Bartonellosis

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Summary

- Bacterial infection with bacilliformis
- Occurs only in certain areas of South America
- Transmission via sandflies of the genus Lutzomyia
- Treatment with ciprofloxacin or chloramphenicol
- Acute disease: febrile haemolytic anaemia, hepatosplenomegaly, lymphadenopathy, bleeding
- Chronic disease leads to chronic angiomatous skin lesions

General

The genus *Bartonella* currently contains 19 species of bacteria which infect erythrocytes of vertebrate hosts. It is expected that new species will be identified in the future.

In 1992, the *Bartonella* genus consisted of a single species but by 2007, this had increased to 19 officially recognised species. At present, humans are the sole reservoir for only two species: *B. quintana* and *B. bacilliformis.* Exceptionally, infections with other Bartonella species occur and result in bacteraemia or endocarditis (*B. elizabethiae, B. clarridgeiae, B. vinsonii vinsonii, B. vinsonii arupensis* and *B. vinsonii berkhoffii*). In 2007, a newly recognized *Bartonella* species was isolated from a patient with bacteraemia. It grew slowly in BACTEC bottles (blood culture bottles) could not been visualised with Gram staining but stained with acridine-orange. The proposed name is *B. rochalimae*. The infected patient had recently travelled to Peru where she visited places in the Andes mountains. It is possible that some cases of Oroya fever are actually due to infection with this new bacterium.

Bartonella baciliformis	Oroya fever, verruga peruviana, asymptomatic carriers
Bartonella quitana	Trench fever, bacillary angiomatisis, endocarditis, chronic bacteraemie
Bartonella henselae	Cat-scratch disease, bacillary angiomatosis, visceral peliosis, endocarditis, septicaemia
Bartonella clarridgeiae	Cat-scratch disease (rare)
Bartonella elizabthea	Endocarditis
Bartonella washoensis	Cardiac disease

Bartonella grahamii	Neurorentinitis
Bartonella vinsonii	Endocarditis, fever and neurological disease

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Bartonelle baciliformis or Carrion's disease

History

South American-bartonellosis, (Carrión's disease, Oroya fever, verruga peruana, verruga peruviana) results from infection with the bacterium *Bartonella bacilliformis* and is transmitted by **sandflies**. The infection manifests itself in **two very different clinical forms** with the causal connection being recognised by the young Peruvian doctor Daniel Alcides Carrión.

Pre-Columbian mummies with histologically confirmed verruga lesions have been discovered in Peru and bartonellosis occurred in Francisco Pizarro's army (1471-1541). During the Inca era, the disease was called "Sirki," which means "warts in blood." In Peru between 1869 and 1873 more than 7000 workers building the Lima-La Oroya railway died from the disease at Cocachacra, 65 kilometers from Lima, 1600 meters above sea level. The name "Oroya fever" refers to this, although in the mining town of La Oroya (altitude 3800 m), strangely enough there was no transmission of Oroya fever. In 1936 a large epidemic was seen in the Guaitara valley on the border between Colombia and Ecuador. An epidemic occurred in 1980 in Ecuador and another in 1987 in Peru with a death rate of 88% in the untreated patients. Now and then there have been isolated cases or small outbreaks. In 1997 there was an outbreak in the area of Cuzco, Peru. In an outbreak in Zumba, Ecuador (1995-96), large numbers of dead rodents were found around the places where the cases had occurred. This finding led to the hypothesis that bartonellosis could have an animal reservoir.

Daniel Alcides Carrión

Daniel Alcides Carrión (1858-1885) was a medical student in Lima, Peru. He was required to prepare an original thesis and choose to study the epidemiology and clinical manifestations of verruga peruviana. His home was in Cerro de Pasco, a mining town high in the Andes where he had

seen many cases. These left a deep impression on the young man. He told a classmate that he hoped “to make an important contribution to aching humanity”. He became concerned with the difficulty in diagnosing verruga peruviana before the typical eruption started. The appearance of the skin lesions was preceded by fever and anaemia, but there was a lot of confusion between the prodromal phase of verruga and other febrile disorders such as malaria. Carrión wanted to determine the incubation period and early symptoms of verruga, so he decided to inoculate himself with some fluid from a chronic skin lesion of a verruga patient. Many friends and professors tried to dissuade him. On the morning of August 27, 1885, Carrión was in the Nuestra Senora de las Mercedes ward of the Dos de Mayo Hospital in Lima. A 14-year-old boy named Carmen Paredes was admitted with verruga on his right eyebrow. Assisted by Dr Chavez, a young ward physician, Carrión used a lancet to inoculate his own arm with blood taken from that verruga. He kept a diary afterwards. The first symptoms started after 21 days, with discomfort and pain in his left ankle. Two days later he developed fever, chills, abdominal pain and generalised pain in bones and joints. He had anorexia and noted severe thirst. His urine became dark red and scanty. He developed jaundice. A week later, he became too ill to continue his diary. His classmates took over this task and were surprised at how quickly anaemia developed. A systolic heart murmur developed and grew in intensity. A few days later, muscle fasciculations appeared in his arm muscles. He said to his friends: “Up to today, I thought I was only in the invasive stage of the verruga as a consequence of my inoculation, that is, in the period of anaemia that precedes the eruption. But now I am deeply convinced that I am suffering from the fever that killed our friend, Orihuela. Therefore, this is the evident proof that Oroya fever and the verruga have the same origin, as Dr Alarco once said.” This insight was the essence of Carrión’s experiment. He had not set out to prove the single cause of verruga peruviana and Oroya fever. He only intended to study the incubation period and prodrome of verruga. When a completely different disease developed, he was lucid enough to understand the full meaning of his experiment. On October 3, he became delirious and two days later he fell into a coma and died at midday. He became a hero of Peruvian medicine and is remembered to this day. The day of his death, October 5, is celebrated yearly as the “Dia de la Medicina Peruana”. His burial vault – where doctors pay tribute – is in the Hospital Nacional Dos de Mayo in Lima. The Peruvian National University in Cerro de Pasco carries his name.


PTE. VERRUGAS
CARGA MAXIMA 60 TNS.
LONGITUD 21 m.
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Puente ‘Verrugas’ in the Andes, a railway bridge on the trail Lima – La Oroya (Peru). The name refers to a bartonellosis epidemic in 1869-1873. Copyright ITM

Picture of Dr Daniel Alcides Carrion, on the road Lima – La Oroya. In this area of the Western Andes in Peru, there was a bartonellosis epidemic in 1869-1873. The disease is also known as Oroya fever or Carrion’s disease. Photo Dr Van den Enden. Copyright ITM

Aetiology

Barton described the pathogen in 1909, but he thought that it was a protozoon. The Japanese bacteriologist Hideyo Noguchi demonstrated the bacterial nature of the pathogen. *Bartonella bacilliformis* is a **small Gram-negative coccobacillus** (0.6-1 µm), which takes Giemsa and Warthin-Starry stain. The pathogen has one or more polar flagella. It replicates within the vascular endothelium and erythrocytes. The bacterium is **related to rickettsiae**. The bacillus grows quickly (extracellularly) on non-living culture media with blood or on chicken embryos at 25-28°C. Numerous

related organisms are animal pathogens.

Distribution

The disease caused by *Bartonella bacilliformis* **only occurs in certain narrow high valleys of the western-most slopes of the Andes at altitudes between 500 and 3200 meters in Peru, Ecuador and Colombia**, between 2° N and 13° S. Whether endemic cases occurred in Chili, Bolivia, Guatemala and Honduras is very doubtful. Sporadic cases of so-called “bartonelloses” have been reported in Africa, (Niger, Sudan), in Asia (Pakistan) and in the USA, but it is still not clear whether there is a connection with Carrión’s disease. Our knowledge about *Bartonella* and related bacteria has largely increased in recent years but is still very incomplete.

Transmission

A sandfly, *Lutzomyia verrucarum*, and perhaps a few related species, is responsible for transmission. Transmission only occurs at night and is seasonal, particularly during the rains. It was formerly assumed that the **reservoir was purely human, but this was recently cast into doubt** (there may be a rodent reservoir). In some of the inhabitants in the endemic valleys bacteria can be found in the blood, but these carriers are usually without any symptoms. These **latent infections** which are likely to have been contracted in childhood probably give **stable immunity**. It is only if non-immune populations enter the endemic area that epidemics occur, sometimes on a large scale, such as in wars or when large public works are being carried out. Tourists may be at risk for the disease.

Clinical aspects

The **clinical range is wide**, going from **asymptomatic infections** via serious febrile forms with acute **haemolytic anaemia**, to the **angiomatous skin lesions** which can be present from the onset or can be preceded by the febrile stage. The mortality of untreated cases varies between epidemics and ranges from 10-40% after 2-3 weeks. The disease is less severe in children and the mortality is far lower. If the course of the disease is favourable, the **fever can last for 3 to 4 months**. In 40-50% of cases of Oroya fever, **concurrent salmonellosis** (generally Salmonella typhimurium) complicates the illness and makes the prognosis less favourable. The superinfection causes fever with gastrointestinal symptoms and a deterioration of the patient’s general condition.

Oroya fever or Acute Carrion”s Disease

Key clinical aspects

1. Incubation takes approximately **3 to 8 weeks** (range 10-210 days). It begins insidiously with:

2. Irregular **intermittent febrile** attacks with shivering

3. Rapidly worsening **anaemia** with tachycardia, pallor and (sub)icterus

4. Severe **headache** with bone and joint pain. This may persist after the fever has ended

5. Enlargement of the **liver and spleen**, slightly painful on palpation

6. Generalised painful **swollen lymph nodes**

7. Myocarditis, pulmonary oedema and anasarca (generalised oedema)

8. **Haemorrhagic diathesis** as a result of the endothelial lesions: petechiae and tendency to thrombosis. Necrotic foci are found in the liver, spleen and bone marrow.

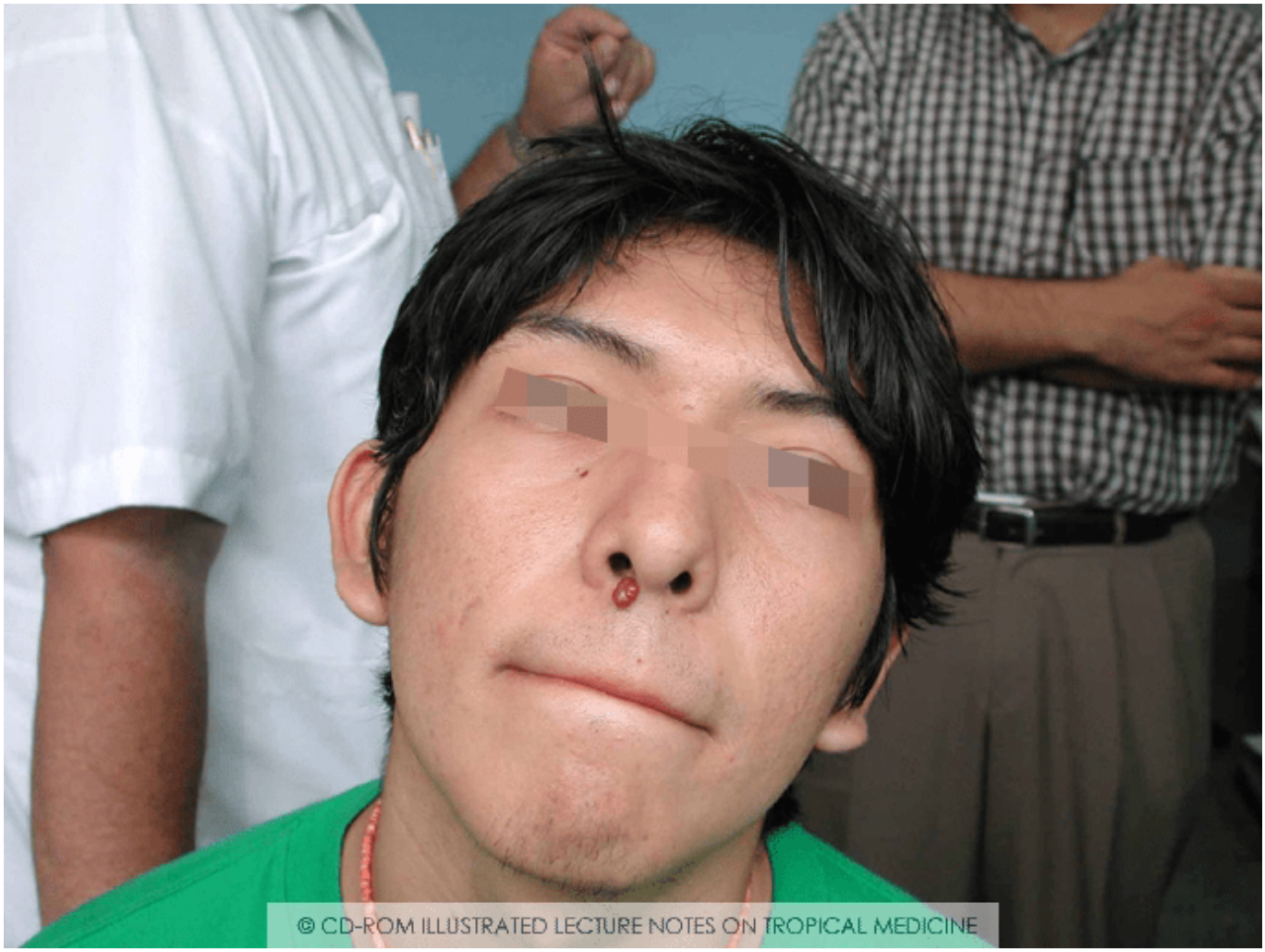
9. **Neutrophilia**

10. Spontaneous abortion, foetal death or transplacental transmission can occur.

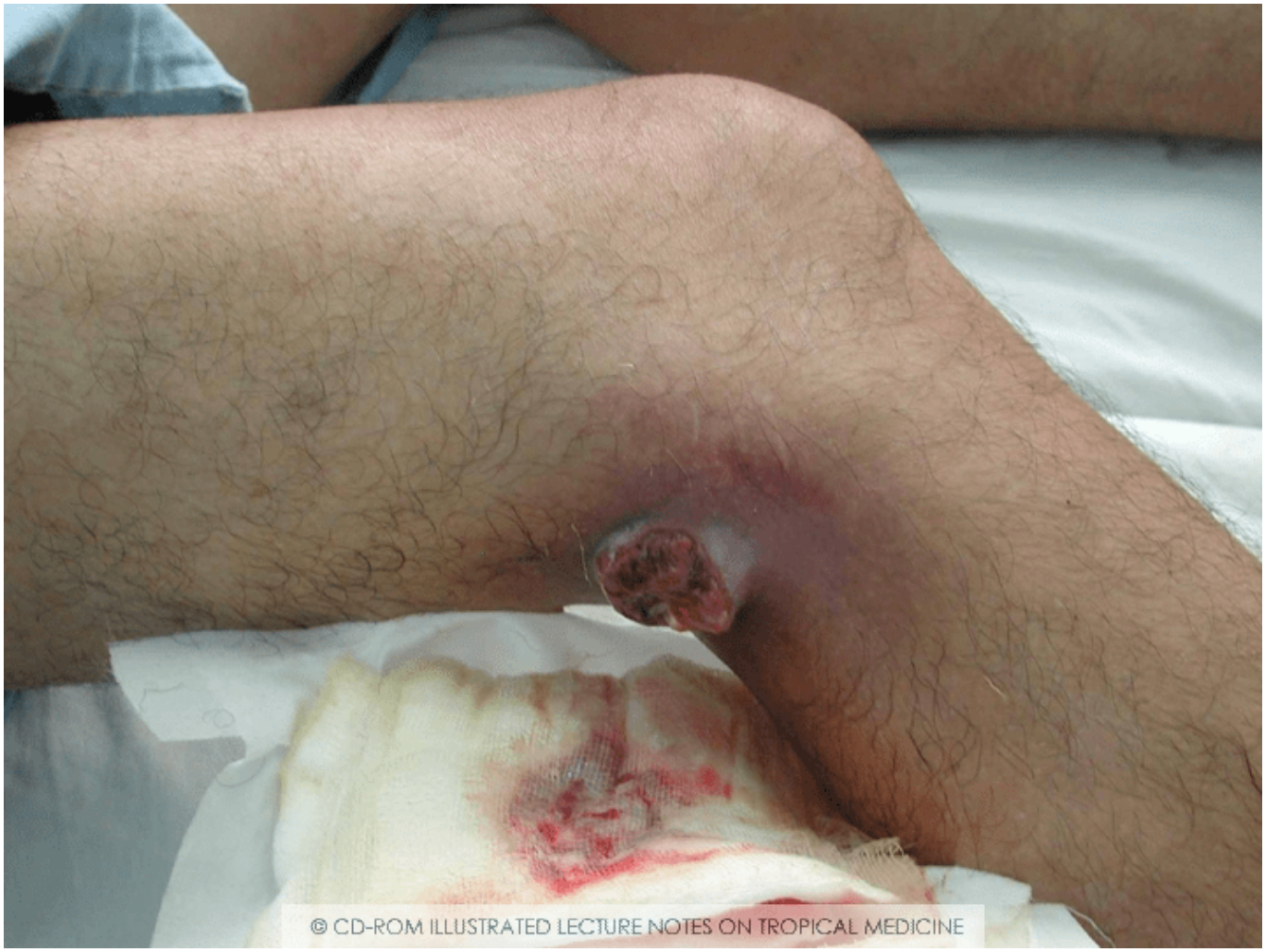
11. **Neurobartonellosis** due to involvement of the CNS takes the form of meningo-encephalitis with or without convulsions and with high mortality. Myelitis also occurs with spastic or flaccid paraplegia with sequelae which can be permanent. There is pleiocytosis of the CSF. More focal and transient lesions of the spinal cord or of the cranial nerves are seen at the verruga stage.

Verruga peruana or Chronic Carrion’s Disease

This is the chronic eruptive stage of infection with Bartonella bacilliformis. The painless wart-like skin eruption results from the abnormal growth of blood vessels with the appearance of haemangiomas and the formation of angioblastic nodules. At this stage Bartonella can still be found in the endothelial cells, but they are only very rarely found in the erythrocytes.



Verruga peruviana in chronic bartonellosis (infection with *Bartonella bacilliformis*). Do not confuse this lesion with a granuloma pyogenicum. Copyright Alexander von Humboldt Institute, Peru



Bacillary angiomatosis. Ulcer due to infection with *Bartonella henselae*. Copyright Alexander von Humboldt Institute, Peru

The skin eruption usually **appears 6 to 14 weeks after the acute stage.** Both pathological conditions can be present at the same time. The skin eruption may initially be accompanied by a mild fever and arthralgia. The eruption is polymorphic. Some lesions disappear quickly, others persist or grow for some time only to shrivel and disappear, generally without leaving scars. There are three forms:

Miliary form: the lesions are small (< 0.5 cm), very numerous and mainly found on the face, on the extensor surface of the limbs and on the trunk. They are initially macular and grow to small vascular, sometimes pedunculated and protruding nodules. Lesions are also present on the digestive and genito-urinary mucosa. Dysphagia, haematemesis, melaena, haematuria and metrorrhagia can occur.

Nodular form: the nodules are larger, less numerous, deeper, chronic and mainly found around the elbows and knees. The mucous membranes are spared. The lesions appear in cycles for 2 to 3 months.

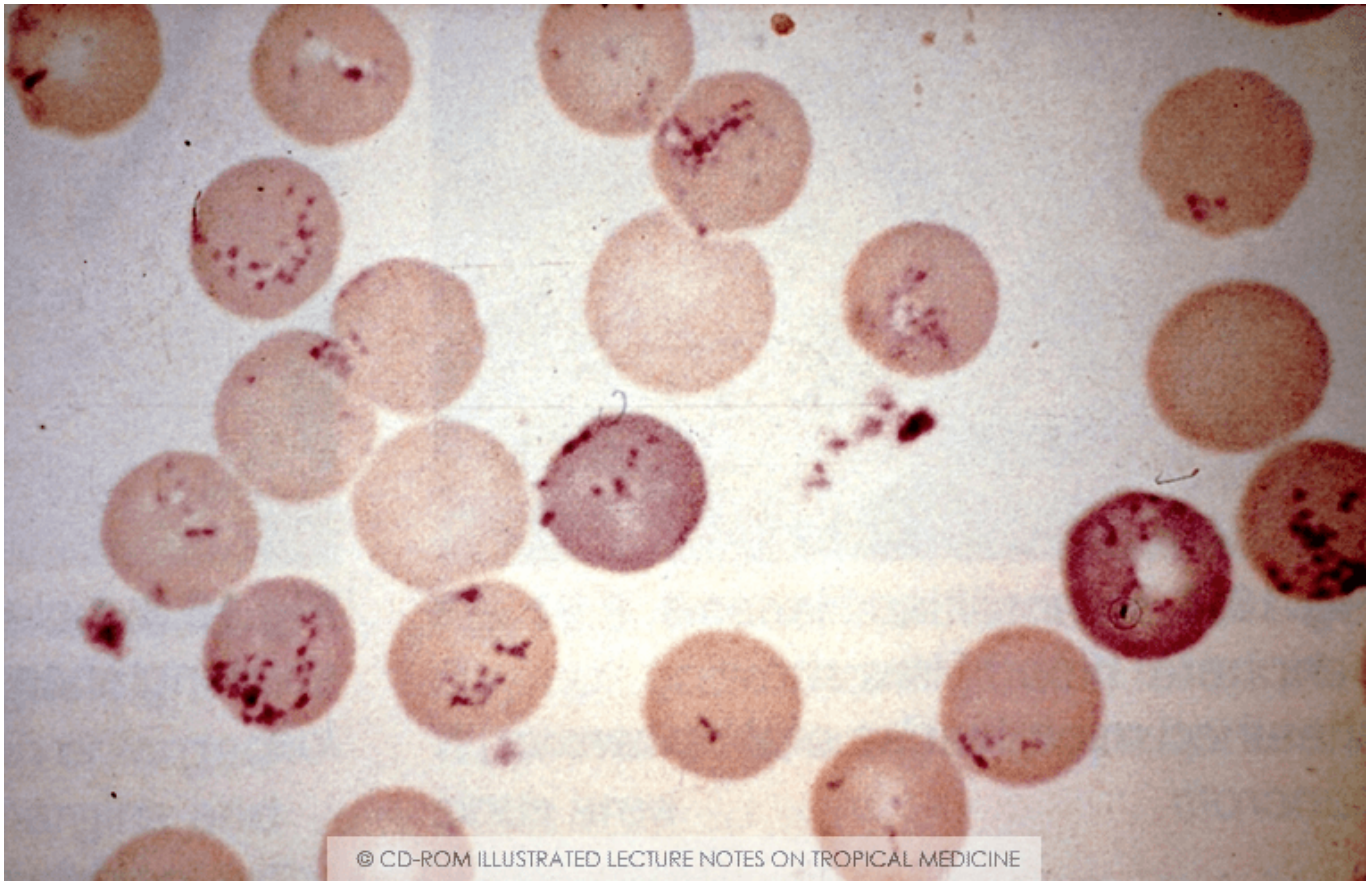
Mular form: there are isolated pseudotumoural haemorrhagic nodules which macroscopically resemble granuloma pyogenicum.

Immunity

Immunity is **gradually acquired during the acute stage**, so that the disease becomes **limited to the wart-like lesions** of the skin and mucous membranes which subsequently heal completely and permanently. In experimentally infected monkeys the **disease can be reversed** from the verruga stage to the febrile haemolytic stage by splenectomy. The same probably occurs in humans. The prognosis of verruga is good. They evolve in spurts and the lesions generally heal spontaneously in less than 6 months.

Diagnosis

The diagnosis is based on the endemicity, the clinical characteristics, full blood count, the presence of *Bartonella* in blood smears (Giemsa stain), blood cultures or tissue cultures from skin lesions or even the histological examination of the latter. More than 70 percent of patients with acute Oroya fever have a positive blood culture for *B. bacilliformis*, although there may be a delay of more than 14 days for the organism to grow in culture. *B. bacilliformis* is fastidious and requires Columbia agar, an enriched blood medium, for growth, which occurs most readily at 25 to 28°C.



Bartonella bacilliformis in red blood cells

In the differential diagnosis, consideration is given to malaria, dengue, viral hepatitis, babesiosis, bacillary angiomatosis in AIDS patients, typhus, typhoid fever, Yaws, Kaposi's sarcoma, haemangiomas, pyogenic granuloma and various skin tumours. In mild forms, the number of Bartonella in the blood smear can fall below the detection limit. The degree of haemolysis is then very limited, and the infection is extremely difficult to diagnose if no serology is available. PCR, Immunofluorescence, ELISA and Western Blot among others are used for diagnosis.

Treatment

Until recently **chloramphenicol** was the drug of choice but **ciprofloxacin** has now been shown to give better results. Both are also effective in Salmonella infections (in absence of resistance).

Chloramphenicol is administered at doses of 4 g/day for 5 days. Ciprofloxacin is given as 500 mg BD.

The fever disappears in less than 48 hours. The mortality rate of Oroya fever can be largely reduced with antibiotic therapy. Late development of the verruga stage is possible despite correct treatment.

Ciprofloxacin or rifampicin for 2 to 3 weeks can be used in the verruga stage.

Disease control

Spraying with insecticides, especially those which retain their activity for long periods interrupts transmission. However, control measures are not essential in endemic areas because of the immunity of the adult population. Individual protection consists of avoiding spending the night in exposed biotopes and the use of insect repellents or mosquito nets treated with permethrin/deltamethrin.

Although theoretically possible vaccination is not used.

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Bartonella quintana or Trench fever

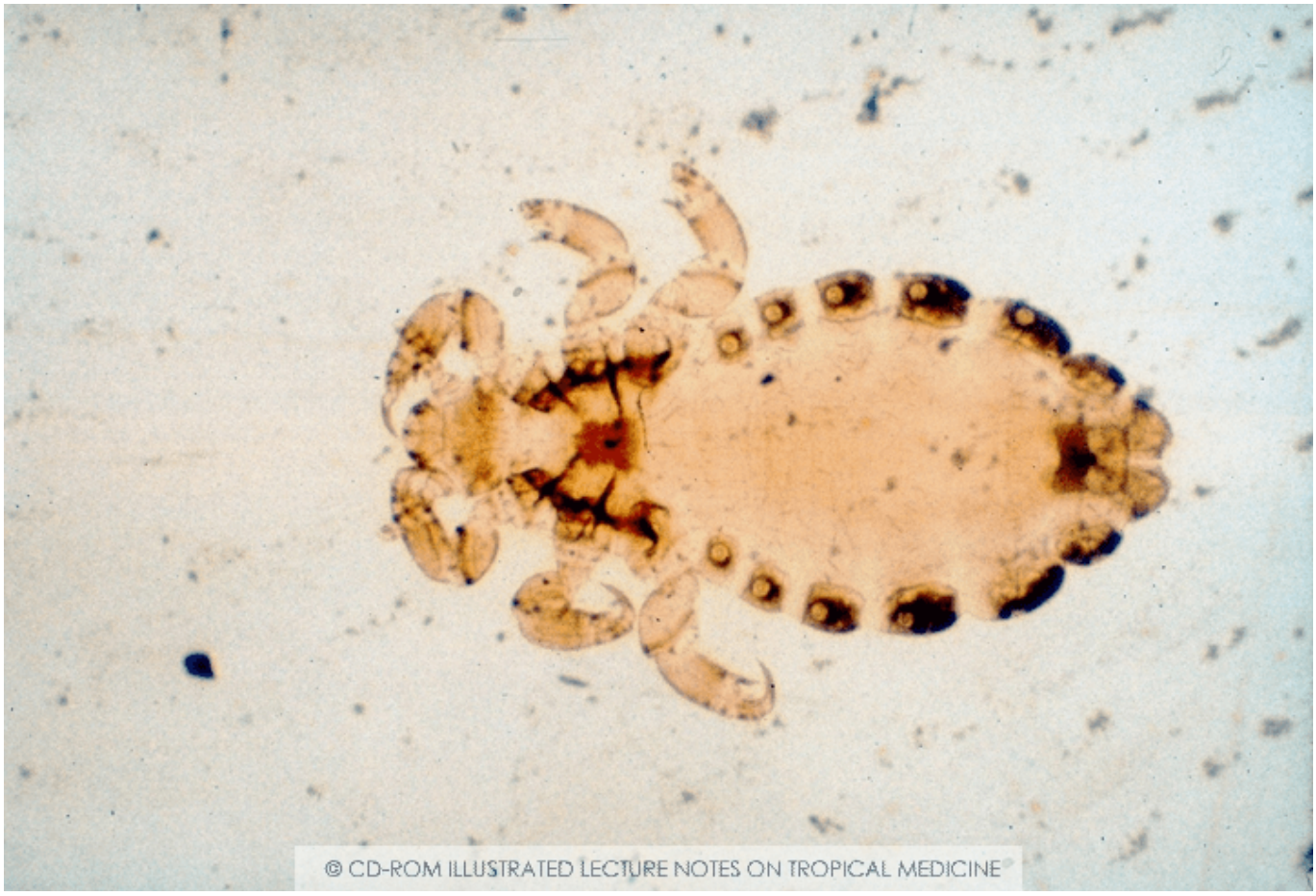
General

Bartonella quintana is a very small Gram-negative intracellular rod-shaped bacterium responsible for a range of clinical presentations. Infections with this bacterium are **linked to louse infestation** and occur where **people lack access to adequate water to maintain personal hygiene, such as homeless encampments in high-income countries and refugee camps and remote rural areas in low-income-countries**. The bacterium is **not recognized by routine bacterial culture**. **Trench fever** was the first clinical manifestation of infection with *Bartonella quintana* to be recognized. The name refers to its association with the German and Allied troops in the First World War. It is estimated that more than one million people were infected during the war. British troops took the disease to Mesopotamia during Lawrence of Arabia. After the war, the incidence fell very sharply. The disease broke out again during the Second World War with large-scale epidemics. As the taxonomic understanding improved over the years, the pathogen underwent several name changes: *Rickettsia quintana, Rickettsia weigli, Rochalimaea quintana* and finally, *Bartonella quintana.*

The 1.6 Mb genome of *Bartonella quintana* has been sequenced. It is closely related (maybe a degenerative form) to *B. henselae,* which can be considered a shortened version of the *Brucella melitensis* genome.

Transmission

The natural reservoir is still uncertain. The **body louse** *Pediculus humanus corporis* is the **predominant vector**. These insects bite an average of 5 times per day. The bacteria multiply in the lice. *Bartonella quintana* survives up to a year in louse faeces. Since *B. quintana* propagates in the intestinal lumen of the body louse, not in the intestinal epithelial cells, infection probably results from contact with contaminated louse feces. **Wounds caused by scratching** facilitates the entry of the **bacteria in louse faeces**. *Bartonella quintana* has also been detected in *Pulex irritans* fleas, cat fleas, cat dental pulp, monkey fleas, and has been isolated from *Pediculus humanis capitis*, the human head louse. The significance of this latter finding is still unclear, but recent genomic studies link head lice infestation to *B. quintana* bacteremia in low-resource settings (e.g.; rural Senegal). Recent studies identify *B. quintana* in various macaque species, but more studies of possible reservoir hosts are needed.



Pediculus humanus, human louse. Copyright ITM

Clinical aspects

The clinical spectrum of trench fever was described in 1919 via experimental infections in volunteer soldiers. In 1949, an accidental epidemic among 104 laboratory workers resulted in 90 symptomatic cases, which were described in detail. The incubation period varies from **15 to 25 days** (sometimes extremes of 3-38 days are mentioned). Infection can lead to several distinct clinical forms:

The patient **may have no or very few symptoms while having *B. quintana* bacteremia (bloodstream infection).** They may be afebrile. People can be asymptomatic carriers and act as a reservoir. *B. quintana* bacteremia is chronic may last many months or years (the most extended duration recorded is 8 years, though more recent studies describe a period of up to one year). In 1995 *B. quintana* was found in the blood in 14% of people without homes in Marseilles, who presented without symptoms or with general, vague unspecific symptoms.

Chronic endocarditis can occur. The main characteristics are fever, splenomegaly and heart murmurs. The symptoms can be divided into (a) symptoms of infection such as fever, weight loss, malaise, nocturnal sweating, clubbing, enlargement of the spleen, anemia and mycotic aneurysms, (b) heart murmurs and heart failure, (c) embolic phenomena such as CVA or a peripheral arterial embolism, (d) vasculitis such as microscopic haematuria with or without renal failure, splinter hemorrhages under the nails, Osler's nodules (painful lesions on the fingers), Roth's spots on the retina. As the bacterium is not identified by routine 5-day bacterial culture, *B. quintana* endocarditis is referred to as a common type of **culture-negative infective endocarditis.**

Classical trench fever. The patient develops a fever which persists for 5 days. This is accompanied by severe headache and muscle pain, particularly in the legs ("shin pain"). Retro-ocular pain, red conjunctivae, spleen enlargement, and leukocytosis can occur. After a fever-free interval, the fever can return. These cycles can recur 3-5, even up to 8 times. The term "quintan fever" derives from the recurring five-day attacks. Mortality is very low. The pathogen may be present in the human body long after the symptoms have disappeared. Classical trench fever is rarely described in contemporary times.

Continuous fever can develop for several weeks (typhoidal form), accompanied by splenomegaly.

The pathogen can be isolated from cutaneous angioproliferative skin lesions in patients with bacillary angiomatosis (*Bartonella henselae* can also be cultured from similar lesions). Many of these patients are immune-deficient (HIV). The pathogen is phagocytosed by endothelial cells and survives in a vacuole. Angiogenic factors are secreted by the pathogen or the host's response to infection, leading

to the proliferation of endothelial cells, with typical neovascularisation. **Bacillary angiomatosis** is characterized by the emergence of a few to hundreds of skin lesions, from a few mm to several cm in diameter. They are reddish-purple and may be ulcerated, resembling a pyogenic granuloma or Kaposi's sarcoma. The lesions bleed heavily when injured. They can also affect the lymph nodes, bone, bone marrow, liver and spleen. The growth of new blood vessel cells resembles the late stages of the skin lesions of verruga peruviana triggered by *Bartonella bacilliformis*. The pathogen can be detected by Warthin-Starry staining.

Diagnosis

The pathogen is not identified by routine bacterial culture (5-day incubation), but can be cultured axenically which takes a long time (up to 45 days) and requires special techniques. It is best to use a combination of cultures on solid medium, liquid medium and cell cultures. Since *Bartonella* is a facultative intracellular bacterium, to release the bacterium from the erythrocyte, lysis techniques such as "freeze-thaw" or the lysis-centrifugation system (Isolator) are recommended for the cultivation of *Bartonella* sp. from blood. Inoculation of material from the Isolator tube and tissue onto freshly made chocolate agar plates facilitates the growth of the organism. For isolation, incubation in a humid atmosphere with 5% to 10% CO2 for several weeks is required. Serologically, antibodies display a great deal of cross-reactivity. Indirect immunofluorescent antibody (IFA) testing is the reference serologic method. IgG of > 1/50 indicates *Bartonella* infection. Endocarditis patients usually have titers of > 1/800. It is sometimes possible to reveal the bacteria in biopsy material using a Warthin-Starry stain (a complex silver stain) or immunohistochemistry. At present, PCR has a central role.

Treatment

Not much is known about the treatment of this pathogen. To treat classical trench fever and bacillary angiomatosis, administration of doxycycline or azithromycin is recommended. In treating endocarditis and chronic bacteremia, it is preferable to use doxycycline with either gentamicin or rifampicin, as well as considering surgery in cases of endocarditis. Bacillary angiomatosis takes 4-12 weeks to treat.

Not much is known about this pathogen. In vitro it is susceptible to beta-lactam antibiotics and it can also be killed in vitro by gentamicin, doxycycline, rifampicin, erythromycin and the new macrolides. To treat classical trench fever, once-daily administration of azithromycin or doxycycline is recommended.

In treating endocarditis, it is preferable to use doxycycline with gentamicin or rifampicin as well as

considering surgery. Bacillary angiomatosis takes 4-12 weeks to treat.

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Bartonella henselea or Cat-scratch disease

Key clinical aspects

This disease manifests itself mainly as a rather slow-healing ulcer with chronic lymphadenitis (98%) or rarely as a systemic condition (2%). An **ulceroglandular syndrome** which must be distinguished from tularemia, mycotic and mycobacterial infections. Sometimes there is **Parinaud's oculoglandular** syndrome (which can resemble sarcoidosis) or one of the rarer forms, such as retinitis with papilloedema.

The condition is caused by *Bartonella henselae* and very rarely by *Afipia felis*. The latter pathogen derives its name from the "Armed Forces Institute of Pathology in the USA, where the bacterium was first identified in 1988. Infection is contracted by cat scratches or bites and possibly also by infected cat fleas. *Bartonella henselae* has also been recovered from ixodid ticks, though the role of ticks in transmission of bartonellosis is not clear yet. It is useful to know that cat bites can also transmit other dangerous infections such as plague, tularemia, sporotrichosis, nocardiosis and infections with *Pasteurella multocida* and *Capnocytophaga canimorsus*.

Bacteraemia with *B. henselae* can persist in cats for months (asymptomatic for the animal). A biopsy of the skin lesion or an affected lymph node can help to cement the diagnosis. Antibodies against *B. henselae* can be detected serologically. In lymphadenitis azithromycin for 5 days is first line treatment, alternatively clarithromycin, ciprofloxacin or doxycycline for 7-10 days can be used.

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