

Bartonella Outline

- Introduction
- Oroya Fever / Carrion Disease
- Cat Scratch disease and Trench Fever
- Other Bartonella spp.







1

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- Oroya Fever / Carrion Disease
- Cat Scratch disease and Trench Fever
- Other Bartonella spp.



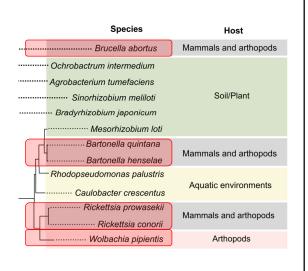




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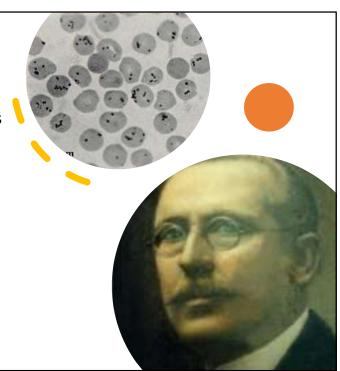
Bartonella

- The genus Bartonella is a member of the class Alphaproteobacteria
- Closely related to Brucella;
- Rickettsiaceae are more distantly related.
- 1993: unification of the genera Bartonella and Rochalimaea as a single genus
- 1993: removal of the family Bartonellaceae from the order Rickettsiales



Bartonia

- The genus Bartonella, synonymous with Bartonia, was described in 1913 and referred to the human erythrocyte-adherent organisms originally described by Dr. Alberto Leonardo Barton in 1909.
- Dr. Barton was an Argentine-born Peruvian microbiologist who discovered Bartonella bacilliformis



5

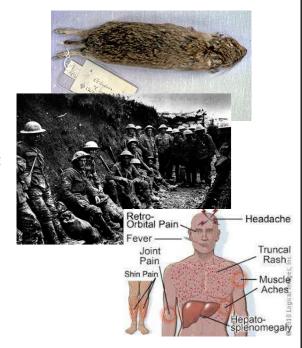
Andes

Limited to the Andes mountain regions of South America, *B. bacilliformis* infection received little attention outside its endemic zone until related bacteria, originally classified in the genus Rochalimaea, were found to be pathogens in individuals with AIDS in the early 1990s



Rochalimaea

- The former genus Rochalimaea, previously grouped with Bartonella in the order Rickettsiales, had long contained only two member species:
 - Rochalimaea vinsonii, the "Canadian vole agent," and
 - Rochalimaea quintana, the agent of trench fever, a debilitating but selflimited human illness so named after it affected numerous military personnel in World War I.



7

Bartonella

- Except for sporadic outbreaks, trench fever was rarely reported after World War I.
- However, R. quintana reemerged in the 1990s as a pathogen causing a debilitating and fatal disease in patients with AIDS and in urban homeless individuals.
- Two new species pathogenic to humans also were identified
 - · Rochalimaea henselae
 - Rochalimaea elizabethae

Bartonella vs. Rochalimaea

- Bartonella bacilliformis
- Rochalimaea quintana
- Rochalimaea henselae
- Rochalimaea elizabethae

9

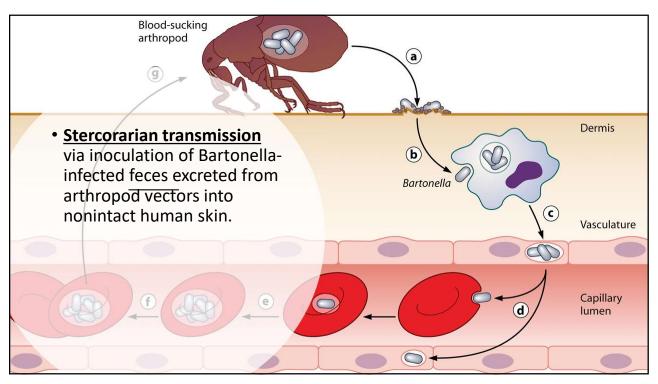
Bartonella vs. Rochalimaea

- Bartonella bacilliformis
- Bartonella quintana
- Bartonella henselae
- Bartonella elizabethae
- DNA analysis of dental pulp from ancient human remains provides evidence that B. henselae and B. quintana have infected humans since antiquity.

Bartonella

- Bartonella spp. are primarily infectious agents of nonhuman mammals. Humans are incidental hosts for most Bartonella spp.
 - The exceptions are B. quintana and probably B. bacilliformis, for which the definitive mammalian reservoir is believed to be humans.

11



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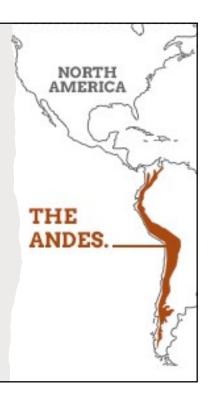




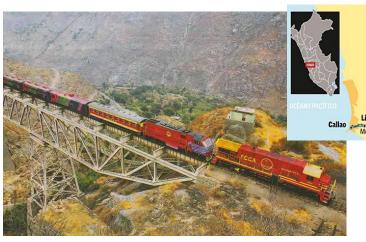
13

Bartonella bacilliformis

- Natural transmission of B. bacilliformis infection is mainly confined to the Andes mountain range in Peru, Ecuador, and Colombia at altitudes between 500 and 3200 m.
- This is presumed due to the limited regional distribution of the sand fly vectors (genus Lutzomyia [formerly Phlebotomus]) of B. bacilliformis.
- No nonhuman vertebrate reservoirs have been identified for B. bacilliformis.



Bartonella bacilliformis: History



 Between 1870-1890, 7,000 railroad workers died building the highest railroad in the world (Oroya's railroad 3,800 meters above sea level)

Carretera Central Ferrocarril Central Carretera afectada Deslizamientos en vía férre en 2008

15

Bartonella Bacilliformis: History

- The long-suspected link between Oroya fever and verruga peruana was confirmed tragically in 1885 by <u>Daniel</u> <u>Carrión</u>, a medical student who injected himself with blood from a verruga peruana lesion and subsequently died of Oroya fever (05-OCT-1885).
- The eponym "Carrión disease" has since denoted the full spectrum of B. bacilliformis infection.



Bartonella bacilliformis: History

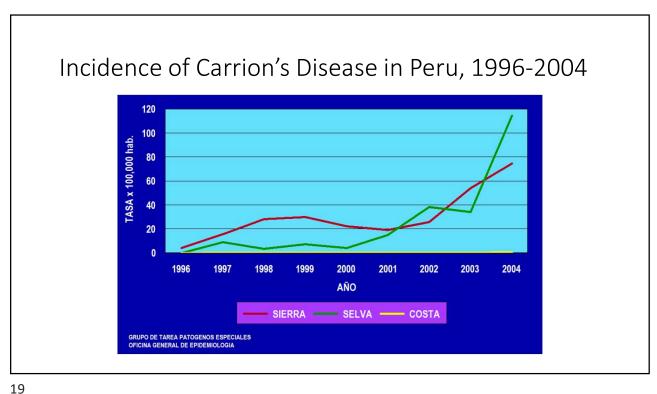
- In 1905 Alberto Barton discovered the agent of Oroya fever and named it 'endoglobular body'.
- Mortality rates for the acute febrile phase varied around 40-90% in the pre-antibiotic era.

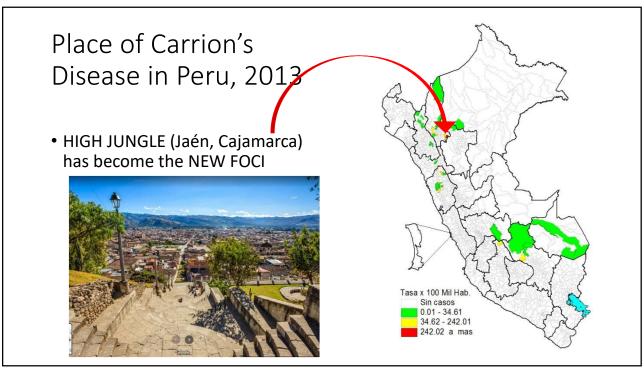
• In 1913, Towsend discovered the vector of the disease ("Titira"-Phlebotomus) (Today, Lutzomyia)

17

Bartonella bacilliformis: Epidemiology

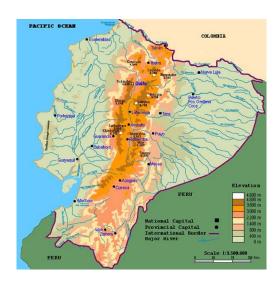
- In Peru, the disease is endemic at an altitude between 500-3,200 meters above sea level.
- Cases have been reported from the Andean valleys and high rain forest.





Bartonella bacilliformis: Epidemiology

 Ecuador has reported cases in the coast at only 150 m above sea level



21

Bartonella bacilliformis: Epidemiology

- Colombia has reported only 2 cases of Carrion's disease in the last 60 years.
- It is not a public health concern in Colombia



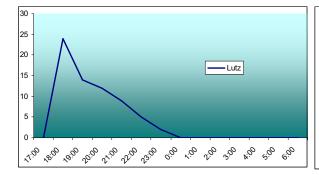
Lutzomya

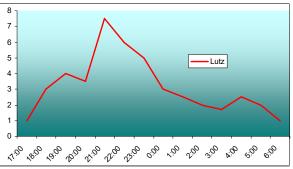
- L. verrucarum (+++): Western Inter-Andean Valleys (Lima, Chachapoyas, etc.)
- L. peruensis : (Cuzco)
- L. robusta, L. maronensis (Cajamarca, etc.)
- L. serrana (Monzón, Huánuco)



23

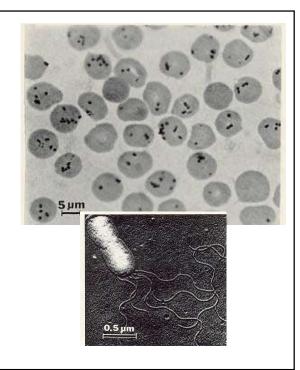
HOURLY ACTIVITY OF LUTZOMYA



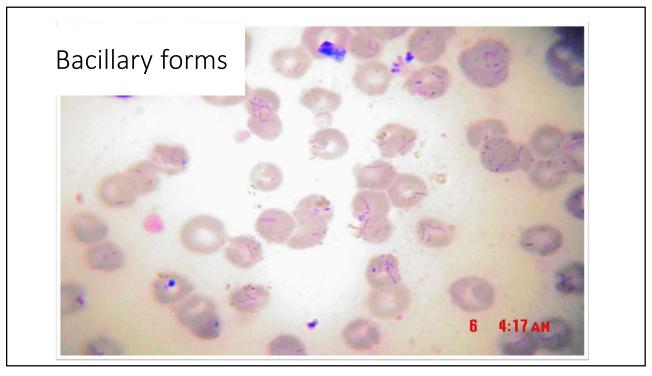


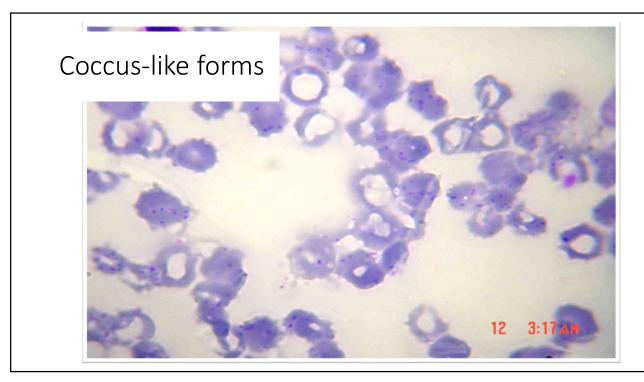
The agent

- Bartonella bacilliformis.
 - A pleomorphic Gram negative bacilli.
 - Direct Giemsa and Wright stains of blood are useful for the diagnosis.
 - The bacterium has a polar flagella on electronic microscopy



25





Bartonella Bacilliformis Clinical Manifestations: <u>Oroya Fever</u>

- acute hematologic disease resulting from primary B. bacilliformis bacteremia and erythrocyte invasion
- develops 3 to 12 weeks after cutaneous inoculation with infected sand fly feces.
- In its mildest insidiously developing form, a febrile illness can last less than a week and go unrecognized, giving rise to subsequent cutaneous manifestations that are the first-recognized clinical findings.
- When illness onset is abrupt, high fever, chills, diaphoresis, anorexia, prostration, headache, and mental status changes are associated with rapidly developing, profound anemia resulting from bacterial invasion and destruction of erythrocytes.

Bartonella Bacilliformis Clinical Manifestations: <u>Oroya Fever</u>

Symptoms/Sign	Occurrence
Pallor	97%
Hepatomegaly	82%
T > 38 °C	78%
Cardiac murmur	78%
Jaundice	71%
Lymphadenopathy	69%
Tachycardia	56%
Splenomegaly	29%
Anasarca	9%

29



Bartonella Bacilliformis Clinical Manifestations: Oroya Fever

 Intense myalgias and arthralgias, abdominal pain and emesis, jaundice, lymphadenopathy, thrombocytopenia, and complications such as seizures, delirium, meningoencephalitis, obtundation, dyspnea, hepatic/gastrointestinal dysfunction, and angina pectoris can occur during this stage, believed to be a consequence of the anemia and microvascular thrombosis, with subsequent end-organ ischemia.

31

Neurobartonellosis

 Mental alteration, ranging from somnolence to coma.



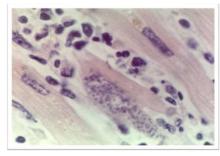


Cardiovascular Bartonellosis

Sign/Symptom	Occurrence
Congestive Heart Failure	62.5%
Cardiac Tamponade	17.5%
Myocarditis	2.5%
Endocarditis (2004, first case)	







33

Bartonella Bacilliformis Clinical Manifestations: <u>Oroya Fever</u>

- Without antimicrobial therapy, the fatality rate is high for the severe,
- abrupt form of bacteremic illness, Oroya fever.
- With appropriate treatment in the modern era, mortality is reported to be less than 10%.
- For survivors, convalescence is associated with a decline of fever and disappearance of bacteria on blood smears, but also a temporarily increased susceptibility to subsequent (opportunistic) infections,

Bartonella Bacilliformis Clinical Manifestations: Oroya Fever

- Temporary increased susceptibility to Oportunistic infections
 - Salmonella infections (Salmonella typhi/paratyphi)
 - Toxoplasma reactivation,
 - TB reactivation
 - Disseminated histoplasmosis
- Asymptomatic persistent bacteremia with B. bacilliformis infection can occur in up to 15% of survivors of acute infection.
- Both the Oroya fever survivors and asymptomatically bacteremic individuals are suspected to serve as the reservoir for B. bacilliformis.

35

Laboratory Diagnosis

Method	Acute Phase	Eruptive Phase	Asymptomatic Phase
Smear	+:	+	•
Blood culture	+	+	+
Biopsy culture		+	•
Histology	*	+	•
Serology	+	+	+
PCR	+:	+	+

Acute Phase Treatment

- Ciprofloxacin (+++) (+/- Ceftriaxone)
 - some reports of intrinsic and in vivo fluoroquinolone resistance suggest that fluoroquinolones may not provide optimal treatment.
- Cloramphenicol (+++)
- Amox/clav < 14 years.
- Azithromycin
- Rifampin
- · PRBC Transfusion
- · Corticosteroids: Coma
- · Folic acid
- Diuretics
- · Pericardiocentesis

37

Bartonella Bacilliformis Clinical Manifestations: Verruga Peruana

- the eruptive phase of B. bacilliformis infection, usually become evident within weeks to months after resolution of untreated acute infection.
- This late-stage manifestation is characterized by crops of skin lesions marked by an evolution of stages: miliary → then nodular → and subsequently what are called "mulaire lesions"

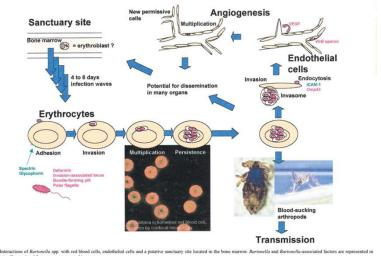






Peruvian Wart Histology

• Histology of active lesions demonstrates vascular proliferation with occasional bacteria evident in interstitial spaces. Bacterial invasion of/replication within endothelial cells (long believed to be the cause of cytoplasmic inclusions first described by Rocha Lima) is actually rare.



39

Peruvian Wart ddx

- Angioma,
- Granuloma pyogenicum (Botriomicoma)
- Bacillary angiomatosis
- Kaposi's sarcoma
- Fibrosarcoma
- Leprosy.
- Malignant lymphoma
- Reticuloendotheliosis
- Molusco contagioso, varicela











• The nodules may develop at one site while receding at another.







• Mulaire lesions are the most superficial and obviously vascular: often bulbous, engorged with blood, and prone to ulceration and bleeding.

• Subsequently, fibrosis of mulaire lesions can occur.



47

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Bartonella quintana

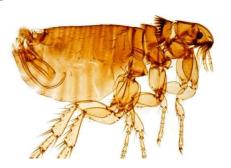
- · globally distributed
- the only identified vector of B. quintana is <u>Pediculus humanus</u>, the human body louse.
- Outbreaks of trench fever (also known as Wolhynia fever, Meuse fever, His-Werner disease, shin bone fever, shank fever, and quintan or 5-day fever) have been focal and widely separated.
- Clusters of trench fever cases usually are associated with conditions of poor sanitation and personal hygiene and are significantly associated with exposure to body lice.



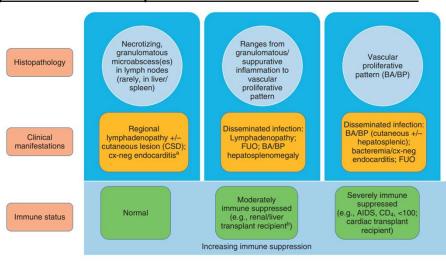
49

Bartonella henselae

- · globally distributed
- the major arthropod vector is the cat flea, Ctenocephalides felis
- infection of domestic cats occurs worldwide, with the prevalence in cats being higher in warm, humid climates, where fleas are more prevalent.
- Prevalence of bacteremia in cats varies but tends to be higher among feral animals
- The amount of B. henselae in blood in infected cats can reach extremely high levels yet cats are usually asymptomatic.
- USA: higher incidence among children (age 5–9 years) and women, and in southern regions
- Additional Bartonella spp. also have been identified in cat fleas.
- Other types of fleas, as well as ixodid and Dermacentor ticks, have been found to harbor various Bartonella spp., but transmission to humans via ticks has not yet been demonstrated.



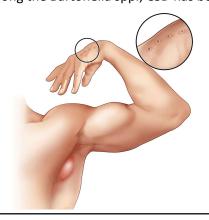
B. henselae and B. quintana Clinical Manifestations Depend on the Species and Immune Status



51

B. henselae and B. quintana Clinical Manifestations Cat-Scratch Disease

- "Typical CSD" (uncomplicated; in immunocompetent hosts) is characterized by regional lymphadenopathy.
 - represents 88% to 89% of CSD cases overall.
- Among the Bartonella spp., CSD has been associated nearly exclusively with B. henselae.





B. henselae and B. quintana Clinical Manifestations Cat-Scratch Disease

- Historically, the diagnosis of a case of typical CSD required fulfillment of 3 of the 4 following criteria:
 - 1. history of an animal (usually cat or dog) contact, with the presence of a scratch or primary skin or eye lesion;
 - Aspiration of "sterile (culture-negative)" pus from the lymph node, or culture and other laboratory testing that excluded other etiologic possibilities;
 - 3. a positive CSD skin test; and
 - Skin test antigen, originally described by Hanger and Rose, was prepared by heating saline-diluted "sterile (culture-negative)" pus aspirated from CSD lymphadenitis at 56°C for 72 hours.
 - It was never standardized or produced commercially.
 - 4. a lymph node biopsy revealing pathology consistent with CSD.

53

B. henselae and B. quintana Clinical Manifestations Cat-Scratch Disease

- "Typical CSD" (uncomplicated) is characterized by regional lymphadenopathy.
 represents 88% to 89% of CSD cases overall.
- A primary cutaneous papule or pustule develops approximately 3 to 10 days after an animal contact (most commonly a kitten or feral cat with flea infestation) at a site of inoculation (usually from a scratch) and it may last for 1 to 3 weeks.
- Regional lymphadenopathy ipsilateral to the inoculation site (usually head, neck, or upper extremity) that develops in 1 to 7 weeks is the most prominent and common manifestation (>90% of typical cases) and the one that usually prompts medical evaluation





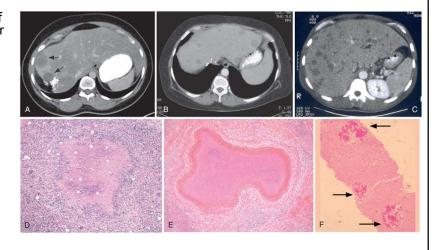
B. henselae and B. quintana Clinical Manifestations Cat-Scratch Disease

- Typical (uncomplicated) cat-scratch disease
- Atypical (complicated) cat-scratch disease is a disseminated infection developing in 5%-14% of patients that may involve almost any organ system.
 - In patients with immunocompromise, it may also present as vasoproliferative disease (bacillary angiomatosis and bacillary peliosis hepatis).

55

B. henselae and B. quintana Clinical Manifestations Cat-Scratch Disease

- Hepatic manifestations of Bartonella henselae occur often when infection disseminates in either immunocompetent or immunocompromised patients, but histopathologic characteristics differ markedly depending on host immune status.
- Other sites:
 - Muscle
 - Bone
 - Brain
 - Eye



B. henselae and B. quintana Clinical Manifestations

Cat-Scratch Disease

- Ocular manifestations of CSD include
 - Parinaud oculoglandular syndrome (an atypical form of CSD lymphadenitis),
 - neuroretinitis
 - vascularocclusive events,
 - retinitis,
 - · choroiditis, and
 - optic nerve granuloma.



FIG. 234.10 Atypical cat-scratch disease: Parinaud oculoglandular syndrome, a granulomatous conjunctivitis, is associated with ipsilateral regional lymphadenopathy (usually preauricular and, less commonly, submandibular).

57

B. henselae and B. quintana Clinical Manifestations

Cat-Scratch Disease

- Neuroretinitis
 - often manifests with a sudden loss of visual acuity, usually unilaterally, and sometimes preceded by an influenza-like syndrome or development of unilateral lymphadenopathy.
 - The most striking retinal manifestation is papilledema associated with macular exudates in a star formation
 - Optic disk swelling was the second most common finding

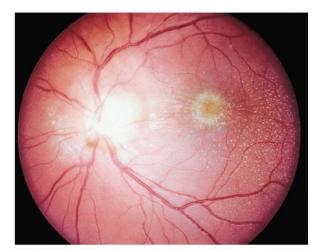


FIG. 234.11 Atypical cat-scratch disease (CSD): neuroretinitis is one of the more common complications of CSD. The striking papilledema associated with stellate macular exudates is among the most common manifestations of CSD neuroretinitis.

Treatment of Cat-Scratch Disease

 There have been anecdotal reports of the utility of various agents in the treatment of CSD. However, in the immunocompetent host, only azithromycin has been demonstrated to accelerate the resolution of typical CSD lymphadenopathy.

59

B. henselae and B. quintana Clinical Manifestations Bacteraemia ("trench fever")

- B. quintana >>> B. henselae
 - Note: B. quintana infection may present as trench fever (primary infection), chronic bacteremia, endocarditis, or bacillary angiomatosis.
- characterized by a self-limited fever, often with a 5-day periodicity (quintan pattern).
- incubation period may span 3 to 38 days before the usually sudden onset of chills and fevers.
- Fever
 - limited form \rightarrow a single bout of fever lasts 4 or 5 days.
 - typical periodic form → 3 to 8, febrile paroxysms, each approximately 5 days apart. Patients are often asymptomatic between febrile paroxysms.
 - continuous form → 2 to 6 weeks of uninterrupted fever.
- Afebrile infection with Bartonella is very common; one study found 8 of 10 homeless individuals with active B. quintana bacteremia were afebrile

B. henselae and B. quintana Clinical Manifestations Bacteraemia ("trench fever")

- Other nonspecific symptoms and signs of B. qunintana
 - Headache
 - · retro-orbital pain
 - · Conjunctival injection
 - Myalgias
 - Arthralgias
 - bone pain
 - · Hepatosplenomegaly
 - Rash
 - Leukocytosis
 - Albuminuria
- B. quintana bacteremia has the potential to evolve into long-term persistence if not treated appropriately.

61

B. henselae and B. quintana Clinical Manifestations Bacteraemia ("trench fever")

- Patients living with HIV with advanced immunosuppression (CD4+ cell
- count <100/mm3) are more likely to develop severe and prolonged bacteremia with B. quintana or B. henselae.
- In these patients Bartonella bacteremia has been associated with
 - cutaneous BA (B. henselae or B. quintana),
 - hepatic and splenic BP (B. henselae),
 - Granulomatous hepatitis (B. henselae),
 - infiltration of the bone marrow (B. henselae),
 - FUO (B. quintana and B. henselae), and
 - endocarditis (B. quintana >>> B. henselae).

B. henselae and B. quintana Clinical Manifestations Fever of Unknown Origin and Endocarditis

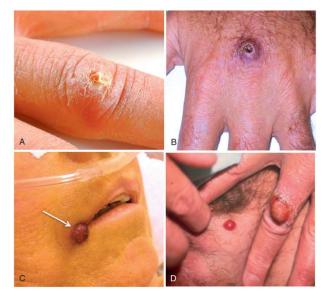
- Both B. henselae and B. quintana can present as FUO
- Bartonella spp. are recognized as the first or second most important causes of blood culture-negative endocarditis (first in north America, secondary to Coxiella burnetii in Europe)
- Endocarditis → Immunocompetent hosts
 - B. quintana → absence of a history of valvular abnormalities
 - B. henselae → much less frequent, most often occurs in patients with underlying valvular pathology or congenital heart disease (CHD).

63

B. henselae and B. quintana Clinical Manifestations

Bacillary Angiomatosis

- BA → Immunocompromised
 - solid-organ transplant (SOT) recipients
 - persons living with HIV (CD4+ cell count <100/mm3)
- The degree of host immunocompromise determines the clinical cutaneous manifestations



B. henselae and B. quintana Clinical Manifestations

Bacillary Angiomatosis



Cutaneous BA – firm, dry, hyperkeratotic lesion on the leg (pretibial region) of a man with AIDS



Cutaneous BA - pedunculated, vascular lesion on the thigh of a woman living with AIDS, systemic symptoms, and inguinal adenopathy.



Cutaneous BA, presenting with numerous, painful angiomatous nodules within an indurated, erythematous plaque that developed over the biopsy site of the right thigh mass in the patient shown in (A)



Cutaneous BA in a man with AIDS and multiple comorbid opportunistic infections.

65

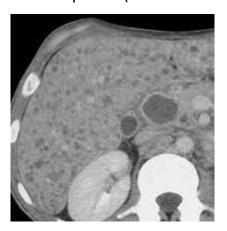
Bacillary Angiomatosis

- 1993
- AIDS

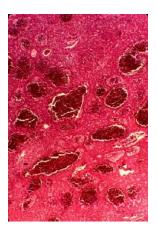


B. henselae and B. quintana Clinical Manifestations Bacillary Peliosis (BP) Hepatis

• BP Hepatitis (B. henselae only)



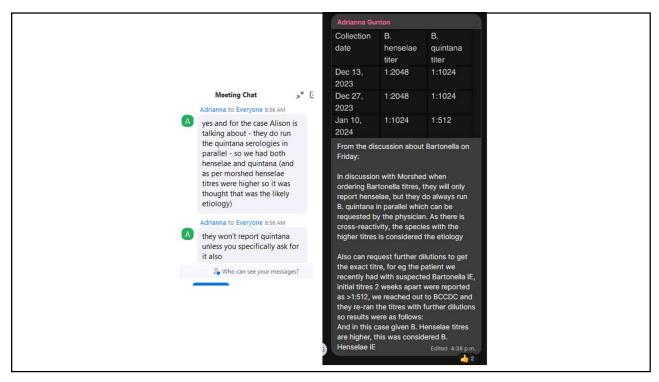




67

Treatment of Bartonella Infections in Immunocompromised Hosts

- For B. henselae or B. quintana, in vitro susceptibilities often do not predict in vivo response to therapy
- Indeed, in contrast to in vitro sensitivities, CSD and BA/BP have developed in, and Bartonella has been cultured from, HIV-infected patients or SOT recipients while receiving ongoing therapy with TMP-SMX, β -lactam antibiotics, or fluoroquinolone antibiotics. Thus these antibiotics are not recommended for empirical treatment of B. quintana or B. henselae.
- In contrast, therapy with rifampin, tetracyclines, or macrolides (even a single dose) dramatically reduced culture recovery of B. quintana or B. henselae from blood and BA/BP lesions.
- the recommended initial agent of choice to treat Bartonella infections is doxycycline or erythromycin for a minimum of 3 months.
- For severe illness, rifampin can be added to doxycycline, although interactions with antiretroviral therapy or immunosuppressants should be considered.
- Azithromycin or clarithromycin is can be considered an alternative treatment.



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Common Human Pathogens

- · Bartonella bacilliformis
- · Bartonella henselae
- · Bartonella quintana

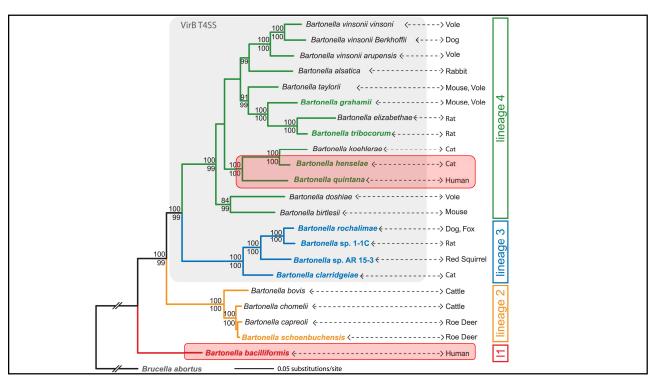
Uncommon/Suspected Pathogens

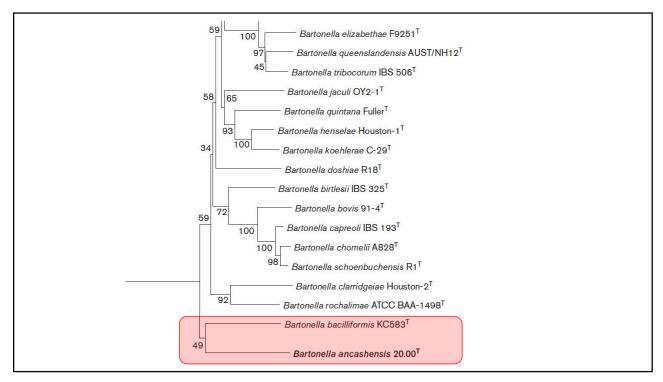
- Bartonella alsatica
- Bartonella ancashensis
- · Bartonella clarridgeiae
- · Bartonella doshiae
- Bartonella elizabethae
- Bartonella grahamii
- · Bartonella koehlerae
- Bartonella rochalimae
- Bartonella schoenbuchensis
- · Bartonella tribocorum
- Bartonella vinsonii subsp. arupensis

Not Identified as Human Pathogens

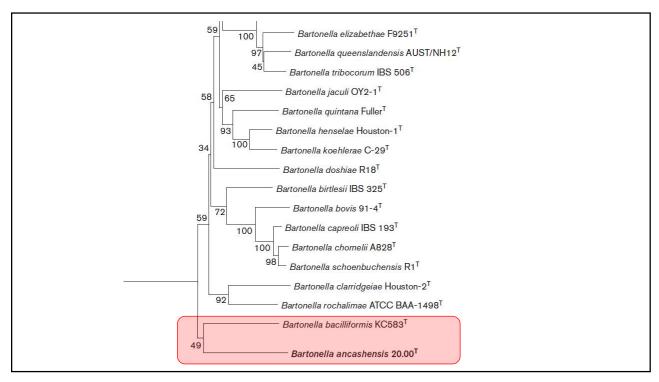
- · Bartonella acomydis
- · Bartonella apis
- · Bartonella birtlesii
- Bartonella bovis
- · Bartonella callosciuri
- Bartonella capreoli
- · Bartonella chomelii
- Bartonella coopersplainsensis
- Bartonella florencae
- · Bartonella fuyuanensis
- · Bartonella heixiaziensis
- · Bartonella jaculi
- Bartonella japonica
- · Bartonella pachyuromydis
- · Bartonella peromysci
- Bartonella queenslandensis
- Bartonella rattaustraliani
- · Bartonella senegalensis
- Bartonella silvatica
- · Bartonella talpae
- Bartonella taylorii
- Bartonella vinsonii subsp. berkhoffii
- Bartonella vinsonii subsp. vinsonii

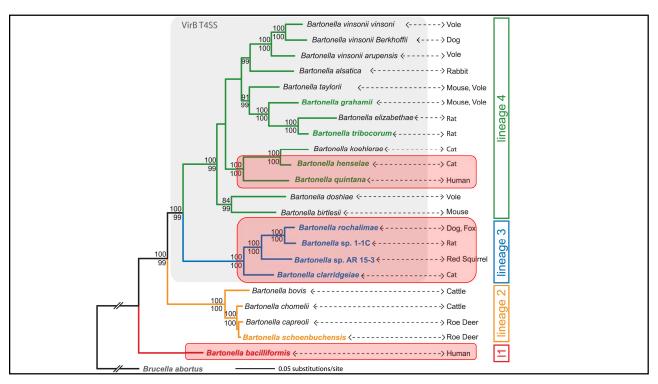
71











The NEW ENGLAND JOURNAL of MEDICINE

Bacteremia, Fever, and Splenomegaly Caused by a Newly Recognized Bartonella Species

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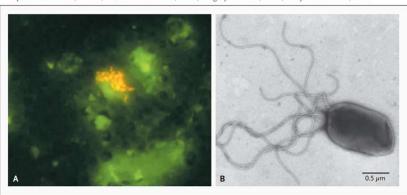


Figure 1. Bartonella rochalimae in a Blood Specimen from the Patient.

A broth culture of a blood specimen from the patient shows clusters of bacteria (stained with acridine orange) among the erythrocytes (which appear green) (Panel A). Transmission electron microscopy of the BMGH isolate after negative staining shows an organism with multiple, unipolar flagella (Panel B).

77

Common Human Pathogens

- · Bartonella bacilliformis
- · Bartonella henselae
- · Bartonella quintana

Uncommon/Suspected Pathogens

- · Bartonella alsatica
- Bartonella ancashensis
- Bartonella clarridgeiae
- Bartonella doshiae
- Bartonella elizabethae
- Bartonella grahamii
- Bartonella koehlerae
- · Bartonella rochalimae
- Bartonella schoenbuchensis
- Bartonella tribocorum
- Bartonella vinsonii subsp. arupensis

Not Identified as Human Pathogens

- · Bartonella acomydis
- Bartonella apis
- Bartonella birtlesii
- Bartonella bovis
- Bartonella callosciuri
- Bartonella capreoli
- · Bartonella chomelii
- Bartonella coopersplainsensis
- · Bartonella florencae
- Bartonella fuyuanensis
- Bartonella heixiaziensis
- Bartonella jaculi
- Bartonella japonica
- Bartonella pachyuromydis
- · Bartonella peromysci
- Bartonella queenslandensis
- Bartonella rattaustralianiBartonella senegalensis
- Bartonella silvatica
- Bartonella talpae
- Bartonella taylorii
- Bartonella vinsonii subsp. berkhoffii
- Bartonella vinsonii subsp. vinsonii

