

Leptospirosis and Typhoid

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History

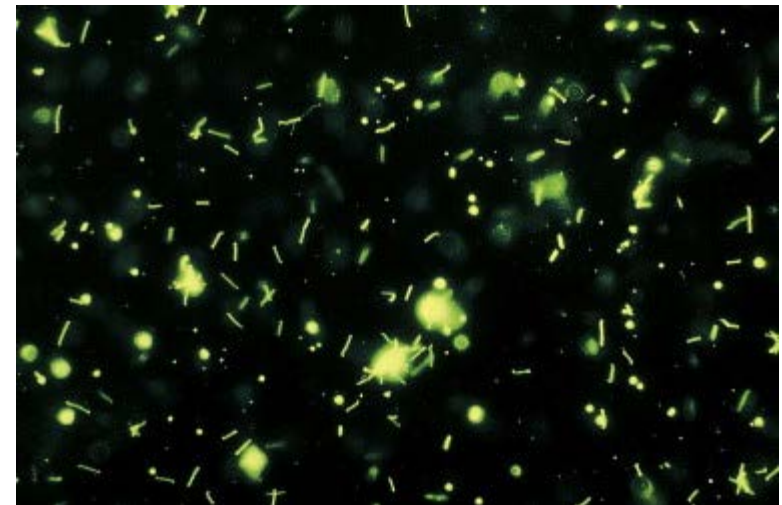
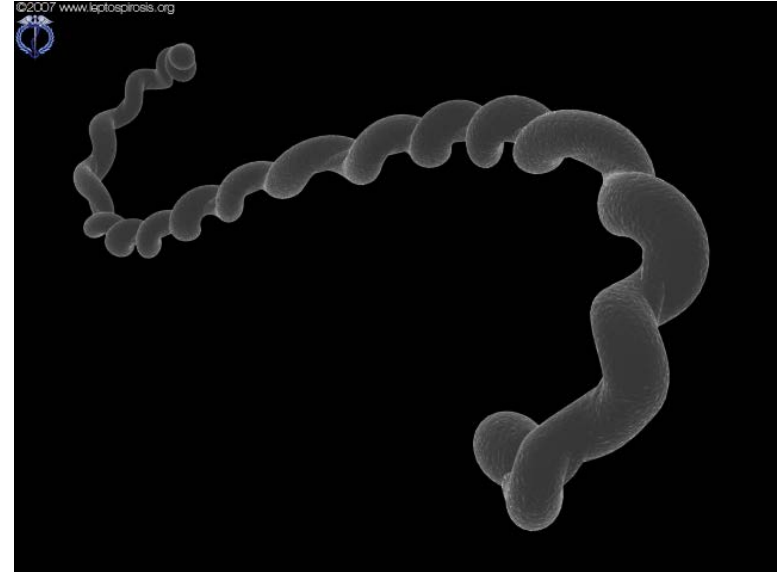
- Severe syndrome with fever, profound jaundice and renal dysfunction described in Germany in 1886.
- *Leptospira* visualized first in a patient suspected of yellow fever



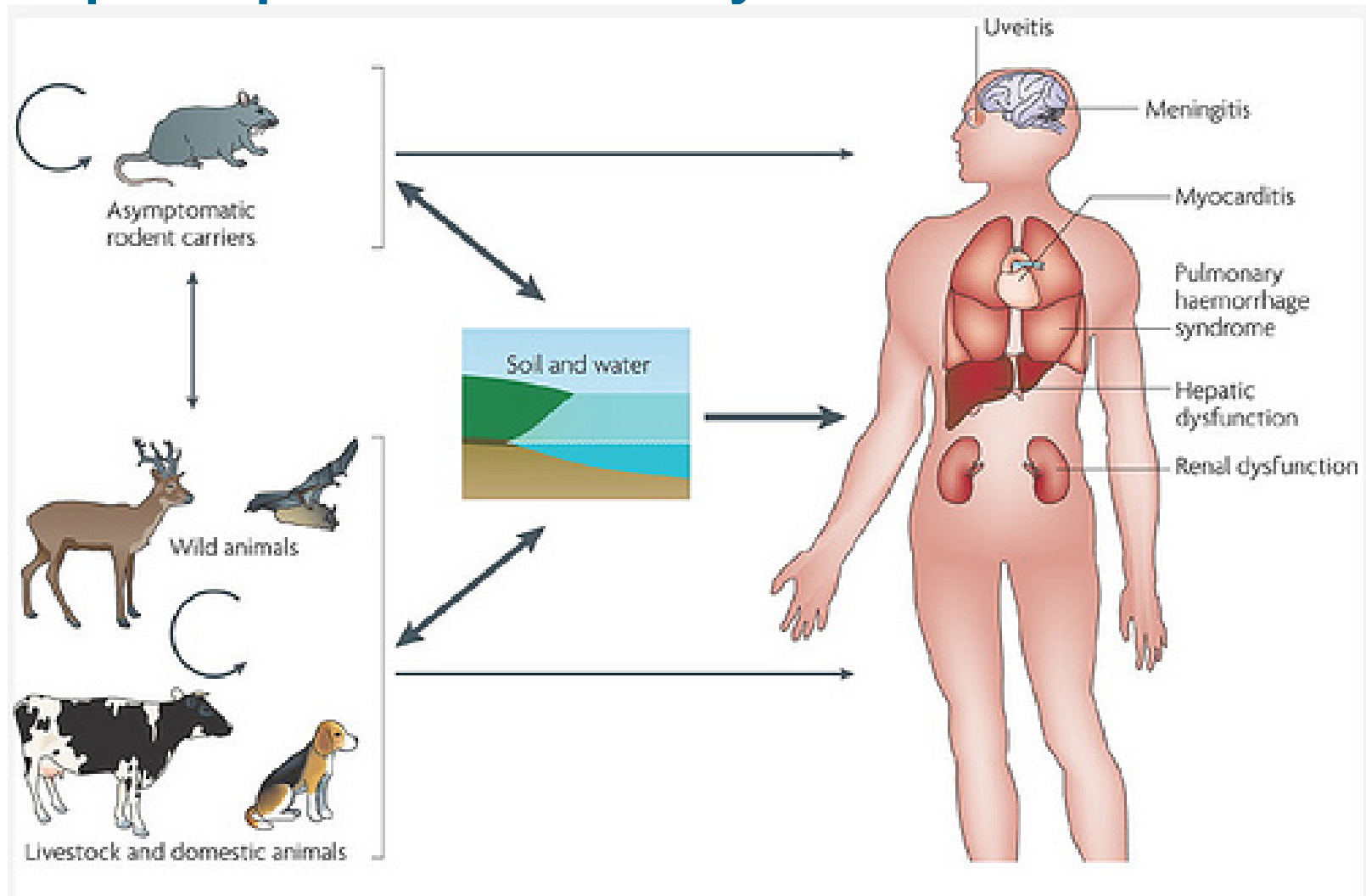
Adolf Weil

Microbiology

- Zoonosis of global distribution
- Gram negative, curved, motile spirochete
- *L. interrogans* and *L. biflexa*
- Maintained in the environment by renal infection of carrier animals



Leptospirosis life cycle



Epidemiology

- 3-5 million cases per year, 100-120,000 deaths
- Endemic in resource poor areas of Asia and Africa
 - Worst cases in young children and elderly
- Epidemics have occurred in Asia, Middle East, South and Central America
- Transmission after contact with urine or direct contact (veterinarians, butchers, hunters)
- Mostly imported to US
 - 9% acquired via consumption of contaminated Gulf Coast seafood

TABLE 4. Waterborne-disease outbreaks (n = 14) associated with untreated recreational water, by state — United States, 2005

State	Month	Class*	Etiologic agent	Predominant† illness	No. of cases (deaths) (n = 171)	Type	Setting
California	Jul	IV	Unidentified [§]	Skin	2	Lake	Lake
California	Jul	IV	<i>Leptospira</i>	Lep	3	Stream	Stream
Florida	Jul	I	Unidentified [¶]	Other	24	Ocean [¶]	Beach
Florida	Nov	II	<i>Leptospira</i>	Lep	43	Stream	Adventure race
Maine	Jul	III	Unidentified	AGI	10	Lake	Swimming beach
Massachusetts	Jul	IV	<i>Shigella sonnei</i>	AGI	5	Lake	Lake
Michigan	Jun	IV	Copper sulfate	ARI	3	Lake	Lake
Minnesota	Jun	IV	<i>Escherichia coli</i> O157:H7	AGI	4	Lake	Swimming beach
Minnesota	Jul	IV	<i>S. sonnei</i>	AGI	12	Lake	Swimming beach
Minnesota	Aug	IV	Norovirus	AGI	8	Lake	Swimming beach
New York	Jul	III	<i>Cryptosporidium</i>	AGI	27	Lake	Swimming beach
New York	Aug	III	Unidentified**	AGI	13	Lake	Lake
Oklahoma	Jul	IV	<i>Naegleria fowleri</i>	Neuro	2 (2)	Unknown††	Unknown
Pennsylvania	Jul	IV	<i>S. sonnei</i>	AGI	15	Lake	Swimming beach

* On the basis of epidemiologic and water-quality data provided on CDC form 52.12 (available at http://www.cdc.gov/healthyswimming/downloads/cdc_5212_waterborne.pdf) (see Table 1).

† Skin: illness, condition, or symptom related to skin; Lep: leptospirosis; Other: undefined or mixed illness, condition, or symptom. AGI: acute gastrointestinal illness; ARI: acute respiratory illness; Skin: illness, condition, or symptom related to skin; and Neuro: neurologic condition or symptoms (e.g. meningitis).

§ Etiology unidentified: clinical diagnosis of cercarial dermatitis (caused by avian schistosomes).

¶ Etiology unidentified: whereas certain swimmers had symptoms consistent with seabathers eruption (caused by jellyfish larvae), a majority of persons affected in this outbreak experienced systemic, flu-like illnesses which might have been related to another etiology. Swimmers alternated between marine and chlorinated swimming venues.

** Etiology unidentified: illness was most consistent with norovirus infection on the basis of clinical syndrome.

†† Whereas an interactive fountain at a water park was a common exposure for both case-patients, other potentially shared and untreated recreational water exposures could not be ruled out.

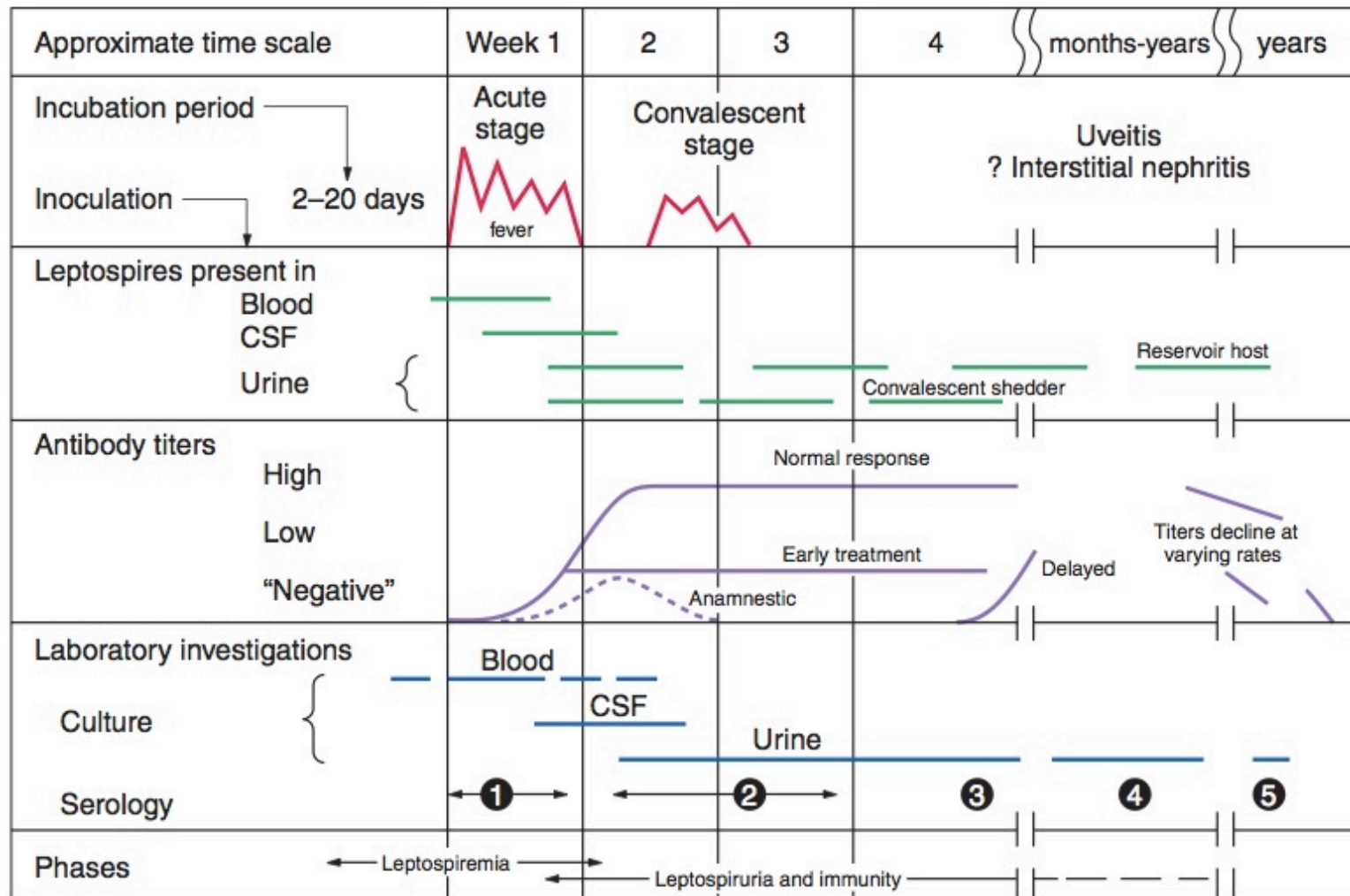
Pathogenesis

- Entrance to the body through cuts and abrasions, mucosal membranes and inhaled droplets
- Hematogenous dissemination
- Systemic **vasculitis**
- Immune-mediated mechanisms
- **(HLA) DQ6** as an independent risk factor for leptospirosis
- **LipL32** is a major target of the human immune response and related to tubulo-interstitial nephritis

Clinical presentation

- **Self-limited Illness**
 - 90% of patients
 - Incubation period 10 days (5 to 14 days)
- **Severe disease**
 - Renal and liver failure
 - Pneumonitis
 - Hemorrhagic diathesis

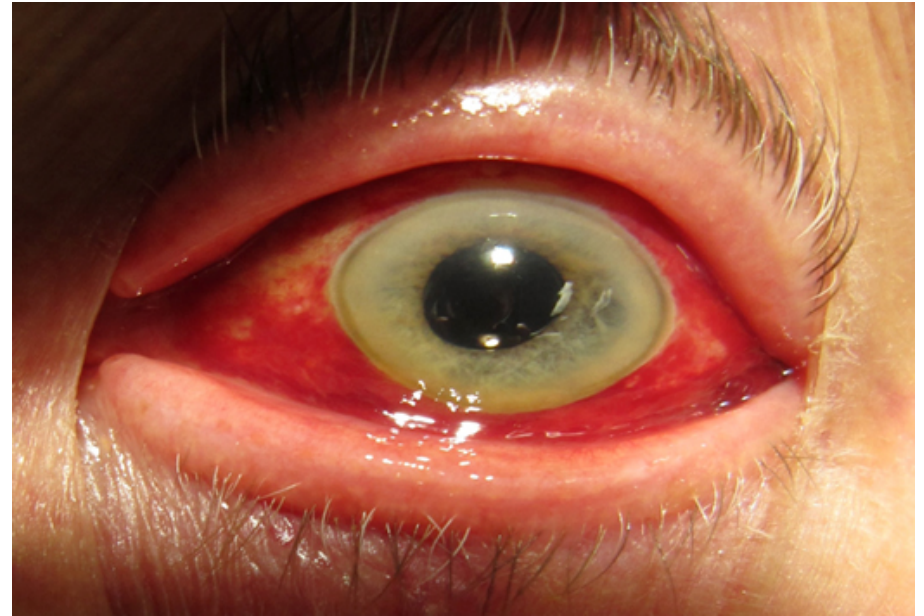
Natural History of Leptospirosis



Clinical manifestations of patients hospitalized with Leptospirosis

Sign or symptom	Puerto Rico	China	Vietnam	Korea	Brazil	India
Jaundice	49	0	2	16	93	34
Headache	91	90	98	70	75	92
Conjunctival suffusion	99	57	42	58	29	35
Vomiting	69	18	33	32	--	--
Myalgia	97	64	79	40	94	68
Cough	24	57	20	45	--	--
Hepatomegaly	69	28	15	17	--	--
Lymphadenopathy	24	49	21	--	--	15
Diarrhea	27	20	29	36	--	--
Hemoptysis	9	51	--	40	20	35

Clinical Manifestations of Leptospirosis



- Weil's disease
- Aseptic meningitis in 80% cases
- Altered conscious status predictor of death (5-15%)

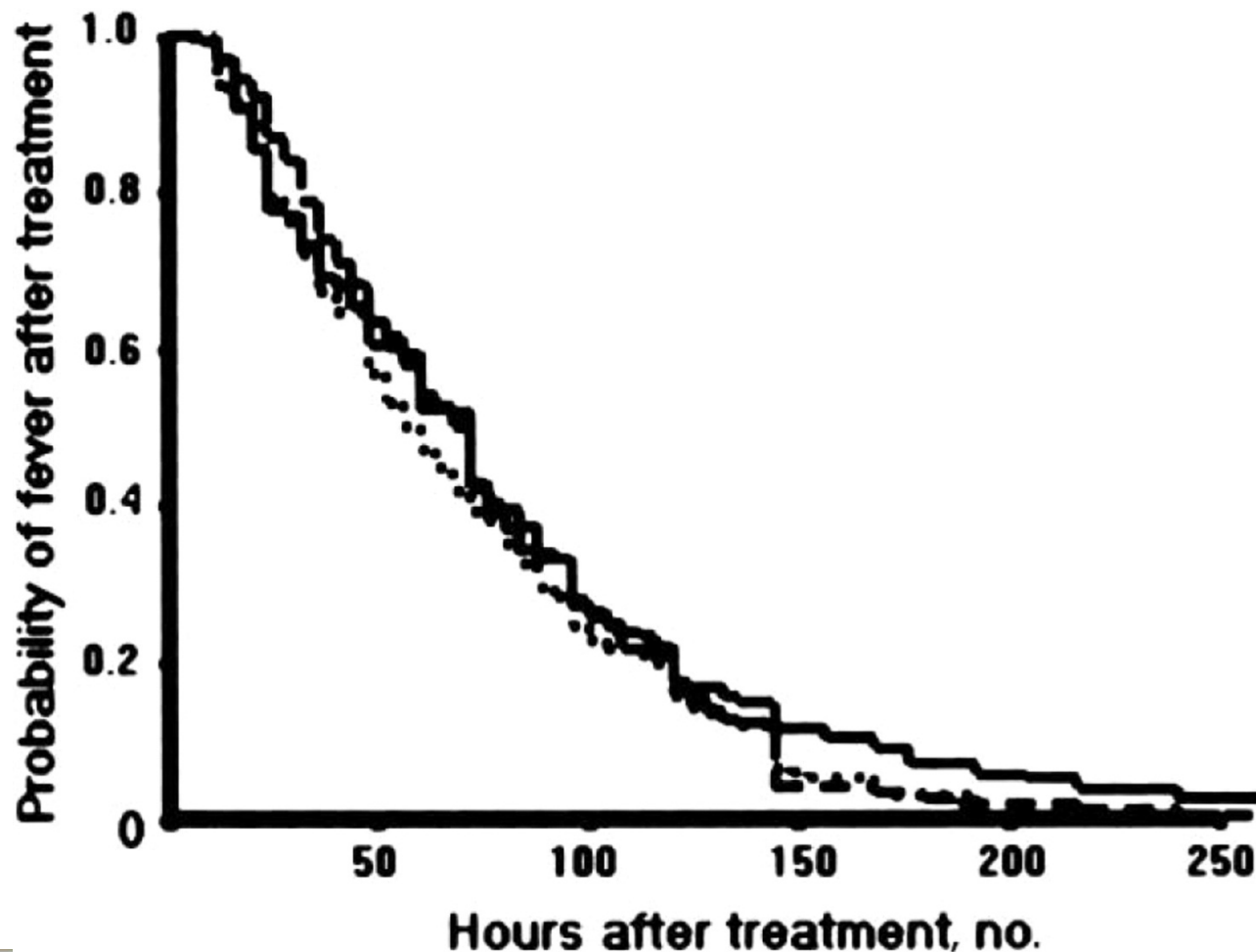
Diagnosis of Leptospirosis

- Direct detection
 - Darkfield microscopy of urine or blood (S0.4/S0.6)
 - PCR serum, urine, fluids
 - Isolation by culture first 10 days of illness (EMJH)
- Indirect detection
 - MAT acute & convalescent titers (4x or 1:800)
 - IgM after 5 days of illness

Treatment of Leptospirosis

- Moderate-Severe disease
 - Penicillin G 1.5 MU q 6 hrs
 - Ceftriaxone 1 gm q 24 hrs
 - Ampicillin 1 gm q 6 hrs
- Mild cases
 - Doxycycline 100 mg BID PO
 - Amoxicillin 500 mg PO q 6 hrs
- Chemoprophylaxis
 - Doxycycline 200 mg once a week

Kaplan-Meier plot of the duration of fever after treatment among patients with leptospirosis.



What antibiotic works better for Lepto?

Patient group, outcome	Patients given penicillin G sodium	Patients given doxycycline	Patients given cefotaxime	<i>P</i>
All patients (<i>N</i> = 520)				
Death at ≥48 h after treatment	5 (2.9)	4 (2.4)	7 (3.9)	.72
Time to defervescence, median h (range)	72 (8–512)	72 (12–264)	60 (8–200)	.42
Duration of hospitalization, median days (range)	6 (2–38)	6 (2–29)	5 (2–37)	.30
Reason for subsequent antimicrobial treatment				.08
Inadequate clinical response ^a	16 (9.3)	11 (6.6)	12 (6.6)	
Other diagnosis ^b	9 (5.2)	5 (3.0)	4 (2.2)	
Nosocomial infection	3 (1.7)	5 (3.0)	1 (.6)	
Adverse event	2 (1.2)	1 (.6)	...	
Patients with confirmed leptospirosis (<i>n</i> = 256)				
Death at ≥48 h after treatment	2 (1.2)	2 (1.2)	...	
Time to defervescence, median h (range)				
For all patients	72 (12–240)	72 (12–264)	60 (8–192)	.56
For patients with no previous or concomitant antimicrobial treatment ^c	70 (16–240)	58 (12–216)	56 (12–192)	.43
Duration of hospitalization, median days (range)	6 (2–21)	5 (2–28)	5.5 (3–37)	.93
Reason for subsequent antimicrobial treatment	9 (10.3)	9 (11.1)	2 (2.3)	.19
Inadequate clinical response ^a	6 (7.0)	6 (7.4)	0	
Nosocomial infection	2 (2.2)	3 (3.7)	2 (2.3)	
Adverse event	1 (1.1)	

NOTE. Data are no. (%) of patients, unless indicated otherwise.

^a Continued to have high fever or deterioration of vital signs after ≥48 h of treatment with study drug.

^b Diagnosis other than leptospirosis was obtained after entry into the study.

^c *N* = 164.

Typhoid Fever

History

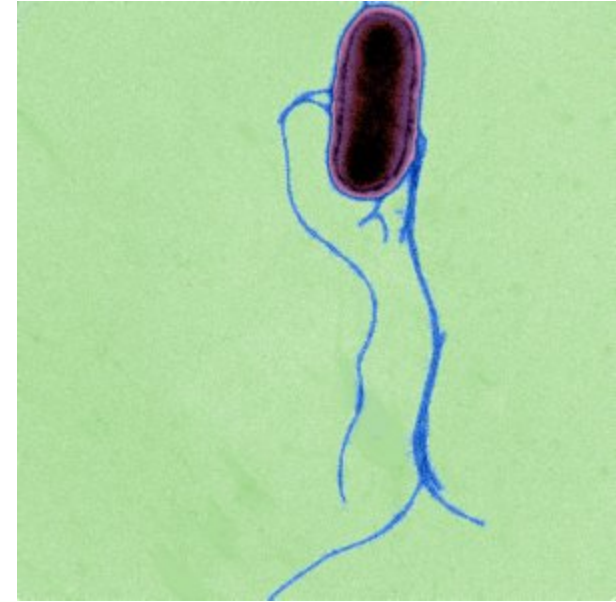
- French: “boil of the intestine”
- *Pierre Louis* (1829) called the enteric fever *typhoide* (typhus like)
- Eberth (1880) *Bacillus typhosus*
- Widal (1896) described reaction
- Woodward (1948) found that chloramphenicol cleared typhoid fever
- Spanish-American war 1/5 soldiers died of TF



Pierre A. Louis

Salmonella typhi

- Gram negative enterobacteria
- *Salmonella choleraesuis* species
- Infects only humans
- 1-4% of infected patients become carriers
 - *Women and older ages*
- Acquired through contaminated food or water
- Survives environment and reproduces in milk without changing appearance



Pathogenesis

- Bacterial invasion and multiplication within the mononuclear phagocytic system
 - Mucosal penetration (M cells)
 - Incubation 7-14 days
 - Dissemination and organ invasion
 - Hemophagocytic macrophages in liver and spleen
- Endotoxin
- DIC
- Immunity: humoral and cellular

Clinical Manifestations

- Incubation 7-14 days
 - 10-20% subjects with diarrhea after ingestion
- Symptoms:
 - Fever, headaches and abdominal pain
- XX

Details of operations and description of intestinal perforation sites for 27 patients with typhoid perforation.

Characteristic	Value (n = 27)
Pertoneal fluid present	27
Pseudomembrane present	27
Procedure performed	
Simple closure by suture	2
Wedge excision and simple closure	13
Drainage	6
Ileostomy	4
Perforations	
Mean no. (range)	1.4 (1–5)
Distance from ileocecal junction, mean mm (range)	419 (20–1800)
Diameter, mean mm (range)	6.6 (1–25)
Edge of perforation	
Rolled	27
Punched	2
Tissue appearance	
Fragile	26
Normal	0
Erythematous	27
Swollen/inflamed	27
Pancreas normal	27
Gastrointestinal tract inflamed around site	27
Liver condition	
Normal	2
Congested	3
Gastrointestinal bleeding	1

NOTE. Data are no. of patients, unless otherwise indicated.

Clinical manifestations of hospitalized patients with Typhoid Fever

Symptom	Frequency (%)
Fever and weakness	99
Headache, anorexia	85
Abdominal pain, nausea, chills	50
Diarrhea	45
Constipation	40
Cough or chest discomfort, vomiting	35
Confusion	25
Epistaxis	10
Dysuria, seizures	2

Complications of Typhoid Fever

- Intestinal perforation (3% of hospitalized)
 - *1-3rd week of illness*
 - *Severe abdominal pain and peritoneal signs*
- Intestinal hemorrhage (15%)
- Neuropsychiatric manifestations
 - *Delirium, stupor, seizures, meningitis*
- Urinary: 25% excrete *S. typhi*
- Relapse in 5-10% of untreated patients

Quiz...

- What is the real name of “Typhoid Mary”?
- Where was she from?

Chronic carriers

- Source of infection in the community
- Excretion of *S. typhi* > 1 year
- 20% will excrete for 2 months, 10% for 3 months
- Source of carrier state: gallbladder
- Detection, treatment and isolation of carriers imperative for public health



Mary Mallon

Response to treatment with azithromycin or ceftriaxone among patients with cultures positive for *Salmonella enterica serovar Typhi*

Characteristic	Azithromycin (n = 32)	Ceftriaxone (n = 36)
Clinical cure by day 7, n/N (%)	30/32 (94)	35/36 (97)
Clinical cure by day 30, n/N (%)	25/25 (100)	26/32 (81)
Duration of fever, mean days ± SD	4.5 ± 1.9	3.6 ± 1.6
Microbiological cure by day 8, n/N (%)	32/32 (100)	35/36 (97)
Positive blood culture result on day 3	12 (38) ^a	0
Positive blood culture result on day 8	0	1 (3)
Positive stool culture result on day 8	0	0
Positive stool culture result on day 30	0	0
Relapse	0	5 (14) ^b
Laboratory value on day 8, mean ± SD		
Hemoglobin, g/dL (NR, 11–18 g/dL)	10.4 ± 1.8	11.0 ± 1.5
WBC count, ×10 ³ cells/mm ³ (NR, 4.5 ×10 ³ to 10.5 ×10 ³ cells/mm ³)	5.7 ± 1.8	6.4 ± 1.9
Platelet count, ×10 ³ cells/mm ³ (NR, 150 ×10 ³ to 350 ×10 ³ cells/mm ³)	367 ± 136	418 ± 133
Total bilirubin, mg/dL (NR, 0.2–1.0 mg/dL)	0.3 ± 0.2	0.33 ± 0.2
AST, U/L (NR, 0–33 U/L)	48 ± 36	42 ± 23
Blood urea nitrogen, mg/dL (NR, 7–18 mg/dL)	8.5 ± 6.3	9.2 ± 2.9
Serum creatinine, mg/dL (NR, 0.7–1.5 mg/dL)	0.4 ± 0.2	0.5 ± 0.1

NOTE. Data are no. (%) of patients, unless otherwise indicated. Times indicated are days after the initiation of therapy. AST, aspartate aminotransferase; NR, normal range

^a P < .001.

^b P < .05.

Treatment

- Prompt diagnosis
- Chloramphenicol effective and available in developing countries
- Ampicillin, amoxicillin and TMP-SMX
- MDRTF – Fluoroquinolones and 3rd generation cephalosporins
 - 100% cure rates, no relapses
 - Duration 10-14 days

Additional treatment

- High-dose dexamethasone reduces mortality (Hoffman et al)
 - *Initial 3 mg/kg*
 - *Followed by 1 mg/kg/dose x 8 doses (q 6 hrs)*
- Fluid and electrolyte balance
- Antipyretics only if very high fever (>39.5C)
- Treatment of carriers: ampicillin or fluoroquinolones for 3 months

Dosage and Schedule for Typhoid Fever Vaccination

Vaccination	Age, years	Dose (mode of administration)	No. of doses	Dosing interval	Boosting interval
Oral, live, attenuated Ty21a vaccine					
Primary series	≥6	1 capsule (oral)	4	48 h	NA
Booster	≥6	1 capsule (oral)	4	48 h	Every 5 years
Vi capsular polysaccharide vaccine					
Primary series	≥2	0.50 mL (intramuscular)	1	NA	NA
Booster	≥2	0.50 mL (intramuscular)	1	NA	Every 2 years