

# *Leptospirosis*

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- Introduction
- Bacteriology
- Epidemiology
- Pathogenesis
- Clinical Features
- Laboratory Diagnosis
- Management

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# Introduction

- Emerging infectious disease
- Resurgence of international interest related to outbreaks following flooding as a result of El Niño related excess rainfall
- Zoonosis
- Ubiquitous

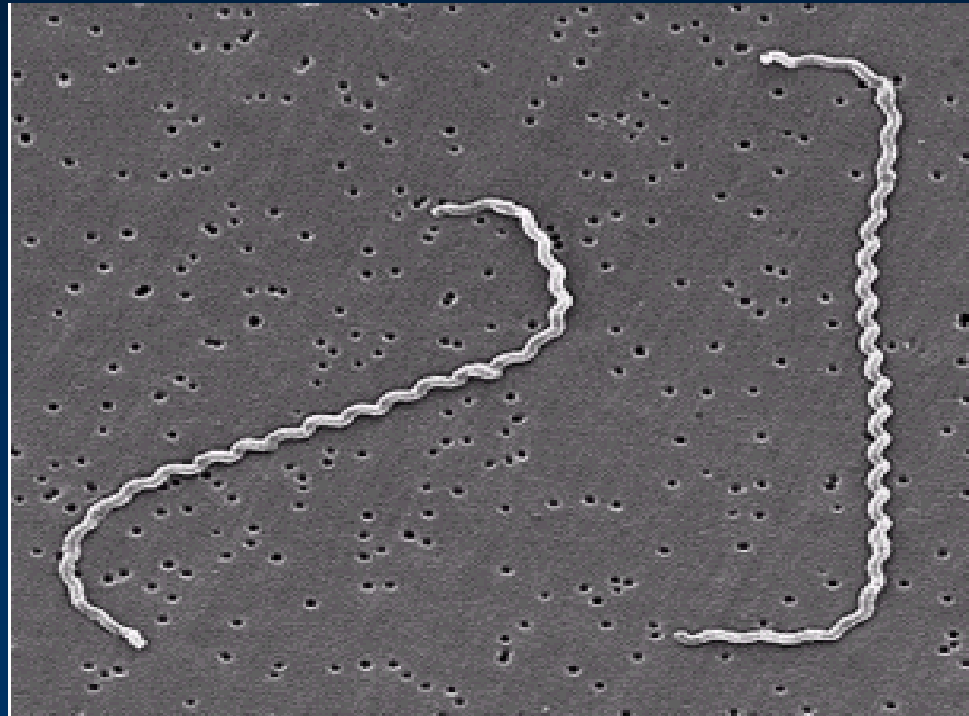
- Wide spectrum of human disease
- Recognized as occupational hazard in ancient China & Japan
- Icteric leptospirosis with renal failure 1<sup>st</sup> reported by Adolf Weil 100 years ago
- Etiology of leptospirosis was 1<sup>st</sup> described in 1915 independently in Japan & Germany

- 2 documented cases in HK in last 15 yrs
- Exact local / global incidence unknown; it's likely that many mild cases were left undiagnosed

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- Epidemiology
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# Biology

- Gram negative spirochaetes
- $0.1\mu\text{m} \times 6 - 20\mu\text{m}$
- Right handed helix with helical amplitude of  $0.1$  to  $0.15\mu\text{m}$  and wavelength of  $0.5\mu\text{m}$
- Pointed ends bent into distinct hooks
- Two axial flagella with polar insertions



- All leptospire are morphologically indistinguishable
- Typical double membrane structure
- LPS similar to G -ve bacteria but less endotoxic

- Obligate aerobes
- Optimal growth temp: 28 – 30°C
- Use long-chain fatty acids as sole carbon source for metabolism
- Grow in media enriched with vitamins, growth factors and ammonium salts
- Produce catalase & oxidase

# Classification & Taxonomy

- Serological v.s. genotypic
- Serologic:
  - Phenotypic
  - *L interrogans* (pathogenic) v.s. *L biflexa* (saprophytic)
  - Both were subdivided into different serovars; >200 for *L interrogans* & >60 for *L biflexa*
  - Serovars that are antigenically related → serogroups

- Genotypic:
  - By means of DNA hybridization studies
  - In theory, considered to be the correct method of classification taxonomically
  - Problematic as it is incompatible with the serological classification
  - Technically difficult to perform

- Introduction
- Bacteriology
- **Epidemiology**
- Pathogenesis
- Clinical Features
- Laboratory Diagnosis
- Management

# Epidemiology

- The most widespread zoonosis in the world
- Reliable incidence data are not available because of non-specific nature of illness & diagnostic capabilities are limited in countries with highest burden of diseases
- More common in warm-climate places & developing countries

- Disease was maintained in nature by chronic infection of renal tubules in maintenance hosts
- Most important maintenance hosts are small mammals
- Distinct variations in maintenance hosts & the serovars they carry throughout the world

- Factors determined extent of transmission:
  - Climate
  - Population density
  - Degree of contact
  
- Route of acquisition:
  - Abrasions & cuts in skin
  - Mucous membrane / conjunctiva
  - ? Intact skin after prolonged immersion in water
  - Inhalation of aerosols / water
  - Ingestion of water
  - Animal bites
  - Mother to infant

TABLE 5. Documented outbreaks of leptospirosis associated with water

Place and yr	No. of cases	Exposure	Source of infection	Presumptive serogroup	Reference
Lisbon, Portugal, 1931	126	Drinking from water fountain	Contamination by rat urine	Unknown	315
Greece, 1931	31	Drinking water in a cafe	Contamination by rat urine	Unknown	457
Philadelphia, 1939	7	Swimming in a creek	Contamination by rat urine	Icterohaemorrhagiae; serovar icterohaemorrhagiae isolated from one case	272
Georgia, 1940	35	Swimming in a creek	Contamination by offal and a dead cow	Unknown	75
Wyoming, 1942	24	Swimming in a pool	Unknown	Canicola	120
Okinawa, 1949	16	Swimming in a pond	Unknown	Autumnalis	236
Alabama, 1950	50	Swimming in a creek	Suspected to be pigs	Pomona	503
Georgia, 1952	26	Swimming in a creek	Suspected to be dogs	Canicola	628
Russia, 1952	Not stated	Swimming in a lake	Suspected to be pigs and/or rats	Canicola	597
Japan, 1953	114	Swimming in a river	Suspected to be dogs	Canicola; serovar canicola isolated	396
Russia, 1954	62	Drinking and bathing in well water	Contamination by pigs	Serovar pomona isolated	68
South Dakota, 1956	3	Swimming in a river	Unknown	Pomona	304
Florida, 1958	9	Swimming in a stream	Contamination by cattle and/or pigs	Serovar pomona isolated from pigs	121
Iowa, 1959	40	Swimming in a stream	Contamination by cattle	Serovar pomona isolated from two cases and from cattle	79
Washington, 1964	61	Swimming in a canal	Suspected to be cattle	Pomona; serovar pomona isolated from cattle	414
Tennessee, 1975	7	Swimming in a creek	Unknown	Grippotyphosa	26
Buenos Aires, Argentina, 1976	10	Swimming in a drainage canal	Suspected to be pigs	Pomona; Pomona serogroup isolated from patients	93
Italy, 1984	35	Drinking from water fountain	Dead hedgehog in header tank	Australis	92
Missouri, 1985	4	Kayaking in creek during flooding	Unknown	Djasiman	306
Morón, Cuba, 1986	6	Swimming in a canal	Suspected to be dogs	Canicola	277
Okinawa, Japan, 1987	22	Swimming in a pool or jungle training	Unknown	Shermani	130
Kauai, Hawaii, 1987	8	Swimming in a river	Suspected to be cattle	Australis; serovars bangkok and bataviae isolated	320
São Paulo, Brazil, 1987	23	Swimming in a pool with river water	Unknown	Pomona	153
Illinois, 1991	5	Swimming in a pond	Unknown; several animal species seropositive	Grippotyphosa; serovar grippotyphosa isolated from patients and water	302
Kauai, Hawaii, 1992	8	Swimming in a waterfall	Unknown	Australis; serovar bangkok isolated	321
Costa Rica, 1996	9	White water rafting	Unknown	Unknown	482
Barbados, 1997	2	Swimming in a pond	Unknown	Serovar bim isolated from one case	542a
Illinois & Wisconsin, 1998	74	Swimming in a lake	Unknown	Unknown	98

- ‘At-risk’ activities:
  - Occupational:
    - Direct contact: farmers, veterinarians, abattoir workers, meat inspectors, rodent control workers, etc
    - Indirect contact: sewer workers, miners, soldiers, septic tank cleaners, fish farmers, canal workers, farmers, sugar cane cutters, etc
  - Recreational:
    - Swimming, canoeing, rafting, fresh water fishing, caving, etc
  - Avocational:
    - Bare foot walking in damp conditions, gardening with bare hands, contamination of drinking water, etc

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- Epidemiology
- **Pathogenesis**
- Clinical Features
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# Pathogenesis

- Toxin production:
  - LPS: endotoxic but potency is low
  - Haemolysin: sphingomyelinase, phospholipase C, pore forming protein
  - Cytotoxin
- Outer envelope: antiphagocytic component
- Outer membrane proteins: role in interstitial nephritis

- Immune mechanisms:
  - Immune complex mediated inflammation:
    - deposition of immune complexes in kidney interstitium, wall of small blood vessels
    - Circulating immune complex level fall concurrently with clinical improvement
  - Cross reaction of anti-leptospiral antibodies to body tissue → uveitis
  - Autoantibodies: anti-platelet, anticardiolipin, ANCA
  - Apoptosis: stimulated by LPS via induction of TNF- $\alpha$

- Introduction
- Bacteriology
- Epidemiology
- Pathogenesis
- **Clinical Features**
- Laboratory Diagnosis
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# Clinical Features

- Wide spectrum of presentations
  - Mild or subclinical infection, especially those who have frequent exposure
  - Self-limiting systemic illness for 90% of patients who had initial exposure
  - Severe, potentially fatal illness illness accompanied by any combination of liver failure, renal failure & pneumonitis with bleeding diathesis
- Severe disease in human frequently due to *seovar icterohaemorrhagiae*

- The specific serovars involved depend largely on geographic location & ecology of maintenance hosts, e.g. serovar *lai* is common in SE Asia
- Biphasic clinical presentation
- Incubation period: 5 – 14 days
- Septicaemic phase lasted about 1 week
- Immune phase: characterized by antibody production & excretion of leptospire in urine
- Complications usually develop during the 2<sup>nd</sup> week, associated with localization of leptospire within tissue

# Anicteric Leptospirosis

- Febrile illness of sudden onset
- Chills, headache, myalgia, abdominal pain, conjunctival suffusion, rash
- Lasting about 1 week
- Fever may recur after a remission of 3 - 4 days
- Aseptic meningitis may occur
- Mortality is almost nil
- DDX: viral infection, HIV seroconversion, dengue, glandular fever, Hantavirus infection, rickettsiosis, typhoid, brucellosis, malaria

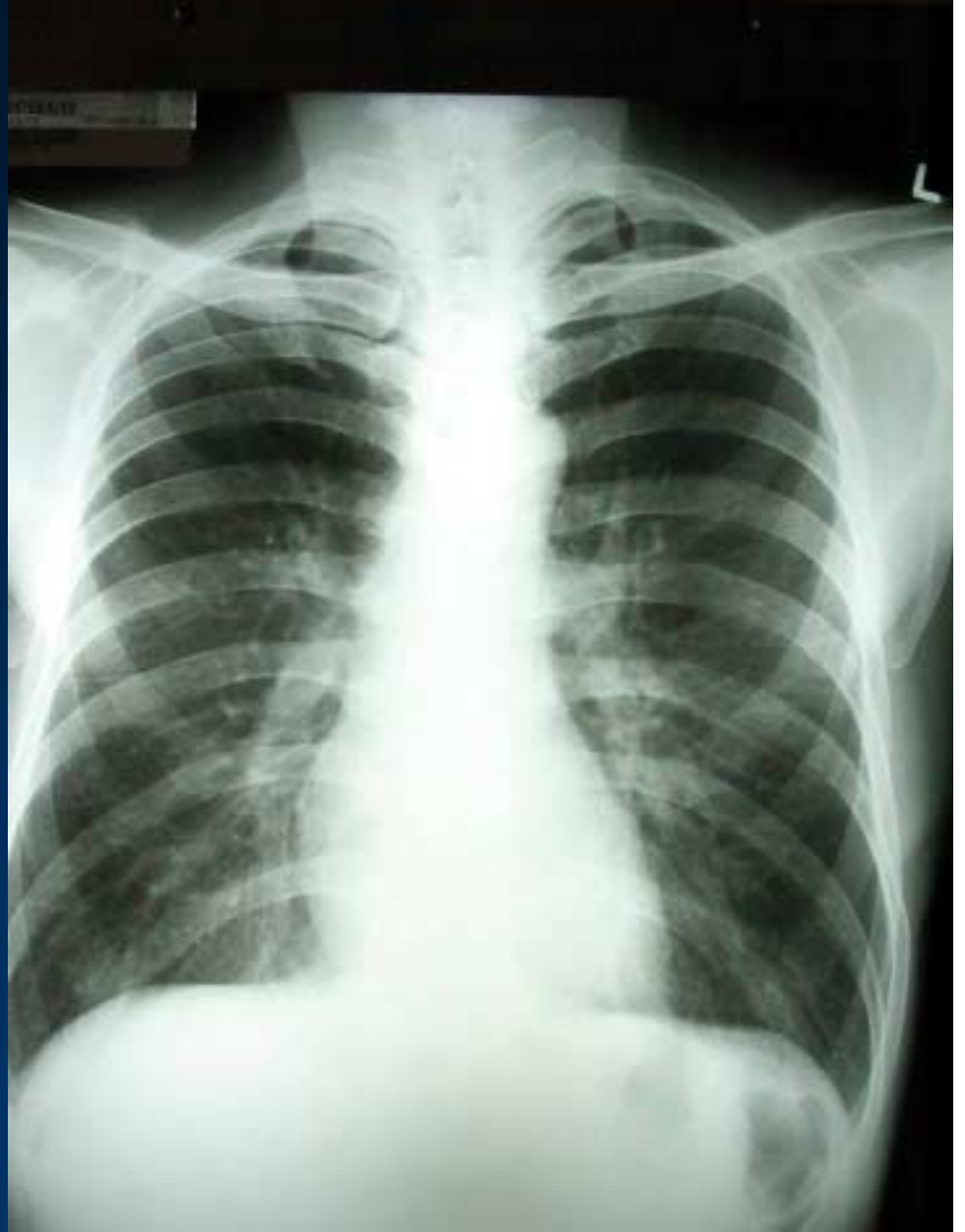
# Icteric Leptospirosis

- 5 – 10 % of cases
- Mortality: 5 – 50 %
- Acute phase illness preceded by few days' of improvement, with high fever and rapid progression to liver failure, renal failure, pneumonitis, cardiac arrhythmia or circulatory collapse

- Liver damage
  - Resulted from injury of liver capillaries in the absence of frank hepatocellular necrosis
  - Hepato +/- splenomegaly  $\geq 25\%$
  - Bilirubin may be grossly elevated
  - moderate rise of transaminase & mildly elevated ALP
  - hypoprothrombinaemia was uncommon
  - CPK (MM fraction) may be grossly elevated

- Renal damage:
  - Mainly due to interstitial nephritis
  - Abrupt onset of renal impairment with progression to oliguria during 2<sup>nd</sup> week of illness
  - Frequently associated with jaundice
  - Accompanied by thrombocytopenia without evidence of DIC

- Pulmonary damage:
  - May occur in the absence of renal or liver failure
  - Pulmonary haemorrhage
  - Cough, dyspnea, haemoptysis, ARDS
  - Radiographic changes include diffuse small opacities which may coalesce, pleural effusion



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- Cardiac damage:
  - Myocarditis, coronary arteritis and aortitis
  - Strong association with pulmonary involvement in several case series
  - Presented with features of CHF, arrhythmia & sudden circulatory collapse

# Ocular Involvement

- Conjunctival suffusion
- Uveitis which may persists for long time
- Immune phenomenon

# Other Complications

- Infection in pregnancy associated with abortion and fetal death
- Other reported complications: CVA, rhabdomyolysis, TTP, acalculous cholecystitis, erythema nodosum, epididymitis, nerve palsy, GBS, reactive arthritis

# Chronic or Latent Infection

- Possibility of chronic infection, like those produced by other spirochetal infection, was suggested
- Other than uveitis, objective evidence is lacking to support this view currently

# Immunity

- Largely humoral
- Immunity is strongly restricted to the homologous serovar or closely related serovars

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# General Lab Findings

- Anicteric disease:
  - Elevated ESR
  - WCC from below normal to moderately elevated
  - slight elevation of transaminase, ALP and bilirubin
  - Proteinuria, sterile pyuria +/- microscopic haematuria, hyaline & granular casts
  - LP: normal to slightly elevated pressure, normal glucose, normal or slightly elevated protein, elevated WCC with lymphocyte predominance

- Severe cases:
  - Elevated WCC with left shift, thrombocytopenia, renal impairment, deranged liver function with disproportional rise of bilirubin, grossly elevated CPK

# Microscopic Demonstration

- Dark field microscopy / immunofluorescence / appropriate staining
- Specimen: body fluid e.g. blood, urine, CSF
- Insensitive and non-specific

# Isolation of Leptospire

- 1<sup>st</sup> week: blood, CSF, dialysate
- Urine: beginning of 2<sup>nd</sup> week. Duration of excretion varies
- Special semi-solid medium containing 5-fluorouracil
- Slow growing, examined weekly with dark field microscopy for 13 weeks before being discarded
- Identification by serological or molecular techniques . Limited number of labs which can perform the identification

# Serological Diagnosis

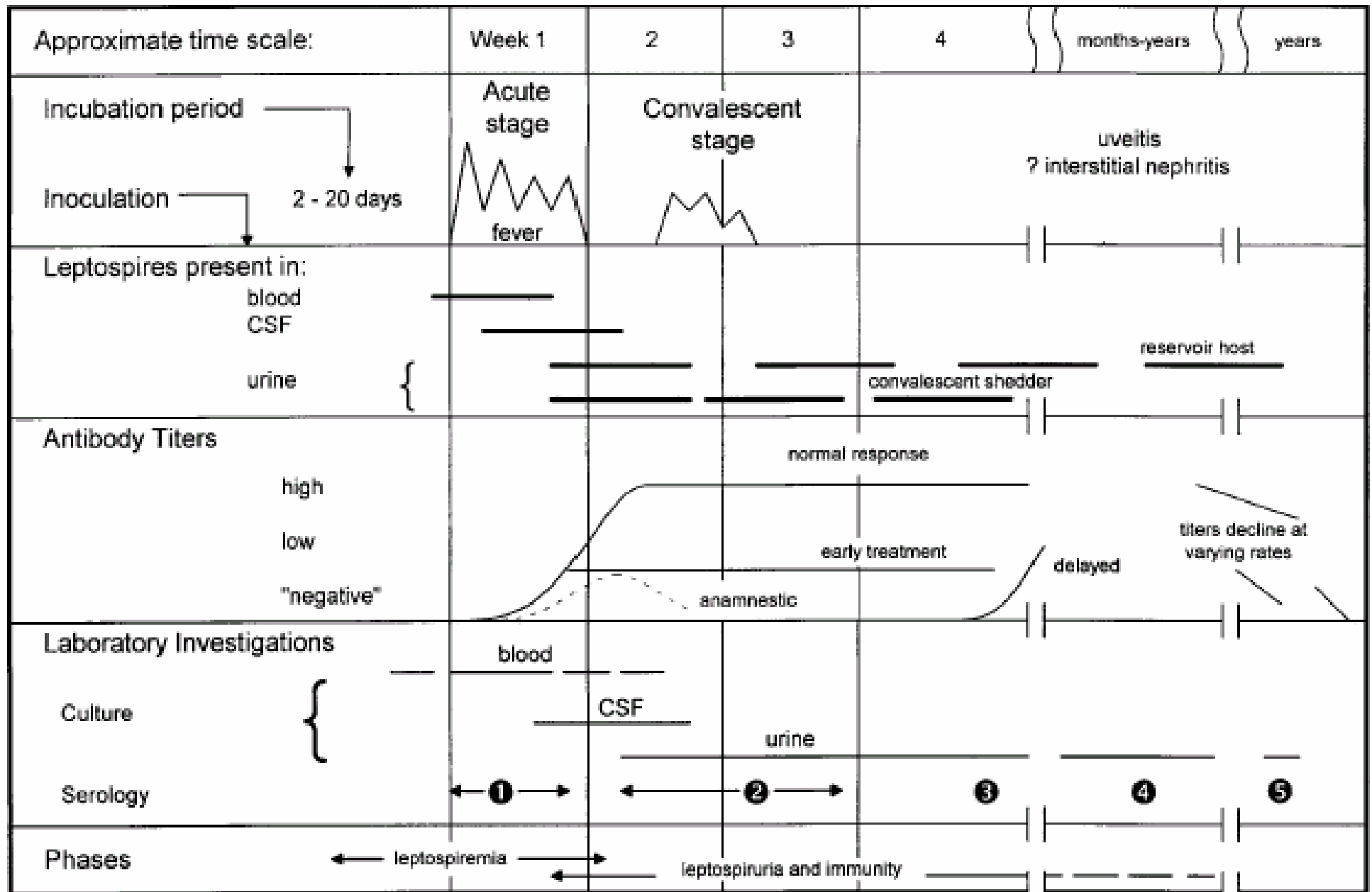
- Antibodies start to appear in blood about 5 – 7 days after onset of illness
- Gold standard: microscopic agglutination test (MAT)
- CDC case definition: a titre of  $\geq 200$  with clinically compatible illness
- Cut-off value depends on seroprevalence

- Titres following acute infection may be extremely high ( $\geq 25600$ ) and take months or even years to fall to low level
- Rarely, seroconversion may be delayed for many weeks after recovery
- “paradoxical response” vs. “anamnestic response”

- Other serologic methods: RIA / ELISA
- More sensitive and comparable specificity to MAT
- Commercial dipstick test methods available for rapid diagnosis

# Molecular Diagnosis

- PCR based methods for diagnosis
- Restriction endonuclease (REA), restriction fragment length polymorphism (RFLP), PCR based methods and PFGE for identification



NB 1,2: acute phase sample; 3 convalescent phase sample; 4,5: follow-up sample

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# Treatment

- Out-patient management for those with mild symptoms
- LP sometimes required for relief of headache
- Admitted for observation for those with more severe symptoms
- ICU care for those with icteric leptospirosis

## Dupont H et al. CID 1997 Sep; 25: 720-4

- Retrospective study in an emergency department between 1989 and 1993
- 68 patients, 56 (82%) were discharged from the hospital, and 12 (18%) died
- Independent predictors of mortality:
  - dyspnea (OR, 11.7; 95% CI, 2.8–48.5;  $P < 0.05$ )
  - oliguria (OR, 9; CI, 2.1–37.9;  $P < 0.05$ )
  - WCC  $> 12,900/\text{mm}^3$  (OR, 2.5; CI, 1.8–3.5;  $P < 0.01$ )
  - repolarization abnormalities on electrocardiograms (OR, 5.9; CI, 1.4–24.8;  $P < 0.01$ )
  - alveolar infiltrates on chest radiographs (OR, 7.3; CI, 1.7–31.7;  $P < 0.01$ )

- McClain JB et al. Ann Intern Med 1984 May; 100(5): 696-8
  - 29 patients
  - randomised, double-blinded trial with doxycycline 100 mg orally twice a day or placebo for 7 days; followed for 3/52
  - Duration of illness before therapy and severity of illness were the same in both groups
  - Doxycycline reduced the duration of illness by 2 days and favorably affected fever, malaise, headache, and myalgias. Treatment prevented leptospiruria

- Watt G et al. Lancet 1988 Feb 27; 1(8583): 433-5
  - 42 patients
  - 7-day course of i.v. penicillin (6 MU/day) on severe, advanced leptospirosis in a randomised, placebo-controlled, double-blind fashion
  - Fever >2x as long in the placebo group (11.6 [SD 8.34] days vs. 4.7 [4.19] days,  $p < 0.005$ )
  - Creatinine rise persisted >3x as long in the placebo group (8.3 [8.46] days vs. 2.7 [1.90] days;  $p < 0.01$ )
  - Penicillin also shortened the hospital stay and prevented leptospiruria

- Takafuji ET et al. NEJM 1984 Feb 23; 310(8): 497-500
  - Randomized, double-blind, placebo-controlled field trial
  - Doxycycline (200 mg) or placebo on a weekly basis and at the completion of training to 940 volunteers from two U.S. Army units deployed in Panama for approximately three weeks of jungle training.
  - 20 cases of leptospirosis occurred in the placebo group (an attack rate of 4.2 per cent), as compared with only one case in the doxycycline group (attack rate, 0.2 per cent, P less than 0.001), yielding an efficacy of 95.0 per cent

- Drugs of choice:
  - Severe disease:
    - Penicillin 1.5MU q6h iv
    - Ampicillin 0.5 - 1 gm q6h iv
  - Mild disease:
    - Doxycycline 100mg BD po
    - Ampicillin 500 – 750mg q6h po
    - Amoxicillin 500mg q8h po

N.B. Watch out for Jarisch-Herxheimer rxn
- Doxycycline 200mg once weekly for prophylaxis

- Panaphut et al. CID 2003 Jun 15; 36: 1507-13
  - A prospective, open-label, randomized trial in Northern Thailand
  - 173 patients with severe leptospirosis were randomly assigned to be treated with either intravenous ceftriaxone (1 g daily for 7 days) or intravenous penicillin G (1.5 million U every 6 h for 7 days)
  - Primary outcome: time to fever resolution
  - Median duration of fever was 3 days for both groups.
  - Ten patients (5 in each group) died of leptospirosis infection
  - No statistically significant differences in the duration of organ dysfunction

# Immunization

- Limited success so far
- Needs to give vaccine containing serovars representative to those present in the population to be immunized

# Summary

- A ubiquitous pathogen with protean manifestations
- High index of suspicion: fever + constellations of C/F (esp. conjunctival suffusion) + appropriate hx of exposure
- Serology for Dx
- Supportive care + antimicrobial therapy; watch out for complications

*Thank You!*