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SEIZURES AND COMA IN A TRAVELLER RETURNING FROM THE TROPICS

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TRANSPARENCY DECLARATION

No conflicts of interest relating to this presentation

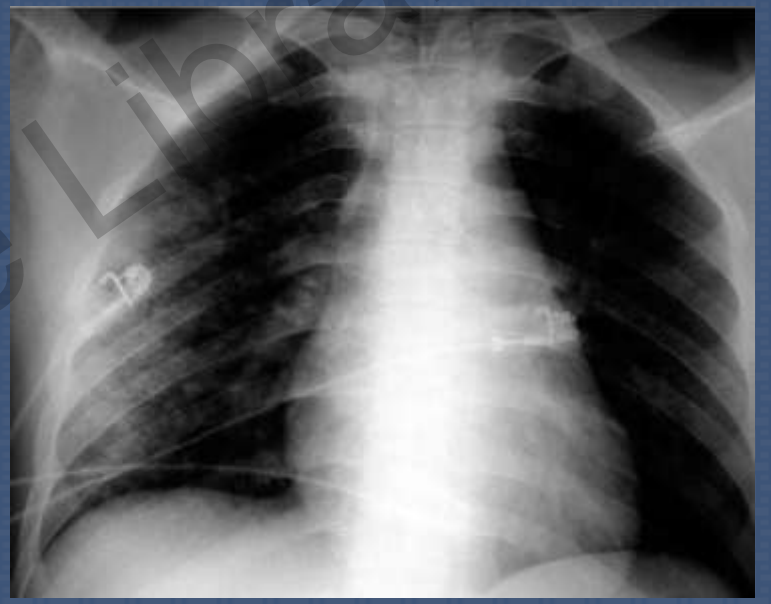
CASE PRESENTATION

- Male 28 years old, without significant medical history
- Spent 8 days in Malaysia with his girlfriend (including a 2 day trip in Malaysian Borneo district for rafting)
- Residence in 5 star hotel, no consumption of non-commercial food or drinks
- No contact with animals or insect bites
- Malaria prophylaxis with atovaquone proguanil and good anti-mosquito protective measures
- Pre-travel consultation: had previous effective vaccination against hepatitis B and A
- He had a superficial abrasion in his left foot during outdoor activities without evidence of infection

CASE PRESENTATION

- Day 3 of his return:mild symptoms of illness, fever 38.0°C, sore throat, headache
  - Treated with paracetamol, symptoms disappeared after 48 hours of bed rest
- On day 14, he develops new fever up to 39°C, malaise, myalgias, retroorbital headache, vomiting, diarrhea and mild erythematous rash of the trunk
  - His girlfriend found him unconscious at home
  - On the way to the hospital he developed seizures

CASE PRESENTATION



- Glasgow coma scale 5
- Meningism
- Dyspnoea, tachypnea (RR 32/min), Hypoxia (SaO2 90%, FiO2 0.6)
- Bilateral Ronchi, Xray: bilateral alveolar –interstitial infiltrates, peripherally
- Oliguria, metabolic acidosis pH 7.29; base excess, – 6.1 mmol/L
- Electrocardiogram (ECG): sinus tachycardia (110bpm) with inferolateral T wave inversion
- Arterial blood pressure 90/55 mmHg

CASE PRESENTATION
LAB TESTS AT HOSPITAL ADMISSION

- HT 30%
- HB 9.2mg/dL
- PLT 70 000/mm3
- WBC 13 000 /mm3 (Poly 48%, Lympho 40%, Eo 0.2%)
- Urea 120mg/dL
- Creatinine 4.8 mg/dL
- Gluc 95mg/dL

ALT 1228 IU/L

AST 2301 IU/L

ALP 430 IU/L

Gt 65 IU/L

Tbil 14.1 mg/dL

Dbil 10.9 mg/dL

Urinalysis: granular casts, WBCs, protein ++

Q1: WHICH IS THE MOST PROBABLE DIAGNOSIS?

1. Malaria
2. Viral Encephalitis/meningitis
3. Typhoid fever
4. Rickettsial infection
5. Eosinophilic meningitis
6. All the above
7. Other

RELATIVE RISKS FOR TRAVELLERS

Risk	Illness
High	Acute viral gastroenteritis, *E coli* enteritis, upper respiratory infection
Moderate	Salmonella, shigella, campylobacter, giardia, hepatitis A, gonorrhoea, chlamydia, herpes simplex, dengue, Epstein-Barr, malaria (without chemoprophylaxis)
Low	Malaria (with chemoprophylaxis), amoebiasis, leptospirosis, typhoid, cholera, HIV, HBV, syphilis, chancroid, Lyme, schistosomiasis, tuberculosis, ascariasis, enterobiasis, strongyloidiasis, trichuriasis, rubella, rubeola, rickettsioses, borreliosis, tropical sprue
Very low	Yellow fever, rabies, anthrax, plague, trypanosomiasis, viral haemorrhagic fevers, filariasis, flukes, toxocariasis, diphtheria, legionella, tularaemia, melioidosis, poliomyelitis, echinococcosis, trichinosis, gnathostomiasis, anisakiasis, yaws, pinta, LGV

Spira A, Lancet 2003; 361: 1459–69

Q2: WHAT FURTHER TESTS WOULD YOU ASK?

1. Brain MRI
2. Malaria testing
3. Serology for WNV, CHIKGV, Dengue, arboviruses, rickettsiae, leptospira and tuberculosis testing
4. All the above
5. Other

CASE 2
ON ADMISSION

Radiology

- U/S abdomen: mild hepatomegaly and splenomegaly
- Brain C/T: non significant

Lumbar puncture

- Lymphocytic pleocytosis (385 cells/mm3, lymphocytes 90%)
- Gluc: within normal range
- Protein slightly elevated
- Gram stain and latex negative
- PCR for bacterial pathogens: negative

CASE PRESENTATION

- Over the next 2 days, his condition deteriorated
- High fevers, tachycardia (heart rate, 120/min), hypotensive (BP 80/64 mmHg), hypoxia (PO_2, 71.9 mmHg; FIO_2, 0.6), jaundice (bilirubin, 18.5mg/dL), progressive renal failure (creatinine, 6.1 mg/dL)
- On day three in the ICU
  - The white cell count was 16 400/mm3 and the platelet count dropped to 10 000/mm3
  - He became anuric (renal replacement treatment started), developed new seizures and ARDS
  - He developed rrhabdomyolysis with creatinine phosphokinase (8037 IU/L [RR, 0–250 U/L])

MANAGEMENT

- Intubation/mechanical ventilation
- Fluids+inotropes, PLT-blood transfusions
- Artesunate+doxycycline iv
- Ceftriaxone
- Serial malaria smears

ED EVALUATION OF THE FEBRILE TRAVELER

1. What infections are **possible** given the patient's travel history
2. What infections are **probable** given the patient's medical history and presentation
3. What infections are **life-threatening** or **contagious** or both

PRACTICAL APPROACH TO AN III TRAVELER WITH SEIZURES AND COMA

Diagnosis

- **Basic blood work (CBC, BMP, LFT, urinalysis, blood cultures)**
- **Thick and thin blood film**
- **Imaging studies (CT, MRI)**
- **Lumbar puncture**
- **Special tests (EEG)**
- **Serology and viral identification**

Han M, Neurologist. 2005 January ; 11(1): 30–44

BMP indicates basic metabolic panel; CBC, complete blood picture; EEG; electroencephalogram; LFT, liver function test

LABORATORY RESULTS

- Thick and thin blood films examined twice for malaria parasites were negative
- Blood cultures were negative
- Targeted testing was negative for:
  - Dengue fever , CHIKG (serology)
  - WNV (serology and PCR in blood and CSF)
  - Rickettsia (serology), Leptospiras (serology)
  - Influenza viruses A and B (antigen, serology)
  - Adenovirus, Enteroviruses (PCR)
  - Toxoplasma (serology)
  - Legionella (urine antigen, serology)
  - Cytomegalovirus (serology, PCR), Epstein–Barr virus (serology)
  - HIV (ELISA , PCR)

Q3: WHAT ARE YOUR THOUGHTS NOW?

1. Malaria
2. Viral Encephalitis
3. Rickettsial infection
4. Leptospirosis
5. All the above are still possible
6. Other

PRE TRAVEL COUNSELLING-MALAYSIA

Malaria √

Areas with malaria: Present in rural areas of Malaysian Borneo (Sabah and Sarawak Provinces) and to a lesser extent in rural areas of Peninsular Malaysia.

Estimated relative risk of malaria for US travelers: Low.

Drug resistance: Chloroquine.

Malaria species: *P. falciparum* 40%; *P. vivax* 50%; remainder *P. Knowlesi, P. malariae, and P. ovale. P. knowlesi* reported to cause 28% of cases in Sarawak and known to cause cases in both Malaysian Borneo and Peninsular Malaysia.

Recommended chemoprophylaxis: Atovaquone-proguanil, doxycycline, or mefloquine.

Yellow Fever √ (not required)

Requirements: Required if traveling from a country with risk of YFV transmission and ≥1 year of age, including transit >12 hours in an airport located in a country with risk of YFV transmission

Other Vaccines to Consider

Routine, hepatitis A & B, typhoid, Japanese encephalitis, and rabies

http://wwwnc.cdc.gov/travel/yellowbook/2014

PRACTICAL APPROACH TO AN III TRAVELER

Travel history: date and places visited	√
Fever: duration, pattern	Biphasic?
Potential exposures:	
Travel to rural areas	√
Sexual exposure	?
Freshwater swimming	√
Climatic conditions, season (rainy)	√
Ingestion of contaminated food	X
Insect or animal bites	X
Exposure to ill people or injuries	√
Vaccination history	√
Use of prophylactic medication and compliance	√
Use of protective equipment	√
Immune status	√

Adapted from Spira A, Lancet 2003; 361: 1459–69

INCUBATION PERIODS

PATHOGENS CAUSING CNS INVOLVEMENT IN THE RETURNED TRAVELLER

Short (<10 days)

- Viral haemorrhagic fevers
  - Dengue Fever
  - Yellow Fever
  - Arboviral infections
- Enteric bacterial infections (including paratyphoid)
- Enteric viral infections
- Rickettsioses: louse, flea-borne, typhus
- Pneumonia, Influenza
- Anthrax
- Bacterial meningitis

Medium (11-21 days)

- Malaria (particularly P. falciparum)
- Typhoid fever
- Leptospirosis
- Rickettsioses: scrub typhus, spotted fever group, Q fever
- Brucellosis
- Enteric protozoal infections
- Enteric hepatitis
- Strongyloides
- Lyme
- African trypanosomiasis

Long (>30 days)

- Malaria
- Viral hepatitis
- Schistosomiasis
- Tuberculosis
- Amoebic liver abscess
- Enteric protozoal infections
- Enteric helminthic infections
- HIV
- Rabies
- Leishmaniasis
- American trypanosomiasis

PRACTICAL APPROACH TO AN ILL TRAVELER WITH SEIZURES AND COMA

Management

- Treat potential life-threatening complications
- Assess for neurologic emergencies (status epilepticus, stroke, spinal cord compression)
- Consider empiric broad-spectrum antibiotic, antiviral or antiparasitic coverage for very ill patients
- Consult tropical or travel medicine expert

CNS INVOLVEMENT AND FEVER AND THROMBOCYTOPENIA/PETECHIAES

- Severe malaria
  - Coma, lethargy, delirium, seizures, retinal haemorrhages
- Dengue Haemorrhagic Fever
- Leptospirosis, Rickettsial infections
  - Mental Status changes, seizures
- Meningococcaemia,
- Yellow fever, viral haemorrhagic fevers,

Spira AM, Lancet. 2003 ;361(9367):1459-69

DIFFERENTIAL DIAGNOSIS OF PHYSICAL FINDINGS FOR SOME TRAVEL DISEASES

Lymphadenopathy	•Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, lymphogranuloma venereum, Lassa fever
Hepatomegaly	•Malaria, leishmaniasis, amoebic liver abscess, typhoid, hepatitis, leptospirosis
Splenomegaly	•Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue
Jaundice	•Hepatitis, malaria, leptospirosis, relapsing fevers, cholelithiasis, pancreatitis
Petechiae/ecchymosis	•Meningococcaemia, yellow fever, dengue, rickettsioses, viral haemorrhagic fevers, envenoming, leptospirosis
Nystagmus/diplopia	•Rabies, botulinum poisoning, neurotoxic snakebite envenoming

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Q4: IS DIAGNOSIS OF MALARIA EXCLUDED SO FAR?

1. Yes
2. No

Q5: IS DIAGNOSIS OF LEPTOSPIROSIS EXCLUDED SO FAR?

1. Yes
2. No

PITFALLS

- Malaria (serial smears, requires lab experience, rapid diagnostic methods, PCR, *P. knowlessii* infection difficult to diagnose)
- Leptospirosis (no optimal testing method)
  - Phase-specific diagnostic methods, early diagnosis difficult
- Rickettsia (fatal if not treated early, difficult to diagnose early)
- Biphasic fever
  - Dengue and leptospirosis

Spira AM, Lancet. 2003 ;361(9367):1459-69

CASE PRESENTATION

- The patient succumbed on the 10th ICU day due to multiorgan failure
- Brain haemorrhage was demonstrated on MRI
- Broad spectrum antibiotics had been added to cover nosocomial sepsis
- Fever never responded to treatment

Q6: WHICH TEST LED TO THE DIAGNOSIS?

1. PCR and/or rapid test for malaria
2. Dark field urine microscopy and repeat serology/PCR for *Leptospira spp*
3. Repeat serology for Dengue fever
4. Other

Q7:
WHICH IS THE MOST PROBABLE DIAGNOSIS?

1. Malaria
2. Dengue haemorrhagic fever
3. Leptospirosis
4. Other

DIAGNOSIS

PCR in the urine was positive for *Leptospira interrogans*

LEPTOSPIROSIS

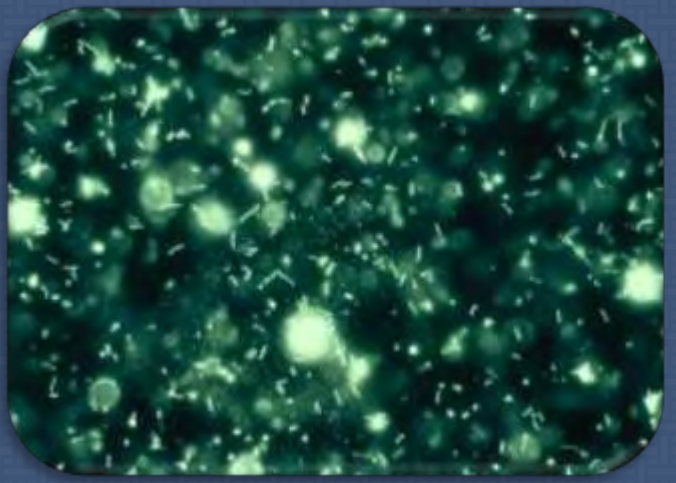
- A zoonosis of worldwide distribution (World Health Organization, 1999), caused by infection with pathogenic spirochaetes of the genus *Leptospira*
- The disease is maintained in nature by chronic renal infection of carrier mammals, which excrete the organism in their urine
- It has been recognized as an emerging infectious disease, in part because of recent large-scale outbreaks associated with recreational activities

Faine et al., 1999, Levett, 2001, Morgan et al., 2002, Sejvar et al., 2003

THE CAUSATIVE BACTERIUM

- Order Spirochaetales – Treponema, Borrelia, Leptospira
- Family – Leptospiraceae
- Genus – Leptospira, 26 serogroups, 250 serovars
- interrogans, biflex, icterohemorrhagica

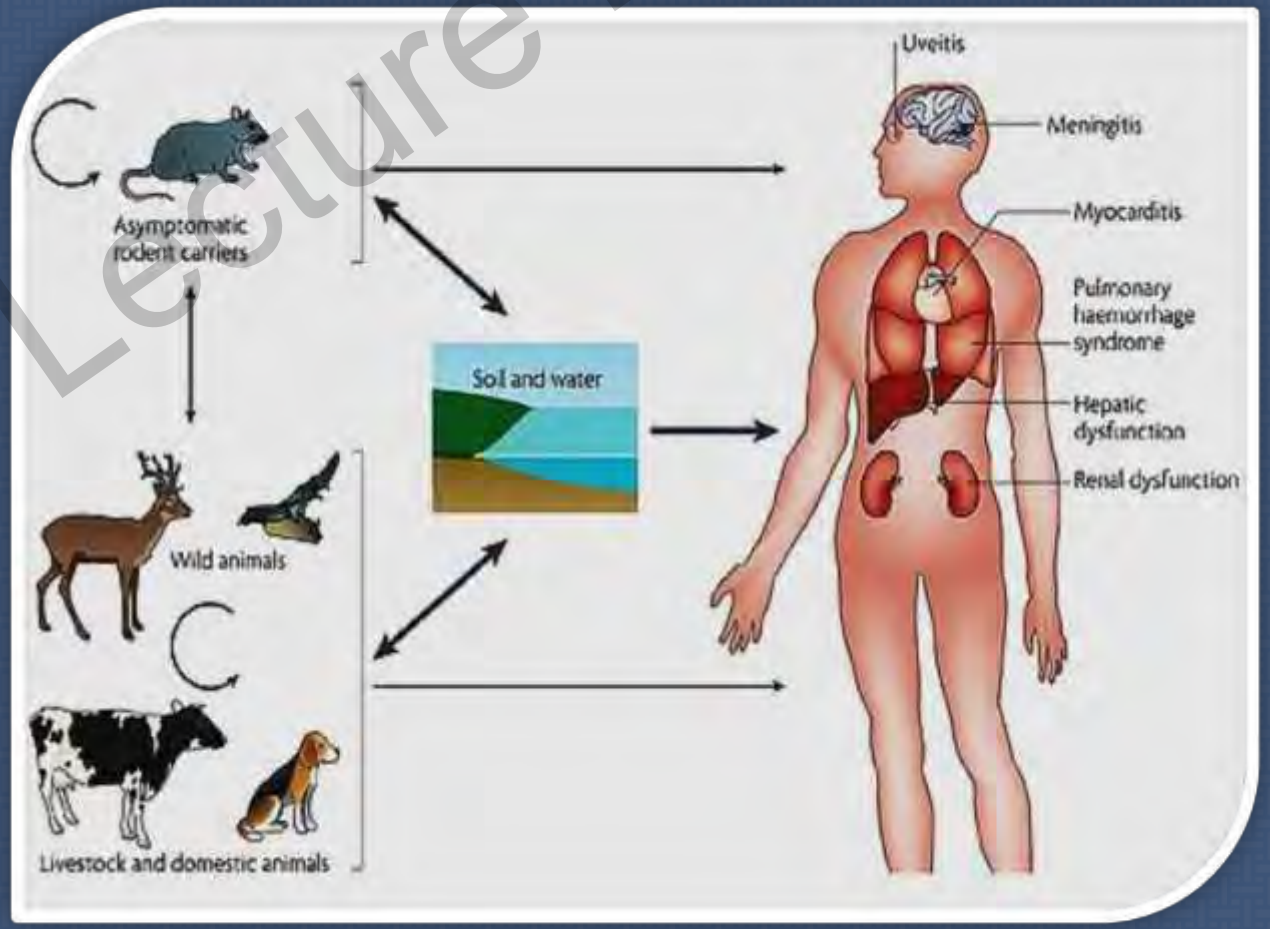
Long, Thin, Highly Coiled



Dark Field Microscopy

LEPTOSPIROSIS

- First description by Weil in 1886 synonyms: Rice fever, mud fever, canicola fever, leptospira jaundice etc
- Humans become infected through direct exposure to infected animals or their urine, or through indirect contact via contaminated water or soil, or inhalation of droplets infected from animal urine



RISK GROUPS

Rural > Urban

Male > Female (10 : 1)

Occupational exposure

Farmers – Rice, Sugarcane, Vegetables

Sewerage workers; Abattoirs, Butchers

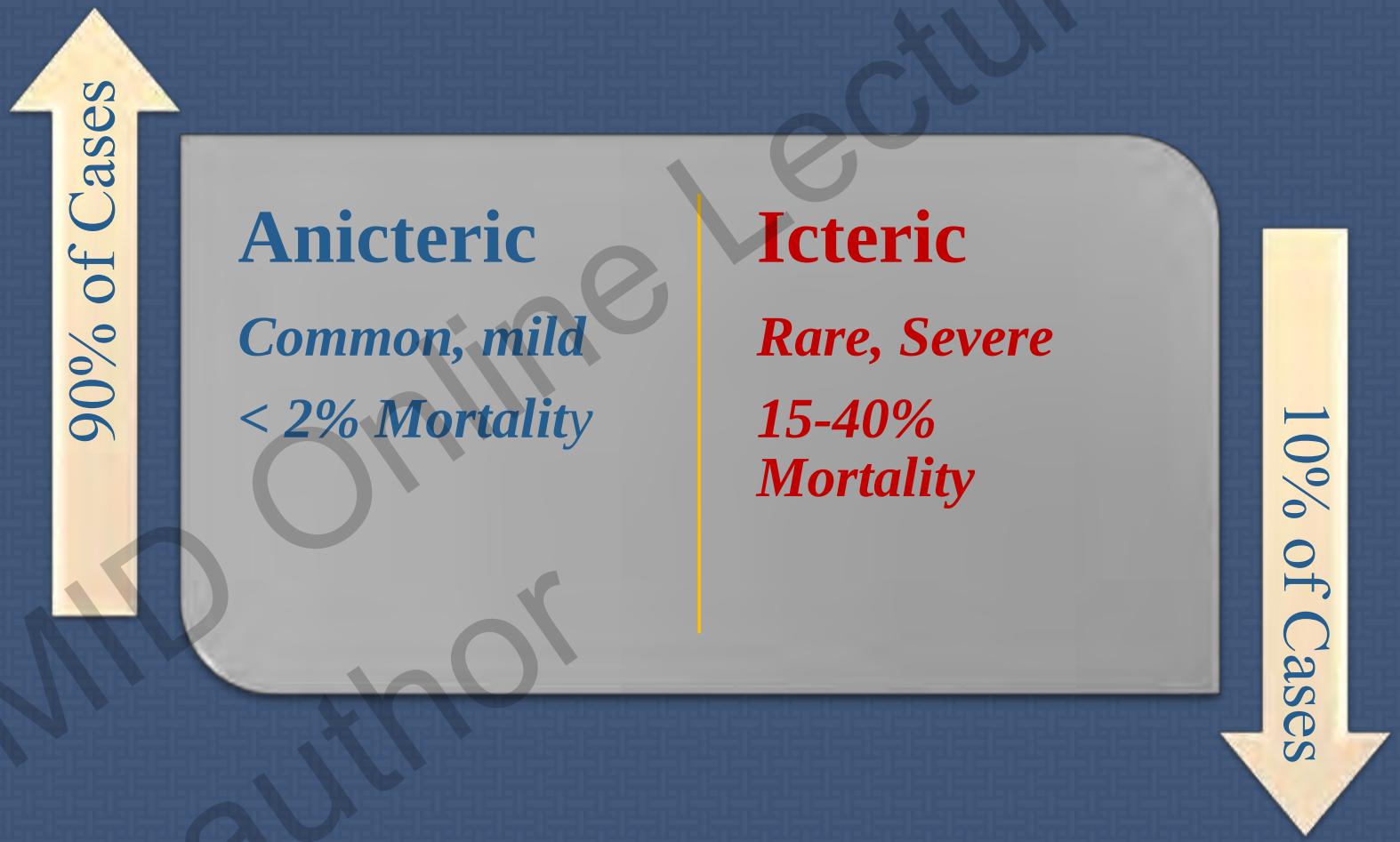
Vetenarians, Lab staff, Miners, Soldiers

Fishermen – Inland (not on the sea)

Recreational activities

Swimming, Sailing, Marathon runners, Gardening

CLINICAL PRESENTATION



	Anicteric leptospirosis		Iceteric leptospirosis (Weil's syndrome)	
Fever	First stage 3-7 days (Septicemic)	Second stage 0 days-1 month (Immune)	First stage 3-7 days (Septicemic)	Second stage 10-30 days (Immune)
Important clinical findings	Myalgia, headache, abdominal pain, vomiting, conjunctival suffusion, fever	Meningitis, uveitis rash, fever	Jaundice, hemorrhage, renal failure myocarditis	
Leptospires present	Blood, CSF, Urine		Blood, CSF, Urine	

ICTERIC LEPTOSPIROSIS

LIVER

Jaundice, occurs in 4-6 days

Serum bilirubin markedly increased (20-40 mg/dl)

AST/ALT mild elevations

Hepatocellular necrosis/intrahepatic steatosis

KIDNEYS – Mild to Severe

Urinalysis : Hematuria / Pyuria / Proteinuria

Renal Failure: Pre renal azotemia, Oliguric / Non Oliguric

HEMORRHAGIC MANIFESTATIONS

Hemorrhagic Fever - Vascular injury

Respiratory, Gastrointestinal, Renal & Genital tracts

Hemorrhagic Pneumonitis

Hemoptysis / Respiratory failure

Occurs in 2nd week (as early as 24-48 hours)

CARDIAC INVOLVEMENT

Cardiac manifestations

- Hemorrhagic Myocarditis
- Cardiomyopathy / Cardiac failure
- Arrhythmias, Hypotension / Death
- Atrial fibrillation / Conduction defects

ECG changes

- Non Specific ST-T changes
- Low voltage complexes

CNS AND OCULAR INVOLVEMENT

Aseptic Meningo-encephalitis

It is rare; It occurs in the Immune phase

CSF – proteins ⇑, lymphocytes ⇑

Convulsions, Encephalitis, Myelitis & Polyneuropathy

Ocular manifestations

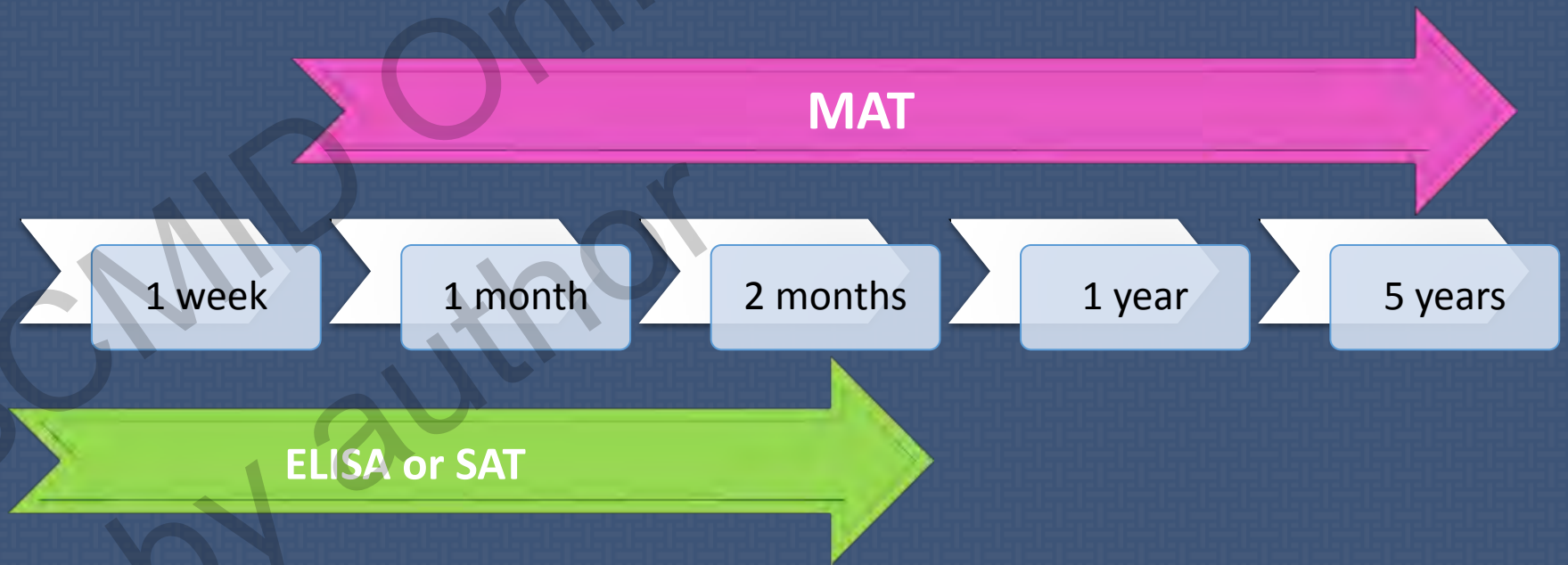
Late complication; Conjunctival suffusion/hemorrhage

Anterior uveitis, Iritis, Iridocyclitis, chorioretinitis

Occurs in 2 weeks to 1 yr. (average 6 months)

LABORATORY TESTS FOR DIAGNOSIS OF LEPTOSPIROSIS

- Early diagnosis difficult: Culture for Leptospira (delays), PCR variable, genus specific
- IgM ELISA / (M)SAT: Microscopic Slide Agglutination Test (>5day)
- Diagnosis of leptospirosis is usually accomplished retrospectively by serology
- Microscopic agglutination test (MAT); Sero conversion or 4 fold rise/ high titer



Levett, 2003

WHO GUIDE - FAINE'S CRITERIA

2	• Headache	5	• Rain fall
2	• Fever	4	• Contaminate H_20
2	• Temp > 39 F	1	• Animal contact
4	• Conjn. suffusion	15	• ELISA IgM + ve
4	• Meningism	15	• SAT positive
4	• Muscle pain	15	• MAT high titer
1	• Jaundice	25	• MAT rising titer
1	• Alb, ⇑ creatinine	Definite	• Culture positive

Score of 25 or more – Presumptive Diagnosis
Score of 20 to 25 – Possible case of leptospirosis

TREATMENT

Mild-start Rx. early

Oral Treatment 7 to 10 day

- Doxycycline 100 mg b.i.d
- Amoxicillin 500 mg q.i.d
- Ampicillin 500 mg q.i.d

Severe-start intensive Rx.

IV Treatment 5 to 7 days

- Benzyl Penicillin 20L q.i.d
- Ampicillin 1G q.i.d
- 3rd gen Ceftriaxone 1G od/ Cefotaxime 1G t.i.d

Jarisch Herxheimer Reaction

TAKE HOME MESSAGE FOR THE RETURNING TRAVELER:
FEBRILE PATIENT WITH CNS INVOLVEMENT

Except from "classic" CNS infections (viral/bacterial meningitis, encephalitis, protozoan infections of the brain), physicians should exclude:

- **MALARIA**
- **Dengue (can be fatal, particularly in repeat infections /DHF)**
- **Rickettsia/Leptospira**
  - **Can be fatal if not treated early**
  - **Difficult to diagnose**

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THANK YOU