Rickettsial diseases

November 24, 2010

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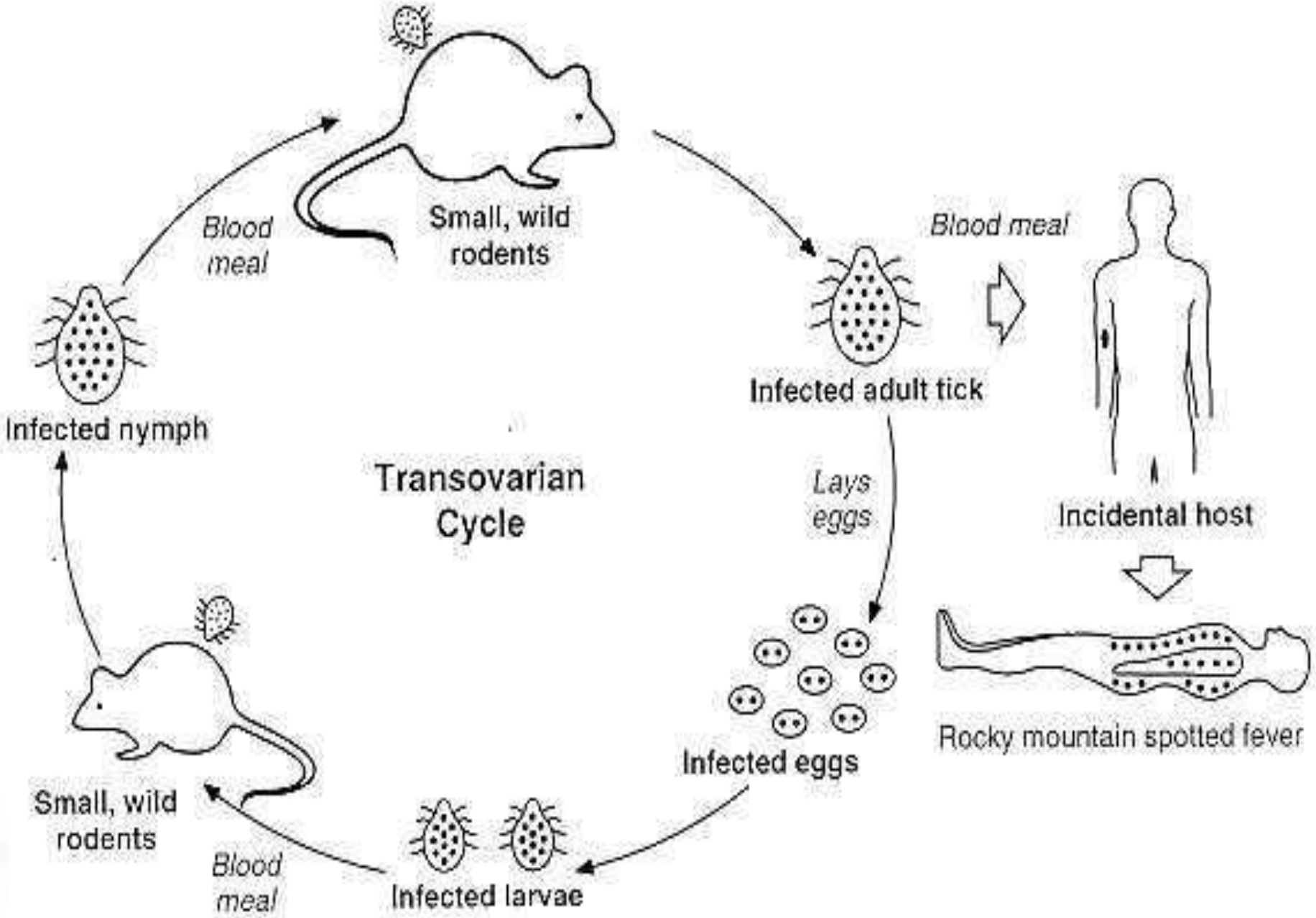
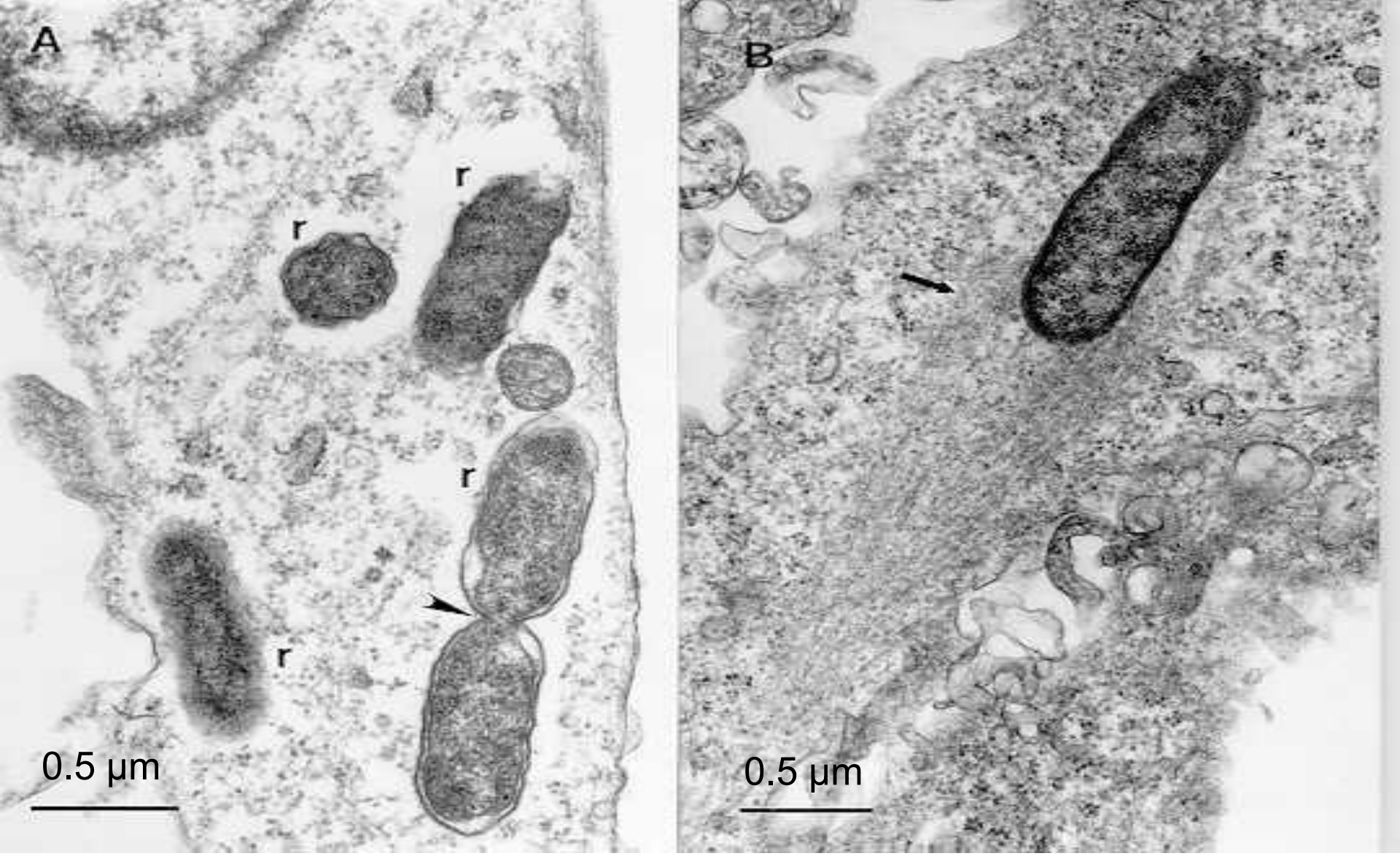
Introduction - rickettsiae

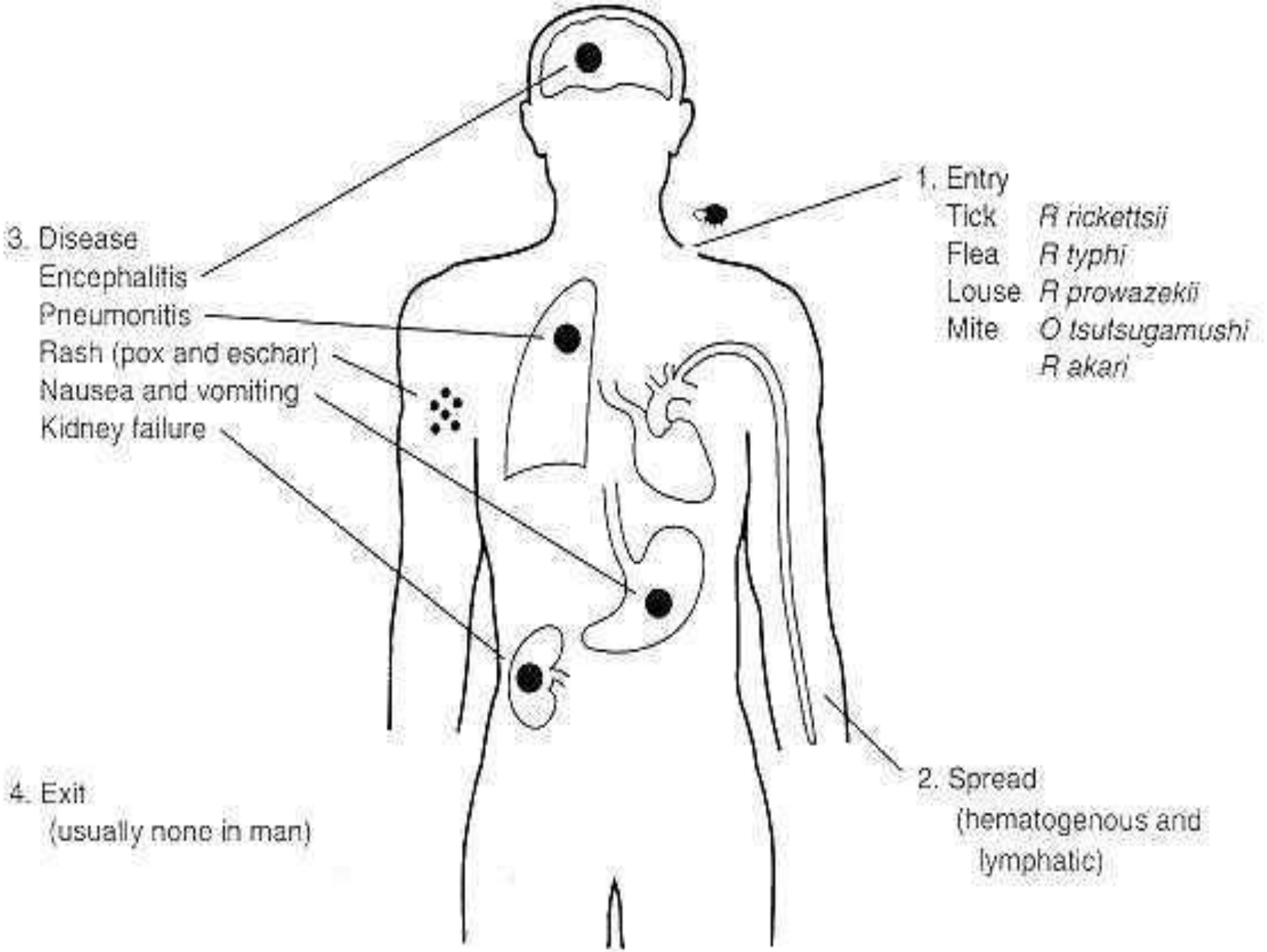
- Gram-negative coccobacilli and short bacilli that grow strictly in eukaryotic cells (obligately intracellular location)
- The pathogenic rickettsiae move through mammalian reservoirs
- Transmitted by insect or tick vectors
- Except for louse-borne typhus, humans are incidental hosts
- Coxiella burnetii (the agent of Q fever) survive for an extended period outside of the reservoir or vector and for its extreme infectiousness can cause pneumonia.
- Clinical infections with rickettsiae can be classified into six general groups:
  - (1) tick-, flea–borne spotted fever group (SFG)
  - (2) louse–borne typhus group rickettsial diseases;
  - (3) chigger-borne scrub typhus;
  - (4) tick-borne ehrlichioses and anaplasmosis;
  - (5) neorickettsiosis (sennetsu fever);
  - (6) Q fever.


Small, wild rodents
Blood meal
Infected nymph
Transovarian Cycle
Infected adult tick
Blood meal
Incidental host
Lays eggs
Infected eggs
Rocky mountain spotted fever
Small, wild rodents
Blood meal
Infected larvae



(A) Rickettsia conorii (r) in the culture of human endotelial cells – localized in the cytoplasm. (B) This rickettsia is moving to the cytoplasm of the host cells using actin filaments of the host cells.

Disease	Organism	Vector(s)	Geographic Range	IP	Dura-tion
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor andersoni* *D. Variabilis* *Amblyomma cajennense* *Rhipicephalus sanguineus*	United States United States Central/South America Mexico	2–14	10–20
Mediterranean spotted fever[a]	*R. conorii*	*R. sanguineus*	Southern Europe, Africa, Middle East, Central Asia	5–7	7–14
African tick-bite fever	*R. africae*	*A. hebraeum, A. variegatum*	Sub-Saharan Africa, West Indies	4–10	?
Rickettsialpox[a]	*R. akari*	*Liponyssoides sanguineus*	United States, Ukraine, Croatia	10–17	3–11
Cat-flea typhus	*R. felis*	*Ctenocephalides felis*	North and South America, Europe	8–16	8–16
Epidemic typhus	*R. prowazekii*	*Pediculus humanus corporis*	Worldwide	7–14	10–18
Brill-Zinsser d.	*R. prowazekii*	— [b]	Worldwide	Years	7–11
Murine typhus	*R. typhi*	*Xenopsylla cheopis*	Worldwide	8–16	8–16
Scrub typhus[a]	*Orientia tsutsugamushi*	*Leptotrombidium deliense*	Asia, Australia, New Guinea, Pacific Islands	6–21	6–21


1. Entry
Tick R rickettsii
Flea R typhi
Louse R prowazekii
Mite O tsutsugamushi
R akari
2. Spread
(hematogenous and
lymphatic)
3. Disease
Encephalitis
Pneumonitis
Rash (pox and eschar)
Nausea and vomiting
Kidney failure
4. Exit
(usually none in man)

Classification according the clinical course

Very severe course

Species	Disease	Vector	Distribution
R. prowazekii	Epidemic typhus	Louse (veš)	Worldwide
R. rickettsii	Rocky Mountain SF	Tick (klíště)	America
O. tsutsugamushi	Scrub typhus	Mite (roztoč)	SE-Asia, Australasia

Classification according the clinical course

Mild or intermediate course

Species	Disease	Vector	Distribution
R. typhi (mooseri)	Endemic typhus	flea	Worldwide
R. felis	Flea typhus	Flea	USA, Europe
R. conorii	Fièvre boutonneuse	tick	Mediterranean, Africa (India?)
R. africae	African Spotted Fever (SF)	tick	Africa, Caribbean
R. sharoni	Israeli SF	tick	Middle East
R. sibirica	North Asian SF	tick	Siberia, Mongolia
R. japonica	Japanese SF	tick	Japan
R. australis	Queensland SF	tick	Australia
R. honei	Flinders Island SF	tick	Australia
R. mongolotimonae	Atypical fièvre boutonneuse	tick	Asia, Europe, Africa
R. helvetica	Influenza syndrome	tick	Europe
R. slovaca	Insufficient data	tick	Europe
R. akari	Rickettsialpox	mite	USA, Africa

RECENT CLASSIFICATION

- α-proteobacteria (*Rickettsiales*)

  „spotted fever“ group:

  – *Rickettsia rickettsii* – RMSF)
  – *R. conorii*, *R. africae*, … - Tick typhus

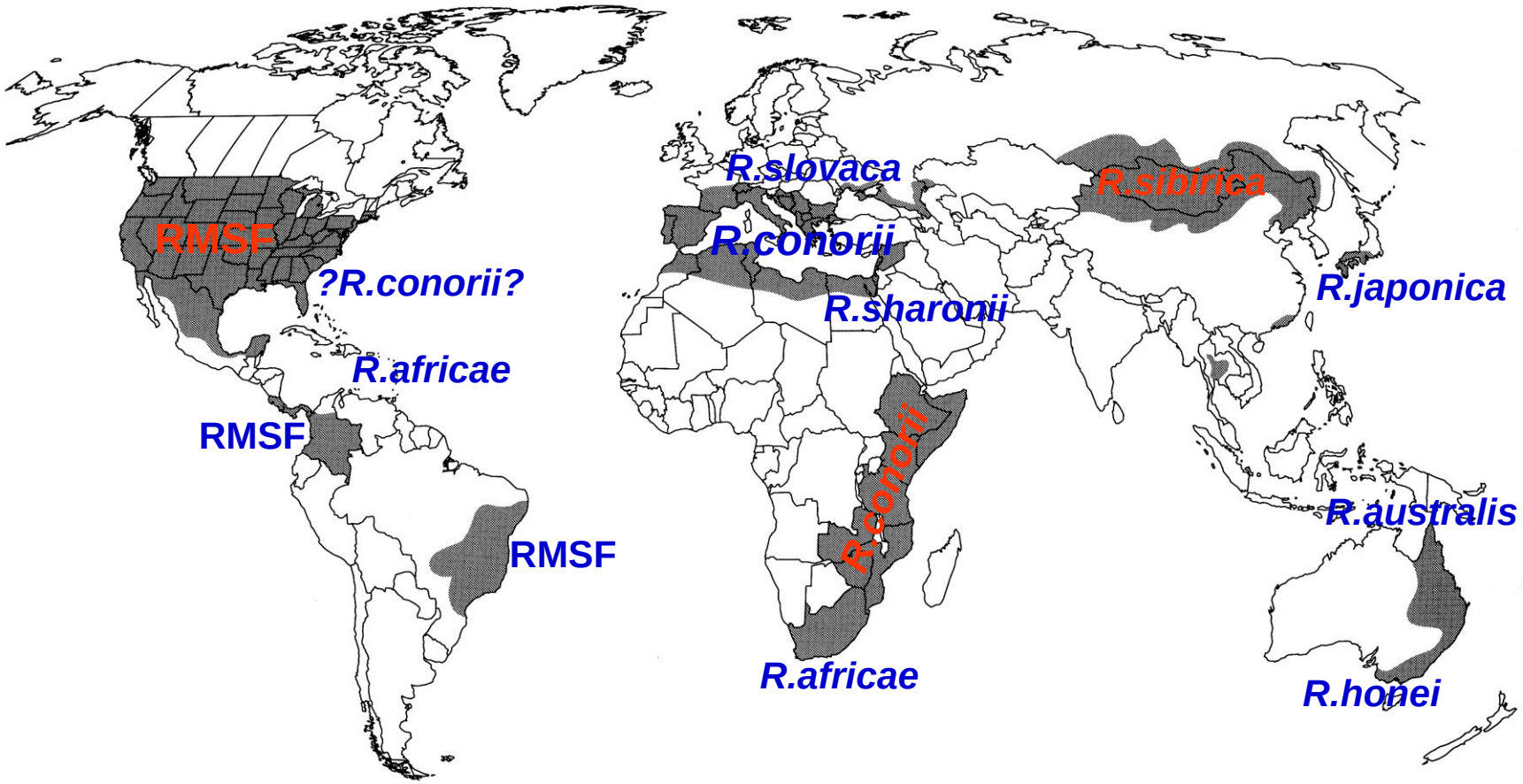
  Ehrlichiosis:

  – *Anaplasma phagocytophilum* – human granulocytic anaplasmosis (HGA); 1994
  – *Ehrlichia ewingii* – granulocytic ehrlichiosis – dog, deer, (human)
  – *Ehrlichia chaffeensis* – human monocytic ehrlichiosis (HME); 1986

  Neorickettsia sennetsu – Far East, 1953, sy IM

- γ-proteobacteria
  – *Coxiella burnetii* – Q fever
  – *Francisella tularensis* - tularemia

TICK-BORNE RICKETTSIOSES

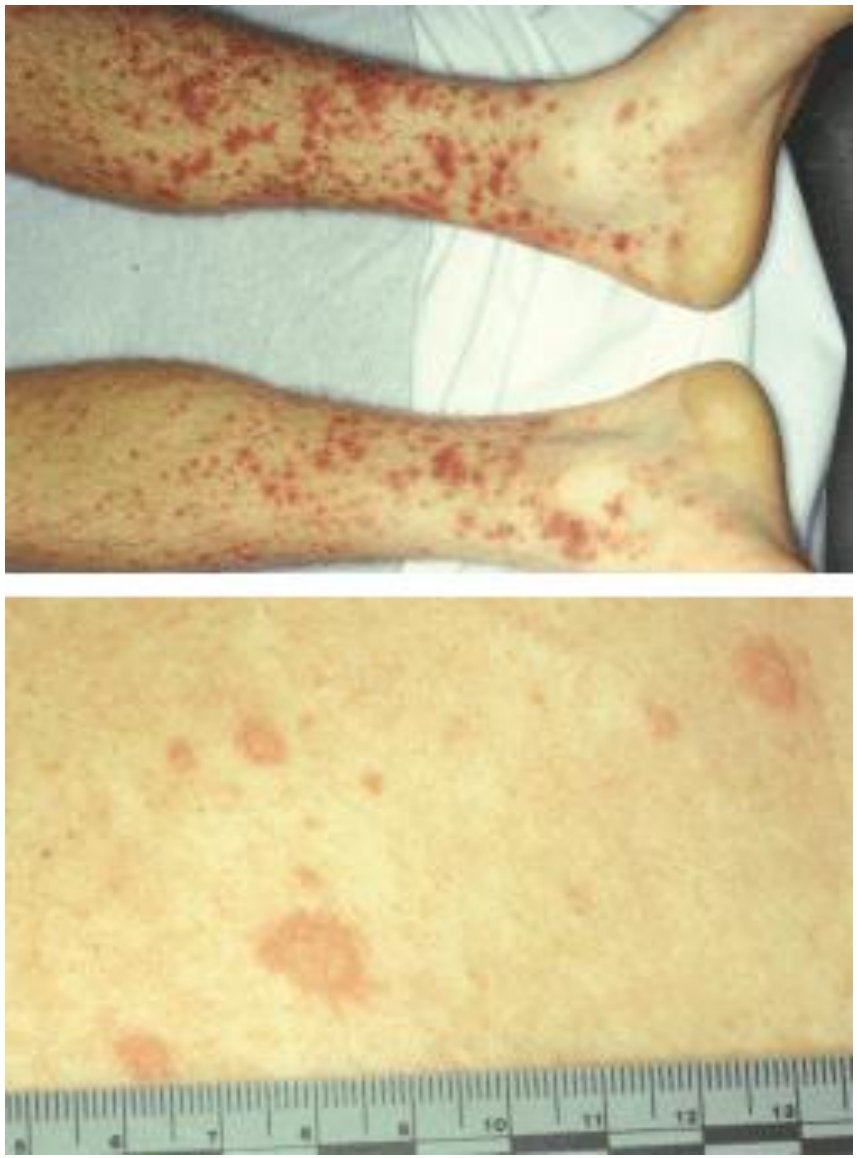


R. conorii – prokázána u klíšťat v Indii a Pákistánu

- *R. honei* – prokázána u klíšťat v Thajsku

Upraveno podle
Sexton DJ & Walker DH.
Infectious Tropical
Diseases, 2000

RMSF



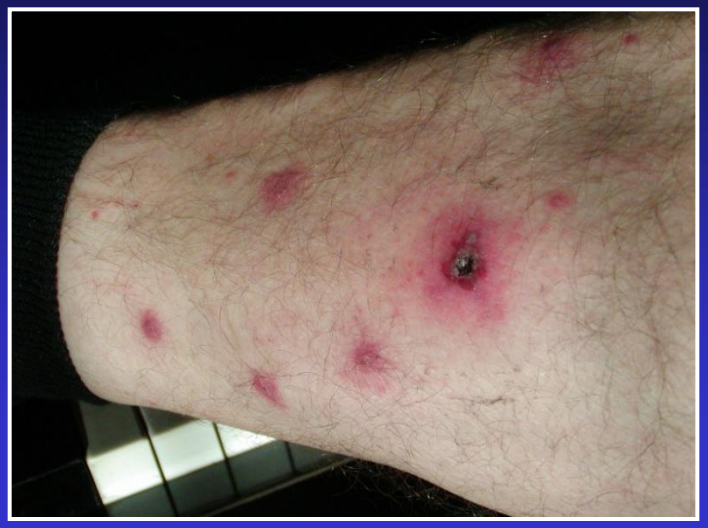
Top: Petechial lesions of Rocky Mountain spotted fever on the lower legs and soles of a young, otherwise-healthy patient.

Bottom: Close-up of lesions from the same patient.

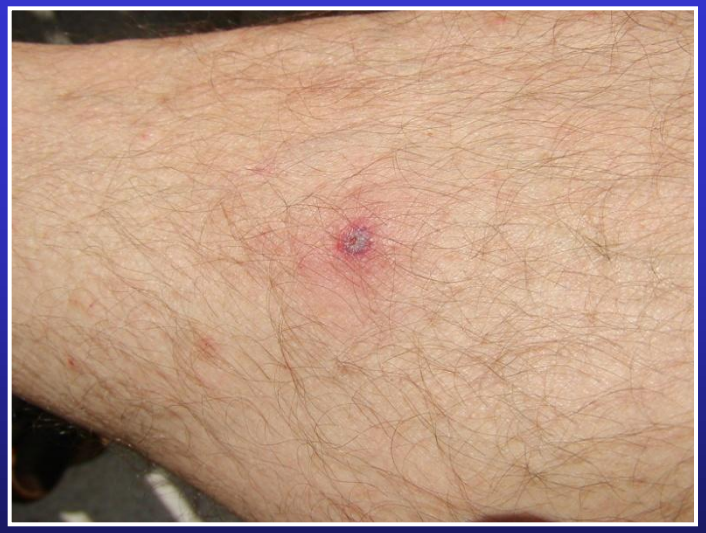
Tick typhus - Etiology

- Mediterranean spotted fever (*R. conorii*) is prevalent in southern Europe (below the 45th parallel), all of Africa, and southwestern and south-central Asia. The tick vector and reservoir is *R. sanguineus*, the brown dog tick.
  - The name of this disease varies with the region: Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever
  - High fever, rash, and an inoculation eschar (tâche noire) at the site of the tick bite.
- African tick-bite fever (*R. africae*) is in rural areas and follows bites by ticks of cattle and wild animals (*Amblyomma hebraeum* and *A. variegatum* ticks, which readily feed on humans)
  - Cases occur throughout sub-Saharan Africa and in the Caribbean islands.
  - The average incubation period is 7 days (range, 4 to 10 days).
  - The illness is mild and consists of headache, fever, eschar at the tick bite site, and regional lymphadenopathy.
  - Amblyomma ticks often feed in groups, and several ticks may be found on one patient - multiple eschars.
  - Rash is frequently lacking or transient and may be vesicular.
  - African tick-bite fever is the most prevalent rickettsiosis worldwide and frequently imported to Europe.
- *Rickettsia japonica* causes Japanese spotted fever.
  - fever, cutaneous eruption, and an inoculation eschar.
- In Europe, *R. slovaca* after a *Dermacentor* tick bite manifest as an eschar and regional lymphadenopathy.

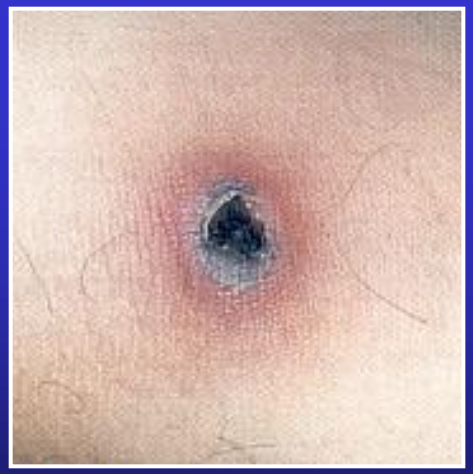
SKIN ESCHAR



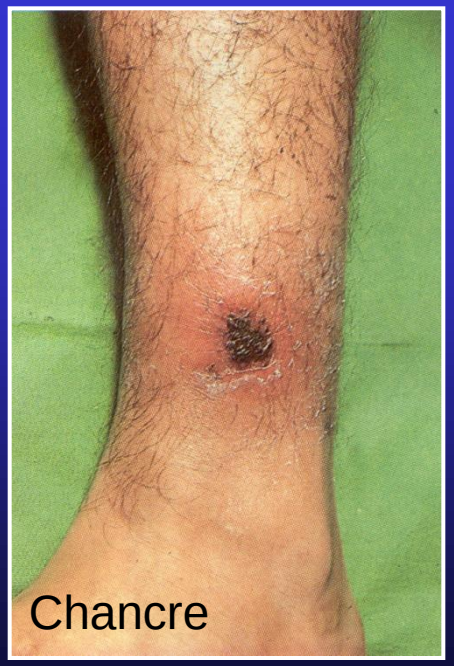
- Tick typhus
- Rickettsialpox (*R. acari*)
- Scrub typhus (*O. tsutsugamushi*)
- Tularemia
- Trypanosomal chancre
- Antrax



Inoculation eschar
tick typhus

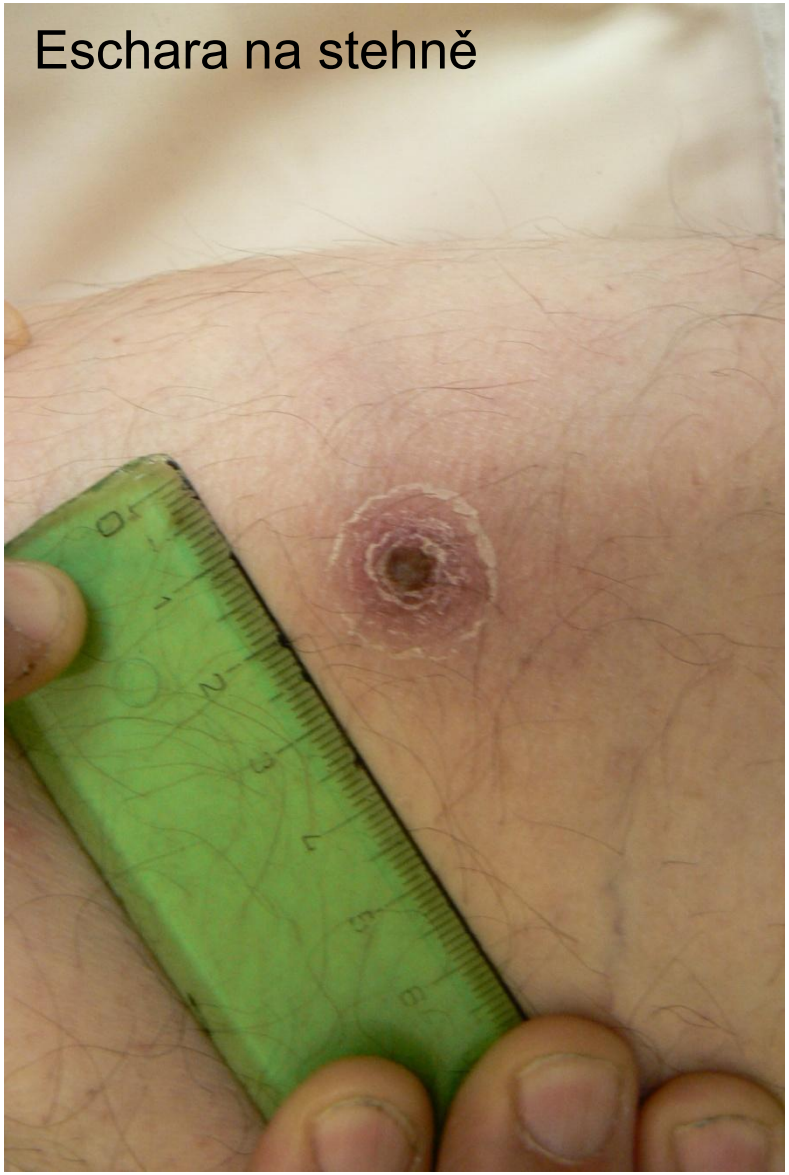


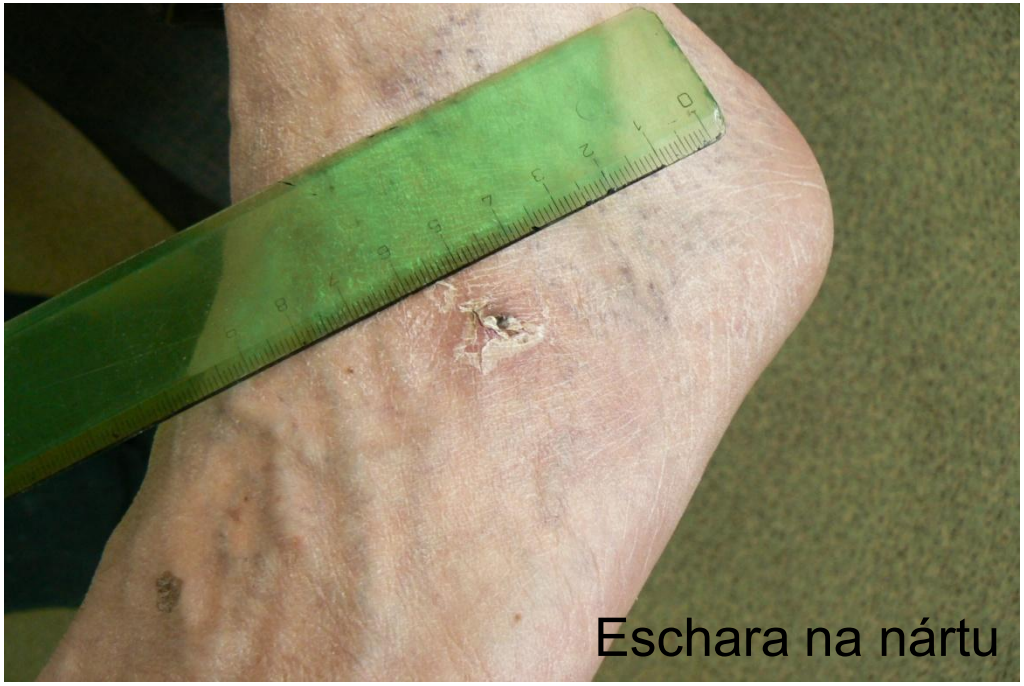
Rickettsialpox

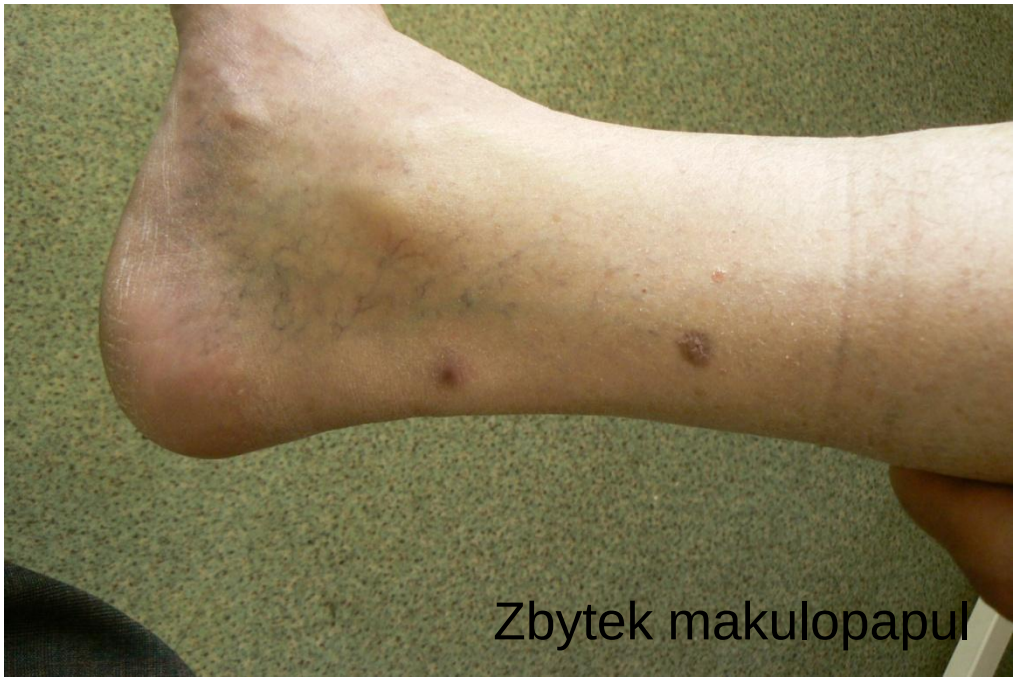


Chancre

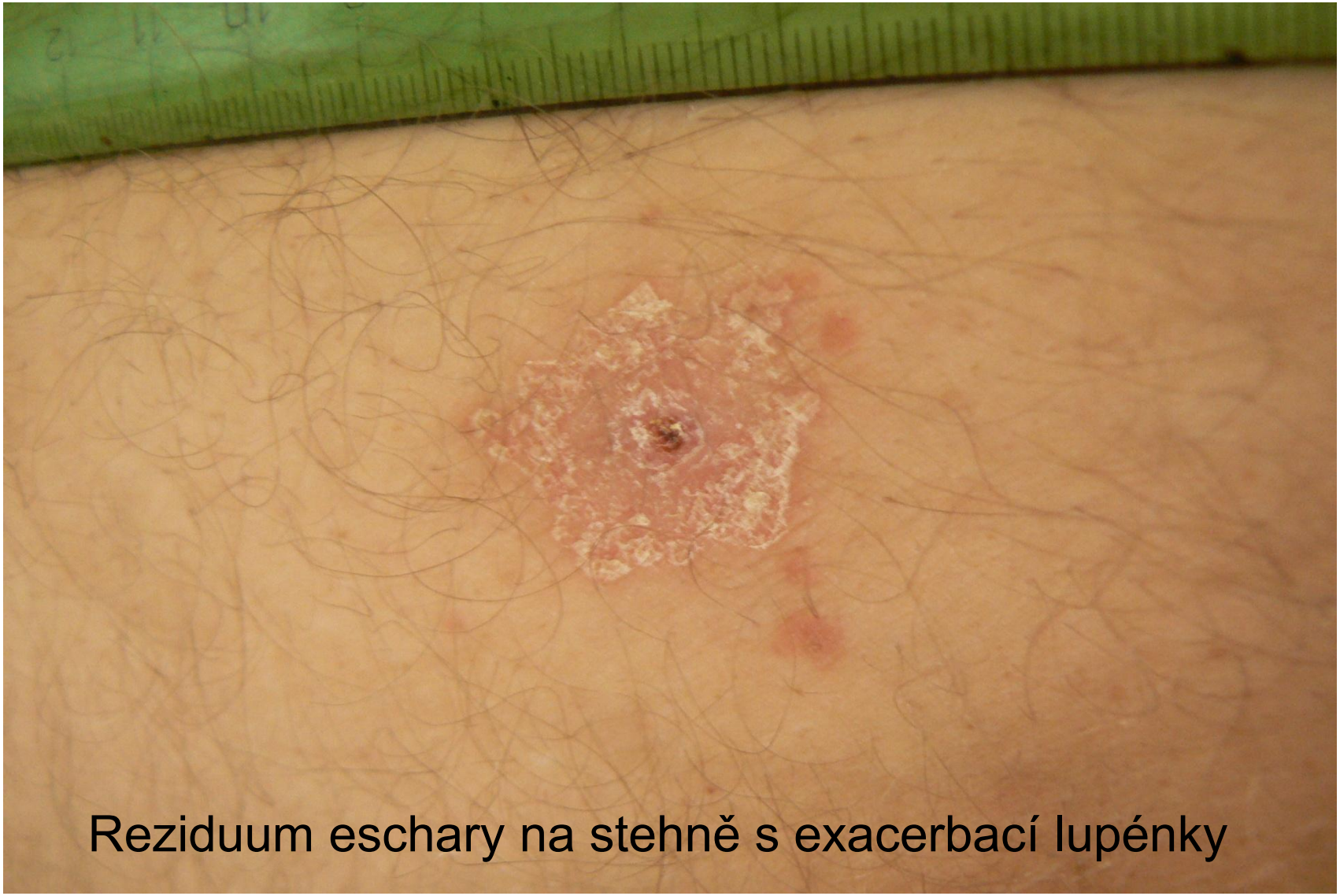
Pacient č. 4, po 14 dnech





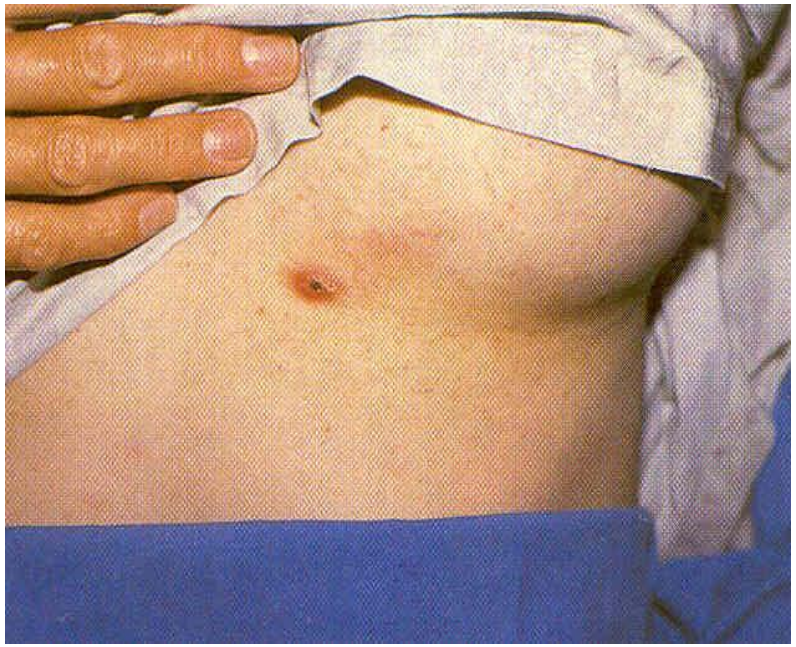


Pacient č. 5, po 3 týdnech

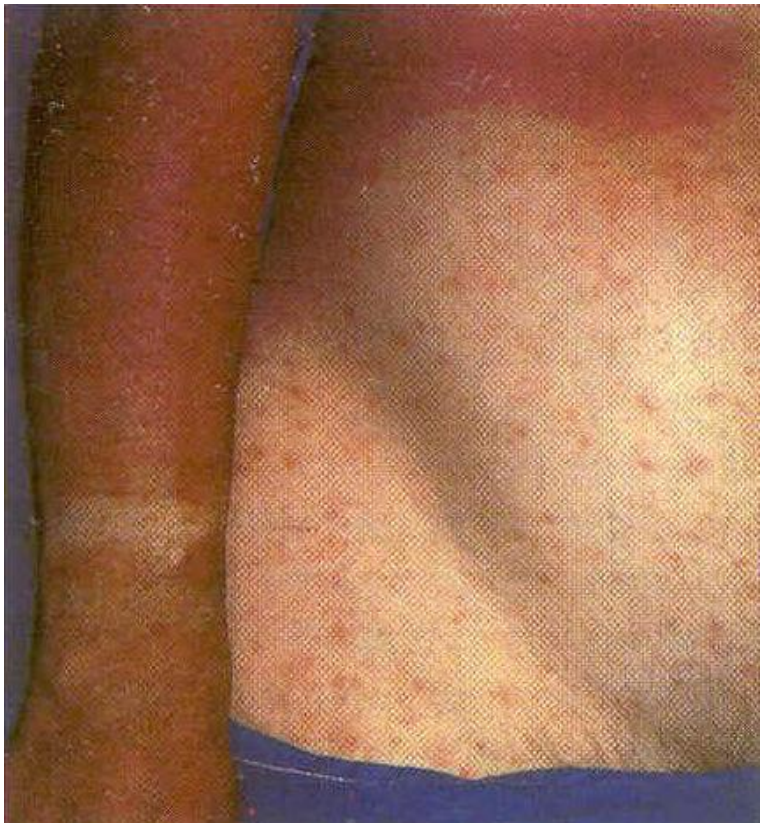


Reziduum eschary na stehně s exacerbací lupénky

RICKETTSIOSIS – ESCHAR AND RASH



Tick typhus – eschar (France)



Tick typhus – exanthema

Laboratory diagnostics

- The diagnosis of these tick-borne spotted fevers is based on clinical and epidemiologic findings
- It is confirmed by cell-culture isolation of rickettsiae, by PCR of skin biopsies (a method not available in most laboratories), or by serology.
- The serologic identification of infection with a specific species requires cross-adsorption. In an endemic area, patients presenting with fever, rash, and/or a skin lesion consisting of a black necrotic area or a crust surrounded by erythema should be considered to have one of these rickettsial spotted fevers.

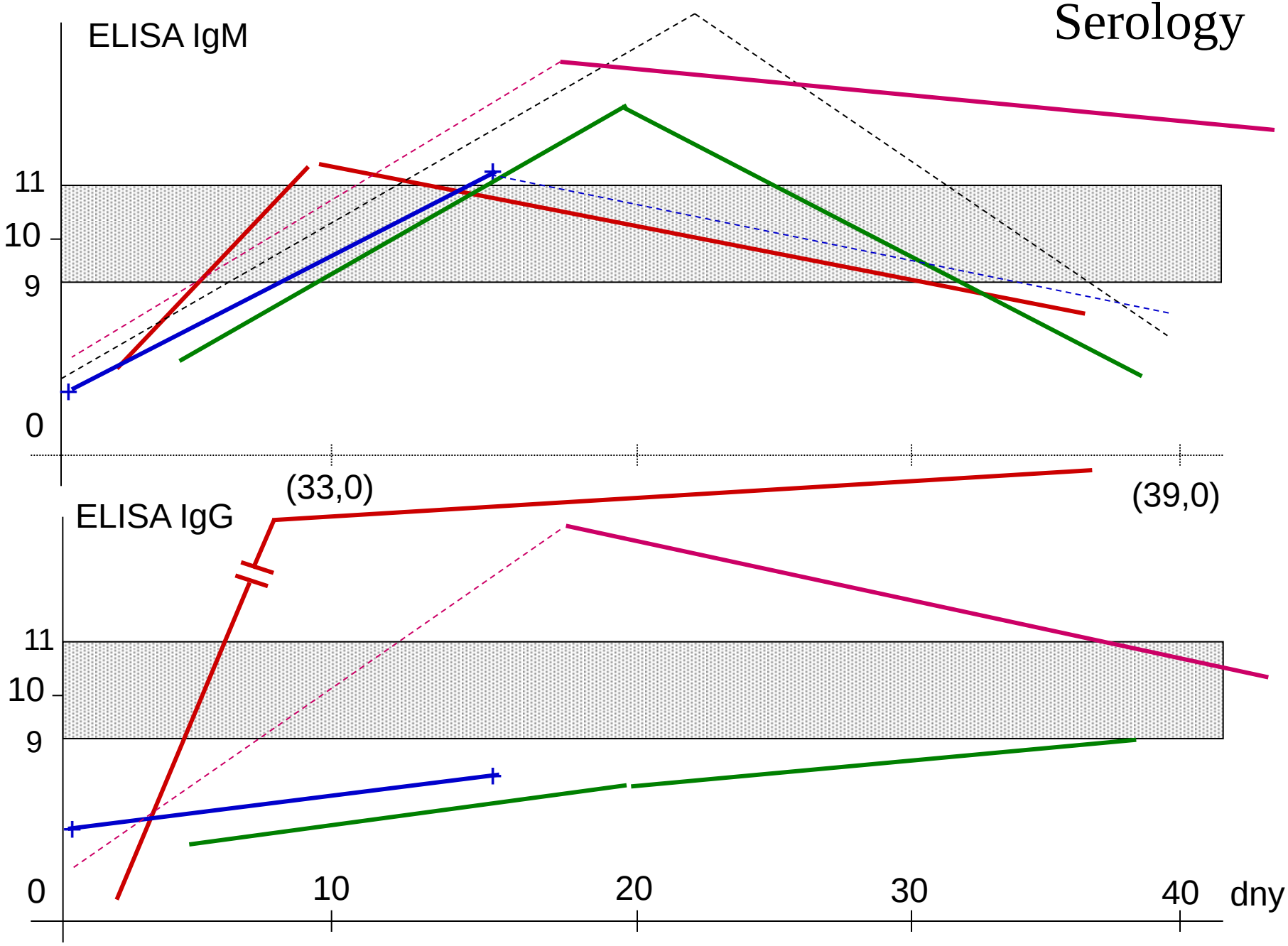
LABORATORY DIAGNOSIS OF RICKETSIOSIS

- Serology
- Skin biopsy and antigen detection in endothelial cells
- PCR

Onemocnění	Původce	OX19	OX2	OXK
Tick tyfhus	*R. conorii, R. africae*	+	+	+
RMSF	*R. rickettsii*	+++	+	-
Epidemic tyfhus	*R. prowazekii*	+++	+	-
Murine tyfhus	*R. typhi*	+++	+	-
Scrub tyfhus	*O. tsutsugamushi*	-	-	+++
Tranch fever	*Bartonella quintana*	-	-	-
Q fever	*Coxiella burnetii*	-	-	-

R. rickettsii v endotel. buňkách (zdroj CDC)

Serology



ELISA: R. conorii Ag, Vircell, Španělsko. Dr. V. Skokanová, ZÚ Praha 2, Dittrichova 17, 234118111

ENDEMIC MURINE TYPHUS (FLEA-BORNE)

- Murine typhus was postulated to be a distinct disease, with rats as the reservoir and fleas as the vector, by Maxcy in 1926. By the end of World War II, murine typhus was known to be a global disease.
- *R. typhi* is maintained in mammalian host/flea cycles, with rats (*Rattus rattus* and *R. norvegicus*) and the Oriental rat flea (*Xenopsylla cheopis*) as the classic zoonotic niche.
- Infected rats appear healthy, although they are rickettsemic for ~2 weeks.
- Cases of endemic typhus occur year-round, mainly in warm (often coastal) areas. and during the warm months of summer and early fall in other locations.
- Patients seldom recall a flea bite or exposure to fleas

Clinical Manifestations

- IP of murine typhus averages 11 days, with a range of 8 to 16 days
- Prodromal symptoms of headache, myalgia, arthralgia, nausea, and malaise developing 1 to 3 days before the abrupt onset of chills and fever
- Nearly all patients experience nausea and vomiting early in the illness.
- The duration of untreated illness averages 12 days, with a range of 9 to 18 days
- Rash is present in only 13% of patients at the time of presentation for medical care
- In half of the remaining patients appearing an average of 2 days later: initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles.
- Rash never appearing in the other half.
- Pulmonary involvement is frequently prominent in murine typhus;
  - 35% of patients have a hacking, nonproductive cough
  - 23% of patients who undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions
  - Bibasilar rales are the most common pulmonary sign.
- Less common clinical symptoms and signs include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice.

Complications

- Respiratory failure requiring intubation and mechanical ventilation
- Hematemesis
- Cerebral hemorrhage
- Hemolysis (in patients with G6PD deficiency and some hemoglobinopathies)
- The illness is severe enough to necessitate the admission of 10% of hospitalized patients to an intensive care unit
  - Greater severity is generally associated with old age, underlying disease, and treatment with a sulfonamide drug; the case-fatality rate is 1%.

Laboratory findings

- Anemia and leukopenia early in the course,
- Leukocytosis late in the course,
- Thrombocytopenia
- Hyponatremia, hypoalbuminemia
- Mildly increased serum levels of hepatic aminotransferases, and prerenal azotemia.

EPIDEMIC TYPHUS (LOUSE-BORNE)

- Epidemic typhus due to infection with R. prowazekii is transmitted by the human body louse (Pediculus humanus corporis), which lives on clothes and is found in poor hygienic conditions. Lice acquire R. prowazekii when they ingest a blood meal from a rickettsemic patient. The infected louse defecates during its blood meal, and the patient autoinoculates the organisms by scratching. Lice die within 1 to 2 weeks after infection, turning red because of intestinal perforation.
- This epidemic form of typhus is related to poverty, cold weather, war, and disasters and is currently prevalent in mountainous areas of Africa, South America, and Asia. A large outbreak involving 100,000 people in refugee camps in Burundi occurred in 1997, a small focus was reported in Russia in 1998, sporadic cases have been reported from Algeria, and annual outbreaks have occurred in Peru.
- Brill-Zinsser disease is a recrudescent, mild form of epidemic typhus occurring years after the acute disease, probably as a result of immunosuppression or old age. Strains of R. prowazekii indistinguishable from classic strains were isolated from patients with recrudescent typhus. Furthermore, R. prowazekii was isolated from the lymph nodes of patients undergoing elective surgery who had had typhus years earlier. Thus the typhus rickettsiae can remain dormant for years and can reactivate with waning immunity.
- Rickettsiae, particularly R. prowazekii, are potential agents of bioterrorism. R. prowazekii and R. typhi have dormant forms that survive extracellularly for long periods, and all rickettsiae are highly infectious when inhaled as aerosols.

Clinical Manifestation

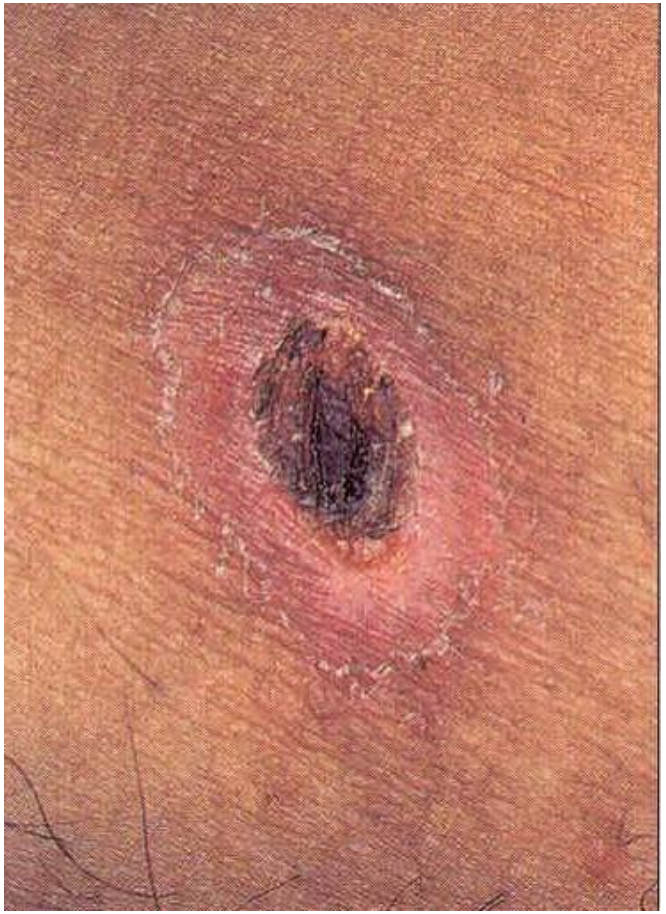
- After an incubation period of ~1 week (range, 7 to 14 days), the onset of illness is abrupt, with prostration, severe headache, and fever rising rapidly to 38.8° to 40.0°C (102° to 104°F).
- Cough is frequently prominent, occurring in 70% of patients.
- Myalgias are usually severe.
- A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving all of the body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent. The rash is frequently absent or not detected on black skin in Africa, where 60% of patients have spotless epidemic typhus.
- Photophobia, with considerable conjunctival injection and eye pain, is frequent.
- The tongue may be dry, brown, and furred.
- Confusion and coma are common.
- Skin necrosis and gangrene of the digits as well as interstitial pneumonia in severe cases.
- Untreated disease is fatal in 7 to 40% of cases, with outcome depending primarily on the condition of the host

Prevention

- Prevention of epidemic typhus involves control of body lice. Clothes should be changed regularly, and insecticides should be used every 6 weeks to control the louse population.

SCRUB TYPHUS

- Orientia tsutsugamushi.
- O. tsutsugamushi is maintained in nature by transovarian transmission in trombiculid mites, mainly of the genus Leptotrombidium.
- The disease is endemic in eastern and southern Asia, northern Australia, and islands of the western Pacific Ocean. Scrub typhus is also found in tropical areas of India, Sri Lanka, Bangladesh, Myanmar, Thailand, Malaysia, Laos, Vietnam, Kampuchea, China, Taiwan, the Philippines, Indonesia, Papua New Guinea, northern Australia, and islands of the South Pacific Ocean; in temperate areas of Japan, Korea, far-eastern Russia, Tadzhikistan, the mountains of northern India, Pakistan, and Nepal; and in nontropical areas of China, such as Tibet and Shangdong Province.
- Those infected include indigenous rural workers, residents of suburban areas, and westerners visiting endemic areas for professional or recreational purposes.



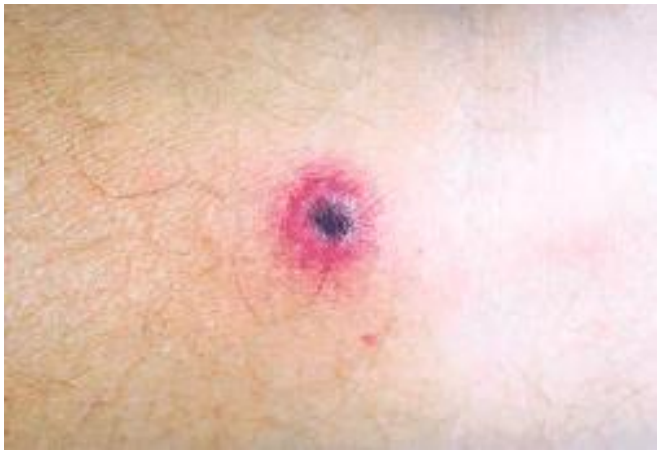
Scrub typhus

Clinical Manifestations

- The illness varies in severity from mild and self-limiting to fatal. After an incubation period of 6 to 21 days (usually 8 to 10 days), the onset of disease is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms.
- The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash—signs that are seldom observed in indigenous patients.
- Severe cases typically include prominent encephalitis and interstitial pneumonia as key features of vascular injury. Severe illness in persons with G6PD deficiency has been accompanied by hemolysis. The case-fatality rate for untreated classic cases is 7% but would probably be lower if all relatively mild cases (which are underdiagnosed) were included.
- Treatment: Some cases of scrub typhus in Thailand are caused by O. tsutsugamushi strains that are resistant to doxycycline or chloramphenicol. These strains are susceptible to rifampin, and azithromycin and clarithromycin have been used successfully in small numbers of patients.

Rickettsialpox

- was first described in 1946 by a general practitioner in New York City and soon afterwards was shown to be caused by a distinct species, R. akari. This organism was isolated from mice and their mites (Liponyssoides sanguineus), which maintain the organisms by transovarian transmission.

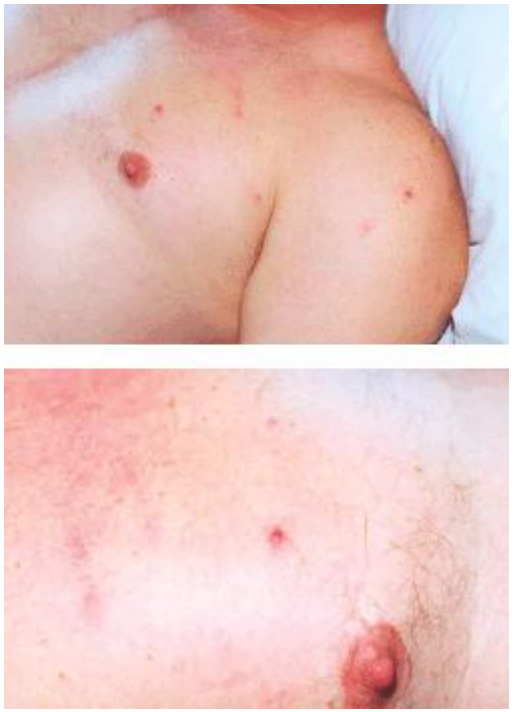


Eschar at the site of the mite bite in a patient with rickettsialpox

Clinical Manifestations

- A papule forms at the site of the mite bite. This lesion develops a central vesicle that becomes a 1- to 2.5-cm painless black crusted eschar surrounded by an erythematous halo.
- Enlargement of the lymph nodes draining the region of the eschar suggests initial lymphogenous spread. After an incubation period of 10 to 17 days, during which the eschar and regional lymphadenopathy frequently go unnoticed, the onset of illness is marked by malaise, chills, fever, headache, and myalgia.
- A macular rash appears 2 to 6 days after onset and evolves sequentially into papules, vesicles, and crusts that heal without scarring. In some cases the rash remains macular or maculopapular.
- Some patients suffer nausea, vomiting, abdominal pain, cough, conjunctivitis, or photophobia. Untreated rickettsialpox is not fatal, with fever lasting 6 to 10 days.

Rickettsialpox

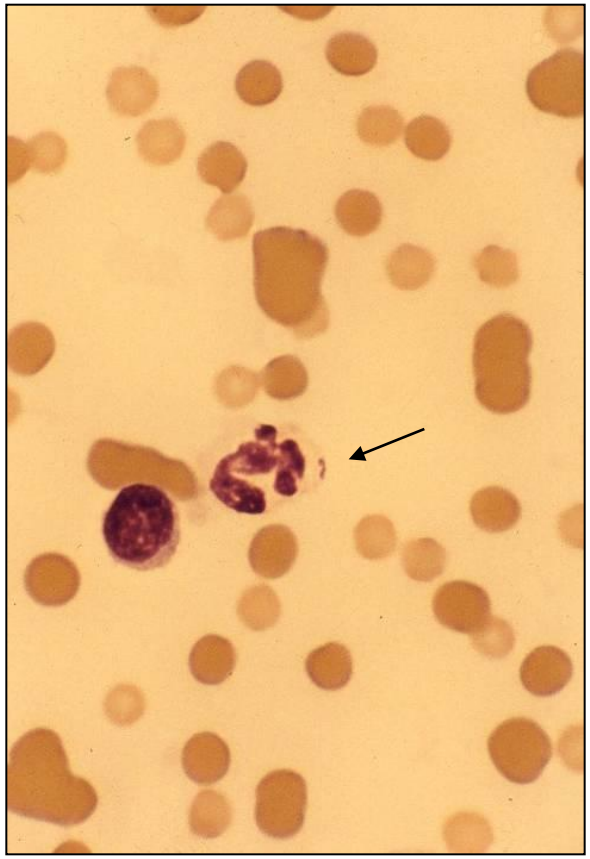


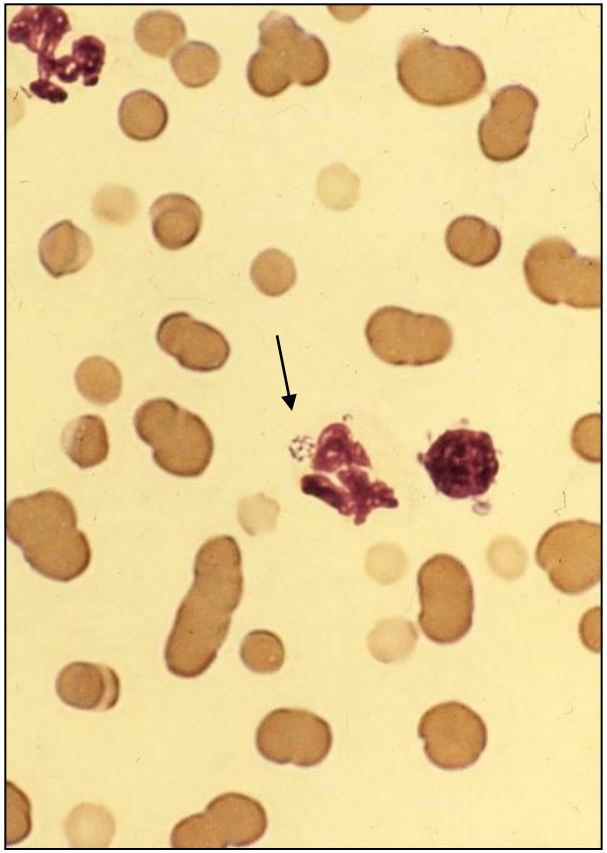
Papulovesicular lesions on the trunk of the patient with rickettsialpox. Bottom: Close-up of lesions from the same patient

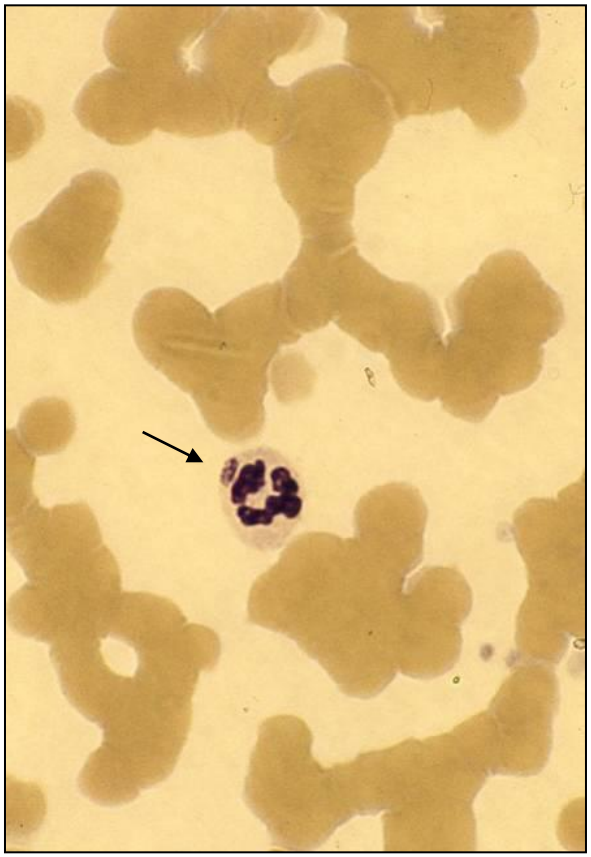
DIAGNOSTICS AND TREATMENT OF RICKETTSIAL INFECTIONS

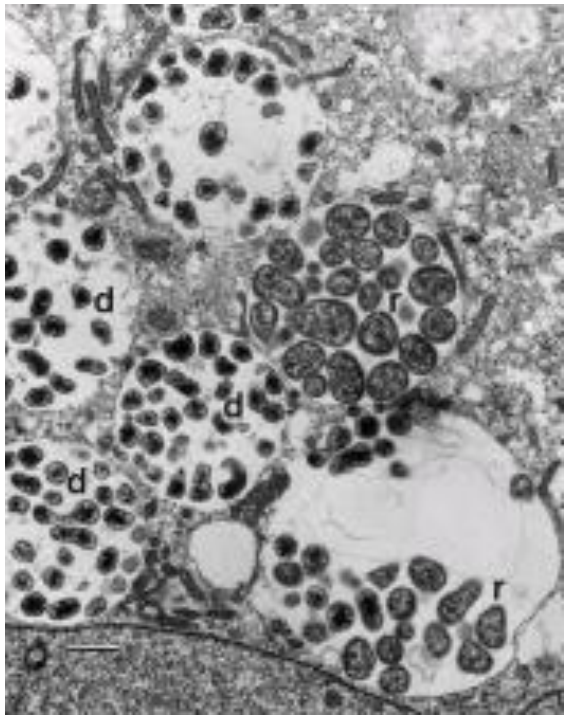
Mediterranean spotted fever, Japanese spotted fever, Queensland tick typhus, Flinders Island spotted fever, African tick-bite fever	Isolation of rickettsiae by shell-vial culture; serology, IFA (IgM, ≥1:64; or IgG, ≥1:128); skin biopsy immunohistochemical detection of rickettsiae; PCR amplification of DNA from tissue specimens	**Doxycycline (100 mg bid PO for 1–5 days) *or* Ciprofloxacin (750 mg bid PO for 5 days) *or* Chloramphenicol (500 mg qid PO for 7–10 days)** ***or* (in pregnancy)** **Josamycin[a] (3 g/d PO for 5 days)**
Rickettsialpox	IFA: seroconversion to a titer of ≥1:64 or a single titer of ≥1:128; cross-adsorption to eliminate antibodies to shared antigens necessary for a specific diagnosis of the spotted fever rickettsial species; skin biopsy immunohistochemistry	**Doxycycline (100 mg bid PO for 1–5 days) *or* Ciprofloxacin (750 mg bid PO for 5 days) *or* Chloramphenicol (500 mg qid PO for 7–10 days)** ***or* (in pregnancy)** **Josamycin[a] (3 g/d PO for 5 days)**
Endemic (murine) typhus	IFA: fourfold rise to a titer of ≥1:64 or a single titer of ≥1:128; immunohistology: skin biopsy; PCR amplification of *R. typhi* or *R. felis* DNA from blood; dot ELISA and immunoperoxidase methods also available	**Doxycycline (100 mg bid PO for 7–15 days) *or* Chloramphenicol (500 mg qid PO for 7–15 days)**
Epidemic typhus	IFA: titer of ≥1:128; necessary to use clinical and epidemiologic data to distinguish among louse-borne epidemic typhus, flying-squirrel typhus, and Brill-Zinsser disease	**Doxycycline (200 mg PO as a single dose or until patient is afebrile for 24 h)**
Scrub typhus	IFA: titer of ≥1:200; PCR amplification of *O. tsutsugamushi* DNA from blood of febrile patients	**Doxycycline[b]** (100 mg bid PO for 7–15 days) ***or* Chloramphenicol (500 mg qid PO for 7–15 days *or* (for children)** **Chloramphenicol** (150 mg/kg per day for 5 days)

	HMEHuman	Anaplasmosis	Ehrlichiosis Ewingii
Etiologic agent	*E. chaffeensis*	*A. phagocytophila*	*E. ewingii*
Tick vector(s)	*Amblyomma americanum*, *Dermacentor variabilis* (dog tick)	*Ixodes scapularis* (deer tick), *I. ricinus*, *I. pacificus*	*A. americanum*
Seasonality	April through September	Year-round (peak: May, June, and July	April through September
Major target cell	Monocyte	Granulocyte	Neutrophil
Morulae seen	Rarely	Frequently	Rarely
Antigen used in IFA test	*E. chaffeensis*	*A. phagocytophila*	*E. chaffeensis* as surrogate
Diagnostic titer	Fourfold rise or a single titer of ≥1:128; cutoff for negative titer, 1:64	Fourfold rise; cutoff for negative titer, 1:80	No established criteria
Treatment of choice	Doxycycline	Doxycycline	Doxycycline
Mortality	2–3%	<1%	None reported









Ehrlichia chaffeensis microcolonies (morulae) within cytoplasmic vacuoles manifest as two morphologic forms: reticulate cells (r) and dense-core cells (d). Bar = 1 μm.