



MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE

**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE**

Lecture № 7

LEPTOSPIROSIS
CONGO-CRIMEAN HAEMORRHAGIC FEVER
HAEMORRHAGIC FEVER WITH RENAL SYNDROME
YELLOW FEVER

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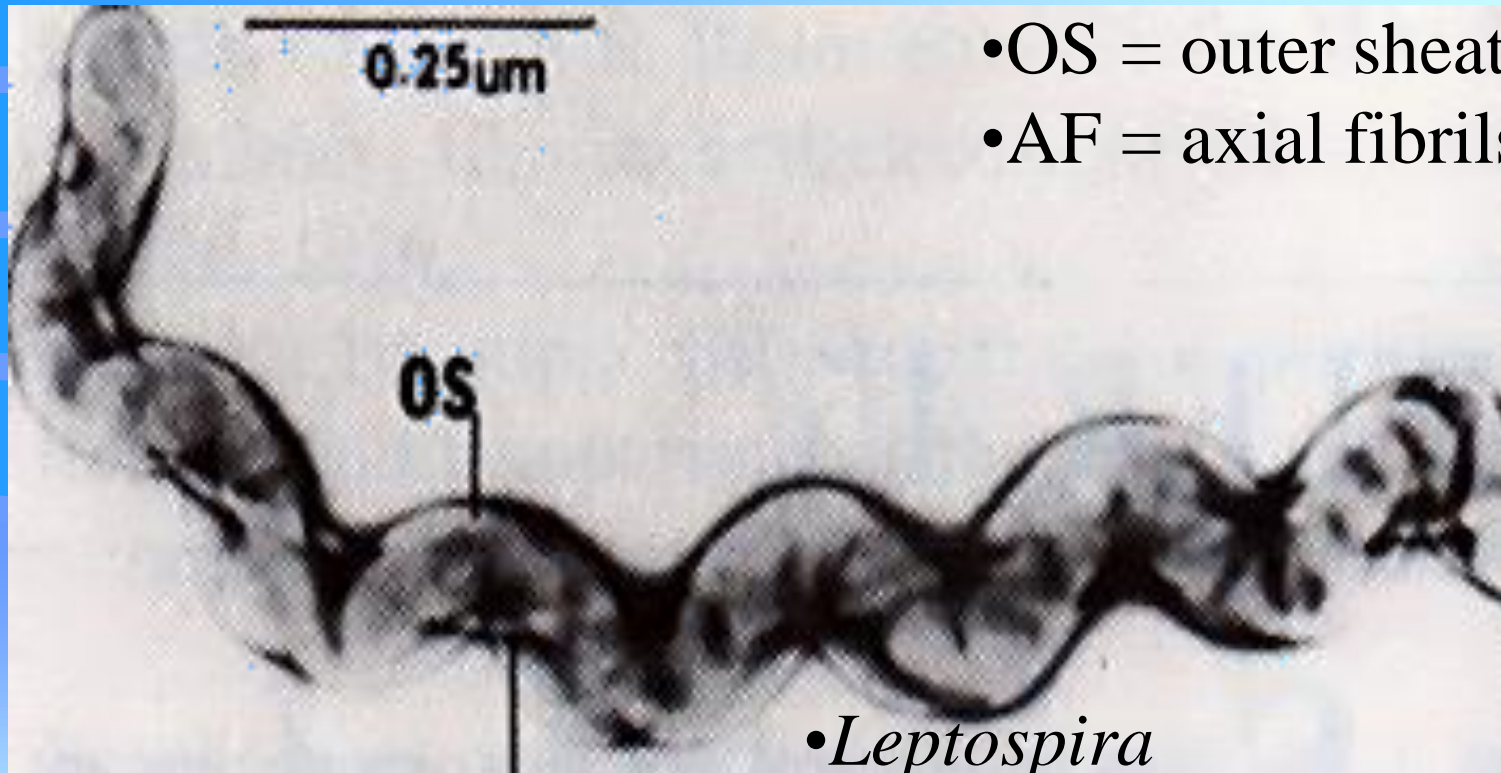
Leptospirosis – definition

- **Zoonosis** of global distribution,
- caused by infection with **pathogenic spirochetes of the genus *Leptospira*.**
- Most human infections are probably asymptomatic.
- The spectrum of illness is extremely wide, ranging **from undifferentiated febrile illness to severe multisystem disease** with high mortality rates.
- The extreme variation in clinical presentation is partly responsible for the **significant degree of under-diagnosis.**

Leptospirosis – etiology

- Leptospire are Gram (-), thin, tightly coiled spirochetes. The cells have pointed ends, one or both of which is usually bent into a characteristic hook. Motility is conferred by the rotation of two axial flagella underlying the membrane sheath, which are inserted at opposite ends of the cell and overlap in the central region. Because of their small diameter, leptospire are visualized by dark-field microscopy.
- Historically, the genus *Leptospira* was classified into two species, *L. interrogans* and *L. biflexa*, comprised of pathogenic and nonpathogenic strains, respectively. Within each species, large numbers of serovars were differentiated using polyclonal agglutinating antibodies. Serovar specificity is conferred by lipopolysaccharide (LPS) O-antigens. More than 250 serovars of pathogenic leptospire have been described; because of the large number of serovars, antigenically related serovars were grouped into serogroups, for convenience in serologic testing.

Leptospira interrogans



- OS = outer sheath
- AF = axial fibrils

• AF

• *Leptospira
interrogans*

Leptospirosis – etiology

- Leptospire are now classified into a number of species defined by their degree of genetic relatedness, determined by DNA reassociation.
- There are currently 20 named species genomospecies. These include both pathogenic and nonpathogenic strains, and some species contain both pathogens and nonpathogens. This classification is supported by 16S RNA gene sequencing, but is quite distinct from the former serologic classification.

Species of *Leptospira* and Some Pathogenic Serovars

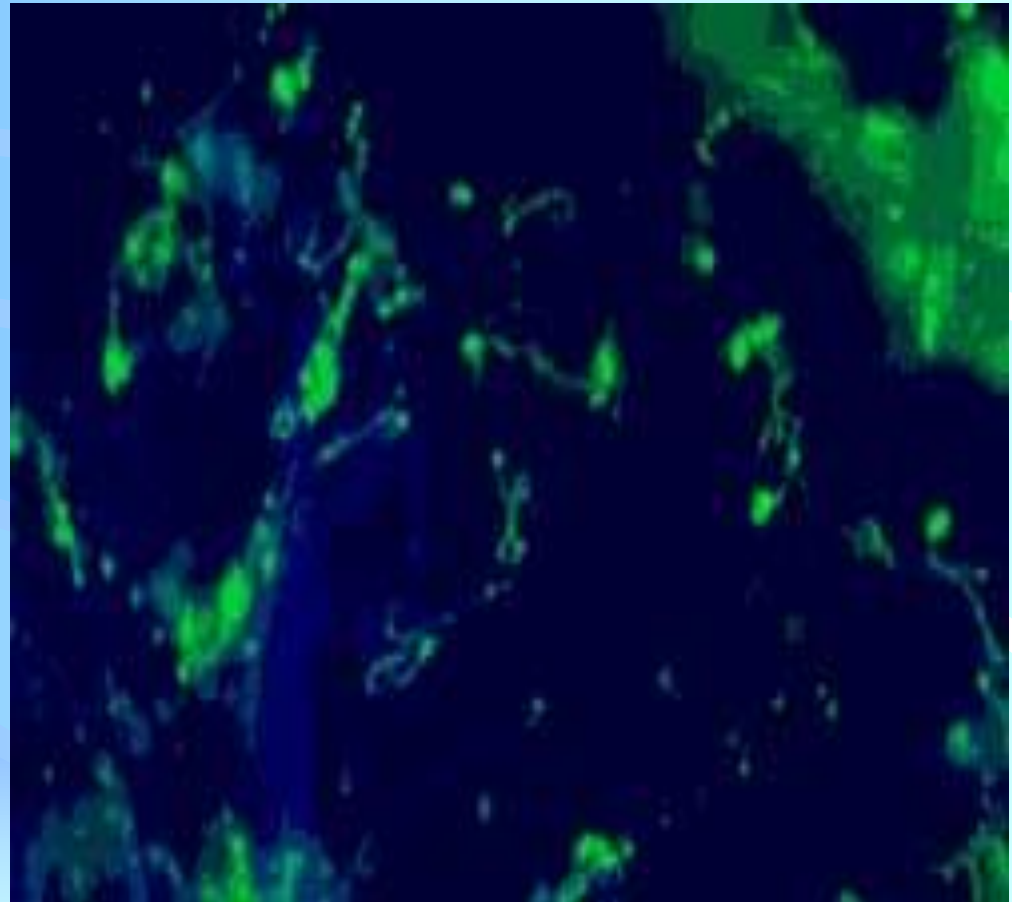
- **Species and Selected Pathogenic Serovars**

- ❖ *L. interrogans* Icterohaemorrhagiae, Copenhageni, Canicola, Pomona, Australis, Autumnalis, Pyrogenes, Bratislava, Lai
- ❖ *L. noguchii* Panama, Pomona
- ❖ *L. borgpetersenii* Ballum, Hardjo, Javanica
- ❖ *L. santarosai* Bataviae
- ❖ *L. kirschneri* Bim, Bulgarica, Grippotyphosa, Cynopteri
- ❖ *L. weilii* Celledoni, Sarmin
- ❖ *L. alexanderi* Manhao 3
- ❖ *Leptospira* genomospecies 1 Sichuan
- ❖ *L. fainei* Hurtsbridge
- ❖ *L. meyeri* Sofia
- ❖ *L. inadai* indeterminate

- **Selected Non-Pathogenic Serovars**

- ❖ *L. wolbachii* non-pathogens
- ❖ *L. biflexa* non-pathogens
- ❖ *L. parva* non-pathogens
- ❖ *Leptospira* genomospecies 3 non-pathogens
- ❖ *Leptospira* genomospecies 4 non-pathogens
- ❖ *Leptospira* genomospecies 5 non-pathogens

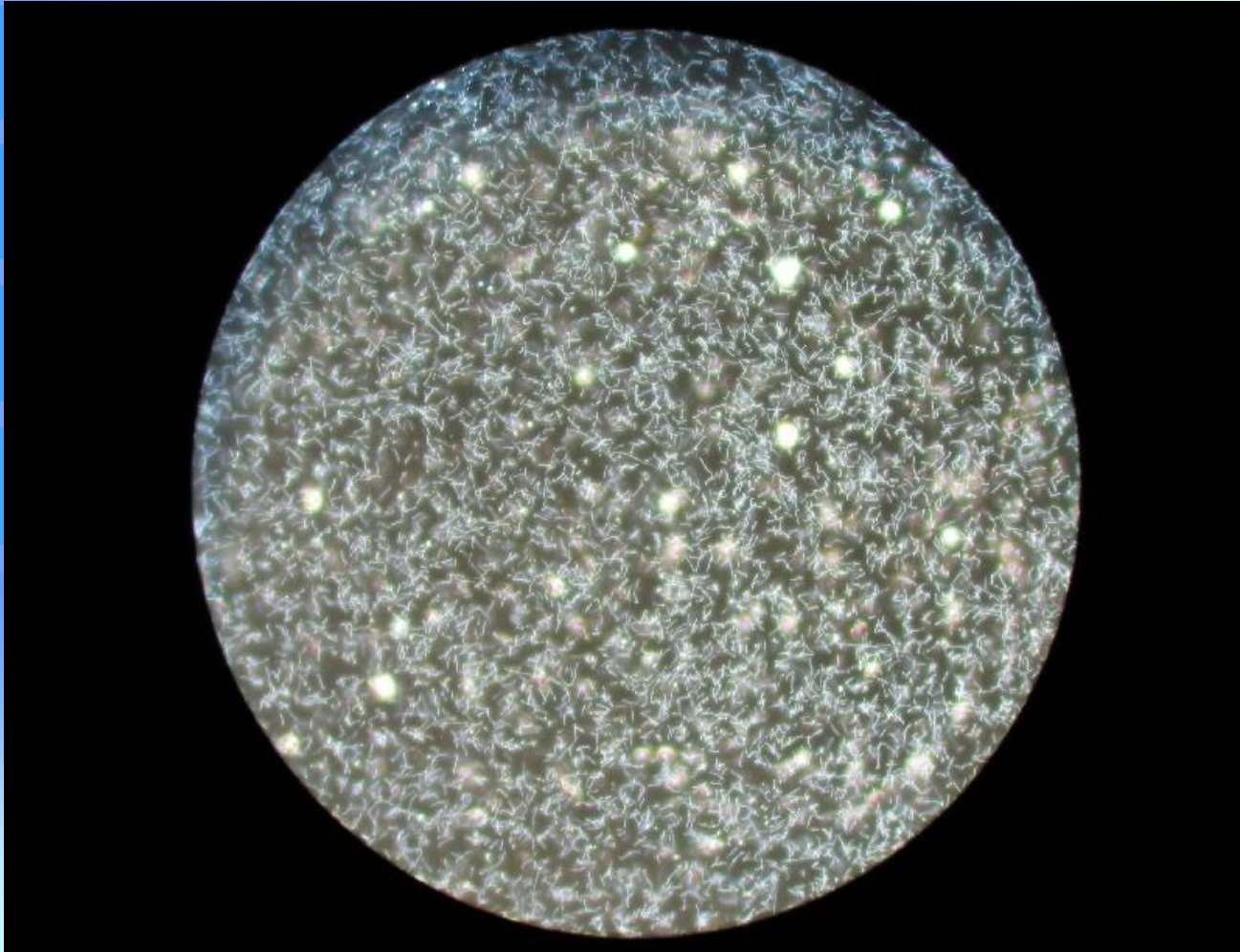
Leptospira



Leptospira –
dark-field microscopy



Leptospira –
dark-field microscopy



Leptospirosis – epidemiology

- Leptospirosis is endemic throughout the world. Human infections are endemic in most regions and the peak incidence occurs in the rainy season in tropical regions and the late summer to early fall in temperate regions. Outbreaks may follow periods of excess rainfall. The incidence of leptospirosis is probably grossly underestimated, because of limited diagnostic capacity in the regions where the burden of disease is greatest.
- Leptospirosis is maintained in nature by chronic renal infection of carrier animals. The most important reservoirs are rodents and other small mammals, but livestock and companion animals are also significant sources of human infection. Infection of carrier animals usually occurs during infancy, and **once infected, animals may excrete leptospires in their urine intermittently or continuously throughout life.**
- **Infection occurs through direct or indirect contact with urine or tissues of infected animals.** **Direct contact** is important in transmission to veterinarians, workers in milking sheds on dairy farms, abattoir workers, butchers, hunters, and animal handlers (transmission has been reported to children handling puppies and to dog handlers). **Indirect contact is more common,** and is responsible for disease following exposure to wet soil or water. The great majority of cases are acquired by this route in the tropics, either through occupational exposure to water as in rice or taro farming, or through exposure to damp soil and water during a **professional activities.**
- **Recreational exposures** have become relatively more important, often in association with adventure tourism to tropical endemic areas.

Leptospirosis – pathogenesis

- Leptospires enter the body through cuts and abrasions; mucous membranes or conjunctivae; and aerosol inhalation of microscopic droplets; ingestion is probably not an important route of entry, but provides access to oral mucosae. **Leptospires are carried in the blood throughout the body.** A **systemic vasculitis** occurs, facilitating migration of spirochetes into organs and tissues and accounting for a broad spectrum of clinical illness. Severe vascular injury can ensue, leading to pulmonary hemorrhage, ischemia of the renal cortex and tubular epithelial cell necrosis, and destruction of the hepatic architecture resulting in jaundice and liver cell injury with or without necrosis.
- The mechanisms by which leptospire
- s cause disease are not clearly understood. Potential virulence factors include attachment, toxin production, immune mechanisms, and surface proteins. **Leptospiral lipopolysaccharide exhibits weak endotoxic activity but a number of serovars produce hemolysins, which may act as sphingomyelinases, phospholipases or pore-forming proteins.**
- **Immune-mediated mechanisms** have been postulated as one factor influencing the severity of symptoms. In humans, the significance of circulating immune complexes, anticardiolipin antibodies, and antiplatelet antibodies is unproven.
- Much recent work has focused on the **role of surface lipoproteins**, many of which are thermoregulated, with expression occurring in vivo at mammalian body temperatures. The major surface lipoprotein, LipL32, is highly conserved among pathogenic serovars. **LipL32 is a major target of the human immune response and appears to be involved in pathogenesis of tubulointerstitial nephritis.**

Leptospirosis – clinical manifestations

- Leptospiral infection is associated with a very broad spectrum of severity, ranging from subclinical illness followed by seroconversion to **two clinically recognizable syndromes: a self-limited, systemic illness seen in roughly 90% of infections, and a severe, potentially fatal illness (so called Weil's disease) accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis.**
- The disease may have **two distinct phases**, an **initial septicemic stage** that is followed by a temporary decline in fever that is followed by an **immune phase** in which the severe symptoms occur.

Leptospirosis – clinical manifestations

- The mean incubation period is 10 days, ranging from 5 to 14 days.
- The acute, septicemic phase of illness begins abruptly with high, remittent fever (38° to 40° C) and headache, chills, and myalgias; conjunctival suffusion; abdominal pain; anorexia, nausea, and vomiting; diarrhea; cough and pharyngitis; a pretibial maculopapular cutaneous eruption occurs rarely. Conjunctival suffusion and muscle tenderness, most notable in the calf and lumbar areas, are the most characteristic physical findings. Other less common signs include lymphadenopathy, splenomegaly, and hepatomegaly. The acute phase lasts from 5 to 7 days. Routine laboratory tests are nonspecific but indicative of a bacterial infection. Leptospire can be recovered from blood and CSF during the acute phase of illness, but meningeal signs are not prominent in this phase. Leptospire may also be recovered from urine, beginning about 5 to 7 days after the onset of symptoms. Urinalysis reveals mild proteinuria and pyuria, with or without hematuria and hyaline or granular casts. Death is exceedingly rare in the acute phase of illness.

Leptospirosis – clinical manifestations

- Defervescence is followed by the **immune phase** of illness, which generally lasts from 4 to 30 days. The disappearance of leptospire from the blood and cerebrospinal fluid (CSF) coincides with the appearance of IgM antibodies. The organisms can be detected in almost all tissues and organs, and in urine for several weeks, depending on the severity of the disease. In addition to the acute phase symptoms described in the preceding paragraph, the immune phase may be characterized by any or all of the following signs and symptoms: jaundice, renal failure, cardiac arrhythmias, pulmonary symptoms, aseptic meningitis, conjunctival suffusion with or without hemorrhage; photophobia; eye pain; muscle tenderness; adenopathy; and hepatosplenomegaly .

Leptospirosis – clinical manifestations

- **Aseptic meningitis**, with or without symptoms, is characteristic of the immune phase of illness, occurring in up to 80% of cases. In endemic populations a significant proportion of all aseptic meningitis cases may be caused by leptospiral infection. Symptomatic patients present with an intense, bitemporal and frontal throbbing headache with or without delirium. A lymphocytic pleocytosis occurs, with total cell counts generally below 500/mm³ . CSF protein levels are modestly elevated between 50 and 100 mg/mL; the CSF glucose concentration is normal. Severe neurologic complications such as coma, meningoencephalitis, hemiplegia, transverse myelitis, or Guillain-Barré syndrome occur only rarely.

Leptospirosis – clinical manifestations

- The most distinctive form of severe illness that may develop after the acute phase of illness is Weil's disease, characterized by impaired hepatic and renal function. More severe cases may progress directly from the acute phase without the characteristic brief improvement in symptoms to a fulminant illness, with fever greater than 40° C and the rapid onset of liver failure, acute renal failure, hemorrhagic pneumonitis, cardiac arrhythmia, or circulatory collapse. Mortality rates in patients developing severe disease have range from 5% to 40%!!!
- In jaundiced patients, disturbance of liver function is disproportional to the rather mild and nonspecific pathological findings. Conjugated serum bilirubin levels may rise to 80 mg/dL, accompanied by more modest elevations of serum transaminases, alanine aminotransferase, and aspartate aminotransferase, which rarely exceed 200 U/L. This is in marked contrast to viral hepatitis. Jaundice is slow to resolve, but death due to liver failure almost never occurs in the absence of renal failure.

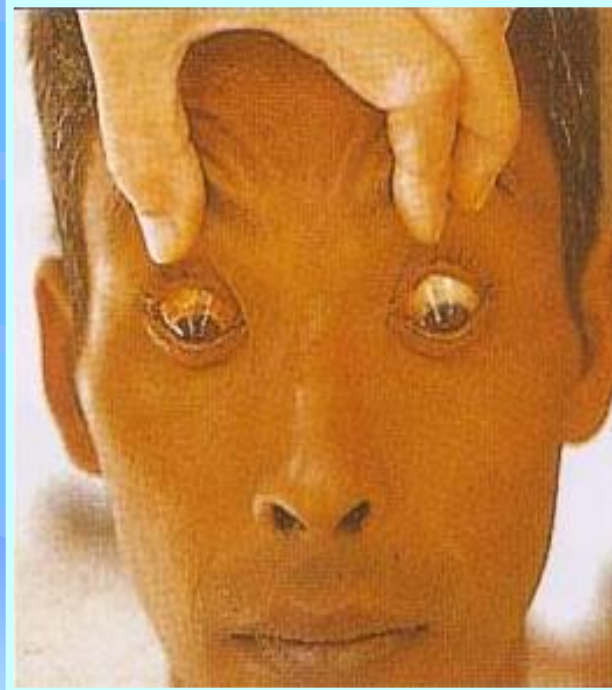
Leptospirosis – clinical manifestations

- **Acute renal failure** is characterized by a rapid onset of uremia and oliguria during the second week of illness, frequently accompanied by jaundice. The blood urea nitrogen level is usually below 100 mg/dL, and the serum creatinine level is usually below 2 to 8 mg/dL during the acute phase of illness. Thrombocytopenia occurs in the absence of disseminated intravascular coagulation and may accompany progressive renal dysfunction. Renal biopsy reveals acute interstitial nephritis; immune-complex glomerulonephritis may also be present. Renal injury is compounded by concomitant dehydration, causing hypovolemia and hypotension; the development of anuria is a poor prognostic sign.

Leptospirosis – clinical manifestations

- **Severe hemorrhagic pneumonitis and acute pulmonary distress syndrome** can be prominent manifestations of infection and may occur in the absence of hepatic and renal failure. Frank hemoptysis can arise simultaneously with the onset of cough during the acute phase of illness; auscultatory examination may be normal. With progressive pulmonary involvement, radiographic abnormalities seen most frequently in the lower lobes evolve from small nodular densities (“snowflake-like”) to patchy alveolar infiltrates; confluent consolidation is uncommon. Bibasilar rales may be present when radiographic involvement is extensive.
- **Congestive heart failure** occurs rarely. However, nonspecific electrocardiographic changes are common. In more than half of patients receiving continuous cardiac monitoring, cardiac arrhythmias may occur, including atrial fibrillation; flutter and tachycardia; and cardiac irritability, including premature ventricular contractions and ventricular tachycardia. Atrial fibrillation is associated with more severe disease. Cardiovascular collapse with shock can develop abruptly and in the absence of aggressive supportive care can be fatal. At autopsy, **interstitial myocarditis** with inflammatory involvement of the conduction system is seen.

*Leptospirosis –
jaundice and conjunctival haemorrhages*



Leptospirosis – skin haemorrhages



Leptospirosis – clinical forms

- According to presence or not of jaundice:
 - ❖ Anicteric
 - ❖ Icteric
- According to severity:
 - ❖ Mild
 - ❖ Moderate
 - ❖ Severe(Weil's disease)

Leptospirosis – complications

- Ocular – iridocyclitis → risk of blindness
- Profuse bleeding
- Hypochloraemic uremia
- Cholestasis
- Secondary pneumonia
- Otitis
- Pyelonephritis
- Arthritis

Leptospirosis – laboratory findings

- Depending o f severity – mild to marked leucocytosis, neutrophilia and left shift, lymphopenia; extremely increased erythrocytes' sedimentation rate; thrombocytopenia, increased blood urea nitrogen (BUN) and serum creatinine levels (depending of severity and phase of renal involvement), increased serum bilirubin with prevalence of conjugated fraction), slightly elevated transaminases (more often ASAT > ALAT), increased creatin kinase, increased fibrinogen and c-reactive protein, metabolic acidosis.

Leptospirosis – diagnosis

- By clinical and epidemiological data.
- Microbiological – direct darkfield microscopy, immunofluorescent microscopy (IFA).
- Serological – microagglutination test (MAT) –
after 7th day of the clinical onset.

Leptospirosis – management and treatment

- **Admission at Infectious Ward immediately!!!**
- **Etiological** – penicillin 10-16 g/day intravenously; allergy or severe forms – ceftriaxon 2-4 g/day.
- **Supportive** – adequate fluid-saline infusions, corticoids (methylprednizolon, dexamethasone – in brain edema), diuretics (furosemide), hepatoprotective (L-ornitine, ademethionine), gastroprotective (famotidine), hemostatic, substitution of blood-cells-losses with blood products. **ARF requires immediately assessment with nephrologist and decision of dialysis no later then 48th hour (aim – prevention of brain and lung edema – leading factors to death)!!!**

Leptospirosis – prophylaxis

- Observation of the contacts within 14 days.
- Killing of the rodents.
- Sanitary measures and control of cooking, storage and consumption of the foods.
- Vaccine – limited administration.

Bunyavirid Hemorrhagic Fevers

- The family Bunyaviridae comprises more than 200 animal viruses classified into four major genera (*Bunyavirus*, *Phlebovirus*, *Nairovirus*, and *Hantavirus*) readily distinguished by genetic, morphologic, biochemical, and immunologic characteristics. The circulation of the viruses in nature via arthropod-vertebrate cycles or chronic infection of vertebrates leads to disease distributions that are determined by ecologic circumstances, can be highly focal, and depend on weather and climatic variables. Caused by viruses in the genus *Bunyavirus*, California encephalitis (CE) is the common childhood central nervous system (CNS) disease reported every year, making CE second in importance only to St. Louis encephalitis among the mosquito-borne viral diseases in the United States. La Crosse (LAC) virus is responsible for most cases of CE, although a number of other antigenically related viruses compose the CE group, including California and Jamestown Canyonviruses. Although not endemic in the Americas, Rift Valley fever (RVF), Crimean-Congo hemorrhagic fever (CCHF), and Hantaan (HTN) viruses cause serious and fatal acute disease with hemorrhagic manifestations (hemorrhagic fever with renal syndrome [HFRS]) on other continents. Relatives of HTN virus, isolated initially in Korea in 1978, are present in wild rodents throughout Eurasia, where they also cause HFRS, and other relatives in the Americas (e.g., Sin Nombre virus [SNV]) are implicated as causes of severe pulmonary edema and shock.

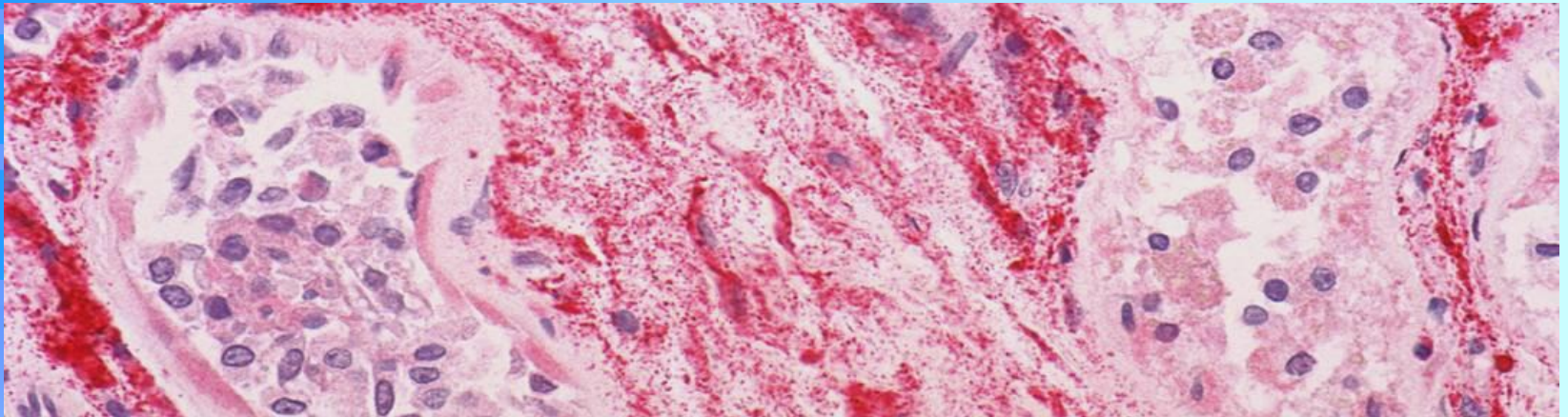
Crimean-Congo haemorrhagic fever (CCHF) – definition

- **Acute life-threatening viral infectious disease with endemic distribution, transmitted by ticks. Classical manifestations include severe toxicity, haemorrhagic syndrome, conjunctival suffusions, high mortality rate and risk of nosocomial infections.**

Crimean-Congo haemorrhagic fever – etiology

- Causative agent – Crimean-Congo haemorrhagic virus, genus nairovirus, Bunyaviridae family – RNA virus. Without antigenic variability.
- ❖ Viral morphogenesis usually occurs intracellularly, with virions maturing by budding from the Golgi complex and endoplasmic reticulum into vesicles.
- ❖ Virus is unstable on environmental factors and disinfectants.

Crimean-Congo haemorrhagic virus



Crimean-Congo haemorrhagic fever – epidemiology

- CCHF virus is transmitted by ticks. The principal vectors belong to the genus *Hyalomma*.
- ❖ Immature stages feed on hares, hedgehogs, and ground-feeding birds, whereas adults parasitize large wild and domestic animals.
- ❖ This virus is widely distributed in the southwestern Russia, the Balkans, the Middle East, central Asia, western China, and Africa.

Crimean-Congo haemorrhagic fever – pathogenesis

- CCHF is a severe hemorrhagic fever with shock, disseminated intravascular coagulation, frequent extensive bleeding, and severe thrombocytopenia. The virus infects the reticuloendothelial system and frequently involves hepatocytes extensively, leading to icteric hepatitis. Mortality rates range from 20% to 35%.
- **Portal of entry** – the skin, rarely – mucosa of the oral cavity and conjunctiva.
- **The transmission of virus** is by tick biting, after removing of tick and by contact with blood of patient.
- The virus enters into the circulation → reticuloendothelial system – replication → secondary massive viraemia – clinical onset → localization in the tissues and organs – vassal endothelium, liver, spleen, bone marrow, kidneys etc.
- It is considered that the cellular disorders are immunogenic but not from direct viral cytopathic effect. Disseminated intravassal coagulation (DIC) appears commonly. **Severe endovasculitis, thrombocytopenia, liver coagulopathy and DIC are reasons for severe bleeding.**
- **Multiorgan disorders** – hepatitis, bone marrow insufficiency, renal involvement to acute renal failure, acute respiratory distress syndrome, myocarditis, endotoxic shock, involvement of CNS (brain edema, aseptic meningitis and meningoencephalitis), alkaline-acid dysbalance, metabolic acidosis with high risk for lethal outcome.

Crimean-Congo haemorrhagic fever – clinical manifestations

- Incubation period – from 2 to 15 and more days. At nosocomial infection – to 6 days. Three clinical periods:
- ❖ Prehaemorrhagic period – sudden onset with fever and conjunctival suffusions. The temperature rises up to 39-40⁰ C, severe weakness, prostration, strong headache, myalgia, arthralgia, nausea, vomiting, common diarrhea, dizziness to collapse; (+) succusio renalis, marked palpatory pain in lumbar region, uncommon transient prodromal rash. Intensive hyperemia on the face, pharynx, neck and upper thoracic region, conjunctival suffusions; uvular and gingival swelling, easily gingival bleeding. On the soft palate red patches, petechial and maculous enanthema.

Crimean-Congo haemorrhagic fever – clinical manifestations

- ❖ **Haemorrhagic periods** (from 2 to 10 days) – **haemorrhagic syndrome** **appears** after decreasing of the temperature – gingival bleeding with specific subdental grayish line, bleeding of manipulations' sites, epistaxis, skin haemorrhages; visceral bleeding with poor prognosis.
- **General intoxication** – depression, drowsiness, stupor to coma or excitation due to brain edema; cranial paralysis, seizures, aseptic meningitis.
- **Acute myocarditis.**
- **Hepatic dysfunction** with hepatomegaly and mild to moderate jaundice.
- Very severe status – full prostration, drowsiness, aphonia, tanatophobia.
- In severe forms – **acute renal failure (ARF).**
- **Shock** is possible in this period – endotoxic, haemorrhagic, cardiogenic or complex.
- ❖ **Convalescent period** – for long time.

Crimean-Congo haemorrhagic fever – haemorrhagic syndrome



Crimean-Congo haemorrhagic fever – clinical forms

- **Haemorrhagic** – with marked haemorrhagic syndrome. According to severity it is mild, moderate, severe or fulminant (severe intoxication, massive multi-site bleeding resulting in haemorrhagic shock and acute renal failure (ARF), fast evolution and often lethal outcome.
- **Ahaemorrhagic** – with intoxication and conjunctival suffusions, without haemorrhages, with good prognosis – in immunized and after prophylaxis.
- **Unapparent** (asymptomatic) – in immunized in endemic areas.

Crimean-Congo haemorrhagic fever – complications

- Endotoxic shock
- Haemorrhagic shock
- Acute renal failure
- Otitis
- Bacterial parotitis
- Secondary pneumonia
- Pyelonephritis
- Hypopituitarism.

Crimean-Congo haemorrhagic fever – laboratory findings

- **Blood cells:**
 - ❖ **in initial period** marked leucopenia with neutropenia and left shift, lympho- and monocytosis with immature forms, moderate thrombocytopenia;
 - ❖ **in haemorrhagic period** (especially at severe forms) – anaemia; leucocytosis with neutrophilia and left shift, lymphopenia, monocytosis, marked thrombocytopenia, slightly elevated erythrocytes' sedimentation rate; common increased serum bilirubin and transaminases, decreased haemostatic parameters.
- **Urinalysis** – albumins, erythrocytes, casts.

Crimean-Congo haemorrhagic fever – diagnosis

- CCHF virus recovers from the blood of acutely ill patients in cell cultures or suckling mice.
- Antigen detection ELISA is useful in diagnosis, particularly of severe cases.
- The polymerase chain reaction provides additional sensitivity with no loss of specificity.
- Antibodies detectable by a variety of methods generally appear within 5 to 14 days of onset and coincide with clinical improvement.
- ELISA detection of IgM antibodies is a reliable definitive method.
- **Because of the aerosol hazard to laboratory personnel, acute samples must be handled with care, and attempts to isolate these two agents should be restricted to facilities with maximal containment.**

Crimean-Congo haemorrhagic fever – treatment

- Immediately admission in Infectious Ward at regimen of life-threatening infections.
- **Etiologic** – studies in vitro and in laboratory animals suggest that ribavirin might be effective in the treatment of severe CCHF, and clinical experience with the drug in CCHF supports its use.
- ❖ Antihaemorrhagic hyperimmune immunovenin in dose 0,3 to 0,6 ml/kg intravenously (18-36 ml single dose, for children 6-9 ml); at severe forms –in dose 0,5-1,0 ml/kg.
- **Supportive** – fluid-saline replacements, corticoids, blood transfusions.

Crimean-Congo haemorrhagic fever – prophylaxis

- Desacarisation of the livestock in endemic areas, **use of tick repellents**.
- Vaccination of the risk groups.
- Defense by wears and gloves.
- Observation of the contact people within 15 days.
- Administration of 3 ml antihaemorrhagic hyperimmune immunovenin intravenously – single dose.

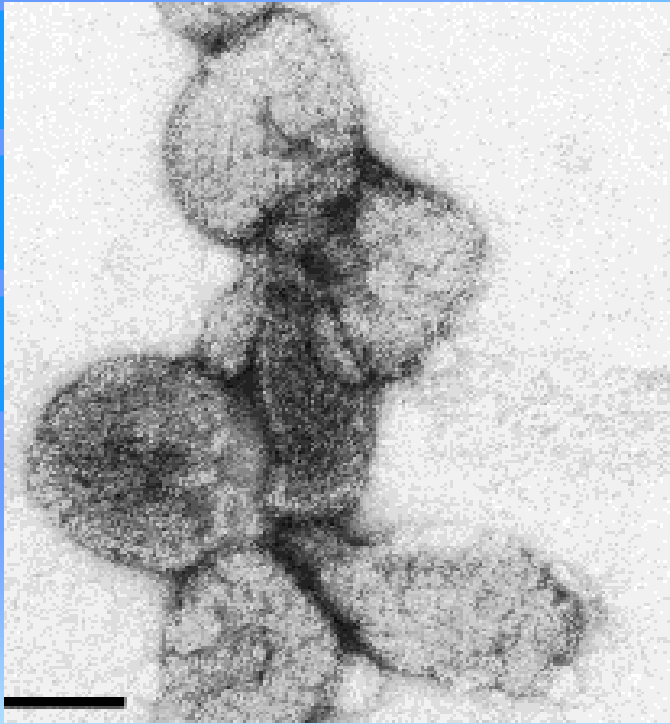
Haemorrhagic fever with renal syndrome (HFRS) – definition

- **Acute endemic zoonosis with fever, intoxication, conjunctival suffusions, haemorrhagic syndrome and renal involvement to acute renal failure (ARF).**

Haemorrhagic fever with renal syndrome – etiology

- **Causative agents** – four RNA viruses – Hantaan, Puumala, Seul, Dobrava, belonging to genus Hantavirus, Bunyaviridae family.
- Stable in environmental, unstable on disinfectants.

Hantavirus



Haemorrhagic fever with renal syndrome – epidemiology

- Aerosols of virus-contaminated rodent urine or perhaps feces are thought to represent the principal vehicle for the transmission of hantaviruses; disease has also followed the bite of infected rodents (saliva contains virus). Infections from *Apodemus* or *Clethrionomys* are acquired principally by persons visiting or working in forests and on farms. Depending on the circumstances, the incidence may be highest in summer or in fall and early winter. Disease is maximal in “highrodent” years, when suburban residents may be exposed to dispersing infected rodents.
- ❖ Infection with Seoul virus from *Rattus norvegicus* may occur on farms or in residential areas. Indeed, cases of HFRS, traced to nontraveling residents of urban Seoul, Korea, were the first clues to the existence of the virus. Rat-borne disease has striking seasonal prevalence (winter-spring) in China and Russia. In addition, infection, human disease, and even death have been linked to infected laboratory rats in Korea, Japan, Belgium, France, and the United Kingdom. Rat colonies are apparently infected by the introduction of infected laboratory rats or by contact with wild rats bearing the virus.
- ❖ Deer mice are numerous and readily enter human dwellings and outbuildings, particularly when mouse populations are high or in autumn when food and cover are scarce. Abundant rodent populations led to a large number of cases in the southwestern United States in summer 1993 and resulted in the first discovery of the virus. Most hantavirus epidemic years have been associated with increased rodent populations.

Haemorrhagic fever with renal syndrome – pathogenesis

- Portal of entry – mucosa of gastrointestinal tract and skin abrasions, inhalation of contaminated dust → transitory viraemia → replication in reticuloendothelial system → secondary viraemia. Because of vaso- end neurotropism **the virus localizes in the vasa and renal endothelium** → dystrophic and necrotic changes appear → haemorrhagic diathesis. Involvements of the liver, lungs, myocardium, bone marrow, nervous and endocrine system have been observed.
- The kidneys are major target – acute tubulointerstitial haemorrhagic nephritis and rare tubular necrosis → OBH.
- The destructive mechanisms in different organs probably are immunogenic because the virus does not possess direct cytopathic effect.
- The damage of vascular endothelium, liver and bone marrow results in haemorrhagic syndrome.
- HFRS is disease with multiorgan disorders, clinical variability and severe course.

Haemorrhagic fever with renal syndrome – clinical manifestations

- The hallmarks of clinical infection by HTN, Dobrava, Seoul, and Puumala viruses as well as other Eurasian hantaviruses are **fever, thrombocytopenia, and acute renal insufficiency** pathologically typical of acute interstitial nephritis.
- ❖ **The incubation period**, typically 2 weeks, may vary from 5 to 42 days. In the severe form of HFRS exemplified by HTN virus infection, patients who survive full-blown disease progress through
 - **febrile (toxic),**
 - **hypotensive,**
 - **oliguric, and**
 - **polyuric clinical stages** and may require weeks or months to recover from general asthenia.

Haemorrhagic fever with renal syndrome – clinical manifestations

- **In the toxic phase,**
 - ❖ patients complain of headache, abdominal and lower back pain, dizziness, and, often, blurred vision.
 - ❖ Conjunctival injection and petechiae occur over the upper trunk and soft palate. An erythematous flush that blanches on pressure is characteristically seen on the torso and face.
 - ❖ Leukocyte levels are normal or more likely elevated, often exceeding 20,000/mm³. The differential count shows a left shift, immature myeloid cells, and atypical lymphocytes as well, confirming the decreased thrombocyte count.
 - ❖ At the end of the febrile period (**4 to 7 days**), many patients experience **severe shock.**
 - ❖ Those surviving then must endure varied grades of renal insufficiency that can include anuria, oliguria, mucosal bleeding diathesis, electrolyte and acid-base abnormalities, hypertension, and pneumonitis complicated by pulmonary edema.

Haemorrhagic fever with renal syndrome – clinical manifestations

- After 3 to 10 days, **polyuria** begins with its attendant stresses on the fluid and electrolyte balance. The fatality rate in Asian HFRS averages about 5%: one third during the shock phases and two thirds (cerebrovascular accidents and pulmonary edema) during the renal phases of illness.
- ❖ Hemodynamic changes result from massive acute capillary leak syndrome of uncertain cause and equally poorly understood shock-inducing mechanisms.
- ❖ The renal lesions, predominantly in medullary tubules, are possibly related to systemic and intrarenal hemodynamic factors and the influence of immunopathologically released kinins and cytokines.

Haemorrhagic fever with renal syndrome – clinical manifestations

- The milder form of HFRS caused by Puumala virus and often referred to as nephropathia epidemica is rarely hemorrhagic and is fatal in less than 1% of clinical cases. Abdominal pain and hypospheneria may be manifestations. Up to 90% of Puumala virus infections are asymptomatic. Proteinuria, creatinine level elevation, and leukocytosis, although common, are much less severe than for HTN virus infection.
- Seoul virus also causes a mild to moderately severe HFRS in Eurasia with more prominent hepatic involvement than classic HFRS.

Haemorrhagic fever with renal syndrome – haemorrhagic syndrome



Haemorrhagic fever with renal syndrome – clinical forms

- According to severity – mild, moderate, severe and fulminant.
- Atypical:
 - ❖ Ahaemorrhagic
 - ❖ Without renal involvement
 - ❖ Without haemorrhages and ARF.

Haemorrhagic fever with renal syndrome – complications

- Secondary bacterial pneumonia
- Abscesses
- Bacterial parotitis
- Sepsis
- Rupture of renal cortex
- Glaucoma
- Retinal ablation, blindness
- Thrombophlebitis
- Hypophyseal necrosis.

Haemorrhagic fever with renal syndrome – laboratory findings

- In initial phase leukocyte count is normal or decreased. The differential count shows a left shift, immature myeloid cells, and atypical lymphocytes as well, confirming the decreased thrombocyte count.
- In hypotensive phase – moderate leucocytosis with neutrophilia and left shift; anaemia appears.
- In oliguric phase – extremely increased nitrogen parameters; increased transaminases and serum bilirubin levels, hypoproteinemia, decreased haemostatic parameters.
- In urine – decreased urine output with low density, in sediment – erythrocytes, leucocytes, casts, fibrin and **pathognomonic fatty degenerated epithelial cells.**

Haemorrhagic fever with renal syndrome – diagnosis

- From clinical and epidemiological data.
- HFRS virus recovers from the blood of acutely ill patients in cell cultures or suckling mice.
- All hantavirus patients have both IgM and IgG ELISA antibodies present when admitted to the hospital.
- Hantaviruses can be recovered only with difficulty in cell culture or animal hosts, but the agent can be detected in blood or tissues by reverse transcription – polymerase chain reaction or in tissues by immunohistochemical staining.

Haemorrhagic fever with renal syndrome – management and treatment

- Immediately admission in Infectious Ward. Незабавна хоспитализация.
- **Etiologic treatment** – by ribavirin and alfa interferon – controversial results.
- **Supportive treatment** – fluid-saline infusions, vitamins, corticoids.
- **Management of acute renal failure.**

Haemorrhagic fever with renal syndrome – prophylaxis

- Deratization.
- Control on the cookin, storage and consumption of the foods.
- Education of the risk groups.

Flaviviruses

- The family Flaviviridae comprises at least 68 viruses, of which 29 cause human illness. The prototype virus, yellow fever (L. flavus, yellow) was isolated in 1927. New flaviviruses continue to be isolated from arthropod vectors and wild animals, and this group of agents is certainly among the “emerging viruses”. Flaviviruses are transmitted by mosquitoes or ticks, and some are zoonotic infections spread between rodents or bats without involving arthropod vectors.

Flaviviruses

- All important human infections are caused by flaviviruses transmitted by mosquitoes or ticks. In two cases, dengue and yellow fever, humans serve as viraemic hosts in the transmission cycle, but the remainder use intermediate wild or domestic animals, and humans are "dead-end" hosts that do not contribute to transmission. **Flavivirus infections are not communicable.** Geographical distribution of the disease is often circumscribed by the range of vector and host and provides a clue to the diagnosis of human infections. **An important feature of arthropod virus transmission is the requirement for an extrinsic incubation period in the vector, generally lasting 7 to 14 days, representing the interval of virus replication in the vector between feeding on a viraemic host and ability to transmit by refeeding on a second host.**

Flaviviruses

- Flaviviruses are small (37-50 nm) spherical particles consisting of a lipid-protein bilayer envelope surrounding a nucleoprotein core containing the single-stranded, positive-polarity RNA genome. Viruses attach to as yet undefined cell receptors by means of the envelope (E) protein spike protruding from the virion surface. After virus entry and uncoating, replication occurs in the cytoplasm. Virions mature and accumulate in the endoplasmic reticulum and are released by exocytosis or cell lysis.

Flaviviruses

- The genome organization has been fully elucidated and consists of approximately 11000 nucleotides that encode 10 viral proteins, three of which make up the virus particle and seven of which are non-structural proteins remaining in the infected cell. From the medical standpoint, the most important gene products are the E protein, which subserves virus attachment and contains antigens stimulating humoral immunity, and two non-structural (NS) proteins, NS1 and NS3, that serve as targets for immune clearance.

Flaviviruses

- Disease syndromes associated with flaviviruses include non-specific febrile illness, fever with arthralgia and rash, haemorrhagic fever, and central nervous infection (aseptic meningitis or encephalitis).
- Pathogenesis is mediated by direct viral injury to infected cells or, in some cases (e.g. dengue haemorrhagic fever) perhaps indirectly by cytokines released from cells during the process of immune clearance.
- Because the clinical illness is rarely pathognomonic (except in an epidemic), the physician must use epidemiological information and specific laboratory tests to arrive at an accurate diagnosis.
- Vaccines are available or in advanced development for prevention of a number of flavivirus infections, but no effective antiviral drugs have been discovered and treatment is supportive and symptomatic.

Yellow fever – clinical manifestations

- Subclinical or abortive infections are frequent, and only about 1 in 10 to 20 infections results in clinical disease with jaundice.
- In its classical form, disease onset occurs abruptly after an incubation period of 3 to 6 days.
- The initial phase of illness (“period of infection”), during which time virus is present in the blood, is characterized by fever, chilliness, severe headache, lumbosacral pain, generalized myalgia, nausea, and severe malaise or prostration.

Yellow fever – clinical manifestations

- **On examination**, the patient is febrile, with a relative bradycardia, conjunctival injection, and a coated tongue reddened along the edges. Within several days, the patient may recover transiently (“period of remission”), only to relapse (“period of intoxication”) with increasing systemic symptoms, jaundice, albuminuria, oliguria, haemorrhagic manifestations (especially “black vomit” haematemesis), delirium and stupor, metabolic acidosis, and shock. The prognosis in those who exhibit this full-blown syndrome is poor, and over 50 per cent succumb between the seventh and tenth day after onset.

Yellow fever – complications

- The kidney shows acute tubular necrosis. Focal myocarditis, and brain edema and petechial haemorrhages are found and may contribute to the pathogenesis of the disease. Some patients recover from the acute hepatic infection, only to die of complications of acute tubular necrosis and renal failure. Those who recover, do so without permanent effects or postnecrotic cirrhosis. Late deaths during convalescence have been attributed to cardiac arrhythmias, but this complication requires confirmation.

Yellow fever – laboratory findings

- Clinical laboratory tests reveal leucopenia, and chemical signs of hepatic dysfunction and renal failure. The bleeding diathesis is believed due principally to decreased synthesis of clotting factors by the liver, but disseminated intravascular coagulation has been described in a few cases and may have a role. As yet unidentified vasoactive mediators are probably responsible for terminal events and shock. **Pathological findings in the liver are characteristic, showing midzonal necrosis and eosinophilic degeneration of hepatocytes (Councilman bodies).**

Yellow fever – diagnosis

- Specific diagnosis may be accomplished during the period of infection by examination of serum for isolation of virus, demonstration of viral genome by polymerase chain reaction, or by antigen detection by monoclonal antibody-enzyme immunoassay.
- Serological methods (especially IgM enzyme immunoassay) are useful, but cross-reactions with other flaviviruses present problems for diagnosis, particularly in Africa where multiple heterologous flaviviruses abound.
- Postmortem diagnosis may be accomplished by histopathological examination of the liver, with or without immuno-cytochemical analysis to detect yellow-fever viral antigen. **Liver biopsy should never be performed on living patients, as it may precipitate lethal haemorrhage.**

Yellow fever – management and treatment

- Treatment is symptomatic.
- Intensive care and counter measures to acid-dosis, shock, and other pathophysiological disturbances would probably save lives but have not been available where most cases occur. Patients with renal failure may require dialysis.
- No specific antiviral drug is available.

Yellow fever – prophylaxis

- Yellow fever is a preventable disease. The live, attenuated 17D vaccine is produced in a number of countries from chicken embryos. The vaccine is delivered as a single 0.5 ml subcutaneous dose and induced long-lasting immunity in over 95 per cent of those immunized. Immunity is probably lifelong; **for travel certification, revaccination is recommended every 10 years.** Reactogenicity is minimal.

**THANK YOU
FOR THE ATTENTION !**