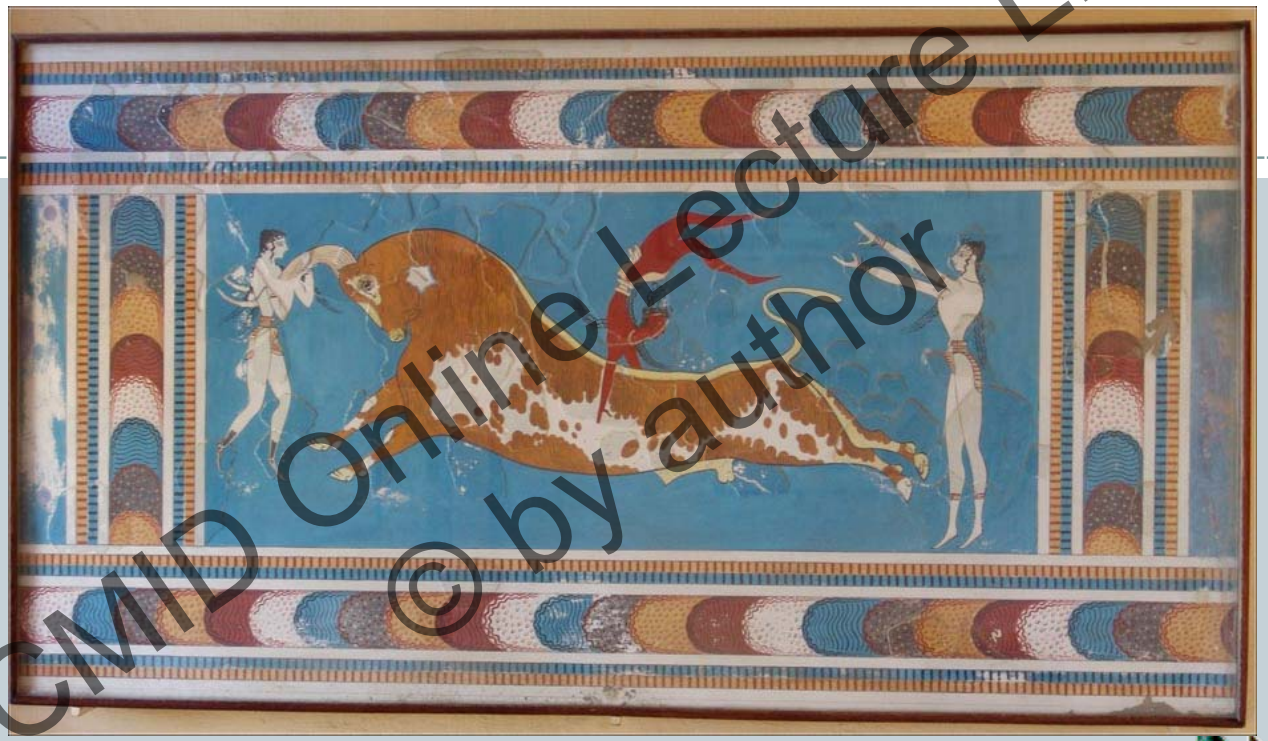
Case presentation
R. typhi infection



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Case presentation

- A 30 yo man presented with a 12-day history of high fever with rash, chills, frontal headache, anorexia, malaise, non-productive cough and left upper quadrant pain

History

- pensioner
- recent contact with sheep and rats
- medical history (-)

Physical examination

- Fever 39°C
- HR 110/min, SBP 110 mmHg
- Diffuse macular rash on trunk and extremities
- Mild hepatomegaly
- Auscultation (-)

Significant laboratory findings upon admission

- WBC count 4.300/μL
- Platelets 80.000/μL
- ESR 113 mm
- SGOT 152 U/L, SGPT 179 U/L,
- γGT 193 U/L, ALP 227 U/L
- Na^+ 130 mEq/L
- Urea 90, Creatinine 1.5
- Albumin 2.9 g/dL
- Hematuria
- Proteinuria
- Serial blood and urine cultures (-)
- CXR (-)
- Serology for Parasitic Viral infections (-)

Diagnosis?

Causes of fever - rash - headache

Bacterial Infections

- RMSF
- Boutonneuse fever
- Endemic typhus
- Epidemic typhus
- Scrub typhus
- Ehrlichiosis / Anaplasmosis
- Lyme disease
- Tularemia
- CSD
- Psittacosis
- Plague
- Leptospirosis
- Pasteurella wound infection
- Mycobacterium marinum
- Folliculitis
- Secondary syphilis
- Gonococcal septicemia
- Meningococcemia
- Toxic shock syndrome
- Typhoid fever

Parasitic infections

- Cutaneous leishmaniasis
- Schistosomiasis
- Trypanosomiasis
- Toxoplasmosis
- Malaria

Viral infections

- Childhood viral infections if inadequately immunized
- HIV infection
- Viral haemorrhagic fevers

Other

- Allergic reactions
- Kawasaki disease

Clinical course

- Patient was diagnosed as having a lower respiratory tract infection
- Initial treatment: ceftriaxone IV

Clinical course (2)

3 days later:

- Fever, rash & cough persisted
- Creatinine titres increased to 1.9

- New CXR performed → infiltrates involving lower pulmonary fields and bilateral pleural effusions

Rickettsial Serology

- Serology (IFA) for atypical pathogens → *Rickettsia typhi* acute infection

	Day 3 of hospitalization
IgM	1:6,400
IgG	1:15,360
IgA	1:400

Treatment and outcome

Doxycycline per os on day 5

- Defervescence within 48 hours
- Rash and dyspnea subsided within 76 hours
- Creatinine gradually returned to normal
- Discharge on day 19 after completing 2 weeks of doxy

Day after admission	Day 3	Day 25
IgM	1:6,400	1:3,200
IgG	1:15,360	1:7,680
IgA	1:400	1:50

Murine / endemic typhus

- Flea-borne infection (main vector: rat flea *Xenopsylla cheopis)* caused by *Rickettsia typhi*

Humans

- accidental hosts after contact with fleas
- typically infected in conditions requiring close proximity with rats (markets, grain stores, breweries, garbage depots)
- High frequency in temperate and subtropical coastal regions during warm months
- Endemic in Mediterranean, African countries, Southeast Asia, Texas USA
- Mostly in areas with large rat populations

Pathophysiology of R. typhi infection

Rickettsiae cause systemic endothelial injury

→ lymphohistiocytic vasculitis of almost any organ

→ increased microcirculation permeability → leakage of serum, albumin, electrolytes

→ consumption of platelets and leukocytes at site of vascular inflammation

Walker et al. Am J Clin Pathol 1989

Table 1. Clinical manifestations in 83 patients with murine typhus on the island of Crete (1993–97)

Clinical manifestations	Patients affected *n*	(%)
Fever	83	(100)
Headache	73	(88)
Chills	72	(87)
Rash	66	(80)
Malaise	46	(55)
Anorexia	44	(53)
Myalgia	37	(45)
Non-productive cough	23	(28)
Perspiration	21	(25)
Conjunctivitis	21	(25)
Splenomegaly	19	(23)
Hepatomegaly	18	(22)
Nausea/vomiting	15	(18)
Arthralgia	10	(12)
Abdominal pain	9	(11)
Diarrhoea	9	(11)
CNS involvement	8	(10)
Confusion	8	(10)
Acute renal failure	4	(5)
Lymphadenopathy	3	(4)
Iritis	2	(2)

Gikas et al. Trans R Soc Trop Med Hyg 2002

Laboratory tests

Laboratory test	Abnormality detected	Percentage
AST titre	> 1-fold elevation	86
LDH levels	Mild levation	82
Serum albumin	Hypoalbuminemia	82
ALT titre	> 1-fold elevation	64
Platelet count	Thrombocytopenia	51
Red blood cell count	Mild anemia	25-50
CPK levels	> 1-fold elevation	42
Serum sodium	Mild hyponatremia	37
White blood cell count	Leucopenia	7

Gikas et al. Trans R Soc Trop Med Hyg 2002

Study (n)	**Gikas, 2002. (83)**	**Adjemian, 2010. (33)**	**Dumler, 1991. (80)**	**Silpapojakul 1993. (137)**	**Tselentis, 1992. (49)**	**Phongmany, 2006. (41)**	**Taylor, 1986. (200)**
Classic Triad	Not specified All 3 observed in **high** Percentage	Not specified Rash was at **low** percentage	Not specified Rash was at **low** Percentage	Not specified Rash was at **low** Percentage	Not specified All 3 observed in **high** Percentage	Not specified Rash at **low** Percentage	Not specified
Complications	**Acute renal failure** 5% Pulmonary infiltrates 5% Pleural effusion 2%	9 (27%) required ICU (pneumonia coagulopathy **acute renal failure**)	Neuropsych. abnormalities 7.5% **Renal failure** 6.3% CNS involvement 5% Respiratory failure 3.8% Jaundice 2.5% Hematemesis 1,3%	Jaundice 10.9% Altered consciousness 2.2% Seizures 2.2%	**Acute renal failure** 2%	Dyspnea 12.5% Meningism 5.1%	Not specified 2 fatalities Reported
Deaths due to Infection	0	0	**2 (2.5%)**	**2 (1.5%)**	0	0	**2 (1.0%)**

Diagnosis

Indirect immunofluorescence assay (IFA)

- Reference method for serodiagnosis
- Antibodies are usually detected 7-15 days after disease onset

Individual laboratories determine their cut-off titres based on local seroprevalence data:

- Unité des Rickettsies (Marseille-France)

→ IgG > 1:64 and/or IgM > 1:32

Serological diagnosis:

- IFA titre ≥ cut-off titre, OR
- 4-fold increase in antibody titre in acute-and convalescent-phase specimens (2 & 4 weeks after disease onset)

Brouqui et al. CMI 2004

Treatment in adults

Antibiotic	Dosage and duration	Comments
Doxycycline	Adults: 100 mg orally every 12 hours Duration of 7-15 days, or at least 48 hours after defervescence	The most efficient antibiotic against *R. typhi* in vitro Defervescence within mean 2.9 days Drug of choice for nonpregnant adults
Chloramphenicol	50 mg/kg/day orally or intravenously in 4 doses, up to 2 g /day. Duration until 4-5 days after defervescence	Alternative when doxycycline is contraindicated Drug of choice for pregnant, but not for parturient (risk of gray baby syndrome) Defervescence within mean 4.0 days Risk of fatal aplastic anaemia
Ciprofloxacin	500 mg orally or intravenously every 12 hours	Effective in vitro Used on a small number of patients, with controversial results Defervescence within mean 4.2 days

Gikas, Tsioutis. In: Tropical and Emerging Infectious Diseases. 2010.

Treatment considerations in children

Doxycycline

- drug of choice for children
- risk of teeth discoloration in children <8 yo is minimal when treatment duration is 7-10 days
- 5 mg/kg/day in 2 doses (maximum 100 mg)

Chloramphenicol

- a potential alternative in severe cases
- risk of aplastic anaemia
- 150/mg/kg/day

American Academy of Pediatrics (Ed.), 22nd ed, 1991.
Raoult, Drancourt. AAC 1991

Thank you for your attention