

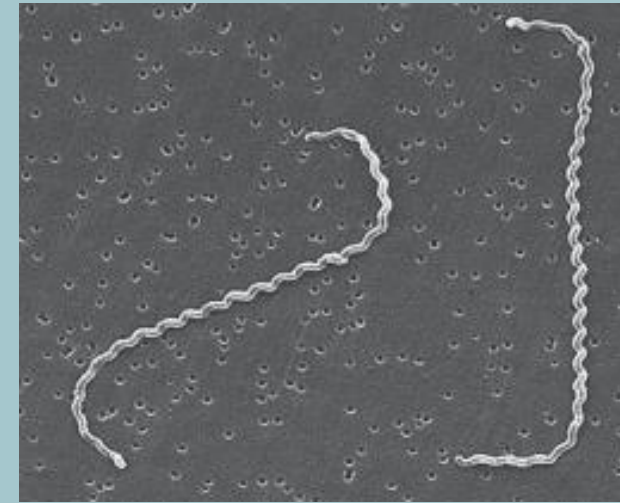
LEPTOSPIROSIS

Introduction

- Leptospirosis Is A Zoonotic Disease With Worldwide Distribution And Increasing Prevalence.
- Infection Is Caused By The Spirochete *Leptospira*, With Common Exposure Being Contaminated Fresh Water.
- Most Infections Are Asymptomatic
- Symptoms Range From A Mild, Self-limiting, Non-specific Febrile Illness To Fulminant Respiratory And Renal Failure.

History

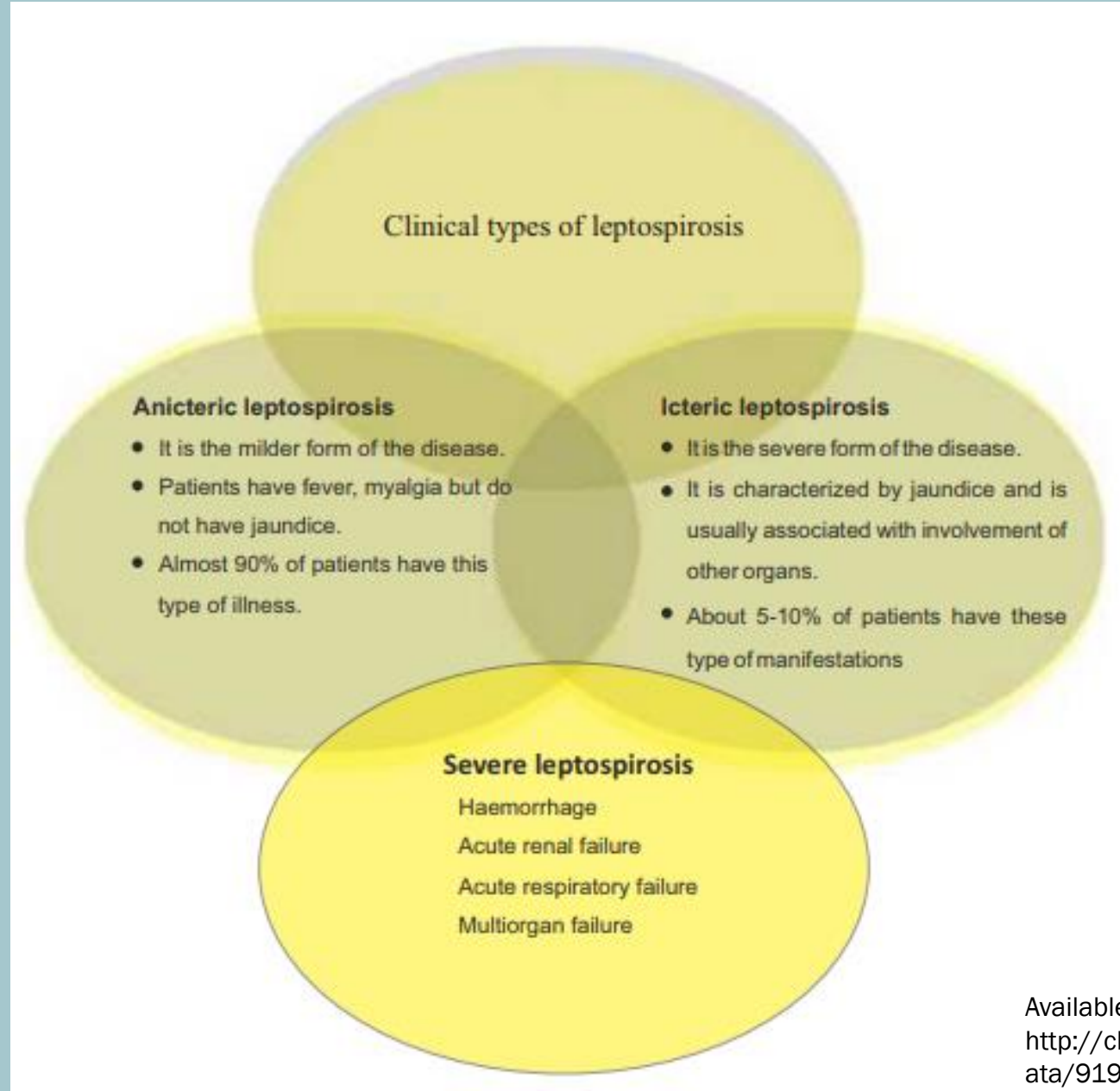
- Also known as – field fever, eye cather's yellows, 7- day fever, cane-field fever
- Disease was first described by Adolf Weil in 1886
- Leptospira was first observed in 1907 from a post mortem renal tissue slice
- World War I - where the sodden conditions of trench warfare favoured infection
- *L. icterohaemorrhagiae* was identified as the causative agent in pre-World War II outbreaks in Japan



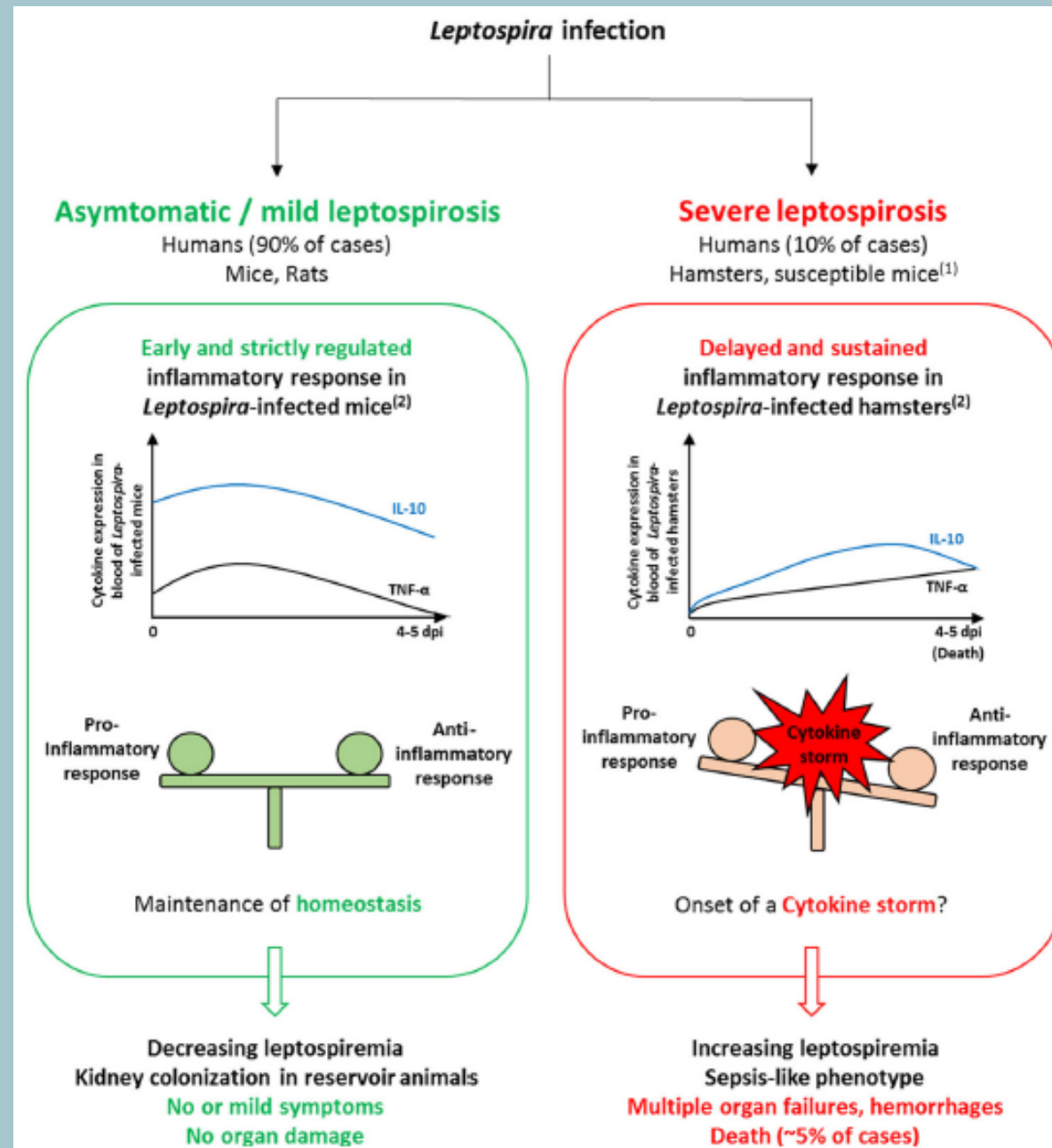
SCOPE OF THE PROBLEM

- Number of human cases worldwide is not well- documented
- annual incidence of this disease is estimated at 10 to 100 per 100,000 in tropical regions and 0.1–1.0 per 100,000 in temperate areas
- During outbreaks and in high-risk groups, 100 or more per 100 000 infected • 7-10 million peoples are infected annually.

Clinical types of Leptospirosis



Pathophysiology of leptospirosis



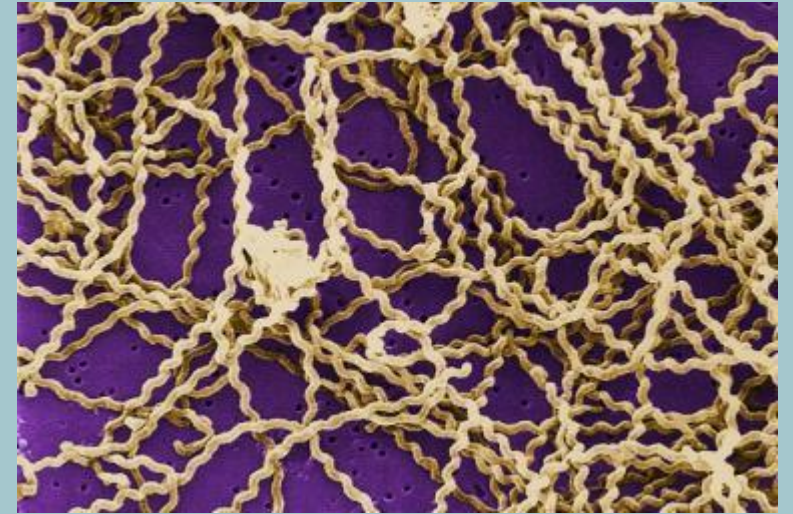
Cagliero J et al. Front Cell Infect Microbiol. 2018; 8: 204.

Risk factors for Leptospirosis

Environmental risk factors	Occupational risk groups	Recreational activities
▪ Rainfall and flooding ▪ Contaminated environment – Poor sanitation – Inefficient solid waste disposal – Inadequate drainage facilities and open drains – Presence of rodents, cattle, pigs and dogs – Walking bare foot – Wading through contaminated water – Absence of indoor toilets – Living in overcrowded residential areas (urban slums) – Outdoor manual work.	▪ Farmers – Rice, sugarcane, vegetables, cattle, pigs ▪ Sewage workers ▪ Abattoir workers, butchers ▪ Veterinarians, laboratory staff ▪ Miners ▪ Fishermen—Inland ▪ Soldiers	▪ Swimming in fresh water ▪ Sailing ▪ Marathon runners ▪ Gardening ▪ Adventure travel ▪ Water sports ▪ Ecotourism

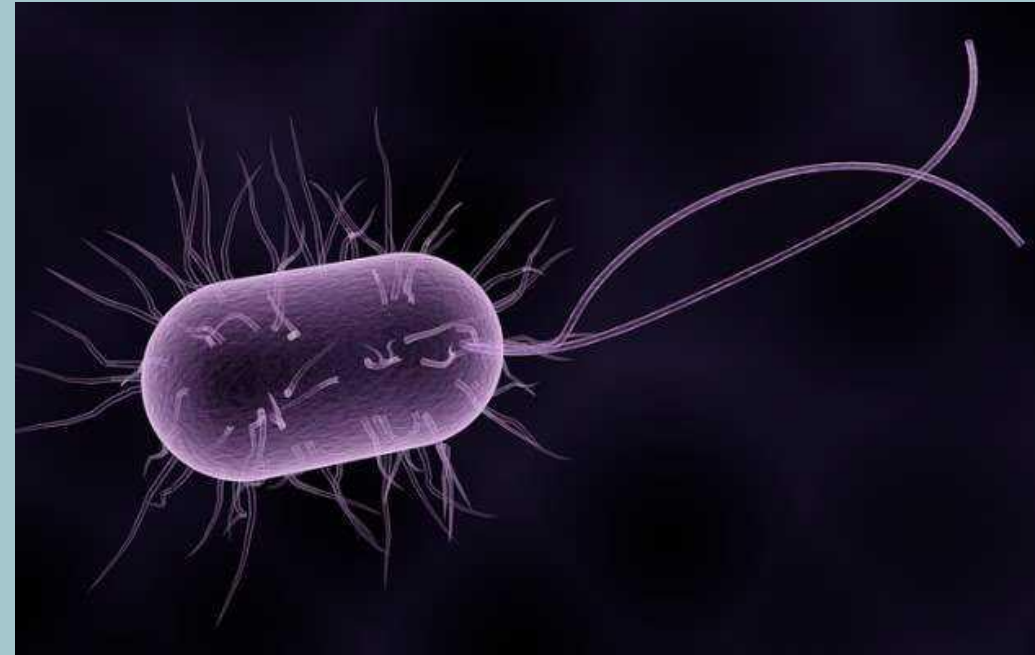
AGENT

- Corkscrew-shaped bacteria - spirochete
- Thin and light motile
- Only strains of *L.interrogans* are pathogenic – visible by dark field illumination and silver staining
- 21 species identified; 13 species detected in human cases.



AGENT

- About 250 pathogenic serovars based on diverse sugar composition of lipopolysaccharide on surface
- Antigenically related serovars are grouped into 24 serogroups - identified using the microscopic agglutination test (MAT)
- Given serogroup is often found in more than one species, suggesting that the LPS genes that determine the serovar are exchanged between
- Source of infection: urine of infected animals – entire life time in case of rodents
- Animal reservoirs: wild and domestic – Especially rodents – rats, mice, moles – particularly *R. norvegicus* and *Mus musculus* – Cattle, sheep, goats, buffalo, pigs, horses – through grazing – Dogs



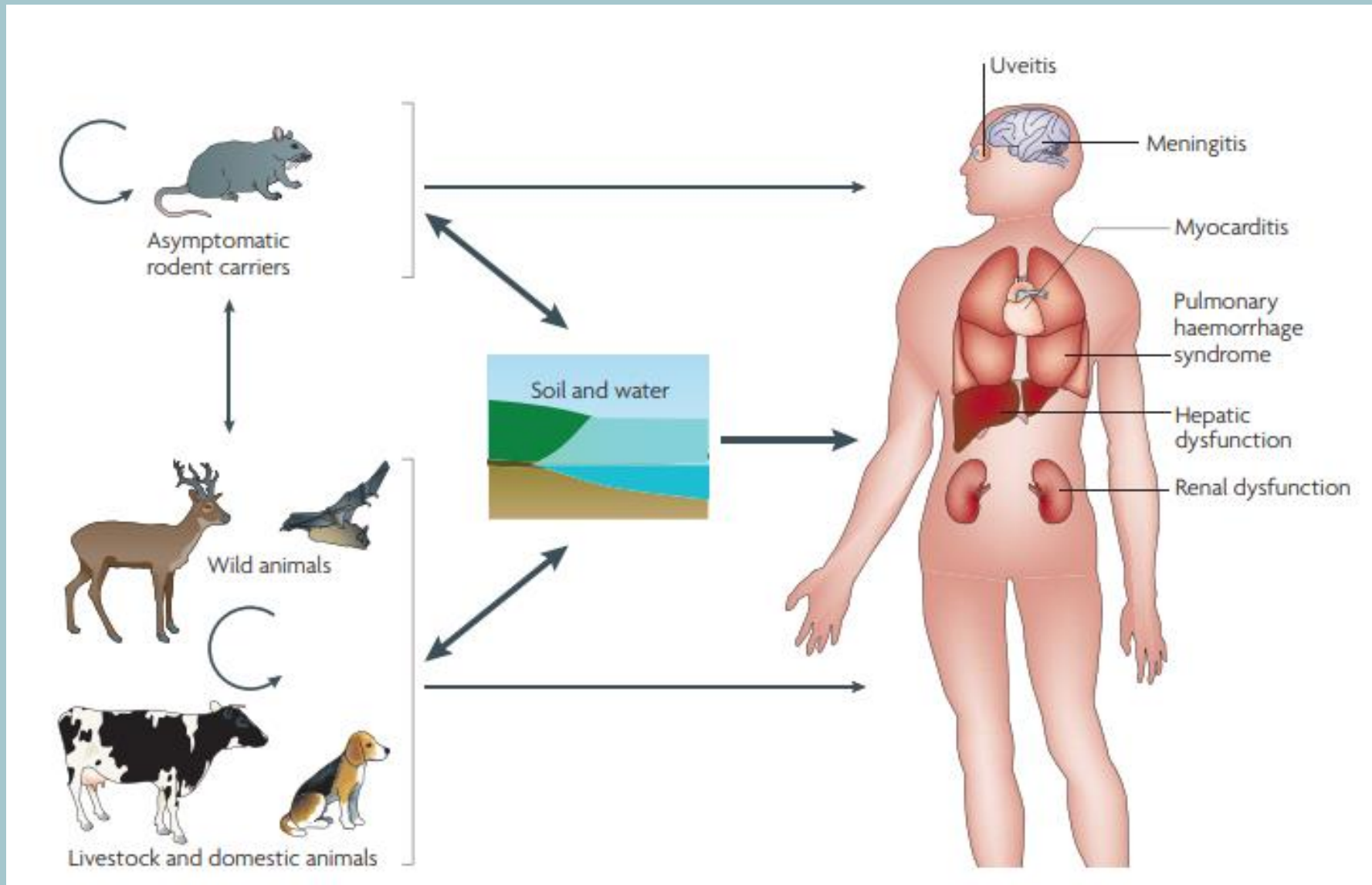
HOST

- Human infection is accidental
- AGE: Children acquire infection from dogs more frequently
- OCCUPATION: veterinarians, slaughterhouse workers, farmers, sewer maintenance workers, waste disposal facility workers, and people who work on derelict buildings; Rowers, kayakers and canoeists also sometimes
- IMMUNITY: serovar specific immunity

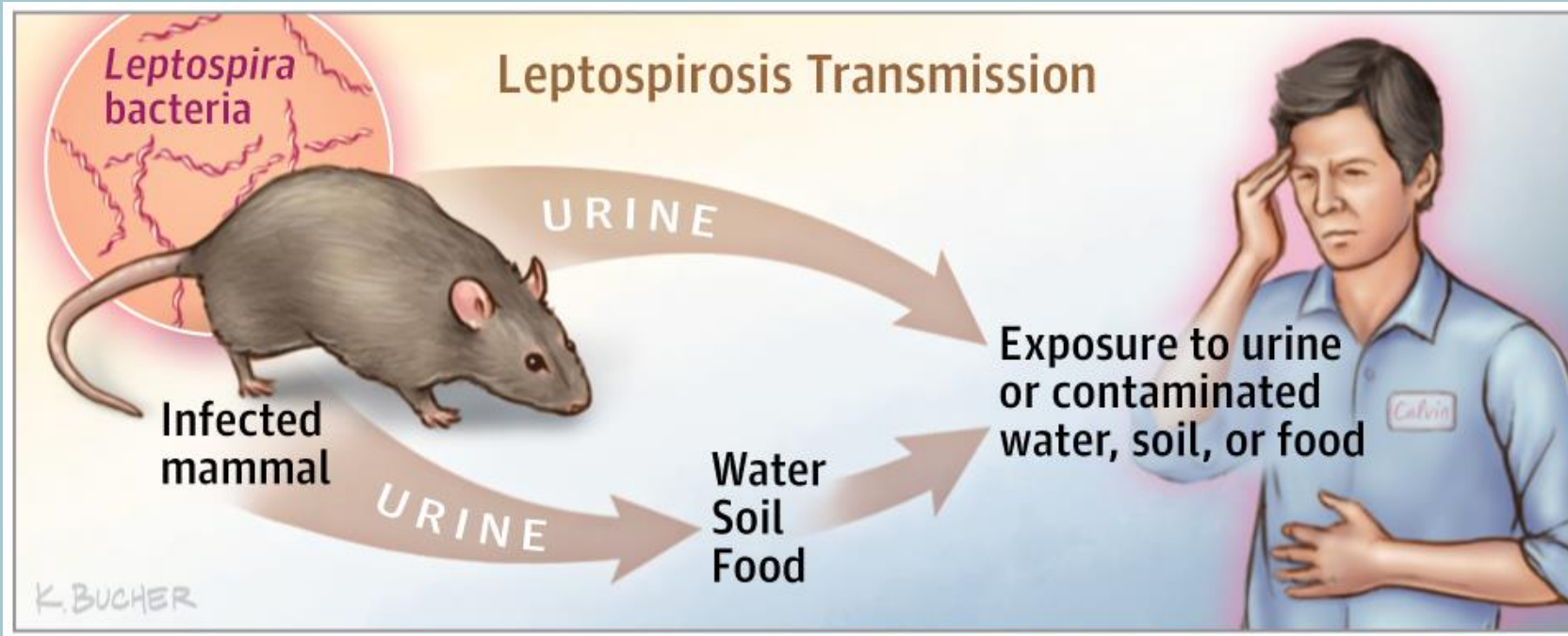
ENVIRONMENT

- Leptospira shed in urine survive for weeks in soil and water – high level of environmental contamination were carrier animals frequently urinate
- Poor housing
- Limited water supply
- Inadequate waste disposal

Life cycle of leptospirosis



TRANSMISSION

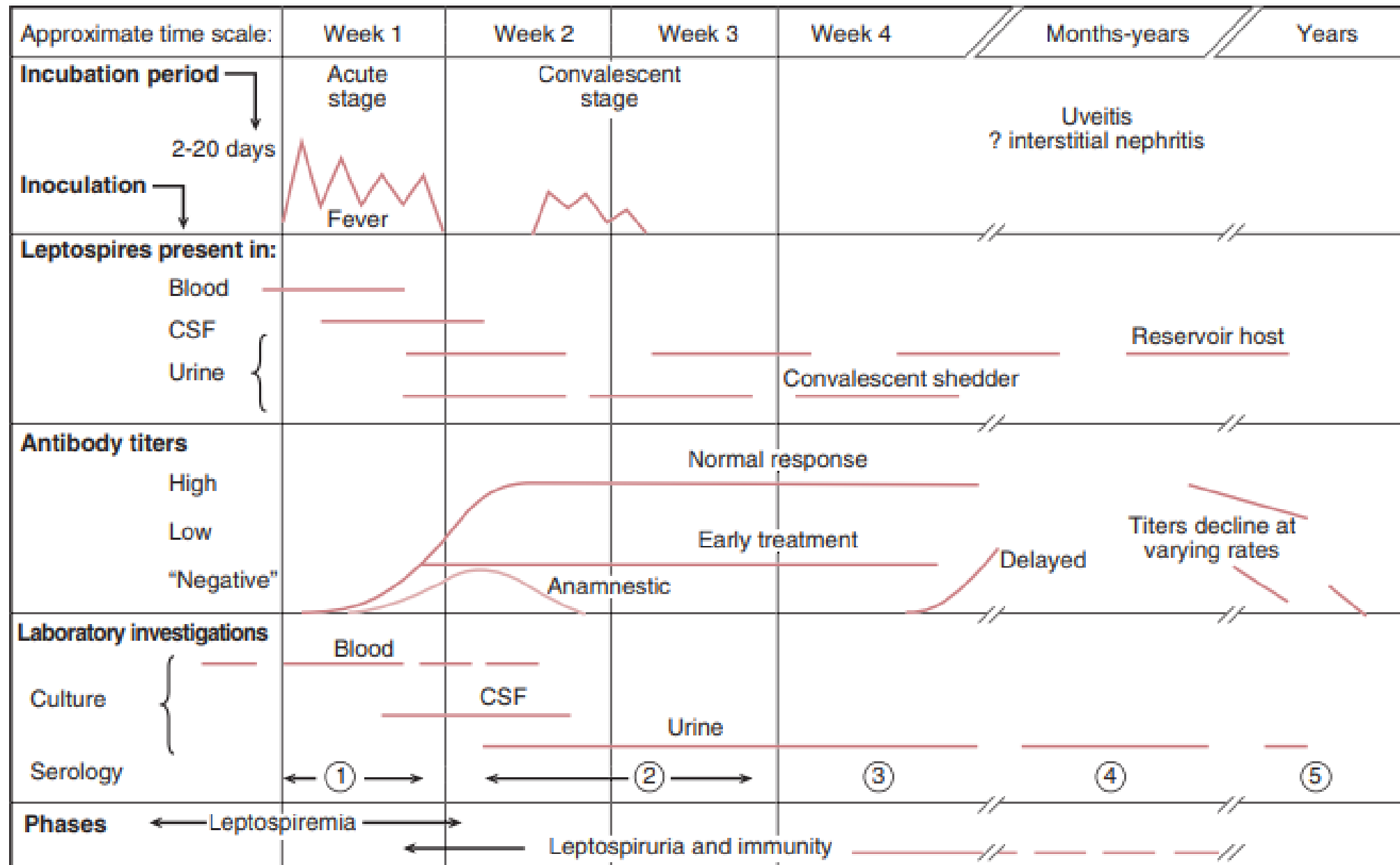


- **DIRECT CONTACT:** skin abrasions or intact mucous membrane
- **INDIRECT CONTACT:** – broken skin with contaminated soil, water or vegetation – ingestion of contaminated food or water
- **DROPLET INFECTION:** breathing air polluted with droplets of urine – like while milking cattle

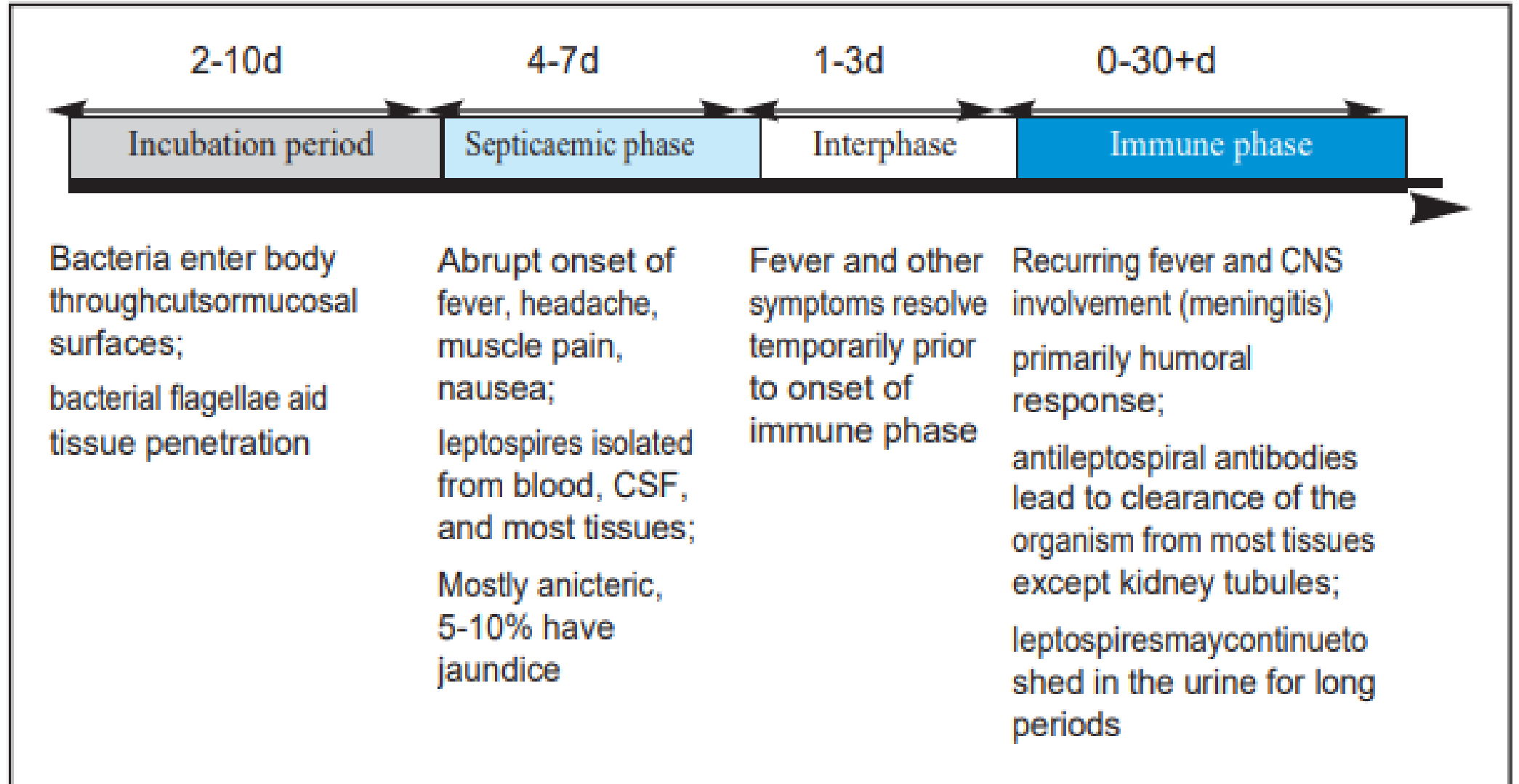
SIGNS & SYMPTOMS

- Incubation period: 7–12 days
- Biphasic disease - sudden fever with chills, intense headache, severe myalgia, abdominal pain, conjunctival suffusion, and occasionally a skin rash
- First phase (septicemic phase) - 3–7 days
- Disappearance of symptoms coincides with the appearance of antibodies and disappearance of bacteria from bloodstream - Patient asymptomatic for 3–4 days
- Second phase - more severe symptoms

Biphasic nature of Leptospirosis



Typical course of leptospirosis



Clinical criteria

- History of fever within past 2 weeks and at least two of the following clinical findings: myalgia, headache, jaundice, conjunctival suffusion without purulent discharge, or rash (i.e. maculopapular or petechial); OR
- At least one of the following:
 - Aseptic meningitis
 - GI symptoms (abdominal pain, nausea, vomiting, diarrhoea)
 - Pulmonary complications (cough, breathlessness, haemoptysis)
 - Cardiac arrhythmias, ECG abnormalities
 - Renal insufficiency (anuria, oliguria)

Complications of Leptospirosis

- Jaundice
- Acute kidney injury
- Pulmonary hemorrhage
- ARDS
- Neuroleptospirosis
- Hypotension
- Thrombocytopenia
- Myocarditis
- Ocular complications
- Hypokalemic paralysis



Organs affected in Leptospirosis

Organ	Clinical features	Investigations reveal
Kidney	Decrease in urine output, features of uremia	Increase in Serum Creatinine, Increase in Blood Urea
Liver	Jaundice, hepatomegaly	Increase in Serum Bilirubin with normal or mildly elevated SGPT and SGOT and increased CPK
Lungs	Cough, haemoptysis, dyspnoea with increase in respiration rate and basal creps	X ray chest shows lower and mid zone opacities.
Heart	Hypotension, irregular pulse	ECG reveals the type of arrhythmia
Blood	Bleeding tendencies	Decrease in platelet count
Brain	Altered consciousness with neck rigidity	CSF shows increase in cells, increase in protein, normal sugar

Differential diagnosis of Leptospirosis

- Malaria
- Dengue
- Typhoid
- Tuberculosis
- Scrub typhus
- Influenza
- Pneumonia
- Urinary tract infection
- Sepsis
- Viral hepatitis

DIAGNOSIS

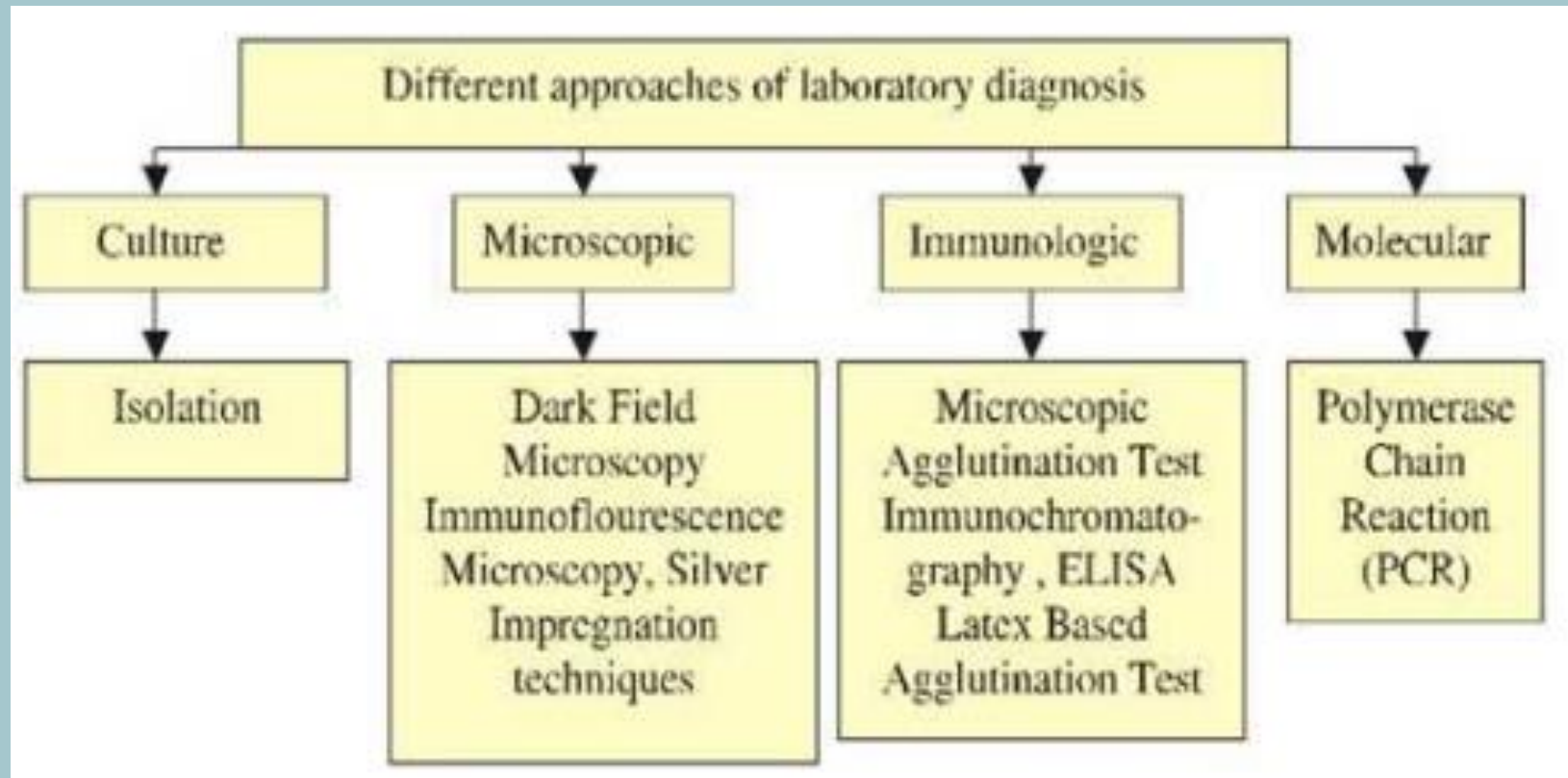
- Difficult to diagnose clinically; laboratory support is indispensable
- Supportive:
 - Leptospira agglutination titer of ≥ 200 but < 800 by Microscopic Agglutination Test (MAT) in one or more serum specimens
 - Demonstration of anti-Leptospira antibodies in a clinical specimen by indirect immunofluorescence
 - Demonstration of Leptospira in a clinical specimen by dark-field microscopy,
 - Detection of IgM antibodies against Leptospira in an in acute phase serum specimen.

DIAGNOSIS

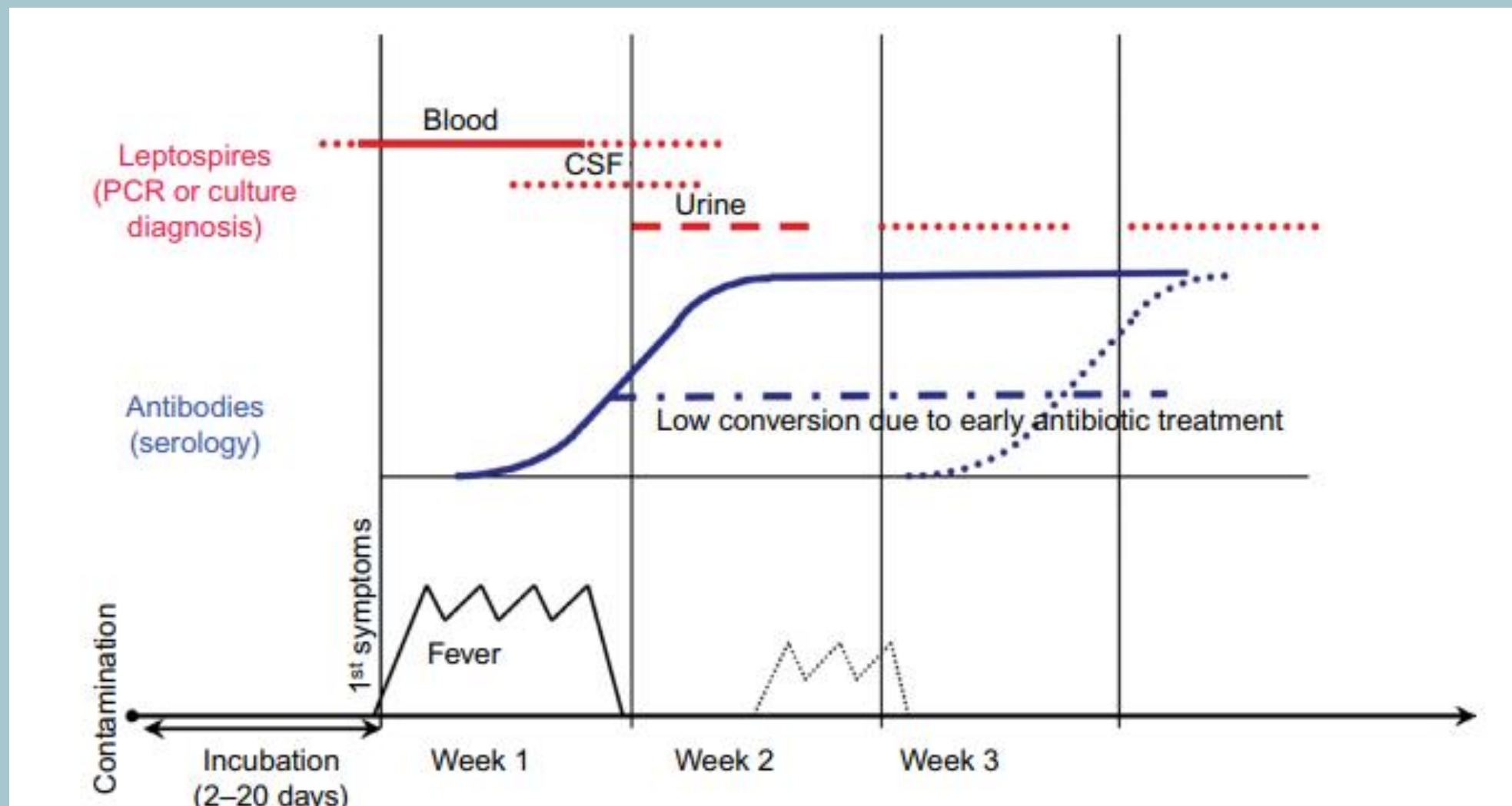
■ Confirmed:

- Isolation of *Leptospira* from a clinical specimen
- Fourfold or greater increase in *Leptospira* agglutination titer between acute- and convalescent-phase serum specimens studied at the same laboratory
- Demonstration of *Leptospira* in tissue by direct immunofluorescence
- *Leptospira* agglutination titer of ≥ 800 by Microscopic Agglutination Test (MAT) in one or more serum specimens
- Detection of pathogenic *Leptospira* DNA (e.g., by PCR) from a clinical specimen.

Protocol for laboratory diagnosis



Diagnosis of leptospirosis



Case definition

- **Suspect:** Which consists of only clinical features.
 - Acute febrile illness ($\geq 38.5^{\circ}\text{C}$) and/or severe headache with:
 - Myalgia
 - Prostration and/or
 - Conjunctival suffusion
 - History of exposure to leptospira-contaminated environment

Case definition

- **Probable (At primary health care level) :** Which consists of clinical features + Rapid diagnostic tests.
 - Suspect case with any two of the following:
 - Calf tenderness
 - Cough with or without hemoptysis
 - Jaundice
 - Hemorrhagic manifestations
 - Meningeal irritation
 - Anuria/oliguria and/or proteinuria
 - Breathlessness
 - Cardiac arrhythmias
 - Skin rashes

Available at : <http://clinicalestablishments.gov.in/WriteReadData/919.pdf>.
Accessed on 12-06-2020.

Case definition

- **Probable (At Secondary and Tertiary Health Care Levels):** Which consists of clinical features + Rapid diagnostic tests.
 - Based on availability of laboratory facilities a probable case of leptospirosis is a suspect case with a positive rapid IgM test. And/ Or
 - Supportive serologic findings (i.e. a MAT titer equal to 200 in a single sample) And/Or
 - Any three of the following:
 - Urinary findings: Proteinuria, pus cells, blood
 - Relative neutrophilia (> 80%) with lymphopenia
 - Platelets less than 100,000/cu mm
 - Elevated serum bilirubin more than 2 mg%; liver enzymes moderately raised (Serum alkaline phosphatase, S amylase, CPK).

Available at : <http://clinicaestablishments.gov.in/WriteReadData/919.pdf>.
Accessed on 12-06-2020.

Case definition

- **Confirmed:** Which consists of clinical features + positive MAT/ PCR/Culture
 - Isolation of leptospires from clinical specimens
 - Positive PCR result
 - Seroconversion from a negative to positive or fourfold rise in titer by MAT
 - Titer by MAT of 400 and greater in a single sample.
 - Where laboratory capacity not well established: Positive by two different rapid diagnostic tests could be considered as laboratory confirmed case

Indian guidelines for treatment

■ Mild leptospirosis

- Doxycycline 100 mg bd for 7–10 days
- Amoxycillin 500 mg qid for 7–10 days
- Ampicillin 500–750 mg qid for 7–10 days
- Azithromycin 500 mg od for 3 days

■ Severe leptospirosis

- Penicillin 1.5 million units IV qid for 7 days
- Ceftriaxone 1 g IV od for 7 days
- Start treatment before 5 days
- Empiric therapy recommended (WHO)

Indian guidelines for treatment

- Fluid therapy
 - Indication: Hypovolemia/Hypotension/Hemorrhage
 - Fluids: IV saline/Blood transfusion
- Acute kidney injury
 - Mild: Fluid therapy/Diuretics
 - Severe: Dialysis
- ARDS/Pneumonia
 - Ventilatory support

Prophylaxis

- Chemoprophylaxis may be considered for those who are high risk of exposure to potentially contaminated sources
- Farmers soldiers, rescue teams and those who involved in adventurous sports are at high risk of exposure.
- Oral doxycycline 200 mg once a day given once weekly throughout period of exposure is recommended drug for prophylaxis

Prevention & control

- Control of infection source (e.g. rodent control, animal vaccination)
- Interrupt transmission route (e.g. wearing protective clothing, refrain from contact with infected animals and from swimming in contaminated water, provide clean drinking-water)
- Prevent infection or disease in human host (e.g. vaccination, antibiotic prophylaxis, information to doctors, veterinarians, risk groups and the general population.
- VACCINATION – of pets and occupational risk persons

CLINICAL TRIAL

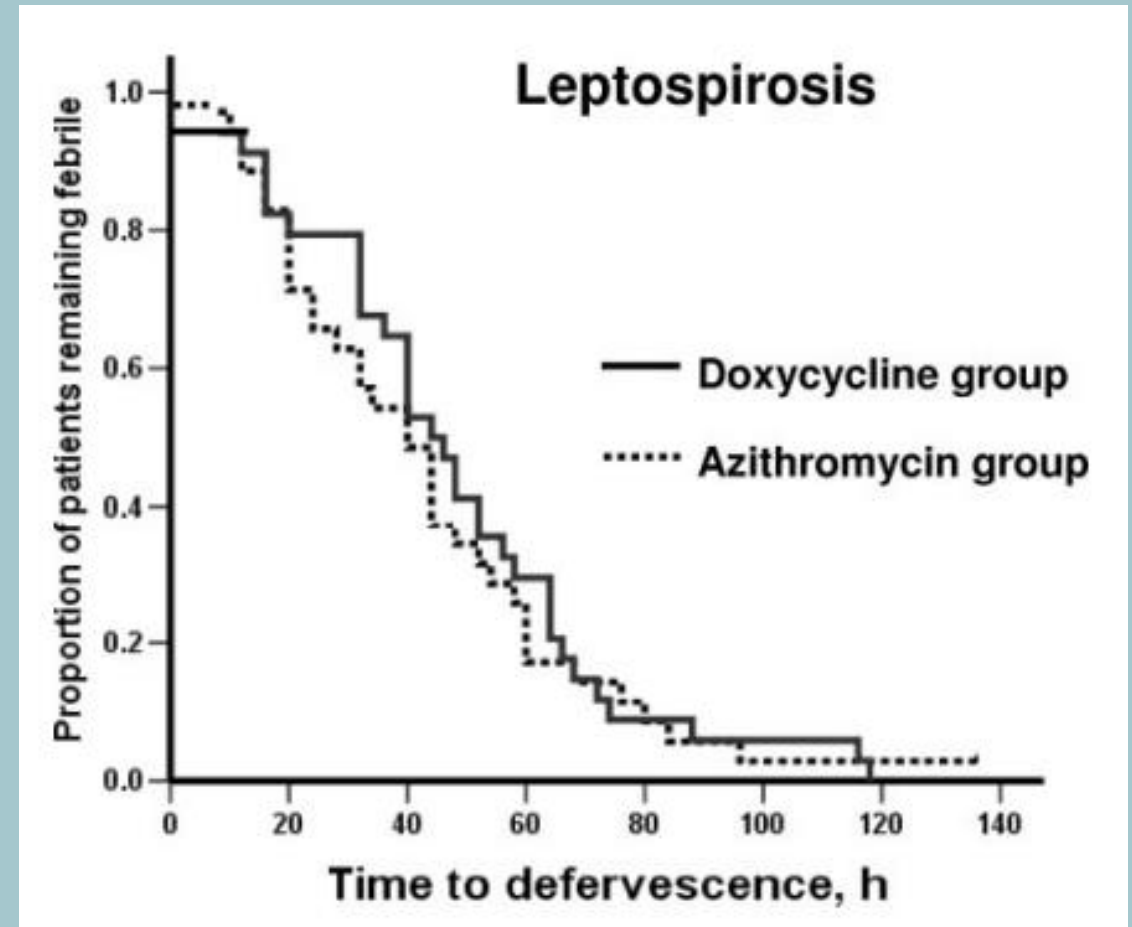
Comparison of Doxycycline vs Azithromycin in Leptospirosis

- Methods: 296 patients were enrolled in the study.
- Patients were randomly allocated to receive either oral doxycycline (200 mg in the first dose, followed by 100 mg every 12 h for 7 days) or a 3-day course of azithromycin (1 g initially, followed by 500 mg once daily for 2 days)
- The cure rate, fever clearance time, and adverse drug events were compared between the two study groups.
- Patients were discharged when defervescence had been achieved and maintained for at least 48 h.
- A follow-up visit was scheduled for 1 to 2 weeks after initial sampling to obtain convalescent-phase serum samples for serological analysis.

Results

- Within 48 h after initiation of treatment, 19 patients (55.9%) in the doxycycline group and 23 patients (65.7%) in the azithromycin group became afebrile ($P = 0.33$).
- The median time to fever clearance was 45 h (range, 8 to 118 h) in the doxycycline group and 40 h (range, 8 to 136 h) in the azithromycin group, respectively ($P = 0.45$)

Conclusion: Doxycycline is an effective choice for the treatment of both leptospirosis with comparable fever clearance compared to Azithromycin



Summary

- Leptospirosis is a zoonotic disease with worldwide distribution and increasing prevalence.
- Leptospirosis is under reported and under diagnosed in India due to a lack of awareness of the disease and lack of appropriate laboratory diagnostic facilities.
- Combining clinical expertise and awareness with confirmatory laboratory back up dramatically increases the recognition of patients with leptospirosis.
- Antibiotics are chosen based on certainty of diagnosis, cost, availability.
- Oral doxycycline at the dose of 200 mg twice daily is drug of choice for leptospirosis, azithromycin and oral penicillins are reasonable alternatives.