



**MEDICAL UNIVERSITY – PLEVEN**  
**FACULTY OF MEDICINE**  
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,  
PARASITOLOGY AND TROPICAL MEDICINE**

**Lecture № 10**

**RICKETTSIAL DISEASES**  
**BOUTONEUSE FEVER**  
**Q-FEVER**

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# Vasculopathic rickettsial diseases of the spotted fever and typhus groups

- **Etiological agents**

These bacteria measure approximately 0.3 x 1.0  $\mu\text{m}$  and have a cell wall typical of Gram-negative bacteria. Components of the outer membrane include a 120-kDa surface protein, a 17-kDa lipoprotein, and lipopolysaccharides. Differences in the lipopolysaccharide antigens are the principal basis for the traditional antigenic separation of the spotted-fever and typhus groups.

# Epidemiology

The epidemiology of these rickettsioses is determined by the encounter between man and the infected arthropod vectors. The seasonal incidence and geographical distribution are determined by the vector's activity.

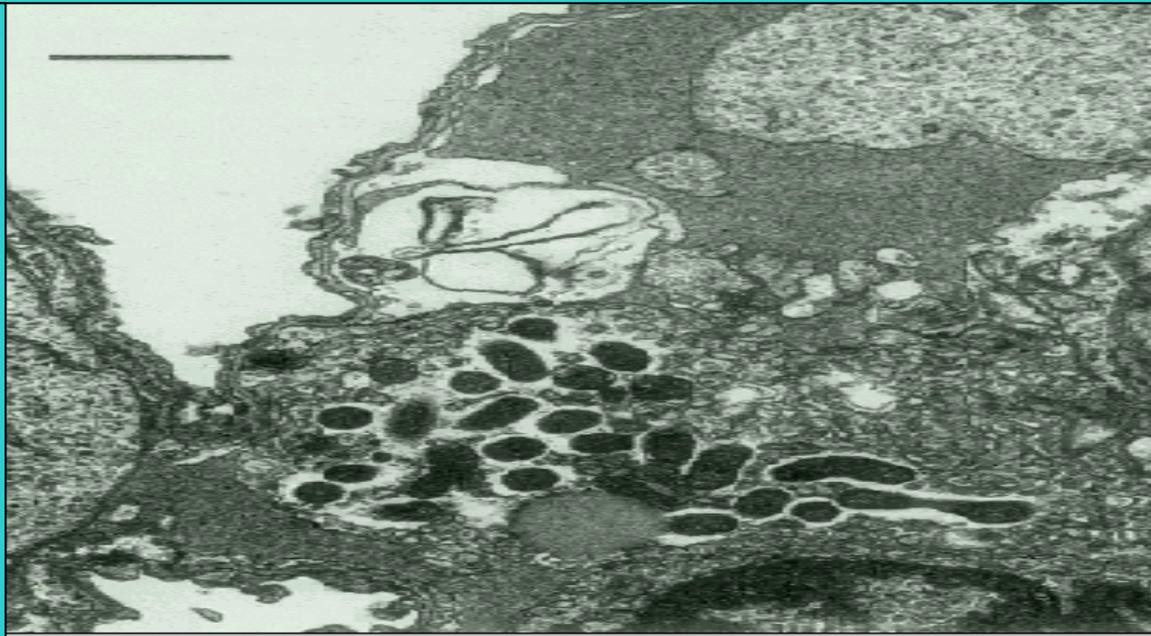
# Epidemiology

- Spotted-fever group rickettsiae are transmitted to man by secretion of infected tick saliva into the blood pooled at the site of the bite. It is possible that fluid or feces of infected ticks crushed between the fingers could enter a cutaneous wound or be rubbed into the conjunctival membrane.
- Typhus-group rickettsiae are transmitted to man by infected louse or flea feces deposited on human skin during arthropod feeding, with subsequent scratching of the organisms into the skin.

# Pathogenesis

- Rickettsiae of some species of the spotted-fever group frequently invade endothelial cells at the cutaneous portal of entry, proliferate, and cause a **focus of dermal and epidermal necrosis, an eschar**.
- Rickettsiae spread via the bloodstream to all parts of the body, where they come in contact with the endothelial cells lining the blood vessels.
- After their attachment to the endothelial cell membrane, phagocytosis is induced and rickettsiae escape from the phagosome into the cytosol, where they proliferate by binary fission.
- Epidemic typhus rickettsiae reach massive numbers intracellularly until the endothelial cell bursts, a dramatic pathogenic event, with further spread of the rickettsiae to other cells.
- Rickettsial lipopolysaccharides are essentially non-endotoxic in the quantities present during human infections, and there is no evidence of any rickettsial exotoxin.

# *Spotted fever rickettsiae*

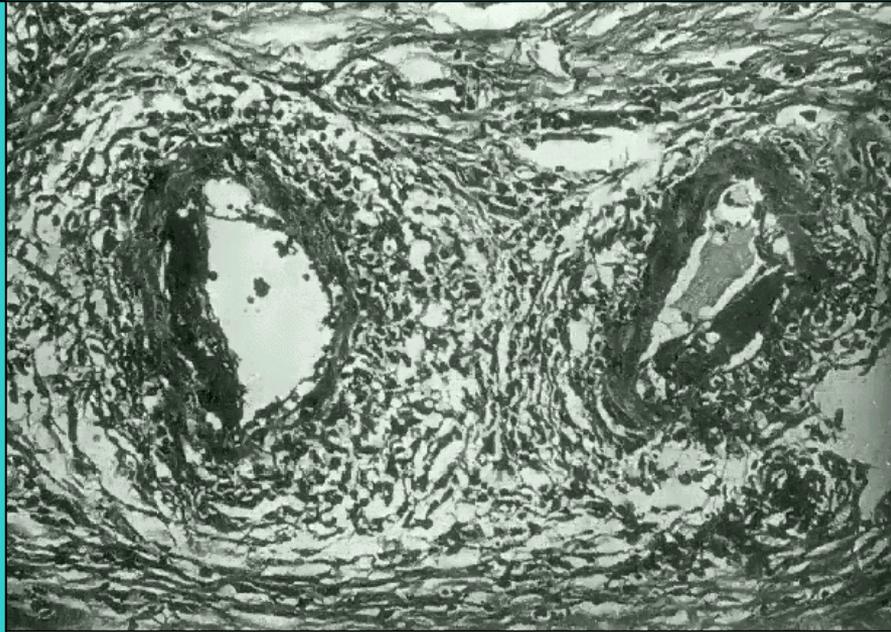


**Fig. 1** Electron photomicrograph of spotted fever rickettsiae in the cytosol of a pulmonary vascular endothelial cell (generously provided

# Pathogenesis

- Host immune, inflammatory, and coagulation systems are activated with apparent overall benefit to the patient. It has been suggested that some cytokines and inflammatory mediators, such as interferon- $\gamma$ , tumour necrosis factor- $\alpha$ , kallikrein, kinin, prostacyclin, thromboxane, and leukotrienes, cause some of the pathological manifestations of rickettsial diseases. It is very likely that host factors such as interleukin (IL)-1, tumor necrosis factor- $\alpha$ , and IL-6 are involved in fever and the acute-phase response.
- Injury to endothelium results in multifocal deposition of platelet plugs, which minimize the formation of petechia. This utilization of platelets in more extensive disease results in thrombocytopenia, but very rarely hypofibrinogaemic disseminated intravascular coagulation.
- The haemostatic thrombi are usually non-occlusive and thus seldom cause microinfarcts.

## *Rickettsial injury to two adjacent blood vessels*

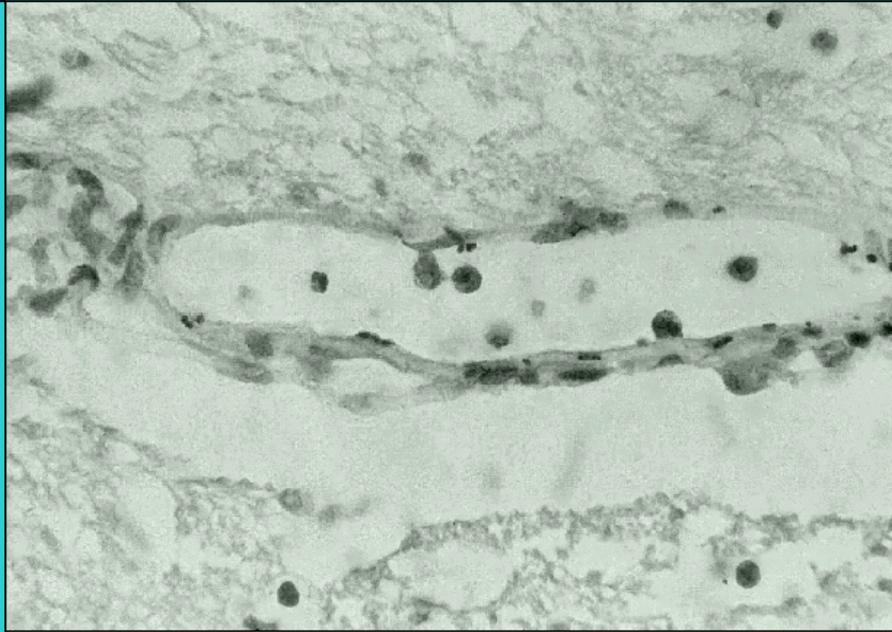


**Fig. 2** Severe rickettsial injury to two adjacent blood vessels with intramural and perivascular infiltration by host immune and phagocytic cells and non-occlusive mural thrombi that are not causing distal ischaemia but are plugging foci of severe damage to the vessel wall.

# Pathogenesis

- Progressive, disseminated infection and injury to endothelial cells cause increased vascular permeability, oedema, hypovolaemia, and signs and symptoms resulting from multifocal vascular injury in affected organs.
- Infection of the pulmonary microcirculation and the resulting increase in vascular permeability produce non-cardiogenic pulmonary oedema or acute respiratory distress syndrome, a life-threatening condition that may require supplemental oxygen and mechanical ventilation.

# *Rickettsia rickettsii*

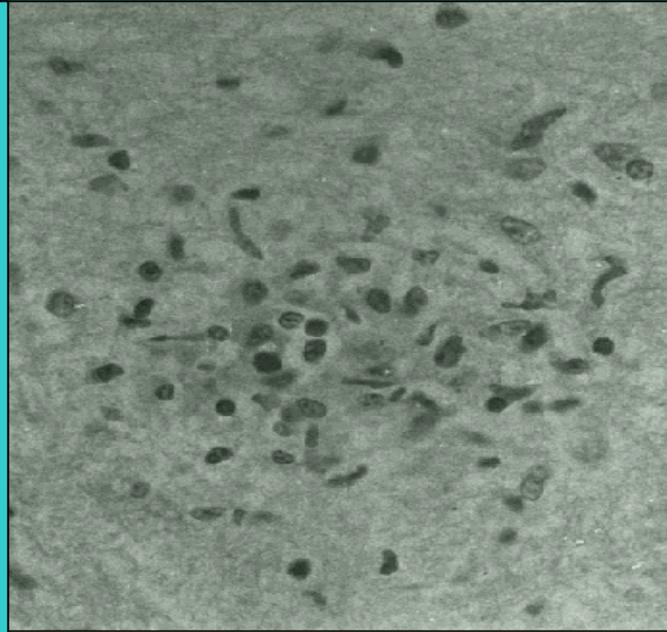


**Fig. 3** Immunoperoxidase-stained *Rickettsia rickettsii* appear as dark bacilli in endothelial cells of a cerebral blood vessel with perivascular oedema but no host immune-cell infiltration.

# Pathogenesis

- Although the host immune lymphohistiocytic response to rickettsial infection of the myocardial microcirculation is often described histologically as interstitial myocarditis, cardiac dynamics indicate that myocardial function is preserved. Arrhythmias may, at least in part, result from vascular lesions affecting the conduction system. The local effects of the vascular lesions in the brain, coupled with hypoperfusion, are associated with coma and seizures in severe cases, and the multifocal infectious lesions in the dermis are the basis for the maculopapular, sometimes petechial, rash.

# *Epidemic typhus fever*



**Fig. 4** Epidemic typhus fever. The typical lesion of rickettsial encephalitis is exemplified by the typhus nodule in the brain of a patient (death about 12th

# Pathogenesis

- Acute renal failure occurs in severe cases, usually as prerenal azotaemia or less frequently as acute tubular necrosis associated with severe hypotension. Rickettsial vascular lesions also are observed in the wall of the gastrointestinal tract, pancreas, liver, skeletal muscle, and other organs; these seem to be the basis for frequent nausea, vomiting, abdominal pain, and mild-to-moderate elevations in serum aminotransferases and variable elevations in serum creatine kinase.

# Clinical manifestations

- The incubation period of rickettsial diseases generally ranges from a few days to 2 weeks with an average of 1 week after cutaneous inoculation or deposition of the organisms by the tick, louse, or flea.
- The onset of rickettsioses is clinically non-specific, with malaise, chills, fever, myalgia, and headache that is often severe. The next few days' symptoms – anorexia, nausea, vomiting, abdominal pain, photophobia, and cough – suggest systemic involvement. **A rash usually appears after 3 to 5 days of illness,** is often absent at the time of presentation for medical care, and does not appear at all in a substantial portion of patients.

# Clinical manifestations

- The rash is frequently difficult to detect in patients with darkly pigmented skin. Initially, it consists of macular or maculopapular lesions, 1 to 5 mm in diameter, representing foci of numerous contiguous endothelial cells infected by rickettsiae and a surrounding zone of varying degrees of vasodilatation and dermal oedema. When compressed, these erythematous lesions blanch. In later stages of more severe disease, the intensely infected blood vessels in the centre of the maculopapule are breached and a petechia appears. At this stage, compression of the rash does not blanch the haemorrhagic focus.

# Clinical manifestations

- Pulmonary endothelial infection often results in cough and may cause pulmonary oedema, radiographic infiltrates, hypoxaemia, dyspnoea, and pleural effusions in severe cases.
- Neurological manifestations parallel the severity of illness, being absent in mild cases, consisting of lethargy in moderate cases, and, in severe cases, developing early and progressing to confusion, delirium, stupor, ataxia, coma, focal neurological signs, and seizures. Rickettsial infection of the blood vessels in the meninges, brain, and spinal cord may cause pleocytosis of the cerebrospinal fluid, usually 10 to 100 cells/ $\mu$ l with variable proportions of mononuclear and polymorphonuclear leucocytes, and/or an increased protein concentration; the glucose concentration is usually normal.

# Laboratory findings

- Although serum aminotransferases and bilirubin may be elevated, jaundice is observed in less than 10 per cent of patients, and hepatic failure does not occur.
- The white blood-cell count is usually normal, but an increased proportion of immature myeloid cells may be present.
- Mild anaemia may develop during the course of illness.
- The acute-phase reaction occurs in many patients, with increased concentrations of some plasma proteins, including C-reactive protein, haptoglobin,  $\alpha$ 1-antitrypsin, fibrinogen, factor VIII, and the third and fourth components of complement, and a decrease in transferrin.
- Hypoalbuminaemia is probably the result of leakage of this plasma protein into the interstitial space because of increased permeability of the microcirculation.

# Management and treatment

- **Etiologic treatment** – spotted-fever and typhus-group rickettsioses respond favourably to treatment with doxycycline (200 mg/day for adults and children greater than 45kg, and 4.4 mg/kg body weight per day for smaller children), tetracycline (2 gm/day in four divided doses for adults and 25 mg/kg body weight per day in four divided doses for children), or chloramphenicol (2 g/day in four divided doses for adults and 50 mg/kg body weight per day in four divided doses for children). Fluoroquinolones are active against rickettsiae, and ciprofloxacin (200 mg, intravenously every 12 h or 750 mg orally every 12 h), ofloxacin (200 mg orally every 12 h), and pefloxacin (400 mg intravenously or orally every 12 h) have been used successfully to treat boutonneuse fever.

# Management and treatment

- Epidemic typhus fever has been treated effectively under field conditions with a single, 200 mg dose of doxycycline. Treatment is generally continued for 2 or 3 days after defervescence to avoid relapse of the infection.
- Intravenously administered doxycycline or chloramphenicol is employed when oral treatment cannot be used because of vomiting or coma. Josamycin (3 g/day for 8 days) have been used to treat rickettsioses during pregnancy when the tetracyclines are contraindicated.

# Management and treatment

- **Supportive treatment** includes careful replacement of intravenous fluid volume to correct hypotension, hypoperfusion, and prerenal azotaemia; this may require monitoring of pulmonary capillary-wedge pressures to lessen the possibility of precipitating or exacerbating pulmonary oedema. Hyponatraemia is rarely severe enough to be life threatening, and homeostasis of serum sodium usually occurs within 48 hours of initiation of antirickettsial treatment and fluid replacement. Severely ill patients may suffer seizures and should then be given anticonvulsants. Severe thrombocytopenia may warrant platelet transfusions, but heparin should not be given.

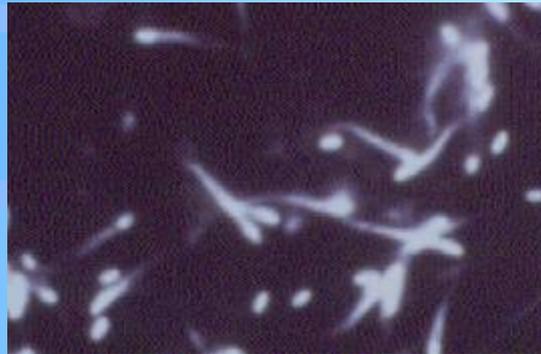
# **Mediterranean spotted fever (Boutonneuse fever) – definition**

- **Acute rickettsial infectious disease manifested by :**
- **intoxication and conjunctival suffusions,**
- **primary affect on the place of tick biting,**
- **generalized maculopapulous rash**
- **hepatosplenomegaly.**

# Boutonneuse fever – etiology

- Causative agent – Rickettsia conorii
- Gram (-) intracellular pathogen. The better replication is intra nuclearly.
- Unstable in environmental.

# *Rickettsia conorii*



# Boutonneuse fever – epidemiology

- The changes in the ecology of *R. conorii*, which is particularly associated with the tick *Rhipicephalus sanguineus*, that might explain the upsurge in cases have not been elucidated. *R. conorii* is maintained in *Rh. sanguineus* transovarially and is transmitted to humans by tick bite. The peak of cases along the Mediterranean coast of southern Europe occurs in July and August when immature stages of the tick predominate.

# *Ripicephalus sanguineus* and *Ixodes ricinus*



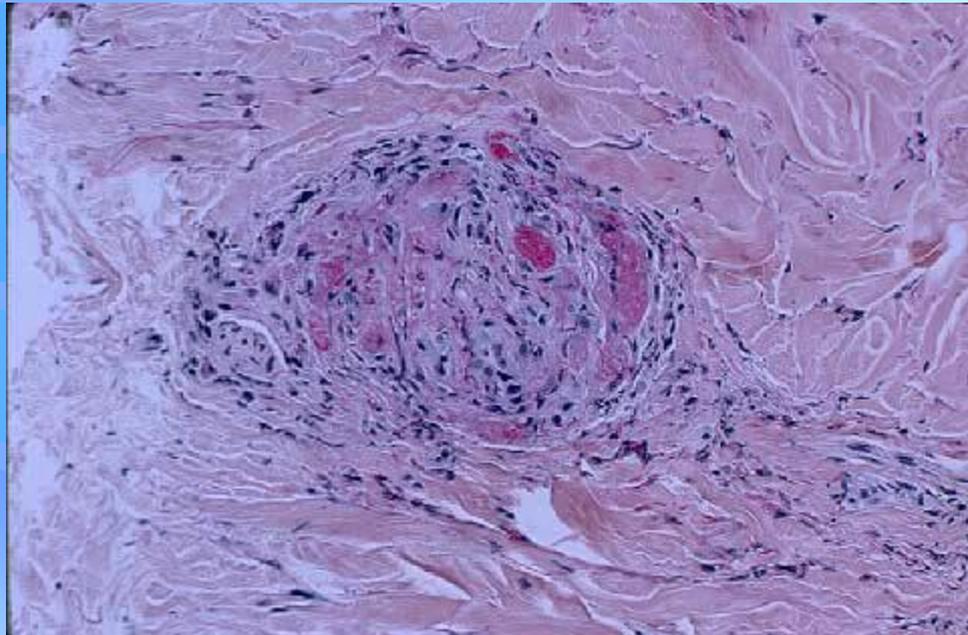
# Boutonneuse fever – pathogenesis

- The pathological basis for tissue injury in boutonneuse fever is illustrated by the tache noire (black spot) or eschar at the site of the infective tick bite. Endothelial infection and injury by *R. conorii* causes perivascular oedema and dermal and epidermal necrosis. The necrosis is apparently not secondary to thrombosis, which is usually absent or inconsequential. Reduction in the number of rickettsiae in the eschar is associated with a perivascular influx of lymphocytes and macrophages.

# Boutonneuse fever – pathogenesis

- Autopsies of fatal cases of boutonneuse fever show systemic vascular infection and injury by *R. conorii*, with lesions in the brain, meninges, lungs, kidney, gastrointestinal tract, liver, pancreas, heart, spleen, and skin including sites of peripheral gangrene. Clinical and experimental studies support the premise that direct rickettsial injury of infected endothelial cells is the major pathogenic event. Hepatic biopsies taken during the course of non-fatal boutonneuse fever contain multifocal hepatocellular necrosis with a predominantly mononuclear cellular response.

# *Boutonneuse fever – vasculitis*



# Boutonneuse fever – clinical manifestations

- During the incubation period of boutonneuse fever (3 to 7 days), a red papule appears at the site of the tick bite and progresses to develop into an eschar in approximately 70 per cent of diagnosed cases. It is often associated with regional lymphadenopathy. Subsequently, onset of illness is marked by fever, sometimes accompanied by headache and myalgias. The rash most often appears on the fourth day of illness but may be delayed, is maculopapular, and involves the palms and soles. It is petechial in only 10 per cent of patients and fails to appear at all in some patients.

*Boutonneuse fever –  
primary affect – tache noire*



*Boutonneuse fever –  
primary affect – tache noire*



*Boutonneuse fever –  
primary affect and specific rash*



*Boutonneuse fever –  
specific rash*



# Boutonneuse fever – clinical manifestations

- Other signs and symptoms may include nausea, vomiting, cough, dyspnoea, conjunctivitis, stupor, meningism, lymphadenopathy, and hepatomegaly. Increased vascular permeability manifested as mild oedema, hypoalbuminaemia, and arterial hypotension characterizes the pathophysiology of boutonneuse fever. Clinical laboratory evaluation (aggregate data) reveals anaemia in one-third of patients, with blood haemoglobin concentration of less than 100g/l in 11 per cent of patients occurring particularly in severe cases.

# Boutonneuse fever – clinical manifestations

- The white blood-cell count is usually normal, with leucopenia in 18 per cent and leucocytosis in 28 per cent of patients. Platelet counts less than  $100 \cdot 10^9/l$  are detected in 12.5 per cent of the patients. Hyponatraemia of less than 130 mmol/l occurs in 23 per cent; hypocalcaemia of less than 2.1 mmol/l in 38 per cent is presumably related to the hypoalbuminaemia. Hypoproteinaemia is observed in 23 per cent of patients.

# Boutonneuse fever – clinical manifestations

- Serum urea and creatinine concentrations are elevated in 25 and 17 per cent of patients, respectively. Serum concentrations of aspartate and alanine aminotransferases are increased in 39 and 37 per cent, respectively, and serum bilirubin is greater than 20  $\mu\text{mol/l}$  in 9 per cent. Severe illness occurs in 6 per cent of patients and may be manifested by cutaneous purpura and other haemorrhagic phenomena, neurological signs, altered mental status, respiratory symptoms and hypoxaemia, acute renal failure, thrombocytopenia, and often even death.

# Boutonneuse fever – diagnosis

- In the acute stage of illness, laboratory diagnosis can be established by immunohistological demonstration of *R. conorii* in a biopsy of the tache noire or rash, or in circulating endothelial cells separated from the peripheral blood by magnetic beads coated with a monoclonal antibody to an endothelial cell-membrane antigen, as described above. *R. conorii* can be isolated by intraperitoneal inoculation in guinea-pigs or in cell culture.
- Diagnostic serological methods currently used include the indirect immunofluorescent antibody assay and latex agglutination test, both of which have commercially available reagents, as well as the indirect immunoperoxidase assay and complement fixation test. Western immunoblots have demonstrated that antibodies are directed mainly at the major 120- and 190-kDa surface proteins and lipopolysaccharides.

# Boutonneuse fever – management and treatment

- **Etiologic** – doxycyclin 2 x 100 mg/day 7-10 days. Alternative – fluoroquinolones are active against rickettsiae, and ciprofloxacin (200 mg, intravenously every 12 h or 750 mg orally every 12 h), ofloxacin (200 mg orally every 12 h), and pefloxacin (400 mg intravenously or orally every 12 h) have been used successfully to treat boutonneuse fever.
- **Supportive treatment** includes careful replacement of intravenous fluid volume to correct hypotension, hypoperfusion, and prerenal azotaemia; this may require monitoring of pulmonary capillary-wedge pressures to lessen the possibility of precipitating or exacerbating pulmonary oedema. Hyponatraemia is rarely severe enough to be life threatening, and homeostasis of serum sodium usually occurs within 48 h of initiation of antirickettsial treatment and fluid replacement. Severely ill patients may suffer seizures and should then be given anticonvulsants.

# Boutonneuse fever – prophylaxis

- Specific – there is no vaccine to protect against *R. conorii*.
- Non specific:
  - ❖ education,
  - ❖ personal prevention,
  - ❖ cares for dogs.

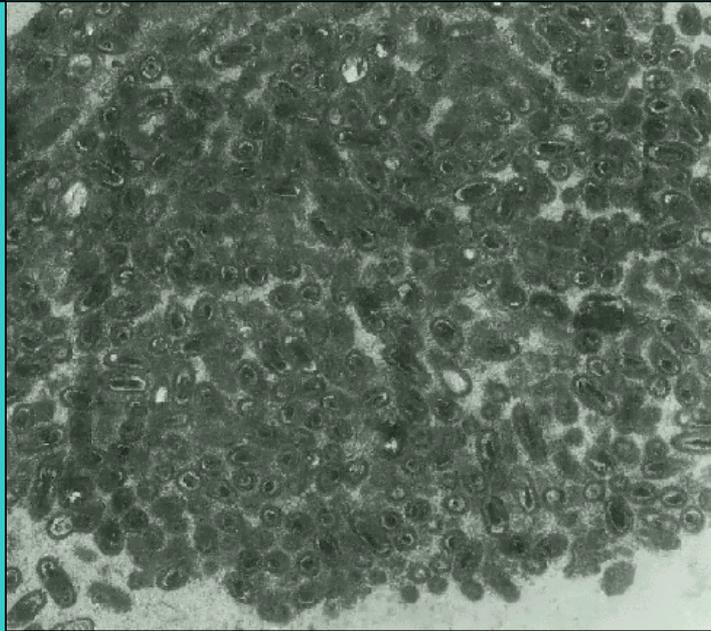
# **Coxiella burnetii infections (Q fever) – etiology**

- **Causative agent – Coxiella burnetii**

This micro-organism has a Gram-negative cell wall and measures 0.3  $\mu\text{m}$ .

- ❖ It is the sole species of its genus and, while it is a member of the family Rickettsiaceae.

# *Coxiella burnetii*



**Fig. 1** Transmission electron micrograph showing *Coxiella burnetii* cells within a macrophage in the heart valve of a patient with Q fever endocarditis. The dark material in the centre of each cell is condensed

# Q fever – epidemiology

- Q fever is a zoonosis.
- There is an extensive wild-life and arthropod (mainly ticks) reservoir of C. burnetii.
- Domestic animals are infected through inhalation of contaminated aerosols or by ingestion of infected material.
- Man becomes infected after inhaling organisms aerosolized at the time of parturition or later when organisms in dust are stirred up on a windy day.
- Infected cows have shed C. burnetii in milk for up to 32 months while sheep shed the organism in faeces for 11 to 18 days postpartum.
- Infected cattle, sheep, and goats are the animals primarily responsible for transmitting C. burnetii to man. Some studies have suggested that ingestion of contaminated milk is a risk factor.
- Percutaneous infection, such as when an infected tick is crushed between the fingers.
- Vertical transmission from mother to child has been infrequently reported.
- Person-to-person transmission has been documented on a few occasions.

# Q fever – clinical manifestations

- Man is the only known almost always to develop illness following infection with *C. burnetii*. There is an incubation period of about 2 weeks (range 2-29 days) following inhalation of *C. burnetii*. A dose-response effect has been demonstrated experimentally and clinically. In cattle-related outbreaks of Q fever those who cleaned up the products of conception had the shortest incubation period and the most severe illness. *C. burnetii* is one of the most infectious agents known to man; a single micro-organism is able to initiate infection. The resulting illness in man can be divided into acute and chronic varieties.

## Q fever – clinical manifestations and clinical forms

- **Acute Q fever**

- Self-limiting febrile illness:

- ❖ The most common manifestation of acute Q fever is a self-limiting febrile illness. In areas where Q fever is endemic, 12 per cent or more of the population have antibodies to *C. burnetii* – most of these infections are subclinical.

## Q fever – clinical manifestations and clinical forms

- **C. burnetii pneumonia** – this is the most commonly recognized manifestation of Q fever. The onset is non-specific with fever, fatigue, and headache. The headache may be very severe, occasionally so severe that it prompts a lumbar puncture. A dry cough of mild to moderate intensity is present in 24 to 90 per cent of patients. About one-third have pleuritic chest pain. Nausea, vomiting, and diarrhoea do occur in 10 to 30 per cent of patients. Most cases of *C. burnetii* pneumonia are mild; however, about 10 per cent of cases are severe enough to require admission to hospital; rarely, assisted ventilation is necessary.

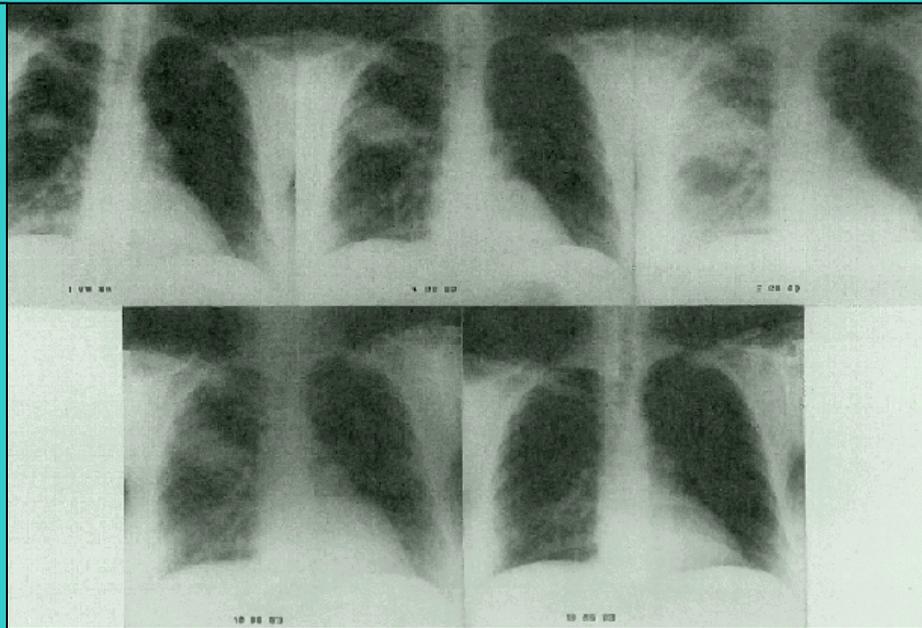
## Q fever – clinical manifestations and clinical forms

- ❖ Death is rare in Q fever pneumonia and is usually due to comorbid illness. Examination of the chest reveals crackles but frequently there are no abnormal findings. The physical findings of consolidation are present in 30 per cent of cases. The white blood-cell count is usually normal; it is elevated in one-third of patients. There may be mild elevation of liver enzymes, two to three times normal. Reactive thrombocytosis is surprisingly common, occurring in 60 per cent of patients and often reaching values of  $700$  to  $800 \cdot 10^9/l$ . Microscopic haematuria is a common finding.

## **Q fever – clinical manifestations and clinical forms**

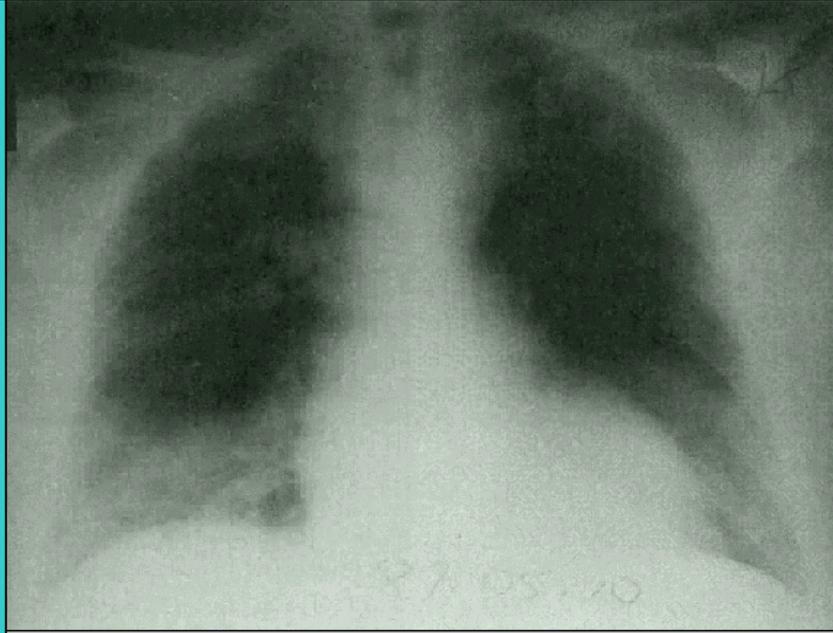
- The chest radiographic manifestations of Q fever pneumonia are usually indistinguishable from those of any bacterial pneumonia. However, rounded opacities are suggestive of this infection. Some investigators have reported delayed clearing of the pneumonia; however, in our experience resolution is usually complete within 3 weeks.

## *Q fever pneumonia – radiographic manifestations*



**Fig. 2** Serial chest radiograph of a 35-year-old patient with Q fever pneumonia. The first radiograph (1 August 1989) shows a right upper-lobe, round opacity that increases in size over the next 6 days. The pneumonia has completely cleared by 19 September 1989.

## *Q fever pneumonia – radiographic manifestations*



**Fig. 3** Portable anteroposterior chest radiograph of a 72-year-old male with Q fever pneumonia. Note the bilateral lower-lobe opacities. This radiographic picture is indistinguishable from pneumonia due to any other microbial agent.

# Q fever – clinical manifestations and clinical forms

- **Q fever – hepatitis** – the liver is probably involved in all patients with acute Q fever. There are three clinical pictures:
  - ❖ pyrexia of unknown origin with mild to moderate elevation of liver function tests;
  - ❖ a hepatitis-like picture; "incidental hepatitis". In incidental hepatitis the chief manifestation of Q fever is infection of another organ system with mild elevation of liver function tests. Liver biopsy reveals the distinctive "doughnut" granuloma, consisting of a granuloma with a central lipid vacuole and fibrin deposits.

# Q fever – clinical manifestations and clinical forms

- **Q fever** – neurological manifestations – encephalitis, encephalomyelitis, toxic confusional states, optic neuritis, and demyelinating polyradiculoneuritis are uncommon manifestations of Q fever.
- **Q fever** – rare manifestations – these include myocarditis, pericarditis, bone marrow necrosis, lymphadenopathy, pancreatitis, mesenteric panniculitis, erythema nodosum, epididymitis, orchitis, priapism, and erythema annular centrifugum.

## Q fever – clinical manifestations and clinical forms

- **Chronic Q fever** – the usual manifestation of chronic Q fever is that of culture-negative endocarditis. Seventy per cent of these patients have fever and nearly all have abnormal native or prosthetic heart valves. Hepatomegaly and or splenomegaly occur in about half of these patients and one-third have marked clubbing of the digits A purpuric rash due to immune complex-induced vasculitis and arterial embolism occur in about 20 per cent of patients. Hyperglobulinaemia (up to 60 g/l) is common and is a useful clue to chronic Q fever in a patient with the clinical picture of culture-negative endocarditis.

**THANK YOU  
FOR ATTENTION !**