

CCM Inter-hospital Grand Round

Not Simply Jaundiced

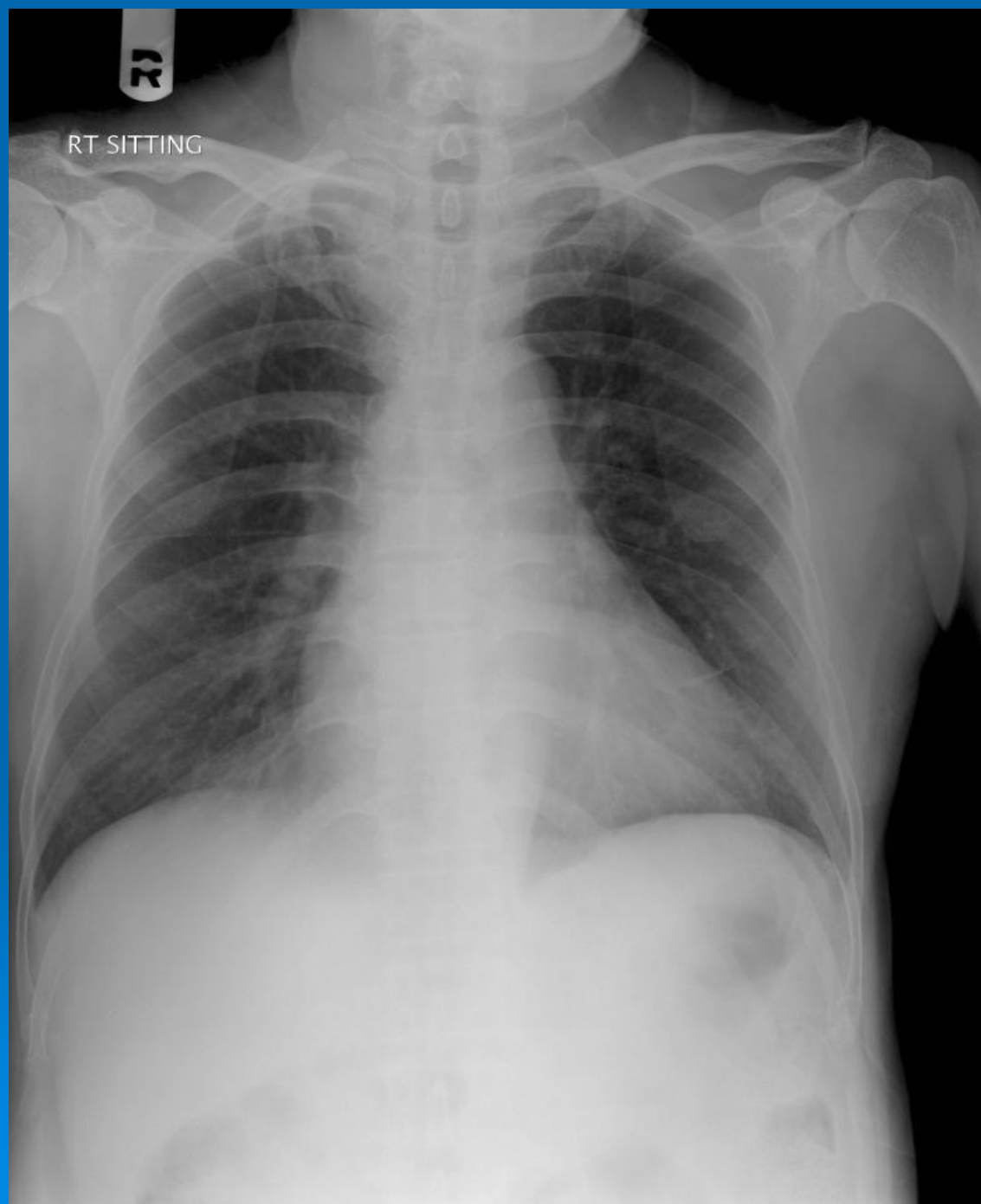


Case

- 61/M
- Ex-smoker, Ex-drinker
- Lives alone in Shek Kip Mei Estate
- HT
- Atypical chest pain, normal coro 6 years ago
- Anxiety
- Right chest wall lesion with Bx one year ago showed papillary eccrine adenoma

Case

- Complained of fever, cough, sputum, runny nose to CMC AED
- Fever for 3 days
- No abdominal pain



Case

➤ Triage to OLMH Medical

Progress in OLMH Medical

- P/E on arrival to OLMH
 - Chest and Abdomen NAD
- Blood test:
 - WCC 8.5, Hb 11.7, Plt 86
 - RFT normal
 - LFT Bil 36, ALP109, ALT 177, Amylase 137
- Put on augmentin

Progress in OLMH Medical

- Found RUQ pain, desaturation on day 4
- Blood tests on day 3
 - RFT normal
 - LFT Bil 129, ALT 131, ALP 136

Progress in OLMH Medical

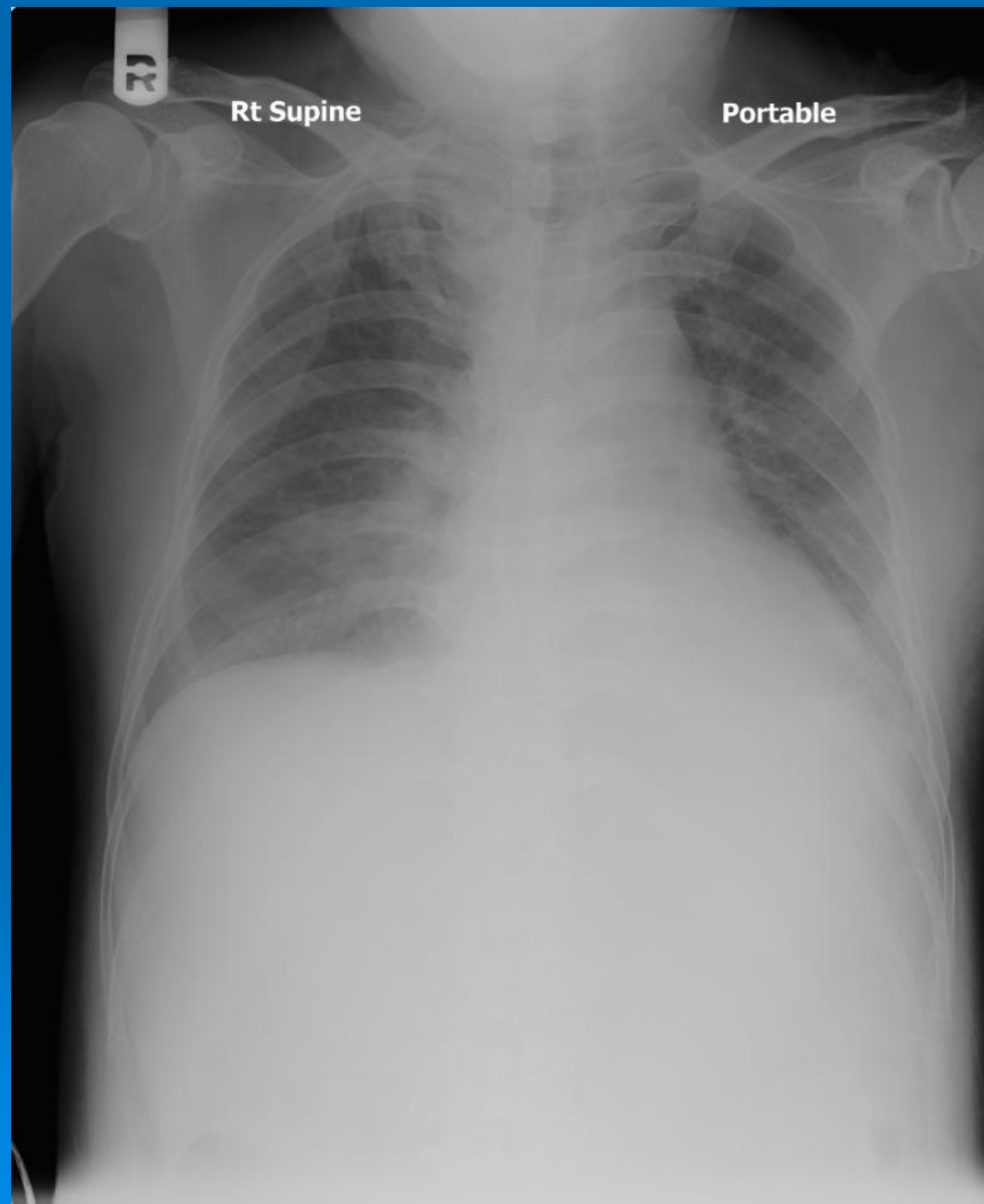
- USG abdomen -> Distended GB with increased wall thickness. No gall stone. Biliary tree not dilated. CBD 0.67cm. No ascites.

Progress in OLMH Medical

- Surgical team was consulted
 - Impression: cholangitis
 - suggested intervention
- Patient was transferred to CMC Surgery through AED

Progress in CMC Surgery

- Arrived CMC surgery on day 4 evening
- Fever
- Epigastric tenderness



Progress in CMC Surgery

➤ Blood tests:

- RFT Ur 15.5, Cr 233
- LFT Bil 238, ALT 109, ALP 158, Amylase 266
- Blood gas: pH 7.04, pCO₂ 16.7, pO₂ 77, HCO₃ 9.5, BE -12.7

Progress in CMC Surgery

- Repeat septic workup
- Put on suplerazon
- ICU was consulted on next day morning (day 5)

Progress in ICU

- Alert, BP 170/62, HR 120/min
- Chest – bilateral crepitations
- Abdomen - epigastric tenderness
- Repeated septic workup, antibiotic – sulperazon and ampicillin

Progress in ICU

➤ Bedside USG

- No SOL in liver. CBD 7mm. Mildly distended GB containing sludges and with thickened wall. Murphy's sign negative. Right renal cyst. No hydronephrosis.

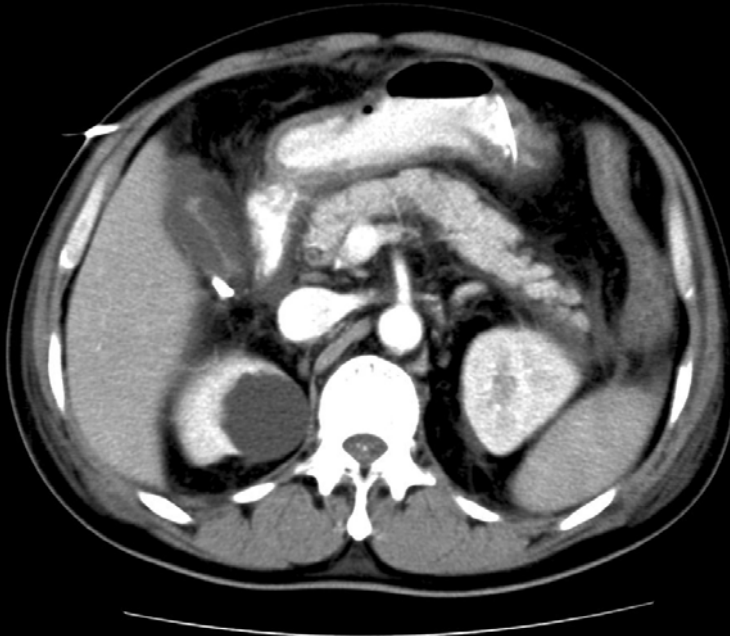
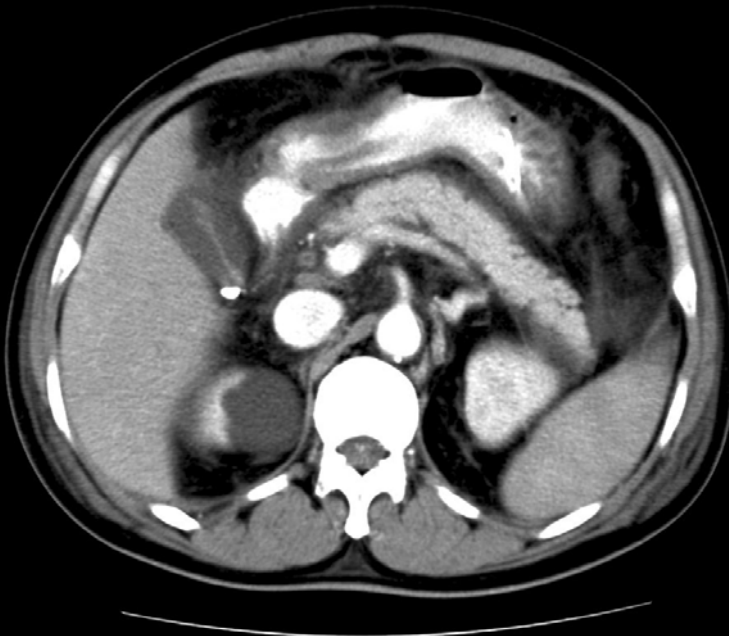
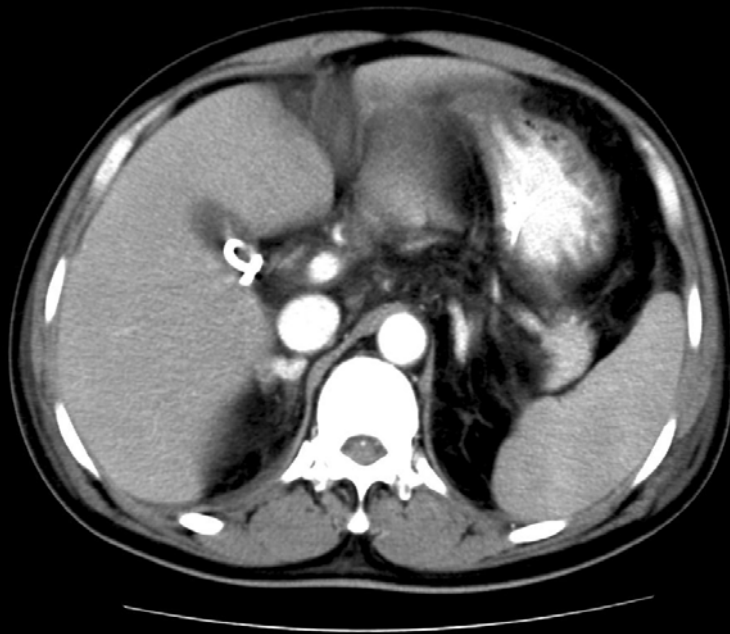
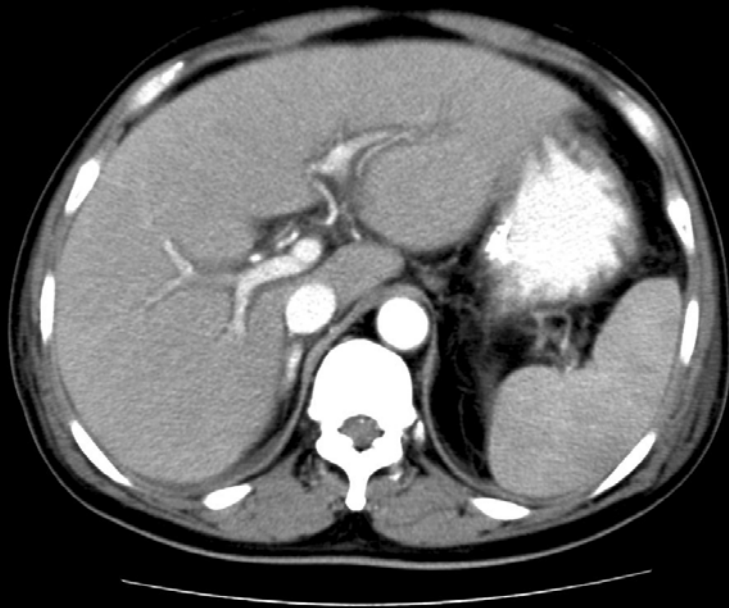


Progress in ICU

- Discussed with hepatobiliary team
 - Impression: acaculous cholecystitis with sepsis and cholestatic jaundice
- Suggested immediate USG guided transhepatic drainage of gall bladder

Progress in ICU

- Intubation, required high PEEP and O2
- Not required inotropic support
- Urgent USG guided cholecystostomy was done
 - Clear bile



Progress in ICU

➤ CT abdomen

- Pigtail catheter in gallbladder with diffuse thickened wall, no stone and no evidence of biliary obstruction, diffuse peri-portal edema, inflammatory changes noted in retroperitoneum, no free gas, no lymph node

Progress in ICU

➤ WAIT...

- Lesion in right anterior chest wall



Progress in ICU

- ? Eschar
- Computer search
- Attended AED one week before for fever

Progress in ICU

- AED MO wrote a referral letter to GOPD
 - Wound on right side after climbing
 - 1cm healed wound with mild erythema
 - ? Insect bite
 - Please monitor temp and rash

Progress in ICU

- Suspected arthropod related infection
- Discussed with microbiologist -> change to levofloxacin (Bile gram stain -ve)
- More blood tests...

Progress in ICU

➤ Blood

- Leptospira IgM antibody –ve
- Malaria smear –ve
- Hantavirus IgG/IgM antibody –ve
- Dengue virus IgM antibody –ve

Progress in ICU

➤ Blood

- Weil-Felix
 - OX K:40
 - OX19: <20
 - OX 2: <20
- C/ST - no growth

➤ What's else?

Progress in ICU

➤ Skin biopsy of eschar

- Extensive necrosis in epidermis, focal necrosis in dermis
- Infiltrated by polymorphous lymphoid cells comprising small lymphocytes, activated lymphocytes and larger cells with irregular hyperchromatic nuclei and scant cytoplasm
- Immunostains show all lymphoid cells are T-cells (CD3+/CD20-)
- Immunofluorescent stains all negative
- → suspicious of T cell lymphoma

Progress in ICU

- No palpable peripheral LN
- CT – no intra-abdominal LN
- Bone marrow
 - Active trilineage haemopoiesis and increased histiocytes with haemophagocytosis. No evidence of lymphoma or malignancy
- Scar -> healing

Progress in ICU

- Extubated D5 ICU admission
- Improving trend but fever
- Further history
 - Hiking in Shek Kip Mei two weeks ago
 - Insect bite over right anterior chest wall

Progress in ICU

- First rickettsia antibody titre from DH a/v on D9 ICU
 - Spotted fever group <128
 - Typhus group <128
 - Orientia tsutsugamushi 4096
- Scrub typhus with multi-organ failure
- Reported to DH

Progress in ICU

- Change to doxycycline on D10 ICU admission
- Fever down
- Discharge to general ward on D12 ICU admission
- Discussed with pathologist, skin biopsy slides reviewed → can be reactive changes

Progress in CMC

- Cholangiogram through cholecystostomy -
> no biliary obstruction
- Removed drain
- Short course of rehab in medical ward
- Hospital stay 26 days (OLMH + CMC)

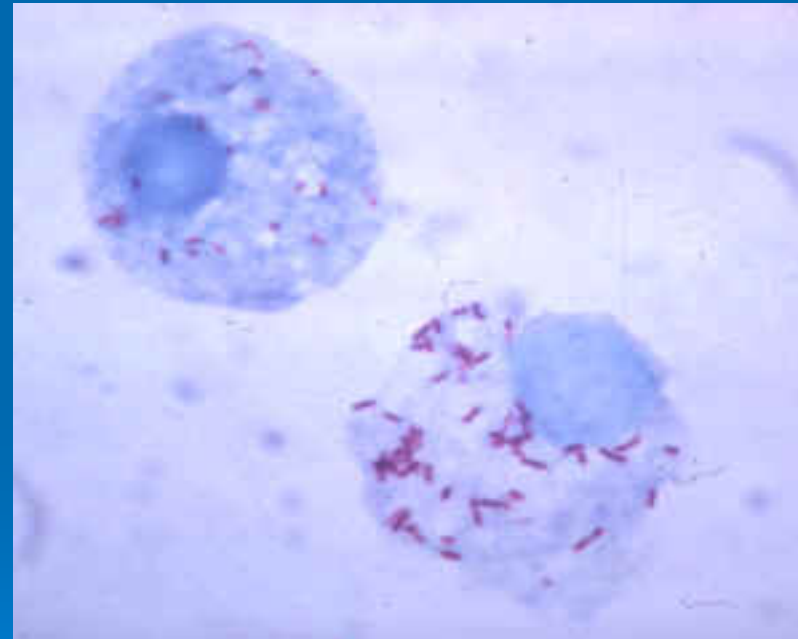
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Scrub Typhus



Rickettsia

- Small
- Gram –ve
- Aerobic
- Coccobacilli
- Obligate intracellular parasites



3 Important groups

➤ Spotted Fever group

- Rocky Mountain Spotted Fever

➤ Typhus group

- Epidemic (Louse-borne) typhus
- Murine (Endemic, Flea-borne, Urban) typhus

➤ Scrub Typhus group

- Scrub typhus (Tsutsugamushi disease)

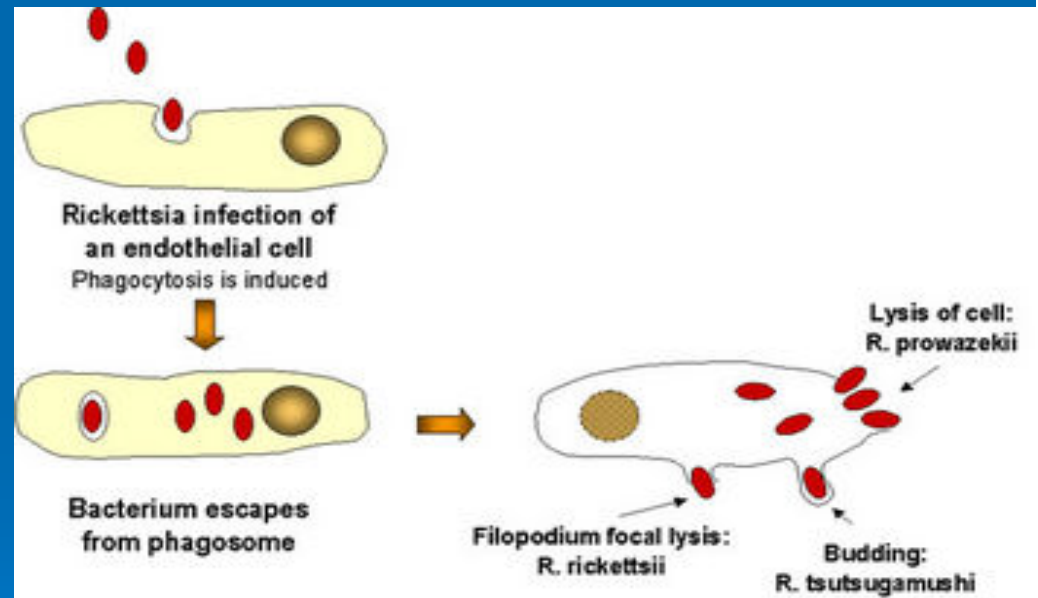
Japanese *tsutsugamushi* scrub typhus mite, from *tsutsuga* sickness + *mushi* insect

Table 1 Characteristics of Spotted Fever, Scrub Typhus and Murine Typhus

	Spotted Fever ¹⁻⁴	Scrub Typhus ^{1, 3, 5, 6}	Murine Typhus ^{1, 6, 7}
Causative agent	The spotted fever group comprises a large group of tick- and mite-borne zoonotic infections that are caused by closely related rickettsiae, e.g. <i>Rickettsia conorii</i> , <i>R. rickettsii</i> and <i>R. japonica</i> .	<i>Orientia tsutsugamushi</i> (previously known as <i>Rickettsia tsutsugamushi</i>)	<i>Rickettsia typhi</i> (previously known as <i>R. mooseri</i>)
Major vectors	Ticks (e.g. <i>Rhipicephalus sanguineus</i> — the brown dog tick, <i>Rhipicephalus appendiculatus</i> , <i>Haemaphysalis leachi</i> , and <i>Amblyomma hebraeum</i>)	Larval stage (chigger) of trombiculid mites (e.g. <i>Leptotrombidium deliense</i>)	Fleas (e.g. <i>Xenopsylla cheopis</i>)
Major reservoirs of vectors	Rodents and domestic dogs	Rodents	Small rodents like rats, such as <i>Rattus norvegicus</i> and <i>Rattus rattus</i>
Incubation period	2 to 14 days (usually 5 to 7 days)	6 to 21 days (usually 10 to 12 days)	1 to 2 weeks (usually 12 days)
Clinical manifestation	- A mild to severe febrile illness of a few days to two weeks. - There may be a primary lesion or eschar at the site of the arthropod bite. - Rash is common and may persist for one week. - Regional lymph nodes may enlarge.	- Eschar may appear at the bite wound and is associated with lymphadenopathy. - After about five days of febrile illness, maculopapular rash may appear on the trunk and extend to the extremities. The rash usually disappears in a few days. - Rarely, tremors, delirium, nervousness, slurred speech or deafness may develop in the second week of illness.	- Abrupt onset of fever, severe headache, chills and myalgia are early clinical features. - Around 50% of the patients will develop maculopapular rash over the trunk and extremities. - Nausea, vomiting and cough are not uncommon.
Prognosis	Prognosis is largely related to the timeliness of initiation of appropriate therapy.	- Renal failure, septicaemia and encephalopathy may occur in severe cases. - Deaths are rarely encountered with prompt recognition and early appropriate treatment. - Repeated attacks are possible as a result of heterologous infection from different strains.	- The clinical course is usually uncomplicated. Children usually experience minimal neurologic changes. - One attack confers lifelong immunity.
Case fatality rate	Less than 3%	- In untreated cases, the rate varies from 0-30%, according to area, strain of infectious agent and previous exposure to disease. - Consistently higher among older people.	- Overall less than 1% but risk increases with age.
Treatment	Tetracycline and chloramphenicol	- Tetracycline, doxycycline and chloramphenicol - Azithromycin and rifampicin have been used successfully in pregnant patients.	- Tetracycline, doxycycline and chloramphenicol

Mechanism

- Proliferates intracellular
- Subsequently spreads throughout the body via blood stream or lymphatics
- Tropism for endothelial cells



➤ Net effects

- Endothelial injury
 - Lymphohistocytic vasculitis
- Wide spread rickettsii-induced vasculitis
 - Minute foci of haemorrhage
 - Increased vascular permeability
 - Vascular thrombosis and haemorrhage in severe case
 - Wide spread organ dysfunction

Complication

- Hypotension
- Cardiac involvement
 - Arrhythmia, myocarditis
- Pulmonary involvement
 - Non-cardiogenic pulmonary edema
 - Pneumonitis
- CNS
 - Encephalitis
- GI & Hepatic injury
 - Hepatic cell death and elevation of liver enzyme
- Mortality
 - ~ 20-40% in untreated patients (scrub typhus)
 - ~ 2-5% (scrub typhus)

➤ Infectious DDX

- Leptospirosis
- Viral haemorrhagic fever
- Dengue
- Malaria
- Typhoid

➤ Co-infection

Scrub Typhus

- *Orientia tsutsugamushi* (previously called *Rickettsia tsutsugamushi*)
- First described by the Chinese in the third century
- Did not appear in the western literature until the end of the nineteenth century.
- Knowledge about scrub typhus increased dramatically during World War II

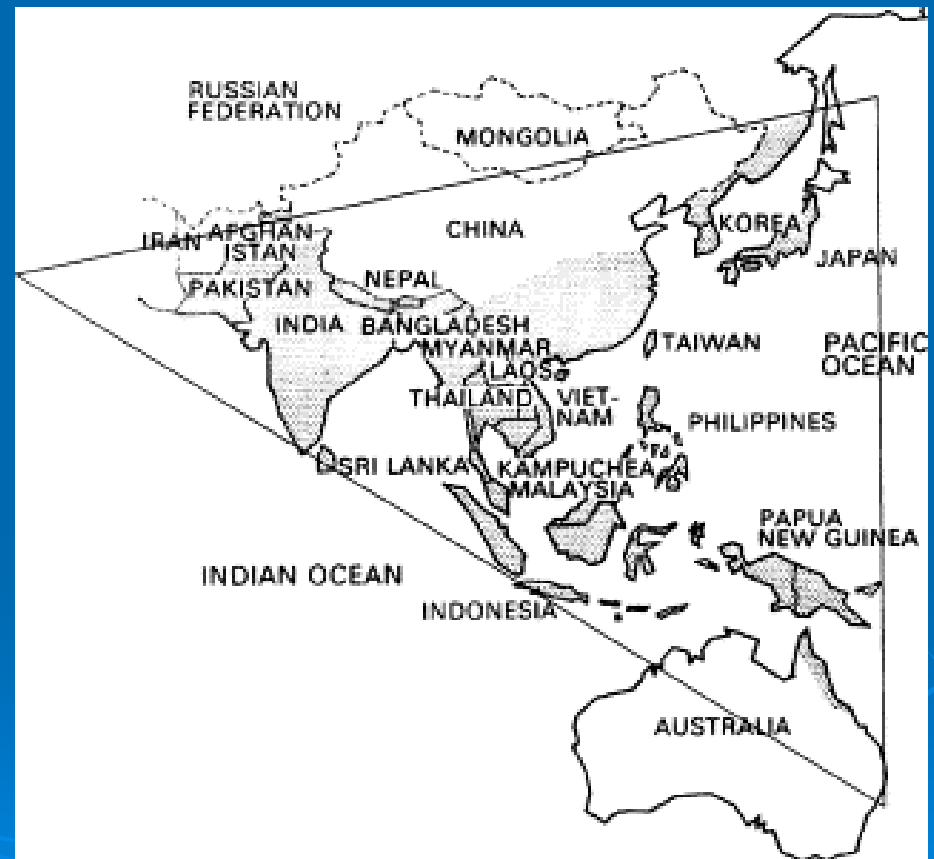
Scrub Typhus

➤ *O. tsutsugamushi*

- unique in that it is released from infected cells by budding from the plasma membrane of host cells
- may then be phagocytosed by adjacent cells while still coated with its original host cell membranes
- phospholipase A2 appears to be involved as a mediator of entry into host cells with subsequent release from phagosomes and injury to the host cell

Scrub Typhus

- Asia Pacific rim
- Endemic in Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia, and Queensland, Australia

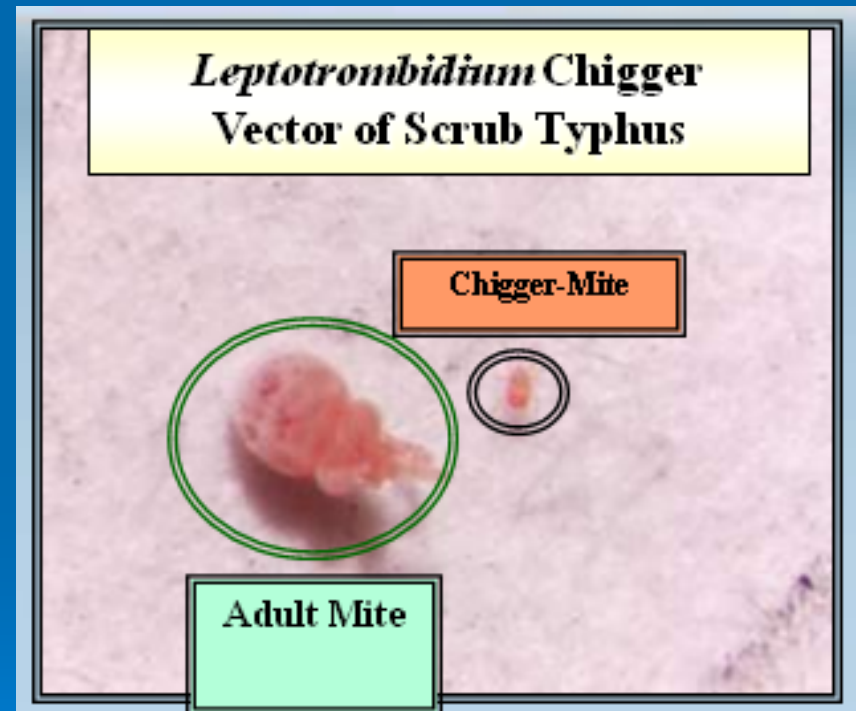


Scrub Typhus

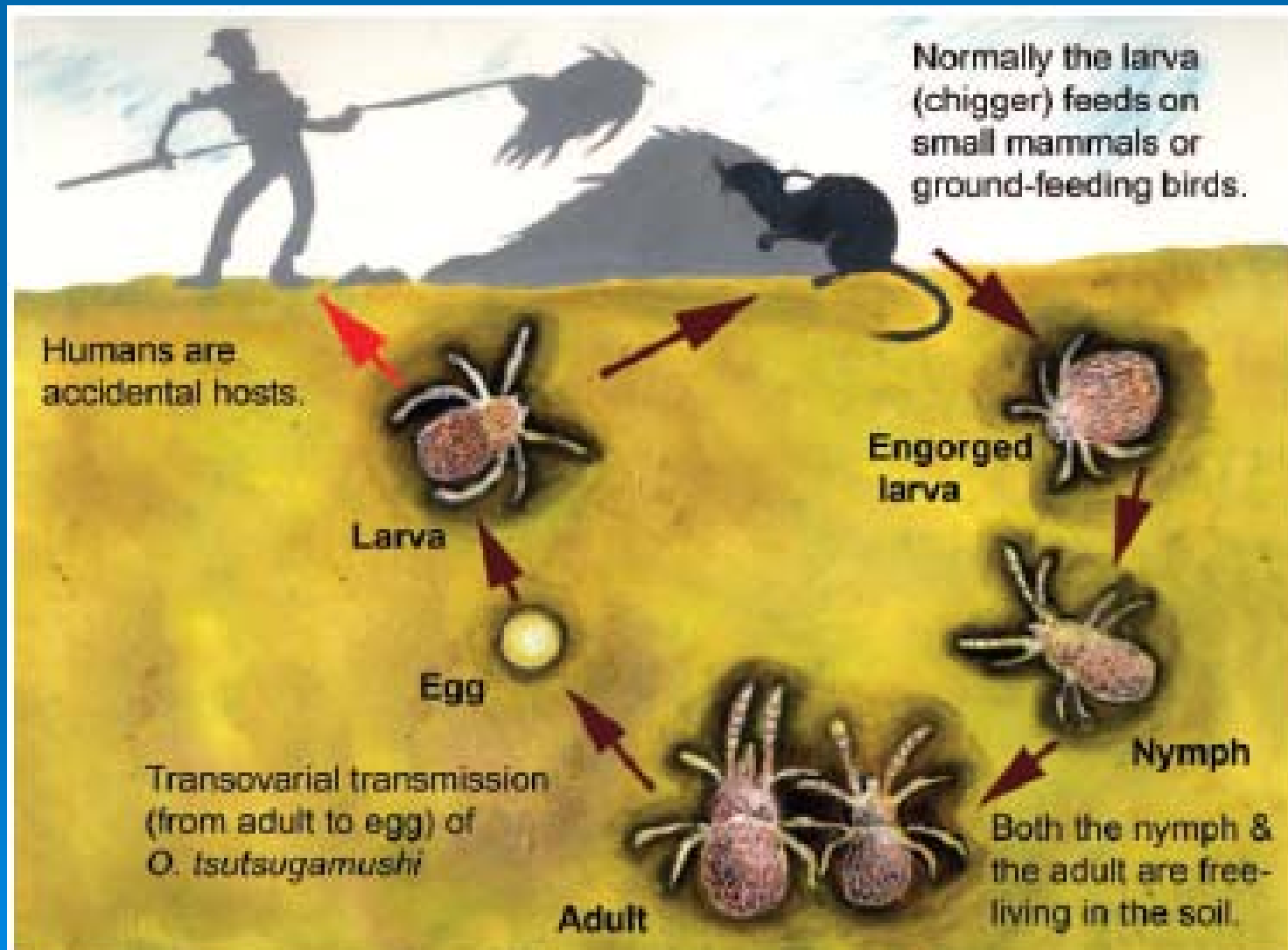
➤ Vectors

- larval trombiculid mites of the genus *Leptotrombidium*
- (also known as chiggers)

➤ Incubation period 7-10 days



Scrub Typhus



Diagnosis

➤ Diagnosis

- Clinical and epidemiological
 - Recall tick bite ?
- Imaging
- Blood tests
- Biopsy

Table 1 Reported clinical symptoms in scrub typhus patients

Authors	Tattersall ⁶	Berman and Kundin ⁷	Ogawa and colleagues ⁸	Jensenius and colleagues ^{9,10}
Year of publication	1945	1973	1998	2004, 2006
Number of cases	500	87	462	23
Location	India/Burma	South Vietnam	Japan	Thailand, Burma, Vietnam, and Malaysia, Papua New Guinea, The Philippines, Korea, India
Population	Soldiers and local	Soldiers	Local	Travelers
Fever (%)		100	98	100
Rash (%)	64	34	93	50
Headache (%)	100	100	46	100
Eschar (%)	11	46	87	55
Adenopathy (%)	92	85	52	85
Splenomegaly (%)	47	43		43
Hepatomegaly (%)	64	34	36	NR
Elevated transaminases (%)	NR	NR	87	15

NR = not reported.



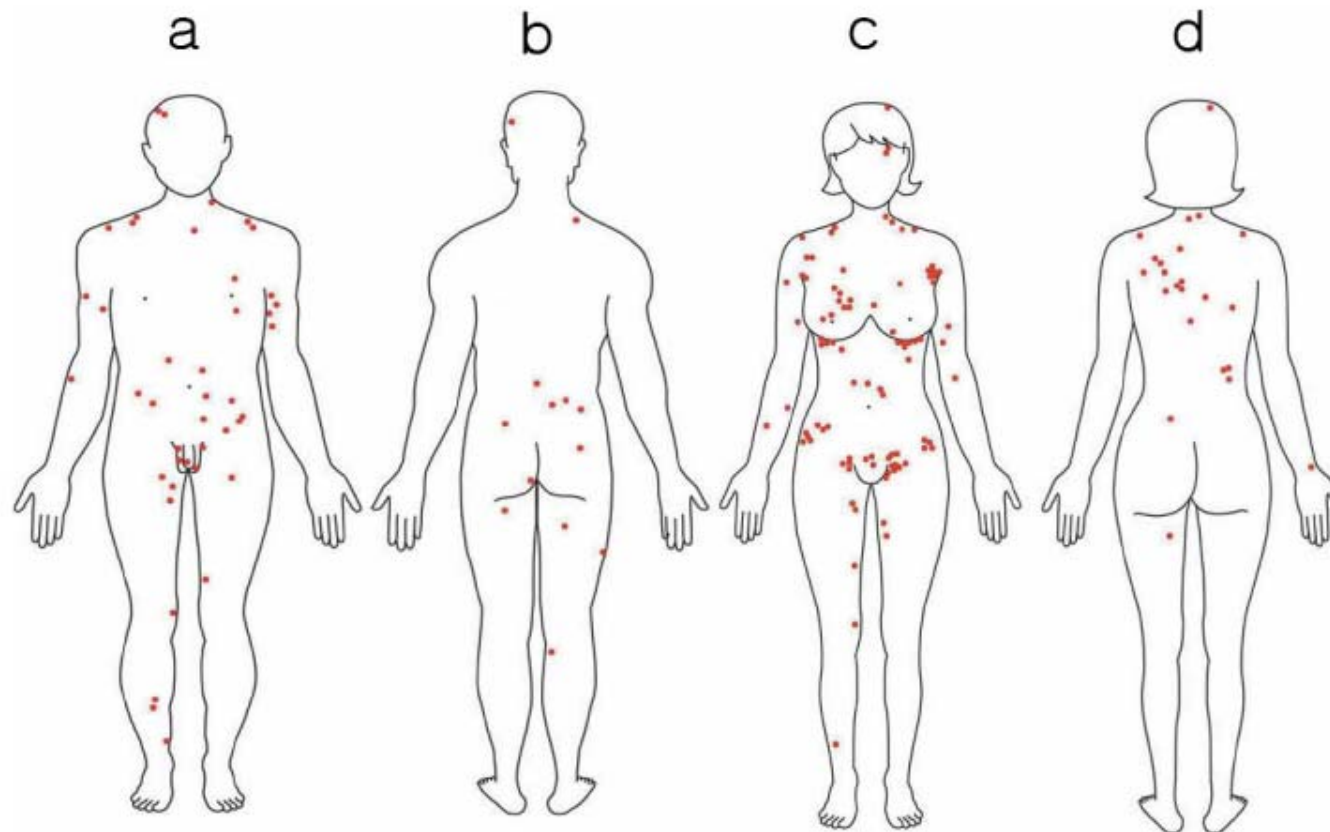


FIGURE 1. Sites that manifest an eschar in scrub typhus patients: (a) male front, (b) male back, (c) female front, (d) female back. This figure appears in color at www.ajtmh.org.



Scrub Typhus Mimicking Deep Neck Infection Inter Med 47: 1997-2000, 2008

Liver function tests in scrub typhus patients

	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	T-Bili (mg/dL)	PT (sec)	ALB (g/dL)
No.	28	24	19	1	13	5	6
Median	148	120	168	82	0.9	10.75	2.7
IQR	73–175	83–206	117–201	0	0.5–1.2	10.25–11.20	1.9–3.0
Range	14–461	24–538	76–485	0	0.4–8.9	9.8–11.6	1.8–3.5
Rate of abnormality (%)	89.3% (25/28)	91.7% (22/24)	84.2% (16/19)	—	38.5% (5/13)	0	83.3% (5/6)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ -glutamyl transpeptidase; T-Bili, total bilirubin; PT, prothrombin time; ALB, albumin; No., number; IQR, interquartile range.

TABLE 1. Demographic and clinical characteristics and outcome.

	Case 1	Case 2	Case 3	Case 4
Month/year of admission	October 2005	October 2005	November 2005	November 2006
Age (yr), gender	12, F	14, M	11, F	10, M
Days of illness at a myocarditis episode	7	8	8	9
Other signs/symptoms	Cough, dyspnoea	Headache, drowsiness	Headache, abdominal pain	Jaundice, hepatomegaly
Eschar lesion(s)	A few	One	None	None
Haematological parameters				
Haematocrit (%)	32.8	25.7	40	18
WBC (/mm ³)	3900	8300	8980	12,900
Platelet count (/mm ³)	25,000	47,000	39,300	55,000
<i>O. tsutsugamushi</i> IFA titre				
Blood sample 1 (days of fever)	IgM 1:800, IgG 1:1600 (7)	IgM 1:800, IgG 1:200 (7)	IgM 1:200, IgG 1:400 (8)	IgM >1:400 (10)
Blood sample 2 (days of fever)	-	IgM 1:1600, IgG 1:3200 (14)	IgM 1:400, IgG 1:1600 (14)	-
Cardiac parameters				
Chest radiograph	CTR 60%, mild venous congestion	CTR 65%, bilateral pulmonary infiltration, pleural effusion	CTR 45%	CTR 60%, venous congestion
Electrocardiogram	Low voltage, ST-T changes, wide QRS, PVCs, ventricular tachycardia	Low voltage, ST changes, PVCs	ST-T changes, prolonged PR	Low voltage, ST-T changes, ventricular tachycardia
Echocardiogram	Mild LA & LV dilation, EF 45%	Mild LA & LV dilation, EF 26%	EF 37%	Mild LA & LV dilation EF 36%, pericardial effusion
Creatine kinase-MB (normal 0.63–5 U/L)	6.9	37	21	42.3
Cardiac troponin-T (normal <0.01 ng/ml)	0.05	<0.01	0.036	0.065
NT-proBNP (normal 5–391 pg/ml)	2972	4465	1350	>35,000
Treatment				
Anti-rickettsial antibiotic(s), no. of days illness at receiving	IV chloramphenicol, 7	Oral doxycycline, 5 IV chloramphenicol, 7	IV chloramphenicol, 7	IV chloramphenicol, 10
	Case 1	Case 2	Case 3	Case 4
Other supportive treatment	Dopamine, dobutamine, epinephrine, amiodarone, prednisolone, on ventilator	Dopamine, dobutamine, methylprednisolone, IVIG 2 g/kg, intra-aortic balloon pump, on ventilator	Dopamine, dobutamine, methylprednisolone	Dopamine, dobutamine, milrinone, amiodarone, methylprednisolone, on ventilator
Outcome	Died day 10, ventricular tachycardia, shock	Alive: EF recovered by 1 wk	Alive: EF recovered by 1 wk	Died day 13, ventricular tachycardia, shock

CTR, cardiothoracic ratio (normal <50%); EF, ejection fraction of left ventricle (normal ≥50%); IV, intravenous; PVC, premature ventricular contractions.

TABLE 1
Characteristics and clinical course of eight scrub typhus patients with ARDS*

No.	Age (years), Sex	Underlying diseases	Complications	Antibiotics course	A day	I day	Duration of ventilation	Outcome
1	66, F	None	Acute hepatic failure Acute renal failure Urinary tract infection	Penicillin plus ceftriaxone, doxycycline	Day 14	Day 9	7 days	Survived
2	70, F	HTN	UGI bleeding Pneumonia (<i>Pseudomonas Aeruginosa</i>)	Cefamazin plus gentamicin, Oxytetracycline	Day 9	Day 4	9 days	Survived
3	71, M	COPD	Acute hepatic failure UGI bleeding Urinary tract infection	Piperacillin plus amikacin, doxycycline	Day 2	Day 3	13 days	Survived
4	44, F	None	Acute hepatic failure UGI bleeding CVP line infection	Penicillin plus ceftriaxone, doxycycline, Clindamycin	Day 7	Day 8	27 days	Survived
5	24, F	Pregnancy (31 weeks)	Pre-eclampsia	Penicillin plus ceftriaxone, oxytetracycline	Day 2	Day 5	10 days	Survived
6	24, F	None	Acute hepatic failure	Levofloxacin, Doxycycline	Day 7	Day 8	8 days	Survived
7	75, M	DM COPD	Acute hepatic failure Seizure UGI bleeding Pneumonia (<i>Acinetobacter baumannii</i>) (<i>Conynebacterium</i>)	Ceftriaxone plus Amikacin, Doxycycline, Teicoplanin	Day 9	Day 4	35 days	Died
8	69, M	COPD Gouty	Acute hepatic failure Acute renal failure UGI bleeding	Penicillin plus Ceftriaxone, Doxycycline, Ceftizoxime	Day 16	Day 14	9 days	Died

* ARDS = acute respiratory distress syndrome; A day = the day when antibiotic use was started. I day = the day when the patient was intubated after the onset of illness; HTN = hypertension; UGI = upper gastrointestinal; COPD = chronic obstructive pulmonary disease; CVP = central venous pressure; DM = diabetes mellitus.

TABLE 1
Clinical descriptions of 92 hospitalized patients with rickettsial infections*

Clinical observations	%	Clinical observations	%
Possible exposure	65.2	Scrub typhus	37.0
Recalling insect bite	19.6	Death	0.0
Fever	98.9	Major organ dysfunctions	23.9
Headache	65.2	ICU admission	14.1
Myalgia	40.2	Prolonged LOS > 10 days	26.1
Rash	65.2	Correct initial diagnosis	10.9
Eschar (site of eschar: trunk)	52.2 (75.0)	Doxycycline therapy (within 3 days of admission)	85.9 (55.4)
Lymphadenopathy	22.8	Ever received macrolide	17.4
Hepatomegaly	13.0	Ever received fluoroquinolone	38.0
Splenomegaly	15.2	USG of liver performed	57.6
Abnormal LFT result	92.4	Lumbar puncture	12.0
Peak ALT > 3 times ULN	42.4	Urine RBC $\geq$ 1+	39.1
Peak bilirubin > 2 times ULN	15.2	Urine protein $\geq$ 1+	50.0
Platelet count < 140×10^9 /L	60.9	Urine WBC $\geq$ 1+	7.6
WBC > 11×10^9 /L	17.4		
Urea > 9 mmol/L	15.2		

Comparisons of patients with life-threatening rickettsiosis who required intensive care support (n = 13) with those who survived without intensive care (n = 79)*

Characteristics	ICU (n = 13)	Non-ICU (n = 79)	P
Clinical (%)			
Age, years, mean $\pm$ SD	52.2 $\pm$ 15.6	48.3 $\pm$ 14.1	NS
Male sex	61.5	55.7	NS
Scrub typhus	80.0	38.8	0.019
Possible exposure	53.8	31.6	NS
Fever	100	98.7	NS
Headache	53.8	67.1	NS
Rash	46.2	68.4	NS
Eschar	61.5	51.3	NS
Hepatosplenomegaly	23.1	14.1	NS
Pulmonary infiltrates	76.9	10.1	< 0.001
Oxygen desaturation	69.2	2.5	< 0.001
ARDS	53.8	0	< 0.001
Hypotension	66.7	1.3	< 0.001
Acute renal failure	30.8	2.5	0.003
Severe jaundice	38.5	6.3	0.004
Encephalopathy	38.5	6.4	0.005
Cardiac failure	7.7	1.3	NS
Delay in doxycycline therapy, days, mean $\pm$ SD	4.4 $\pm$ 3.9	2.9 $\pm$ 2.5	NS
Laboratory† (mean $\pm$ SD)			
Sodium (mmol/L)	130.4 $\pm$ 5.4	132.9 $\pm$ 3.9	0.050
Urea (mmol/L)	9.6 $\pm$ 6.3	5.2 $\pm$ 3.5	< 0.001
Creatinine (μ mol/L)	127.4 $\pm$ 88.0	91.5 $\pm$ 25.8	NS
Bilirubin (μ mol/L)	65.7 $\pm$ 105.2	18.9 $\pm$ 23.6	NS
Alanine aminotransferase (IU/L)	136.6 $\pm$ 90.4	145.5 $\pm$ 124.9	NS
Alkaline phosphatase (IU/L)	221.2 $\pm$ 134.8	172.1 $\pm$ 117.5	NS
White blood cell count $\times 10^9$ /L	11.8 $\pm$ 6.3	7.3 $\pm$ 3.5	0.026
Platelet count $\times 10^9$ /L	102.9 $\pm$ 42.1	129.5 $\pm$ 67.3	NS
INR	1.2 $\pm$ 0.1	1.1 $\pm$ 0.1	0.006
APTT (sec)	45.7 $\pm$ 12.1	36.4 $\pm$ 7.9	0.019
C-reactive protein (mg/dL)	140.2 $\pm$ 133.8	86.0 $\pm$ 62.2	NS

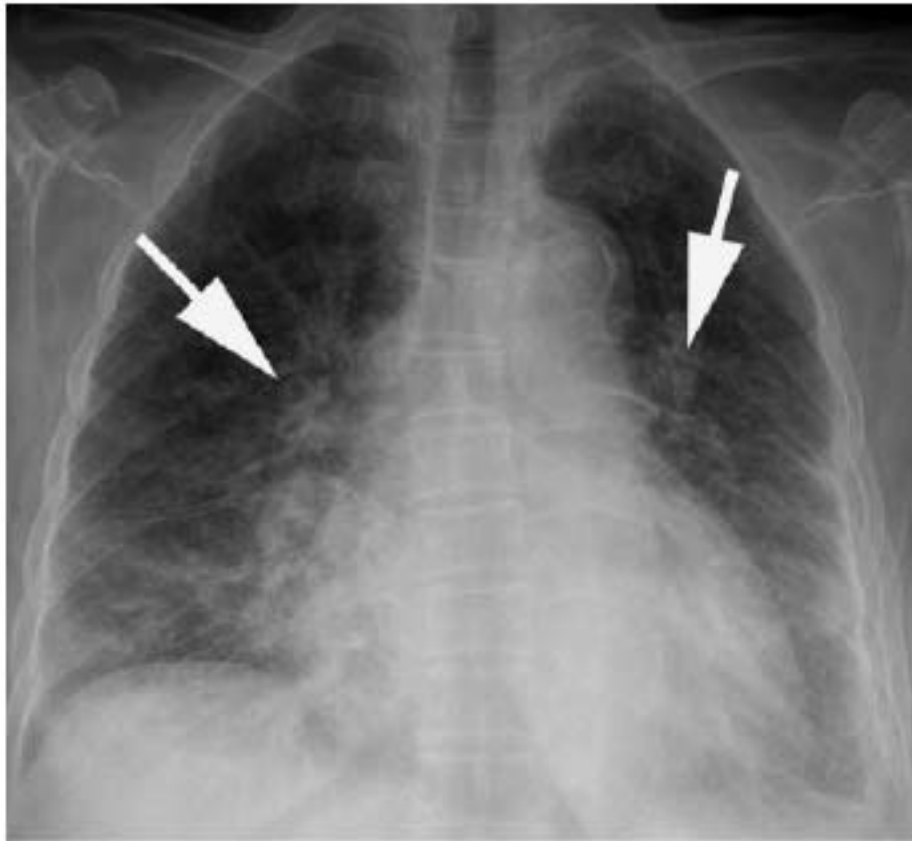
TABLE 3
Factors associated with life-threatening illnesses in hospitalized patients with rickettsial infections*

Clinical outcomes	Variables in the final multivariate model	Odds ratio (95% confidence interval)	<i>P</i>
ICU admission	Pulmonary infiltrates	25.2 (3.9–160.9)	0.001
	White blood cell count (per unit)	1.3 (1.0–1.5)	0.033
Major organ dysfunction	Delayed doxycycline (per day)	1.2 (1.0–1.5)	0.046
	Scrub typhus	3.3 (1.0–10.7)	0.051
Prolonged hospitalization > 10 days	Age (per year)	1.1 (1.0–1.1)	0.058
	Major organ dysfunction	10.0 (2.3–43.9)	0.002
	Delayed doxycycline (per day)	1.4 (1.1–1.9)	0.014

* ICU = intensive care unit.

Imaging

- Chest
- Abdomen
- Soft tissue



4.

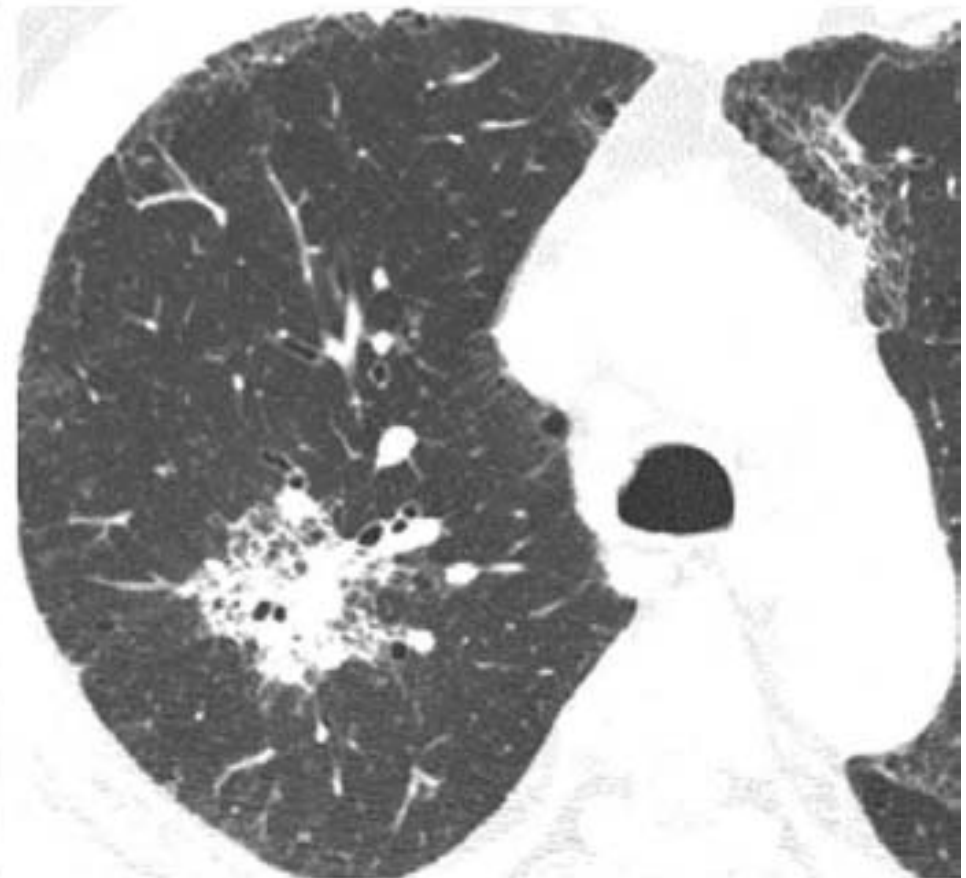


5.

Figures 4, 5. Chest radiographic findings of scrub typhus. (4) Initial radiograph in a 75-year-old woman shows septal lines, ground-glass opacity, peribronchial cuffing (arrows), redistribution of pulmonary vasculature, and an increased cardiothoracic ratio, as well as bilateral pleural effusion. Follow-up radiograph (not shown), obtained 4 days after treatment, revealed a decrease in the extent of parenchymal opacity. (5) Initial radiograph in a 66-year-old man shows multiple foci of reticular and patchy opacity in both lungs. Follow-up radiograph (not shown), obtained 5 months after treatment, showed resolution of the parenchymal lesions.

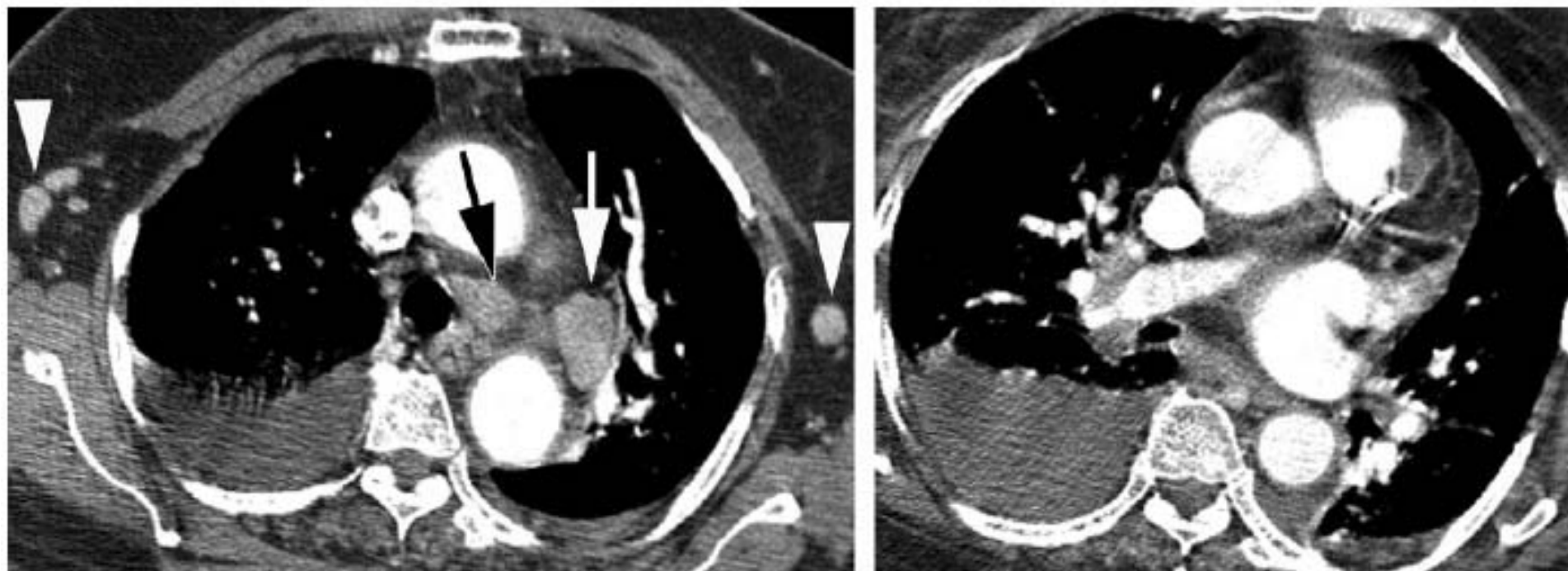


a.



b.

Figure 6. Scrub typhus in a 68-year-old man with previously diagnosed usual interstitial pneumonia. **(a)** Initial chest radiograph shows patchy opacity (arrow) in the upper lobe of the right lung and areas of reticular and ground-glass opacity near the base in both lungs, findings suggestive of usual interstitial pneumonia. **(b)** Axial thin-section (1.0-mm collimation) CT image obtained with lung window settings shows a focal area of ground-glass opacity in the upper lobe of the right lung. Follow-up thin-section CT images obtained 2 weeks later and 17 months later (not shown) revealed resolution of the parenchymal opacity in the right upper lobe.



a. **b.**

Figure 9. Scrub typhus in a 76-year-old woman. Axial contrast-enhanced CT images obtained with mediastinal window settings (**a** at a higher level than **b**) show enlarged bilateral hilar, mediastinal (arrows in **a**), and axillary (arrowheads in **a**) lymph nodes, as well as bilateral pleural effusion.

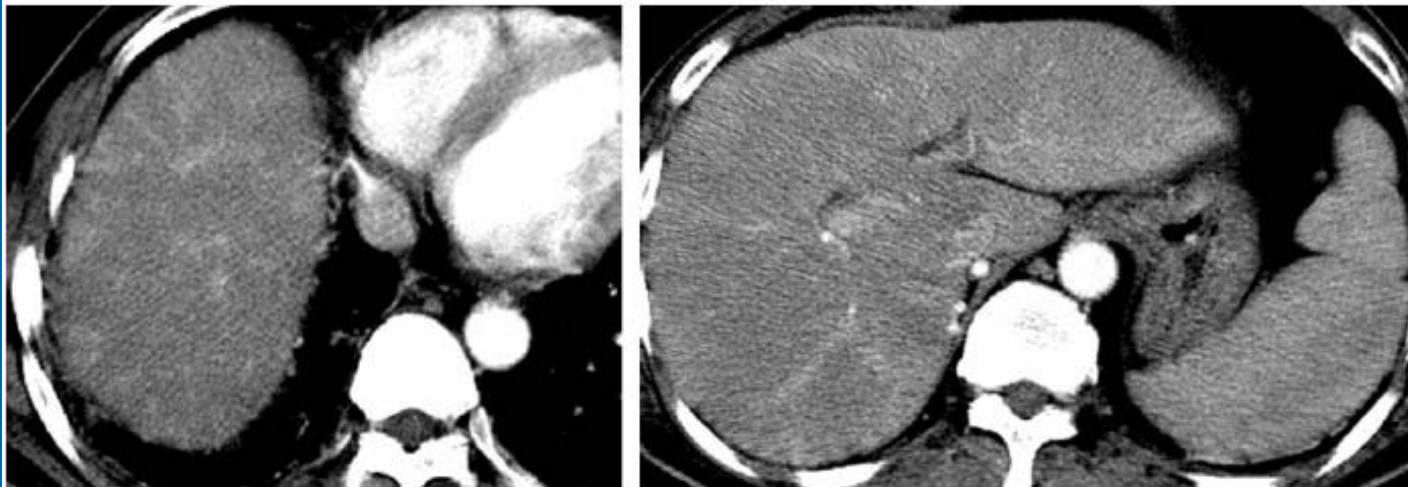


a.



b.

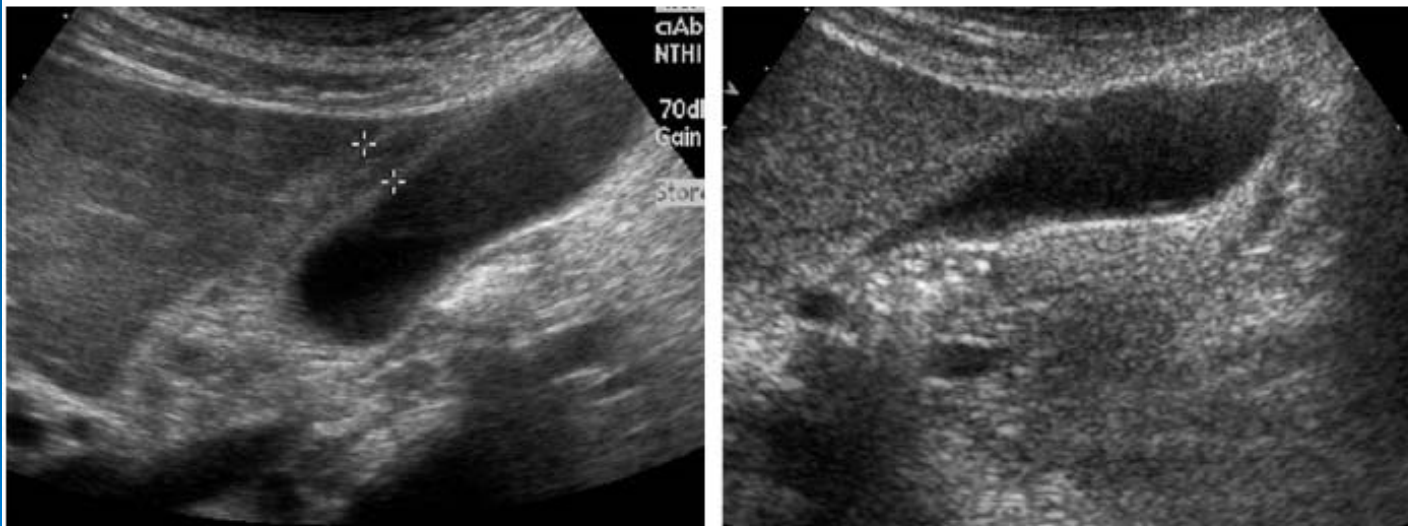
Figure 10. Acute respiratory distress syndrome in a 47-year-old woman with scrub typhus. **(a)** Initial anteroposterior chest radiograph shows diffuse ground-glass opacity in the right lung and the lower zone of the left lung and a small amount of pleural effusion in both lungs. **(b)** Follow-up anteroposterior chest radiograph obtained 6 days later shows extensive airspace consolidation in both lungs, a feature suggestive of acute respiratory distress syndrome.



a.

b.

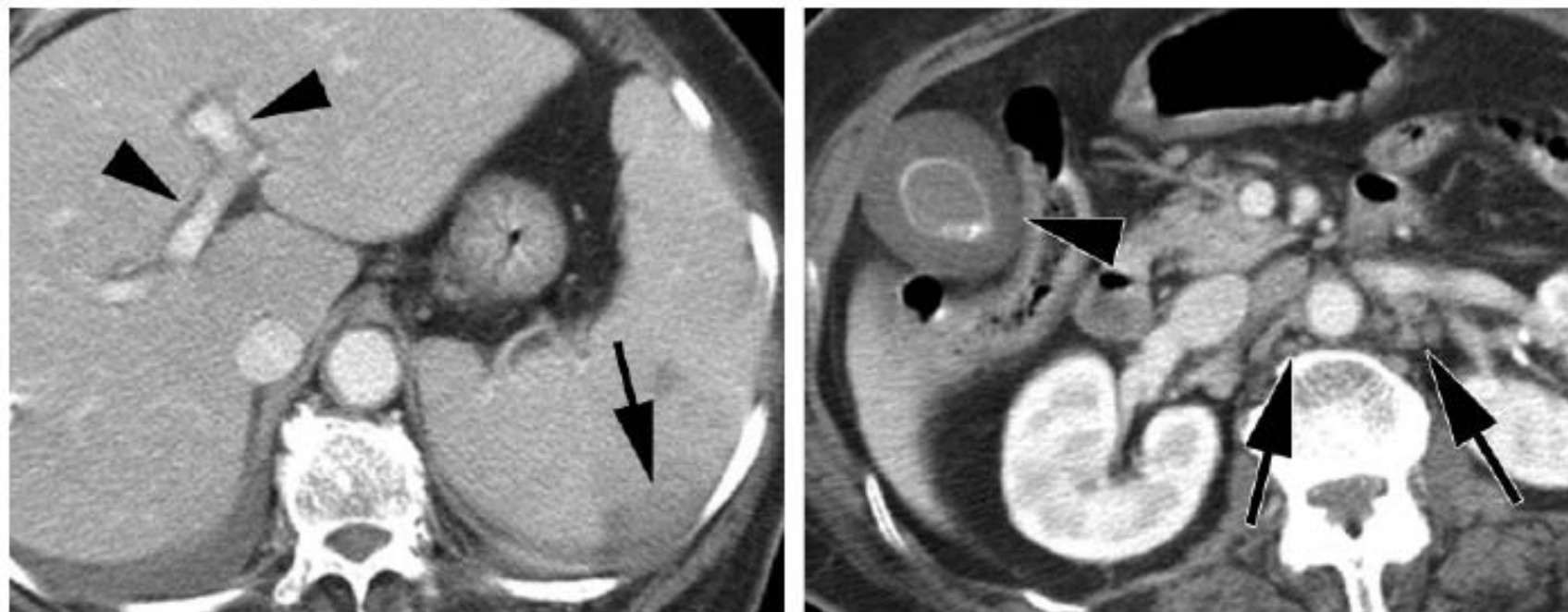
Figure 13. Scrub typhus in a 50-year-old man. Arterial phase dynamic CT images (**a** at a higher level than **b**) show mild inhomogeneous enhancement of the hepatic parenchyma as well as splenomegaly.



a.

b.

Figure 14. Scrub typhus in a 52-year-old man. (**a**) Longitudinal US image shows gallbladder wall thickening and gallbladder distention. (**b**) Transverse US image, obtained at follow-up 2 weeks after appropriate treatment, shows decreased gallbladder wall thickening.



a.

b.

Figure 16. Scrub typhus in a 78-year-old woman. **(a)** Contrast-enhanced abdominal CT image demonstrates a wedge-shaped hypoattenuated lesion (arrow) in the spleen, a finding indicative of a splenic infarct. Periportal areas of low attenuation (arrowheads) also are visible throughout the hepatic parenchyma. **(b)** Contrast-enhanced abdominal CT image, obtained at a level 2 cm inferior to **a**, depicts gallbladder wall thickening (arrowhead), a tiny gallstone, and enlarged lymph nodes (arrows) in the aortocaval and para-aortic regions.

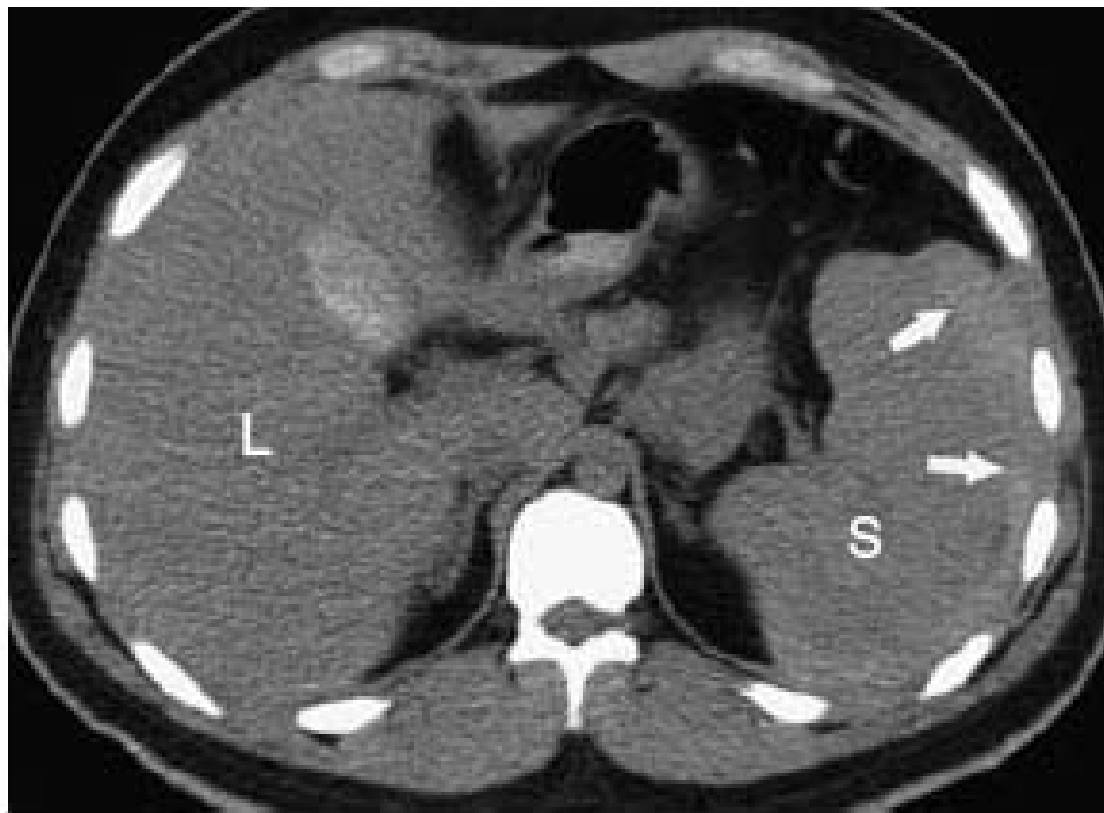


Figure 1. Non-enhanced axial CT scan showed relatively high-density fluid accumulation (arrows) in the left subphrenic space. It is consistent with spontaneous hemoperitoneum. (L, liver; S, spleen).

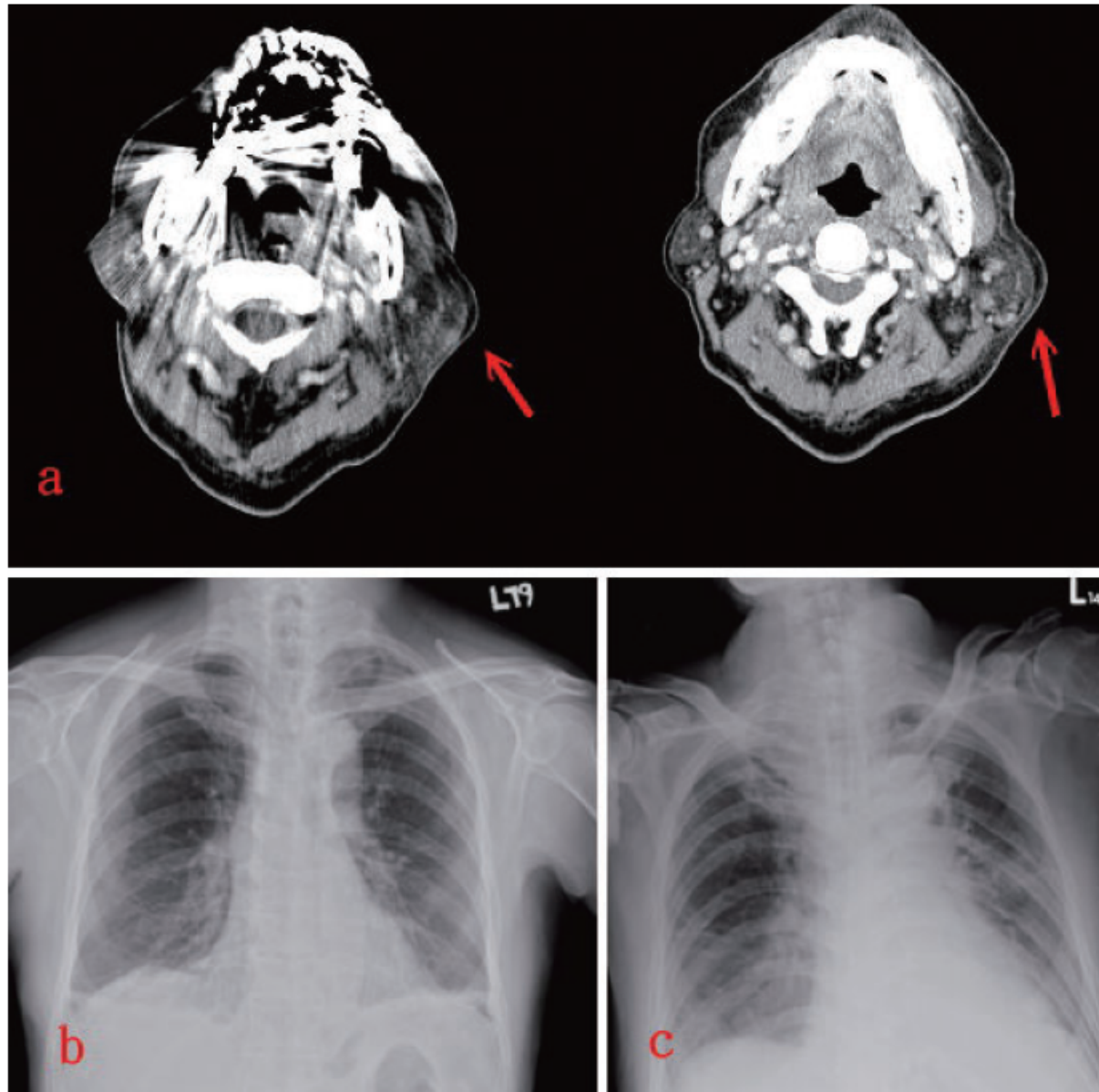


Figure 1. Computer tomography showed apparent swelling of left neck (a). Chest film appeared mildly increased infiltration on bilateral lung fields on the first hospital day (b) and progressed after two days (c).



Scrub Typhus Mimicking Deep Neck Infection Inter Med 47: 1997-2000, 2008

Labarotory tests

➤ Old vs New Techniques

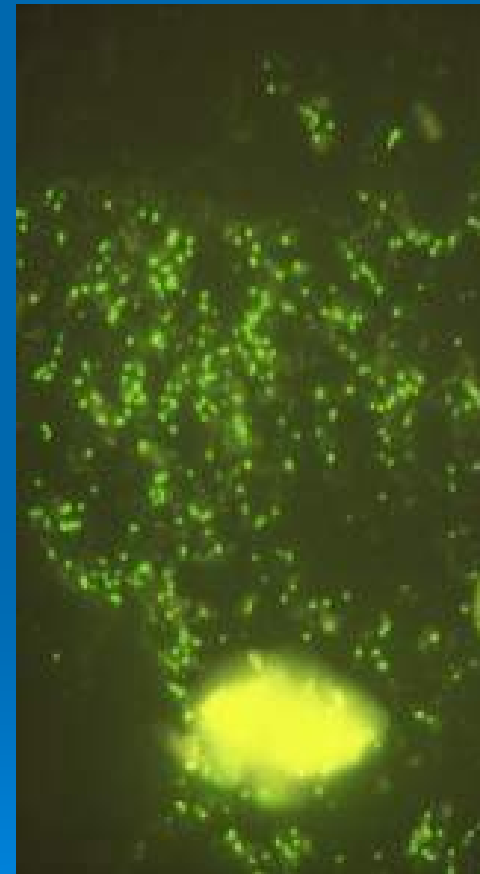


Old Technique

- 1. Giemsa Stain
- 2. Weil-Felix Proteus Agglutination Test
 - relies on the fact that *Rickettsia* and *Proteus* OX strains have common antigens.
 - for the presence & type of rickettsial disease based on the agglutination of X-strain *Proteus vulgaris* with suspected *Rickettsia* in a patient's blood serum sample.
 - OX2 – Spotted fever group
 - OX19 – Typhus and Rocky Mountain Spotted Fever
 - OXK – Scrub typhus
 - Lacks sensitivity and specificity
- 3. Complement Fixation Test (CFT)
 - serological test to detect specific antibody or specific antigen in a patient's serum.

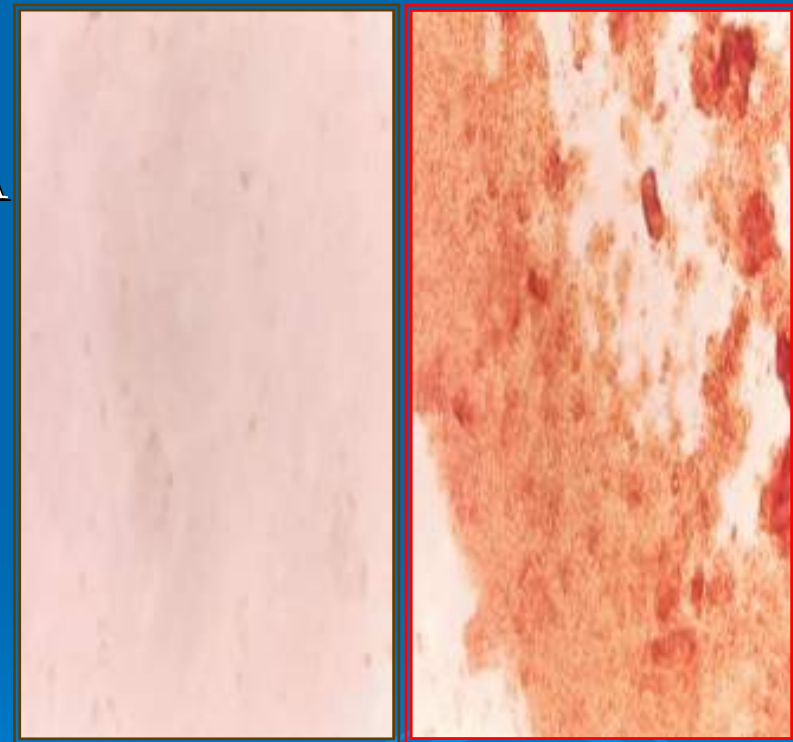
New Technique

- 1. Indirect Immuno-Fluorescence (IFA)
 - Used to detect antibodies in serum or other body fluids.
 - The specific antibodies are labeled with a compound that makes them glow an apple-green color when observed microscopically under a fluorescence microscope.



New Technique

- 2. Indirect Immuno-Peroxidase (IIP)
 - IIP= is a modification of IFA technique that replaces the fluorochrome with peroxidase.
 - Slide is observed using a bright-field microscope.
 - Staining reaction is positive when *O. tsutsugamushi* particles stain light brown.



Control

Infected

New Technique

- 3. Enzyme-linked Immunosorbent Assay (ELISA)
 - one of the most reliable techniques to detect antibody against scrub typhus infection
 - procedure is the principal for development of recent rapid diagnostic kits.
 - Pan-Bio ® Rapid diagnostic enzyme dot blot immunoassay (*PanBio Pty. Ltd, Brisbane, Australia*)
 - Standard Diagnostics (SD) BioLine Tsutsugamushi-Assay (*Standard Diagnostics Inc. Yongin-si, Kyonggi-do, Korea*)

New Technique

- 4. PCR (Polymerase Chain Reaction)
 - A real time quantitative PCR (rtq-PCR) also provide quantitative information on *O. tsutsugamushi*, especially in chigger specimens

Comparison of the accuracy and performance characteristics of assays for acute diagnosis of scrub-typhus infection

Format	Assay	Acute sensitivity	Specificity	Cost/sample	Time	Ease	Setting	Comments
Isolation	<i>In vitro</i> isolation (cell culture) ⁹	+	+++++	+++++	7–60 days	+	BSL3 reference laboratory	- Isolation of BSL3 agent - Requires infrastructure - Biocontainment issues - Retrospective diagnosis
Isolation	Mouse inoculation ¹⁰	+	+++++	+++++	5–30 days	+	BSL3 reference laboratory	- Technically demanding - Isolation of BSL3 agent - Requires animal facilities - Biocontainment issues - Retrospective diagnosis
Serology	IFA ¹⁹	++	+++	++++	2 hours	++	Reference laboratory/hospital	- Serology gold standard - Requires propagation and purification of BSL3 agents as antigen for assay - Requires fluorescence microscope - Standardization problems - Requires paired samples (retrospective diagnosis)
Serology	IIP ³	++	+++	+++	2 hours	++++	Reference laboratory/Hospital	- Serology gold standard - Requires propagation and purification of BSL3 agents as antigen for assay - Requires light microscope only - Standardization problems - Requires paired samples (retrospective diagnosis)
Serology	Weil–Felix OX-K ²⁰	+	++	+	6–18 hours	++++	Primary hospital	- Poor sensitivity for acute disease - Requires paired samples (retrospective diagnosis)
Serology	Rapid point-of-care tests (e.g., Integrated Diagnostics Dip-S-Ticks) ²⁰	++	+++	+++	< 30 minutes	+++++	Primary hospital	- Does not require specialized equipment - Rapid and simple
Genetic	Real-time PCR (16S, 56 kDa, 47 kDa, <i>groEL</i>) ^{13,15}	+++	+++++	+++	3 hours	+++	Reference laboratory/hospital	- Expensive equipment - Requires infrastructure - Sensitivity dependent on sample type and timing - Possible contamination issues
Genetic	Loop amplification (<i>groEL</i>) ¹³	+++	+++++	++	2 hours	++++	Primary hospital	- Simple - Inexpensive - Possible contamination issues

Biopsy of an eschar or rash

- Pathological hallmark of scrub typhus is a lymphohistiocytic vasculitis.
- Histologic changes in biopsies of eschars
 - Focal areas of cutaneous necrosis surrounded by a zone of intense vasculitis
 - Perivascular collections of lymphocytes and macrophages.
 - Thrombosis of small blood vessels can also occur
 - Demonstration of these typical vasculitic changes can be diagnostic, even when rickettsiae are not demonstrable by fluorescent antibody conjugates

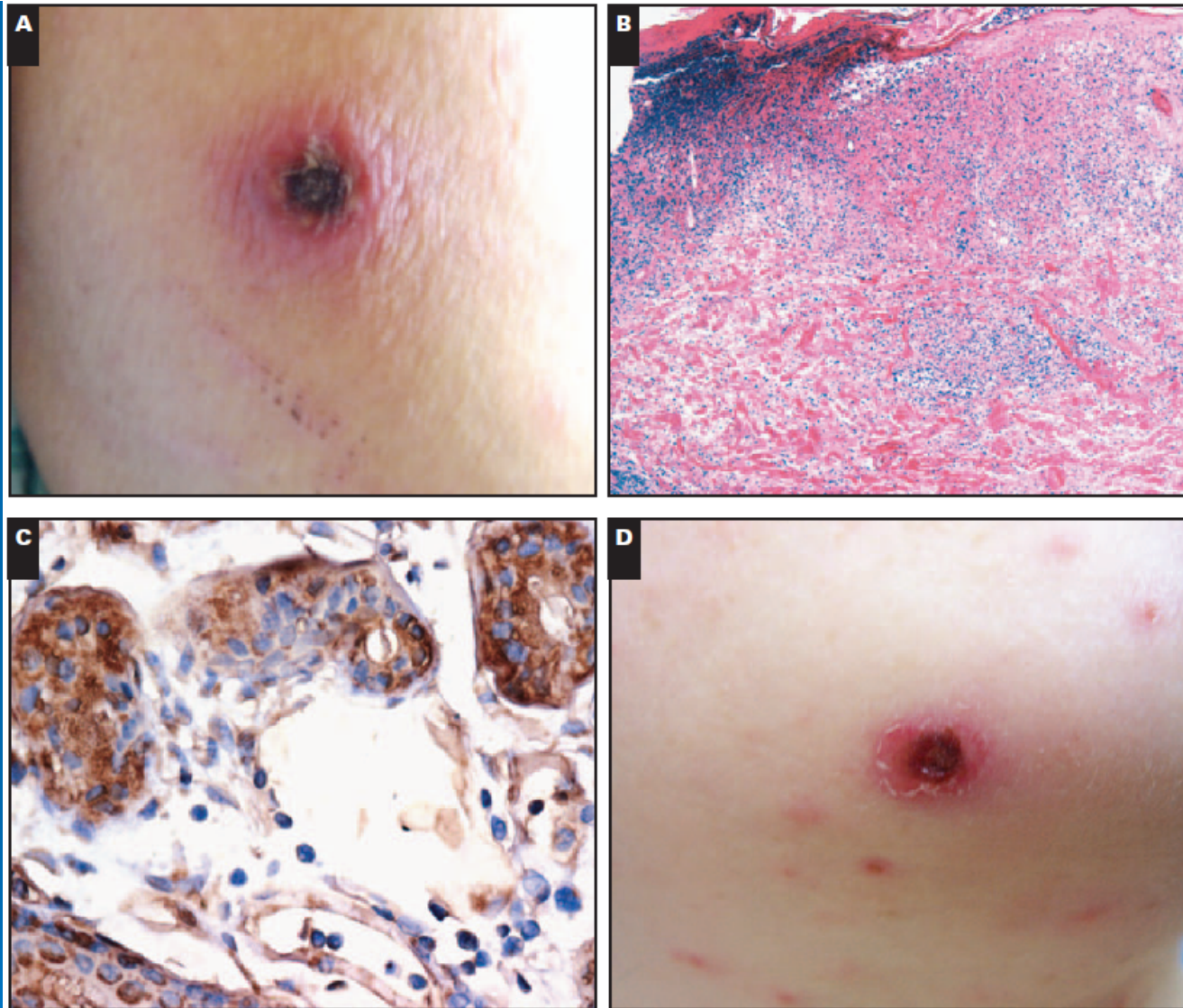


Image 1 Histopathologic findings and immunohistochemical staining of the eschar from a patient with scrub typhus (**A**, **B**, and **C**) and of the eschar-like lesions from a patient with chickenpox (**D**, **E**, and **F**). **A**, Eschar from the right shoulder of a patient with scrub typhus. **B**, Confluent epidermal necrosis with dermal vascular dilatation and perivascular inflammation was identified. Infiltration of mononuclear cells such as lymphocytes and macrophages was observed. **C**, Positive immunohistochemical staining of the vascular endothelial cells, sweat glands and a few scattered mononuclear cells around the small blood vessels and sweat glands was demonstrated. **D**, Eschar-like lesion from the submental area of a patient with chickenpox.

Diagnosis

- Clinical suspicious
- Laboratory confirmation
 - Serology, PCR
 - +/- Biopsy

Treatment

- Cochrane review in 2009 – Antibiotics for treating scrub typhus
 - Four trials involving 451 adults met the inclusion criteria
 - One small study did not demonstrate a difference between tetracycline with chloramphenicol (participants afebrile after 48 hours, Risk Ratio 1.00; 95% confidence interval 0.07 to 15.26)
 - Two small trials did not show a difference between doxycycline and tetracycline (participants afebrile after 48 hours, Risk Ratio 0.46; 95% confidence interval 0.12 to 1.75)
 - One trial showed rifampicin to be more effective than doxycycline (for eliminating fever, Risk Ratio 0.41; 95% confidence interval 0.22 to 0.77; no relapses in either group)

Treatment

➤ Doxycycline

- Standard treatment regimen consists of 200 mg of doxycycline daily for 3–14 days or 2.2 mg/kg body weight per dose administered twice daily (orally or intravenously) for children weighing <100 lbs. (45.4 kg) – CDC recommendation

➤ Chloramphenicol

- No significant differences in outcomes in patients treated with doxycycline and those patients treated with chloramphenicol

Treatment

- Strains with reduced susceptibility to tetracycline
 - Azithromycin
 - Combination with rifampicin
- Resistance
 - In Thailand
 - Azithromycin
 - Clarithromycin
 - Rifampicin
 - In Korea
 - Roxithromycin

Treatment

➤ Pregnancy

- Azithromycin is considered safer than other antibiotic in pregnant women

Treatment

Treatment and pregnancy outcomes of pregnant women with scrub typhus who were given a single dose of azithromycin*

Patient	Age (years)	GA at onset of scrub typhus (weeks)	Treatment outcome	GA at delivery (weeks)	Birth weight (g)	Fetal outcome
1	27	29	S	41	2,800	Healthy
2	31	10	S	40	3,200	Healthy
3	28	21	S	38	1,800	Healthy
4	30	29	S	40	3,600	Healthy
5	22	30	S	NA	NA	NA
6	33	20	S	40	2,800	Healthy
7	34	15	S	37	2,800	Healthy
8	29	16	S	40	3,700	Healthy
9	34	16	S	39	3,290	Healthy

* GA = gestational age; S = success; NA = not available.

Treatment

Treatment and pregnancy outcomes of pregnant women with scrub typhus in review series*

Patient	Age (years)	GA at onset of scrub typhus (weeks)	Antibiotics	Treatment outcome	GA at delivery (weeks)	Birth weight (g)	Fetal outcome	IgM titers of cord blood
A [13]	27	19	Azithromycin	S	Term	NA	Healthy	NA
B [13]	37	24	Azithromycin	S	Term	NA	Healthy	NA
C [6]	26	< 4	Azithromycin	S	–	–	Preclinical loss	–
D [6]	30	26	Azithromycin	S	NA	NA	NA	NA
E [7]	17	28	Ciprofloxacin	F	–	–	Stillbirth	–
F [7]	20	NA	Ciprofloxacin	F	–	–	Stillbirth	–
G [7]	21	11	Ciprofloxacin	F	–	–	Abortion	–
H [7]	32	16	Cefuroxime	F	–	–	Stillbirth	–
I [7]	24	30	Chloramphenicol	S	36	1,800	NA	NA
J [8]	33	29	Chloramphenicol	S	29	950	Neonatal death	Negative
K [16]	31	34	Chloramphenicol†	S	34	2,200	Neonatal ST	Positive
L [15]	NA	NA	Tetracycline†	S	Term	NA	Neonatal ST	Positive
M [14]	34	32	Minocycline	S	40	3,900	Healthy	Negative

* GA = gestational age; S = success; NA = not available; F = failure; ST = scrub typhus.

† Two mothers were treated after they delivered children.

SCRUB TYPHUS DURING PREGNANCY AND ITS TREATMENT: A CASE SERIES AND REVIEW OF THE LITERATURE *Am. J. Trop. Med. Hyg.*, 75(5), 2006, pp. 955–959

Prevention

- No effective vaccine/ chemoprophylaxis

Mite Control



HK Data (CHP)

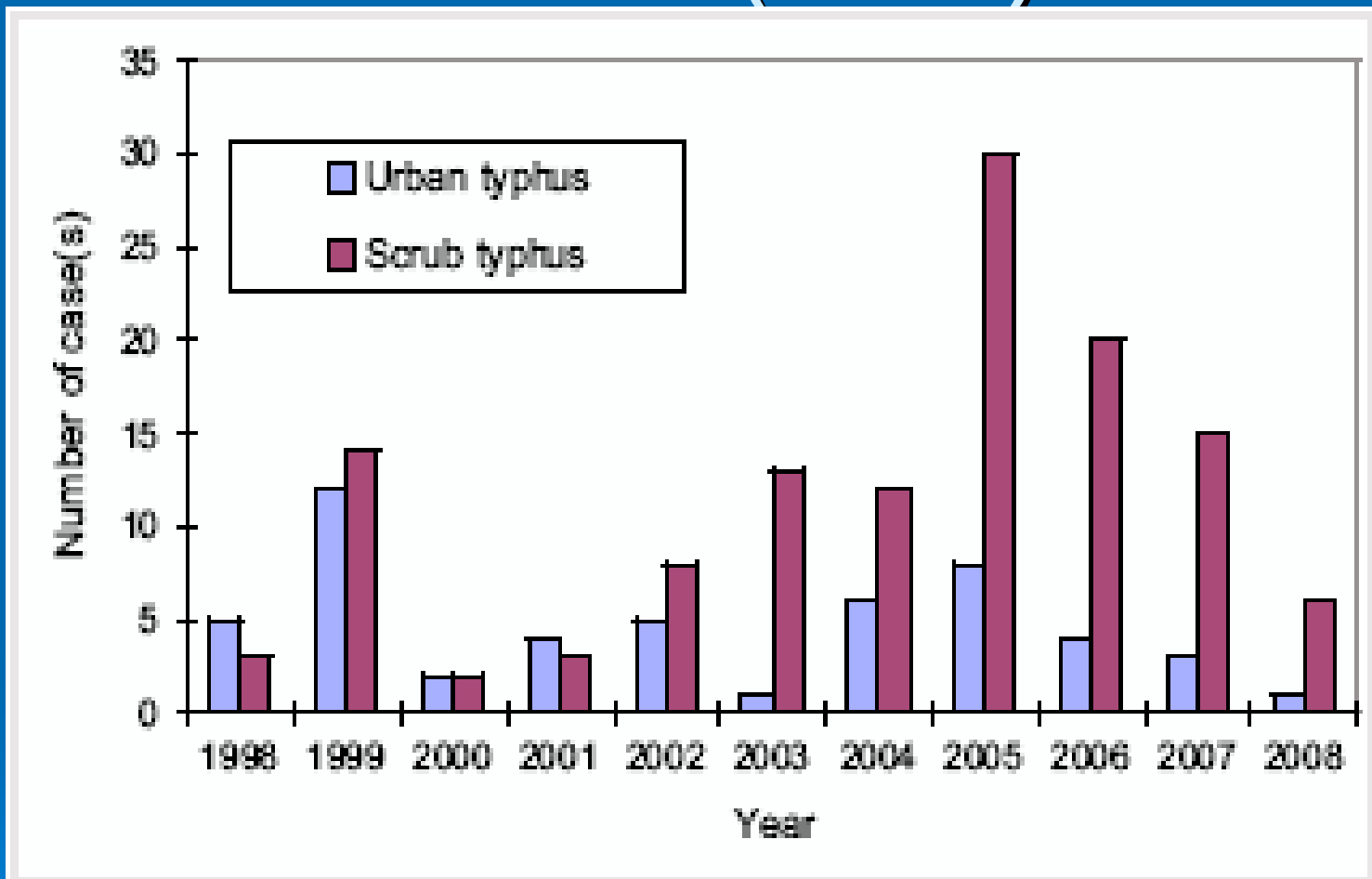
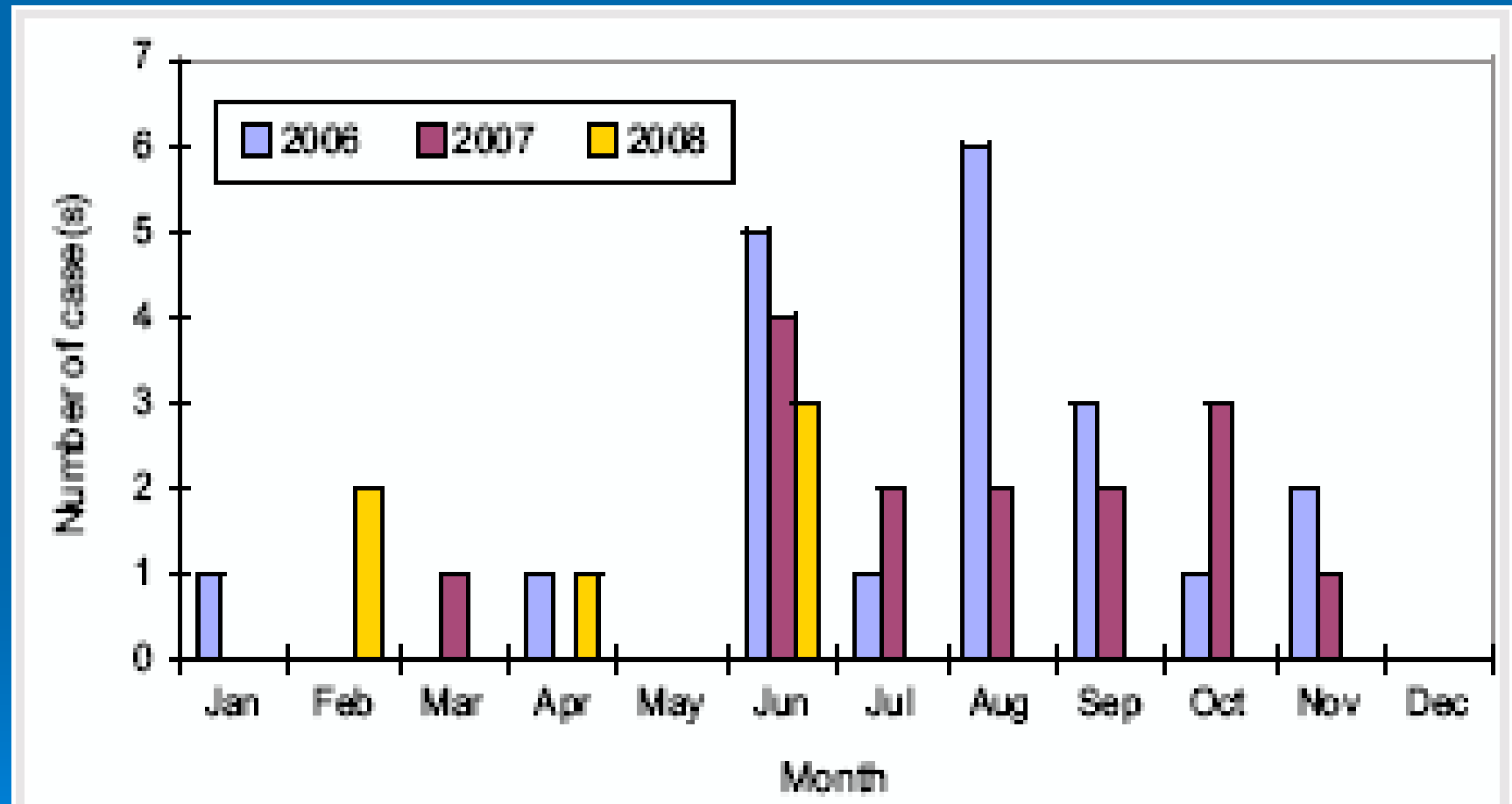


Figure 1 – Number of confirmed typhus fever case(s), 1998 to 2008 (as of June 30).

HK Data (CHP)



HK Data (CHP)

- 41 confirmed cases Jan 2006 – Jun 2008
- Local cases - 93%
- Fever - 100%
- Rash - 61%
- Headache - 59%
- Myalgia - 39%
- Eschar - 46%
- Deranged LFT - 88%
- Low platelet count - 68%

HK Data (CHP)

- All had history of exposure to vegetated areas
- Only seven cases (17%) had a clear recollection of being bitten by insects during the incubation period

HK Data (CHP)

- Field investigations conducted by the Pest Control Advisory Section of the Food and Environmental Hygiene Department
 - areas near the residence of the patients were the most common suspected places of contracting the disease (24%)
 - hiking trails (22%)
 - rural workplaces (15%)
 - other outdoor environments (15%)

HK Data (CHP)

- ICU care 20%
- No fatal case

Statistic in 2009

Disease		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Typhus and other rickettsial diseases	<i>Scrub typhus</i>	0	1	0	2	1	1	3	5	4	2	1	0	20
	<i>Urban typhus</i>	1	0	0	0	0	0	0	0	1	1	2	0	5
	<i>Spotted fever</i>	2	1	1	1	0	1	4	0	1	1	0	0	12
	<i>Unclassified</i>	0	0	0	0	0	1	0	1	0	0	0	0	2

Guidelines on the Prevention of Tick and Mite-Borne Diseases



Vector borne diseases in scrubby areas

Contracting vector borne diseases in local scrubby areas is uncommon but does occur. Some ticks and mites inhabiting the scrubby areas may carry vector borne diseases. **Scrub typhus** and **tick-borne spotted fever** are some of the diseases transmitted in the scrubby areas locally. Therefore, preventive measures should be taken when visiting the rural areas to avoid contracting these diseases.

Scrub Typhus

Scrub typhus is transmitted by Trombiculid mites. Symptoms include fever, headache and conjunctival congestion.

Biology of Trombiculid Mites

Trombiculid mites are small, only 1-2 millimetres in length, and red in colour. Some wild rodents may carry the larvae of the mites on their bodies.

The mite larvae bite animals and suck blood, a behaviour conducive to disease transmission. On man, the larvae congregate at areas where clothing is tight against the skin such as around the waist or the ankles.

Prevention of Scrub Typhus

Scrub typhus can be prevented by:

- Applying insect repellent on body as well as clothing
- Wearing light coloured long sleeved clothes and long trousers
- Avoiding sitting or lying on scrubby areas
- Avoiding hanging clothes on scrubs or trees
- Disinfesting your pets regularly

Tick-Borne Spotted Fever

Tick-borne spotted fever is transmitted by ticks belonging to family Ixodidae and Argasidae. Symptoms include fever, muscular and joint pain.

Biology of Vector Tick

Mammals such as dogs and rodents may carry ticks on their bodies.

Most larval ticks cluster at tips of grasses or leaves and seek for their preferred animals. They pierce their mouthpart deep into the skins of animals or humans to obtain blood whilst transmitting the disease. Crushing of infective ticks or its feces into human abrasions or the eyes could also be a way to have the disease contracted.

Prevention of Tick-Borne Spotted Fever

Tick-borne spotted fever can be prevented by:

- Applying insect repellent on body as well as clothing
- Wearing light coloured long sleeved clothes and long trousers
- Avoiding sitting or lying on scrubby areas
- Avoiding brushing the long grasses beside the paths
- Disinfesting pets regularly
- Do not feed stray dogs



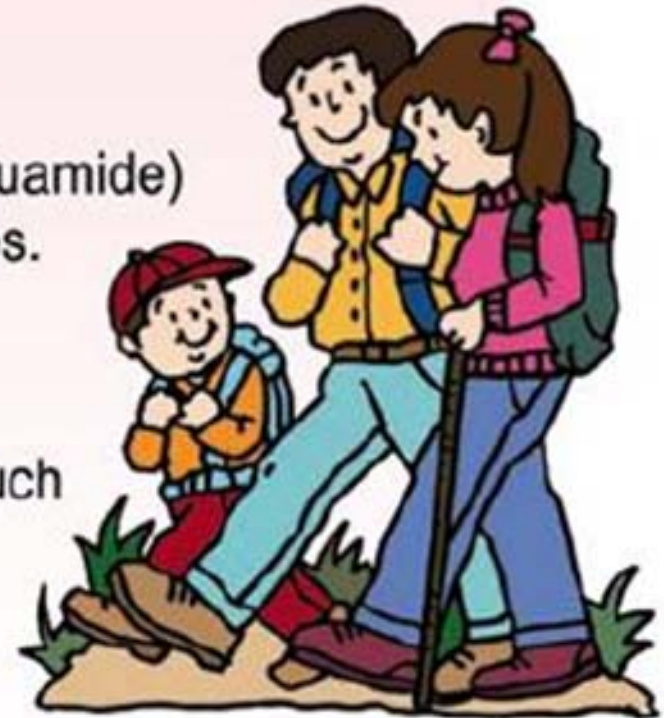
Summary

- Scrub typhus
- Septicaemia, MOF in severe case
- DDx and coinfection
- Laboratory confirmation
 - Serology
 - PCR
- Treatment is effective

Advice to visitors and hikers

Personal protection

- 🍷 Wear light-coloured long-sleeved clothes and long trousers;
- 🍷 Tuck pants legs into socks or boot tops;
- 🍷 Apply insect repellent containing 10% - 30% concentration of DEET (N, N-diethyl-meta-toluamide) to the clothes and the exposed parts of bodies. Pay close attention to the product labels, especially when applying on children; and
- 🍷 Avoid applying odour-producing cosmetics such as perfume and body lotion during outdoor activities.



Thank you

