

Rickettsia an Overview

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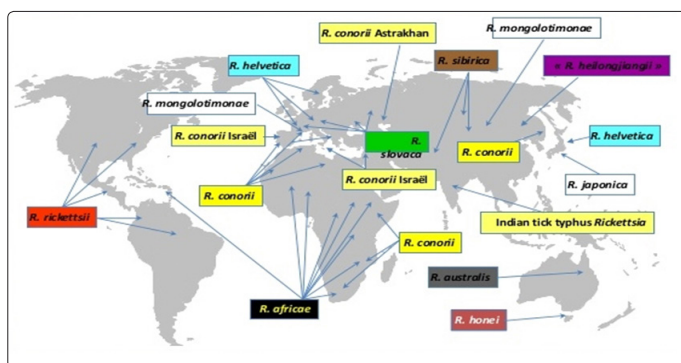
Introduction

A diverse collection of organisms, maintained in nature through a cycle involving reservoir in mammals and arthropod vectors. Rickettsial diseases are largely unmeasured but quite high worldwide. Diseases caused by Rickettsia and Orientia species are collectively called Rickettsioses. All rickettsioses exist as zoonoses. Moreover, all rickettsiae are found in infected arthropods, which generally serve as the natural hosts and can transmit the infection to the next generation of ticks, mites, chiggers, or fleas. Greater clinical awareness and high index of suspicion are the key factors.

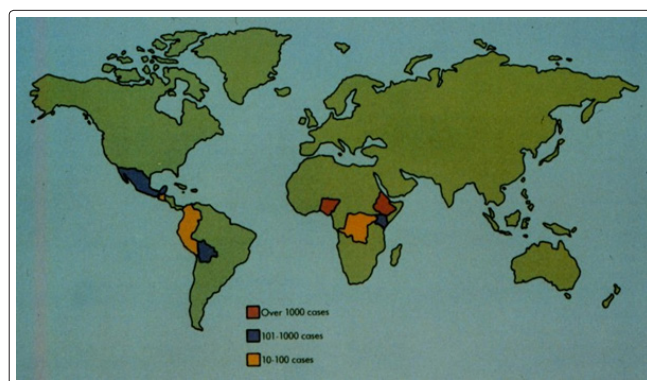
History

In 1910, the first case of Mediterranean spotted fever (MSF) was reported in Tunis. The typical inoculation eschar was described in 1925 in Marseille. In the 1930s, the roles of the brown dog tick, *Rhipicephalus sanguineus*, and the causative agent *Rickettsia conorii* were described. For several decades, *R. conorii* was considered to be the only agent of tick-borne SFG rickettsioses in Europe and Africa. Was rediscovered in USA in 1990. In a similar manner, *Rickettsia sibirica* (in the former USSR and China) and *Rickettsia australis* (in Australia) were believed to be the sole tick-borne rickettsial agents associated with these respective locations.

Global Distribution-India, China, Brazil, France, Mexico, USA, Africa, Spain



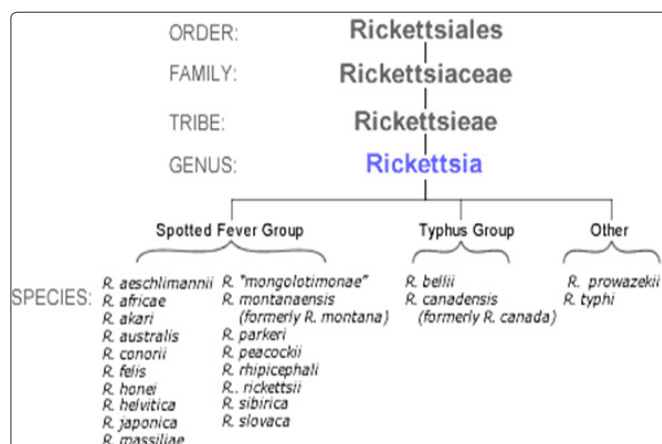
Epidemic Typhus-Incidence



Rickettsia Reporting

In India, reported cases are underestimated due to lack of community based data. Cases are found in J & K, Himachal, Assam, Rajasthan, WB, Kerala, TN, Maharashtra and Uttaranchal. In 2012 India reported 45.6% cases of spotted fever and 30.7% of scrub typhus. Untreated cases have fatality rate of 30-35%.

Classification



The family Rickettsiaceae is taxonomically divided in 3 genera

- *Rickettsia* (11 species) – obligate intracellular parasites which do not multiply within vacuoles and do not parasitize white blood cells.
- *Ehrlichia* (2 species) – obligate intracellular parasites which do

not multiply within vacuoles but do parasitize white blood cells.

- Coxiella (1 species) – obligate intracellular parasite which grows in vacuoles of host cells.
- Bartonella (3 species) – intracellular parasite which attacks the red blood cell is excluded now.

Commonest Rickettsiae

The rickettsial pathogens to be encountered during travel:

- R. africae (African tick-bite fever),
- R. conorii (Mediterranean spotted fever),
- R. rickettsii (known as both Rocky Mountain spotted fever and Brazilian spotted fever),
- O. tsutsugamushi (scrub typhus), and
- R. typhi (murine or flea-borne typhus).

Rickettsia

Rickettsia are genus of nonmotile, Gram negative, nonspore-forming, highly pleomorphic bacteria and obligate intracellular that can be present as cocci (0.1 µm), rods (1–4 µm long), or thread (10 µm long). The term rickettsia, named after HOWARD Taylor Ricketts, is often used interchangeably for any member of Rickettsiales. Being obligate intracellular parasites, the Rickettsia survival depends on entry, growth, & replication within the cytoplasm of eukaryotic host cells (endothelial cells). They spread by arthropod vectors-lice, fleas, mites, ticks.

General Features

They occur singly, in pairs, or in strands. Most species are found only in the cytoplasm of host cells, but those which cause spotted fevers multiply in nuclei as well as in cytoplasm. Have DNA & RNA & they use host ATP. In lab, cultivation in living tissues-embryonated chicken eggs or vertebrate cell cultures.

Cell Wall Structure

The cell wall of the typical rickettsia is very similar to that of Gram-negative bacteria (contains diaminopimelic acid and lacks teichoic acid). The typical envelope consists of 3 major layers: an innermost cytoplasmic membrane, a thin electron dense rigid cell wall and an outer layer (trilaminar).

Intracytoplasmic mesosomes and ribosomes are also seen. With no discrete nuclear structures. They occupy a position between bacteria and viruses.

Pathogenicity

In their arthropod vectors, the rickettsia multiply in the epithelium of the intestinal tract; they are excreted in the feces, but occasionally gain access to the arthropods salivary glands. They are transmitted to man, via the arthropod saliva, through a bite. In their mammalian host, they are found in the endothelium of the small blood vessels of the brain, skin and heart.

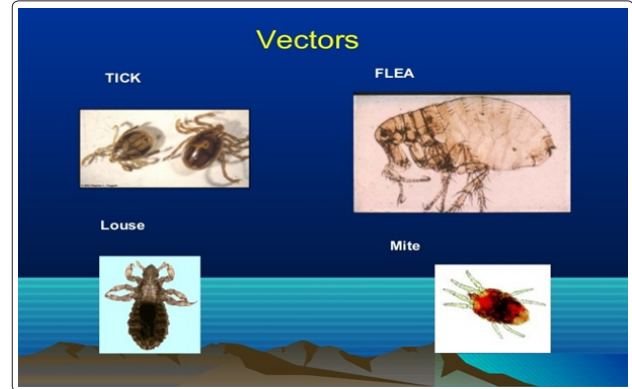
Pathogenicity-Hyperplasia

Hyperplasia of endothelial cells and localized thrombus formation leads to obstruction of blood flow, with escape of RBC's into the surrounding tissue. Inflammatory cells also accumulate around the affected segments of blood vessels.

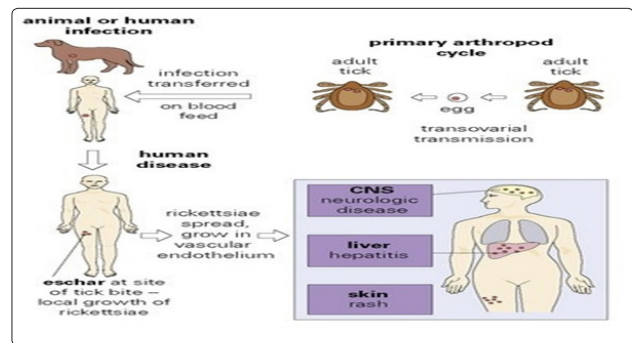
Pathogenicity-Angitis

Angitis appears to account for some of the more prominent clinical manifestations, such as petechial rash, stupor and terminal shock. Death is ascribed to damage of endothelial cells, resulting in leakage of plasma, decrease in blood volume, and shock.

Vectors



Life Cycle



Rickettsia Transmission

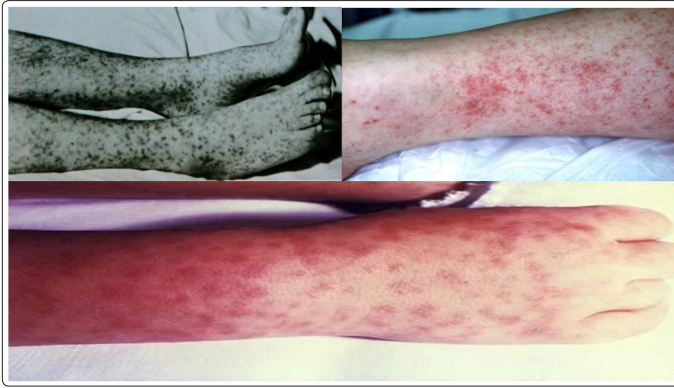
TRANSMISSION

- Bite of infected ticks and mites
- Contamination of the skin wounds with the feces of infected lice and fleas.
- The rickettsia present in the dried excreta of insects may also enter through the conjunctiva or even through inhalation.
- In ticks and mites transovarial and transstadial transmission of rickettsia occurs
- Spread through the blood stream to infect vascular endothelium in the skin, brain, lungs, heart, kidneys, liver, gastrointestinal tract and other organs.

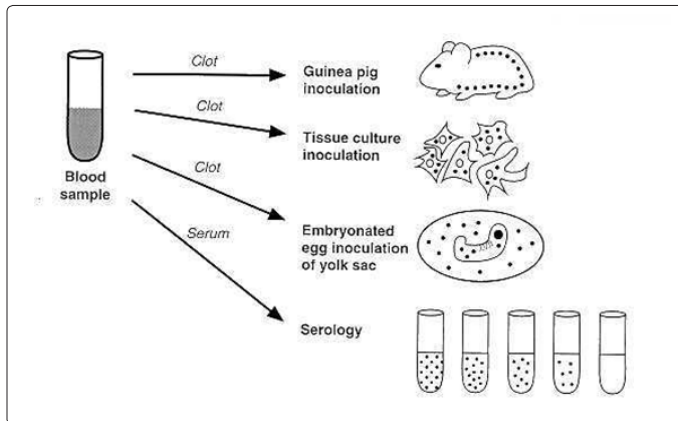
Clinical Features

Symptoms: Fever, chills, headache, myalgia's, rash, Escher (black ulceration) may develop at site of inoculation. Rash: haemorrhages in the skin (Not seen in 10% cases) – Develops after 3 days. Incubation: 2-14 days after tick bite [average 7 days] Patient may not recall painless tick bite.

RASH of Rocky Mountain Spotted Fever-RMSF



Laboratory Diagnosis



- Specimen: Blood & skin biopsy.
- Culture: Tissue culture or chick embryo.
- Direct detection in clinical specimen: PCR Immunofluorescence
- Serological diagnosis: Detection of rising titers of anti-rickettsial antibodies by ELISA. Weil-elix reaction: no longer used because it is non-specific.
- Presumptive lab diagnosis is based on the finding of rickettsial-like organisms in tissue or blood. Although the organisms are gram-negative, they only weakly take the counter stain, safranin. Therefore, special staining procedures are used. Infected tissue stains:
 - Macchiavello stain--organisms are bright red against the blue background of the tissue.
 - Castaneda stain--blue organisms against a red background.
 - Giemsa stain--bluish purple organisms.

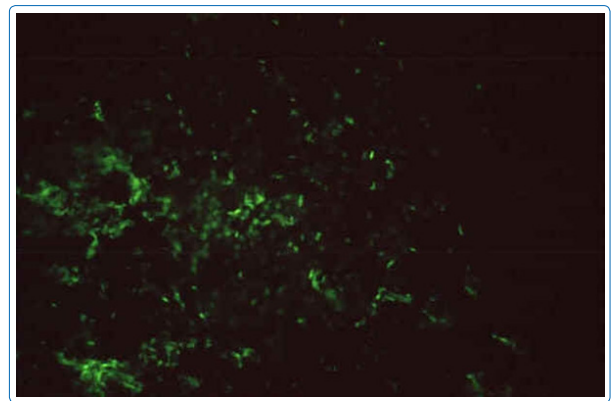
Laboratory Diagnosis Weil-Felix Test

Confirmative diagnosis is based on a serological reaction (Weil-Felix reaction) in which the titer of the agglutinins in the patient's serum against the Proteus strains OX-19, OX-2 and OX-K are determined which have no etiological role in rickettsial infections, but share antigens in common with certain rickettsia. Use of WF test (high specificity) is acceptable in conditions where definitive investigations are not possible and it is still not entirely obsolete but has to be interpreted in the correct clinical context. The antigens are alkali stable polysaccharide haptens which are distinct from group-specific & type-specific antigens. In interpreting the results, it must be kept in mind that Proteus infections are fairly common (especially in the urinary tract) and that they, too, may evoke antibodies to the Proteus-OX strains. The test is positive 7 days after initial infection.

Laboratory Diagnosis

A more specific complement fixation test is available but does not show positive results until 14 days into the infection. The indirect fluorescent antibody test is also useful for IgM and IgG antibodies against rickettsia. In fact, this is the diagnostic test of choice for ehrlichiosis. Indirect fluorescent antibody of patient's serum and latex agglutination. In these tests, the antigen is known and the unknown is the antibodies to Rickettsia in serum. Antibodies are detected 2-3 weeks after onset of disease with FA. Latex agglutination can be positive earlier. Direct Immunofluorescence-100% specific and 70% sensitive-within 3-4 days of illness. The recognition of multiple distinct tick-borne Spotted Fever Group rickettsioses during the last 20 years has been greatly facilitated by broad use of cell culture systems and the development of molecular methods for the identification of rickettsiae from human samples and ticks. PCR assays and immunohistochemical analyses may be helpful, but useful results are highly dependent upon the specimen submitted (whole-blood in ehrlichiosis). If an eschar is present, a swab / biopsy sample of the lesion can be evaluated by PCR and provides a species-specific diagnosis. A buffy coat may provide presumptive evidence of infection.

IFA reactions of a positive human serum on Rickettsia rickettsii grown in chicken yolk sacs, 400X



Treatment

The drugs of choice for the treatment of rickettsial diseases are chloramphenicol and tetracycline. Each of these is highly toxic, especially in children, and must be used with care. The sulfonamides stimulate rickettsial growth and thus are contraindicated in the treatment of these diseases.

- Supportive Care
- Possible blood transfusion and platelets if counts too low
- Steroids and anti-inflammatory drugs??

Complications

- Gastro-intestinal symptoms,
- Respiratory failure,
- Encephalitis
- Renal failure.
- Mortality is high when the disease progresses.

This is usually due to the late development of the rash and the difficulty of diagnosing the disease



Classification



Group	Disease	Organism	vector
Typhus group	Epidemic Typhus	R. prowazekii	Lice
	Epidemic Typhus	R. Typhi	Rat, flea
Spotted fever group	Rocky mountain spotted fever	R. Rickettsii	Tick
	Trench fever	R. Quintana	Lice
Scrub typhus Group	Scrub typhus	R. Tsutsugamushi	Mite
Q fever group	Q fever	C. Burnetii	Ticks, lice
Rickettsial pox grou	Rickettsial pox	R. Akari	mite

Table 48-4: Epidemiology of Rickettsia species causing human diseases

Species	Vector	Reservoir	Disease
<i>Rickettsia prowazekii</i>	Louse	Humans	Epidemic typhus and Brill-Zinsser disease
<i>Rickettsia typhi</i>	Rat flea	Rat	Endemic typhus
<i>Rickettsia rickettsiae</i>	Tick	Ticks, wild rodents	Rocky Mountain spotted fever
<i>Rickettsia akari</i>	Gamasid mite	Mouse	Rickettsial pox
<i>Rickettsia conorii</i>	Tick	Rodents	Boutonne fever
<i>Rickettsia australis</i>	Tick	Unknown	Queensland tick typhus

Specie	Disease	Mode of transmission	Geographical distribution
<i>R. Rickettsii</i>	Rocky Mountain spotted fever	Bite of tick	North & America
<i>R. prowazekii</i>	Epidemic typhus	Louse faeces	Africa, North & South America
<i>R. typhi</i>	Murine (endemic) typhus	Flea faeces	Tropics
<i>O. tsutsugamushi</i>	Scrub typhus	Bite of mite	Asia & Australia

Diseases

- Louse-borne: European epidemic typhus (*Rickettsia prowazekii*), Brill's disease (*Rickettsia prowazekii*), Trench fever (*Bartonella quintana*)
- Flea-borne: Endemic murine typhus (*Rickettsia typhi*), Cat scratch fever / Bacillary angiomatosis / (*Bartonella henselae*)
- Mite-borne: Scrub typhus (*Orientia/Rickettsia tsutsugamushi*), Rickettsial pox (*Rickettsia akari*)
- Tick-borne: Rocky Mountain spotted fever (*Rickettsia rickettsiae*), North Asian tick typhus (*Rickettsia sibirica*), Fiebreboutonneuse (*Rickettsia conorii*), Queensland tick typhus (*Rickettsia australis*), Q-fever (*Coxiella burnetii*), Spotted fever (*Rickettsia rhipicephali*), Ehrlichiosis (*Ehrlichia canis*, *Ehrlichia chaffeensis*)
- Fly-borne: Oroya fever / Verrugaperuana (*Bartonella bacilliformis*)

Coxiella burnetii [1]

Disease/Bacterial Factors

- strict intracellular pathogen
- multiplies in cytoplasmic vacuole
- stable in harsh environments

Reservoirs

- sheep goats, ticks, mammals birds

Transmission

- inhaled airborne particle – unpasteurized milk

Geography/Season

- Global rare in Canada and USA
- not seasonal

Control

- Tetracycline
- Chloramphenicol

Risk?

- Livestock handlers
- patients with prosthetic/ damaged heart valves

C. burnetii differs from other rickettsia in that it is enclosed in a persistent vacuole during growth and division. Six to ten daughter cells will form within a host cell before the cell ruptures and releases them

- No arthropod vector
- Q fever

Q fever

Entry: aerosol from infected placenta of sheep goat's cattle

Spread: blood stream

Disease: Pneumonitis endocarditis, granulomas

No Exit, since the bacteria usually infect cattle, sheep, and goats, people who are at highest risk for infection are: Farmers, Veterinarians, People who work around sheep, People who work in the dairy industry, People who work in a meat processing facilities, People who work in research laboratories with livestock and with *C. burnetii*, People who live close to a farm

Q Fever-Complications

Sometimes Q fever can persist or come back. This can lead to more serious complications if infection in heart, liver, lungs, Brain. You're at high risk of developing chronic Q fever if you: Have an existing heart valve disease and / or blood vessel abnormalities. Have a weakened immune system Are pregnant

Ehrlichia chaffeensis

Disease/Bacterial Factors

- Ehrlichiosis
- Strict intracellular parasite
- Vector lone star tick?

Transmission

- break in skin via infected tick

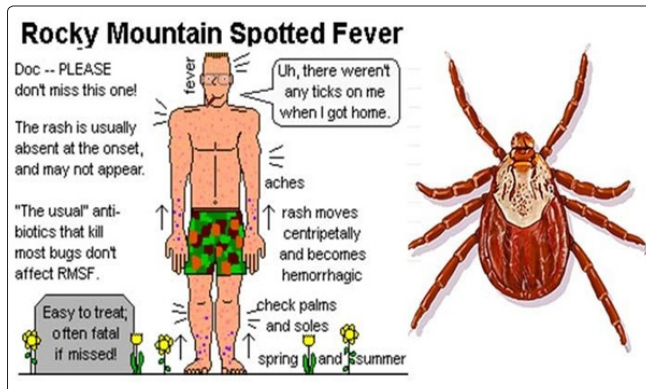
Geography/Season

- Common in Southeast, mid-Atlantic and South Central USA
- Most common May June July

Control

- Tetracycline, chloramphenicol
- Control of tick vector

Rocky Mountain spotted fever RMSF



Rickettsia Rickettsii-RMSF

Rickettsia Rickettsii-RMSF

- Rocky Mountain spotted fever
- Intracellular parasite that multiplies in host cytoplasm
- Transmission
 - ticks are primary reservoir and vector
 - Risk?
 - Requires 24-48 hour exposure to feeding tick
- Geography/Season
 - Western Hemisphere, southeast Atlantic and south central USA
 - April-Sept

Control

- Tetracyclines & chloramphenicol
- Avoid tick infested areas
- Insect repellent
- remove ticks

RMSF-Symptoms

The symptoms of Rocky Mountain spotted fever typically begin between 2 and 14 days after getting a tick bite. Symptoms come on suddenly and usually include:

- High fever, which may persist for 2 to 3 weeks
- chills
- Headache & muscle aches
- Nausea & vomiting
- Poor appetite and fatigue
- Abdominal pain

RMSF-Vectors

Though RMSF is caused by bacteria, you can only be infected with the bacteria via a tick bite. There are many different types of ticks. Types that may be vectors, or carriers, of RMSF include the:

- American dog tick (*Dermacentor variabilis*)
- Rocky Mountain wood tick (*Dermacentor andersoni*)
- Brown dog tick (*Rhipicephalus sanguineus*)

RMSF-Treatment

Treatment for Rocky Mountain spotted fever involves an oral antibiotic known as Doxycycline. It's the preferred drug for treating both children and adults. If pregnant, prescribe Chloramphenicol.

RMSF-Complications

If it isn't treated right away, RMSF can cause damage to the lining of blood vessels, tissues, and organs. Complications of RMSF include:

- Meningitis, leading to seizures and coma
- inflammation of the heart and lungs
- Kidney Failure
- Gangrene of the fingers and toes
- enlargement of the liver or spleen
- death (if not treated)
- Severe cases of RMSF end up with long-term health problems:
 - neurological deficits
 - deafness or hearing loss
 - muscle weakness
 - Partial paralysis of one side of the body.

Rickettsia Typhi

Disease/Bacterial Factors: strict intracellular pathogen

Transmission: break in skin via infected flea

Reservoir: rodents, cats, opossum, racoons & skunks

Vectors: rat & cat fleas

Geography Season: Global, Southeast & gulf states of USA

Control: tetracycline's, chloramphenicol, Control of rodent vectors

Risk? : People in crowded areas infested with rodents

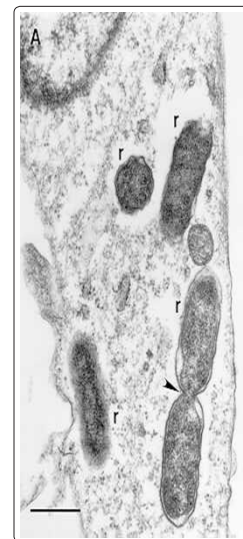
Rickettsial Pox

R. akari - Clinical infection is biphasic

First phase: a vesicle develops at the mite bite site and the organisms multiply; within one week they have spread systemically.

Second phase: fever, severe headache and chills, sweats, myalgias and photophobia. After 2-3 days a papulo-vesicular rash forms and spreads over the body.

Rickettsia Conorii [2]



- Gram negative short rods
- Transverse Binary Fission
- Multiple in cytoplasm
- Long filaments under poor nutritional conditions, undergo rapid/multiple division into the typical short rod forms when fresh nutrients added
- Attach to "tail" of host actin filaments
- actin provides propulsion

Rickettsia Conorii

Boutonneuse fever (BF), also known as Mediterranean spotted fever (MSF), is transmitted by the dog tick *Rhipicephalus sanguineus*. The tick bite causes a characteristic rash and a distinct mark—namely, *atche noire* (black spot) at the site of the bite.

The etiologic agent for BF is *Rickettsia conorii*, which is endemic in the Mediterranean basin & also associated with Marseilles fever, Kenya tick typhus, South African tick fever, Indian tick typhus, and Israeli tick typhus.

Rickettsia Prowazekii

Disease/Bacterial Factors

- Louse-borne typhus, Brill-Zinsser Disease

Transmission

- humans are primary reservoir
- inoculation through break

Vector

- human louse, squirrel fleas

Geography/ Season

- central & south America
- no season

Risk?

- Persons in crowded unsanitary conditions
- close contact with infected persons

Control

- tetracycline's, chloramphenicol
- Louse control

Rickettsia Prowazekii Epidemic Typhus

Epidemic typhus, also called louse-borne typhus, is an uncommon disease caused by *Rickettsia prowazekii*.

Epidemic typhus is spread to people through contact with infected body lice. Though epidemic typhus was responsible for millions of deaths in previous centuries, it is now considered rare.

Prevention-No Vaccine

Avoid tick - infested areas wear protective clothing and use repellents. Ticks are difficult to eradicate as they can survive for 4 years without feeding.

The proper use of insect or tick repellents on skin or clothing, self-examination after visits to vector-infested areas, and wearing protective clothing are ways to reduce risk. These precautions esp for immune compromised patients as they are more susceptible to severe disease.

Prevention

Ticks live in grassy, brushy, or wooded areas, or even on animals, so spending time outside camping, gardening, or hunting will bring you in close contact with ticks. Protect yourself, your family, and your pets. Use EPA registered insect repellents-DEET, picaridin, IR3535, Oil Lemon Eucalyptus, or 2-undecanone. Always follow product instructions. Do not use insect repellent on babies younger than 2 months old. Do not use products containing oil of lemon eucalyptus (OLE) or para-menthane-diol (PMD) on children less than 3 yrs of age.

Prevention-After Coming Indoors

Check your clothing for ticks - Any ticks that are found should be removed. Tumble dry clothes in dryer on high heat for 10 mins to kill ticks on dry clothes. If the clothes are damp, additional time may be needed. If the clothes require washing first, hot water to be used. Cold and medium temperature water will not kill ticks effectively. Shower soon after being outdoors. Showering within 2 hours of coming indoors is very helpful. Showering may help wash off unattached ticks & it's a good chance for tick check

Prevention-After Going Outdoors

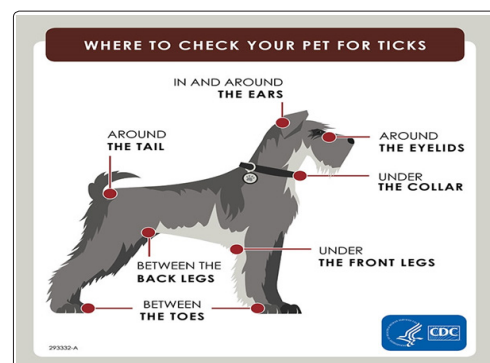
Check your body for ticks after being outdoors. Conduct a full body check upon return from potentially tick-infested areas, which even includes your back yard. Use a hand-held or full-length mirror to view all parts of body. Check your body and your child's body for ticks:

- Under the arms
- In and around the ears
- Inside belly button
- Back of the knees
- In and around the hair
- Between the legs and around the waist

Prevention

To prevent bites

Avoid densely wooded areas. Mow lawns, rake leaves, and trim trees in your yard to make it less attractive to ticks. Tuck your pants into your socks & your shirt into your pants. Wear sneakers or boots (not sandals). Wear light colored clothing so you can easily spot ticks. Apply insect repellent containing DEET. Permethrin is also effective, but only to be used on clothing, not skin. Check your clothes and body for ticks every three hours. Perform a thorough check of your body for ticks at the end of the day. Ticks prefer warm, moist areas, so be sure to check your armpits, scalp, and groin area. Scrub your body in the shower at night.



Emerging Rickettsial Diseases

- TIBOLA [3] – Tick-borne lymphadenopathy
- First case in France 1997
- *R. slovaca*
- Painful lymph nodes in region of tick bite.
- DEBONEL [4] –Dermacentor borne necrosis eschar lymphadenopathy
- On scalp region with characteristic eschar and erythema
- Without treatment last for 18 months

Latest

- New tick causes epidemic of Rocky Mountain spotted fever
- The brown dog tick is more likely to bite people and spread the often fatal bacterial infection, experts say.



- A recent molecular study has confirmed the causative agent involved in a large epidemic of Rocky Mountain spotted fever (RMSF) in humans and dogs in Mexicali, in Baja California, Mexico. Because Mexicali is a town adjacent to the border with the US, investigators now concern that epidemic may be spreading stateside
- The tick is present in U.S. and is moving northward.

Take Home

There exist many unique tick-associated rickettsiae for which a role in human disease has yet to be determined. Several of these rickettsiae satisfy the first component necessary for a potential tick-borne pathogen, i.e., they reside in a tick species with a natural proclivity to bite humans. Potentially fatal

The combined efforts of investigators around the world have reduced the concept of “one continent, one pathogenic tick-borne rickettsia” to an anachronism. Subsequent investigations will surely lead to discovery of new tick-borne rickettsial diseases in future.asm.org. Respond to Tetracycline and Doxycycline [5, 6,7].

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