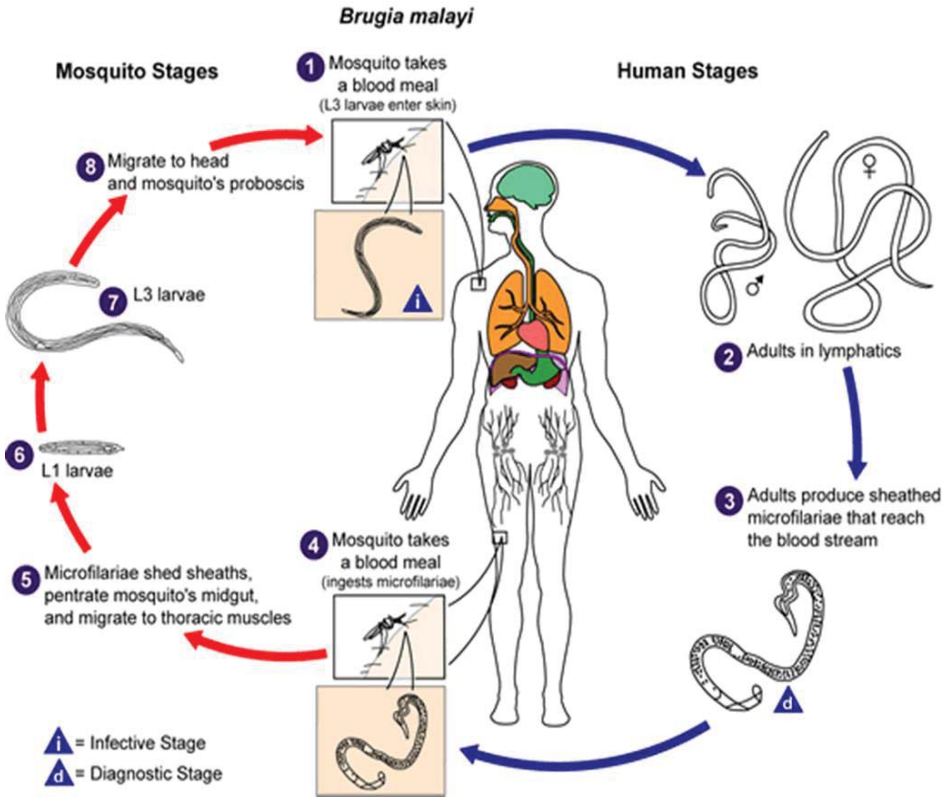

Fig. 18. – Life Cycle of Brugia malayi

The infective larvae are deposited onto the skin during the mosquitos' next blood meal. The larvae crawl into the open wound, migrate through the subcutaneous tissues, and finally reach the peripheral lymphatics where they mature into adult worms. Microfilariae are released into the blood stream approximately 6 to 12 months after the infecting bite.

Pathogenesis. Microfilariae in blood do not cause any pathology. The adult worm does not seem to cause blockage of the vessel. The adult lymphatic parasite causes a parasite-specific local inflammatory reaction with both cell-mediated and humoral components, which lead to hypertrophy of the vessel walls. This results in vessel dilatation and intraluminal polyposis, which diminish normal lymphatic function. The resulting lymphedema is reversible in its early stages. Following worm death there is necrosis and granulomatous reaction with infiltration of plasma cells, eosinophils, and giant cells. With progression, fibrosis and obstruction of lymph flow within the vessel leads to irreversible elephantiasis of the affected part. At an uncertain point during the clinical evolution of the lymphatic insufficiency, repeated limb bacterial infections in

previously damaged vessels may in some individuals become superimposed on other processes. The relative contribution to disease evolution of each of the components and the degree of interindividual variability are incompletely defined at present. Recently, Wolbachia, which are symbiotic bacteria coexisting inside filarial worms, have been implicated as factors in filarial inflammation in animal models but relevance in human disease is not yet established (4).

Clinical Manifestations. Most infected individuals remain clinically asymptomatic microfilaria carriers even though sub-clinical lymphatic damage is often present. Those with clinical manifestations present a spectrum of disease including filarial fevers, acute adenolymphangitis, chronic lymphatic obstruction, and tropical pulmonary eosinophilia.

In the early stages of disease a syndrome of ***filarial fevers*** characterized by general malaise, low-grade fevers, headaches, and pain associated with lymphangitis or lymphadenitis can occur. Affected lymph nodes may be enlarged and tender, and the skin overlying infected lymphatics may be thickened, firm, tender, and edema-tous.

Acute episodes of filarial inflammation due to W. bancrofti frequently affect the male genitalia and can lead to complications including funiculitis, epididymitis, orchitis, hydrocele, and elephantiasis of the scrotum. In many areas the most common chronic manifestation of disease is hydrocele with no history of acute inflammatory episodes. A genital examination is mandatory in all males in endemic areas. Chyluria may develop if the obstructed, swollen lymphatic channels rupture into the urinary tract. The legs are more commonly involved than the upper extremities in bancroftian filariasis. In contrast to the common involvement of male genitalia in bancroftian filariasis, brugian filariasis is more likely to present clinically as lymphadenitis and lymphangitis as a result of a predilection of Brugia species to involve the superficial inguinal lymphatics. Filarial lymphadenopathy is seen commonly in infected children; before puberty, adult worms can be detected by ultrasonography of the inguinal, crural, and axillary lymph nodes and vessels. Death of the adult worm triggers an acute inflammatory response, which progresses distally (retrograde) along the affected lymphatic vessel, usually in the limbs and is termed acute filarial lymphangitis. If present, systemic symptoms, such as headache or

fever, are generally mild.

In postpubertal males, adult Wuchereria bancrofti organisms are found most commonly in the intrascrotal lymphatic vessels and can be visualized on ultrasound examination. Inflammation resulting from adult worm death, in this area, may present as funiculitis, epididymitis, or orchitis. A tender granulomatous nodule may be palpable at the site of the dead adult worms.

The chronic manifestations of lymphedema and/or hydrocele will develop in approximately 30% of LF infected persons. Lymphedema mostly affects the legs, but can also occur in the arms, breasts, and genitalia. Most people develop these symptoms years after being infected. Recurrent secondary bacterial infections of the affected extremity, characterized by severe pain, fever and chills, hasten the progression of lymphedema to its advanced stage, known as elephantiasis.

Filarial hydrocele is thought to be the consequence of lymphatic damage caused by adult worms. Chyluria, which results from rupture of dilated lymphatics into the renal pelvis, can occur as a manifestation of bancroftian filariasis. Microscopic hematuria and proteinuria are also found in LF infected patients.

Elephantiasis of the lower extremities involves the entire leg in bancroftian filariasis, whereas the leg above the knee maintains a relatively normal contour in brugian filariasis. Involvement of the upper extremities, breasts, and other areas of the body is relatively infrequent in both forms of lymphatic filariasis. Patients with chronic disease may be microfilaremic but most often are not, having previously cleared their acute infection. Acute attacks of adenolymphangitis may continue even with far advanced lymphedema and may be accompanied by a cellulitis that is bacterial in origin.

Tropical pulmonary eosinophilia is a hypersensitivity syndrome found mainly in southern India, where it is most common in young adult men. Symptoms include low-grade fever, nocturnal asthma, cough, fatigue, and weight loss.

Associated findings include interstitial infiltrates on chest radiographs, marked eosinophilia, and high levels of serum immunoglobulin E. Subjects with this syndrome mount an intense immune response in vitro to the parasite and usually have no circulating microfilariae. If left untreated, tropical pulmonary eosinophilia can result in chronic restrictive lung disease.

Diagnosis. Clinical case definition – Hydrocoele or lymphoedema in a resident of an endemic area for which other causes of these findings have been excluded. Laboratory criteria for diagnosis – Microfilaria positive, antigen positive or biopsy positive.

The definitive parasitologic diagnosis is based on the demonstration of microfilariae in blood samples. In patients with lymphatic filariasis from regions where nocturnal periodicity is common, blood specimens should be obtained between 10 PM and 2 AM. Microfilariae in blood can be detected by Giemsa-stained thick smears, although this method is generally less sensitive than concentration techniques that use centrifugation (Knotts test) or filtration through a 5 Bμm polycarbonate membrane filter. Species identification is based on size, staining characteristics of the sheath, and arrangement of nuclei in the tail. The presence of eosinophilia and elevated titers of specific antifilarial antibodies in serum help support the diagnosis but are only variably present. Antifilarial antibody tests do not distinguish between the eight human filarial species and often cross-react with Strongyloides species and other helminthes. Antibodies may be present in those with exposure and in those with past but not current infection. Adult worms may be found incidentally in asymptomatic persons in diverse body tissues but lymph node biopsy is not indicated in suspected filariasis unless malignancy is also a concern. An enzyme-linked immunosorbent assay and rapid card test for the detection of circulating antigens of W. bancrofti are commercially available but are not approved by the U.S. Food and Drug Administration (FDA). Circulating antigen tests are the most sensitive diagnostic modality available for W. bancrofti and can be done on serum drawn at any time of day or night. Ultrasound techniques have been used to visualize rapidly moving (“dancing”) adult worms in the dilated scrotal lymphatics of infected men. Such findings are pathognomonic of filarial parasites, but the technique is less sensitive than other modalities. Abnormalities detected by lymphoscintigraphy are not specific for filarial disease.

Treatment. Both diethylcarbamazine (DEC) and ivermectin, given as single doses, have been shown to be very effective in reducing microfilaraemia, especially when administered together, or singly with a single dose of albendazole. Both symptomatic and asymptomatic patients with lymphatic filariasis should be treated with diethylcarbamazine (DEC) (6 mg/kg/day in three divided doses for 2

to 3 weeks). DEC is FDA-approved but at the present time is only available through the Centers for Disease Control (CDC) Drug Service. DEC is non-toxic but dying parasites can cause adverse reactions including fever, chills, headache, dizziness, nausea, vomiting, and arthralgias, which usually occur in the first 24 to 36 hours. The magnitude of the reaction is directly proportional to the number of circulating microfilariae. In those with high levels of microfilaremia, treatment can be initiated with single doses of 50 to 100 mg of DEC on the first 2 days or patients can be pre-medicated with steroids. Adenolymphangitis due to dying adult worms may occur. In individuals who will not be returning to areas of transmission, attempted adulticidal therapy, which requires repeated or prolonged courses of DEC, is recommended. However, less than 25% of patients treated aggressively in this way clear all adult worms. If the patient remains microfilaremic, at least two repeat courses at 1-month intervals should be considered. Patients with lymphedema or elephantiasis should receive low-dose DEC daily for at least a year in an attempt to determine whether any reversible component of the chronic disease is present. In trials to date, single dose albendazole has been demonstrated to have adulticidal and microfilaricidal activity in lymphatic filariasis, but appropriate dosing regimens for attempts at prolonged curative treatment of individual patients with albendazole alone or an albendazole plus DEC combination have yet to be determined.

DEC is contraindicated in patients who may also have onchocerciasis. Prior to DEC treatment for lymphatic filariasis, onchocerciasis should be excluded in all patients with a consistent exposure history due to the possibility of severe exacerbations of skin and eye involvement (Mazzotti reaction). In addition, DEC should be used with extreme caution in patients with circulating Loa loa microfilarial levels >2,500/mm^3 due to the potential for life-threatening side effects, including encephalopathy and renal failure. Neither steroids pre-treatment nor slow dose escalation prevents these complications. Consultation with a tropical medicine specialist is recommended in these scenarios.

The drug ivermectin kills only the microfilariae, but not the adult worm; the adult worm is responsible for the pathology of lymphedema and hydrocele. Some studies have shown adult worm killing with treatment with doxycycline (200 mg/day for 4-6 weeks).

Treatment of complications due to chronic lymphatic obstruction is difficult. Limb elevation, massage, use of elastic stockings, and careful skin care with early antimicrobial therapy can help minimize bacterial superinfections of affected limbs.

Prevention and Control. Although it may be difficult for residents of endemic areas to avoid mosquito bites, temporary visitors should use repellants and mosquito nets. DEC has some value as a prophylactic agent in a dose of 10 mg/kg on 2 consecutive days each month. Attempts to control the mosquito vectors have failed owing to the development of resistance to insecticides. Yearly mass treatment with single dose albendazole plus DEC or albendazole plus ivermectin is being utilized by the global lymphatic filariasis elimination program to reduce the load of microfilariae in treated individuals and thereby to decrease transmission (16).

ONCHOCERCIASIS. Onchocerciasis is endemic in 34 countries of Africa, the Arabian peninsula and the Americas. Chronic infection with the parasite Onchocerca volvulus is commonly manifested by dermatologic or ocular disease that may progress to disabling dermatitis and blindness. The long-term disability that results from this filarial infection is responsible for a significant negative social and economic impact in endemic areas of equatorial Africa, Latin America, and the Arabian peninsula.

Epidemiology. An estimated 17,7 million people worldwide are infected with O. volvulus, most of whom live in equatorial Africa in a broad belt stretching from the Atlantic Coast on the west to the Indian Ocean and Red Sea on the east. The greatest number of infected persons is found in Cameroon, Nigeria, the Congo, Uganda, and Ethiopia. Approximately 100,000 individuals suffer from onchocerciasis in Latin America where scattered foci exist in Guatemala, Mexico, Venezuela, Brazil, Colombia, and Ecuador. Onchocerciasis is also endemic in Yemen and southwestern Saudi Arabia.

Humans are the definitive host of this parasite, although similar species are found in other mammals. O. volvulus larvae are transmitted to humans by black flies of the genus Simulium. The insect vector breeds along free-flowing waterways that have sufficient forest canopy to protect the black flies from excessively intense sun and heat. The black flies deposit their eggs on rocks, sticks, and

vegetation along the rapidly flowing bodies of water from which the developing larvae and pupae derive their nutrients. Consequently, onchocerciasis, or river blindness, is clustered around rivers and streams. The disease has a higher prevalence in men than in women in many communities because of greater exposure during daily activities such as fishing, farming, washing, and water collection.

Approximately 1% to 4% of all infected individuals will become blind; however, as many as half of adults in hyperendemic areas may develop this complication. A much higher prevalence of skin disease and other forms of ocular involvement is found in endemic regions than of blindness. The prevalence of infection rises with age such that almost all members of a village may be infected by early adulthood. The debilitating effects of chronic dermatitis and severe ocular disease tend to affect adults in their third to fifth decades of life at a time when they are the heads of households. The impact of this disease on some rural communities can be devastating in terms of the severe, personal discomfort and negative economic effects stemming from reduced productivity and time away from work.

Life Cycle. Microfilariae in the skin are ingested by female black flies while they are taking a blood meal from an infected individual. Once ingested, the immature worms penetrate the fly's intestinal wall and migrate to the thoracic flight muscles where they molt twice. The infective third-stage larvae migrate into the proboscis after 6 to 12 days of development and are then deposited on human skin when the fly bites. The larvae enter the bite wound and migrate into the subcutaneous tissues, where they molt twice over several months to become mature male and female worms. The adults become encapsulated in fibrous nodules in the subcutaneous tissue and deeper fascial planes during their growth and maturation. The female adult measures 23 to 50 cm in length and about 250 to 450 Bμm in diameter; the males are 2 to 5 cm long and 125 to 210 Bμm wide. After a prepatent period of 9 to 20 months, fertilized female worms release millions of microfilariae during their estimated life span of 8 to 10 years. The microfilariae are motile, are unsheathed, and measure 220 to 360 Bμm long. The host's immune response to dead and dying microfilaria is responsible for the clinical manifestations of this disease (fig. 19).

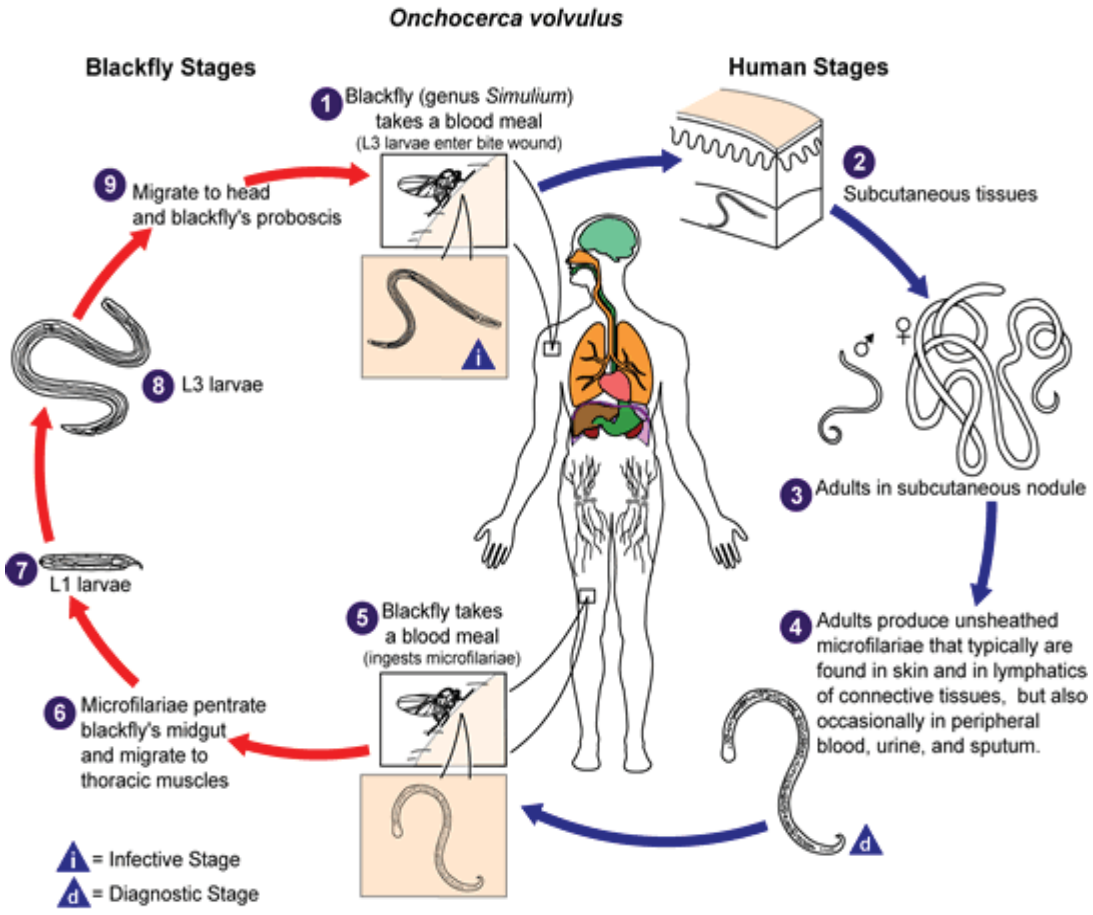

Fig. 19. – Life Cycle of Onchocerca volvulus

Pathophysiology. The skin, lymph nodes, and ocular tissues are the principal sites of infection. More frequent, intensive exposures lead to greater levels of infection. Histopathologic examination of the skin reveals a low-grade, chronic inflammatory process that may progress to dermal atrophy, loss of elastic fibers, and fibrosis. Live microfilariae do not appear to induce any host response, whereas the dead worms cause inflammation that increases with severity the longer the infection persists. The nodules containing adult worms, known as onchocercomata, have an outer fibrous capsule, a thin layer of chronic inflammation, and an inner inflammatory cell infiltrate around the adult worm.

A punctate keratitis develops around dead microfilaria in the outer eye, which with long-term, heavy infection progresses to sclerosing keratitis and iridocyclitis, finally culminating in blindness. A chronic, nongranulomatous inflammatory process in other parts of the eye can result in anterior uveitis, chorioretinitis, and optic atrophy.

The host reaction to the microfilariae, resulting from cell-

mediated immunity to parasite antigens, appears to be the driving force behind the skin and ocular damage. Individuals who manifest the most vigorous immune responses appear more likely to experience severe disease. A multiplicity of factors including host inflammatory mediators, especially eosinophils, and parasite antigens contribute to the complex immunopathogenesis of onchocerciasis.

Clinical Manifestations. Intense pruritus and intermittent urticarial or papular eruptions localized to one region of the body and conjunctivitis are early manifestations of disease. These may be the only signs and symptoms in nonresidents of endemic areas who usually have lighter infections. Chronic inflammation of the skin can result in hyperpigmentation and, later, a loss of elasticity, a widespread maculopapular rash, hypopigmentation, scaling, and edema. Depigmentation, thickening, and eventually a shiny, atrophic epidermis may develop in long-standing infections. The increased fragility of the skin can lead to areas of breakdown, which places the patient at risk for bacterial super-infection. A classification and grading system of the cutaneous changes of onchocerciasis has been developed in an attempt to standardize interpretation of skin involvement. Dermal manifestations of the disease in Africa more commonly involve the lower trunk, buttocks, and lower extremities, whereas they are more prominent around the head and neck in Central America. Lymph node involvement parallels the sites of skin involvement in these two geographic regions. It is usually manifested as non-tender lymphadenopathy although secondary obstructive changes in the groin region can lead to a hanging groin. A hypergic form of onchocerciasis known as sowda characterized by hyperpigmentation, papular eruptions, swelling, and regional lymphadenopathy, usually limited to one extremity, is common in Yemen and Sudan, but has also been observed elsewhere in Africa and Latin America. In contrast to sowda, in which skin snips reveal few microfilariae, the more common, nonreactive form of onchocerciasis tends to be symmetric with many microfilariae present in skin snips.

Onchocercomata are firm, nontender, and freely mobile subcutaneous or dermal nodules that usually measure 1 to 2 cm. If they are attached to periosteum, the nodules may be immobile. The nodules often occur in clusters in areas where lymphatics converge, including the skull, scapula, intercostal areas, iliac crests, and sacrum. The nodules tend to predominate in the lower part of the body in infected Africans, whereas they are more common in the upper

regions of the body in Central Americans.

Early ocular involvement is usually manifested by punctate keratitis and conjunctivitis associated with local irritation and increased tearing. Any part of the eye can be involved from the cornea to the posterior segment, including the retina and optic nerve. Slit-lamp examination may reveal living and dead microfilariae in the cornea, limbus, anterior chamber, retrolental space, vitreous humor, and retina. Additional ophthalmologic manifestations of onchocerciasis include sclerosing keratitis, iridocyclitis, chorioretinitis (which may cause progressive narrowing of visual fields), and optic neuritis and atrophy. Persistent anterior uveitis can lead to meiosis, pupillary distortion, and glaucoma. Sclerosing keratitis, the primary cause of blindness in onchocerciasis, typically develops after decades of infection.

Diagnosis. Clinical case is defined in an endemic area if a person has fibrous nodules in subcutaneous tissues. Laboratory criteria for confirmation:

One or more of the following:

• Presence of microfilariae in skin snips taken from the iliac crest

• Presence of adult worms in excised nodules

• Presence of typical ocular manifestations, such as slit-lamp observations of microfilariae in the cornea, the anterior chamber, or the vitreous body.

Samples of skin are usually taken with a corneoscleral biopsy instrument or razor blade from commonly infected sites, such as the upper portion of the body in Central Americans and the lower part in Africans. The skin is weighed and then placed in saline or tissue culture media. Microfilariae that emerge from the skin specimen are counted after incubation at room temperature for 30 minutes to 3 hours. They must be distinguished microscopically from the smaller microfilariae of M. perstans. The skin snips provide a measure of the intensity of infection; less than 10 microfilariae per milligram of skin are present in light infections, whereas more than 100 are found in heavy infections. Skin snips should be taken from several standard sites including the iliac crest, buttocks, calf, and scapula to ensure reliable sampling.

Because the diagnosis of onchocerciasis based on skin snips is highly specific but relatively insensitive, better serologic and molecular diagnostic tests have been sought. Serologic tests, which use a combination of recombinant O. volvulus antigens, appear to be useful

for determining the seroprevalence of infections (18). In addition, a rapid-format card test for the detection of IgG4 antibodies to antigen Ov16 has been shown to be sensitive and specific for the diagnosis of onchocerciasis in patients in Africa and Latin America. Polymerase chain reaction-based tests of skin snips is another highly sensitive approach to diagnosis.

Treatment. Although DEC was the standard therapy for nearly half a century, it has largely been supplanted by ivermectin. Ivermectin has been consistently demonstrated to be well tolerated, acceptable to endemic communities, and highly effective in eliminating microfilariae. Ivermectin is administered as a single oral dose of 150 to 200 Bμg/kg on an empty stomach at least 2 hours before the next meal. Although many treated subjects have little or no reaction to treatment, some may have increased pruritus, fever, headache, edema, and conjunctivitis or blurring of vision. Adverse reactions usually occur in the first 24 to 48 hours of therapy and last for 5 to 10 days. A minority will develop a maculopapular rash characteristic of the Mazzotti reaction after treatment with ivermectin; more serious reactions such as hypotension or worsening ocular disease are rare. The frequency and severity of adverse reactions to treatment are directly proportional to the intensity of infection. Skin snips should be taken every 6 to 12 months to monitor the response to treatment and to select patients who will need retreatment.

Repeated courses of ivermectin at 6-month intervals lead to a progressive reduction of skin microfilariae counts as well as a decrease in the prevalence of punctate corneal opacities and microfilariae in the anterior chamber of the eye. The intensity and frequency of adverse reactions diminish with later treatments. Although ivermectin is not macrofilaricidal, three monthly courses of the drug appear to be effective in reducing the numbers of male O. volvulus worms, preventing embryogenesis to the microfilarial stage in females, and progressively reducing the numbers of viable female worms. Even annual treatment with ivermectin results in an irreversible decline in microfilariae production of about 30% per treatment.

Contraindications to ivermectin therapy include pregnancy, breast-feeding during the first 3 months postpartum, age younger than 5 years, central nervous system disorders such as meningitis that may increase the permeability of the blood-brain barrier, and a history of allergy to the drug. If a serious Mazzotti-like reaction occurs during

treatment, symptomatic therapy with fluids, antipyretics, antihistamines, and corticosteroids should be used.

Older treatments for, such as suramin and diethylcarbamazine should not be used. Suramin has multiple systemic toxicities that limit its use in the presence of other less toxic and effective therapies. Diethylcarbamazine accelerates the development of onchocercal blindness (tab. 16).

Table 16. – Treatments for *Onchocerca volvulus*

Usage/Drug	***Adult Dose***	***Pediatric dose***
To kill microfilariae: ivermectin	150 mcg/kg orally in one dose every 6 months	150 mcg/kg orally in one dose every 6 months
To kill macrofilariae: doxycycline*	200 mg orally daily for 6 weeks	200 mg orally daily for 6 weeks

* Doxycycline is not standard therapy, but several studies support its use and safety. Treatment with ivermectin should be given one week prior to treatment with doxycycline in order to provide symptom relief to the patient. If the patient cannot tolerate 200 mg PO daily of doxycycline, 100mg PO daily is sufficient to sterilize female *Onchocerca*.

Surgical removal of nodules containing adult worms should be strongly considered if the nodules are in the head region because of an increased risk for ocular involvement. Nodulectomy has been widely practiced in Latin America but not in Africa, where many nodules are deeper in the subcutaneous tissues or are situated adjacent to bones or joints.

Prevention and Control. Success at controlling the disease in West Africa was achievedthrough the strategy of larviciding for vector control in order to interrupt transmission; since 1988 this has been combined with treatment by ivermectin, a safe, effective drug. The global strategy for controlling onchocerciasis is based onthe yearly administration of ivermectin to affected populations. The first step is to map the endemicity of onchocerciasis in known or potentially endemic areas. The second is to implement cost-effective and sustainable ivermectin delivery, focusingon methods involving community treatment.

LOAOASIS. L. loa is a filarial parasite endemic to the rain forests of equatorial West and Central Africa where an estimated 20 million people are infected. Risk is highest in southeastern Nigeria,

Cameroon, Gabon, Central African Republic, Equatorial Guinea and the Democratic Republic of Congo. Loiasis is transmitted to humans by tabanid flies of the genus Chrysops.

Life cycle (fig. 20). Adult worms migrate and reside in subcutaneous tissues where they cause transient swellings. They occasionally migrate across the eye, hence the name eyeworm. The adult females measure about 6 cm in length and 0.5mm in width; the males are 3,2 cm by 0,4 mm. Sheathed microfilariae deposited by the adult females migrate from the subcutaneous tissues to the blood stream. Peak levels of microfilaremia occur at midday. After ingestion in a blood meal by the vector deerfly, the microfilariae develop into infective third-stage larvae, which are released into the bite wound when the fly feeds. The larvae mature to adults in the subcutaneous tissue and reproduce sexually to reinitiate the cycle.

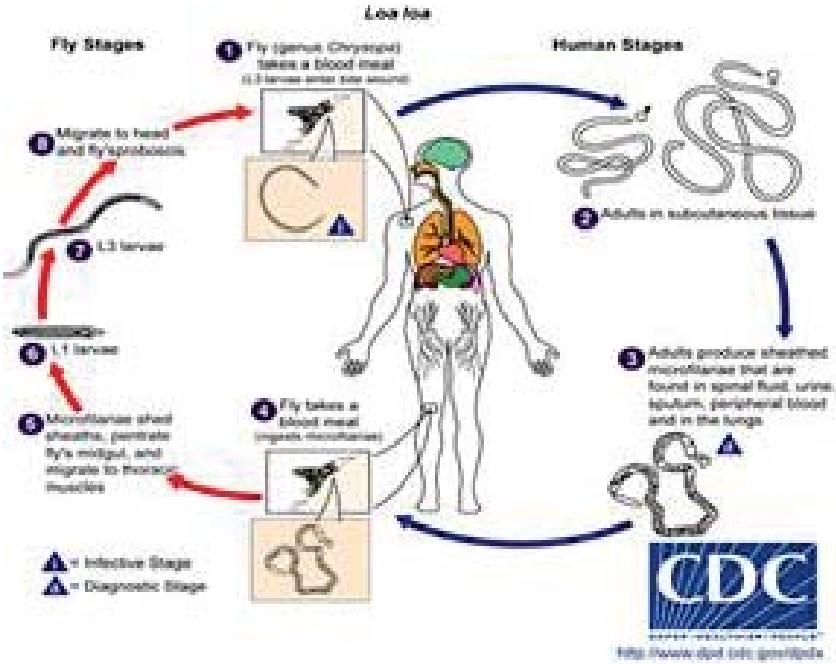

Fig. 20. – Life cycle of loaoasis

Infected people are frequently asymptomatic despite having heavy microfilaremia and an intense blood eosinophilia. Migration of the adult worms through subcutaneous tissue results in painful, angioedematous eruptions known as Calabar swellings. The forearms, wrists, and periorbital tissues are most commonly affected. These transient skin swellings last 1 to 2 days; are frequently preceded by localized pain and pruritus; and may be associated with fever, arthralgias, and urticaria. Migration of the adult worm across the conjunctiva and sclera can

precipitate an intense conjunctivitis. Visitors to endemic regions who develop loiasis often have exaggerated allergic reactions to the migratory worms characterized by more frequent Calabar swellings and cutaneous symptoms as well as higher levels of eosinophilia, parasite-specific immunoglobulin E, and lymphocyte blastogenic responses to parasite antigen. However, these individuals are amicrofilaremic 90% of the time. Rare, potentially life-threatening complications include cardiomyopathy, encephalitis, nephropathy, and pulmonary disease. The microfilariae of L. loa have been encountered in a variety of aberrant locations including ascites and pleural and joint effusions.

Diagnosis. Identification of characteristic microfilariae in thick or thin smears of blood taken during the day and stained with Wright or Giemsa stain establishes the diagnosis of loiasis. Concentration techniques, as for lymphatic filariasis, may be necessary in patients with low levels of microfilaremia. Short-term visitors are often amicrofilaremic so the diagnosis may need to depend on the characteristic exposure history, clinical presentation, blood eosinophilia, and elevated antifilarial antibody titers. O. volvulus, M. perstans, M. ozzardi, and M. streptocerca all cause overlapping syndromes and must, if epidemiologically possible, be ruled out by a complete search for microfilariae in blood and skin. An adult L. loa excised while crawling across the conjunctiva or under the skin provides a definitive diagnosis.

Treatment. Loa loa, unlike many other filarial parasites, doxycycline is not an effective treatment (tab. 17).

Table 17. – Treatment of Loiasis

Treatment	*Indication*	*Adult Dose*	*Pediatric Dose*
Diethylcarbamazine (DEC)	Symptomatic loiasis with MF/mL <8,000	8–10 mg/kg orally in 3 divided doses daily for 21 days	8–10 mg/kg orally in 3 divided doses daily for 21 days
Albendazole	Symptomatic loiasis, with MF/mL <8,000 and failed 2 rounds DEC OR Symptomatic loiasis, with MF/ml ≥8,000 to reduce level to <8,000 prior to treatment with DEC	200 mg orally twice daily for 21 days	200 mg orally twice daily for 21 days
Apheresis* followed by DEC	Symptomatic loiasis, with MF/mL ≥8,000	N/A	N/A

MF = microfilariae of L. loa

* Apharesis should be performed at an institution with experience in using this therapeutic modality for loiasis

DEC (6 to 10 mg/kg/day for 21 days) effectively eliminates microfilariae and is reliably adulticidal in most individuals with repeated courses. Subjects with high levels of microfilaremia may develop intense allergic reactions to the dying parasites characterized by fever, nausea, urticaria, and rarely encephalitis.

In any patient with microfilaremia, a test dose of 25 mg of DEC should be given on day 1 followed by 50 mg the following day and then 400 mg/day for 7 to 21 days. Corticosteroids may be given as an adjunct to decrease the initial inflammatory reaction. With microfilaremia greater than a few hundred microfilariae per milliliter of blood DEC-induced inflammatory reactions to dying microfilariae may progress to encephalopathy and death. If available, apheresis to remove circulating microfilariae can be performed before initiating DEC therapy in these individuals. If this latter option is not available for highly microfilaremic individuals, limited data support the use of albendazole (200 mg twice a day for 21 days) as it appears to be moderately adulticidal but without any effect on the microfilariae. Ivermectin is microfilaricidal but has no adulticidal effect and may also cause toxic encephalopathy in highly microfilaremic individuals. If epidemiologically appropriate, onchocerciasis must be carefully ruled out before the initiation of DEC therapy for loiasis in order to prevent toxicity due to dying O. volvulus microfilariae. A 21-day course of albendazole is indicated for those failing multiple courses of DEC. DEC has also been used successfully as a prophylactic agent in long-term visitors to endemic regions. Migrating adult worms should be surgically removed, especially if they are found in the conjunctiva.

MANSONELLA PERSTANS. M. perstans is found commonly in rain forests in tropical Africa, and less so in Central and South America, and the Caribbean. This parasite is transmitted by midges of the Culicoides genus with host reservoirs including humans and chimpanzees. The adult worms normally live in the peritoneal cavity of their host but have also been found in pleural and pericardial spaces. Unsheathed microfilariae are released into the blood without periodicity. Infected residents of endemic regions are often asymptomatic, although they may have vague joint or cutaneous complaints and eosinophilia. Visitors to endemic areas may develop angioedema, serositis, arthralgia, fever and neurologic manifestations. Demonstration of characteristic microfilariae in blood smears

confirms the diagnosis; eosinophilia and positive antifilarial titers are often present. No reliable therapy exists. DEC and ivermectin seem ineffective. Albendazole (400 mg twice a day for 10 days) has given the best results. Microfilaremia does not decrease until 30 days or more after treatment.

MANSONELLA STREPTOCERCA. Streptocerciasis is a common filarial infection in parts of Central and West Africa and has recently been found in Uganda as well. M. streptocerca is transmitted by midges of the genus Culicoides. The adult females, which measure approximately 3 cm in length, live in the subcutaneous tissue. The unsheathed microfilariae are about 200 Bμm long, have a distinctive, and can be found in the skin. Clinical manifestations of infection include pruritus, axillary or inguinal adenopathy, and a chronic dermatitis with hypopigmented macules or papules that resemble those of leprosy but are not anesthetic. Skin snips incubated in saline usually reveal the presence of the microfilariae. Caution must be used to avoid confusion with the larger microfilariae of O. volvulus. Treatment with DEC (6 mg/kg/day for 2 weeks) is effectively microfilaricidal and adulticidal but may exacerbate the pruritus. Single dose ivermectin (150 Bμg/kg) is microfilaricidal and concomitantly kills O. volvulus microfilariae-these two infections are co-endemic in many areas.

MANSONELLA OZZARDI. Mansonelliasis, the filarial infection caused by M. ozzardi, is found only in parts of Central and South America and in certain Caribbean islands. Midges of the genus Culicoides or black flies of the Simulium group serve as vectors. The location of adult worms is unclear. The microfilariae in the blood have a characteristic sharp tail and are nonperiodic. Clinical manifestations of this usually asymptomatic infection are ill-defined but may include chronic arthritis and pruritus. Therapy with DEC is generally ineffective. Single-dose therapy with ivermectin may be effective, but experience with this agent is limited.

DIROFILARIA AND OTHER ZOONOTIC FILARIIDS. Filarial nematodes of the genus Dirofilaria are responsible for two syndromes in humans. Transmission of Dirofilaria immitis (dog heartworm) larvae from dogs to humans by mosquitoes can lead to the

development of a granulomatous pulmonary nodule. Subcutaneous dirofilariasis results from the accidental infection of humans by Dirofilaria repens, whose natural hosts are dogs and cats, or by Dirofilaria tenuis, a parasite of the subcutaneous tissue of raccoons.

The larvae of D. immitis are commonly found in mosquitoes in urban areas of the United States, especially in the Southeast. Accidental infection of humans has been described in the United States, Japan, Australia, and Western Europe. The adult worms of this parasite are unable to develop fully in humans.

Life cycle of Dirofilaria immitis (fig. 21). During a blood meal, an infected mosquito (Aedes, Culex, Anopheles, Mansonia) introduces third-stage filarial larvae of Dirofilaria immitis into the skin of the definitive host, which is usually a domestic dog or coyote in the United States (although a wide variety of other animals can also be infected, including felids, mustelids, pinnipeds, beaver, horses, and humans), where they penetrate into the bite wound (the number 1). In the definitive host, the L3 larvae undergo two more molts into L4 and adults. Adults reside in pulmonary arteries, and are occasionally found in the right ventricle of the heart (the number 2). Adult females are usually 230-310 mm long by 350 µm wide; males are usually 120-190 mm long by 300 µm wide.

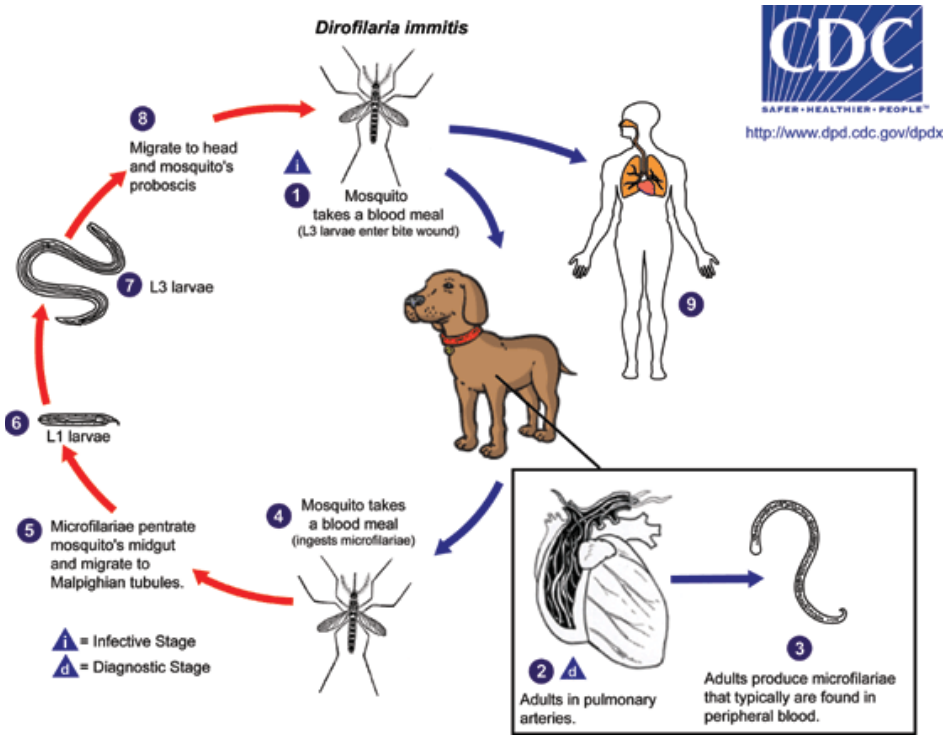

Fig. 22. – Life cycle of Dirofilaria immitis

Adults can live for 5-10 years. In the heart, the female worms are capable of producing microfilariae over their lifespan. The microfilariae are found in peripheral blood (the number 3). A mosquito ingests the microfilariae during a blood meal (the number 4). After ingestion, the microfilariae migrate from the mosquito's midgut through the hemocoel to the Malpighian tubules in the abdomen (the number 5). There the microfilariae develop into first-stage larvae (the number 6) and subsequently into third-stage infective larvae (the number 7). The third-stage infective larvae migrate to the mosquito's proboscis (the number 8) and can infect another definitive host when it takes a blood meal (the number 1). In humans (the number 9), D. immitis larvae tend to follow the same migratory pathway as in the canine host, ending up in the lungs, where they often lodge in small-caliber vessels, causing infarcts and typical "coin lesions" visible on radiographs.

Life cycle of Dirofilaria tenuis (fig. 22). During a blood meal, an infected mosquito (Aedes, Anopheles, and possibly others) introduces third-stage filarial larvae of Dirofilaria tenuis onto the skin of the raccoon definitive host (but also occasionally humans), where they penetrate into the bite wound (the number 1). In the definitive host, the L3 larvae undergo two more molts into L4 and adults, the latter of which resides in subcutaneous tissues (the number 2).

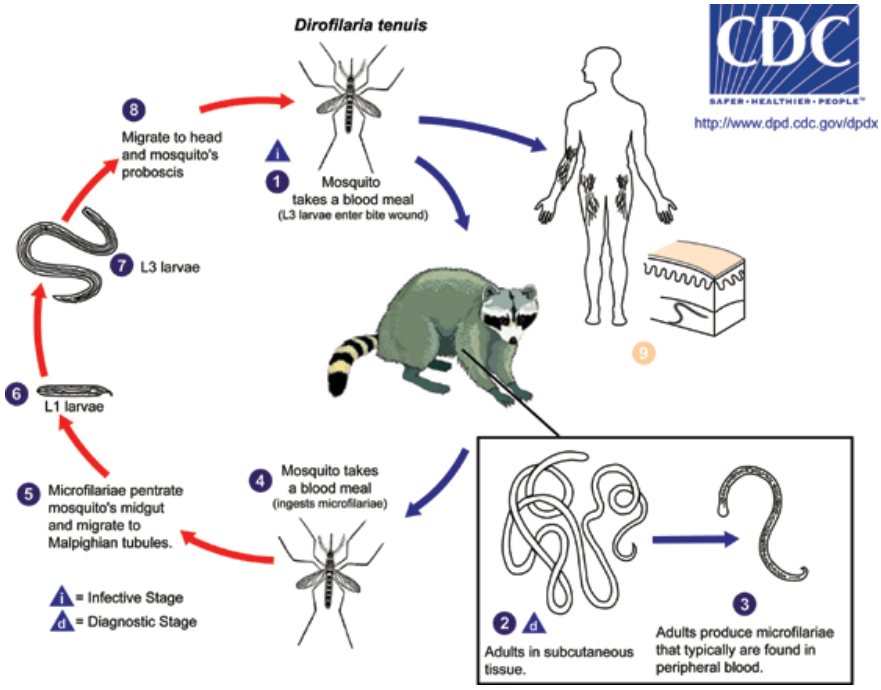

Fig. 22. – Life cycle of Dirofilaria tenuis

Adult females are usually 80-130 mm long by 260-360 μm wide; males are usually 40-50 mm long by 190-260 μm wide. Adults can live for 5-10 years. In subcutaneous tissue, the female worms are capable of producing microfilariae over their lifespan. The microfilariae are found in peripheral blood (the number 3). A mosquito ingests the microfilariae during a blood meal (the number 4). After ingestion, the microfilariae migrate from the mosquito's midgut through the hemocoel to the Malpighian tubules in the abdomen (the number 5). There the microfilariae develop into first-stage larvae (the number 6) and subsequently into third-stage infective larvae (the number 7). The third-stage infective larvae migrate to the mosquito's proboscis (the number 8) and can infect another definitive host when it takes a blood meal The number 1. In humans (the number 9), D. tenuis may wander in the subcutaneous tissues for months, but finally is encapsulated in a granulomatous nodule, but may also be found around the eye or on the conjunctiva. Because of this, the infection in humans was first known as Dirofilaria conjunctivae.

Clinic. Infected individuals are usually asymptomatic, although there may be cough, chest pain, hemoptysis, and fever in up to 44%. Chest radiographs commonly reveal a solitary, peripheral pulmonary nodule, most often in the lower lobes, which, when it is excised, will reveal a granulomatous reaction surrounding an intact dead worm or worm fragments within an arteriole. Surgical excision of the nodule, often performed to rule out malignant neoplasm, fulfills the dual purposes of diagnosis and treatment of pulmonary dirofilariasis. Antifilarial serology is unreliable and unproven and peripheral eosinophilia is present in less than 10%. No additional therapy is necessary because this infection is self-limited.

Subcutaneous dirofilariasis is a rare, cosmopolitan infection that is probably acquired by humans from the usual animal host by a mosquito vector. Because humans represent a dead-end host, the larvae are unable to mature to adults, and therefore microfilariae are never observed. Granulomatous, subcutaneous nodules may be found in the conjunctiva, chest wall, and extremities. The lesion develops slowly during many weeks into a nodule that may be painful and erythematous. Diagnosis is made by identification of the worm in biopsy specimens, a procedure that also serves as treatment.

ANCYLOSTOMIASIS

An estimated 1.3 billion people worldwide are infected with the hookworms Ancylostoma duodenale and Necator americanus. N. americanus is more commonly found in the Americas, equatorial Africa, Southeast Asia, Polynesia, and Australia whereas A. duodenale is more prevalent in northern Africa and north and southwest Asia. Although the distributions of these two species were formerly thought to be discrete, surveys have shown that ranges overlap in parts of Asia, Africa, and South America. Ancylostoma ceylanicum, a minor nematode species, which is primarily a pathogen of large felines such as panthers and tigers, uncommonly infects humans in parts of Southeast Asia and Suriname. Although many individuals have light, asymptomatic infections, heavy worm burdens can cause significant gastrointestinal blood loss, iron deficiency anemia, and rarely, death.

Morphology. The hookworm life cycle is similar to that of A. lumbricoides with the nuance that the penetration of unbroken skin by infective larva initiates the infection. There are no reservoir hosts for either species of hookworm.

The adult worms are small, ranging from 9 to 13 mm in length. Morphologic differences of the mouth parts of adult worms help to differentiate the two species. N. americanus adults have two pairs of rounded, chitinized cutting plates, whereas A. duodenale adults have two pairs of cutting teeth. The adult worms obtain their nutrients from the consumption of villous tissue and blood sucked directly from their site of attachment to the intestinal mucosa. The A. duodenale adult is responsible for the loss of 0,1 to 0,2 mL of blood per day; the adult of N. americanus accounts for the loss of 0,01 to 0,02 mL of blood daily through direct ingestion of blood and focal hemorrhages produced at the site of intestinal attachment. Proteases and anticoagulants released by the worms play a role in the pathogenesis of the blood loss.

Life cycle. Adult females of A. duodenale produce up to 30,000 eggs per day, whereas females of N. americanus produce 5,000 to 10,000 eggs per day. Eggs passed in the feces contain a segmented ovum that will undergo larval maturation and hatch within 1 to 2 days in soil, if the necessary conditions of temperature and moisture are present. The freshly hatched rhabditiform larvae pass through a free-

living cycle in the soil during which they molt twice and then become sheathed, filariform larvae that are infectious to humans. If soil conditions are suitable, the larvae can survive for months. Humans are infected by penetration of the skin, most commonly through the feet. Infection with A. duodenale may occur by the oral route. The larvae migrate through the venous system to the pulmonary arterial circulation where they cross into the alveoli and then are passively carried up the bronchi to the trachea and larynx. The migrating larvae of N. americanus undergo maturation in the lung, whereas those of A. duodenale do not. On reaching the pharynx, the larvae are swallowed and reach the small intestine approximately 3 to 5 days from the time of skin penetration. During the next 4 to 6 weeks, the worms become mature. Intestinal survival is an average of 4 years for N. americanus and 5 years for A. duodenale. In some regions where reinfection is common, the filariform larvae of A. duodenale may remain dormant in skeletal muscle and then later complete their development when the external environmental conditions have again become favorable for parasite development in the soil.

Epidemiology. The prevalence of hookworm infection varies substantially from region to region, with rates as high as 90% described. The prevalence tends to be higher in rural than in urban areas. The age-specific prevalence in tropical regions peaks in schoolchildren and then levels off in adulthood. Hookworm infections used to be common in the rural southeast of the United States and Puerto Rico, but the frequency has dropped as socioeconomic conditions have improved. Survival of hookworm larvae is optimal in moist, sandy, or loamy soil with ambient temperatures of 24B°C to 32B°C. The practices of using the same site for defecation and not wearing footwear facilitate infection. Because A. duodenale can also be acquired by the oral route, contamination of fresh produce with nightsoil contributes to the transmission of hookworms.

Clinical Manifestations. A dermatitis characterized by intense pruritus, edema, and erythema followed later by a vesiculopapular eruption may occur at the skin entry site of the filariform larvae. This cutaneous manifestation of infection, known as ground itch or cooliевЂ™s itch, may last as long as 2 weeks and is more common in individuals in endemic areas who are presensitized to hookworms. Although pulmonary symptoms can occur during the larval migration, they tend to be mild in comparison with A. lumbricoides, unless the

initial infection is heavy, in which case dyspnea and cough may occur. During worm maturation in the intestine, there may be abdominal pain, steatorrhea, and an intense peripheral eosinophilia with 1,000 to 4,000 cells per mm^3.

Complications. Lighter worm burdens tend to result in no or only mild symptoms, whereas heavier infections can be complicated by severe iron deficiency anemia from chronic intestinal blood loss and hypoalbuminemia secondary to a protein-losing enteropathy. These complications are manifested by fatigue, peripheral edema, dyspnea, high-output heart failure, pale skin, and other manifestations of chronic iron deficiency anemia. The hypoproteinemia that results from chronic infection may lead to a kwashiorkor-like state characterized by growth impairment, facial and lower extremity edema, dermatitis, and hair loss. Factors influencing the severity of anemia include the iron content of the individual's diet, the underlying iron stores, and the intensity and duration of infection. Chronic hookworm anemia contributes to physical and intellectual growth retardation.

Diagnosis. The diagnosis is established by the identification of characteristic hookworm eggs in direct stool smears. Concentration techniques may be necessary in light infections. Fresh or preserved stool specimens should be examined because the eggs may hatch into rhabditiform larvae, which can be misinterpreted as Strongyloides larvae. Such distinctions are critical to the selection of optimal therapeutic agents. Hookworm ova can be confused with those of Oesophagostomum species, which appear identical, or ova of Trichostrongylus species, which tend to be much larger. A. duodenale and N. americanus can be differentiated by the examination of adult worms or third-stage larvae.

Therapy. The main goal of treatment in endemic regions is to reduce the worm burden below the level of clinical significance. Infected people in nonendemic areas should be treated. Mebendazole, albendazole, and pyrantel pamoate are effective treatments for hookworm infections. However, the failure of a single-dose regimen of mebendazole suggests that the development of resistance to the benzimidazoles may interfere with the utility of these drugs in the near future. The safety of the benzimidazole agents, mebendazole and albendazole, has not been established in infants. Pyrantel pamoate is available as a suspension and is an effective therapy for hookworm

infections in infants. Oral iron supplements should be given to rectify the iron deficiency anemia. Chemotherapy of hookworm infections and correction of the associated anemia result in improved physical fitness and catch-up growth in endemic populations.

Mebendazole, 100 mg PO bid – 3 d. Albendazole, a 400 mg PO once, Pyrantel pamoate, 11 mg/kg PO – 3 d (max 1 g). Dosage is the same for children as for adults. Albendazole should be taken with food. Albendazole is not FDA-approved for treating hookworm infection.

Prevention and Control. Three major aspects of prevention include the sanitary disposal of feces, chemotherapy, and public health education. Correct use of latrines helps to contain the hookworm larvae. In regions where fresh human fecal matter is used as manure (nightsoil), it should be treated to kill the larvae by composting or through the addition of chemicals such as sodium nitrate, ammonium sulfate, or calcium superphosphate. Protective footwear and education about the mode of transmission may prove helpful in geographic locales where percutaneous rather than oral transmission is more common.

LARVA MIGRANS SYNDROME

Larva migrans is a condition in humans caused by the migratory larvae of certain nematodes, humans being a dead-end host, and was first reported in 1952.

Nematodes causing such zoonotic infections are Baylisascaris procyonis, Toxocara canis, Toxocara cati, and Ascaris suum. These nematodes can infect but not mature in humans and after migrating through the intestinal wall, travel with the blood stream to various organs where they cause inflammation and damage. Affected organs can include the liver, heart (causing myocarditis) and the CNS (causing dysfunction, seizures, and coma) – Visceral form. Cutaneous larva migrans is a condition where nematodes such as Ancylostoma braziliense migrate to the skin. A special variant is ocular larva migrans where usually T. canis larvae travel to the eye.

Etiology. Toxocariasis is an illness of humans caused by larvae (immature worms) of either the dog roundworm (Toxocara canis), the cat roundworm (Toxocara cati) or the fox (Toxocara canis).

Toxocariasis is often called visceral larva migrans (VLM). Depending on geographic location, degree of eosinophilia, eye and/or pulmonary signs the terms ocular larva migrans (OLM), Weingarten's disease, Frimodt-Møller's syndrome, and eosiniphilic pseudoleukemia are applied to toxocariasis. Other terms sometimes or rarely used include nematode ophthalmitis, toxocaral disease, toxocarose, and covert toxocariasis. This zoonotic, helminthic infection is a major cause of blindness and may provoke rheumatic, neurologic, or asthmatic symptoms. Humans normally become infected by ingestion of embryonated eggs (each containing a fully developed larva, L2) from contaminated sources (soil, fresh or unwashed vegetables, or improperly cooked paratenic hosts).

Toxocara canis and Toxocara cati are perhaps the most ubiquitous gastrointestinal worms (helminths) of domestic dogs and cats and foxes. There are many 'accidental' or paratenic hosts including humans, birds, pigs, rodents, goats, monkeys, and rabbits. In paratenic hosts the larvae never mature and remain at the L2 stage.

Cats, dogs and foxes can become infected with Toxocara through the ingestion of eggs or by transmission of the larvae from a mother to her offspring. Transmission to cats and dogs can also occur by ingestion of infected accidental hosts, such as earthworms, cockroaches, rodents, rabbits, chickens, or sheep.

Eggs hatch as second stage larvae in the intestines of the cat, dog or fox host (for consistency, this article will assume that second stage larvae emerge from Toxocara eggs, although there is debate as to whether larvae are truly in their second or third stage of development). Larvae enter the bloodstream and migrate to the lungs, where they are coughed up and swallowed. The larvae mature into adults within the small intestine of a cat, dog or fox, where mating and egg laying occurs. Eggs are passed in the feces and only become infective after several weeks outside of a host. During this incubation period, molting from first to second (and possibly third) stage larva takes place within the egg. In most adult dogs, cats and foxes, the full lifecycle does not occur, but instead second stage larvae encyst after a period of migration through the body. Reactivation of the larvae is common only in pregnant or lactating cats, dogs and foxes. The full lifecycle usually only occurs in these females and their offspring.

Second stage larvae will also hatch in the small intestine of an accidental host, such as a human, after ingestion of infective eggs. The

larvae will then migrate through the organs and tissues of the accidental host, most commonly the lungs, liver, eyes, and brain. Since L2 larvae cannot mature in accidental hosts, after this period of migration, Toxocara larvae will encyst as second stage larvae (fig. 23).

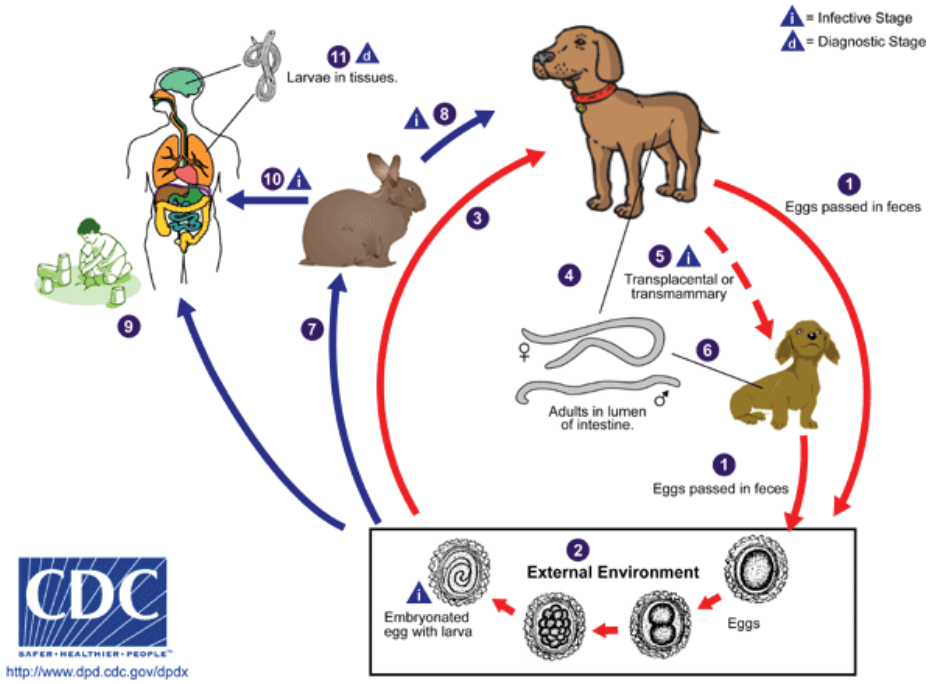

Fig. 23. – Life cycle of Toxocaras

Clinic. Physiological reactions to Toxocara infection depend on the host's immune response and the parasitic load. Most cases of Toxocara infection are asymptomatic, especially in adults. When symptoms do occur, they are the result of migration of second stage Toxocara larvae through the body.

Covert toxocariasis is the least serious of the three syndromes and is believed to be due to chronic exposure. Signs and symptoms of covert toxocariasis are coughing, fever, abdominal pain, headaches, and changes in behavior and ability to sleep. Upon medical examination, wheezing, hepatomegaly, and lymphadenitis are often noted.

High parasitic loads or repeated infection can lead to visceral larva migrans (VLM). VLM is primarily diagnosed in young children, because they are more prone to exposure and ingestion of infective eggs. Toxocara infection commonly resolves itself within weeks, but chronic eosinophilia may result. In VLM, larvae migration incites inflammation of internal organs and sometimes the central nervous system. Symptoms

depend on the organ(s) affected. Patients can present with pallor, fatigue, weight loss, anorexia, fever, headache, rash, cough, asthma, chest tightness, increased irritability, abdominal pain, nausea, and vomiting. Sometimes the subcutaneous migration tracks of the larvae can be seen. Patients are commonly diagnosed with pneumonia, bronchospasms, chronic pulmonary inflammation, hypereosinophilia, hepatomegaly, hypergammaglobulinaemia (IgM, IgG, and IgE classes), leucocytosis, and elevated anti–A and –B isohaemagglutinins. Severe cases have occurred in people who are hypersensitive to allergens; in rare cases, epilepsy, inflammation of the heart, pleural effusion, respiratory failure, and death have resulted from VLM.

A case study published in 2008 supported the hypothesis that eosinophilic cellulitis may also be caused by infection with Toxocara. In this study, the adult patient presented with eosinophilic cellulitis, hepatosplenomegaly, anemia, and a positive ELISA for T. canis.

Diagnostics. Finding Toxocara larvae within a patient is the only definitive diagnosis for toxocariasis; however, biopsies to look for second stage larvae in humans are generally not very effective. PCR, ELISA, and serological testing are more commonly used to diagnose Toxocara infection. Serological tests are dependant on the number of larvae within the patient, and are unfortunately not very specific. ELISAs are much more reliable and currently have a 78% sensitivity and a 90% specificity. A 2007 study announced an ELISA specific to Toxocara canis, which will minimize false positives from cross reactions with similar roundworms and will help distinguish if a patient is infected with T. canis or T. cati. OLM is often diagnosed after a clinical examination. Granulomas can be found throughout the body and can be visualized using ultrasound, MRI, and CT technologies.

Treatment. Toxocariasis will often resolve itself, because the Toxocara larvae cannot mature within human hosts. Corticosteroids are prescribed in severe cases of VLM or if the patient is diagnosed with OLM. Either albendazole (preferred) 400 mg PO 14-21 days or mebendazole (“second line therapy”) 200 mg PO 14-21 days may be prescribed. Granulomas can be surgically removed, or laser photocoagulation and cryoretinopexy can be used to destroy ocular granulomas.

Cutaneous larva migrans (abbreviated CLM) is a skin disease in humans, caused by the larvae of various nematode parasites of the

hookworm family (Ancylostomatidae). The most common species causing this disease in the Americas is Ancylostoma braziliense. These parasites live in the intestines of dogs, cats and wild animals and should not be confused with other members of the hookworm family for which humans are definitive hosts, namely Ancylostoma duodenale and Necator americanus.

Colloquially called creeping eruption due to its presentation, the disease is also somewhat ambiguously known as "ground itch" or (in some parts of the Southern USA) "sandworms", as the larvae like to live in sandy soil. Another vernacular name is plumber's itch. The medical term CLM literally means "wandering larvae in the skin".

Hookworm eggs are shed in infected dog (or other animal) feces to the ground, where they then develop over a period of 1-2 weeks into the infectious larval form (filariform larvae). The filariform larvae can burrow through intact skin that comes into contact with soil or sand that is contaminated with feces. Although they are able to infect the deeper tissues of animals (through to the lungs and then the intestinal tract), humans are incidental hosts and the larvae are only able to penetrate the upper dermis of the skin and thus create the typical wormlike burrows visible underneath the skin. These parasites apparently lack the collagenase enzymes required to penetrate through the basement membrane deeper into the skin (fig. 24).

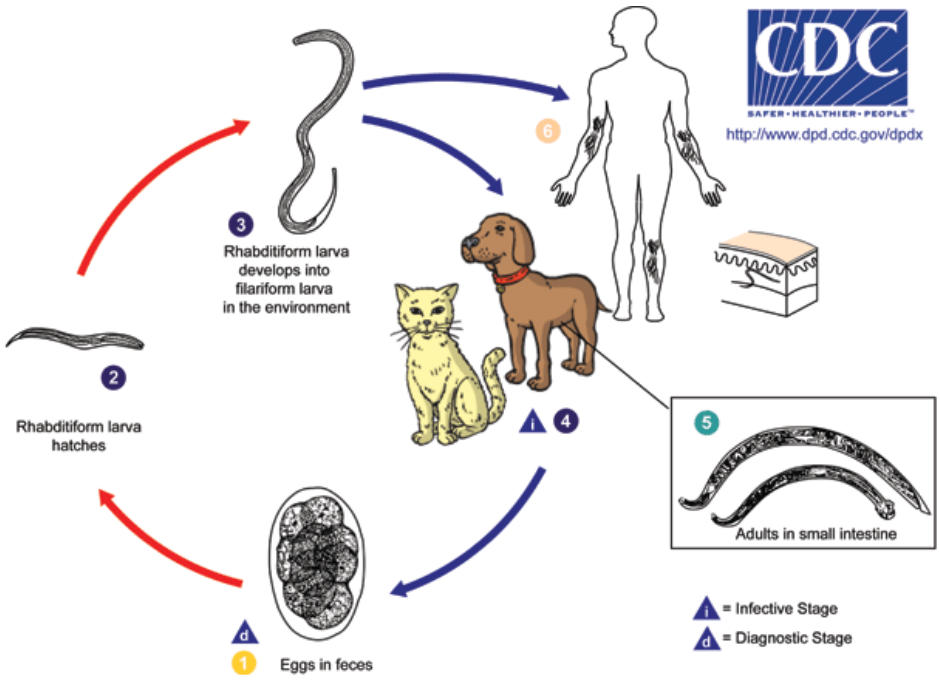

Fig. 24. – Life cycle of Ancylostomatidae

Symptoms. The infection causes a red, intensely pruritic (itchy) eruption. The itching can become very painful and if scratched may allow a secondary bacterial infection to develop. Cutaneous larva migrans usually heals spontaneously over weeks to months and has been known to last as long as one year. However, the severity of the symptoms usually causes those infected to seek medical treatment before spontaneous resolution occurs. Following proper treatment, migration of the larvae within the skin is halted and relief of the associated itching can occur in less than 48 hours (reported for thiabendazole).

This is separate from the similar cutaneous larva currens which is caused by strongyloides. Larva currens is also a cause of migratory pruritic eruptions but is marked by 1) incredible speed on the order of inches per hour 2) perianal involvement due to autoinfection from stool and 3) a wide band of urticaria.

Treatment and prevention. CLM can be treated in a number of different ways:

Systemic (oral) agents include albendazole (trade name Albenza) and ivermectin (trade name Stromectol)).

Another agent which can be applied either topically or taken by mouth is thiabendazole (trade name Mintezol)), an anti-helminthic. When taken orally, this medication is known to cause nausea. A topical preparation can be made by mixing the ground pills in vaseline. This mixture can be spread lightly on the lesion and held in place with a plaster. This produces local tissue levels sufficient to kill the parasite without the systemic side effects when taken orally.

Topical freezing agents, such as ethylene chloride or liquid nitrogen, applied locally can freeze and kill the larvae, but this method has a high failure rate due to the fact that the larvae are usually located away from the site of the visible skin trails. Additionally, this is a painful method which can cause blistering and/or ulceration of the skin and it is therefore not recommended.

It is recommended to use Benadryl or some anti-itch cream (i.e. Cortizone or Calamine lotion). This will help relieve some of the itch.

Wearing shoes in areas where these parasites are known to be endemic offers protection from infection. In general, avoiding exposure of skin to contaminated soil or sand offers the best protection. In some areas dogs have been banned from beaches in an attempt to control human infection.

STRONGYLOIDIASIS

Strongyloides stercoralis was first described in the 19th century in French army personnel returning from Indochina. It remains a significant cause of disease in many tropical and subtropical regions and, less commonly, in temperate climates such as North America (33). The unique ability of this nematode to replicate within its host for decades and its potential to cause massive infections with high mortality rates in immunocompromised patients make it a clinically significant pathogen. Although S. stercoralis is the usual cause of human strongyloidiasis, Strongyloides fuelleborni, an intestinal nematode of old-world primates, may be responsible for occasional human infections in central Africa and New Guinea. The ability of S. fulleborni to maintain sustained endogenous infections in humans has not been established.

Life Cycle (fig. 25). S. stercoralis has a complex life cycle with a free-living soil phase and a parasitic phase. The free-living phase is initiated when second-stage, rhabditiform larvae are excreted by an infected host into moist, shaded soil. Under proper conditions, the larvae molt twice to become free-living adult worms. In contrast with the intestinal phase, the free-living cycle is not sustained, and thus is not thought to be a significant factor in the amplification of infection.

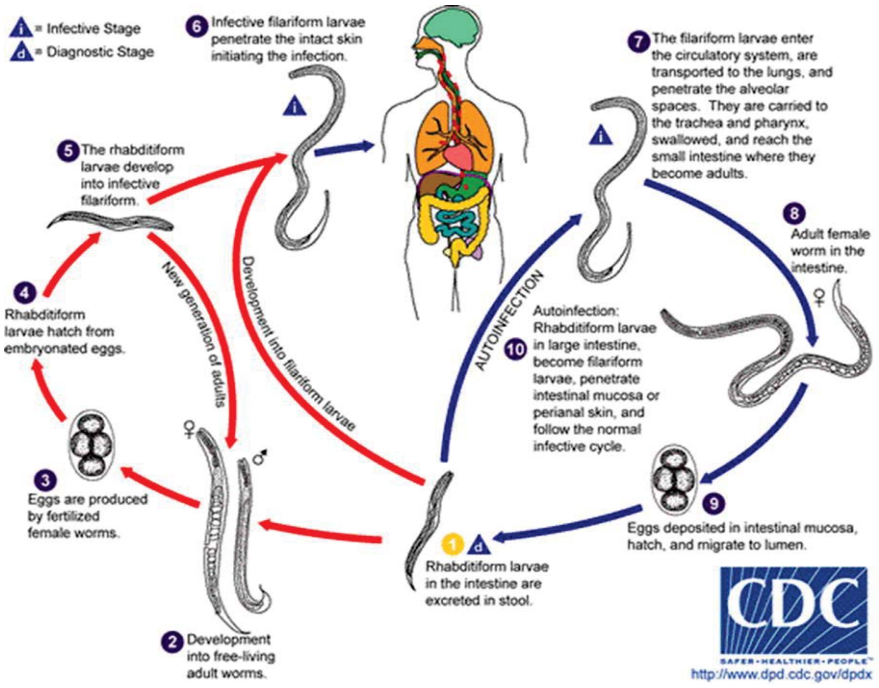

Fig. 25. – Strongyloides stercoralis life cycle

The initial infection occurs when humans come in contact with fecally contaminated soil that contains the third stage filariform larvae. The larvae respond to vibration by penetrating the skin of the host. The larvae are transported through the blood stream to the pulmonary circulation where they penetrate the alveoli, migrate up the tracheobronchial tree to the pharynx, and are then swallowed. The larvae undergo a final molt in the duodenum and upper jejunum to become the 2-mm long gray-white adults. Interestingly, the parasitic host cycle is maintained by adult females, which reproduce by parthenogenesis (i.e., in the absence of male worms). Females release small numbers of eggs into the bowel lumen. The time from initial skin penetration to the excretion of eggs is approximately 25 to 30 days. Eggs quickly hatch within the lumen, releasing first stage larvae; for this reason, ova of S. stercoralis are rarely seen in stool samples. The larvae then molt in the colon to become second-stage, rhabditiform larvae, which may be passed in feces to contaminate soil or may undergo an additional molt to form the infectious third-stage, filariform larvae. The filariform larvae are infectious, and can penetrate either the bowel mucosa, resulting in internal autoinfection, or penetrate the perianal skin resulting in external autoinfection. External autoinfection is increased when fecal-contaminated clothes remain in close contact with perianal skin. This process of autoinfection allows S. stercoralis to persist in its host for decades. Immunocompromised hosts may harbor many infective larvae in their intestines, which can lead to a hyperinfection syndrome, a difficult to treat and frequently fatal complication of chronic strongyloidiasis.

Epidemiology. S. stercoralis is estimated to infect as many as 100 to 200 million people worldwide. Infection is endemic in many less developed, tropical areas of the world where warmth, moisture, and poor sanitation allow the soil stages to flourish. There is some evidence to suggest that dogs, cats, or monkeys may also serve as nonhuman reservoirs of infection. In the United States, strongyloidiasis can occasionally be found in recent immigrants from Southeast Asia, in rural areas of the Southeast, and in institutionalized settings where personal hygiene and sanitation are inadequate. Accurate estimates of the prevalence of strongyloidiasis are hindered by difficulties identifying the low numbers of larva and near absent ova in routine stool samples. The importance of autoinfection has been emphasized by the detection of symptomatic disease three to four

decades after exposure in ex-prisoners of war who had worked on the railroad between Myanmar (formerly Burma) and Thailand during World War II.

Clinical Manifestations. The symptomatic spectrum of Strongyloides ranges from subclinical in acute and chronic infection to severe and fatal in hyperinfection syndrome and disseminated strongyloidiasis, which have case-fatality rates that approach 90%. In either case, patients' symptoms are a result of the parasite's larval form migrating through various organs of the body.

Acute strongyloidiasis.

The initial sign of acute strongyloidiasis, if noticed at all, is a localized pruritic, erythematous rash at the site of skin penetration. Patients may then develop tracheal irritation and a dry cough as the larvae migrate from the lungs up through the trachea. After the larvae are swallowed into the gastrointestinal tract, patients may experience diarrhea, constipation, abdominal pain, and anorexia.

Chronic strongyloidiasis.

Chronic strongyloidiasis is generally asymptomatic, but in patients with clinical disease gastrointestinal and cutaneous manifestations are the most common. Of the gastrointestinal complaints, epigastric pain, postprandial fullness, heartburn, and brief episodes of intermittent diarrhea and constipation are the most frequent. Less commonly, patients may present with fecal occult blood, or massive colonic and gastric hemorrhage. Presentations resembling inflammatory bowel disease, specifically ulcerative colitis, are rare. Also rare, but documented, are endoscopic exams revealing pathology similar to pseudopolyposis.

Cutaneous symptoms include chronic urticaria and the pathognomonic larva currens- a recurrent serpiginous maculopapular or urticarial rash along the buttocks, perineum, and thighs due to repeated auto-infection. It has been described as advancing as rapidly as 10 cm/hr.

Rarely, patients with chronic strongyloidiasis have complained of arthritis, cardiac arrhythmias, and signs and symptoms consistent with chronic malabsorption, duodenal obstruction, nephrotic syndrome, and recurrent asthma.

Up to 75% of people with chronic strongyloidiasis have mild peripheral eosinophilia or elevated IgE levels.

Hyperinfection syndrome and disseminated strongyloidiasis are

most frequently associated with subclinical infection in patients receiving high-dose corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD) exacerbations. Subsequent impaired host immunity leads to accelerated autoinfection and an overwhelming number of migrating larvae. Whereas in chronic strongyloidiasis and in hyperinfection syndrome the larvae are limited to the GI tract and the lungs, in disseminated strongyloidiasis the larvae invade numerous organs. Left untreated, the mortality rates of hyperinfection syndrome and disseminated strongyloidiasis can approach 90%.

The following are signs and symptoms that can be seen with hyperinfection syndrome and disseminated strongyloidiasis:

Gastrointestinal manifestations: abdominal pain, nausea, vomiting, diarrhea, ileus, bowel edema, intestinal obstruction, mucosal ulceration, massive hemorrhage, and subsequent peritonitis or bacterial sepsis.

Pulmonary manifestations and findings: cough, wheezing, dyspnea, hoarseness, pneumonitis, hemoptysis, respiratory failure, diffuse interstitial infiltrates or consolidation on chest radiographs.

Neurologic findings: aseptic or gram-negative meningitis, larvae have been reported in the CSF, meningeal vessels, dura, epidural, subdural, and subarachnoid spaces.

Systemic signs and symptoms: peripheral edema and ascites secondary to hypoalbuminemia from protein losing enteropathy.

Recurrent gram negative bacteremia/sepsis from larvae carrying bacteria that penetrate mucosal walls.

Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH).

Peripheral eosinophilia is frequently absent.

Cutaneous manifestations.

Recurrent maculopapular or urticarial rash most commonly found along the buttocks, perineum, and thighs due to repeated auto-infection, but can be found anywhere on the skin.

Larva currens - pathognomonic serpiginous or urticarial rash that advances as rapidly as 10cm/hr.

Diagnosis. The diagnosis is established by demonstrating characteristic, motile rhabditiform larvae in stool or duodenal fluid specimens. Concentration techniques such as the Baermann funnel method, fecal culture, and serial sampling are often necessary because

larval output is often sporadic and low. The use of duodenal aspirates, mucosal biopsies, or the string test (Enterotest') can increase the likelihood of diagnosing strongyloidiasis. In contrast to normal hosts, patients with the hyperinfection syndrome may have large numbers of larvae present in sputum, bronchial washings, cerebrospinal fluid, urine, and ascitic fluid.

Patients with acute or chronic infections may have a moderate eosinophilia (10% to 25%), but this is usually absent in cases of hyperinfection. Most infected subjects will have S. stercoralis' specific immunoglobulin G detectable by enzyme-linked immunosorbent assays. These assays are both sensitive and specific, and are now available in reference laboratories.

Treatment. For φcute and chronic strongyloidiasis first line therapy is Ivermectin, in a single dose, 200 μg/kg orally for 1-2 days. Relative contraindications:confirmed or suspected concomitant Loa loa infection. persons weighing less than 15kg, pregnant or lactating women. In recent years, ivermectin has replaced thiabendazole as the drug of choice for treating strongyloidiasis. Thiabendazole remains a useful alternative choice for treatment; however, its efficacy is variable and its use may be complicated by multiple side effects including nausea, vomiting, dizziness, rash, and hallucinations. Albendazole, which has excellent activity against hookworm, the larvae of which are occasionally confused with S. stercoralis larvae, has only modest efficacy in the treatment of strongyloidiasis. Patients with the hyperinfection syndrome tend to be refractory to treatment, which may need to be both prolonged and repeated. Intensive supportive therapy, antimicrobial coverage for secondary bacterial infections, and nutritional supplementation are necessary adjuncts to antiparasitic drugs in patients with overwhelming S. stercoralis infection.

DRACUNCULIASIS

Dracunculiasis, also known as guinea worm disease or dracontiasis, develops after the ingestion of water contaminated with copepods infected with Dracunculus medinensis. A chronic skin ulcer from which the adult worm protrudes is the main manifestation of disease. Dracunculiasis is responsible for significant morbidity and decreased agricultural productivity in endemic populations.

Epidemiology. Dracunculiasis remains endemic in rural populations in several countries in sub-Saharan Africa. A worldwide eradication campaign has successfully reduced the incidence of disease from more than 3 million cases in 1986 to less than 100,000 cases in 1999. The prevalence of dracunculiasis exhibits seasonal variation. The frequency of infection increases with age until the second or third decade of life. Greater exposure to infected water through agricultural activities or the collection of water for domestic use places certain groups at higher risk for infection. Sources of drinking water such as step wells or ponds that require people to walk down into the water are necessary for continued transmission of this parasite.

Life Cycle of D. medinensis (fig. 26). Human infection is acquired after drinking water containing copepods (Cyclops) harboring the third-stage larvae of the parasite. The larvae penetrate the intestinal mucosa to reach the retroperitoneum, where they mature into adult worms during a 12-month period. The adult female migrates to the skin surface to form a blister from which a portion of the worm protrudes. Water exposure leads to the release of many first-stage larvae from the wound, which are in turn ingested by copepods.

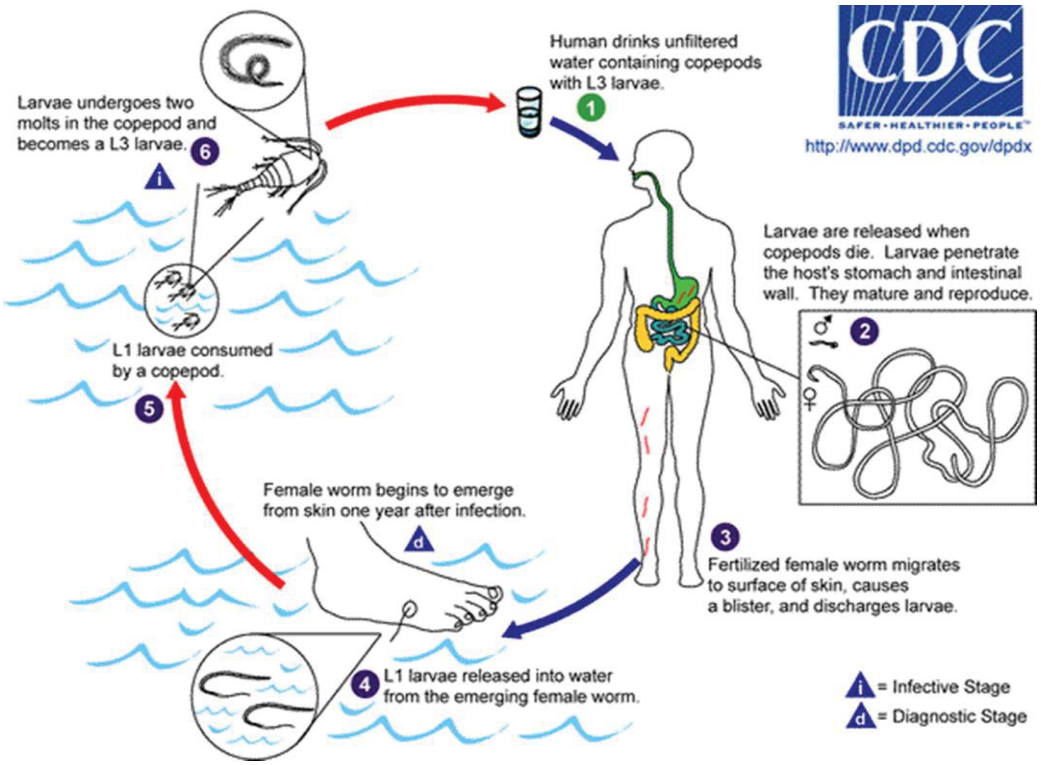

Fig. 26. – Life Cycle of D. medinensis

After a period of about 10 days, the larvae mature to a new infective stage. The adult females of D. medinensis range from 70 to 120 cm in length; the males, uncommonly observed in infected humans, measure only 3 to 5 cm.

Clinical Features. Prodromal symptoms of urticaria, fever, nausea, vomiting, diarrhea, and dysphoria may precede the formation of a skin blister. The lesion is initially pruritic and erythematous and then progresses to form a vesicle that may measure several centimeters in diameter. After the blister ruptures, the adult female protrudes to a distance of several centimeters. The ulcers are painful and occur most commonly in the lower extremities, although many other locations are possible. Multiple ulcers may be present, with greater numbers directly correlating with the degree of disability suffered. The adult worm intermittently discharges a milky white fluid containing larvae and is gradually resorbed or completely extruded. The healing process may take many weeks or even months, during which the affected person is incapacitated. Secondary bacterial infections with abscess formation are common complications whereas tetanus is rare. If the ulcer formation occurs during a critical agricultural period or the school year for children, the resulting disability can have significant negative social and economic impact. The proximity of an ulcer to a joint may lead to arthritis and long-term disability due to joint contractures.

Diagnosis. The clinical picture is diagnostic. A case of dracunculiasis is defined as an individual exhibiting or having a history of a skin lesion with the emergence of a Guinea worm. Larvae can be seen on microscopic examination of fluid discharged from the ulcer. Attempts to develop serologic tests for the diagnosis of the infection during the prepatent period have been unsuccessful.

Treatment. Optimal management of GWD involves the following steps:

First, each day the affected body part is immersed in a container of water to encourage more of the worm to come out. To prevent contamination, the infected person is not allowed to enter drinking water sources. Next, the wound is cleaned.

Then, gentle traction is applied to the worm to slowly pull it out. Pulling stops when resistance is met to avoid breaking the worm. Because the worm can be as long as one meter, full extraction can take from several days to weeks.

The worm is then wrapped around a rolled piece of gauze or a

stick to maintain some tension on the worm and encourage more of the worm to emerge. This also prevents the worm from slipping back inside.

Afterwards, topical antibiotics are applied to the wound to prevent secondary bacterial infections.

The affected body part is then bandaged with fresh gauze to protect the site. Medicines, such as aspirin or ibuprofen, are given to help ease the pain of this process and reduce inflammation.

These steps are repeated every day until the whole worm is successfully pulled out.

Accidental rupture of the worm will precipitate severe systemic reactions manifested by fever, anaphylaxis, and urticaria with late complications including abscess formation and chronic ulceration. Surgical extraction of the unerupted worm under local anesthesia effectively shortens the removal time and associated period of disability. Tetanus immunization is recommended.

Prevention. The Guinea Worm Eradication Program (GWEP) includes a group of national and international partners whose purpose is to support the global eradication of Guinea worm disease (GWD). GWEP provides these guidelines for interventions that focus on preventing the spread of GWD: surveillance (case detection) and case containment, provision of safe drinking water, vector control using a chemical larvicide, health education and community mobilization.

Many of these interventions are provided by village volunteers, people who are selected by the community to work with the GWEP. Village volunteers are the backbone of the program. In their communities, they identify and treat people with GWD and prevent them from contaminating drinking water sources (case containment). They also distribute filters and provide community health education.

Health education and community mobilization are important aspects of GWD eradication. Activities include: teaching communities about the disease and how it is spread. People are educated during household visits by GWEP volunteers and staff and through organized events, such as worm weeks. Helping villagers take action against the disease. Preventing people with worms from entering and contaminating water supplies. Using water filters to protect against GWD.

Helping villagers understand the need for safe chemical larvicide in their water supplies.

CESTODES (TAPEWORMS)
GENERAL CHARACTERISTICS OF TAPEWORMS (CESTODES)

Tapeworms are parasites of the vertebrate digestive tract and about 4000 species are known. The true tapeworms, class Cestoda, belong to the phylum Platyhelminthes, the most highly specialized of the metazoan parasites. All adult members of this class are endoparasites of the alimentary tract or associated ducts of vertebrates. Their life cycle includes at least one intermediary host, in which the tapeworm undergoes one phase of development.

Almost all tapeworms require at least two hosts with the definitive host being a vertebrate, although intermediate hosts can be invertebrates.

General Structure of Tapeworms:

- Head region (scolex): contains suckers and hooks used to attach to a host organism.
- Proglottids: square body segments used for reproduction.
- Tapeworms are usually monoecious (have both male and female reproductive organs).
- A proglottid is fertilized by another proglottid in the same or a different strobila.
- Shell-encased embryos form in the uterus and exit the proglottid via a uterine pore or the entire proglottid may detatch and pass out of the host.

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Cestodiasis is the term for being infected with a cestode. Adult cestodiasis occurs when a human is infected with an adult tapeworm. Adult cestodiasis is the commonest form and is generally not very harmful. However, heavy infestation can lead to physical damage to the wall of the gut or perhaps blockage of the intestines.

Clinically important cestodes pathogenic to man are:

- Taenia solium (pork tapeworm)
- Taenia saginata (beef tapeworm)
- Diphyllobothrium latum (fish or broad tapeworm)
- Hymenolepis nana and H. diminuta (dwarf tapeworm and rat tapeworm respectively)
- Echinococcus granulosus and E. multilocularis (cause hydatid disease)

Life cycle

This involves two hosts: a definitive and an intermediate. Humans are involved as either definitive host or intermediate host.

Humans are as definitive host in Teniasis**,**

Humans are as intermediate host in cysticercosis.

TENIASIS

Cestodiasis is the term for being infected with a cestode. Adult cestodiasis occurs when a human is infected with an adult tapeworm.

***Epidemiology*.** Teniasis is caused by Tenia solium or T. saginata. These cestodes have a worldwide distribution but incidence is higher in developing countries. Infection rate is as low as 1 per 1000 in most of North America and as high as 10% in the third world. Pork tapeworm shows a higher incidence but this is dependent on dietary habits. T. saginata worms can be found worldwide in countries where cattle are raised for human consumption. The frequency of beef tapeworm has decreased in developed countries owing to stricter meat inspection practices, better hygiene, and significantly better sanitary facilities. In developing countries, particularly in pastoral societies and rural areas, where sanitary installations are not an element of the culture and where human excrement is disposed of on open ground, used to fertilize, or even used for medicinal purposes (12), both T. saginata and T. solium continue to flourish.

Morphology. . saginata can be up to 4 to 6 meters long and 12 mm broad; it has a pear-shaped head (scolex) with four suckers but no hooks or neck. It has a long flat body with several hundred segments (proglottids). Each segment is about 18 x 6 mm with a branched uterus (15-30 branches). The egg is 35 x 45 micrometers, roundish and yellow-brown. It has peripheral radial striations and contains an

embryo with 3 hooklets.

T. solium is slightly smaller than T. saginata. It has a globular scolex with four suckers and a circular row of hooks (rostellum) that gives it a solar appearance. There is a neck and it has a long flat body (0.1 meter in length). The proglottids are 5 x 10 mm with a 7-12 branch uterus. The eggs of T. solium and T. saginata are indistinguishable.

Life cycle (fig. 27). A tapeworm larval cyst (cysticercus) is ingested with poorly cooked infected meat; the larva escapes the cyst and passes to the small intestine where it attaches to the mucosa by the scolex suckers. The proglottids develop as the worm matures in 3 to 4 months. The adult may live in the small intestine as long as 25 years and pass gravid proglottids with the feces. Eggs extruded from the proglottid contaminate and persist on vegetation for several days and are consumed by cattle or pigs in which they hatch and form cysticerci.

Pathology and pathogenesis. Clinical features. Light infections remain asymptomatic, but heavier infections may produce abdominal discomfort, epigastric pain, vomiting and diarrhea.

Complications. Acute surgical abdomen, appendicitis, or obstructed bile or pancreatic ducts.

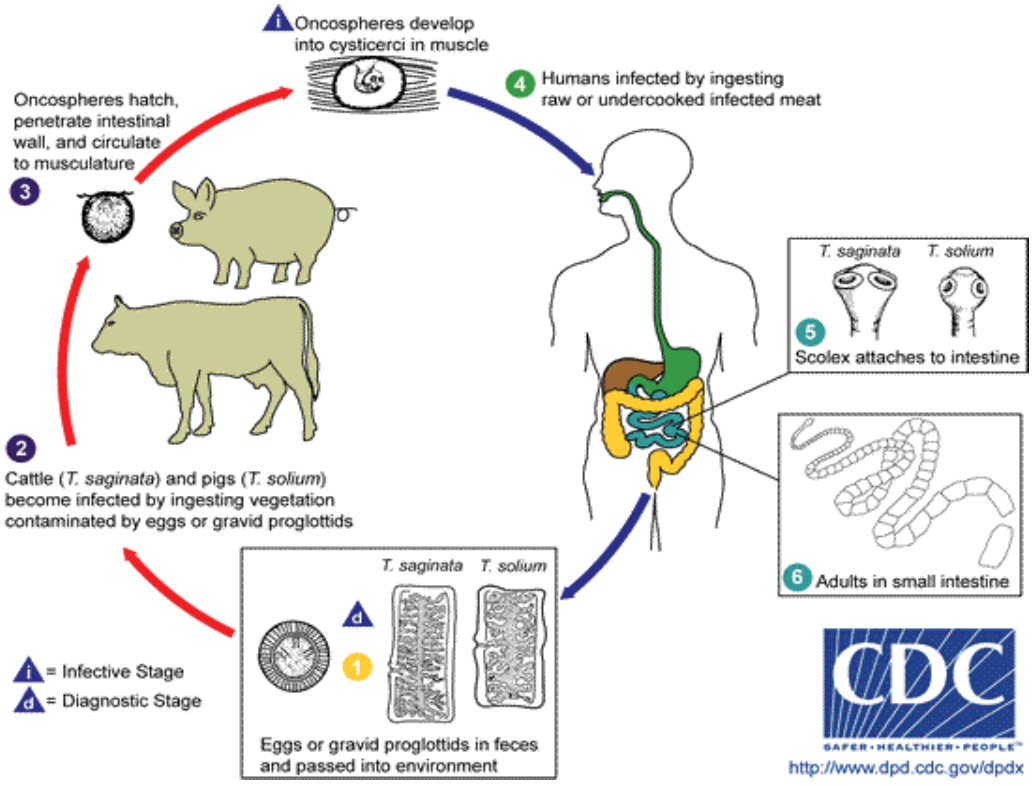

Fig. 27. – Life cycle Tenia solium and T. saginata

Human cysticercosis. Human cysticercosis is caused by the development of T. solium oncospheres to the larval stage, or cysticercus, in the interstitial tissues of humans. Because the oncospheres are transported passively from the intestinal wall through the circulation, they can lodge in almost any tissue, but cysticerci are most frequently found in brain, skeletal muscle, and subcutaneous tissues. By far the most important clinicopathologic picture is the one these parasites produce in the CNS. Cysticercosis is the most common parasitosis affecting the CNS and a major cause of neurological disease. It is considered an emerging public health problem and been reported to be increasing in countries that receive immigrants from countries where the tapeworm is endemic.

The incidence of cerebral cysticercosis can be as high 1 per 1000 population and may account for up to 20% of neurological case in some countries (e.g., Mexico); cysticercosis ocular involvement occurs in about 2,5% of patients and muscular involvement is as high as 10% (India).

Clinical Manifestations. The clinical manifestations of NCC are secondary to location, number of cysts, and inflammatory response of the host. The clinical signs and symptoms are generally the result of the inflammatory host response to the cysticerci in the brain tissue. The neurologic picture it produces is complex and pleomorphic; often, it can be asymptomatic.

The principal sites and approximate frequency of brain cysticerci are as follows: parenchyma, approximately 60%; subarachnoid space, meningobasal and cortical, approximately 40%; ventricular system, approximately 10%; mixed areas, more than 50%; spine, approximately 1%. Parenchymal cysts can be single or multiple. The majority of these larvae, when viable, are 1 or 2 cm in diameter, are filled with fluid, and have an invaginated scolex. They are observed in children and young adults and frequently cause no symptoms. It is surmised that a proportion of these infections are resolved spontaneously by the patients' immune response, leaving small granulomata or calcified cysts that are fortuitously detected on radiographs. In other cases, viable, translucent larvae have been seen with computed tomography (CT) in persons without symptoms.

The symptoms of patients with parenchymal cysts are varied, but most induce epilepsy that includes focal or generalized seizures (30% to 92%) and headache. Cysticercosis has been recognized as a major

cause of late-onset epilepsy in several endemic countries.

When parasites lodge in the ventricular cavities, they may become trapped in lateral ventricles, the fourth ventricle (by far the most frequent ventricular location), or the aqueduct. If the cyst is free, it may cause little inflammatory reaction. The clinical manifestations are the result of obstruction of CSF circulation, which can give rise to hydrocephalus. Acute hydrocephalus is a syndrome characterized by increased intracranial pressure, headache, vomiting, impaired vision, dizziness, and ataxia. Papilledema and mental disturbances are also common in patients with hydrocephalus. The syndrome progresses if the hydraulic problem is not resolved with a ventricular shunt, causing progressive loss of consciousness, decerebration, and death. Cysticerci that lodge in the fourth ventricle exhibit a syndrome of progressive hydrocephalus, with headache, nausea, vomiting, and papilledema associated with disturbances in the cerebellar functions (dizziness, vertigo, and loss of equilibrium and motor coordination). In other cases, the cyst adheres to the base of the fourth ventricle, inducing an inflammatory response with ependymitis characterized by signs of brain dysfunction.

Cysticerci found in the basal cisternae are frequently in clumps or of the racemose type. The racemose cysticercus is a large membranous cyst measuring up to 5 cm in diameter. It often does not have a visible scolex, but it is certainly derived from a taeniid because it has the ultrastructural morphologic feature of taeniid tegumentary bladder walls. The work of Rabiela and coworkers has shown by serial sections that these racemose forms do contain vestiges, or sometime whole scolices, unequivocally belonging to the species T. solium. For reasons that are at present not understood, the parasite located in the ventricles frequently becomes of the racemose type.

In cases in which the inflammatory process advances or increases, it can induce vasculitis or neuritis with local or distant ischemic phenomena, all of which are responsible for further brain damage and functional deterioration.

Cysticerci located in the subarachnoid space are in close contact with the CSF, and it is assumed that the parasites reach the meninges from the ventricles. This form of NCC is almost always associated with severe inflammatory infiltrates, which eventually give a clinical picture of chronic basal meningitis. This complication gives rise to one of the most frequent signs of NCC: increased intracranial

pressure, without focal deficits, which can progress rapidly and cause death if it is not treated. On CT examination, they can be confused with parenchymal cysts.

Diagnosis. NCC should be suspected when the patient is known to live or to have lived in an endemic zone or country or has a clinical history of taeniasis or a family member who does; when there is chronic, persistent, atypical headache that is resistant to ordinary treatment, or seizures in young adults; when there are neurologic symptoms associated with increased intracranial pressure (papilledema); or when a nonsenile person exhibits mental deterioration. CT is the most useful study and in most cases is virtually

CSF analysis is useful and shows lymphocytic pleocytosis and elevated protein content in most cases, eosinophilia in about 50% of cases, and decreased glucose level in about 25% of cases.

By using a combination of ELISA and immunoblotting (enzyme-linked immunoelectrotransfer blot assay), Gottstein and colleagues have been able to identify specific antibodies against T. solium in 92% of serum samples and 100% of CSF samples from patients with cysticercosis. An additional enzyme-linked immunoelectrotransfer blot assay based on affinity of purified glycoprotein antigens and lentil lectin has reported a 98% sensitivity and 100% specificity in detecting antibodies in serum and CSF from patients with confirmed cysticercosis. It is also capable of discriminating cysticercosis from other infections and from no infection. Enzyme-linked immunoelectrotransfer blot assay has been used successfully in numerous field trials. Serodiagnosis with these methods has been extremely useful in epidemiologic studies, and they do aid in the diagnosis of individual cases of suspected NCC. However, definitive diagnosis can be carried out only by CT or magnetic resonance imaging techniques.

Diagnosis of teniosis is based on the recovery of eggs or proglottids in stool or from the perianal area.

Differential Diagnosis of Taenia solium and Taenia saginata Infestations.

Taeniasis can be diagnosed on the basis of the following findings:

- A careful clinical history and questioning of patients about ingestion of raw beef or pork (particularly sausages).

- Discharging of proglottids or worm segments in the stool (loose gravid proglottids in underclothing or bedclothes are indicative of T. saginata).
- Coprologic analysis: three serial stool examinations on three consecutive days by use of perianal swabs or the method of Graham if T. saginata is suspected or the method of Faust, Ritchie, or Kato if T. solium is suspected. If proglottids become available, an effort should be made to fix them and count the uterine branches under the microscope. If the number of branches is 12 or fewer, it can be assumed that the patient has T. solium. The patient should be advised that he or she is a potential risk to other humans, instructed on hygiene measures, and treated as soon as possible. The patient should also be asked to recover the tapeworm (taking all safety precautions and using gloves and a disposable or autoclavable container) and bring it into the laboratory for definitive diagnosis.

From the medical point of view, the specific diagnosis and treatment of Taenia species infestations are important, because of the eggs of T. solium and T. saginata are indistinguishable, the former being the cause of human cysticercosis. Although the identification of the scolex and some morphologic features of the proglottids allows precise diagnosis of the tapeworm species, this is frequently not possible. Well-preserved proglottids and trained personnel, which many countries do not have, are required. In addition, when the proglottids are macerated, it is virtually impossible to establish a definitive diagnosis. Two promising new techniques for the detection of taeniid antigens in stool specimens have been worked out by several groups: (a) antigen capture and detection by enzyme-linked immunosorbent assay (ELISA), and the preparation of specific deoxyribonucleic acid (DNA) probes for the detection of Taenia eggs in stool, which promise rapid, highly sensitive and specific assays that could eventually be used for epidemiologic surveys.

Treatment of Taenia Tapeworms

Praziquantel is the medication most often used to treat active taeniasis, given at 5-10 mg/kg orally once for adults and 5-10 mg/kg orally once for children. If the patient has cysticercosis in addition to taeniasis, praziquantel should be used with caution. Praziquantel is cysticidal and can cause inflammation around dying cysts in those with cysticercosis, which may lead to seizures or other symptoms. Niclosamide is an alternative, given at 2 g orally once for adults and

50 mg/kg orally once for children. For children weighing between 11 and 34 kg, the recommended dose is 1 g. Children younger than 2 years of age are given 0,5 g in one dose, the tablets ground to powder and mixed with water. Niclosamide is tolerated well, and less than 10% of patients report nausea, vomiting, abdominal pain, or exanthema, which are transitory. If the species of Taenia has not been determined, it is recommended that the drug be followed by a laxative 1 hour later to ensure expulsion of the worm. Bendazole is a potent anthelmintic drug with unique broad-spectrum activity indicated in multiple parasitosis. It should not be used in patients with hypersensitivity to the drug, children younger than 2 years or during pregnancy owing to the embryotoxic and teratogenic effects, which have been observed in experimental animals. The recommended dose for treatment of tapeworms is 6,6 mg/kg (two doses of 200 mg each per day on 3 consecutive days).

After treatment, stools should be collected for 3 days to search for tapeworm proglottids for species identification. Stools should be re-examined for Taenia eggs 1 and 3 months after treatment to be sure the infection is cleared.

Cysticercosis. Praziquantel has been shown by various workers in different countries to be an effective drug against parenchymal NCC. The patients are treated with 50 mg/kg daily for 15 days. About 2 or 3 days after the treatment is started, a strong inflammatory reaction occurs, with increased protein levels and cells in CSF, headaches, exacerbation of neurologic symptoms, and edema around cystic lesions, which can be detected by CT. These reactions can be suppressed with steroids and usually last 2 or 3 days. Clinical evidence of improvement is observed about 3 months after treatment. Albendazole, an imidazole, has been used in several trials and is as effective as praziquantel for parenchymal lesions. It has the additional advantage of being considerably less expensive than praziquantel and should be particularly useful in endemic countries where economy is an important factor in health care. Extraparenchymal lesions affecting basal or lateral cisternae, lesions caused by Cysticercus racemosus, and calcified cysts do not improve with praziquantel or albendazole. These types of NCC require surgery for extirpation of the parasite or insertion of valves to drain CSF and relieve increased intracranial pressure due to hydrocephalus.

Prevention. Inspect meat thoroughly. Adequate handling of food e.g. freezing or cooking.

Cysticerci do not survive temperatures <10°C and >50°C. WHO advocate the periodic treatment of tapeworms such as T. solium in endemic areas with albendazole. This can prevent neurocysticercosis at a later stage.

DIPHYLLOBOTHRIASIS

Fish tapeworm (diphyllobothrium latum) infection is distributed worldwide, in the subarctic and temperate regions; it is associated with eating of raw or improperly cooked fresh water fish.

Epidemiology. Infections are acquired by eating raw or undercooked fish, usually from the Northern Hemisphere (Europe, newly independent states of the Former Soviet Union, North America, Asia), but cases have also been reported in Uganda and Chile. Fish infected with Diphyllobothrium larvae may be transported to and consumed in any area of the world. Adequately freezing or cooking fish will kill the parasite.

Morphology. This is the longest tapeworm found in man, ranging from 3-10 meters with more than 3000 proglottids. The scolex resembles two almond-shaped leaves and the proglottids are broader than they are long, a morphology reflected in the organism's name. Eggs are 30 x 50 micrometers in size and contain an embryo with 3 pairs of hooklets

Life cycle of diphyllobothrium latum (fig. 28). Man and other animals are infected by eating uncooked fish that contains plerocercoid larvae (15 x 2 mm) which attach to the small intestinal wall and mature into adult worms in 3 to 5 weeks. Eggs discharged from gravid proglottids in the small intestine are passed in the feces. The egg hatches in fresh water to produce a ciliated coracidium which needs to be ingested by a water flea (Cyclops) where it develops into a procercoid larva. When infected Cyclops are ingested by the freshwater fish, the procercoid larva penetrates the intestinal wall and develops into a plerocercoid larva, infectious to man.

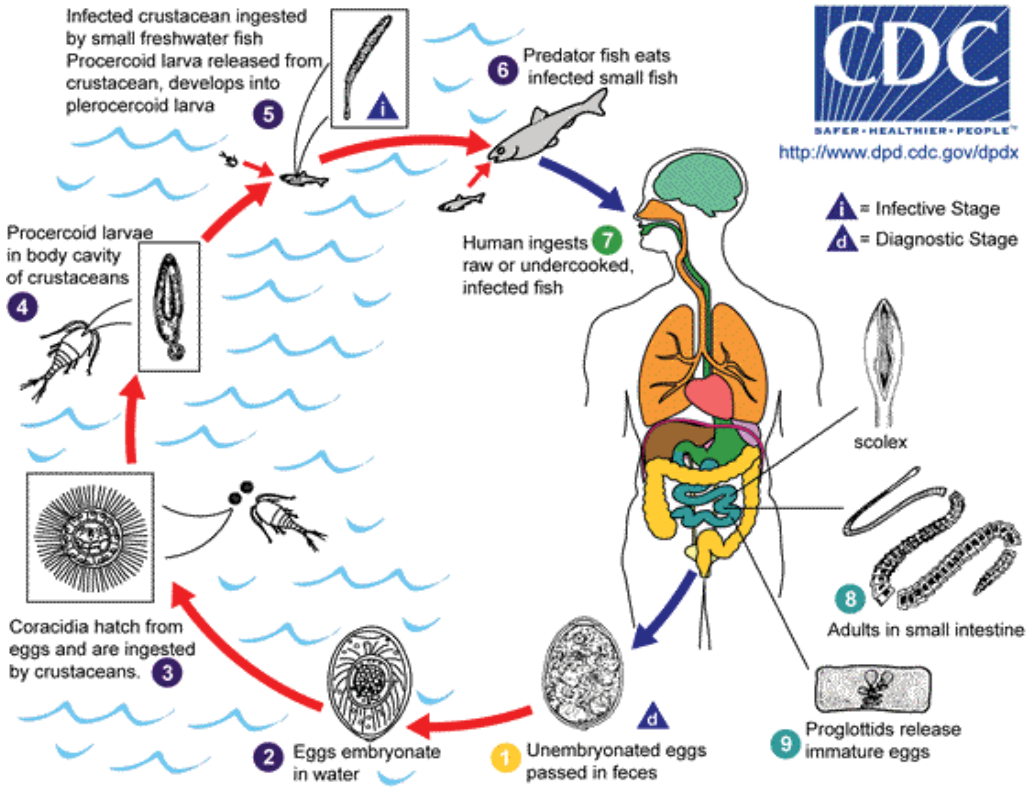

Fig. 28. – Life cycle of diphyllobothrium latum

Clinical manifestation. Depends on the number of worms. Mild infection leads to: Abdominal discomfort; loss of appetite; loss of weight; malnutrition.

B12 deficiency may occur with heavier infections and may lead to anaemia and even subacute combined degeneration of the spinal cord.

Microscopic stool examination for ova and parasites.

Diagnosis. Complete blood cell count: hemoglobin and hematocrit levels may be below or at the lower end of the reference range. he mean cell volume may be above or at the higher end of the reference range. Eosinophilia may be present. Vitamin B-12 level and Folate level deficit

Treatment. Praziquantel, adults, 5-10 mg/kg orally in a single-dose therapy; the dosage for children is the same. (Note: praziquantel should be taken with liquids during a meal).

Alternative:Adults, niclosamide 2 gm orally once; children, 50 mg/kg (max 2 gm) orally once. Niclosamide must be chewed thoroughly or crushed and swallowed with a small amount of water.

Diet: Less than 2% of patients with diphyllobothriasis develop anemia, even in the face of decreased vitamin B-12 levels. Vitamin supplementation may be required in severe cases.

Prevention. Freeze fish for 24 hours. Thoroughly cook fish. Pickling fish. Preventing sewage contamination of fish reservoirs.

HYMENOLEPIASIS

Hymenolepis nana is the cestode that most commonly infects humans, especially school-aged children. It is most often seen in children in countries in which sanitation and hygiene are inadequate. Although the dwarf tapeworm infection rarely causes symptoms, it can be misdiagnosed for pinworm infection. Hymenolepiasis most frequently occurs in warm, dry regions of the developing world, where exposure to human feces results in hand-to-mouth infection. Direct person-to-person spread of H. nana may occur.

This is a relatively small tapeworm (15-40 mm) and tends to infect children. The reservoir is rodents and transmission is oro-faecal. Thus cross infection and autoinfection is common in children

Life cycle (fig. 29). Humans become infected with H. nana when they ingest infective eggs, most commonly by direct fecal-oral exposure. The eggs pass into the ileum and hatch into oncospheres (the larval form), which penetrate the lamina propria of the villus.

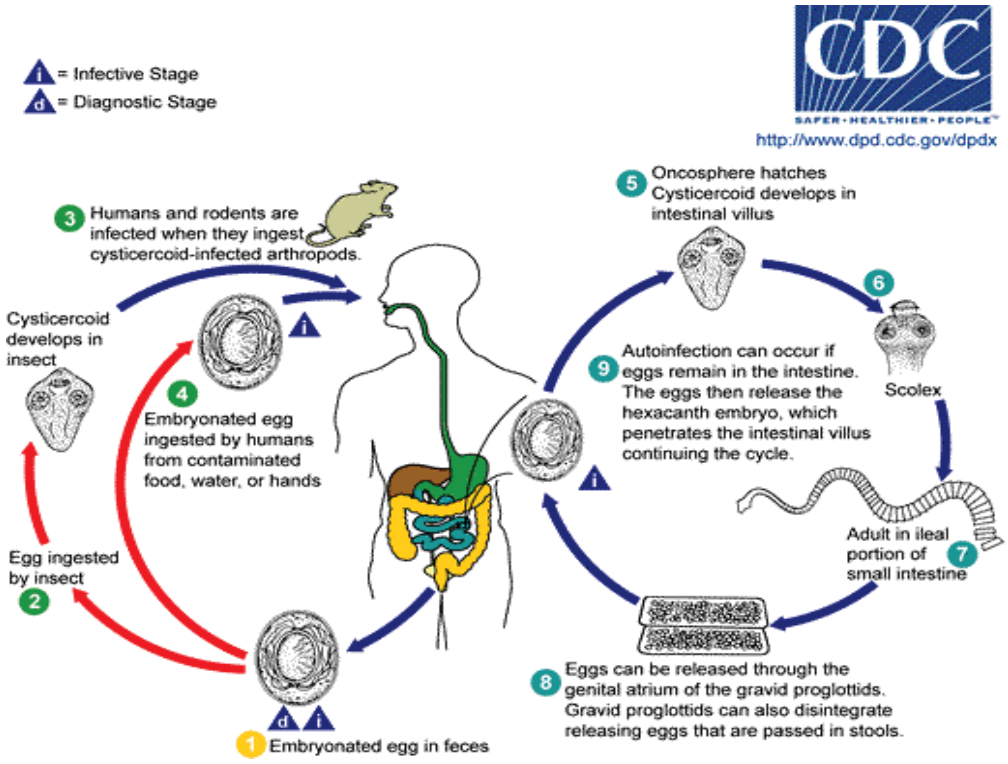

Fig. 29. – Life cycle of H. nana

Within 3-4 days, the larvae mature into the preadult cysticercoid, which then enters the gut lumen to attach to the mucosae of the villus. Mature adults, measuring 35-45 mm in length and comprising 150-200 proglottids, result within about 3 weeks. Self-mating between adjacent proglottids generates hundreds of eggs, some of which penetrate intestinal villa and some of which pass into the feces. Occasionally, rodents may ingest the eggs in feces and serve as incidental hosts and reservoirs for spread of infection.

Clinics. The vast majority of infections produce no symptoms. Symptom frequency seems to correlate with increasing worm burden. Among children with clinical infection, symptoms (in order of decreasing frequency) include restlessness, irritability, diarrhea, abdominal pain, restless sleep, anal pruritus, and nasal pruritus. Rare symptoms include anorexia, increased appetite, vomiting, nausea, bloody diarrhea, hives, extremity pain, headache, dizziness, behavioral disturbances, and seizures.

Diagnosis. One third of infected children have eosinophilia exceeding 5%. Diagnosis is made by discovery of eggs in stool specimens. Sections of the adult worm most often disintegrate before passage into the stool but rarely may be discovered.

Treatment. Praziquantel, adults and children, 25 mg/kg in a single-dose therapy.

Alternatives. Niclosamide: adults, 2 gm in a single dose for 7 days; children 11-34 kg, 1 gm in a single dose on day 1 then 500 mg per day orally for 6 days; children >34 kg, 1,5 gm in a single dose on day 1 then 1 gm per day orally for 6 days.

Nitazoxanide: adults, 500 mg orally twice daily for 3 days; children aged 12-47 months, 100 mg orally twice daily for 3 days; children 4-11 years, 200 mg orally twice daily for 3 days.

Prevention. Emphasize good personal hygiene and proper disposal of sewage. Good handwashing after handling pets should be reinforced. Use contact precautions because H nana eggs in stool are infectious.

ECHINOCOCCOSIS

Echinococcus granulosus and E. multilocularis are causative agents of ***hydatid cysts***. Cystic echinococcosis (CE) is caused by infection with the larval stage of Echinococcus granulosus. CE is found

in Africa, Europe, Asia, the Middle East, Central and South America, and in rare cases, North America. The incidence of human infection about 1 to 2 per 1000 population and may be higher in rural areas of affected regions. The parasite is transmitted to dogs when they ingest the organs of other animals that contain hydatid cysts. The disease is most commonly found in people involved in raising sheep, as a result of the sheep's role as an intermediate host of the parasite and the presence of working dogs that are allowed to eat the offal of infected sheep.

Alveolar echinococcosis (AE) is caused by infection with the larval stage of Echinococcus multilocularis. AE is found across the globe and is especially prevalent in the northern latitudes of Europe, Asia, and North America. The adult tapeworm is normally found in foxes, coyotes, and dogs. Infection with the larval stages is transmitted to people through ingestion of food or water contaminated with tapeworm eggs.

Life cycle *(fig. 30).* The adult Echinococcus granulosus (3 to 6 mm long) (1) resides in the small bowel of the definitive hosts, dogs or other canids. Gravid proglottids release eggs (2) that are passed in the feces. After ingestion by a suitable intermediate host (under natural conditions: sheep, goat, swine, cattle, horses, camel), the egg hatches in the small bowel and releases an oncosphere (3) that penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs. In these organs, the oncosphere develops into a cyst (4) that enlarges gradually, producing protoscolices and daughter cysts that fill the cyst interior. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. After ingestion, the protoscolices (5) evaginate, attach to the intestinal mucosa (6), and develop into adult stages (1) in 32 to 80 days.

The same life cycle occurs with E. multilocularis (1.2 to 3.7 mm), with the following differences: the definitive hosts are foxes, and to a lesser extent dogs, cats, coyotes and wolves; the intermediate host are small rodents; and larval growth (in the liver) remains indefinitely in the proliferative stage, resulting in invasion of the surrounding tissues. With E. vogeli (up to 5,6 mm long), the definitive hosts are bush dogs and dogs; the intermediate hosts are rodents; and the larval stage (in the liver, lungs and other organs) develops both externally and internally, resulting in multiple vesicles. E. oligarthrus

(up to 2,9 mm long) has a life cycle that involves wild felids as definitive hosts and rodents as intermediate hosts. Humans become infected by ingesting eggs (2), with resulting release of oncospheres (3) in the intestine and the development of cysts (4) in various organs.

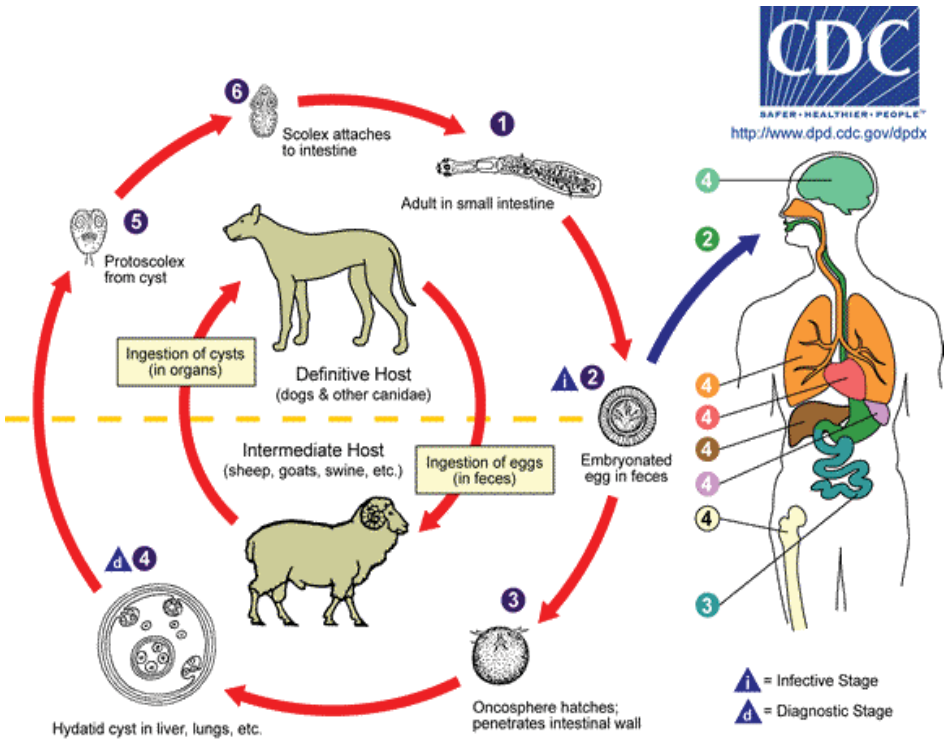

Fig. 30. – Life cycle of Echinococcus granulosus and E. multilocularis

The symptoms, comparable to those of a slowly growing tumor, depend upon the location of the cyst (fig. 24). Large abdominal cysts produce increasing discomfort. Liver cysts cause obstructive jaundice. Peribronchial cysts may produce pulmonary abscesses. Brain cysts produce intracranial pressure and Jacksonian epilepsy. Kidney cysts cause renal dysfunction. The contents of a cyst may produce anaphylactic responses. Loss of appetite is a frequent symptom, and weight loss and weakness may occur.

Cystic Echinococcosis. The incubation period of cystic echinococcosis is often prolonged for several years and most cases of cystic echinococcosis remain asymptomatic until the cysts reach a large enough size to cause dysfunction. Most primary infections in humans consist of a single cyst. The liver is the most common site of the hydatid cysts (98%), followed by the lungs. Cysts in the spleen, kidneys, heart, bone and central nervous system are less common. In secondary echinococcosis, larval tissue spreads from the primary site

and new cysts develop after spontaneous or trauma-induced cyst rupture or after release of viable parasite material during invasive treatment procedures.

Signs and symptoms may include hepatic enlargement with or without a palpable mass in the right upper quadrant, right epigastric pain, nausea, and vomiting. Rupture or leakage usually results in acute or intermittent allergic manifestations.

Alveolar Echinococcosis. The primary infection of alveolar echinococcosis is in the liver (60%), usually the right lobe, but direct extension to contiguous organs, as well as hematogenous metastases to the lungs (20%) and brain (<2%) is not uncommon. Alveolar echinococcosis is inhibited by the host from completing its development and remains in the proliferative stage indefinitely. The larval mass resembles a malignancy in appearance and behavior. In chronic alveolar hydatid infections, the lesion consists of a central necrotic cavity filled with a white amorphous material that is covered with a thin peripheral layer of dense fibrous tissue. Host tissue is directly invaded by extension of the budding and proliferating cyst wall, causing a pressure necrosis of surrounding host tissue. A vigorous inflammatory and fibrous tissue reaction usually surrounds the larval mass. Diagnosis is often delayed until an advanced and inoperable stage; mortality rates have traditionally been high, ranging between 50% and 75%.

Diagnosis. Cystic Echinococcosis. The diagnosis of E. granulosus infection (cystic hydatid disease) is suggested by identification of a cyst-like mass in a person with a history of exposure to sheepdogs in areas where the parasite is endemic. Cystic echinococcosis must be differentiated from benign cysts, cavitary tuberculosis, mycoses, abscesses, and benign or malignant neoplasms. Noninvasive imaging techniques such as CT scans, MRI, and ultrasound imaging are all used for detecting and defining the extent and condition of avascular fluid-filled cysts in most organs. These techniques have proved valuable for diagnosis and preoperative evaluation by staging the condition of the lesion, the extent of the lesion in reference to other organs and vital structures, and identifying the presence of additional occult lesions. Radiography permits the detection of hydatid cysts in the lungs; however, in other organ sites, calcification is necessary for visualization. Ultrasonography has been widely used for screening, clinical diagnosis, and monitoring of

treatment of liver and intra-abdominal cysts. Cyst viability cannot be reliably determined with radiography or parasite antigen detection; calcification can be present in all stages of cysts.

Serologic tests, such as enzyme-linked immunosorbent assay (ELISA) and indirect hemagglutination test, are highly sensitive methods for detecting infection. Specific confirmation can be obtained by demonstrating echinococcal antigens by immunodiffusion procedures or immunoblot assays.

Alveolar Echinococcosis. Alveolar echinococcosis closely mimics hepatic carcinoma or cirrhosis and is more commonly diagnosed in people of an advanced age. Plain radiographs show hepatomegaly and characteristic scattered areas of radiolucency outlined by calcific rings 2 to 4 mm in diameter. The usual CT image of E. multilocularis infection is that of indistinct solid tumors with central necrotic areas and perinecrotic plaque-like calcifications. Serologic test results are usually positive at high titers. Comparing a patient's titers with both purified-specific and shared antigens permits the serologic discrimination between patients infected with E. multilocularis and those infected with E. granulosus.

Treatment involves surgical removal of cyst or inactivation of hydatid sand by injecting the cyst with 10% formalin and its removal within few (4-5) minutes. In cases of inoperable hydatid cysts, or when the general condition of the patient precludes surgery, albendazole, 10 to 15 mg/kg per day for 1 month, or mebendazole, 50 to 150 mg/kg per day for 3 months, may be administered, although the results are unpredictable.

Surgery remains the mainstay in the treatment ot hepatic hydatid disease. Cystectomy and pericystectomy offer a good chance for cure and should be undertaken wherever possible. Occasionally, formal hepatic resection will be required. Radical surgery – either pericystectomy or resection – is possible in 50-85% of cases. In the absence of complications this can be achieved with little mortality and an acceptable morbidity. Recently, laparoscopic peri-cystectomy has been demonstrated to be as safe and effective as open laparotomy in selected cases with hepatic and/or splenic involvement.19 If surgical removal of the cyst is contra indicated, treatment of CE has several alternatives such as PAIR (Puncture, Aspiration, Injection of an heminthicide and Reaspiration), chemotherapy or 'wait and observe' approach. Basically, indications for hepatic surgery include large liver

cysts with putatively multiple daughter cysts; single liver cysts, situated superficially which may rupture spontaneously or as a result of trauma; bacterially superinfected cysts; cysts communicating with binary tree and/or exerting pressure on adjacent vital organs; brain, heart and kidney cysts; spinal and bone cysts. Relative contraindications are inoperable cases as defined for surgical procedures in general; patients with cysts difficult to access; abortive cysts either partly or totally calcified.

Alveolar Echinococcosis. Alveolar echinococcosis requires chemotherapy with or without surgery; radical surgery is the preferred approach in suitable cases. Effective treatment involves benzimidazoles administered continuously for at least 2 years and patient monitoring for 10 years or more since recurrence is possible. This has inhibited progression of alveolar echinococcosis and reduced lesion size in approximately half of treated cases. Intermittent treatment with albendazole is not recommended.

TREMATODOSE. OPISTHORCHIASIS

Opisthorchis viverrini (Southeast Asian liver fluke) is a food-borne trematode parasite from the family Opisthorchiidae that infects the bile duct, characterized by a long course with exacerbations contributing to the development of primary liver cancer. O. viverrini (together with Clonorchis sinensis and Opisthorchis felineus) is one of the three most medically important species in the family Opisthorchiidae.

Etiology. Structurally, O. viverrini is basically similar to C. sinensis and O. felineus. Pathogen is Opisthorchis viverrini – small trematode having dimensions of 4-13x1-3,5 mm and 5,4-10x0,8-1,9 mm respectively. Eggs are small (0,011-0,019x0,023-0,034 mm), have a lid. Opisthorchis viverrini is spread in Thailand, the Lao People's Democratic Republic, Vietnam and Cambodia.

Epidemiology. Opisthorchiasis (opisthorchosis) – oral helminthiasis with natural focal invasion. The final hosts of parasites and pathogens sources are people, cats, foxes, dogs that excrete helminth eggs in feces. Intermediate hosts are freshwater shellfishes – Bithynia laechi, additional hosts are carp fishes. Person is infected with opisthorchiasis when eating raw, salted or low-dried fish

containing live helminth larvae - metacercariae. Fishermen, wood rafters, fish farmers are exposed to infection concerning their profession. Infection usually occurs in the summer-autumn period. Susceptibility to invasion is general, more vivid picture is observed in people coming to endemic foci.

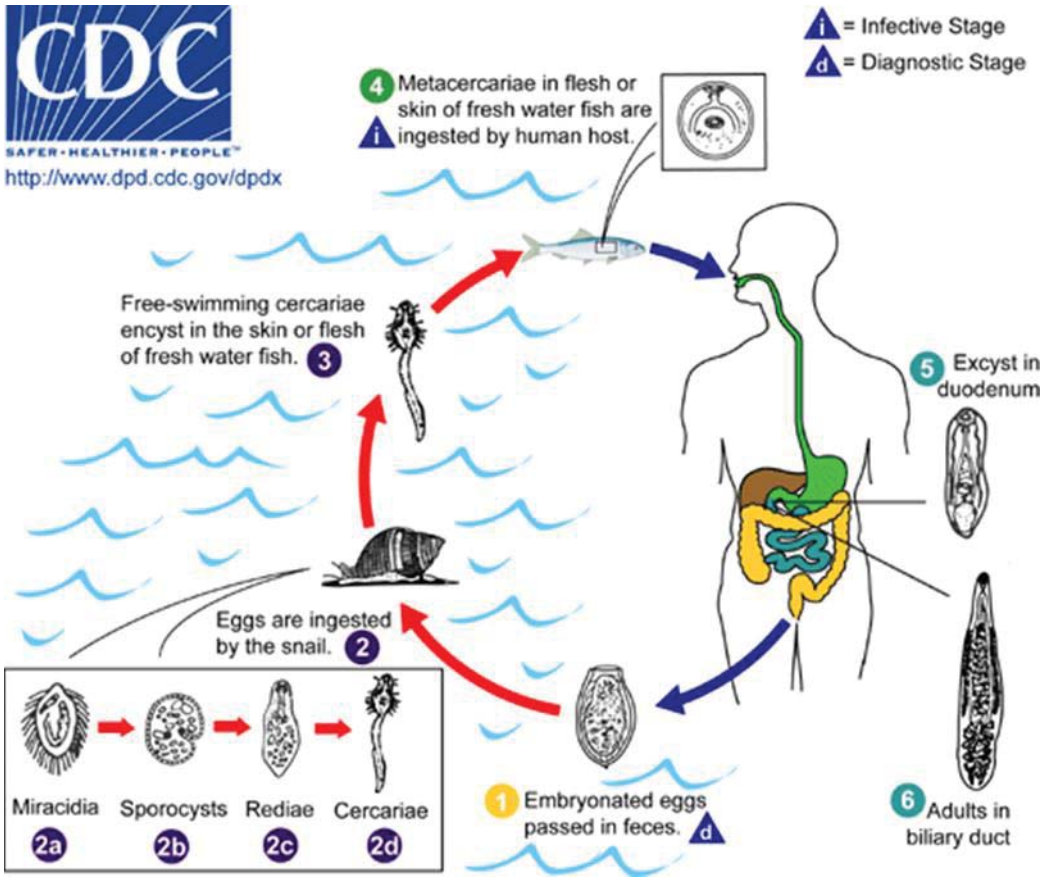

Fig. 31. – Life cycle

The adult flukes deposit fully developed eggs that are passed in the feces[1]*. After ingestion by a suitable snail (first intermediate host)*[2]*, the eggs release miracidia*[2a] *, which undergo in the snail several developmental stages (sporocysts*[2b]*, rediae*[2c]*, cercariae*[2d]*). Cercariae are released from the snail*[3] *and penetrate freshwater fish (second intermediate host), encysting as metacercariae in the muscles or under the scales*[4]*. The mammalian definitive host (cats, dogs, and various fish-eating mammals including humans) become infected by ingesting undercooked fish containing metacercariae. After ingestion, the metacercariae excyst in the duodenum*[5] *and ascend through the ampulla of Vater into the biliary ducts, where they attach and develop into adults, which lay eggs after 3 to 4 weeks*[6]*. The adult flukes (O. viverrini: 5 mm to 10 mm by 1 mm to 2 mm; O. felineus: 7 mm to 12 mm by 2 mm to 3 mm) reside in the biliary and pancreatic ducts of the mammalian host, where they attach to the mucosa.*

Pathogenesis. Ingested larvae are released from shells in the small intestine; in a few hours along the bile duct they penetrate into intrahepatic bile ducts and passages, into the ducts of the pancreas, where after 2 weeks turn into mature marita secreting eggs. Leading pathogenetic mechanisms are toxic and allergic effects of helminth eggs and their metabolites in humans, mechanical damage of the biliary system, impaired secretion and motility of the biliary tract, stomach and duodenum, thereby enhancing secondary infection, occurrence of cholangitis, cholelithiasis. Incidence of primary liver cancer is higher in the foci of infection than in the free areas of helminthiasis.

Clinical picture. The incubation period of the disease is 3-4 weeks. Early phase of infection in endemic foci is usually asymptomatic; malaise, fever, hives, frequent doughy feces, pain in the liver, hypereosinophilia are observed in travellers. In the late phase of invasion are observed colicky pain in the liver and gallbladder, dyspeptic symptoms, sleep disturbance, headache, often pallor, subicteric skin and mucous membranes. A number of patients has the enlargement of the liver and gall bladder, pain in the pancreas. Biochemical methods reveal a minor disorder of the liver and pancreas, hemogram reveals hypereosinophilia (80% or more).

Complications of the disease are liver abscesses, ascending cholangitis, parasitic cysts rupture, peritonitis, primary liver cancer and others. Opisthorchiasis adversely affects the course of a number of infectious diseases (shigellosis, hepatitis, typhoid fever).

Diagnosis involves the detection of O. viverrini eggs in the stool and duodenal contents or ELISA test (Ig G).

Treatment. Praziquantel at 50 mg/kg is highly effective and results in low toxicity. The drug is administered in three doses over 15-20 minutes after eating, taken with milk. Pathogenetic and symptomatic agents are used according to indications. Monitoring the effectiveness of the treatment is carried out after 1-2 months.

SCHISTOSOMIASIS

Schistosomiasis is the second most prevalent tropical disease (following malaria) and a leading cause of severe morbidity in large parts of Africa, Asiaand South America. Six hundred million are at risk; 200 million are infected, of whom 20 million are severely ill, and those

at risk for acquiring infection range from 600 million to 1 billion.

Schistosomiasis (also known as bilharzia) is an infection with blood flukes and is a major infectious diseases. Infection is endemic in many parts of Africa, the Middle East, Southeast Asia, South America, and the Caribbean.

The main goal for WHO is to control the disease, to reduce and even (in some countries) eliminate the risk of schistosomiasis through strong surveillance and control programmes.

Five species of Schistosoma are currently known to infect humans: S. haematobium, S. mansoni, and S. japonicum and the less common S. mekongi and S. intercalatum.

There are 2 types of clinical disease: urinary schistosomiasis (S. haematobium) and intestinal schistosomiasis (S. mansoni, S. japonicum, S. intercalatum, S. mekongi).

Characteristics of the Pathogen. The schistosomes are flatworms (platyhelminths) but differ from other flukes that infect humans in that they have separate sexes. Most other trematodes are hermaphroditic and are found in the intestinal tract or in organs, such as the liver. The lifecycle of schistosomes includes two hosts: a definitive host (i.e. human) where the parasite undergoes sexual reproduction, and a single intermediate snail host where there are a number of asexual reproductive stages.

Adult worms inhabit the venous system draining the urinary bladder or intestines. Adult male worms measure approximately 1 to 1,5 cm in length; the flattened sides of the body curve anteriorly to form the gynecophoric canal, in which adult females usually live. Adult females are rounded and longer than males (1,5 to 2,0 cm) and produce several hundred eggs daily. Epidemiologic evidence indicates that the mean life span of adult schistosomes is 5 to 10 years, although case reports document that viable eggs may be detected in excreta of infected persons as long as 40 years after they depart endemic areas.

Life cycle (fig. 31). Schistosome eggs enter the water when infected people urinate or defecate in or near water. Eggs hatch and the miracidium seeks out a snail. Inside the snail the parasite develops into a sporocyst and asexual reproduction takes place. Cercaria eventually are released into the water. When a schistosome cercaria swims it takes care to avoid UV light which can damage it, but is very sensitive to the scent of humans.

When it senses molecules from human skin it swims rapidly and

jerks around looking for the person. When it makes contact it releases chemicals that soften the skin and it burrows in shedding its tail at the same time. The fluke searches until it finds a capillary and enters it. The capillary is only barely wide enough for the fluke and it moves along using its pair of suckers. Eventually, it reaches a larger blood vessel in which it can float until it reaches the lungs and enters an artery and eventually makes its way to the liver.

Once in the liver, the fluke feeds on blood and begins to mature and develops ovaries or testes depending on its sex. The fluke grows dozens of times larger in the course of a few weeks and then begins to search for a mate. Once paired up, the pair mature sexually and travel from the liver to a permanent home that is species-specific.

In Schistosoma mansoni it is near the large intestine, in S. haemotobium it is the bladder, and in S. nasale, a blood fluke of cows, it is the nose. Once established the pair remain in situ for the rest of their lives. The male consumes blood and feeds the female most of it, which she turns into eggs, which pass out of the host and can begin the life cycle again.

Schsitosomiasis has a low mortality rate, but it is a chronic illness that debilitates the infected person.

Pathogenesis. Disease manifestations due to schistosome infection are a result of the stage of parasite active in the host and its interaction with specific and nonspecific inflammatory and immune responses. Multiple studies have demonstrated that only a proportion of infected persons exhibit disease. Most of them are heavily infected, but the relationship of disease to intensity of infection is not exact. There is evidence that other factors, such as host genetics, nutrition, and intercurrent infection, participate to varying degrees in determining the susceptibility to and the pathologic outcome of schistosomiasis.

Skin penetration by cercariae and the death of some of these organisms in the subcutaneous tissues result in an eruption called swimmers itch, which is associated with humoral, cellular, and local infiltrative responses. A serum sickness-like syndrome (acute schistosomiasis or Katayama fever) occurs in some infected individuals at 6 to 8 weeks, particularly those with heavy infection. This syndrome is thought to be due to the formation of antigen-antibody complexes.

The most significant disease manifestations of schistosomiasis follow egg deposition. As mentioned earlier, a proportion of ova

escape in excreta; those retained in host tissues elicit a series of immunopathologic reactions. The basic host response to parasite eggs is a delayed-type hypersensitivity granulomatous reaction that far exceeds the size of retained ova. These large granulomata account for some of the early obstructive lesions seen in the lower end of ureters in S. haematobium' infected persons and also in the hepatomegaly and interference with portal blood flow seen in S. mansoni, S. japonicum, and S. mekongi infections. Despite multiple immunologic factors that regulate granuloma formation (resulting in smaller granulomatous response in chronically infected persons), another set of more permanent fibrotic responses leads to obstructive and hemodynamic changes that herald significant morbidity.

The multicellular, multistage schistosome infection presents the mammalian host with a variety of antigenic stimuli. The host responds at both systemic and local levels. Serum antibodies and sensitized lymphocytes that react with the different stages of schistosomes are detected after infection. It is remarkable that as long as adult worms live in the venous system, no recognition by the host immune or inflammatory responses can be detected in situ. On the other hand, once ova are deposited, the host recognizes their existence, and the sensitized lymphocytes along with other inflammatory cells and antibodies contribute to granuloma formation. Schistosome egg granulomata are dynamic lesions that are tightly controlled, representing the balance between initiating and down-regulating immune mechanisms. Granuloma formation is further complicated by the subsequent development of fibrosis, which is responsible for the more permanent fibroobstructive and hemodynamic changes seen in schistosomiasis.

Like other worm infections that involve migration through host tissues, schistosome infections are characteristically associated with peripheral as well as tissue eosinophilia. This observation has been related to the role of eosinophils as effector cells in mediating host defense to multicellular organisms. Both oxidative and nonoxidative mechanisms have been linked with eosinophil-induced destruction of schistosome invading stages (schistosomula) and parasite eggs.

Clinical Manifestations. Specific disease manifestations due to schistosomiasis appear in only a proportion of infected individuals.

Symptoms can include anemia, diarrhea, fever, fatigue and van result in organ damage. In children infection can result in reduced

growth and mental development.

Skin penetration by human schistosomes results in the itchy papular eruption known as swimmer itch. Acute schistosomiasis manifests as a febrile illness with lymphadenopathy, hepatosplenomegaly, and eosinophilia. The more characteristic clinical manifestations occur after oviposition. In S. haematobium infection, the main features are hematuria, dysuria, and frequency as well as laboratory evidence of proteinuria and hematuria. Thickening and irregularity of urinary bladder wall and obstructive uropathy with hydroureter and hydronephrosis is observed in a significant proportion of infected persons. In S. mansoni, S. japonicum, and S. mekongi infections, the intestinal phase may be associated with abdominal pain and blood in stools. As egg deposition in the liver increases, hepatomegaly, portal hypertension, splenomegaly, and evidence of portosystemic anastomosis may be seen. These individuals remain asymptomatic for a considerable time, retain good liver function, may bleed several times without progressing to hepatic encephalopathy, but finally succumb to the effects of repeated bleeding or liver failure.

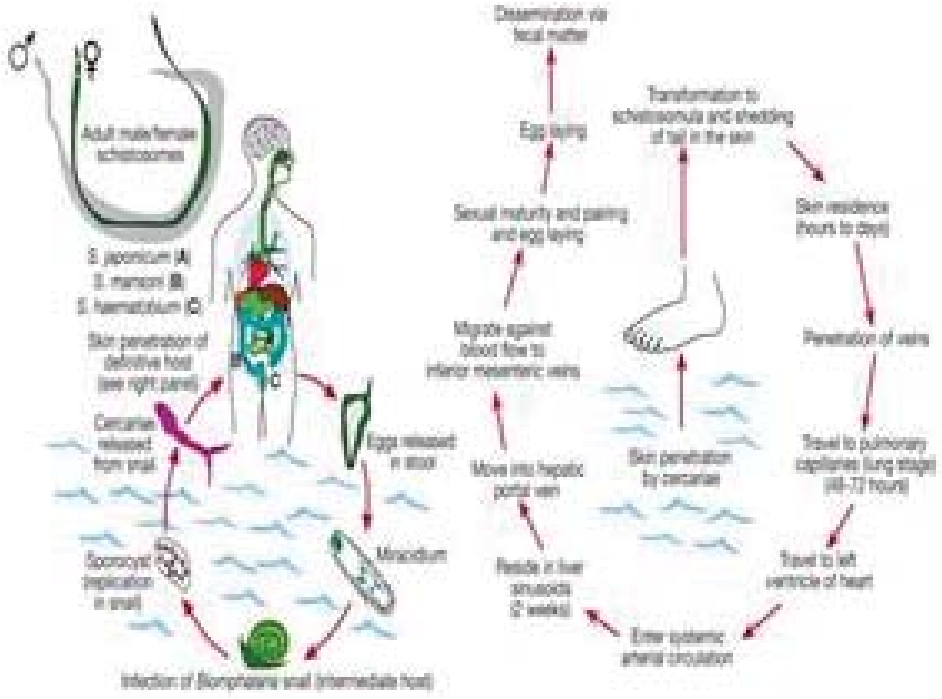

Fig. 32. – Life cycle of schistosomas

Schistosoma Mansoni. The schistosomiasis caused by Schistosoma mansoni is intestinal schistosomiasis.

The S. mansoni parasites are found predominantly in the small

inferior mesenteric blood vessels surrounding the large intestine and caecal region of the host. Each female lays approximately 300 eggs a day (one egg every 4,8 minutes), which are deposited on the endothelial lining of the venous capillary walls. Most of the body mass of female schistosomes is devoted to the reproductive system. The female converts the equivalent of almost her own body dry weight into eggs each day. The eggs move into the lumen of the host's intestines and are released into the environment with the faeces.

Symptoms. Many individuals do not experience symptoms. If symptoms do appear, it usually takes four to six weeks from the time of infection. The first symptom of the disease may be a general ill feeling. Within twelve hours of infection, an individual may complain of a tingling sensation or light rash, commonly referred to as "swimmer's itch", due to irritation at the point of entrance. The rash that may develop can mimic scabies and other types of rashes. Other symptoms can occur two to ten weeks later and can include fever, aching, cough, diarrhea, or gland enlargement.

Schistosoma Japonicum. This parasite has a very wide host range, infecting at least 31 species of wild mammals and therefore it can be considered a true zoonosis.

Schistosoma japonicum is the only human blood fluke that occurs in China. It is the cause of schistosomiasis japonica, a disease that still remains a significant health problem especially in lake and marshland regions.

Infection by schistosomes is followed by an acute Katayama fever (fever, abdominal pain, diarrhoea and allergic reaction).

If left untreated, it will develop into a chronic condition characterized by hepatosplenic disease and impaired physical and cognitive development. The severity of S. japonicum arises in 60% of all neurological diseases in schistosomes due to the migration of schistosome eggs to the brain.

Morphology. The S. japonicum worms are yellow or yellow-brown. The males of this species are slightly larger than the other Schistosomes and they measure ~ 1,2 cm by 0,5 mm. The females measure 2 cm by 0,4 mm. The adult worms are longer and narrower than the related S. mansoni worms

Once the parasite has entered the body and begun to produce eggs, it uses the host’s immune system (granulomas) for transportation of eggs into the gut. The eggs stimulate formation of granuloma

around them. The granulomas, consisting of motile cells, carry the eggs to the intestinal lumen.

When in the lumen, granuloma cells disperse leaving the eggs to be excreted within feces. Unfortunately, about two-thirds of eggs are not excreted, instead they build up in the gut. This can lead to fibrosis in chronic cases. S. japonicum is the most pathogenic of the schistosoma species because it produces up to 3,000 eggs per day, ten times greater than that of S. mansoni.

As a chronic disease, S. japonicum can lead to Katayama fever, liver fibrosis, liver cirrhosis, liver portal hypertension, splenomegaly, and ascites. Some eggs may pass the liver and enter lungs, nervous system and other organs where they can adversely affect the health infected individual.

Schistosome Haematobium. S.Haematobium is endemic in most parts of Africa, West Asia, Portugal and in India. In chronic stage hyperplasia and fibrosis of vesicle mucosa with granular appearance (sandy patch) is observed. Pseudoabscess occurs due to lymphocytes, plasma cells and eosinophils infiltration. Calculi present due to uric acid crystals around eggs. Haematuria is also possible.

Diagnosis. Urinary schistosomiasis is observed in a person with visible haematuria or with positive reagent strip for haematuria. Confirmation **of** urinary schistosomiasis is eggs of S. haematobium in urine (microscope).

Intestinal schistosomiasis is observed in a person with chronic or recurrent intestinal symptoms (blood in stool, bloody diarrhoea, diarrhoea, abdominal pains) or, at a later stage, hepatosplenomegaly. Confirmation of intestinal schistosomiasis is eggs of S. mansoni, or S. japonicum/mekongi in stools (microscope). Microscopic identification of eggs in stool or urine is the most practical method for diagnosis.

Quantitative diagnostic methods (Kato-Katz technique for intestinal forms, urine filtration for S. haematobium) are very important.

Tissue biopsy (rectal biopsy for all species and biopsy of the bladder for S. haematobium) may demonstrate eggs when stool or urine examinations are negative.

An ELISA test can be performed to test for antibodies specific to schistosomes.

Ultrasonographic examination can be performed to assess the extent of hepatic and spleen-related morbidity.

Treatment. The drug of choice for treating all species of schistosomes that infect humans is currently praziquantel. It is administered orally and is extremely effective in either eliminating adult worms or markedly reducing their numbers.

The dose and schedule of praziquantel depend on the Schistosoma species. ***For S. japonicum and S. mekongi***, the recommended dosage is 60 mg/kg of body weight orally in two or three divided doses in 1 day.

The recommended dose for ***S. haematobium, S. mansoni, and S. intercalatum*** is 40 mg/kg as a single oral dose. Follow-up stool or urine examinations for viable eggs should be performed several weeks after therapy to ensure successful treatment. Praziquantel treatment may also reverse the pathologic process if it is instituted early in the course of infection. However, the drug has no detectable effect on reversing the established fibro-obstructive lesions seen in chronic schistosomiasis. The side effects and toxicity of praziquantel are remarkably low.

Prevention. The only reliable method of prevention is to avoid any contact with freshwater bodies in areas known to be endemic for schistosomes. This can easily be achieved for visitors to such areas; the local inhabitants, however, are attracted to these water bodies for many purposes, and in many instances they have no alternative. Another strategy is to stop environmental contamination by excreta of infected persons and so prevent snail infection. In endemic areas, this can be achieved only if cultural and socioeconomic changes are implemented to allow alternative sewage disposal. Several other approaches have been tried, such as the use of widespread chemotherapy and Molluscicides. The availability of praziquantel and other safe, effective, and orally administered antischistosomal agents has encouraged the use of chemotherapy as a strategy for parasite control, and such programs have been reasonably successful. Molluscicides, on the other hand, have proved ineffective except under special circumstances.

The hope for the future prevention and control of schistosomiasis is in vaccine production. This is an ambitious goal, but evidence suggests that several characterized, defined parasite antigens are partially protective in experimental animals. Several candidate vaccines are in phase I clinical trials in humans.

School education, safe water supply and sanitation, environmental management and community participation are important.

PARAGONIMUS WESTERMANI

Infection with Paragonimus species results in fluke encystment in various organs, the most common being the lung fluke infection caused by Paragonimus westermani.

Epidemiology. Different strains of Paragonimus are common in different areas of the world; infection with P. westermani is common in Asia (China, Japan, Korea, Laos, the Philippines, Taiwan, Thailand) but can also be found in West Africa and in South and Central America, including Mexico, Colombia, Costa Rica, and Peru.

Lyfe cycle and pathogenesis (fig. 33). Humans are infected by consuming raw or undercooked crustaceans, including freshwater crabs and crayfish. Metacercariae hatch in the intestine, penetrate the gut into the peritoneal cavity, and migrate through the diaphragm and pleural space to invade the lung parenchyma. Acute clinical symptoms of infection include abdominal pain, diarrhea, fever, malaise, and urticaria followed by chest pain or pressure, malaise, dyspnea, and night sweats. Chronic symptoms include hemoptysis and abscess formation due to pulmonary hemorrhage and necrosis in the inflammation surrounding the parasite and pulmonary fibrosis and bronchiolar damage as a consequence of chronic inflammation. Secondary inflammatory response may lead to bronchopneumonia, bronchitis, bronchiectasis, atelectasis, and vasculitis of the lung. Imaging studies may demonstrate the migratory pathway in the lungs. Ectopic worm cysts may also be found in the intestines, peritoneal cavity, lymph nodes, pleura, diaphragm, heart, subcutaneous tissues, and central nervous system. Diagnosis can be made by examination of expectorated sputum for the characteristic ova. If the patient swallows sputum, eggs may also be noted in the stool.

Time from infection to oviposition (laying eggs) is 65 to 90 days. Infections may persist for 20 years in humans.

Unembryonated eggs are passed in the sputum of a human or feline. Two weeks later, miracidia develop in the egg and hatches. The miracidia penetrate its first intermediate host (snail). Within the snail mother sporocyst form and produce many mother rediae, which subsequently produce many daughter rediae which shed crawling cercariae into fresh water. The crawling cercariae penetrate fresh water crabs and encyst in its muscles becoming metacercaria. Humans

or felines then eat the infected crabs raw. Once eaten, the metacerciaria excysts and penetrates the gut, diaphragm and lung where it becomes an adult worm in pairs.

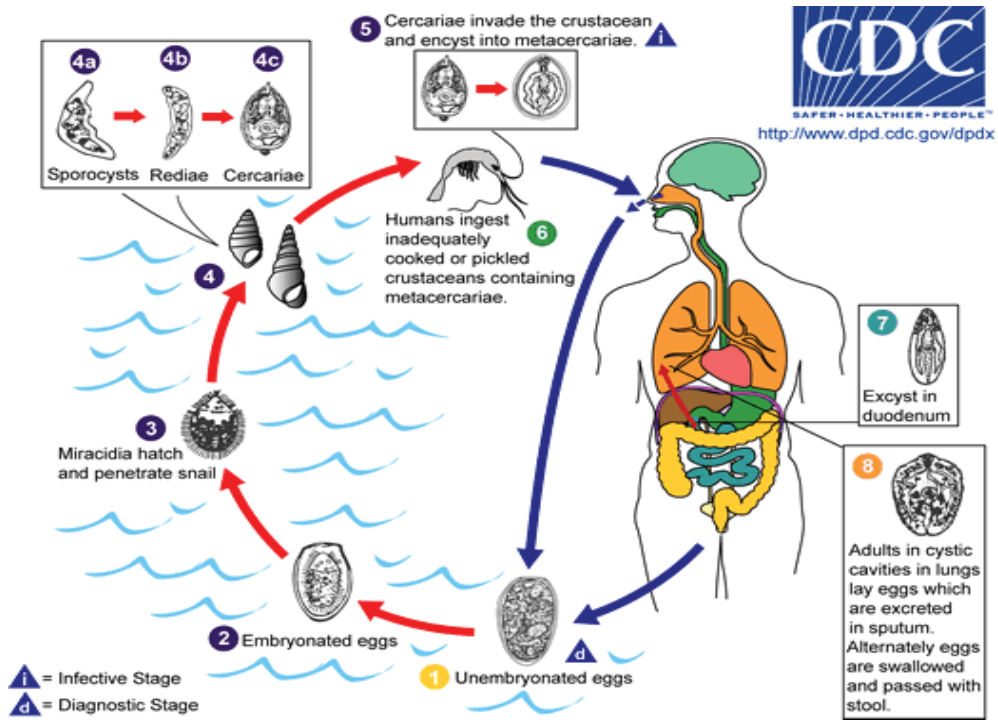

Fig. 33. – Life cycle of Paragonimus westermani

Clinics. Human infection with Paragonimus may cause acute or chronic symptoms, and manifestations may be either pulmonary or extrapulmonary.

The acute phase (invasion and migration) may be marked by:

Diarrhea, abdominal pain, fever, cough, urticaria, hepatosplenomegaly, pulmonary abnormalities, eosinophilia are observed. During the chronic phase, pulmonary manifestations include: cough, expectoration of discolored sputum hemoptysis, chest radiographic abnormalities.

Chronic pulmonary paragonimiasis, the most common clinical pattern, is frequently mild, with chronic cough, brown-tinged sputum (the color being caused by expectorated clusters of reddish brown eggs rather than by blood) and true hemoptysis.

Once inside the lungs, the worm covers itself in granulation tissue, forming a capsule around itself. These capsules can eventually ulcerate and then heal. But if the worm capsules get disseminated into the spinal chord, it can cause paralysis. If a capsule gets into the heart,

it can be fatal. The infection caused by the lung fluke parasite resembles tuberculosis in many respects. The symptoms include a bad cough, bronchitis and coughing up blood. In heavy infestations, lesions may also be found in the lungs, liver and brain.

Treatment. Recommended treatment for paragonimiasis is praziquantel, 25 mg/kg three times daily for 2 or 3 days (reported success rate, 89% to 100%). Resolution of lung fluke infection should be monitored for several months by sputum examination and chest radiographs.

CLONORCHIASIS

Clonorchiasis, or Chinese liver fluke disease, is caused by infection with Clonorchis sinensis. Adult C. sinensis flukes may measure up to 20 mm x 5 mm.

Epidemiology. Clonorchiasis is a common infection of dogs and other fish-eating carnivores (reservoir final hosts) in China, the Democratic People's Republic of Korea, the Republic of Korea and Viet Nam. The transmission cycle is similar to that of both opisthorchiasis viverrini and opisthorchiasis feline. Adult flukes inhabit the bile ducts and lay eggs that are dispersed into the environment during defecation. When they reach fresh water, eggs develop into miracidia that are ingested by various species of aquatic snails.

Life cycle (fig. 34). The miracidia further develop and reproduce asexually into cercariae (larvae). Cercariae leave the snail and swim to penetrate beneath the scales of various species of carp-like freshwater fish where, as metacercariae, they encyst in the subcutaneous tissue. When dogs or other carnivores eat raw fish, the metacercarial cysts hatch in the intestine and the young worms migrate to the bile ducts, thus completing the cycle.

Clinic. Humans may substitute reservoir hosts in the transmission cycle when they eat raw, salted, pickled, smoked, marinated, dried, partially cooked or poorly processed fish, thus ingesting the metacercariae. In humans, acute clonorchiasis may be asymptomatic or scarcely symptomatic in light infections, but if the number of worms is significant (up to several thousands), fever and right upper-quadrant pain are not infrequent and may be associated with intermittent colic pain caused by the worms obstructing the gallbladder.

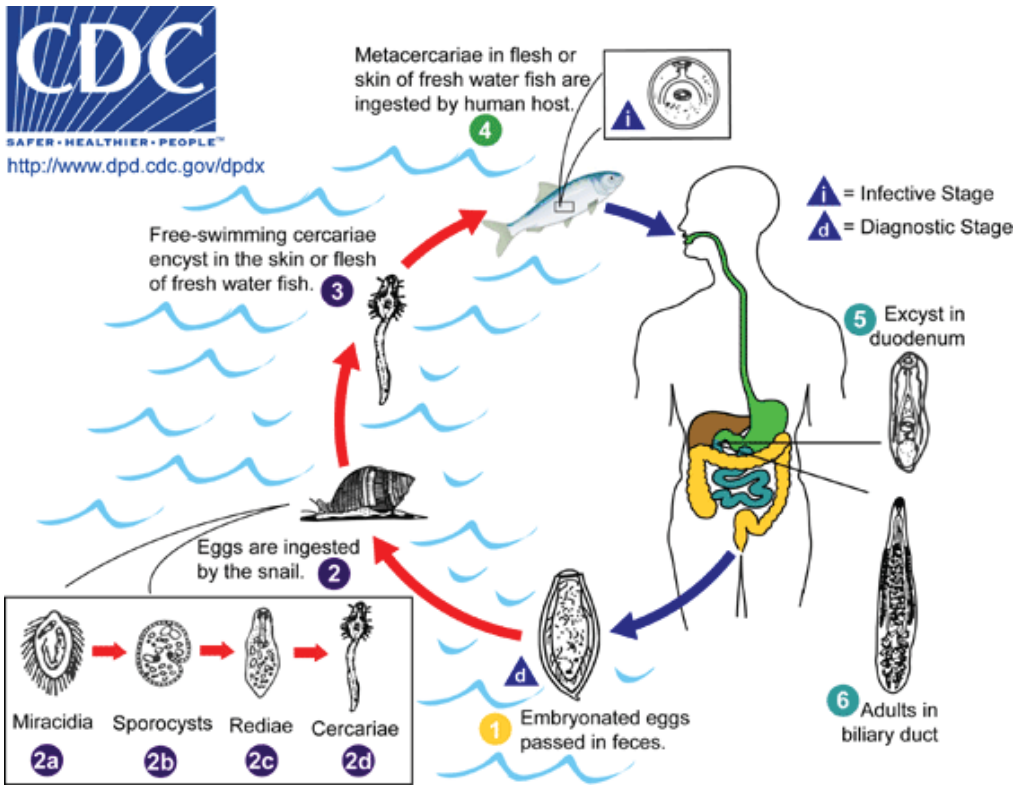

Fig. 34. – Life cycle of Clonorchis sinensis

Chronic clonorchiasis, which results from protracted episodes of re-infection over time, may be most severe. The presence of the worms in the walls of the smaller bile ducts causes chronic inflammation, resulting in fibrosis of the ducts and destruction of the adjacent liver parenchyma. Cholangiohepatitis, or recurrent pyogenic cholangitis, is also frequent. Chronic chlonorchiasis is strongly associated with cholangiocarcinoma, a severe and often fatal form of bile duct cancer. The International Agency for Research on Cancer (IARC) classifies C. sinensis as a Group 1 agent (carcinogenic to humans).

***Diagnosis*.** Diagnosis is made on the basis of the clinical picture, on the anamnestic recall of consuming raw fish, on the detection of eosinophilia, and on typical findings of ultrasound, computed tomography or magnetic resonance imaging scans. Confirmation of diagnosis relies on different types of diagnostic techniques:

1) parasitological techniques to detect Clonorchis eggs in stool samples; their cost and sensitivity may vary according to the type of technique used; they can only be employed in the chronic phase; some techniques, such as the Kato-Katz thick smear, quantify the intensity of infection (allowing estimation of the severity of the infection);

2) immunological techniques to detect worm-specific antibodies in serum samples or worm-specific antigens in serum or stool samples; they are usually more sensitive than the commonly used parasitological techniques; detection of antibodies does not distinguish between current, recent and past infections; their ability to quantify intensity of infection is disputed; stool tests are easier to perform and reportedly better accepted by individuals in endemic areas; these techniques are still at an experimental stage;

3) molecular techniques such as polymerase chain reaction are also at an experimental stage.

Treatment. Praziquantel is the only medicine recommended by WHO for treatment of clonorchiasis. It should be administered at the dose of 25 mg/kg 3 times daily for 2-3 consecutive days or of 40 mg/kg, single administration.

Control. For the purposes of public health control, WHO recommends carrying out community diagnosis at the district level, and implementing preventive chemotherapy with praziquantel at a dosage of 40 mg/kg.

FASCIOLIASIS

Fascioliasis is caused by two species of parasitic flatworms or trematodes that mainly affect the liver. It belongs to the group of foodborne trematode infections and is a zoonosis, meaning an animal infection that may be transmitted to humans.

The two species of trematodes that cause fascioliasis (Fasciola hepatica and F. gigantica) are leaf-shaped worms, large enough to be visible to the naked eye (adult F. hepatica measure 20-30 mm x 13 mm; adult F. gigantica measure 25-75 mm x 12 mm). The disease they both cause is similar.

Epidemiology. Until recently, human cases occurred occasionally but are now increasingly reported from Europe, the Americas and Oceania (where only F. hepatica is transmitted) and from Africa and Asia (where the two species overlap). WHO estimates that at least 2,4 million people are infected in more than 70 countries worldwide, with several million at risk. No continent is free from fascioliasis, and it is likely that where animal cases are reported, human cases also exist.

The life-cycle (fig. 35) of fascioliasis is complex. It involves a final host (where the adult worm lives), an intermediate host (where the larval stages of the worm develop) and a carrier (entailing suitable aquatic plants).

The process starts when infected animals (cattle, sheep, buffaloes, donkeys and pigs but also horses, goats, dromedaries, camels, llamas and other herbivores) defecate in fresh-water sources. Since the worm lives in the bile ducts of such animals, its eggs are evacuated in faeces and hatch into larvae that lodge in a particular type of water snail (the intermediate host).

Once in the snail, the larvae reproduce and eventually release more larvae into the water. These larvae swim to nearby aquatic or semi-aquatic plants, where they attach to the leaves and stems and form small cysts (metacercariae). When the plants with the small cysts attached are ingested, they act as carriers of the infection. Watercress and water-mint are good plants for transmitting fascioliasis, but encysted larvae may also be found on many other salad vegetables. Ingestion of free metacercariae floating on water (possibly detached from carrier plants) may also be a possible mode of transmission.

Symptoms. Most of the clinical knowledge about fascioliasis is based on cases caused by Fasciola hepatica. However, the same principles and clinical features are thought to apply to F. gigantica.

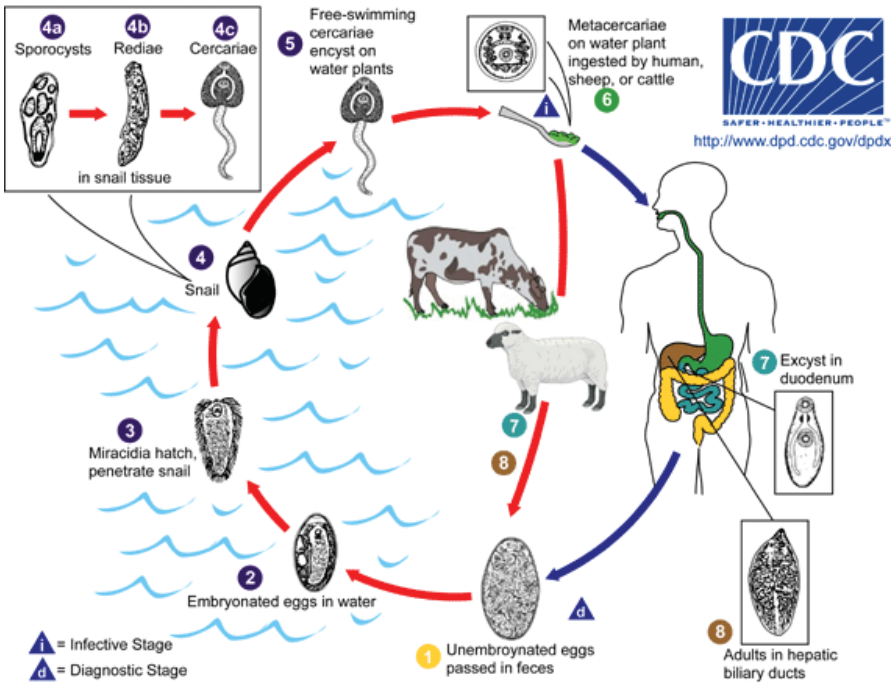

Fig. 35. – Life cycle of Clonorchis sinensis

Fasciola parasites do not multiply in people. Therefore, the parasite burden depends on the inoculum, including the potential for reinfection. The large size of the parasite also can be problematic–for example, can compound the tissue damage and increase the abdominal pain when larval flukes migrate through the liver and can predispose to biliary obstruction during the chronic phase.

Both the acute and chronic phases of infection can be symptomatic or symptom free. Nonspecific clinical features of both phases can include: fever, which can be intermittent; malaise; abdominal pain, in the right upper quadrant, epigastrium, or more diffuse/generalized; other abdominal symptoms (such as anorexia, nausea, vomiting, diarrhea, change in bowel habits, and weight loss) and signs (such as hepatomegaly and jaundice).

Eosinophilia, which is more prominent and less variable during the acute phase than in the chronic phase; anemia, especially in children; and transaminitis (during the chronic phase, laboratory testing also can indicate hepatobiliary obstruction).

The Acute Phase. The acute phase is also referred to as the migratory, invasive, hepatic, parenchymal, or larval phase. Immature larval flukes migrate through the intestinal wall, the peritoneal cavity, the liver capsule, and hepatic tissue and, ultimately, to the bile ducts. The acute phase lasts up to 2 to 4 months and ends when the larvae reach and mature in the bile ducts. Larval migration, especially through the liver, can result in tissue destruction, inflammation, local or systemic toxic/allergic reactions, and internal bleeding. Symptoms, in addition to those listed above, can include urticaria, cough, and shortness of breath. This phase can be life threatening in sheep infected with large inocula of parasites. However, severe illness is uncommon in people, although some young children have intense abdominal pain.

The Chronic Phase (Chronic Fascioliasis). The chronic phase is also referred to as the biliary or adult phase. The chronic phase begins when immature larvae reach the bile ducts, mature into adult flukes, and start producing eggs. The eggs are passed from the bile ducts into the intestine and then into the feces. During this phase, the patient may be asymptomatic for months, years, or indefinitely. The only finding on routine blood testing might be peripheral eosinophilia, which typically is less prominent than during the acute phase.

Some experts differentiate between an asymptomatic latent

phase and a symptomatic obstructive phase, which only some patients experience. The symptoms, if any, can be similar to those during the acute phase or can be more focal/discrete, reflecting: cholangitis and biliary obstruction, which can be intermittent; cholecystitis and gallstones; pancreatitis; and cirrhosis.

On the basis of limited data, the life span of adult flukes in people might be 5 to 10 years, perhaps even longer.

Infection at Ectopic Sites. Fasciola parasites usually go to the liver and bile ducts. However, larval flukes also can migrate to ectopic (aberrant) sites, such as the lungs, subcutaneous tissue, genitourinary tract, or brain. Fasciola parasites at ectopic sites may or may not mature into adult flukes. For example, subadult worms might emerge through the skin.

In addition, F. hepatica and F. gigantica have been reported to cause pharyngeal infection in people who ate raw sheep or goat liver that contained immature flukes. In this unusual scenario, the larval flukes emerge from the liver and attach to the pharyngeal mucosa. Pharyngeal fascioliasis (and other parasitic infections) acquired in this manner from raw liver is also known as halzoun (a local, Middle Eastern term). The clinical features can include dysphagia, dyspnea, bleeding, and airway obstruction.

***Diagnosis*.** Diagnosis of fascioliasis may be suspected on the basis of the clinical picture, on the anamnestic recall of consuming raw vegetables, on the detection of eosinophilia (blood eosinophil count >500-1000 per μl of blood), and on typical findings at ultrasound or computed tomography scans. Confirmation relies on different types of diagnostic techniques.

1) parasitological techniques to detect Fasciola eggs in stool samples; their cost and sensitivity may vary according to the type used; they can only be employed in the chronic phase; some of them allow quantifying intensity of infection (therefore estimating the severity of the infection);

2) immunological techniques to detect worm-specific antibodies in serum samples or worm-specific antigens in serum or stool samples; they are usually more sensitive than the commonly used parasitological techniques; detection of antibodies does not allow distinguishing between current, recent and past infections; their ability to quantify intensity of infection is disputed; stool tests are easier to perform and reportedly better accepted by individuals in endemic areas;

3) molecular techniques such as the polymerase chain reaction are still at experimental stage.

Treatment. Triclabendazole

Triclabendazole is the drug of choice for treatment of fascioliasis. It is the medication recommended by the World Health Organization. It is not yet widely available to treat people. In the United States, it is not approved by the Food and Drug Administration. However, it is available through CDC, under an investigational protocol.

As with all medications, use of triclabendazole should be individualized. It is a benzimidazole compound that is active against immature and adult Fasciola parasites. The therapy usually is effective and safe. Triclabendazole is given orally, with food, to improve absorption.

The medication comes in scored tablets. The dosage is calculated on the basis of the patient's weight. The typical regimen is a single oral dose of 10 mg of triclabendazole per kilogram of body weight (10 mg/kg).

Two-dose (double-dose) triclabendazole therapy can be given to patients who have severe or heavy Fasciola infections (many parasites) or who did not respond to single-dose therapy. Of note, some experts routinely use 2-dose therapy, which might have a higher response rate, on the basis of limited data.

Two-dose therapy means that the patient is given 2 individual doses of 10 mg/kg, separated in time by 12 to 24 hours. In other words, the patient receives a total dose of 20 mg/kg, given in 2 divided doses, 12 to 24 hours apart.

Additional perspective about therapy. Fasciola serologic testing is one of the means that can be used to assess the response to therapy. Seroreversion (loss of detectable antibodies) usually is noted 6 to 12 months after curative therapy.

On the basis of limited data, nitazoxanide might be effective therapy in some patients. The drug is given orally, with food. The dosage regimen for adults is 500 mg po bid (twice a day) for 7 days.

Praziquantel, which is active against most trematodes (flukes), typically is not active against Fasciola parasites. Therefore, praziquantel therapy is not recommended for fascioliasis.

Prevention. No vaccine is available to protect people against Fasciola infection.

In some areas of the world where fascioliasis is found (endemic), special control programs are in place or are planned. The types of control measures depend on the setting (such as epidemiologic, ecologic, and cultural factors). Strict control of the growth and sale of watercress and other edible water plants is important.

Individual people can protect themselves by not eating raw watercress and other water plants, especially from endemic grazing areas. As always, travelers to areas with poor sanitation should avoid food and water that might be contaminated (tainted). Vegetables grown in fields that might have been irrigated with polluted water should be thoroughly cooked, as should viscera from potentially infected animals. Timely treatment with triclabendazole is the quickest way to control morbidity associated with fascioliasis. However, treatment should be complemented, where feasible, by implementing measures that aim to reduce transmission rates, including:

a) information, education and communication, promoting cultivation of vegetables in water free from faecal pollution and thorough cooking of vegetables before consumption;

b) veterinary public health measures, including treating domestic animals and enforcing separation between husbandry and humans;

c) environmental measures such as containment of the snail intermediate hosts and drainage of grazing lands.

METAGONIMIASIS

Metagonimiasis is a disease caused by an intestinal trematode, most commonly Metagonimus yokagawai, but sometimes by M. takashii or M. miyatai. The metagonimiasis causing flukes are one of two minute flukes called the heterophyids. Metagonimiasis was described by Katsurasa in 1911-1913 when he first observed eggs of M. yokagawai in feces (date is disputed in various studies). M. takahashii was described later first by Suzuki in 1930 and then M. Miyatai was describe in 1984 by Saito.

Metagonimiasis is most commonly caused by one of the two smallest flukes known to infect man, Metagonimus yokagawai, also called the Japanese fluke. More rarely, metagonimiasis can arise from

infection with M. takahashii or M. miyatai. Recent studies analyzing the DNA of the three agents causing metagonimiasis found that DNA sequencing supports M. yokagawai and M. takahashii be placed in the same clade, and phylogenic tree analysis supports their genetic similarity. M. miyatai, however, was found to be more genetically distinct, and the authors concluded it should be nominated as a separate species. An additional study examining karyotype data on the three disease-causing agents also supported the nomination of M. miyatai as a separate species.

Trematodes are one class of phylum Platyhelminthes from the order Digenia and are generally referred to as flukes. Metagonimiasis is of the family Herterophyidae.

Eggs. The morphology of the eggs is very important for diagnosis, but is difficult as eggs are very small. Eggs have a smooth, hard shell that is transparent and yellow-brown with a more conventional, ovoid egg shape. They are about the same size as those of Heterophers and Clonorchis, usually measuring 26-28 μm length and 15-17μm width. The egg also has a very slight opercular shoulder, marking the line of cleavage between the shell and operculum, an "escape hatch" for the mircidium. The Clonorchis has more distinctive tapering and a seated operculum that help distinguish it more readily from Metagonimus species.

Adult flukes. The body of the adult disease-causing agent of metagonimiasis is often described as leaf-shaped, similar to most trematodes. It is one of the smallest intestinal flukes, and is only slightly larger than Heteropheres. The most prominent feature is that its ventral sucker is deflected to the right of its midline and is closely associated with the opening of the genital pore. The testes are large and diagonal to each other while the smaller ovary is anterior to the testes and the uterus is filled with eggs. The uterus winds forward to the genital pore and is the largest organ in the body. The size of the adult fluke does not exceed 2,5 mm length by 75 mm width.

Epidemiology. Transmission requires two intermediate hosts, the first of which is snails, most commonly of species Semisucospira libertine, Scoreana, and Thiara granifera, Semisulcospira Snail. Metagonimiasis infections are endemic or potentially endemic in 19 countries including Japan, Korea, China, Taiwan, the Balkans, Spain, Indonesia, the Philippines and Russia. Human infections outside endemic areas may result from ingesting pickled fish or sushi made

from fish imported from endemic areas.

Korea. Food-borne trematodes are currently the most important parasitic infections in Korea and approximately 240,000 Koreans are believed to be currently infected. Of the 240,000 estimated to be infected, 120,000 are caused by M. yokagawai, 20,000 by M. takahashii, and 100,000 by M. miyatai. The national rate of infections among randomly selected people was 1,2% in 1981, 1,0% in 1986, and down to 0,5% in 2004. M. yokagawai infections are found mostly around the large and small streams where sweetfish live and have been identified as endemic foci. M. miyatai and M. takahashii are prevalent along the upper reaches of the big rivers where minnows and carps are caught for eating raw.

Japan. Metagonimiasis is also common in Japan, with 10-15% prevalence rates in populations bordering major rivers and 150,000 estimated infected. Food-borne trematodes are most common in rural areas where traditional food habits are more preserved and raw freshwater fishes are incorporated into the diet. Interestingly, both clonorchiasis and metagonimiasis have become infections of higher social classes in Hong Kong and Japan, owing to their frequent consumption of raw fish.

India. There have also recently been two reported cases in India, a location in which occurrence of infection is almost unknown. The second case, in 2005, was in a 6-year-old female patient presenting with loose watery stools for four days (however more details were not obtained as the patient was both deaf and dumb since birth). Upon examination, M. yokagawai eggs were found in stool, but the patient left and further analysis and treatment could not be completed.

Infection is acquired through the secondary intermediate host, fish, that haven’t been thoroughly cooked. Metacercariae encyst under the scales or in the flesh of fish from fresh or brackish water. Sweetfish (Pecoglossus altevelis) is one of the most common fish species infected, but other include the golden carp (Carassius auratus), common carp (Cyprinus carpio), Zacco temminckii, Protimus steindachneri, Acheilognathus lancedata, and Pseudorashora parva.

Here, ***the life cycle*** of M. yokagawai (fig. 35) will be examined, however, it should be noted M. takahashii and M. miyatai follow similar life cycle pattern. All three species are hermaphroditic and capable of self-fertilization. Embryonated eggs are passed into an aquatic environment (fresh or brackish water) each containing a fully

developed larva, called a miracidium. Development can't proceed past this stage unless the eggs are ingested by the first intermediary host, snails. After the snail host ingests the eggs, miracidia emerge and penetrate the snail's intestines. In the snail tissue, mircadia develop into sporocysts, then rediae, and finally emerge from the snail as cercariae. The cercariae then penetrate the skin or go under the scale of a fresh or brackish water fish and encyst as metacercariae in the tissue. The type of fish that serves as secondary host varies based on location. The host then becomes infected by consuming undercooked, raw, or pickled fish containing the infectious metacercariae. The metacercariae then excyst in the small intestine of the host (human, mammal or bird), and develop into adults. In the small intestine, the adults attach to the walls and develop new eggs.

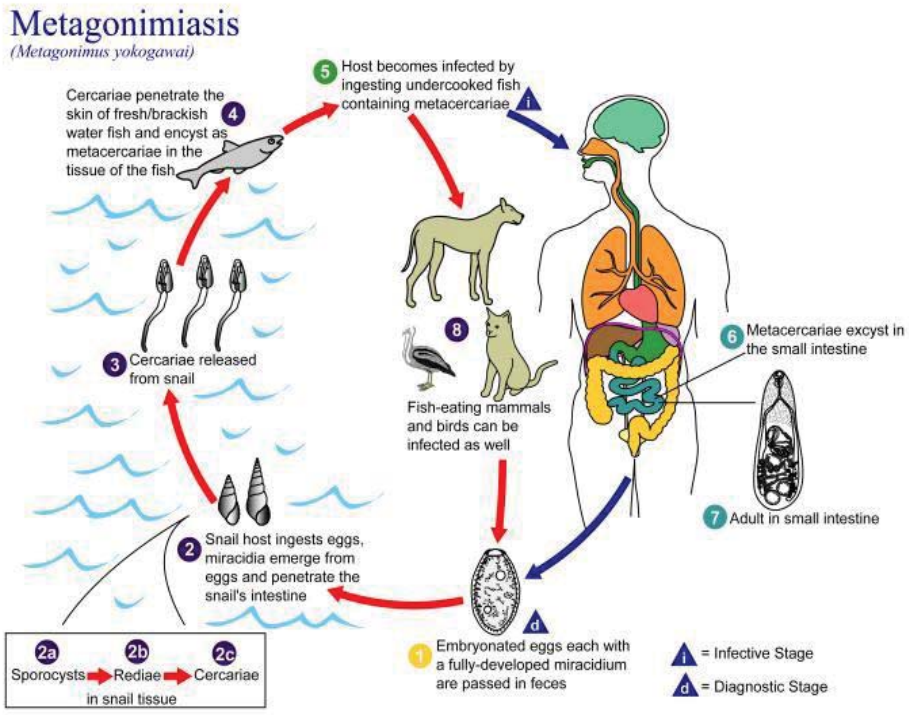

Fig. 36. – Life cycle of Metagonimus sps

Definitive hosts include humans and various fish-eating mammals, primarily dogs, cats, and pigs. Fish-eating birds may also be infected with metagonimiasis.

Clinic. The main symptoms are diarrhea and colicky abdominal pain. Because symptoms are often mild, infections can often be easily overlooked but diagnosis is important. Flukes attach to the wall of the

small intestine, but are often asymptomatic unless in large numbers. Infection can occur from eating a single infected fish source. Peripheral eosinophilia is associated especially in early phase. When present in large numbers, can cause chronic intermittent diarrhea, nausea, and vague abdominal pains. Clinical complaints can also include lethargy and anorexia. In acute metagonimiasis, clinical manifestations are developed only 5-7 days after infection. Heavy infection has also been associated with epigastric distress, fatigue, and malaise.

Occasionally, flukes invade the mucosa and eggs deposited in tissue may gain access to circulation. This can then lead to eggs embolizing in the brain, spinal cord, or heart. Granulomas may form around eggs and can cause seizures, neurologic deficits, or cardiac insufficiency.

An interesting case in Japan found Diabetes Mellitus (DM) to be a sign of chronic infection with intracerebral hemorrhages as the acute sign of aggravation. Two months after administering the appropriate drug, Praziquantel, the ICHs were gone, as was the man's Diabetes Mellitus. This unique case shows the potential of additional symptoms associated with metagonimiasis that are still unknown.

Diagnosis. Metagonimiasis is diagnosed by eggs seen in feces. Only after antihelminthic treatment will adult worms be seen in the feces, and then can be used as part of a diagnostic procedure. A 1993 analysis of the efficacy of ELISA tests to diagnose metagonimiasis implied that simultaneous screening of specific antibodies to several parasite agents are important in serological diagnosis of acute parasitic disease and more research should be done on the efficacy of these methods of diagnosis.

Diagnosis may be difficult because the egg-laying capacity of heterophyids is limited, and therefore sedimentation concentration procedures may be needed to demonstrate eggs in lighter infections. Accurate species identification is also difficult because eggs of most flukes are similar in size and morphology, especially those of Heterophyes heterophyes, Clonorchis and Opisthorchis. It is important to ask where the person may have contracted the disease, find out if they have been to en endemic area, and check for signs and symptoms that would lead to metagonimiasis.

Treatment. Praziquantel is recommended in both adult and pediatric cases with dosages of 75 mg/kg/d in 3 doses for 1 day.

Praziquantel is a Praziniozoquinoline derivative that alters the calcium flux through the parasite tectum and causes muscular paralysis and detachment of the fluke. Prizaquantel should be taken with liquids during a meal and as provided commercially as Biltricide. Praziquantel is not approved by the U.S. Food and Drug Administration (FDA) for treatment of metagonimiasis, but is approved for use on other parasitic infections.

Praziquantel has some side effects but they are generally relatively mild and transient and a review of evidence shows it overall a well-tolerated drug. Possible side effects include abdominal pain, allergy, diarrhea, headache, hepatic dysfunction/hepatitis, nausea or vomiting, exacerbation of porphyries, pruritis, rash, somnolence, vertigo, or dizziness. In fact, in 2002, the World Health Organization recommended the use of Praziquantel in pregnant and lactating women, though controlled trials are still needed to verify this.

Another possible drug option is Tetrachloroethylene, a chlorinated hydrocarbon, but its use has been superseded by new antihelminthic drugs (like Praziquantel). A 1978 study also looked at the efficacy of several drugs on metagonimiasis infection, including bithionol, niclosamide, nicoflan, and Praziquantel. All drugs showed lower prevalence of eggs in feces, however only Praziquantel showed complete radical cure. Therefore the authors concluded Praziquantel was the most highly effective, was very well tolerated, and was the most promising drug against metagonimiasis.

HETEROPHYES

Minute teardrop-shaped flukes found in the small intestines of fish-eating birds and mammals. The eggs are hard to tell apart from other related species so there is no accurate estimate of human infection. The adult flukes range from 1,1 mm to 1,7 mm long and about 0,35 mm at their greatest width. The body of the fluke is covered in scales mostly concentrated at the anterior end. Also there is an oral sucker at the anterior end. Located in the medioanterior of the body is the acetabulum. At the posterior end of the fluke there are two oval testes. The vas deferens leading from the testes expands to form a seminal vesicle and then narrows again to form an ejaculatory duct. The fluke also has female reproductive organs. Located

medioposterior is the fluke's one ovary and leading away from the ovary is the vitellaria. The uterus is a long tube like structure that also leads away from the ovary and joins up with the ejaculatory duct to form the genital duct which leads to a genital sinus. The sinus leads to the genital pore which is lined with 60-90 toothed spines. The genital pore is where the fluke releases its eggs.

Epidemiology. People at high risk for infection are those who live by bay waters including fishermen. Infection is acquired by eating raw fish, a common food in areas of heavy endemicity. In endemic areas, people who live near lake shores or river banks usually have a higher rate and intensity of infection than those living a distance from such areas. It is possible that inhabitants of these areas eat more low-salted or improperly cooked fish and that their fish are obtained from polluted water. It is common practice for people to defecate on the lake shores and river banks or from their boats while fishing. Common in north Africa, Asia Minor, Korea, China, Japan, Taiwan, and the Philippines.

Life cycle (fig. 37). The adult flukes live burrowed between the villi of the host's small intestine. The eggs that are laid contain a miracidium but do not hatch until they are ingested by a snail (Pirenella conica in Egypt or Cerithidia cingula in Japan).

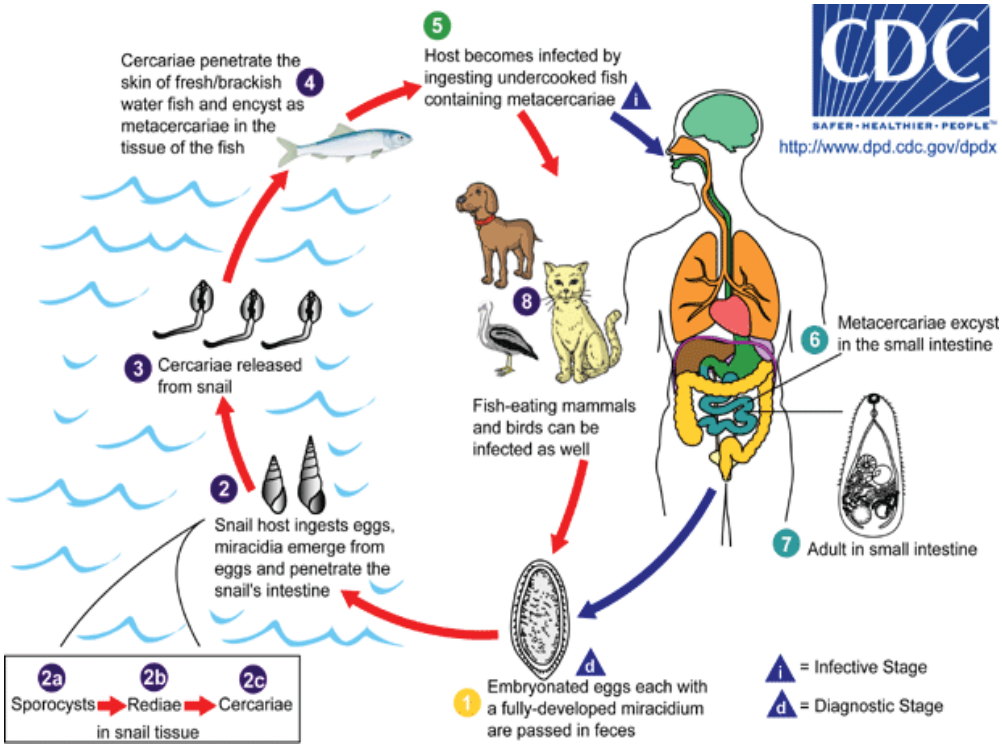

Fig. 37. – Life cycle of heterophyes ethiological agents

Inside the snails gut, the miracidium becomes a sporocyst which then begins to produce rediae. The rediae produce cercariae which then exit the snail, swim toward the surface of the water, and slowly fall back down. On their way down, they contact a fish and penetrate into the epithelium of the fish. Here, the cercariae encyst in the muscle tissue. The definitive host, such as humans or birds, eats the undercooked or raw meat of a fish and ingest the parasite.***Pathology.*** Each worm causes a mild inflammatory reaction at its site of contact with the intestine. In heavy infections which are common cause damage to the mucosa and produce intestinal pain and mucosa diarrhea. Sometimes eggs can enter the blood and lymph vascular systems through mucosa go into the ectopic sites in the body. The heart can be affected with tissue reaction in the valves and myocardium that cause heart failure. Eggs can also get into the brain or spinal cord and cause neurological disorders and sometimes fatalities.

Diagnosis. Diagnosis done by stool examination is difficult when adult worms are not present because the eggs are hard to distinguish from C.sinensis.

The analysis of the efficacy of ELISA tests to diagnose infection implied that simultaneous screening of specific antibodies to several parasite agents are important in serological diagnosis of acute parasitic disease and more research should be done on the efficacy of these methods of diagnosis.

Treatment. Praziquantel, a quinolone derivative. Praziquantel is recommended in both adult and pediatric cases with dosages of 75 mg/kg/d in 3 doses for 1 day.

ARTHROPODS IN THE TROPICS

Arthropod (type Arthropoda) characterized by an outer chitinous skeleton, dismembered body and limbs. Dense chitinous integument inhibit the growth of arthropods, so their life cycle observed molting in different periods of development. Most arthropods dioecious. The greatest medical importance representatives of the classes of arachnids (Arachnida) and insects (Insecta). The study of insects engaged in entomology, arachnids – Arachnology.

Classification arthropods having medical value

TYPE arthropods (ARTHROPODA) class Arachnida

(Arachnoidea) have four pairs of legs, the body is solid

Troop acariform mites (Acariformes)

Family trombiculid mites (Trombiculidae)

Family (Demodicidae) – live in the hair follicles and sebaceous glands

Family of scabies mites (Acaridae) – all stages of parasitic mites in the epidermis

Detachment of ticks (Parasitiformes) – blood-sucking

– Superfamily (Ixodoidea) – proboscis is armed gipostom

Family Ticks (Ixodidae) – «hard» mites, the dorsal surface of the body is covered with armor rogovym

Family argasids (Argasidae) – «soft» ticks, dorsal carapace missing

– Superfamily Gamasid mites (Gamasoidea)

Class Insects (Insecta)

Troop Bedbugs (Hemiptera)

Family of kissing bugs (Triatomidae)

Family of Bed Bugs (Cimicidae)

Troop Cockroaches (Blattoptera)

Order Hymenoptera (Hymenoptera)

Family Ants (Formicidae)

Troop Lice (Anoplura)

Family (Pediculidae): the genus Pediculus, born Phthirus

Detachment of Fleas (Siphonaptera)

Order Diptera (Diptera)

Family Mosquitoes (Culicidae)

Tribe Malaria mosquitoes (Anophelini): Genus Anopheles

Tribe Nemalyariynye mosquitoes (Culicini): Genus Culex, genus Aedes, genus Mansonia, born Culizeta et al.

Family Mosquitoes (Phlebotomidae)

Family Mote (Simulidae)

Family slimies (Ceratopogonidae)

Family of horseflies (Tabanidae)

These family of flies (Muscidae)

Family-louse flies (Hippoboseidae)

Family Ovodov (Hypodermatidae, Gastrophilidiae, Oestridae)

Ticks

Acariformes. Acariformes (order Acariformes) is a large order composed of 40 superfamilies, consisting of free-living and parasitic

species. From the medical point of view the most important superfamilies are: Sarcoptoidea-itch mites, Demodicoidea, Tyroglyphoidea – food mites, and Trombea – harvest mites.

General characteristics. Acariformes are microscopic (0,1-0,3 mm) or mid-sized (1-3 mm) mites. Most often their body has 2 segments: the anterior segment has mouthparts and two pairs of legs, the posterior segment bears two rear pairs of legs, genital opening and anus. Integuments are soft and have different structure. The body can be covered with clypei or enclosed in the hard shell. Lifestyle and practical significance of acariformes are very diverse. Primitive members of the order inhabit the soil, rotting plant litter and other areas of organic residues of plant and animal origin. Most of them are saprophages consuming detritus and flora; necrophages are common as well. Tetranychus urticae, Brevipalpus oncidii and gall causing mites harm plants. Some Oribatida-saprophages living on pastures, are the intermediate hosts of tenia (Anoplocephalata), affecting cattle and causing moniezioz and other helminth infections. Many species are predators. Land parasites can live among animals and humans. Their places of parasitism are various: on the skin surface, inside the skin, in skin glands, feathers, under the skin of birds' metatarsus, under the scales of reptiles, in the insects' trachea, in the mantle cavity of molluscs. There are mites feeding in the larval phase by the blood of spondylics or or hemolymph of insects (red velvet mites).

Role in human pathology. Role in human pathology of acariformes is diverse. Some species of predatory and other mites of this order (Pediculoides ventricosus et al.), coming into contact with the human, try to stick into and drink blood. However, they irritate the skin, causing itching, burning, rash, dermatitis, sometimes nervous and feverish phenomena caused by toxic substances in the tick saliva. Attacks of some species of red velvet mites larvae cause local inflammation, erythema, and sometimes fever in people. This fever is known as autumn fever, or gooseberry disease since the attack of red velvet mites larvae often occurs during harvesting.

A separate unit is devoted to itch mites (Sarcoptidae family). Dermatophagoides scheremetewskyi tick can cause scabies resulting in lesions of the sculp, sometimes face, ears, armpits. Clinical representation of the disease resembles seborrheic eczema. The disease can last for years. Some Dermestidae cause special forms of mange in animals. Demodicidae or follicle mites, living in skin glands

can lead to blockage and inflammation of the glands, the formation of acne and rash. In animals, these mites can cause serious systemic diseases. Products infected by true mites (Tyroglyphoidea superfamily) are filled with mites, their excrements, spoils, skin. Such food used by people may cause catarrhal conditions in the digestive tract. True mites inhaled with the air and dust cause asthma, catarrh of the respiratory tract, ulcers on the mucous membrane of the mouth, which sometimes contain live mites. Sputum can contain mites and sometimes blood. General severe allergic phenomena can be observed. When the contact with ticks is eliminated the symptoms disapear.

Some kinds of red velvet mites are specific carriers of rickettsiae which cause Japanese river fever tsutsugamushi prevalent in South-East Asia. This disease is zoonosis.

Prevention.

To control granary (true) mites warehouses, containers, harvesting and transport equipment, barns should be kept clean and systematic desakarization should be performed. The measures are taken according to granary insects prevention regulations. Food grain is thoroughly dried as mites exist if the humidity is beyond 10%. Seed corn is sprinkled with chalk, vivianite, naphthalene.

Red velvet mites are eradicated byacaricide treatment. Humans use special overalls to defend from larvae of red velvet mites. Sometimes various repellents are used as well.

Parasitiformes.

General characteristics. Order of parasitoformes includes small, medium and large ticks reaching from 0,2 to 30 mm in length. The shells of the body are often developed and can be splitted or joint. Rather rare are ticks with small dorsal shell or without it. The covering is soft, leathery, tensile of various structures. The majority of parasitiformes breed by laying eggs, but viviparous species can be met. The development cycle of the larva includes protonymph, deutonymph and adult phase. Parasitoformes have free or parasitic way of life. They can be saprobes, necrophages, predators, facultative and obligative bloodsuckers. Parasitoformes parasitize mainly on terrestrial vertebrates.

Role in human pathology. Many species suck human blood. This may cause skin irritation, rash, papules, gangrenous pustules, crusts of dried lymph, abscesses and festering sores. Some tick bites are painful due to the toxic action of saliva which causes swelling,

loss of sensation and general symptoms such as fever, headache, poor sleep, increased irritability or, vice versa, depression, muscle weakness, and other phenomena. Intoxication can lead to paralysis in humans and animals, which can lead to death. Though in case of timely tick removal the symptoms disappear.

Many parasitoformes are carriers and keepers of numerous pathogenic agents causing diseases in humans and animals. The order includes large systemic groups of Gamasidae, Argasidae, Ixodidae.

Gamasidae include a large group of small ticks (0,2-2,5 mm) which are quite common. There are free-living and parasitic species among Gamasidae. The parasites feed on the blood of reptiles, birds and mammals. They live in nests, burrows, caves, soil, buildings. Paultry mite (Dermanyssus gallinae) dwells in paultry yard, henhouses and even pet birds in cages. These mites are blood feeders and can attack people, causing skin irritation and dermatitis.

Tropical rat mites (Ornithonyssus bacoti) live in nests and sites of rodent dwellings. During the lifecycle these mites feed on blood, can attack people, causing dermatosis.

Gamasidae are transmitters of rickettsialpox and flea-borne typhus. Some Gamasidae participate in circulation of agents between animals in natural foci of tick-borne encephalitis, tularemia, Query fever, hemorrhagic fever etc.

Argasidae. Argasidae, namely O.papillipes, can provoke severe diseases such as tick-borne relapsing fever (causative agent Borrelia). The size of O.papillipes is 5-8 mm. At the site of a bite a dark-red nodule appears, which later develops into a blister containing blood; severe itch is observed. Spirochaete of relapsing fever are retained in ticks throughout the life and are transmitted in a transphase and transovarian way. Parasitiformes include two suborders: Mesostigmata and Ixodides. The first one as well as others includes Gamasoidea superfamily, the second includes only one superfamily of parasitic Ixodoidea, playing an important role in human pathology.

Ixodidae are spread all over the world. Mora than 1000 species are known and 60 of them inhabit the territory of the former USSR.

Ixodidae are the transmitters of tick-borne encephalitis, Rickettsiosis Sibirica, Query fever, Lyme desease, hemorrhagic fevers, tularemia, pyroplasmosis and other diseases. Ticks get infected through rodents and insect-eaters, coupling, in a transphase and transovarian way. Maintaining the causative agents in the organismfor

several years and transmitting them to litter, the ticks are not only transmitters but keepers of causative agents in nature.

In Belarus the most epidemiologically significant species are Ixodes and Dermacentors.

Taiga tick (Ixodes persulcatus) is distributed in coniferous, deciduous and mixed forests mainly in Siberia and Far East, northern, eastern and central regions of European part of Russia. Adult ticks are active from April to July and parasite in wild and domestic ungulates. Mature ticks are able to starve for about a year. Humans are attacked by imago and nymphs. These ticks are carriers of the spring-summer encephalitis, Lyme disease, ehrlichiosis and other diseases.

Ixodes ricinus is distributed in forest and forest-steppe regions of northern and middle Russia, Europe and mountains of the Crimea and Caucasus. In the South these mites are active in March-July while in the North they are active in July. The term of development is 3-7 years, they hebirnate in all terms of development. The duration of starvation of adult ticks can reach 2-3 years. Ticks feed on different types of wild mammals (moose, hares, hedgehogs, rodents), farm animals, and birds. As a rule humans are attacked by imago and nymphs, transmitting pathogens of tick-borne encephalitis, tick-borne spotted fever, Lyme disease, and other diseases.

Dermacentor marginatus carry pathogens of North Asian tick-borne encephalitis, tularemia, Crimean-Congo hemorrhagic fever, piroplasmosis, etc. Various species of this family are found in the forest area, the steppes and deserts, especially in river valleys with shrubs or pasture areas. Adult ticks are most active from March to June. D.pictus has a 3-host-lifecycle: larvae feed on small rodents, molt and become a nymph. The nymph feeds on rodents, hares and hedgehogs, and then again molts and turns into the adult tick, feeding cattle, sheep, goats, horses.

Representatives of Hyalomma genus are involved in the transmission of the virus causing Crimean hemorrhagic fever. Mites of this genus are large, in the fasting state they reach 6-7 mm. Some species are developed on three hosts, some – on two (larvae and nymphs feed on one host – birds, rabbits; adult mites feed on cattle); there are species developing on only one host.

Fighting the mites includes preventive and destructive activities carried out using insecticides. Facilities for cattle and territories which can be infected with tick-borne encephalitis are desinfected.

Personal prophylaxis should include the use of repellents, wearing high-neck and long-sleeve clothes (overalls), selfexaminations.

The stuck mites must be removed. A thread loop is imposed on a tick as close to the skin's surface as possible and tightened. Then the tick should be pulled upward with steady, even pressure and removed together with the mouth-parts. The tick must not be twisted or jerked, therefore it is not recommended to remove the tick with the tweezers (excluding tweezers, specially designed for this purpose).

Synanthropic flies

These flies belong to Brachicera suborder.

General characteristics.

The development of flies includes 4 phases: eggs, larvae, chrysalices and imago (adult insect).

Flies have a massive body and hemispherical head with slightly curved anteroir surface. Large multifaceted eyes are located on the side parts of the head. Bloodsucking flies have hard proboscis able to penetrate the skin of humans and animals. Flies feed only on liquid food: their saliva contains proteolytic enzymes and dissolve solid substances. Thus, flies have partially external digestion.

Females of most species are oviparous. The larvae go through three stages, and III stage is divided into two phases: feeding and prepupal phase. During the prepupal phase larvae leave sites of feeding in search of place of pupation. Pupae of flies are motionless.

The connection of certain species with humans is determined not only by their feeding features, but by their distribution within human settlements. So, some flies inhabit villages, pastures and wild nature.

Characteristics of some flies.

Aphages and nectarophages.

Poliphages. Adult flies feed on a variety of substances: human and animal feces, human food and food waste, wound and mucous membranes discharges of humans and animals. This group includes Musca domestica (Muscidae family – true flies).

The main sites of M. d. domestica breeding in urban settlements are food waste in garbage rooms, junkyards, food industry enterprises. In the rural areas M. d. domestica breeds in manure. Houseflies in a larval phase can parasite in the human body.

Larvae live in large groups under the substrate surface. In garbage rooms the larvae develop at the sites with food waste. Housefly larvae are thermophilic and actively move to the sites of

substrates with optimal temperature (35-45°). With the onset of prepupal period larvae seek out a cold and dry place where they pupate. Newborn flies coming to the surface can overcome up to 30 cm of soil and more than 1 meter of dry sand, though a layer of rammed ground is impassable for them. That is why mere burying the waste contaminated with larvae, does not protect from flying flies. The soil should be rammed.

During 1-11/2 hours the flies coming to he surface are not able to fly and stay near the sites of breeding. So, contact insecticides should be used.

Flies start feeding 3-3/4 hours after leaving pupae. During the daytime they eat every hour, which makes flies mechanical transmitters of infections. A fly leaves up to 50 spots of excrements within twenty four hours. In large numbers M. domestica greatly annoys people disturbing from rest and labour. It is especially importunate on hot days, when tries to settle on humans to lick up sweat and mucous discharge. In hot countries with low sanitary culture the clouds of flies attack children settling on the face and especially eyes.

Role in human pathology. M.domestica is a mechanical transmitter of many diseases, mostly enteric infections. Feeding on infected feces a fly swallows pathogens or these pathogens stick to flies' body hair. When a fly then settles on human food, the pathogens get there. It is known, that pathogens of a number of enteric infections passing through the fly intestine are viable for twenty-four hours in fly spots.

Facultative hematophagus. Alate flies feed on wound and mucous discharge, human and animal feces, plant sap. They lick up blood, but can not damage skin of humans and animals.

Musca sorbens is a most common type among these flies.

It breeds mostly in human feces on the ground. Musca sorbens is common in open air near feces or at fruit markets, though it can be met in premises.

Usually it attacks humans, licking up sweat, wounds or mucous membranes discharge. These attacks are hardly noticeable.

M. sorbens play an important role in spread of eye diseases. These flies transmit enteric infections as well. Besides, they can carry leprosy and frambesia if they feed on ulcers of infected people with following settling on healthy individuals.

Obligate hematophagus. The main food for alate flies is blood of warm-blooded animals and humans, which is sucked by flies through proboscises. Both males and females are bloodsuckers.

This group includes Stomoxys calcitrans (Muscidae family). Focus of their breeding is animal dung if it is mixed with straw or grass layer. A fly sucks up to 31 mg of blood per one feeding. In hot climate Stomoxys calcitrans breed the whole year round.

Role in human pathology. The bites of Stomoxys calcitrans are very painful. People try to drive them away but hungry flies persistently attack. At the site of the bite burning and itching can be felt, though S. calcitrans saliva is minimally toxic. In mass attacks of Stomoxys calcitrans it becomes impossible for people to worke and have rest.

Stomoxys calcitrans can mechanically transmit pathogens, mostly anthropozoonoses: anthrax, tularemia, staphylococcal infections etc.

Facultative coprophages. The main food for alate flies is human and animal feces and even human food. The most significant in human pathology are Muscina stabulans, Fannia canicularis (Muscidae family), Calliphora uralensis (Calli-phoridae family).

Muscina stabulans is spread everywhere. The basic sites of breeding are human feces. Besides, they can develop in dung of domesticanimals and foodscarps.

The female of Muscina stabulans lays eggs on the substrate, in which the larvae will develop, or on the soil near the sump or even near the food containers. In this case the larvae penetrate under the lid into the food. This is essential for understanding of M. stabulans larvae parasitism cases in the human gut. In the third fase of development the larvae become carnivorous and consume larvae of other flies, including the house ones. Larval development takes about 7 days in summer.

Adult flies live in outdoor facilities, barns and near the sites of breeding.

Role in human pathology.

House fly is a mechanical transmitter of enteric infections pathogens from feces to human food.

Facultative Necrophages. Adult flies prefer feeding on animal carcasses and meet waste as well as human and animal excrements, vegetable waste. The most important in human pathology are members of the family Calliphoridae: Lucilia green blowflies,

Calliphora blue blowflies and others.

Green blowfly – Lucilia sericata. Its body has a metallic green colour, on the head there are nogreen spots.

Tsetse fly (Glossina genus) is distributed throughout Africa. They are bloodsuckers attacking humans and animals. They are biological vectors of trypanosomes, causing sleeping sickness. Tsetse flies' larvae develop in the female uterus and pupate right after the birth.

Role in human pathology

These flies can play role of mechanical transmitters of enteric infectionsflying from feces to food, especially fruits in the gardens and markets.

Control techniques.

The main measures against flies should be considered a sanitary cleaning, including three units: the collection and storage of waste, disposal and decontamination. The most essential element in the fight against flies is the timely removal of waste – before prepupae migration, (at least once in three days). Wastebin should be hermetic and easy to clean. It concerns dung rooms too.These measures prevent waste from being infected and helps to keep wastebins clean, which makes it impossible for larvae to develop in the rests of waste.

The use of insecticides should be considered as an additional measure. It should depend on the level of sanitation: the lower it is, the more insecticides are applied.

The use of larvicides gives, as a rule, high effect in cesspools, as larvae are near the surface of excrements. For the disposal of solid waste the large expenditure norms of preparation is required, otherwise larvicide will not penetrate into the layers with larvae.

The use of insecticides is most effective if desinsection is performed in early spring.

Myiasis

Myiasis is a disease caused by fly larvae-parasites.

In myiasis larvae affect tissues and cavities of the host body.

Depending on the character of parasiting larvae miasis can be divided into seceral groups.

Accidental myiasis

(Intestinal and urinary)

Intestinal myiasis occurs when a person intakes water or food with minor newborn fly larvae by accident. In people with low stomach acidity larvae can stay alive, and even develop in the

intestine. In intestinal myiasis irritation and inflammation of mucosa is observed. Patients feel abdominal pain, sometimes in the anus. Larvae come out with feces, sometimes with vomiting.

Intestinal myiasis can be caused by larvae, which usually develop in decaying substances, but sometimes flies lay their eggs on human food. More often intestinal myiasis is caused by house flies, small gray blowflies, cheese and fruit flies, Eristalis tenax.

Urinary myiasis. This disease may occur in cases when flies lay their eggs on linen soiled with urine or feces, and hatched larvae get into the urethra. Larvae parasiting in the urethra cause pains, sometimes urinary retention. There are cases of urinary myiasis caused by larvae Fannia canicularis and Musca domestica.

Facultative myiasis

Facultative myiasis occurs when flies attracted by the smell of wound discharge or purulent process, lay eggs or larvae (viviparous species). The larvae feed on nekrotized tissues. Larvae at the end of their development leave the wound and pupate in the soil. Parasitizing of larvae is usually harmless and even accelerates wound healing, as larvae excretions contain substances that inhibit the growth of bacteria. However, facultative parasites can cause complications of suppurative disease of the ear, nose, eye conjunctiva. A female fly, settling on the wound, can bring its pathogens. Therefore it is necessary to protect the wound from contamination by flies.

Facultative myiasis more often are caused by the larvae of species which normally breed in carcasses and meat waste, i.e. flies of genera Lucilia, Calliphora etc., and also species, developing in decaying plant materials and manure: houseflies, gray meat flies and others.

Obligatory miasis

Obligatory myiasis is caused by such kinds of flies, larvae of which can only develop as parasites in humans and animals. Obligate myiasis should be distinguished into malignant and benign. Obligatory myiasis also includes thediseases caused by gadfly larvae standing out as a special group, for gadfly larvae do not finish their development in the human body.

Malignant myiasis develops as a result of parasitism of species with rapidly growing larvae (from 3 to 10 days). Females of these species lay large numbers of eggs or larvae on wounds, scratches, and mucous membranes of animals, rarer humans. Through larvae of this

group can not penetrate through the intact skin they destroy the mucous membranes or penetrate through the slightest skin lesions into the subcutaneous tissue, causing necrosis. Due to the rapid and massive development of the larvae their damage can be severe. Parts of the body affected by the larvae become inflamed; suppurations and gangrenous processes appear. Sometimes the larvae penetrate into the bone destroying the periosteum and causing bone necrosis. There are cases of complete destruction of the eyeball by larvae. As a result, the penetration of larvae into the brain can cause encephalitis. Some cases of myiasis are fatal. Patients with malignant myiasis experience severe pain. When larvae stop their development they drop from the wounds and pupate in the soil.

Usually it is not difficult to make diagnosis, as the larvae are easily found in wounds. In the cases when larvae develop deep in the tissues, wound bed content is moving.

Treatment. The wound should be rinsed by antiseptic. Larvae are removed from the wound by forceps. In rare cases incisions are performed to remove larvae.

Prevention. General measures of fly control.

Malignant myiasis in humans are caused by the following species: Wohlfahrtia vigil; Callitroga hominivorax (synonyms: Cochliomyia americana, Chrysomyia hominivorax) Chrysomyia bezziana (Calliphoridae family).

Benign myiasis is caused by single and slowly developing larvae (more than 10 days). It appears in parasiting larvae of Cordylobia anthropophaga (Calliphoridae family). This fly is spread in Africa. It lives in huts and cattlesheds. Eggs (about 500) are laid in sand, especially wetted with urine. Hatched larvae remain under a thin layer of sand. When a person (or animal) walks on the sand larvae come to the surface and penetrate into the feet skin. A person doesn’t notice the moment of penetration, but the growing larva causes pain. Larval development lasts 12-15 days. At the site of its development furuncle-like tumor with fistula appears. Through this fistula larva leaves the body of the host and pupate in the soil. Sometimes the parasitic larvae are found in other parts of the body. In these cases, the larvae penetrate into the skin of lying or sitting person.

Treatment. The larvae is easily removed from the tumor by forceps, the wound heals quickly.

Prevention. Desinfestation, destruction of flies in huts and

cattlesheds, wearing the footwear.

Dermatobia hominis (Cuterebridae family). This fly is spreas from Mexico to Argentina.

When a bloodsucker sits on an animal or human, fly larvae leave the eggs and penetrate into the skin of the host. Around the larvae a tumor with fistula appears. The larva needs 70 days to develop, then it falls out from a tumor and pupate in the soil. Larvae are removed from the tumor with forceps.

Prevention. Fighting with dermatobiasis of domestic ungulates, the use of repellents.

Myiasis is caused by larvae of the gadfly. Gadfly larvae parasitize only at the first age. Cases of further gadfly larvae development in the human body are not marked. Gadflies (pasture species) in adulthood do not eat, as they are aphags.

Gastric horse gadfly, – Gastrophilus intestinalis (Gastrophilidae-gastric gadflies family) is widespread.

Myiasis caused by the larva of this species is called Lee (1874) «Creeping disease». Synonyms: creeping disease, hair-worm, larva migrans, myiasis linearis.

The female glues the eggs to horse hair. People become infected after the contact with infected hair. The larva is embedded in the epidermis of the skin and migrates here, producing damage mechanically, using oral hooks, and chemically, using digestive enzymes. Outside the path, made by larva resembles the healing scratches. Parasitising of larvae causes itching.

Treatment. The larva is removed surgically.

Preventuon. Control of gastrophilosis in horses.

Hypoderma bovis (Hypodermatidae family), Lesser ox warble fly or Hypoderma lineatum De Villers. The hatched from the egg larva penetrates under the skin and migrates through the subcutaneous tissue, getting into the subcutaneous tissue a few months later. Parasitising of larvae is painless.

Treatment. The larva is removed surgically.

Prevention. Control of gastrophilosis in cattle.

Oestrus ovis – Rhinoestrus purpureus (Oestridae family). Females of O. ovis and R. purpureus when flying discharge liquid with larvae into the nostrils of sheep and goats. Infection of humans occurs more often in the pastures. Females splash larvae into the human eyes. Ocular myiasis can be external, when the larva penetrates

into the eyelids, lacrimal sac or mucous membrane, and internal, when the larva gets inside the eyeball. Internal oftalmomyiasis can lead to blindness.

Treatment. The larvae are very mobile, so in oftalmomyiasis the eye first is anesthetized with 3% solution of cocaine or 0,25% solution of tetracaine, and then the larva is removed by washing the eyes with water. If it is not effetive, the larva is removed with tweezers.

Prevention. Control of Oestrus ovis in the sheep breeding regions. Bloodsucking larvae. There is another kind of parasitism of larvae – bloodsucking. The larvae of these flies are temporary parasites and therefore do not cause myiasis. In Africa, Auchmeromyia luteola fly (family Calliphoridae) is widespread, the larvae of which attack humans. Flies spend most of their lives in huts leaving them rarely. The larvae live in the cracks of the earth floor. At night they go out and attack the sleeping on the floor of people.

Prevention. Desinfection with insecticides.

Blood-sucking diptera generally called "gnats"

Gnats are a group of flying bloodsucking diptera attacking people and animals in the open nature. The term “gnat” includes mosquitoes, black-flies, biting midges and horseflies, widespread from the far north to the far south. These insects are widespread in tundra and taiga, where due to local conditions, there are huge areas for mass breeding. Development of eggs, larvae and pupae of mosquitoes occurs in water or in the moist soil, rich in organic remains.

Role in human pathology

In the saliva of blood-sucking insects there is antikoagulin to prevent clotting of blood sucked. The saliva is irritating for human skin: the sting itches badly, burning and pain is felt, a papule or even a painful swelling appeares. In some cases, the reactive process involves the nearest lymph nodes, malaise and fever is observed. Many people develop an allergic reaction. Sensitization sometimes resulting from bites rather often leads to severe anaphylactic states.

The degree of irritating saliva action depends on the type of insect, the individual sensitivity of the subject and the number of bites. People often attacked by insects, develop immunity, in which the skin reaction is sharply reduced. This immunity is specific: the one produced against the bites of Aedes mosquitoes does not reduce the skin reaction to the introduction of mosquito saliva of other genera.

Intrusive mass, often almost continuous attacks of mosquitoes,

developing skin reactions complicated with pustular diseases, cause severe sufferings to people and warm-blooded animals. Mosquitoes affect the health and mood of people, lower the resistance to diseases.

Basic measures of gnat control

Making up the plan on mosquitoes control one should distinguish a plan of total area sanitation from a plan of control during the current season. In the first case, the main attention should be focused on the systematic destruction of the breeding sites of bloodsuckers. Regulation of large and small rivers, construction of dams gidrotehnical land reclamation and drainage of boggs leads to a sharp reduction gnats. Tangible results appear gradually along with economic development of large areas. Though, measures directed on protection of people from the mosquito attacks in the upcoming seasons should be performed as well.

Mosquitoes

Most of the species belong to the genus Aedes (40), the genera Culex includes less species (20), Anopheles – 9, Culiseta (synonym: Theobaldia) – 8 and Megarhinus – 2. Genera Mansonia, Uranotaenia and Orthopodomyia have only one representative.

General characteristics. Adult mosquitoes are slim, winged insects with relatively little head, elongated body and long legs. The development of the embryo in the egg occurs only in humid conditions - on damp soil or water. Mosquitoes breed in temporary and permanent natural ponds, as well as artificial (pools, wetlands, lakes formed after snowmelt, rainfalls, flooding rivers, ditches, wells, irrigation and drainage channels, rice fields, water barrels and so on.). From hatching until pupation a larva actively feeds and grows; while growing it moults 4 times, after 4 stages of development a larva becomes a pupa. In favorable conditions many mosquito species need 4-10 days to complete larvae phase, others need more time for this.

Role in human pathology.

Mosquitoes are annoying bloodsuckers. They play a particularly important role as vectors of human and animal diseases. It has been established that mosquitoes can spread more than 50 viral, bacterial and parasitic diseases, including tularemia, Japanese encephalitis and several other encephalitis, American equine encephalitis and related diseases, lymphocytic choriomeningitis, yellow fever, dengue fever and Rift Valley fever, as well as filariasis and malaria.

Preventive and control measures.

Non-malarial mosquitos control should include activities aimed at the elimination of breeding sites. Insecticides should be applied when it is necessary as an additional measure for the protection of human health. Extensive larvicidal treatment by synthetic insecticides often leads to the development of resistance in mosquitoes, and therefore - to synthesis and use of new insecticides. Currently there are many species of mosquitoes that have developed resistance to specific insecticides.

Anti-larval measures. Rational irrigation measures, clearing of stagnant water from vegetation can reduce or prevent the hatching of mosquitoes. Rather effective is elimination of all kinds of small abandoned reservoirs with favourable conditions for mosquito breeding. A large number of insecticides applied as larvicides against mosquito larvae has been synthesized. In the control of Aedes larvae the most effective is early spring mosquito destruction (Ae. communis, Ae. cataphylla, Ae. intrudens and other monocyclic species). Timely performed treatment of reservoirs dramatically reduces the number of mosquitoes in the season and reduces territory infected by eggs, which provides reduction of mosquito population in the next year spring.

Blackflies

General characteristics. Black-flies are small insects, belonging to several genera of Simuliidae family, their size is 1,5-3 mm. Development of blackflies occurs in streams and rivers. Their larvae and pupae do not live in the still water. Blackflies lay eggs, gluing them to the leaves and stems of plants, rocks and other drown objects. There also live larvae slowly crawling along the substrate.

Role in human pathology. Blackflies mostly make harm as bloodsuckers. In the river valleys blackflies often attack people in the open air. Compared to other blood-sucking insects blackflies' saliva is particularly toxic. Even single bites in the facial area often cause very intense reaction. In the area of mass emergence of blackflies pets sometimes die of intoxication. Attacks of blackflies on people do not lead to such serious consequences only due to the use of protective measures. In case of their absence the long stay in the open air at the sites of blackflies distribution is impossible. Especially affected are people working in the lumber camps, construction of roads, dams, and so on. In Africa, South and Central America, blackflies are the

intermediate hosts of filaria Onchocerca volvulus, which causes onchocerciasis. Along with other blood-sucking insects blackflies can be mechanical vectors of tularemia microbe.

Preventive and control measures.

Currently, the most efficient and cost-effective are anti larval measures. To effectively protect the object from blackflies their breeding within 70-200 km should be excluded, depending on the prevailing wind direction and blackfly species.

Midges

General characteristics. Midges belong to the family Midges are tiny blood-sucking insects (1-2 mm). They resemble small mosquitoes. Genera of bloodsucking midges include Sulisoides Leptoconops, Lasiohelea. The most widespread and massive species are Culicoides pulicaris, C. obsoletus and others.

Role in human pathology. Midges can cause the severe damage as bloodsuckers. At the time of blood-sucking a bite is felt like in an attack of mosquitoes. Most often midges sit on face and neck, crawl into the hair. Skin reaction in some individuals is quite different. In typical cases, at the injection site the reddish papule is formed. General reaction of the organism is moderate. Cases of severe intoxication caused by midges, are unknown.

In the tropics (Africa, South America) midges of Culicoides genus serve as intermediate hosts of filaria – Acanthcheilonema perstans. Midges are also carriers of certain viral infections. Culicoides midges are vectors of pathogens of two viral diseases of farm animals - Pestis africana equorum (horses, donkeys) and febris catarrhalis ovium («blue-tongue»). Along with other blood-sucking arthropods midges can play a certain role in the circulation of tularemia pathogen circulation in natural foci.

Preventive and control measures.

The preventive and control measures against midges and mosquitoes are general. They include forest management, land reclamation and hydrotechnical measures, aim at creation of conditions that prevent breeding of midges and other representatives of gnats. The choice of areas for building of plants, hydraulic works, state farms, settlements and towns is of great importance. Forest clearance, duly cleaning of deadwood provides drying of forest floor and prevention of midges from breeding. In case of impossibility of drainage measures places of midges breeding are treated with

larvicides, sprayed twith a special ground equipment or aircraft. Destruction of mosquito larvae with aircraft usually leads to a sharp decrease in the number of midges. Nets treated with larvicides can reduce the penetration of insects in houses.

Gadflies (Horse-flies)

General characteristics. Gadflies belong to the family Tabanidae. Gadflies are bloodsucking flies of medium and large sizes – from 1 to 3 cm; gadflies have a one-year life cycle, but in the northern and middle latitudes the development of larvae in wet conditions is extended to 2 years. Haematopota attack in cloudy or rainy weather.

Role in human pathology. Gadflies' bites are very painful, cause severe local and general reaction. Horseflies can be mechanical and specific vectors of a number of human and animal infections. Anthrax, tularemia, in tropical Africa - filariasis and loiasis – can be transmitted to humans.

Preventive and control measures.

Gadflies control is mostly performed by area reclamation. Additionally, the places of breeding and inhabitation of gadflies should be treated with insecticides. One of control methods is a device "puddles of death" used on the pastures. For this device small ponds with gadflies are flooded with petroleum. Insects flying there touch the surface and die almost instantly. For extermination of all kinds of gadflies dummy-like traps of Skufyin can be used. The combination of both methods - "puddles of death" and traps – gives a good effect in the extermination of gadflies on pastures. To protect people from gadfly biting repellents and protective clothing is used.

Sandflies

Representatives of Phlebotomidae family in Old World are following: Phlebotomus and Sergentomyia, further subdivided into subgenera. Vectors of human pathogens belong to Phlebotomus genus.

General characteristics. Sandflies are small bloodsucking insects living all over the world, but being thermophilic, populate only the hot and warm zones. All kinds of sandflies are bloodsucking, but only the females suck blood, attacking humans, domestic and wild animals, including rodents and cold-blooded. For the development of eggs, blood food is usually necessary. Gonotrophic harmony is characteristic of sandflies, i.e. one blood intake is enough for eggs maturation. Sandflies are crepuscular and nocturnal insects. Sandflies

live at the areas of human habitation and in the wild, where rodent burrows caves, cracks of rocks, tree hollows serve as shelters and breeding sites. Migration of sandflies plays an important role in the spread of pathogens.

Role in human pathology. Sandfly bites are painful. Itching at the injection site with the following formation of blisters and scratches is observed. Some individuals have even fever, appetite and sleep loss, headaches in multiple bites. Though sandflies are dangerous as they are specific carriers of pappatachi fever, leishmaniasis and Bartonella.

Preventive and control measures. Sandfly control is conducted through extermination of winged insects. The main measure is treatment of houses and outbuilding with DDT emulsion at a dose of 1-2g of active ingredient per 1 m². At the moment there is not enough convincing examples of resistanse to insecticides in Phlebotomus.

Louse (lice – plural)

Lice are parasites of mammals; they have their hosts and generally cannot survive for long if removed from them. Human lice include genera Pediculus and Phthirus of Pediculidae family. Each genus is represented by a single species. The first includes P. humanus, human louse, the second – Phth. pubis-pubic louse. Species P. humanus includes two subspecies: P. humanus capitis – head lice and P. humanus humanus – clothes lice.

General characteristics.

Lice are wingless, relatively small insects: head and pubic lice are 1 to 1,5 mm, clothes lice are 2-4,5 mm. Louse feeds on blood 2-3 times a day, getting to the human body with clothes. Pubic lice, having stuck to the body, remain long at one site, sucking blood periodically. Head lice stick eggs to the hair of the head, close to the sculp; clothes lice stuck eggs to the threads of the fabric, especially in the seams, and sometimes on the hair; pubic lice are typically found in pubic hair.

Role in human pathology. Role in human pathology of lice can be treated in two ways: as ecto-parasites, when they introduce salivary gland secretion into the wound, and, secondly, and as vectors of some transmissible diseases.

Pathological changes include both direct and secondary symptoms, namely itching caused by a severe irritant effect on lice saliva; rough skin; chronic dark pigmentation of the body skin (one of the primary symptoms of lice); mats of hair under the action of secondary infection in scratchings.

Lice as vectors of transmissible diseases have been proved to be the reason for typhus, relapsing fever and five-day fever. Transmitters of these diseases are clothes lice. It can be infected by Rickettsia typhus (Rickettsia prowazecki) in bloodsucking humans in the last 2 days of the incubation period and the period of fever, when the pathogen is present in human peripheral blood. Louse becomes contagious 4-7 days (sometimes 10 days) after feeding and retains its infectivity for life. It has been established by numerous studies that after feeding on a person suffering from typhus rickettsiae get into the louse's stomach penetrate into its epithelium and breed. The cells become overfilled with rickettsia, which are found not only in the stomach, but also in the Malpighian vessels in the body cavity of lice. Rickettsia does not penetrate through intact human skin. In skin itching infected lice feces get into the scratches causing typhus in humans. Infection can also occur when crushing lice on the scratched skin. Infection is possible when rickettsiae get on the mucous membranes of humans.

Preventive and control measures. Control measures can be preventive and eliminative.

High sanitary standard of living – a regular body wash; clean, tidy underwear, clothing, houses – is an essential prerequisite for lice prevention. Even in case of single lice in humans weekly body wash with a simultaneous change of underwear provides rapid destruction of these insects and prevents their breeding. The measures of public control include maintaining the system of state sanitary control in crowded places – railway stations, wharves, hotels, trains, passenger ships and so on. All these activities prevent the development and spread of pediculosis. Insecticides depending on the conditions of their application may be used in the form of dusts, solutions, emulsions, pastes, soaps, and aerosols.

To treat pediculosis and pediculosis pubis drugs with synthetic pyrethroids are currently used: permethrin, cypermethrin, etc.

In the intake of pharmacological drug phenylbutazone, human blood becomes toxic to lice and they die quickly after the blood meal.

Special anti-pediculosis shampoos ("Nitilon", "Nitifor", etc.), gels, soaps, lotions, detergents do affect nit dense shell, so washing should be repeated 2-3 times every 16 days. After drug use, one should wash his/her hair with hot water and vinegar (1 tbsp. per liter of water) to dissolve the adhesive nit substance, after which the eggs are easily combed out.

The radical means of lice elimination is shaving the hair. The shaved hair should be burned. To get rid of clothes lice the linen should be boiled for 20-30 minutes and ironed. In pediculosis pubis sulfuric ointment is used, skin is washed with hellebore tincture, bird cherry or tobacco decoction.

Flea

Fleas constitute an independent order Aphaniptera – small insects of peculiar structure, parasiting on mammals, rarer on birds. Adult fleas feed only on blood. The following fleas have the most epidemiological significance: human flea (Pulex irritans), parasites in humans, can be found on domestic animals; dog flea (Ctenocephalides canis), parasites in dogs, cats, gerbils, occurs in humans; rat flea (Xenopsylla cheopis), parasitic in rats, gerbils, can occur in humans, it is important in the epidemiology of the plague; rat flea (Ceratophyllus = Nosopsyllus fasciatus) parasites in gophers, can occur in humans; it is one of the carriers of the plague; Oropsylla silantievi is a parasite in marmots, tarbagans; it is one of the carriers of the plague.

Role in human pathology. When biting a flea injects saliva secret preventing bloodclotting into the sore. The human skin reacts by urticarial reaction, inflammatory swelling at the injection site. Often there is intense itching, especially in individuals who are sensitive to such injections. In scratchings complications such as pyoderma or eczematization can develop.

Fleas are vectors of infection leading to plague, endemic (murine) typhus, and perhaps even to some other ricketsioses. Fleas can be mechanical vectors in the spread of tularemia in natural foci. But the most dangerous disease transmitted by fleas is the plague. At the moment there are many flea species that have plague bacteria in their natural foci. Human become infected when the infected flea faeces get on the mucous membranes or wounds.

Preventive and control measures. Helpful effective measures to eliminate fleas on the premises are general hygienic measures: everyday wet cleaning, elimination of breeding sites (slits, cracks in floors, walls, etc.). In the mass appearance of fleas the use of insecticides is demanded. To remove insects aerosol insecticides (1 spray per 10 sq.) including "dichlorvos" are uses.

Fleas die within 24 hours, but within 1-2 weeks the eggs are hatched. Getting on the treated surface, they die within 1-2 days. If after 3 weeks the situation does not improve, the procedure should be

repeated.

Personal protection in the environment, where attacks of the infected fleas are possible, is achieved by wearing of special protective clothing, appropriate footwear, and the use of modern repellents.

Cimex lectularius (housebug, bed bug)

General characteristics.

Bed bug belongs to the family Cimicidae (parasitic bugs); represented by two species-Cimex lectularius and Qmex rotundatus. It is a typical parasite of human dwellings, living in the cracks and crevices of the walls, beds, furniture and other items. Bedbug is a relatively small insect, it is 4-5 mm in length and 3 mm in width. Bed bugs are insects with incomplete metamorphosis and throughout its development molt 5 times. Junior development phase (I to IV) are called larvae, older (V) – nymphs.

Bedbugs at all stages of development feed only on blood, being obligate hematophagus. During the day they hide in shelters, and at night go out in search of food. Usually they attack the prey in the dark, but if they are very hungry can hunt in the daytime, especially in hot weather. Bed bugs mainly feed on humans, but can attack and animals (cats, dogs) as well.

Role in human pathology. In mass breeding bed bugs cause great troubles in people, disturbing them from normal sleep and rest. In the summer, especially in the south, when the number of bed bugs is the highest, they are so annoying with their bites, that often make people leave the rooms at night and sleep in the open air. The reaction to the bug bite is different in different people: it may cause painful itching, blisters and scratchings; some people do not react to the bites at all; Moreover, people living in a room heavily populated by bugs, a special kind of "immunity" to their bites develops. Bedbug bite itself is not painful; it is felt only after a bed bug has sucked the blood.

There is assumption that the bed bugs participate in transmission of various diseases, as they can carry pathogens of the plague, typhus and relapsing fever, tularemia, filariasis and others, but the facts of these diseases transmission has not been proven yet. There is evidence that bed bugs can transmit Q fever.

Preventive and control measures.

The use of insecticides directly at the sites of breeding leads to elimination of bed bugs. Spraying is more efficient than dusting, as the latter can not be fixed on mattresses, bedding and vertical surfaces. In

addition, dusts are difficult to use for all kinds of surfaces, and traces of treatment are more visible. The effectiveness of control measures depends on the carefullness with which the spraying is done. In bed processing it is enough to spray transversal and longitudinal beams, springs and frame, not missing a gap where bedbugs hide. After the processing the bed is left uncovered for some time for natural drying. Furniture upholstery must also be carefully processed. In processing of other areas of bed bugs living the enough quantity of liquid should be applied to moisten all surfaces for it to penetrate into all the cracks. The walls must be sprinkled up to the ceiling.

The safest drugs for usage in apartments are microencapsulated preparations. Due to the long-lasting effects of such drugs the risk of relapse during the eggs maturation is reduced. The examples of such drugs are "Ekstermin-F" or "Ksulat C25."

Cockroach

Cockroaches belong to the order Blattoptera. Some species are typical synanthropes, the inhabitants of human dwellings. Sinantropic species include Blattella germanica, German cockroach, or Prussian, and Blatta orientalis, oriental cockroach or waterbug, common all around the world; Periplaneta americana, American cockroach; Schelfordella tartara, found in Central Asia, in houses with earth floors; Polyphage saussurei, Egyptian cockroach, living in Central Asia.

General characteristics.

Cockroach is a quite large insect, with oval, flattened body. Cockroaches are nocturnal insects, polyphages. A necessary condition for the existence of cockroaches is the heat, enough humidity and food. Cockroaches can feed on human foods, as well as debris and human discharges (feces, sputum, and so on).

Role in human pathology. In large number cockroaches can attack sleeping people at night, usually children, and bite epidermis on the open parts of the body. The affected areas are covered with a crust and thickened rim around it appeares. In the corium inflammatory infiltrate sometimes develops. It indicates the toxicity of cockroaches' saliva.

Due to the fact that cockroaches feed on garbage, feces, sputum, as well as human food, makes them the mechanical vectors of pathogens. It is known that pathogens of typhoid fever, dysentery, tuberculosis, leprosy and dysentery amoeba cysts, and helminth eggs are detected in the feces of cockroaches.

Preventive and control measures.

Compliance with health and hygiene standards at working areas and residential buildings, cleaning of food residues, and timely repairations prevents the growth of cockroaches. To eliminate cockroaches insecticides of contact and intestinal action are used: organophosphorus insecticides (trichlorfon, malathion, metilatsetofos, DDVP), carbamates (dikrezil), pyrethrins (pyrethrum), inorganic salts (sodium fluoride, borax), inorganic acids (boric acid).

VENIMOUS AND POISONOUS ANIMALS

A poison is a toxic substance that is eaten or absorbed through the skin. Some frogs and toads are considered to be poisonous because they have poison in their skin. If an animal eats, or even licks, a frog or toad it can get sick from poison in the frog or toad's skin.

Venom is a substance that is injected by a bite or a sting. Venomous animals have a stinger or fangs to inject venom into another animal.

Venom and poison are both toxins that can cause damage to the person whose body they are injected into. Venomous and poisonous are used to classify animals that can cause harm to their victim. These animals inject toxins into the body of their prey to either kill them or paralyze them, making it easier for them to slowly consume them. The classification is based on how the toxin is injected into the body.

Venomous organisms have a special gland and part of the body such as fangs that is used to administer the toxin into the body of the victim. These creatures have sharp fangs or stingers that are used to break the skin and inject the toxin directly into the victim's blood stream. The fangs or stingers are attached to a special gland that is responsible for producing the toxin. Once the skin is broken, the toxin is directly pushed into the blood steam causing it to reach the heart faster. Venom is said to kill the victim faster as it is directly added into the blood stream, making it pass through the body faster.

A poisonous creature, organism or plant do not have special glands to produce this toxin, it is produced by their normal body processes. The toxin is either produced by the body in the form of a liquid sticky substance that can coat the body of the creature or their body may be made of the poisonous substance. However, it is crucial to remember what may be poisonous to humans may not be for another creature. The

poison from the organism or the plant must be consumed or absorbed by the body. If it is eaten or drunk, it will first be processed by the stomach and then will be added to the blood streams. This results in poison killing the victim more slowly.

Venomous creatures include snakes, spiders, butterflies, centipedes, etc. Poisonous organisms include tree bugs, poisonous butterflies, frogs, Rhubarb laves, certain types of berries, etc.

Composition of poison or venom: protein-containing component, enzymephospholipase, hyaluronidase, ach-esterase (ants, bees, lizards, snakes), non protein-containing histamine, serotonine, acetylcholine, norepinefrin, dopamine(coelenterata, ants, snakes), saponins (coelenterata), alkaloids (ants), volatile oils (bees), other formicacid, phenol, hydrogencyanide.

Specific Toxins: saxitoxin, gonyautoxin, brevetoxin(shellfish), mellitin (bees), ciguatoxin, maitotoxin(fish), tetrodotoxin (fish, newts), bufagin, bufotoxin, bufotenine (frogs, toads), gilatoxin (lizard), ammodytoxinA, caudoxin, taipoxin (snakes).

Snakes

In Asian countries 200,000 bites and 15-20,000 snake bite deaths per year occure, (last century). It is estimated that 35,000-50,000 people die of snake bite each year. Snake bite is an important public health problem and occupational, rural domestic hazard in rural SriLanka. Surveys carried out as far back as in 1983 in the Anuradhapura district have shown 110 deaths occurring in the field due to snake bite, when people sought the help of native treatment than the Government health facilities. However, the pattern has changed over the last 2 decades that hospital admissions have increased dramatically. During the year 2005 there were 36861 hospital admissions due to snakebite which caused 134 deaths, whilst number of hospital admissions due to snake bite in 1996 was 27082 and that for 1985 was 3820. The highest incidence of snake bites in Sri Lanka was reported from the North Central Province (NCP), where the vegetation and climate provides an ideal habitat for snakes. With the advent of antivenom, the management of patients with snake bites in the government hospitals made a rapid success even though traditional treatment for snake bite was well established in the Sri Lankan culture. There are around 600 species of snake that are known to be venomous. This is about a quarter of all snake species. The following groups of snakes can be aggressive and are able to inflict dangerous, even potentially lethal bites.

Four families of snakes have venom that is toxic to humans:

Atractaspididae: Burrowing asps, mole vipers, stilleto snakes.

Colubridae: Dispholidus typus (Boomslang), Toxicodryas blandingii (Blanding's Tree Snake).

Elapidae: Cobras, coral snakes, kraits, mambas, sea snakes, sea kraits and Australian elapids.

Viperidae: True vipers and pit vipers, including rattlesnakes.

Venom snakes have a pair of enlarged teeth, the fangs, at the front of their upper jaw. Fangs grooved hollow venom channel.

Venom injects subcutaneously or intramuscularly. Snake venoms are not single toxins but mixture of many components, enzymes such as phosphatidases, roteases, cholinestrases, hyaluronidases, ribonucleases, deoxyribonucleases, lecithinase, polynucleotides toxins and biogenic amines. Most of the time these venoms have diversified and complicated toxic effects. The poison of Indian cobra and Krait also contains distinct substances, a neurotoxin haemolysin, a cardiotoxin, a cholinesterase and non-enzymatic components which produce neuromuscular block.

The venom of vipers contains substances which produce severe haemorrhage, haemolysis, fibrinolysis and extensive damage to various organs while venom of sea snakes damages nerves and muscles producing necrosis of the muscles (Rhabdomyolysis, myoglobinuria). The severity of snake bite depends on various factors like age and health of the victim. Children and elder nourished persons are liable to suffer more from its ill effects. Site of strike is equally important.

A direct strike of the fang is more dangerous than a scratch. Similarly if the poison directly enters the blood stream, the effect is more dangerous. Clothing affords protection. Thus a strike through the cloth shall be less serious.

Bites by large kinds are more dangerous since large snakes inject more poison. Exertion or physical activity like running immediately after a bite is dangerous since it accelerates the dissemination of poison in the body.

A proportion of bites do not result in the injection of venom. About 50% of bites by Malayan pit vipers and Russell’s vipers, 30% of bites by cobras and 5-10% of bites by saw-scaled vipers are dry bites.

The king cobra (ophiophagus hannah)

It is the world’s longest venomous snake – growing up to 5,6 m (18,5 ft) in length. Ophiophagus, literally means “snake-eater” as it eats other snakes. One single bite of this deadly snake can easily kill a

human. This snake is even capable of killing a full-grown Asian Elephant within 3 hours (fig. 38).

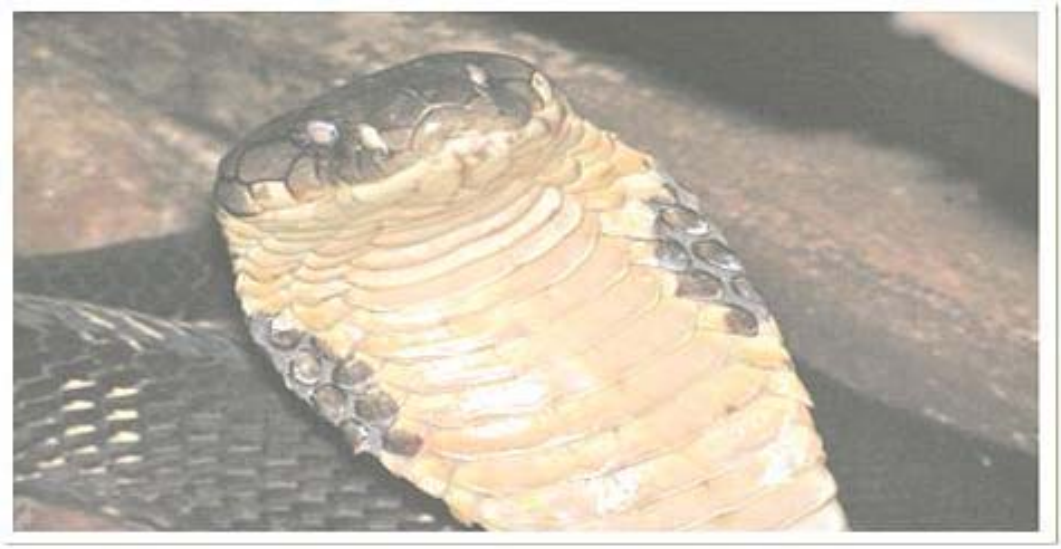

Fig. 38. – The King Cobra (Ophiophagus hannah)

Its venom is not as toxic as other venomous snakes, but King Cobra is capable of injecting 5 times more venom than black mamba and can result in mortality up to 5 times faster than that of the black mamba. It is quite widespread, ranging across South and South-east Asia, living in dense highland forests.

Inland taipan (fig. 39)

Fig. 39. – Inland Taipan

The prize for "The World's Most Venomous Snake" goes to the Inland Taipan of Australia. Just a single bite from this snake contains enough venom to kill 100 human adults or an army of 250,000 mice. Its venom is at least 200 – 400 times more toxic than a common cobra. The Inland Taiwan's extremely neurotoxic venom can kill an adult human in as little as 45 minutes. Fortunately this snake is very shy and there have been no documented human fatalities (all known bites were treated with antivenin).

Black mamba (fig. 40)

Fig. 40. – The black mamba (dendroaspis polylepis)

The black mamba (Dendroaspis polylepis) is the longest venomous snake in Africa, averaging around 2,5 meters (8,2 ft), and sometimes growing up to 4,3 meters (14 ft). Its name is derived from the black colouration inside the mouth rather than the actual colour of the skin which varies from dull yellowish-green to a gun-metal grey. It is the fastest snake in the world, capable of moving at 4,32 to 5,4 metres per second (16-20 km/h, 10-12 mph). The venom of the black mamba consists mainly of potent neurotoxins. Black mamba bites can potentially kill a human within 20 minutes or less

Rattlesnake (fig. 41)

Fig. 41. – Rattlesnake

Rattlesnakes are a group of venomous snakes of the genera Crotalus and Sistrurus of the subfamily Crotalinae ("pit vipers"). There are 32 known species of rattlesnake, with between 65-70 subspecies, all native to the Americas, ranging from southern Alberta and southern British Columbia in Canada to Central Argentina.

Rattlesnakes are predators who live in a wide array of habitats, hunting small animals such as birds and rodents. They kill their prey with a venomous bite, rather than by constricting. All rattlesnakes possess a set of fangs with which they inject large quantities of hemotoxic venom. The venom travels through the bloodstream, destroying tissue and causing swelling, internal bleeding, and intense pain. Some species, such as the Mojave Rattlesnake, additionally possess a neurotoxic component in their venom that causes paralysis and other nervous symptoms.

Clinical features. The clinical picture depends on the quantity of the poison injected. But even if it is non-poisonous, fright and agitations are always present accompanied by tachycardia, sweating and restlessness. In a bite by a poisonous snake symptoms generally appear within a few minutes to as late as 2 hours.

Early symptoms and signs. Increasing local pain (burning, bursting, throbbing) at the site of the bite. Local swelling that gradually extends proximally up the bitten limb and tender painful enlargement of the regional lymph nodes. However, bites by kraits and sea snakes may be virtually painless.

Local Symptoms and Signs. Local pain, local bleeding, bruising, lymphangitis. Enlargement, blistering, local infection and abscess formation, necrosis. Systemic Symptoms.

General Symptoms and Signs. Nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration.

Cardiovascular Symptoms (Viperidae): visual disturbances, dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, pulmonary oedema, conjunctival oedema.

Bleeding and clotting disorders (Viperidae): bleeding from recent wounds (including fang marks,venepunctures etc) and from old partly-healed wounds, spontaneous systemic bleeding.

Neurological disorders (Elapidae, Russell's viper).

Rhabdomyolysis: generalised pain, stiffness and tenderness of muscles, trismus, myoglobinuria, hyperkalemia, cardiac arrest, acute renal failure.

Renal disorders (Viperidae, sea snakes)***:*** loin (lower back) pain, haematuria, haemoglobinuria, myoglobinuria, oliguria / anuria, symptoms and signs of uraemia.

Endocrine disorders: acute pituitary/adrenal insuff. with russell's viper. acute phase: shock, hypoglycaemia; chronic phase (mnths to yrs after): weakness, loss of 2ry sexual hair, amenorrhoea, testicular atrophy, hypothyroidism etc.

Cobra and Krait Bite. There is severe pain at the site, local necrosis and sloughing. Neurotoxic effects (Drowsiness, respiratory paralysis, Blurring of vision, paralysis of palate, tongue and flaccid paralysis of limbs) arc the predominant features and appear after 8-12 hours of bite. These effects are completely reversible provided they are treated at the earliest. Coma and death due to respiratory paralysis may occur.

Viper Bites. There is severe local reaction in the form of swelling and necrosis at the site. Hemorrhagic complications are major manifestations in the form of bleeding from various sites, epistaxis, hematuria, haematemesis and malena. Blood becomes in-coagulable because of consumption coagulopathy. Hypo tension, shock, myocarditis and cardiac failure are other complications.

Renal involvement is a deraded complication and it may be in the form of direct nephrotoxicity acute tubular necrosis and interstitial nephritis. Death generally is due to shock, cardiovascular collapse and renal failure.

The local reaction is not much and signs of poisoning occur within one to 2 hours and are characterized by generalized stiffness, muscle aches, Trismus, Ptosis, paralysis and renal failure later on.

Clinical syndromes of snake bite.

Syndrome 1. Local envenoming (swelling etc) with bleeding/clotting disturbances – Viperidae (all species).

Syndrome 2. Local envenoming with bleeding/clotting disturbances, shock or renal failure (Russell's viper +/-saw-scaled viper). With conjunctival edema (chemosis) and acute pituitary insufficiency (Russell's viper). With Ptosis, External Ophthalmoplegia, facial paralysis etc and dark brown urine (Russell's viper (Sri Lanka & South India), Viperidae (all species)).

Syndrome 3. Local envenoming (swelling etc) with paralysis (Cobra or King Cobra).

Syndrome 4. Paralysis with minimal or no local envenoming (Krait, Sea snake).

Syndrome 5. Paralysis with dark brown urine and renal failure with bleeding/clotting disturbance (Russell's viper (Sri Lanka & South India) or Paralysis with dark brown urine and renal failure no bleeding/clotting disturbances (Sea snake).

Limitations of syndromic approach. The range of activities of a particular venom is wide. Considerable overlap of clinical features caused by venoms of different species of snake. "Syndromic Approach" may still be useful, especially when the snake has not been identified and only monospecific antivenoms are available.

Long term complications of snake bite.

At the site of the bite: chronic ulceration, infection, osteomyelitis or arthritis may persist causing severe physical disability.Malignant transformation may occur in skin ulcers after a number of years.

Management of snake bite

- First aid treatment
- Transport to hospital
- Rapid clinical assessment and resuscitation
- Detailed clinical assessment and species diagnosis

- Investigations/laboratory tests
- Antivenom treatment. Observation of the response to antivenom: decision about the need for further dose(s) of antivenom
- Supportive/ancillary treatment
- Treatment of the bitten part
- Rehabilitation
- Treatment of chronic complications

Identification of the snake is important in planning treatment in certain areas of the world, but is not always possible. Majority of the snake bites are made by non-poisonous ones and it is important to identify the poisonous ones. The poisonous ones are covered with large scales covering greater part of the ventral surface. The mouth contains only one pair of poisonous fangs in the upper jaw placed anteriorly in case of Krait and cobra and posteriorly in viper. As compared to them the non-poisonous ones have small teeth.

In poisonous snakes there are two fang marks along with local reaction while in nonpoisonous there are multiple teeth marks with hardly any local rea ction. In biting it strikes with great speed, opens its jaws, rotates forward the fangs, snaps the jaws together and ejects its venom from the poison gland via the duct and fang into the tissues in one instantaneous movement.

Laboratory investigations. In severe cases there is rise in polymorph leucocyte count with fall in platelet count. There is hypo-fibrinogenemia with abnormal tests of coagulation. Micro Elisa kit for the detection of snake venom and venom antibodies helps in detecting exact circulating venom.

First aid. Protect the person and others from further bites. While identifying the species is desirable in certain regions, risking further bites or delaying proper medical treatment by attempting to capture or kill the snake is not recommended.

Aims of First aid: to retard systemic absorption of venom; Preserve life and prevent complications before receiving medical care, Control distressing early symptoms, Arrange the transport to a place where they can receive medical care.

Useless or Dangerous Methods. Making local incisions or pricks at the site of the bite or in the bitten limb, Attempts to suck the venom out of the wound. Use of snake stones, Electric shock, Topical instillation or application of chemicals, herbs or ice packs.

Recommended first aid methods: reassure the victim who may be very anxious, immobilise the bitten limb with a splint or sling (any movement or muscular contraction increases absorption of venom into the bloodstream and lymphatics); to keep the bitten limb in a functional position and below the victim's heart level so as to minimize blood returning to the heart and other organs of the body.

Do not give the person anything to eat or drink. This is especially important with consumable alcohol, a known vasodilator which will speed up the absorption of venom. Do not administer stimulants or pain medications to the victim, unless specifically directed to do so by a physician. Remove any items or clothing which may constrict the bitten limb if it swells (rings, bracelets, watches, footwear, etc.). Keep the person as still as possible; consider pressure-immobilisation for some elapid bites; avoid any interference with the bite wound as this may introduce infection, increase absorption of the venom and increase local bleeding. A tourniquet must be applied nearest to the site of bite so as to impede the lymphatic flow as well as venous return. The toumiquet should be loosened periodically so that arterial supply of the part is not affected.

The bitten part should be washed well with soap and water. There is a view that incision and suction of the wound removes the poison but this is no longer recommended. Applying ice over the bitten site delays the absorption of venom but again there is a view that cooling may result in irreparable damage of injured tissues by causing ischemia so cooling of the part is not recommended by some authorities.

Besides local measures, general treatment must be instituted. It consists of sedation, (diazepam) antibiotics to cover infection, tetanus toxiod and treatment of shock. An intravenous drip should be set up immediately to correct fluid and electrolyte imbalance. Cardiac, respiratory and renal complications have to be managed appropriately.

Pressure immobilisation method. Ideally, an elasticated, stretchy, crepe bandage, approximately 10 cm wide and at least 4,5 metres long should be used. The bandage is bound firmly around the entire bitten limb, starting distally around the fingers or toes and moving proximally, to include a rigid splint. The bandage is bound as tightly as for a sprained ankle, but not so tightly that the peripheral pulse (radial, posterior tibial, dorsalis pedis) is occluded or that a finger cannot easily be slipped between its layers. Pressure immobilisation is recommended for bites by neurotoxic elapid snakes,

including sea snakes but should not be used for viper bites because of the danger of increasing the local effects of the necrotic venom.

Snake. Do not make attempt to kill it. If the snake has already been killed, it should be taken to the hospital with the patient in case it can be identified. Do not handle the snake with bare hands as even a severed head can bite!

Transport to Hospital. Quickly, but as safely and comfortably as possible. Any movement, especially of the bitten limb, must be reduced to an absolute minimum to avoid increasing the systemic absorption of venom. Any muscular contraction will increase this spread of venom from the site of the bite.

Detailed Clinical Assessment and Species Diagnosis.

- History of the circumstances of the bite and the progression of local and systemic symptoms and signs is very important.
- Site of bite and Time of bite.
- Snake identification.

Early Clues of Severe Envenomation

- Snake identified as a very dangerous one.
- Rapid early extension of local swelling.
- Early tender enlargement of local LN.
- Early systemic symptoms (hypotension, shock), nausea, vomiting, diarrhoea, severe headache, "heaviness" of the eyelids, inappropriate drowsiness or early ptosis/ophthalmoplegia.
- Early spontaneous systemic bleeding.
- Passage of dark brown urine.
- Patients who become defibrinogenated or thrombocytopenic.

Physical Examination. Examination of the bitten part: extent of swelling, tenderness to palpation, LN enlargement and lymphangitis, tense oedema, arterial pulses, compartmental syndrome.

General Examination: Blood pressure, postural drop hypotension indicative of hypovolemia, Heart rate, Petechiae, Purpura & Echymoses, Chemosis, Epistaxis.

Thoroughly examine the gingival sulci, using a torch and tongue depressor, as these may show the earliest evidence of spontaneous systemic bleeding.

Abdominal tenderness may suggest gastrointestinal or retroperitoneal bleeding. Loin pain and tenderness suggests acute renal ischaemia (Russell's viper bites). Intracranial haemorrhage is

suggested by lateralising neurological signs, asymmetrical pupils, convulsions or impaired consciousness.

Neurotoxic Features. Ask the patient to look up and observe whether the upper lids retract fully. Test eye movements, Size and reaction of the pupils. Trismus – Check facial muscles, tongue, gag reflex. Flexors of the neck may be paralysed. Bulbar and Respiratory Paralysis – is inability to swallow secretions, "Paradoxical respiration".

Generalised Rhabdomyolysis. Muscles of the neck, trunk and proximal limbs become tender and painful on movement and may become paralysed. In sea snake bite there is pseudotrismus that can be overcome by sustained pressure on the lower jaw. Myoglobinuria may be evident 3 hrs after bite.

Investigations/laboratory tests. 20 minute whole blood clotting test (20WBCT) (place a few mls of freshly sampled venous blood in a small glass vessel, leave undisturbed for 20 minutes at ambient temperature, tip the vessel once if the blood is still liquid and runs out, the patient has hypofibrinogenaemia as a result of venom-induced consumption coagulopathy).

Haemoglobin concentration/haematocrit: a transient increase indicates haemoconcentration resulting from a generalised increase in capillary permeability (eg in Russell's viper bite). Decrease reflect blood loss or, in the case of Indian and Sri Lankan Russell's viper bite, intravascular haemolysis.

Platelet count: may be decreased – viper. WBC cell count: Early neutrophil leucocytosis in systemic envenoming from any species.

Blood film: fragmented RBC ("helmet cell", schistocytes) are seen in microangiopathic haemolysis.

Plasma/serum: may be pink or brownish if there is gross haemoglobinaemia or myoglobinaemia.

Biochemical Abnormalities. Aminotransferases, creatine kinase, aldolase elevated if there is severe local damage or, particularly generalised muscle damage.

Bilirubin is elevated following massive extravasation of blood. Creatinine, urea or blood urea nitrogen levels are raised in the renal failure. Early hyperkalaemia may be seen following extensive rhabdomyolysis in sea snake bites. Bicarbonate will be low in metabolic acidosis (eg renal failure).

Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidaemia (respiratory or

metabolic acidosis).

Urine Examination. Dipsticks for blood/ Hb./myoglobin. Microscopy for erythrocytes in the urine. Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalised increase in capillary permeability in Russell's viper envenoming.

Antivenom Treatment. Antivenom is immunoglobulin (usually the enzyme refined F(ab)2 fragment of IgG) purified from the serum or plasma of a horse or sheep that has been immunised with the venoms of one or more species of snake. Monovalent or monospecific antivenom neutralises the venom of only one species of snake. Polyvalent or polyspecific antivenom neutralises the venoms of several different species of snakes.

Haffkine, Kasauli, and Serum Institute produce "polyvalent anti-snake venom serum" It is raised in horses using the venoms of the "Big four" (Cobra, Krait, Russell's viper, Saw-scaled viper). Not included are venoms of King Cobra, Sea snakes and Pitvipers and coral snakes.

Antibodies raised against the venom of one species may have cross-neutralising activity against other venoms, usually from closely related species – paraspecific activity. For example, the manufacturers of Haffkine polyvalent anti-snake venom serum claim that this antivenom also neutralises venoms of two Trimeresurus species.

Indications for Antivenom - Systemic Envenoming:

- Haemostatic abnormalities: spontaneous systemic bleeding, coagulopathy, thrombocytopenia (<100 x 109/l);
- Neurotoxic signs: ptosis, external ophthalmoplegia, paralysis;
- Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia, abnormal ECG;
- Acute renal failure: oliguria/anuria, rising blood creatinine/urea;
- Haemoglobinuria/myoglobinuria: dark brown urine, evidence of intravascular haemolysis or generalised rhabdomyolysis (muscle aches and pains);
- Supporting laboratory evidence of systemic envenoming;
- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet);
- Swelling after bites on the digits (toes and especially fingers);

- Rapid extension of swelling (for example beyond the wrist or ankle within a few hours of bites on the hands or feet);
- Development of an enlarged tender lymph node draining the bitten limb;

Antivenom treatment is recommended if and when a patient with proven or suspected snake develops one or more of the signs.

Antivenom treatment should be given as soon as it is indicated. It may reverse systemic envenoming even when this has persisted for several days. When there are signs of local envenoming, without systemic envenoming, antivenom will be effective only if it can be given within the first few hours after the bite.

Contraindications to antivenom. There is no absolute contraindication to antivenom treatment. Patients who have reacted to horse (equine) or sheep (ovine) serum in the past and those with a strong history of atopic diseases (especially severe asthma) should be given antivenom only if they have signs of systemic envenoming. High risk patients may be pre-treated empirically with s/c adrenaline, i/v antihistamines (both anti-H1 anti-H2) and corticosteroid. In asthmatic patients, prophylactic use of an inhaled adrenergic Beta2 agonist may prevent bronchospasm.

Ideal treatment is monovalent antivenom, as this involves administration of a lower dose of antivenom protein than with polyvalent antivenoms. Polyspecific antivenoms can be as effective as monospecific ones, but a larger dose of antivenom protein must be administered to neutralise a particular venom.

Antivenom is given by slow IV inj. (<2 ml/min). This method has the advantage that the doctor/nurse/dispenser giving the antivenom must remain with the patient during the time when some early reactions may develop. It is also economical, saving the use of intravenous fluids, giving sets, canula etc. Reconstituted freeze-dried or neat liquid antivenom is diluted in approximately 5-10 ml of isotonic fluid per kg body weight (ie 250-500 ml of isotonic saline or 5% D in the case of an adult patient) and is infused at a constant rate over a period of about one hour.

Local administration of antivenom at the site of the bite is not recommended! Although this route may seem rational, it should not be used as it is extremely painful may increase intracompartmental pressure and has not been shown to be effective. Antivenom must

never be given by the intramuscular route if it could be given intravenously. Antivenom should never be injected into the gluteal region (upper outer quadrant of the buttock) as absorption is exceptionally slow and unreliable.

Antivenom reactions. Early anaphylactic reactions: usually within 10-180 minutes of starting antivenom – the patient starts itching (often over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. A minority of these patients may develop severe life-threatening anaphylaxis: Hypotension, bronchospasm and angio-oedema. In most cases, these reactions are not truly "allergic". They are not IgE-mediated type I hypersensitivity reactions to horse or sheep proteins. Pyrogenic (endotoxin) reactions are common and usually develop 1-2 hours after treatment. Symptoms include shaking chills (rigors), fever, vasodilatation and a fall in BP. Febrile convulsions may be precipitated in children are caused by pyrogen contamination during the manufacturing process.

Late (serum sickness type) reactions develop 1-12 (mean 7) days after treatment. Clinical features include fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex. Proteinuria with immune complex nephritis and rarely encephalopathy may occur.

At the earliest sign of a reaction antivenom administration must be temporarily suspended. Epinephrine (adrenaline) (0,1% solution, 1 in 1,000, 1 mg/ml) is effective. In pyrogenic reactions the patient must also be cooled physically and with Antipyretics, Intravenous fluids should be given to correct hypovolaemia.

Treatment of late reactions: Chlorpheniramine: adults 2 mg six hourly, children 0,25 mg/kg in divided doses. In those who fail to respond Prednisolone: adults 5 mg six hourly, children 0.7 mg/kg/day in divided doses 5-7 days.

Observation of the response to antivenom. Nausea, headache and generalised aches and pains may disappear very quickly. Spontaneous systemic bleeding (eg from the gums) usually stops within 15-30 minutes. In shocked patients, blood pressure may increase within the first 30-60 minutes and arrhythmias such as sinus bradycardia may resolve. Neurotoxic envenoming of the post-synaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom,

but usually take several hours. Envenoming with presynaptic toxins (kraits and sea snakes) is unlikely to respond in this way. Blood coagulability (as measured by 20WBCT) is usually restored in 3-9 hours. Bleeding from new and partly healed wounds usually stops much sooner. Active haemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal colour.

Recurrence of systemic envenoming. Signs of systemic envenoming may recur in 24-48 hrs. This is attributable to:

1) continuing absorption of venom from the "depot" at the site of the bite,

2) redistribution of venom from the tissues into the vascular space, as the result of antivenom treatment.

Criteria for giving more antivenom. Persistence or recurrence of blood incoagulability after 6 hr of bleeding after1-2 hr; Deteriorating neurotoxic or cardiovascular signs after 1-2 hr.; If the blood remains incoagulable (as measured by 20WBCT) six hours after the initial dose of antivenom, the same dose should be repeated.

This is based on the observation that, if a large dose of antivenom given initially, the time taken for the liver to restore coagulable levels of fibrinogen and other clotting factors is 3-9 hours.

In patients who continue to bleed briskly, the dose of antivenom should be repeated within 1-2 hours. In case of deteriorating neurotoxicity or cardiovascular signs, the initial dose of antivenom should be repeated after 1-2 hours, and full supportive treatment must be considered. Conservative treatment when no antivenom is available.

When antivenom is unavailable. Bite by a species against whose venom there is no available specific antivenom (for example coral snakes - genera, sea snakes) – supportive treatment.

Surgical intervention may be needed but the risks of surgery in a patient with consumption coagulopathy, thrombocytopenia and enhanced fibrinolysis must be balanced against the lifethreatening complications of local envenoming.

Heparin is ineffective against venom-induced thrombin and may cause bleeding on its own account. It should never be used in cases of snake bite. Antifibrinolytic agents are not effective and should not be used in victims of snake bite.

Prophylactic course of penicillin (or erythromycin for penicillin-hypersensitive patients) and a single dose of gentamicin or a course of

chloramphenicol. Booster dose of tetanus toxoid is recommended.

Coelenterata

The Coelenterates are mainly marine animals with some minor exceptions. These animals are two-layered, sessible and free-swimming. The Coelenterates comprise the Cnidaria subphylum and are classified into two basic forms, the polyp and the medusa. One of the characteristic features of the Cnidarians is specific cells with short sensory triggers. These cells contain capsules with coiled threads which have internal tubes. If the sensory trigger of the cell is touched the coiled thread is rapidly ejected. Then the thread straightens and stings the body of the animal or man with venom of the capsule. These cells are called Nematocyst. They are shaped among tentacles around the mouth.

The contact with different types of the Coelenterates produces burning sensation, redness of the skin, itching and eye inflammation in case the venom gets into the eyes with the hands. In some cases these reactions may go away in 30-40 minutes, in others the recovery can take a long period of time.

The observations have shown that the venom of the Nematocyst leads to allergic reactions. After the first sting sensitization to the successive stings occurs which leads to the severe anaphylactic reactions.

Medusae

Gonionemus vertens or “Spider” medusa of the genus Gonionema is extremely dangerous for humans. The genus Gonionema includes 9 species which are common for the Pacific, Atlantic and Indian oceans.

Gonionemus vertens is small medusa, having the shape of the compressed bell or the fleshy mushroom cap which diameter is often not more than 3,5 cm. From the centre of the bell hangs the manubrium, a tubular structure that contains the mouth. The tentacles (about 80) are attached to the edges of the bell. The tentacles have large rings of nematocycts.

Clinics

A sting from Gonionemus vertens causes sharp pain similar to the pain caused by heat. In the location of lesion hyperemia occurs very fast, followed by the edema after 20 minutes. In 30-40 minutes back pain, along with the pain in the limbs, acute pains in the bones, joints and palmus set in. These symptoms are accompanied with cold sensation in

the arms and legs. General weakness and chest tightness occur, breathing becomes labored, and it is followed by choking sensation. The injured person feels uncertain anxiety. Burning sensation in the location of lesion remains for several hours. General critical condition remains from 2 to 4 days. Weakness after the recovery may persist another several days. Some symptoms may cease.

Treatment

One should make intravenous injection of 20% alcohol (10 ml. 3 times a day) or 10% of potassium chloride solution in the same dose, and use 1ml of 1% of pantopon solution for subcutaneous administration; breathe fresh air, use hot-water bottles, drink lots of hot water. The subcutaneous injection of adrenalin, especially, ephedrine which is inserted shortly after venenation leads to good results. Ephedrine ceases breathing, helps to rid of the feeling of anxiety and chest tightness.

Prevention

You should avoid swimming in the medusa habitats in the early and late hours, and in the shallow water under the marine algae. Bathing in the areas of medusa outbreak is forbidden. While bathing it is prohibited to take medusa with hands.

Vertebrata

Fish (eng.), poisson (fren.)

Many species of the venomous fish poison the human with the secretion of the venomous glands of the sharp spines in their fins or the spines on the opercula, tails, rarely, at the bottom of the dorsal fin.

The stings of several species may lead to the serious effects. All that group of fish refers to the active poisonous animals.

In USSR to this group refer rays (family Stingray) which inhabit coastal areas of the Black Sea, the western part of the Azov Sea and the sea coasts of the Russian Far East. Rays can be found in the Atlantic, Indian and Pacific oceans as well.

Stingrays are bottom-lying fish; they are 2 meters in length, with the flat body and long whip-like tail. The tail is equipped with one or several sharp venomous spines with small barbs on the sides.

If they are caught or frightened, they attack with their flexible tails trying to stab the venomous spine of the tail into the victim’s body. The injuries which inflict the human are very dangerous.

The other, no less dangerous, fish called weever fish or scorpion fish, or lesser weever inhabit the Black and Baltic Seas, as well as the

Mediterranean and Atlantic Seas. When caught, lesser weevers are strongly bent, protruding the opercula, trying to prick the victim with their poisonous spines.

Scorpion fish (family Scorpaenidae), less dangerous ones, have a large distribution in the Black Sea, along the coast of the Far-Eastern region and also are common for the Mediterranean Sea and Atlantic Ocean.

These are fish 25 cm in length or abit larger, with big head, slightly squeezed from both sides, slow-moving, living in stones and alga. Their fins are poisonous.

White-edged rockfish belongs to another genus of the same family, they reach 60 cm in length and live at a depth of 200 m. Norwegian **white-edged rockfish lives in** the Arctic Ocean.

The pricks of their fins can be poisonous forhumans.

Another fish, which bites are very dangerous is moray eel. It is widespread in the southern part of Atlantic, Indian Ocean, in the waters of South Korea, Japan and the Mediterranean Sea. According to some authors, the bites of moray eels are poisonous. Other species of poisonous fish, besides the mentioned above, live in the Indian Ocean, warm parts of the Pacific and Atlantic oceans. Teir meat is harmless, edible and many of them are eaten. Poisoning is possible in taking the fish by hands when removing them from the network, as well as during bathing.

The pricks of their fins can be poisonous for humans.

Another fish, which bites are very dangerous is moray eel. It is widespread in the southern part of Atlantic, Indian Ocean, in the waters of the Sea of Japan and the Mediterranean Sea. According to some authors, the bites of moray eels are poisonous. Other species of poisonous fish, besides the mentioned above, live in the Indian Ocean, warm parts of the Pacific and Atlantic oceans. Their meat is harmless, edible and many of species are used for food. Poisoning is possible in taking the fish by hands when removing them from the fishing net, as well as during bathing.

Clinical representation. Symptomatology of poisonings by stabbing fish is quite diverse. Common symptoms are: sharp pain felt at the moment of injection and extending radially from the point of injury, the sense of instinctive fear, rapidly increasing weakness turning into semiconscious state. In some cases there is a loss of consciousness. The victim can develop the following symptoms:

fever, nausea, vomiting, shortness of breath, pain in the heart, sometimes severe convulsions. Edema of the affected limb is observed.

The skin around the wound becomes pale, then red. Tissue necrosis is possible, which can lead to formation of ulcers, abscesses and lymphangites that is considered as complications after poisoning. In severe cases, death occurs within days.

In mild poisoning the symptoms pass after 2-3 days. Nevertheless, in most cases, even in a favorable disease development, the ultimate recovery occurs slowly. The victim needs a complete rest and bed regime for at least a week. Malaise may last for 2 months.

Treatment. The first aid is performed by intensive limb massage towards the site of the injection or extraction of the venom by mouth. The wound must be well washed and a sterile dressing should be imposed. The wounded limb is fixed with splint.

In treatment of patients novocaine blockade is used. 30-40 ml of 0,5% novocaine solution is administered in the area surrounding the wound. If a poisonous prick was made in the thumb, 80-100 ml of novocaine solution must be injected into the arm above the wrist. Accordingly novocaine solution is injected into the damaged lower limb. It is recommended to add antibiotic – penicillin or streptomycin (200 000-250 000 units) – to novocaine solution, prepared for injection. Soluble cortisone preparations are effectiveas well. They are imposed on the affected areas, administered orally or intramuscularly. Antihistamine drugs are prescribed too - diphenhydramine and others. In case of weakened cardiac activity strofantin, camphor, caffeine and other drugs are used. In case of severe pain morphine is administered. With the development of phlegmon and lymphangitis the treatment is carried out under the general rules.

Amphibian

As a rule, there is no any risk for humans from the venom of the cutaneous glands of the Amphibian. The skin of the toad contains a wide range of the saccular glands on the whole body, behind the head, along the edges of the broad neck which are clustered to larger glands called parotid (do not mix with the salivary glands!). The glands secrete the caustic substance of garlic smell.

It is harmless if the substance gets on the healthy human skin. But, if the substance gets into the mucosae it causes burning sensation. It passes quickly after the washing of the suffered area of the mucosa

with fresh cold water. If the venom gets into the mouth and is accidently swallowed, nausea and vomiting occur.

Some species of the African wood frogs which occupy tropical regions constitute a certain threat for humans. When the secretions of their cutaneous glands get on the human skin it causes severe skin irritation, edema and redness. That is why it is necessary to catch frogs with gloves.

Poison Dart Frog. These venomous unique frogs live in the parts of Central and South America. They are brightly colored in red, yellow or orange and often have bold stripes, or crossbars. They seem harmless as they are very small in size reaching only 2-5 cm in length and weighting only a few grams. However, their skin glands produce one of the most powerful poisons in the animal world called batrachotoxin (from the ancient Greek word batrachos-frogs and toxin-poison).

Most Amphibian have the skin which contains complex nitrogenous compounds that affect the victim in different ways. Some compounds can cause local irritation only, others provoke hallucinations or act as vasoconstrictors, ones that contract blood vessels. There are also neurotoxins, which affect the nervous system. Batrachotoxin, in particular, is a nerve poison. Only a drop of this substance that has entered the victim's body can block the transmission of nerve impulses and the heart may stop functioning. Poison dart frogs keep their venom in their skin and sicken or kill anybody who touches, or eats it.

Toxicity and medicine

Chemicals extracted from the skin of Epipedobates tricolor may have medicinal value. This chemical is a painkiller and 200 times as potent as morphine, called epibatidine that has unfortunately demonstrated unacceptable gastrointestinal side effects in humans.

Secretions from dendrobatids can be used as muscle relaxants, heart stimulants and appetite suppressants.

Scorpions (fig. 42)

There exists about 2000 different species of scorpions. Only those of the Buthidea family are harmful to humans. Scorpions have bodies divided into two segments the cephalothorax (also called the prosoma) and the abdomen (opisthosoma). Scorpions prefer to live in areas where the temperatures range from 20°C to 37°C: Buthus – Mediterranean area, from Spain to the Middle East; Buthotus (ie,

Hottentotta) – Across southern Africa to Southeast Asia; Parabuthus – Western and southern Africa; Androctonus – Northern Africa to Southeast Asia; Leiurus – Northern Africa and the Middle East.

Fig. 42. – Scorpion

In terms of venom lethality, the venom of Androctonus australis (found in Australia) and Leiurus quinquestriatus (found in Africa) are the most toxic.

The estimated annual number of scorpion stings is 1.2 million leading to 3250 deaths.

All known scorpion species possess venom and use it primarily to kill or paralyze their prey so that it can be eaten; in general it is fast-acting, allowing for effective prey capture. It is also used as a defense against predators.

The venom is composed of varying concentrations of neurotoxin, cardiotoxin, nephrotoxin, hemolytic toxin, phosphodiesterases, phospholipases, hyaluronidases, glycosaminoglycans, histamine, serotonin, tryptophan, and cytokine releasers

The toxin elimination half-life iso f 4,2-13,4 hours, through the urine. Area of scorpion sting: hands – 70%; remaining on legs, and other regions.

Scorpions are predatory arthropod animals of the order Scorpiones within the class Arachnida. They have eight legs and are easily recognized by the pair of grasping claws and the narrow, segmented tail, often carried in a characteristic forward curve over the back, ending with a venomous stinger. Scorpions range in size from 9

mm (Typhlochactas mitchelli) to 21 cm (Hadogenes troglodytes).

Scorpions are found widely distributed over all continents, except Antarctica, in a variety of terrestrial habitats except the high latitude tundra. Scorpions number about 1,752 described species, with 13 extant families recognised to date.

The body of a scorpion is divided into three parts (tagmata): the head (cephalothorax), the abdomen (mesosoma) and the tail (metasoma).

All known scorpion species possess venom and use it primarily to kill or paralyze their prey so that it can be eaten; in general it is fast-acting, allowing for effective prey capture. It is also used as a defense against predators. The venom is a mixture of compounds (neurotoxins, enzyme inhibitors, etc.) each not only causing a different effect, but possibly also targeting a specific animal. Each compound is made and stored in a pair of glandular sacs and is released in a quantity regulated by the scorpion itself. Of the 1000+ known species of scorpion, only 25 have venom that is dangerous to humans; most of those belong to the family Buthidae.

Death stalker scorpion (fig. 43)

Area of distribution:

Latrodectus geometricus – Africa, USA; Latrodectus curacaviensis – Americas; Latrodectus hystrix – S. Europe, N. Africa, SW Asia; Latrodectus dahli – S. Europe, N. Africa, SW Asia; Latrodectus pallidus – S. Europe, N Africa, SW Asia; Latrodectus mactans U.S.A., warm regions worldwide.

Fig. 43. – Death Stalker Scorpion

Death Starker Scorpion is highly dangerous species because its venom is a powerful cocktail of neurotoxins which causes an intense and unbearable pain, then fever, followed by coma, convulsions, paralysis and death. Fortunately, while a sting from this scorpion is extremely painful, it would be unlikely to kill a healthy, adult human. Young children, the old are at the biggest risk.

Signs and symptoms of scorpion sting: Local symptoms, Early systemic symptoms, Advanced symptoms, Late symptoms, Local symptoms.

Possible local effects: Pain at the site of sting. Some species causes unspeakable pain I heard. (100% victims of Tityus spp experience pain); Itchiness (usually masked by pain); slight to medium swelling; slight bleeding (rare and most likely not related to toxin as only heterometrus scaber seems to have hemolytic components).

Early systemic symptoms. Sweating, Pallor (paleness of skin); Tachypnea (fast breathing); tachycardia (fast heart beat); hypertension (heightened blood pressure); salivation (uncontrolled saliva production) with frothy sputum; respiratory wheezing; stridor (high pitch respiration sound); blurred vision; roving eye movement; oculogyric crisis (cannot control eye movement); slurred speech; dysphagia (cannot swallow properly); pharyngeal spasm (cannot control much of the mouth); drowsiness.

Advanced symptoms. Local tissue effects vary among species. Significant local tissue reaction rules out C exilicauda envenomation. Tapping over the injury site (ie, tap test) may cause severe pain after a sting by C exilicauda. Tachycardia and other dysrhythmias are caused by autonomic effects primarily, although direct myocardial toxicity with arrhythmogenic effects has been described. Hypertension or hypotension may be present.The patient may have hyperthermia. Respiratory arrest and loss of protective airway reflexes are common causes of mortality. Pulmonary edema has been described and may be secondary to cardiogenic causes and to increased capillary permeability

Autonomic effects include the following: Sympathetic overdrive symptoms predominate, causing tachycardia, hypertension, hyperthermia, and pulmonary edema.

Parasympathetic symptoms include hypotension, bradycardia, salivation, lacrimation, urination, defecation, and gastric emptying.

Cranial nerve effects include the following:

Classic roving or rotary eye movements, blurred vision, tongue fasciculations, and loss of pharyngeal muscle control may be observed. Difficulty swallowing combined with excessive salivary secretions may lead to respiratory difficulty.

Somatic effects include the following:

Restlessness and involuntary muscle jerking that can be mistaken for seizures have been described. Presence of true seizures in Centruroides envenomation is controversial and has not been proven to occur. Seizures are described in association with other scorpion envenomations.

Late symptoms. Altered sensorium (changed sensory perception); cyanosis; hypotension; bradycardia; incontinence; seizure; respiratory and cardiac failure; paresis - slight to complete paralysis; altered electrocardiograph; coma.

Lab analysis: increased serum and urine catecholamines (eg. adrenaline) and metabolites; Leukocytosis; hyperkalemia; hyponatraemia; hyperglycaemia (high glucose; due to increased glucocorticoids?); high levels of IL-6, interferon-gamma; Interleukin (IL)–1 levels are elevated in all envenomations.

Treatment. Prehospital Care. Primary assessment of airway, breathing, and circulation takes precedence. Perform endotracheal intubation and vascular access as needed. Emergency Department Care.

Local treatment is discussed as follows: use ice bags to reduce pain and to slow the absorption of venom via vasoconstriction. This is most effective during the first 2 hours following the sting. Immobilize the affected part in a functional position below the level of the heart to delay venom absorption. Calm the patient to lower the heart rate and blood pressure, thus limiting the spread of the venom. Apply a topical or local anesthetic agent to the wound to decrease paresthesia; this tends to be more effective than opiates. Administer local wound care and topical antibiotic to the wound. Administer tetanus prophylaxis. Administer systemic antibiotics if signs of secondary infection occur. Administer muscle relaxants for severe muscle spasms (ie, benzodiazepines).

Systemic treatment is instituted by directing supportive care toward the organ specifically affected by the venom. Establish airway, breathing, and circulation (ie, ABCs) to provide adequate airway,

ventilation, and perfusion. Monitor vital signs (eg, pulse oximetry; heart rate, blood pressure, and respiratory rate monitor). Use invasive monitoring for patients who are unstable and hemodynamic. Administer oxygen. Administer intravenous fluids to help prevent hypovolemia from vomiting, diarrhea, sweating, hypersalivation, and insensible water loss from a tropical environment. Perform intubation and institute mechanical ventilation with end-tidal carbon dioxide monitoring for patients in respiratory distress. For hyperdynamic cardiovascular changes, administration of a combination of beta-blockers with sympathetic alpha-blockers is most effective in reversing this venom-induced effect. Administer atropine to counter venom-induced parasympathomimetic effects. Insulin administration in scorpion envenomation animal experiments has helped the vital organs to use metabolic substrates more efficiently, thus preventing venom-induced multiorgan failure, especially cardiopulmonary failure. Unfortunately, no human studies have been conducted. Administer barbiturates and/or a be nzodiazepine continuous infusion for severe excessive motor activity. The use of steroids to decrease shock and edema is of unproven benefit. Antivenom is the treatment of choice after stabilization and supportive care. There are about six species found around the world and all of them are venomous. Their bites, however, are rarely fatal to humans.

Spider

Most spiders bite humans only in self-defense.

But, recluse spiders and widow spiders, are shy and bite only when they feel threatened. Funnel web spiders' defensive tactics are aggressiveness and their venom. Brazilian wandering spider requires very little provocation (most dangerous spider on the planet).

Karakurts or steppe spiders

Female karakurts are the most dangerous for humans. Karakurts are predators who feed on different arthropodae and live in the semidesert steppe regions and in the footfills of the mountains.

The cases of poisoning is more often observed in the rural areas from May to September and have two waves connected with female migration.

The first wave of bites is explained by the first migration of the karakurts (before their copulation). The second wave of the bites is explained by the migration of spiders after copulation before laying the eggs. When the female lays the eggs, the cases of the human bites become relatively rare.

Clinics

Initially, the human feels stabbing pain which gradually spreads throughout the entire body. The bite is invisible, however, it can be observed under the examination of the bite area with quartz burner with wood's filter.

General poisoning presentation begins in 5-30 minutes after the bite. It causes the pain in the appendicular joints, spasms in the fingers. Sharp pain occurs in the abdomen, and it spreads to the lower back and chest. The stomach muscles are sharply tensed. Along with the pain among other symptoms are paresis and dysesthesia accompanied by hyperemia of the face and the sclerae, eyelid edema. The other symptoms include general muscular tremor, fever, perspiration, jugular venous distention. In view of muscle weakness the injured cannot stand on the feet, in some cases, in 10-15 minutes after the bite. The injured person feels uncertain anxiety, unaccountable fear; he is overwrought and cannot sleep, screams with pain. The stool and urination are detained. The tongue is furred and dry; excessive drooling is observed. There is stammer, difficulty in breathing, tachypnea. The pupillary response is disturbed, and hyperreflexia appears. The body temperature is 38°. Blood and venous pressure increase. There are sharp pains in the abdomen, tension of the tummy muscles.

Stool and urination difficulty lead to the “acute abdomen” presentation.

In case of severe poisoning, the disease lasts to 12 days. In extra severe cases the excitement changes into depression, loss of consciousness, delirium, meningeal symptoms, connected with the increasing of the intracranial and spinal pressure. The poisoning ends in death. In the fatal outcome the symptoms of pulmonary edema appear quite often. Mild cases and intoxication in the middle stages are observed.

Treatment

The most efficient therapeutic effect is reached by the subcutaneous administering of the specific karakurt antitoxin (30-50 ml), which ceases intoxication in the rapid terms at any stage of its development.

If there is no karakurt antitoxin, the patient takes hot baths, drinks lots of hot water, puts hot-water bottles on the lower back, abdomen and limbs. Warming up of the body releases muscle

convulsions and body tremor, assists to the sphincters relaxation, reduces muscle and joints pains. The intravenous infusion of a 25 percent of magnesium sulfate solution (10 ml 2-3 times a day) leads to the rapid removal of intoxication.

Other treatment for serious cases including magnesium sulfate consists of the intravenous infusion of glucose (300 ml of a 5 percent solution) and the subcutaneous administering of morphine (1 ml of a 1 percent solution), atropine (1 ml of a 0,1 percent solution) and caffeine (1 ml of a 10 percent solution). Atropine relieves sphincter's spasms of the urinary bladder and reduces perspiration. In case of urinary difficulty the catheterization is obligatory, and in bloating it is necessary to take valerian (to 50 drops).

Prevention

For the purpose of the karakurts destruction all the flora are burnt out; in autumn and in the early spring cocoons with spiderlings are gathered and burnt out. In the pastures where there is a great number of the karakurts, sheep trample and eat them.

The human must be attentive and follow necessary precautions to prevent the karakurts' bites. In the karakurts' habitats an overnight halt in the open air in the periods of their migration must be avoided. It is recommended to use the mosquito net (curtain) which is especially appropriate in case of the overnight halt in the steppe.

Habitats. Karakurts have a wide distribution all over the world. The karakurts' limit is not further than 50° of the northern latitude. Karakurts can be found in the southern Ukraine, in Moldavia, in the steppe areas of the Crimea and Caucasus, and in the southern Volga region. However, in all these regions the cases of their occurrence are quite rare. They prevail in the Central Asia, occur in Afghanistan, Iran and Turkey; also they are in Africa and Australia.

Black widow

The adult female Latrodectus mactans is 2-3 cm long and has a body length of 2-3 cm. It received this name (red-back spider) because of the distinctive red stripe on its abdomen. The male is seldom seen because the female eats him after mating. That is where the name "black widow" comes from. The male is about four times smaller than the female and is less dangerous. Besides the reddish hourglass-shaped design, it often has four pairs of reddish stripes on the sides of the abdomen.

The black widow is not an aggressive spider. However, bites are

not uncommon. The venom contains neurotoxins and soon after the bite an immediate strong pain is felt. The affected limb starts sweating. Systemic symptoms may develop if the bite is not treated immediately. These include nausea, vomiting, abdominal pain, pyrexia (fever) and in severe cases paralysis may occur.

There is a specific red-back antivenin which is used when signs of systemic envenomation are observed. The pressure-immobilization method is not recommended since it can cause extreme pain in the affected area. Instead, ice packs could be used for relief.

The total venom volume delivered by a single bite is nominal (4 mL), venom has many potent components, among them alkaline phosphatase, ribonucleotide phosphohydrolase, esterase, hyaluronidase, and sphingomyelinase D + accompanied by spider stomach enzymes including hydrolase, protease, and lipase

The brazilian wandering spider (phoneutria nigriventer, or phoneutria keyserling) – fig. 44.

Fig. 44. – The Brazilian Wandering Spider

It is the most venomous spider on earth which consists of 8 species. This spider is not afraid of humans and will aggressively attack any that it feels are a threat, making it very dangerous to approach. Two of the eight species of Brazilian wandering spider are responsible for most bites, and are found in highly populated areas of South-Eastern Brazil and the Amazon. Most bites occur because the spider wanders at night.

The Brazilian Wandering Spider (Phoneutria) or banana spider appears in the Guinness Book of World Records 2007 for the most venomous spider and is the spider responsible for most human deaths.This spider is believed to have the most potent neurotoxic venom of any living spider. Only 0,006 mg (0,00000021 oz) is sufficient to kill a mouse. They are also so dangerous because of their wandering nature. They often hide during daytime in highly populated areas inside houses, clothes, boots, and cars.

Its venomous bite causes not only intense pain, the venom of the spider can also cause priapism – uncomfortable erections lasting for many hours that lead to impotence.

Signs and symptoms. Mild symptoms include nausea, vomiting, fever, rashes, and muscle and joint pain. Anaphylactic shock. Hemolysis and thrombocytopenia. Weakness, necrotising ulcer, DIC, paralysis.

Lab analysis. Blood analysis: leukocytosis, heperkalemia, hyponatremia.

Treatment of spider bite.

Prehospital Care. Pressure immobilization of the bitten limb is not recommended due to the slow and non–life-threatening progression of symptoms. Pressure dressings may also exacerbate pain in the affected area. Ice packs to the bite site and simple oral analgesia may be helpful. Do not administer antivenom in the field due to the risk of a severe allergic reaction. Collection of the spider may aid its proper identification at the emergency department.

Emergency Department Care. In patients with severe symptoms and signs of envenomation, treatment with spider antivenom should be considered. The benefit of treatment with antivenom should be weighed against the risk of its possible complications, including but not limited to, anaphylaxis and serum sickness.

Prevention. Do not approach some species you do not know about.specially venomous ones. During picnic,look carefully around, and check carefully your shoes and towels ect... Clean home thoroughly. Use pesticide in residential areas or at home. Do not tease or try to grab arachnids.

Advantages of toxin. A component of the venom (Tx2-6) is being studied for use in erectile dysfunction treatments. Pesticidal effect. Antiviral effect.

DISTURBANCES IN ORGANS AND SYSTEM IN TROPICAL DISEASES

Fever. Fever is the common symptom in tropical parasitic diseases. It occurs due to disturbances in neurohumoral regulation of heat formation and heat transfer occurring due to microbes toxins and pyrogenic substances which form due to destruction of tissue and blood cells and other components. Phisition should put characteristic of fever when parasitic infection is diagnosed.

There are the following types of temperature curves:

• ***Continuous fever*** (febris contina). It is moderate or high temperature with daily changes of 1 degree Celsius.

• ***Remittent fever*** (febris remittens). It is daily changes of 1 degree Celsius and it can also reach till 2-2,5 degrees Celsius.

• ***Intermittent fever*** (febris intermittens). It is characterizes by big changes in temperature with proper alternation of fever and apyrexic period.

• ***Hectic fever*** (febris hectica). It is characterised by big changes in temperature with rapid decrease to normal or even less.

• ***Indulent fever (febris indulens).*** It is characterizes by increase in temperature from day to day until reaching high number and then decrease to normal and again start to

• ***Irregular fever increase gradually.*** (febris irregularis et atypica). it is characterizes by high moderate temperature with very different daily changes.

Pulmonary Disturbances. Most of the so called tropical eosinophilic pneumonia which are associated with lymphatic filiariasis are the following: Wuchereriosis and Brugiosis where adult helminthes are located in lymphatic systems and as a result of destruction and death of microfilaria in blood vessels cause pathological changes in pulmonary tissue. More eosinophils are present in pulmonary infiltrate.

Clinics are: nocturnal cough, dyspnea, bronchospasm, weakness, sputum is scarce and there is presence of blood.

Serological reaction with antigen of microfilaria is always positive. On x-ray there is increase of vascular pattern, basal pneumonia, miliary focus often taken for tuberculosis.

Generally a course of diethylcarbamazin gives very good results,

that justifies trial of the treatment. In the start of the treatment clinical manifestations of the diseases may sometimes intensify.

Prognosis is favourable but in a number of patients with the current disease there is development of pulmonary hypertension.

In Ancylostomiasis and Strongyloidiasis may arise multifocal helminthic pneumonia which is connected with migration of larvae to lungs. Clinical manifestations consist of: cough, chest pain, dyspnea, wheezing, release of mucous-blood sputum. Increase in temperature develops scattered dry and moist crackles. These changes occur up to 2 weeks and resolve spontaneously but there may be strongyloidiasis relapse connected with auto invasion.

Cardiac Disturbances. American and African trypanosomiasis can cause diffuse myocarditis which appears as tachycardia arrhythmia in ECG. For some patients especially in Chaga's disease myocarditis is the main cause of death. In these cases, in the acute period chemotherapy has good effect and in chronic period the effects are not always positive.

In chronic period there is hypotrophy of myocardium and apex, enlarged width of myocardial wall is decreased and as a result there is formation of aneurysm. Often in the enlarged heart there is formation of thrombi which lead to thromboembolism. In some cases like Japanese Schistosomiasis pulmonary hypertension is caused by presence of eggs in pulmonary artery thus causing blockage. Later in arteries there is formation of aneurysm, atherosclerotic changes and hypertrophy of ventricle.

Clinics: dyspnea, difficulty in expiration, general weakness, symptoms of right heart insufficiency.

On X-ray there is increase of vascular pattern and lymphatic filariasis which can cause pulmonary hypertension associated with pulmonary vasculitis.

Ancylostomiasis occurs with severe anemia which can cause heart problem like cardiac insuffienciency. The more severe the anemia the more severe are the changes. Due to decrease of renal blood supply there is secondary aldosteronemia, sodium retention and appearance of edema.

Clinics: Tachycardia, dyspnea, chest pain, dizziness, edema of limbs and face, cold skin which can be a symptom of cerebral hypoxia.

Treatment is: erythrocyte mass IV, Iron supplement, bed rest.

However antiparasitic drugs should not be given if there is no

improvement in hemodynamic.

Spleen. Splenomegaly is one of the main clinical features of malaria, schistosomiasis and visceral leishmaniasis. Erythrocytes are affected, covered in antibodies immunological complex or complements. These erythrocytes are engulfed by macrophages in spleen thus causing proliferation of macrophages and thickening of pulp of spleen which result in retention of normal erythrocyte in spleen causing an increase in its size.

At the same time changes in spleen cause portal hypertension which cause enlargement of venous sinuses and slowing down of erythrocytes flow in spleen pulp. Sometimes there are severe destruction of spleen tissue, abscesses and hematoma.

Splenectomy decreases chance of patients living in tropical places.

GIT. Changes in GIT in tropical parasitic diseases can be of different symptoms. For some diseases there are specific clinical representations and for other there is only abdominal pain or diarrheal syndrome. In most cases helminthosis occurs without symptoms. Colitic syndrome is the main symptom of acute stage of intestinal amebiasis. Changes occur in proximal colon but rarely in distal. Rectomanoscopy helps in diagnosis of amebic ulcers in sigmoid and rectum. Chemotherapy in these cases is very effective. Perforation of amebic ulcers can cause peritonitis especially in proliferative granulomatous reaction of the caecum. Acute abdomen may be a result of amebic appendicitis. In intestinal schistosomiasis passage of eggs from mesenteric veins to intestinal wall causes formation of micro abscesses and eosinophilic granuloma. Granulomatous processes cause rigidity of intestine and stenosis. There can be formation of anorectal, ischiactic rectal abscesses, fistula and polyps in anal region.

In Japanese schistosomiasis these processes are more severe and most often changes occur in the ileum. Main symptoms: pain and bloody stool which can occur in period of remission and relapse. Rectomanoscopy shows hyperemia of mucosa and granuloma, sometimes ulceration and polyps. Chemotherapy is very effective.

In Chaga's disease 2 main changes occur in GIT: megaesopahgus, megacolon. Changes in the intestine are associated with damage of parasympathetic nerve ganglion and nerve fibers. As a result of degeneration, enlargement and disturbance of peristalsis of esophagus and large intestine occurs, rarely stomach and small

intestine. Positive serological reaction is observed.

Symptoms. Dysphagia starts with difficulty in swallowing of solid food. Pain on swallowing can be present. Enlargement of carotid gland occurs. Salivation in mega colon increases, retention of gas and hardening of stool in the intestine is observed, later there is intestinal blockage. In early stages enema can help but in later stages surgical treatment is required. In severe cases of tropical malaria acute dehydration due to profuse diarrhea occurs. Strongyloidiasis can cause severe diarrhea with dehydration and hypoproteinemia

Liver. In clonorchiasis, orpistorchiasis, fascioliasis, ascariasis changes occur in the bile duct, voluminous changes occur in amebiasis and echinococcosis. Formation of amebic abscess is caused by trophoizoites moving in portal vein to the liver from ulcer in large intestine. Abscesses are mainly found in right liver lobe. Without treatment abscesses can open in diaphragm and lungs. Rarely it can open into abdominal cavity and pericardium. Symptoms: pain and fever. In blood: Leukocytosis with left shift, increased ESR. It is indication for X-ray and echography of the liver.

Complications of echinococcosis. Opening of cyst in the bile duct with liver colic and jaundice, pus formation, acute abdomen, opening of cyst in thoracic cavity, rarely in intestine or blood vessels.

In intestinal and japanese schistosomiasis clinical symptoms occur due to migration of eggs to liver cells, formation of infiltrate of lymphocytes and eosinophils around the eggs, formation of perifocal hepatocellular necrosis. Clinics: painful hepatomegaly, fever, allergic reaction with eosinophilia, diarrhea, splenomegaly.

Chronic stage: fibrotic changes with disturbance of blood circulation, portal hypertension, liver function not affected. In severe cases of malaria: hepatocellular in sufficiency, periportal infiltration, degeneration and necrosis of hepatocytes. Therapy with chloroquine gives positive effect.

Disturbance of lymphatic system. Disturbances in lymphatic system including lymphangitis and lymphadenitis occur with wuchereria and brugia species. The adult filaria is localizd in the lymphatic vessels and nodes. Inflammatory processes in lymphatic system are connected with destruction/death of the helminthes and develop the phenomenon of artoucha. Periodic penetration of microfiliarae in blood happens by recidive inflammatory reaction, after several years chronic disease develops. Disturbances of

lymphatic system manifest in formation of varicose of lymph nodes and cause lymphadenemia. Microscopy shows negative result in this period and diagnosis can be made by skin allergy test and serological reaction. Usually if there is absence of microfilaria in blood, treatment is not given but specific treatment is advised in development of lymphadenemia.

In American Trypanosomiasis there is generalized lymphadenopathy in early stage of the disease.

In African Trypanosomiasis lymphadenopathy happens due to the gambiense variant of the disease. At the beginning lymph nodes are elastic but later they become hard and dense. Diagnosis: puncture of elastic lymph nodes can show presence of trypanosomes.

In early stage of visceral leishmaniasis there is enlargement of lymph nodes of cervical sub muscular and inguinal region.

When puncture of lymph nodes is performed, macrophages may consist of amastigote of leishmania.

Skin. Changes in skin develop in different forms of cutaneous leishmaniasis. In anthroponosis type of leishmaniasis skin changes are: – primary leishmaniasis: ulcer; advance leishmaniasis: diffuse infiltrative skin and tubercular skin. Pathologic process on the skin develops slowly approximately within a year. Skin ulcers develop in approx. 1-3 years, rarely 8-10 years and they are mostly localized on the face and upper limbs. In zoonotic type of skin leishmanisis the pathologic processes develope more rapidly on the skin (3-6 months). Ulcers appear after 10 months and can be localized at any part of the body.

American mucocutaneous leishmaniasis is characterized by disturbance of skin and mucous membrane which develops in pathological processes occuring after 1-2 years (usually after development of skin ulcers).

Ulceronecrotic changes of mucous membrane develop in oral-nasal parts, ears, larynx, respiratory tract and genital organs.

One of the main tropical helminthic disease causing skin changes in many countries is onchocerciasis. Adult onchocerca may go in lymph node and in subcutaneous tissue. These nodes should be resected to decrease the intensity of the disease invasion.

Onchodermatitis develops due to death of microfilariae in skin causing hypersensivity. Skin changes are: papulo-erythrematous rash with intensive itching (most often on thighs and knees);

hyperkeratosis (crocodile skin); atrophic epidermis with depigmentation (leopard skin); secondary changes of skin with trophic disturbances.

In loaosis adult helimnths live and migrate subcutaneously. They have antigen which cause allergic reaction (kalabar edema) on the elbow and forearm.

Ulcerating changes of skin may develop in amebiasis most often in perineal and perianal region thus affecting genital organ or skin of abdomen.

In dracunculiasis when probing of the blister is done, there is development of ulcer in which the end of the helminth can be seen and there can be allergic reaction due to its ineffective removal.

Leprosy symptoms.

Painless skin patch is accompanied by loss of sensation but not itchiness (Loss of sensation is a feature of tuberculoid leprosy, unlike lepromatous leprosy, in which sensation is preserved.)

Loss of sensation or paresthesias where the affected peripheral nerves are distributed. Wasting and muscle weakness is observed. Foot drop or clawed hands may result from neuritic pain and rapid peripheral nerve damage. Ulcerations on hands or feet. Lagophthalmos, iridocyclitis, corneal ulceration, and/or secondary cataract due to nerve damage and direct bacillary skin or eye invasion.

Ocular and CNS disturbances. The eye is more affected in onchocercosis and pathological changes are caused by acute inflammation around microfiliarae which attack the eyeball from the surrounding tissue. The worm enters the conjunctiva and then the sclera followed by the anterior chamber and iris.

Symptoms of keratitis: eye sight does not decrease but patient complains of itching. On investigation with lamp, microfiliarae may be found in aqueous liquor of anterior chamber. After the death of the microfiliarae inflammatory changes in anterior chamber of the eye occur. These changes can affect the surrounding tissues and cause deformation of iris. There may be formation of iritis, glaucoma and cataract and sometimes this can lead to sclerotic keratitis. The optical nerve can be affected: due to microfiliarae in the nerve due to atrophy after corioretinitis.

In laosis migrating helminths enter the eyeball and are found in connective tissue or under the conjunctiva. Migration of helminths causes severe itching, pain and inflammation of the eye. DEK gives

positive result.

In Chaga's disease there is inflammation of the eye and cellulites. In Chaga's disease there is formation of acute meningoencephalitis especially in children.

In tropical malaria there is thrombosis of vessels of retina with decrease of the eye sight. Common cause of death is acute encephalopathy. On autopsy of a patient who died from malaria, there is bleeding in the white matter of the brain, presence of brain edema, obliteration of vessel with parasites and their metabolites and DIC syndrome. Clinics are: Headache of different intensity; Irritation, Disturbance of consciousness which can lead to the loss of consciousness and areflexia. There can be meningeal syndrome in liquor and presence of plasmodium. Effect of chemotherapy is very fast.

In gambiense trypanosomiasis there is chronic meningoencephalitis which without treatment can lead to death. Clinics: headache, irritation, psychosis, hallucination, depression. When the frontal lobe is affected there can be progressive dementia.

Musculo-skeletal system. In dracunculosis there may be arthritis when helminth penetrates inside the joint. There may be immobilization of joint, most often knee joint and ankle. Penetration of dracunculose in tissue causes development of muscular abscesses. In wucherechiosis and brugiosis acute arthritis can occur. These disturbances of the joint are connected with circulating immunological complex.

Urogenital system. In schistosomiasis, eggs of helminths penetrate the bladder through mucosa thus causing damage. The eggs calcify causing development of hyperplasia and papilloma. It can lead to cancer, stone of urinary bladder, disturbance of lymph causing elephantiasis of genital organs. In the end there is development of fibrotic structures, hydronephrosis and pyonephrosis. In early stages chemotherapy is effective.

In lymphatic filiaridosis there can be the following symptoms in male: funiculitis and epidydimitis which should be differentiated from gonorrheal infection but in filiaridosis there is urethritis. Often orchitis is caused by eggs consisting of microfiliarae. In late stages there is development of lymphadenemia and lymphoscrotum. Sometimes there can be chyluria. Symptoms develop due to increased blockage of lymphatic vessels, insufficiency of lymphatic system after site of

blockage cause retrograde flow of lymph, presence of channel between enlarged lymphatic vessels and urinary pathways. In urine there is presence of protein, fat and blood. In this situation surgical treatment should be performed. In female with filiaridosis the appendages and fallopian tube may be affected and thus cause lymphadenemia of vulva. Chemotherapy may stop progression of process and cause regression of several symptoms.

In tropical malaria, acute renal failure may develop which is connected with hypotension, decreased renal perfusion and necrosis of renal tubules. Some patients may develop proliferative glomerulonephritis which do not respond to specific treatment.

Acute hemoglobinuria (hemorrhagic fever) often occurs in patients with deficit of glucose-6-phosphate dehydrogenase, occurring in tropical malaria. This occurs as massive hemolysis due to several preparates (quinine, primaquine, sulfonamides). Treatment with these preparates may cause brain edema and lung edema. On 4^{th} day of malaria nephrozonephritis may occur which is connected with disturbance of kidney tubules.

Disturbances of sexual organs in amebiasis in male occur by sexual transmission and appear as ulcers. In female ulcers appear on genitals and cervix.

Anemia.

In malaria, visceral leishmaniasis, ancylostomiasis, trypanosomiasis, schistosomiasis and amebiasis there may be anemia.

Malaria, visceral leishmaniasis and hepatolienal form of schistosomiasis are connected with the disturbance of spleen, increase destruction of erythrocytes and as well as leukocytes and thrombocytes thus causing pancytopenia.

Direct lysis of erythrocytes occurs in red blood cell by plasmodium parasite. Incorrect lysis of erythrocytes may be due to immunological mechanism.

In ancylostomiasis, urogenital and intestinal schistosomiasis and amebiasis there is hemostasis (bruise) from varicose due to enlargement of vessels and from mucous membrane of urinary bladder and intestine.

Anemia in visceral leishmaniasis causes damage of the skull.

In ancylostoma and necator there can be intensive invasion leading to anemia mostly in patient having large amount of iron in their body. Treatment should be antihelminthic along with diet and iron (ferrum) therapy.

Immunodepression.

Depression of immunological reaction occurs in malaria, african trypanosomiasis, visceral leishmaniasis, schistosomiasis, severe form of onchocerchosis and lymphatic filiariasis.

Immunological disturbance may be connected with B and T lymphocytes, that is why infringement of immunity can be humoral as well as cellular.

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