LEPTOSPIROSIS AND MELIOIDOSIS

EMERGENCY DEPARTMENT CME

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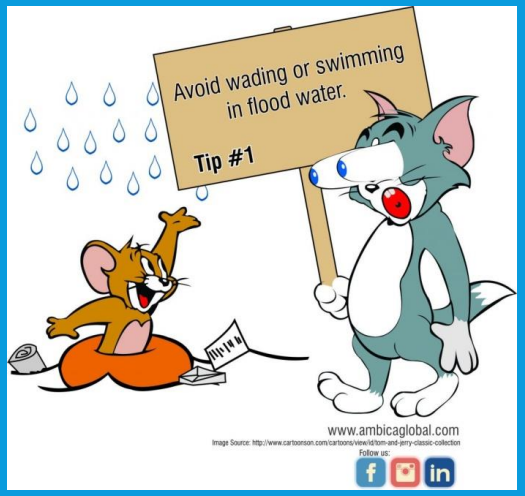
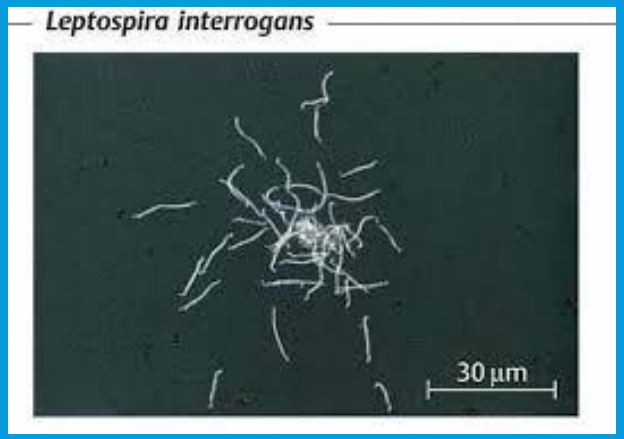
LEPTOSPIROSIS

WEIL'S DISEASE, WEIL-VASILIEV DISEASE, SWINEHERD'S DISEASE, RICE-FIELD FEVER, WATERBORNE FEVER, NANUKAYAMI FEVER, CANE-CUTTER FEVER, SWAMP FEVER, MUD FEVER, STUTTGART DISEASE, AND CANICOLA FEVER[1]





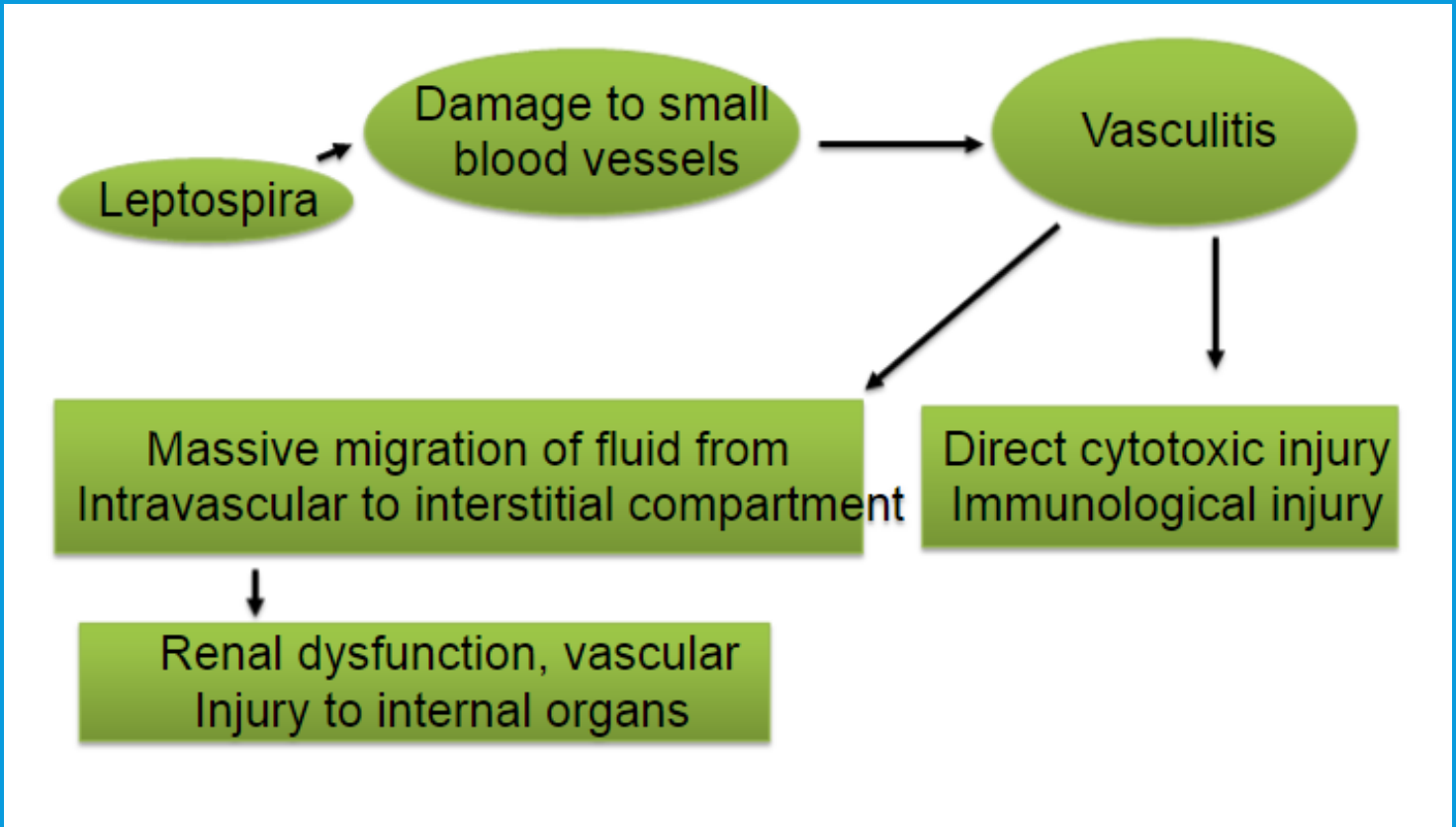
EPIDEMIOLOGY

1. Zoonosis found worldwide
2. Annual incidence ranging from 0.1 to 1 per 100 000 per year in temperate climates; 10 or more per 100 000 per year in the humid tropics [2]
3. Pathogenic *leptospires* belong to the species *Leptospira interrogans* (subdivided into more than 200 serovars with 25 serogroups)
4. *Leptospires* survive best in fresh water, damp alkaline soil, vegetation and mud with temperatures higher than 22°C
5. Starts at the onset of the rainy season and declines as the rainfall recedes

ANIMAL INFECTION [1]	1. Infects wild and domestic animals (rodents most important reservoirs for maintaining transmission) 2. Infection in rodents usually occurs during infancy → persist for long periods in the renal tubules of animals with little or no evidence of disease or pathological changes in the kidney → shed organism intermittently throughout life

HUMAN INFECTION [1]	1. Exposure to environmental sources (animal urine, contaminated water or soil, or infected animal tissue) 2. Common portals of entry: cuts or abraded skin, mucous membranes or conjunctivae 3. Risk factors: occupational exposure (farmers, sewer workers), water recreational activities, household exposure (rodent infestation, poor housing sanitation, flood-prone slums [3])

PATHOPHYSIOLOGY



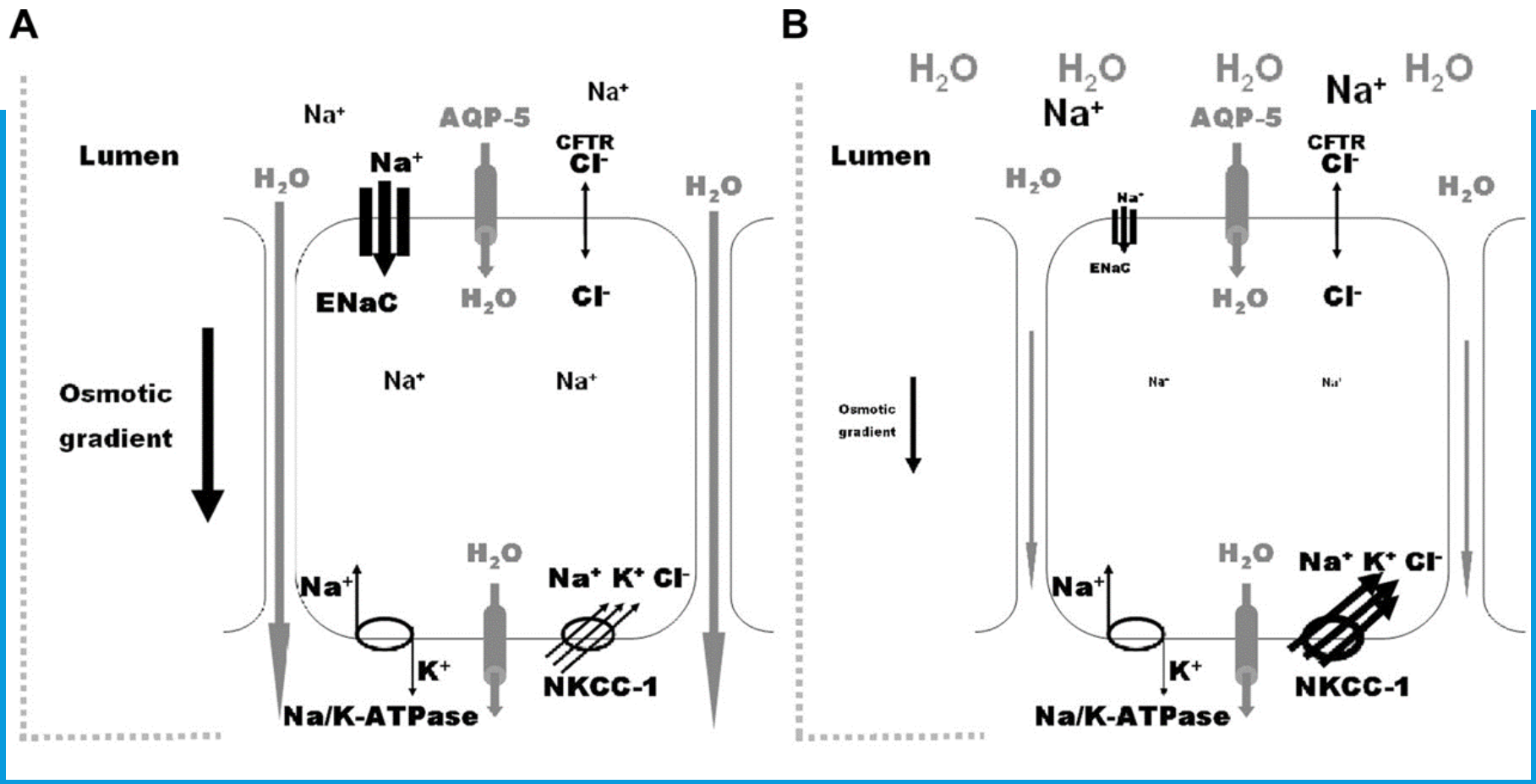


Figure 6 Andrade L, Rodriques AC, Sanches TRC, Souza RB, Seguro AC. Leptospirosis Leads To Dysregulation Of Sodium Transporters In The Kidney And Lung. American Journal Of Physiology. 2007: 292(2)

CLINICAL MANIFESTATION

1. Incubation period is usually 10 days, with a range of 2 to 30 days [2]
2. Clinical manifestations are highly variable. Typically, the disease presents in four broad clinical categories [2]:

i. Mild, influenza-like illness (ILI)

ii. Weil's syndrome characterized by jaundice, renal failure,haemorrhage and myocarditis with arrhythmias

iii. Meningitis / meningoencephalitis

iv. Pulmonary haemorrhage with respiratory failure

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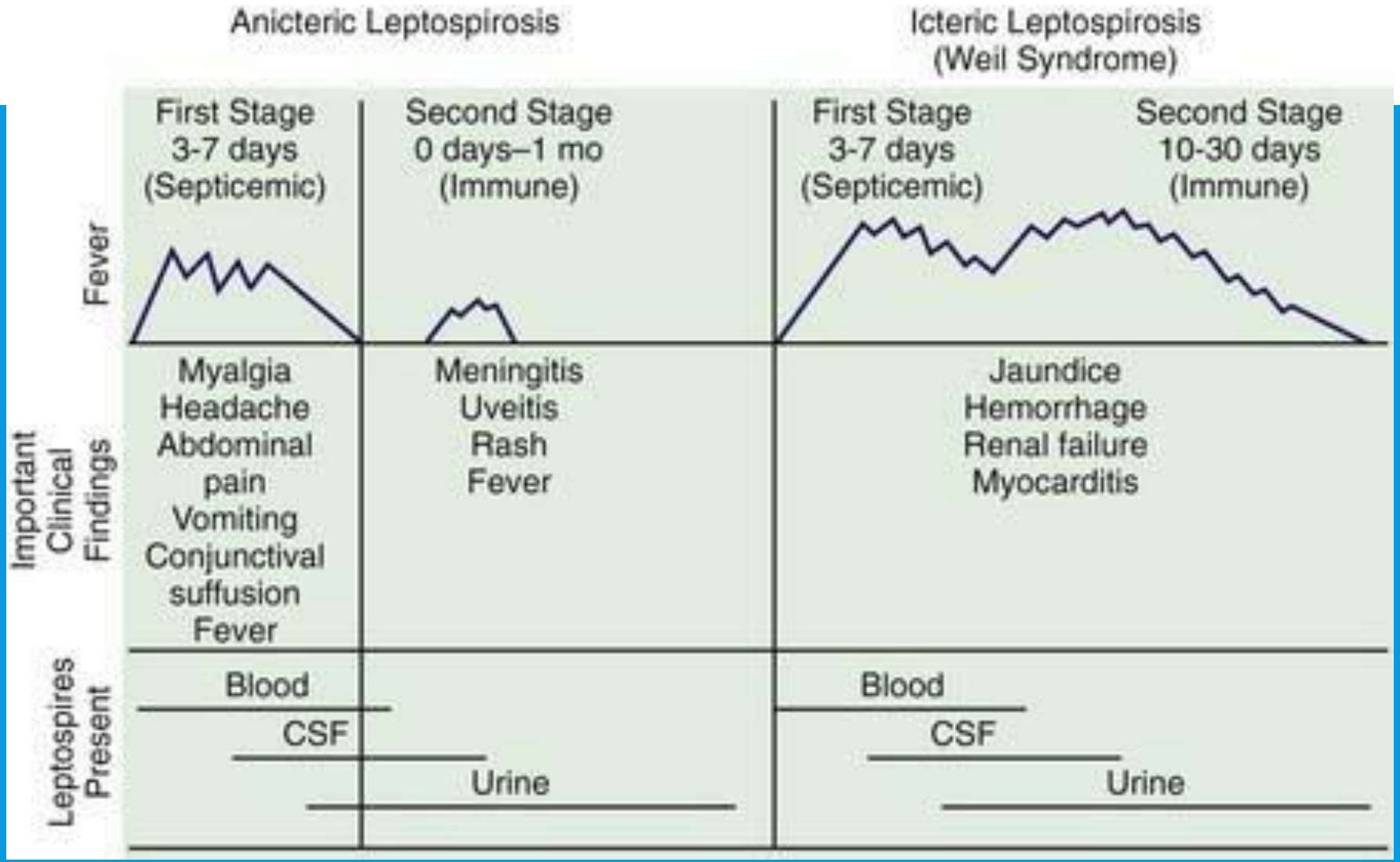
☑ Conjunctival redness

☒ Exudate

80-90 %

About 10%



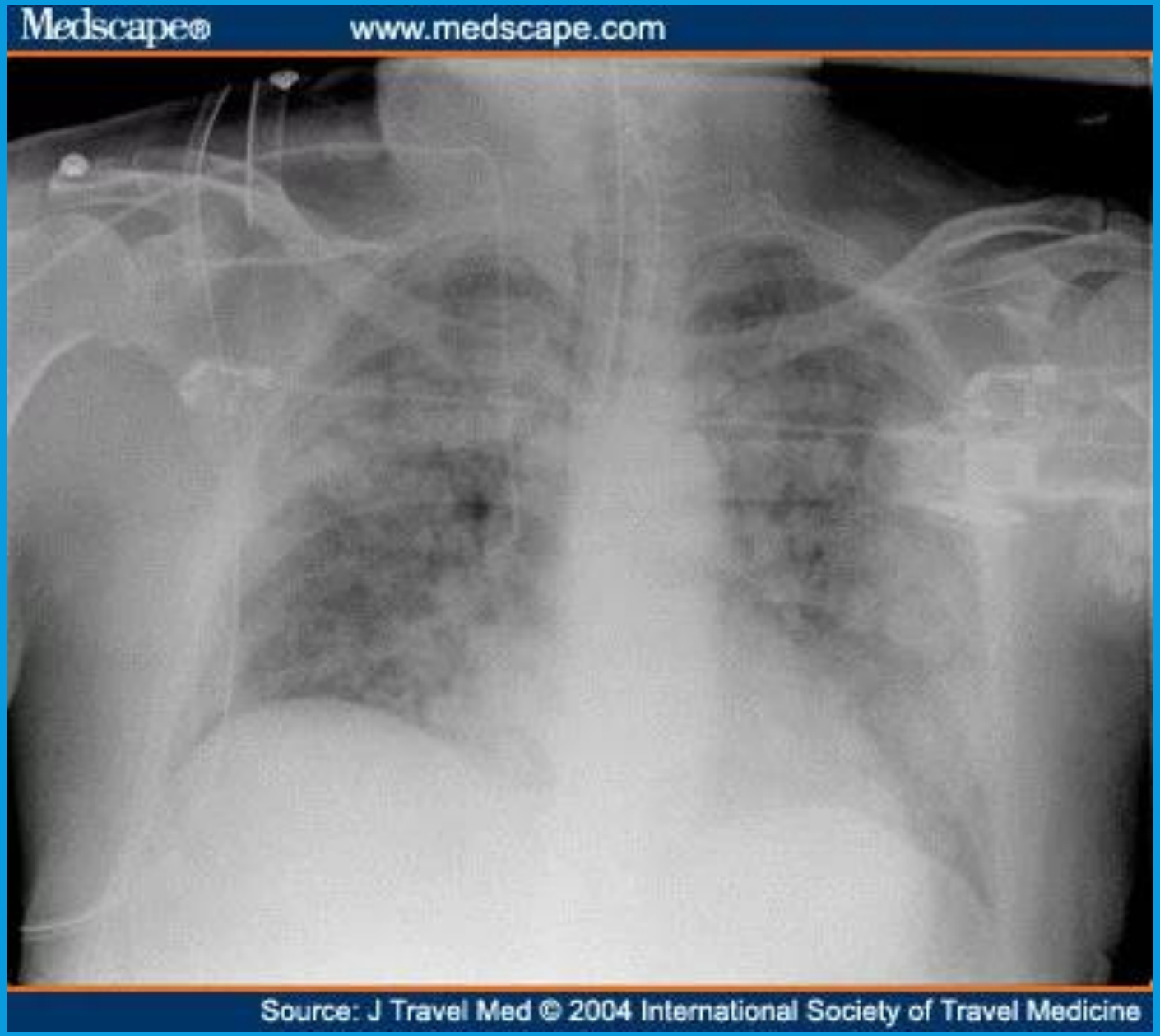
3. Significant predictors of death include pulmonary involvement and CNS disease [4]
4. High case fatality rates associated with jaundice (median mortality 19 percent), renal failure (12 percent) and age >60 years (60 percent) [5]
5. Risk factors for development of severe leptospirosis include delay >2days of initiation of antibiotics from onset of symptoms and infection due to *Leptospira interrogans* serogroup Icterohaemorrhagiae [6]

LABORATORY STUDIES AND IMAGING

PARAMETER	RESULTS
Full blood count	Significant anemia Raised WBC (3000-26000 cells/µL) with left shift Thrombocytopenia
Renal profile	Hyponatremia Hypokalemia Raised urea and creatinine (reduced GFR)
Liver function	Minimal to moderate transaminase elevation Hyperbilirubinemia (1026-1368mmol/L)
Serum creatinine kinase	Markedly raised
Electrocardiogram	Myocarditis, 1st degree heart block
Urinalysis	Proteinuria, pyuria, granular casts and microscopic haematuria

Parameter	Results
CSF analysis	Raised neutrophils Elevated proteins Normal glucose levels
Chest radiograph	Small nodular densities Consolidation Ground glass appearance

Oliguria + WBC > 12900 + ECG repolarisation abnormalities + alveolar infiltrates on chest radiograph
= ADVERSE OUTCOME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DIAGNOSTIC TOOLS

SEROLOGY	Leptospirosis rapid test (ELISA)	Detect mainly IgM antibodies (positive after 5 to 10 days after onset of symptoms) *Can remain detectable for several years *If taken at early stage, need follow-up sample
	Leptospirosis MAT	GOLD standard *Marker for treatment response
CULTURE	Isolation of organism	Blood first 7 days CSF days 4 – 10 Urine ≥ day 7
TISSUE ANALYSIS	PCR or immunohistochemical staining *Post-mortem diagnosis	

CLINICAL CASE	PROBABLE CASE	CONFIRMED CASE
+ History of exposure to water and/ or environment possibly contaminated with animal urine	CLINICAL CASE and positive rapid test	PROBABLE CASE with any of the following laboratory results -MAT (single serum specimen ≥ 1:400 or paired sera of four fold or greater titre) - Positive PCR - Positive culture for pathogenic leptospires - Leptospires in tissues using immunohistochemical staining
+ ANY OF THE SYMPTOMS Headache Myalgia (calf and lumbar region) Arthralgia Conjunctival suffusion Meningism Anuria or oliguria Jaundice Haemorrhage Cardiac arrythmia or failure Skin rash GIT symtoms		

TREATMENT

ADULTS	Mild: PO *doxycycline* (2mg/kg up to 100mg 12-hourly for 5-7 days), *tetracycline*, *ampicillin* or *amoxicillin*
	Severe: IV C-penicillin (2 MU 6-hourly for 5-7 days) *Third generation cephalosporins e.g. *ceftriaxone* and *cefotaxime* also effective
PAEDIATRICS	Mild > 8years: PO *doxycycline* (4mg/kg 12-hourly for 7 days) Mild < 8years: PO *ampicillin* 75-100mg/kg 6-hourly for 7 days) OR PO *amoxicillin* (50ng/kg 6-8hourly for 7 days)
	Severe: IV *penicillin G* (100000 U/kg 6-hourly for 7 days)

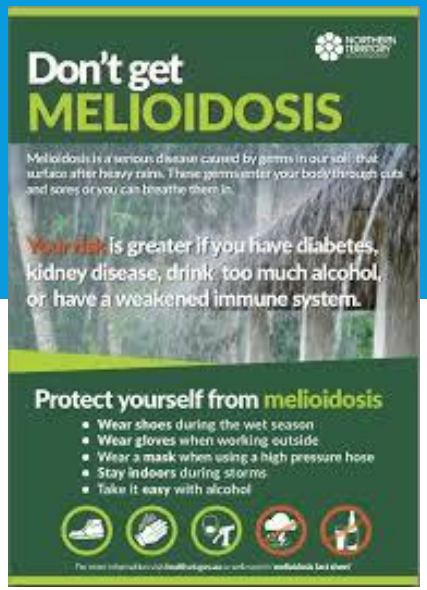
Below are the recommended treatment according to local guidelines :

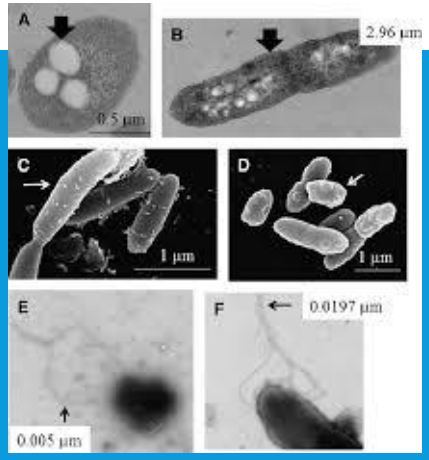
	PPUKM Antibiotic Guideline 2012	MOH Guideline 2011	National Antibiotic Guideline (NAG) 2014
Adult	Benzylpenicillin 1.5 MU q6h IV x 7days **or** Ceftriaxone 1g q12h IV x 7days	Mild : Doxycycline 2 mg/kg per dose (up to 100 mg) PO q12h x 5-7 days **or** Amoxicillin 500mg q6h/1g q8h PO **or** Azithromycin 500mg q24h PO x 3 days Moderate to Severe: Benzylpenicillin 2MU q6h IV x 5-7 days.	Mild : Doxycycline 100mg PO q12h for 5-7 days **or** Azithromycin 500mg PO q24h x 3 days. Moderate to Severe : Benzylpenicillin 2MU IV q6h for 5-7 days **or** Ceftriaxone 1-2gm IV q24h **or** Cefotaxime 1g IV q8h x 7days
Child	-	Mild : < 8years old : Ampicillin 75-100mg/kg/dose PO q6h x7days **or** Amoxicillin 50mg/kg/dose PO q6-8h x 7 days Moderate to Severe : ** Benzylpenicillin G 100, 000 U/kg/dose IV q6h x 7days > 8years old : Doxycycline 4mg/kg/dose PO q12h x 7days	Mild: Amoxicillin 20-50mg/kg PO q6hq8h for 7 days For children > 8 yr: Doxycycline 4mg/kg PO q12h x7 days Moderate to Severe : **Benzylpenicillin 100,000 units/kg IV q6h x 7days **or** Ceftriaxone 80-100mg/kg IV q24h for 7days **or** Cefotaxime 150-200mg/kg/24h IV in 4 divided doses x 7 days.

Pharmacy Department, HCTM, PPUKM. Updates On Leptospirosis In Malaysia. Edition 17, Issue 11.

PROPHYLAXIS

1. Cost effectiveness and risk versus benefits unclear
2. Pre-exposure: PO *doxycycline* 200mg stat then weekly throughout stay OR PO *azithromycin* 500mg stat then weekly throughout stay (pregnant, allergy to *doxycycline*)
3. Post-exposure: PO *doxycycline* 200mg stat then 100mg BD for 5-7 days if symptomatic with first onset of fever OR PO *azithromycin* 1g on Day-1 then 500mg daily for 2 days





MELIOIDOSIS

EPIDEMIOLOGY

1. Caused by facultative intracellular gram negative bacterium, *Bukholderia pseudomallei*
2. Widely distributed environmental saprophyte in soil and fresh surface water in endemic regions
3. Endemic in South East Asia and North Australia. Majority of diagnosed cases are from Thailand, Malaysia, Singapore and northern Australia [7]
4. In Sabah, about 70 cases reported in 2013 with incidence rate of 0.16 per 100, 000 populations per year (Kota Kinabalu reported the highest followed by Penampang and Tuaran) [8]
5. Commonly occurs between ages 40-60 years

TRANSMISSION

1. Acquired from:

i. Inhalation of contaminated dust particles

ii. Direct contact with contaminated soil and water through penetrating wounds, existing skin abrasions, burns

iii. Aspiration of contaminated water

iv. Ingestion of contaminated water

2. *B. pseudomallei* behaves as an opportunistic pathogen

3. Risk factors: Diabetes (57-74% of cases), hazardous alcohol use/ chronic liver disease, chronic renal disease, chronic lung disease, SLE, HIV, malignancy and thalassemia major amongst paediatrics

INCUBATION PERIOD	Ranges from 1-21 days (mean 9 days) *Influenced by inoculation dose, mode of transmission, host risk factors
ACUTE VS CHRONIC INFECTION	1. Acute (symptoms lasting < 2 months before establish diagnosis) VS chronic (symptoms persisting > 2months) 2. Chronic melioidosis present with pneumonia mimicking tuberculosis or non-healing skin ulcer/ abscess
LATENT INFECTION WITH REACTIVATION	Reported latent periods between exposure in endemic regions to development in non-endemic regions as long as 26 to 62 years in the United States and 19 to 24 years in Australia

CLINICAL MANIFESTATION

Presentation	Sign and Symptoms
Presentation	- Community acquired pneumonia - Pneumonia with abscesses involving single or multiple organs - Septicaemia
Other presentations	- Soft tissue infection : Cellulitis, fascilitis, skin absecess/ulcer - Intra abdominal : Single or multiple abscesses in the liver, spleen, kidney or pancreas - Bone and joint infection : Osteomyelitis, septic arthritis - Genitourinary : Prostatic abscess - CNS Infection : Cerebral abscess, meningoencephalitis, encephalomyelitis - Facial : Suppurativeparotitis - Ocular infection : Conjunctival ulser, hypopyon, orbital cellulitis
Asymptomatic	Asymptomatic sero-conversion

Suspect IF

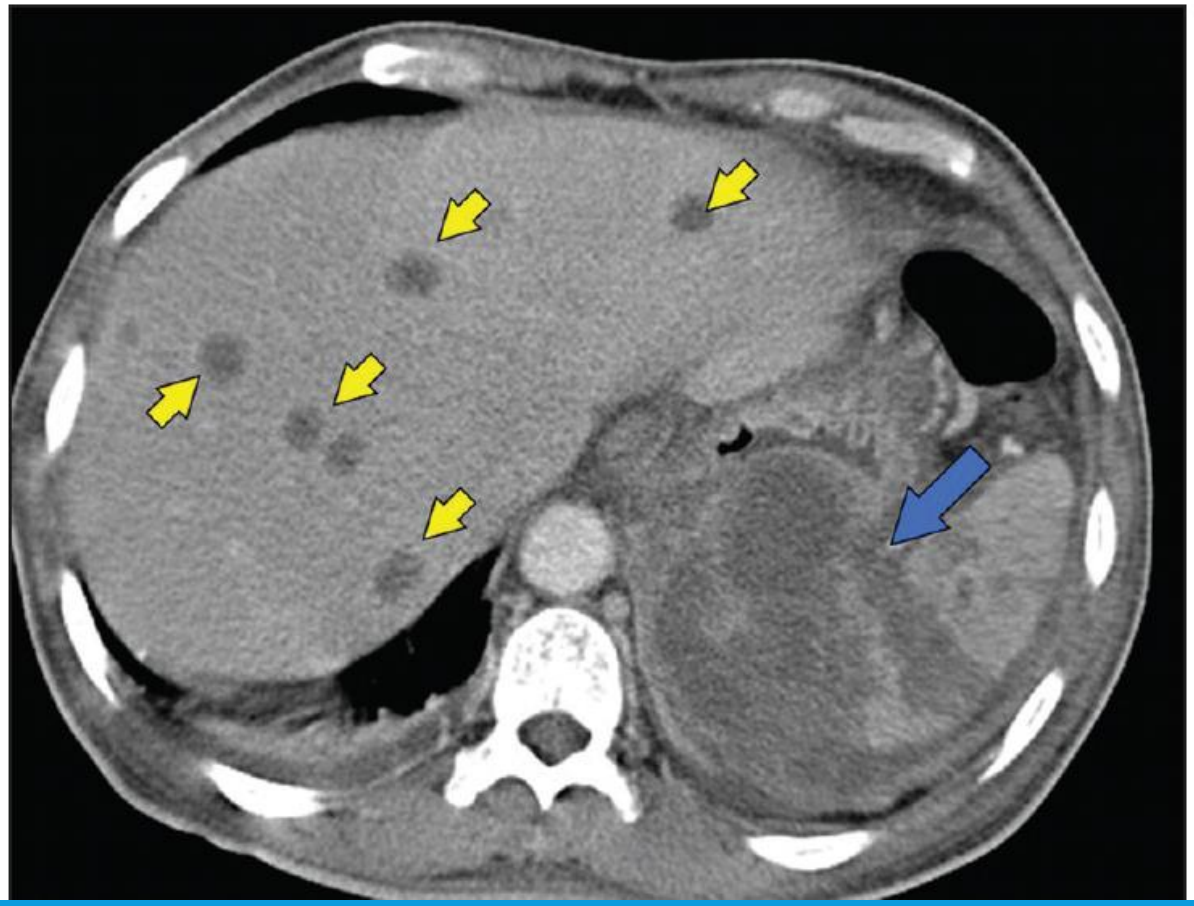
- Patient is residing and/ or working in endemic area
- Patient with diabetes mellitus
- Patient with high grade fever acute or prolonged
- History of exposure to contaminated environment (dust, soil or water)
- Progressive pneumonia (CXRay deteriorating with few hours or 2-3 days) not responding to commonly used antibiotics
- Presence of hepatomegaly and/ or splenomegaly

LABORATORY AND IMAGING

CULTURES	1. Mainstay of diagnosis 2. 2 sets of blood cultures before initiation of antibiotics 3. All suspected patient should have blood, sputum, urine, swab of ulcer, abscess fluid, throat swab and rectal swab
SEROLOGY	Indirect hemagglutination test (IHAT) is available but not a reliable method of diagnosis
MOLECULAR DIAGNOSIS (PCR)	Blood, urine and other involved body secretion
CHEST RADIOGRAPH	1. Acute pneumonia (discrete, diffuse or patchy lobar consolidation, necrotising lesions and pleural effusion) 2. Chronic include cavitating, nodular or streaky infiltrates with fibrotic changes
COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING	CT of abdomen and pelvis should be done routinely for all suspected melioidosis patients

Alsaif HS, Venkatesh SK. Melioidosis: Spectrum of Radiological Manifestations. Saudi Journal of Medicine and Medical Sciences. 2016:4(2)

Figure 6: Hepatosplenic melioidosis. Computed tomography scan showing multiple discrete liver abscesses (arrow heads) in the liver and extensive splenic involvement (blue arrow).



ADULTS	INTENSIVE THERAPY	Life-threatening e.g. intubated patients	IV meropenem (25mg/kg or 1g TDS for at least 2 weeks)
			+ May add PO co-trimoxazole (trimethoprim-sulphamethoxazole) 3-4 tab BD and PO folate 5mg daily
			Consider G-CSF within 72 hours of admission
		Other melioidosis	IV ceftazidime (100mg/kg a day or 2g TDS)
		Localized superficial melioidosis	PO augmentin (amoxicillin/clavunate) 625mg TDS for 12-20 weeks
	ERADICATION THERAPY		PO co-trimoxazole 2-4 tab BD and PO doxycycline 100mg BD for total of 20 weeks OR PO augmentin 625mg TDS

PAEDIATRICS	INTENSIVE THERAPY	IV ceftazidime (50mg/kg 6-8 hourly for at least 2 weeks, 4-8 weeks for deep seated infection)
	ERADICATION THERAPY	PO amoxicillin (20mg/kg)/clavunate 8-hourly for total of 20 weeks OR PO co-trimoxazole (trimethoprim 8mg/kg and sulphamethoxazole 40mg/kg) and PO doxycycline (4mg/kg in 2 divided doses)

Lampir

No. Daftar Melioidosis :

JABATAN KESIHATAN NEGERI SABAH

BUKU RAWATAN MELIOIDOSIS

JABATAN KESIHATAN NEGERI SABAH (JKNS)

Oktober 2016

E. Regim Rawatan

Alahan Ubat (Jika Ada) :

I. Fasa Intensif

Berat badan = ... kg

Ubat	Dos	Tarikh Mula	Tarikh Tamat	Durasi

Tandatangan Pegawai Perubatan:

a. Jadual Rawatan Fasa Intensif

Minggu 1

Tarikh							
Dos 1							
Dos 2							
Dos 3							
Dos 4							

Minggu 2

Tarikh							
Dos 1							
Dos 2							
Dos 3							
Dos 4							

b. Jadual Rawatan Fasa Eradikasi (Bahagian ini ditandatangani oleh pesakit/penyelia sekiranya dos diambil dengan lengkap pada hari tersebut)

Minggu 1-4

No Dos	Tarikh	T/Tangan
1		
2		
3		
4		
5		
6		
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Minggu 5-8

No Dos	Tarikh	T/Tangan
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