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Cat Scratch Disease
and Other
Bartonella Infections

Cat Scratch Fever
Benign Inoculation Lymphoreticulosis
Benign Inoculation Reticulosis
Regional Granulomatous Lymphadenitis
Parinaud's Oculoglandular Syndrome
Bacillary Angiomatosis

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Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control
- Actions to Take

In today's presentation we will cover information regarding the organism that causes cat scratch disease and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures, as well as actions to take if cat scratch disease is suspected.

[Photo: Kittens. Source: Wikimedia Commons]

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THE ORGANISM

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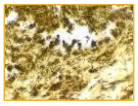
Cat Scratch Disease

- *Bartonella henselae*
  - Gram negative rod
  - Formerly classified as *Rickettsia*
- Two major serotypes/genotypes
  - Type I (Houston I)
  - Type II (BA-TF/Marseille)
- *Bartonella clarridgeiae*



Cat scratch disease is, in most cases, caused by *Bartonella henselae*, a fastidious, pleomorphic, gram-negative rod in the family *Bartonellaceae*. This family, which was once thought to belong to the order Rickettsiales, has been removed from that order. There are two major serotypes/genotypes of *B. henselae*: type I (Houston I) and type II (BA-TF/Marseille). Strain variations are thought to exist within these serotypes. *B. clarridgeiae*, also found in cats, has been implicated in a case of cat scratch disease in a veterinarian.

[Photo: *Bartonella henselae* bacilli in cardiac valve of a patient with blood culture-negative endocarditis. The bacilli appear as black granulations. Source: Warthin Starry/Centers for Disease Control/Wikimedia Commons]

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Other Bartonellae

- Bacillary angiomatosis, peliosis hepatitis caused by *Bartonell*a spp.
  - *B. henselae*
  - *B. quintana*
    - Non-zoonotic pathogen
    - Carried by humans
- Immunocompromised individuals most commonly affected

B. henselae and *B. quintana*, a non-zoonotic pathogen carried by humans, also cause bacillary angiomatosis and peliosis hepatis, mainly in immunocompromised individuals.

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Other Bartonellae

- Dogs, coyotes, humans
  - *B. vinsonii* subsp. *berkhoffii*
- Humans, rodents
  - *B. vinsonii* subsp. *arupensis*
  - *B. elizabethae*
  - *B. washoensis*
  - *B. grahamii*

Other species of *Bartonella* may also be emerging human and/or animal pathogens. All *Bartonella* species are very closely related and may cross-react in serologic assays. *Bartonella* spp. found in animals and implicated in human disease include the following:

- *B. vinsonii* subsp. *berkhoffii* has been isolated from healthy dogs and coyotes. It has also been implicated in cases of canine granulomatous lymphadenitis, granulomatous rhinitis, liver disease, endocarditis, fever of unknown origin, and sudden death. This species may cause endocarditis in people with pre-existing valve disease.
- *B. vinsonii* subsp. *arupensis* has been isolated from the blood of a cattle rancher with fever and heart valve disease. This organism can also be found in rodents.
- *B. elizabethae*, found in rodents, may cause endocarditis in humans.
- *B. washoensis* has been implicated in human cardiac disease. Rodents are probably the reservoir host.
- *B. grahamii*, found in rodents, may cause human uveitis.

Photo: AVMA Press Room Photo Gallery.

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HISTORY

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History

- 1950: Clinical syndrome described
- 1889: Similar disease reported
- 1983: Bacterial cause described
  - Gram negative bacillus
  - Found in lymph nodes of patients
- 1988: Organism successfully isolated and cultured

A clinical syndrome likely to be cat scratch disease (CSD) was first reported in 1950; it was again described in 1889. However, the causative agent was not described until 1983, when Wear et al. discovered a small, pleomorphic Gram-negative bacillus in the lymph nodes of patients with CSD using a Warthin-Starry silver stain. Five years later the organism was successfully isolated and cultured.

Source: Florin TA, Zaoutis TE, Zaoutis LB. Beyond Cat Scratch Disease: Widening Spectrum of *Bartonella henselae* Infection. Pediatrics. 2008:121(5):1413-1425.

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History

- 1991: CSD bacillus named *Afipia felis*
- 1992: *Rochalimaea henselae* isolated
  - Patients with bacillary angiomatosis
  - Refuted role of *A. felis* in CSD
- 1993: Genera *Rochalimaea* and *Bartonella* united
  - *B. henselae* currently recognized as causative agent of CSD

In 1991, the CSD bacillus was named *Afipia felis*, after the Armed Forces Institute of Pathology, where the organism was discovered; in 1992, an organism known as *Rochalimaea henselae* was isolated from HIV-infected patients with bacillary angiomatosis, peliosis hepatis, and fever syndromes. This study, and others, refuted the role of *A. felis* in CSD, in favor of *Rochalimaea* species. In 1993, the genera *Bartonella* and *Rochalimaea* were united; thus, *B. henselae* is currently recognized as the causative agent of CSD.

Source: Florin TA, Zaoutis TE, Zaoutis LB. Beyond Cat Scratch Disease: Widening Spectrum of *Bartonella henselae* Infection. Pediatrics. 2008:121(5):1413-1425.

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EPIDEMIOLOGY

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Geographic Distribution

- Worldwide
  - *B. henselae* type I
    - Eastern U.S.
    - Asia
  - *B. henselae* type II
    - Europe
- Temperate climates
  - Seasonal variation
  - Peak August to October (North)

B. henselae occurs worldwide. *B. henselae* type I is more common in the eastern U.S., where it represents approximately half of all isolates, than in the western states. Type II is the dominant serotype in Europe, and type I in Asia. The incidence of disease is seasonal in temperate but not tropical areas, with the peak incidence from August to October in northern temperate regions.

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Morbidity and Mortality

- Humans
  - 22,000 to 24,000 annual cases in U.S.
  - 3 to 6% of general population seropositive
    - Higher in veterinarians
  - Most cases in children
- Most infections self-limiting
- Death is rare

An estimated 22,000 to 24,000 cases of cat scratch disease are thought to occur in the U.S. each year. Prevalence rates ranging from 1.8 to 9.3 cases per 100,000 persons have been reported. In the U.S., 3.6% to 6% of the general population has antibodies to *B. henselae*. Two studies reported seroprevalence rates of 7% and 51% in veterinarians in the U.S. and Europe, respectively. Any age can be affected, but most cases occur in children, who are more likely to be scratched or bitten. Most infections are self-limiting and death is rare.

[Photo: Veterinarian with pet. Source: AVMA Press Room Photo Gallery]

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Morbidity and Mortality

- Seroprevalence in cats
  - 14 to 55% in U.S.
  - 40 to 70% in warm, humid climates
  - 30% of captive wild felids
- Higher in feral cats vs. pets
- No reported morbidity or mortality

From 14% to 55% of cats in the U.S. have antibodies to *B. henselae*. Seroprevalence rates of 40-70% have been reported in warm, humid parts of the world; these high rates are thought to be related to the increased prevalence of fleas. Feral cats are more likely to be seropositive than pet cats. Approximately 30% of captive wild felids are also seropositive. No morbidity or mortality has been reported in natural infections, to date.

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TRANSMISSION

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Transmission in Animals

- Vector-borne
  - Cat flea (*Ctenocephalides felis*)
    - Flea feces
  - Ticks?
- Other routes?

B. henselae is probably transmitted between cats by cat fleas (*Ctenocephalides felis*). Experimental studies have shown that fleas, or the intradermal inoculation of flea feces, can spread the infection between cats. Transmission is reduced or absent when fleas are controlled. *B. henselae* has also been isolated from ticks but the role of this organism is unknown. Whether *B. henselae* can be spread among cats by other routes is unknown. Oral inoculation of infectious flea feces did not transmit the infection. In one experiment, *B. henselae* was not spread by sexual contact or vertically to kittens.

[Photo: *Ctenocephalides felis*, cat flea. Source: CDC DPDx Image Library]

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Transmission in Humans

- Not well understood
- Patient history usually includes:
  - Cat scratch
  - Cat bite
  - Being licked by cats
- Vector-borne (fleas)?
- Exposure to other animals
  - Other *Bartonella* species?

Transmission to humans is not completely understood. Cases of cat scratch fever are usually reported in people who have been scratched, bitten or licked by cats. It is possible that the source of infection is cat claws or teeth contaminated by flea feces. It has also been suggested, but not proven, that fleas may be able to transmit *B. henselae* directly to humans. In Parinaud's oculoglandular syndrome, a form of cat scratch fever that affects the eye, the site of inoculation is thought to be the eyelid or conjunctiva. This syndrome may occur when patients rub their eyes after contact with a cat. Cases of cat scratch disease have also been reported after exposure to squirrels, dogs, goats, crab claws and barbed wire. Some of these cases could be due to other species of *Bartonella*.

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DISEASE IN HUMANS

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Cat Scratch Disease

- Usually mild, self-limiting
  - Immunocompetent people
- Initial skin rash
- Lymph node enlargement
- Fever, malaise, fatigue
- Complications usually resolve

In immunocompetent people, *B. henselae* causes cat scratch disease, a mild to severe, self-limiting infection. The initial skin rash, seen in 25-90% of patients, consists of one or more small erythematous papules, pustules, macules, vesicles or ulcers at the site of inoculation. One to four weeks later, one or more lymph nodes become enlarged; soon afterward, the skin lesions disappear. The affected lymph nodes are usually painful or tender, and the skin over the nodes is warm, reddened and indurated. Occasionally, the nodes may suppurate. The lymphadenopathy usually lasts for a few weeks to a few months, but in some patients the lymph nodes have remained enlarged for up to 2 years. Other common symptoms are a fever, malaise and fatigue. The fever usually disappears within 2 weeks but fatigue may persist for weeks or months. Less often, there may be headaches, anorexia, vomiting, nausea, weight loss, splenomegaly, generalized pain or a sore throat. Cat scratch disease is usually a self-limiting infection, and the complications generally resolve without sequelae.

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Cat Scratch Disease: Complications

- Parinaud's oculoglandular syndrome
- Encephalitis
- Endocarditis
- Disseminated disease
  - AIDS patients
- Rashes
- Bone/joint lesions
- Pneumonia

Complications and atypical presentations are reported to occur in 5-16% of patients.

- Parinaud's oculoglandular syndrome occurs in 2-6% of patients. This syndrome is characterized by nonpurulent unilateral conjunctivitis, conjunctival granuloma and periauricular lymphadenopathy. It usually resolves without permanent damage.
- Encephalitis has been reported in 1-7% of patients with cat scratch disease. It usually occurs 2 to 6 weeks after the classic symptoms. Cranial or peripheral nerve involvement may include myelitis, optic neuritis with transient unilateral blindness, facial nerve paresis or transient peripheral neuropathies. Patients with myelitis can be extremely weak, with abnormal reflexes, sensory loss and sphincter dysfunction.
- In people with existing heart valve abnormalities, *B. henselae* bacteremia can result in endocarditis.
- Disseminated disease occurs in less than 1% of patients. The usual signs are a persistent spiking fever, hepatosplenomegaly and abdominal pain. *B. henselae* can cause bacteremia and systemic disease in immunocompromised individuals, particularly people with AIDS.
- Other reported complications include transient nonspecific maculopapular or nodular rashes, thrombocytopenic purpura, osteolytic lesions, arthritis, synovitis and pneumonia.

[Photo: Girl receiving an eye examination. Source: Amanda Mills/CDC Public Health Image Library]

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Bacillary Angiomatosis and Bacillary Peliosis

- Bacillary angiomatosis
  - Vascular proliferative disease of skin and/or internal organs
  - Usually an AIDS-related disease
- Peliosis hepatitis
  - Rare
  - Blood-filled cysts and sinusoidal dilatation of the liver

B. henselae also causes bacillary angiomatosis (epithelioid angiomatosis), a vascular proliferative disease of the skin and/or internal organs. Bacillary angiomatosis can occur in immunocompetent persons, but is most often an AIDS-related disease. The most apparent symptoms are one to hundreds of cutaneous papules and nodules, which may resemble granulomas, Kaposi's sarcoma (violaceous nodules), or lichenoid violaceous plaques. They vary in size from pinhead-sized to 10 cm in diameter. Subcutaneous nodules resembling a common abscess may also be seen. In addition, bacillary angiomatosis can involve the internal organs, including the heart, brain, liver, spleen, larynx, lymph nodes and gastrointestinal tract. Peliosis hepatis is a rare condition, caused by *B. henselae* as well as other pathogens, drugs and toxins. It is characterized by multiple blood-filled cysts and sinusoidal dilatation in the liver. The symptoms of peliosis hepatis may include fever, nausea, vomiting, diarrhea and hepatosplenomegaly. In some cases, it may be an incidental finding at necropsy. Peliosis hepatis can be seen in some patients with bacillary angiomatosis.

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Diagnosis

- History and physical examination
- Culture
  - Slow, specialized media required
- PCR
  - Can differentiate Bartonellae
- Serology
  - Indirect immunofluorescence
  - ELISA

Most cases of cat scratch disease are diagnosed by the history and physical examination. *B. henselae* infections can be confirmed by culture of the organism, PCR or serology.
Isolation of *B. henselae* is difficult, but may be accomplished using specialized media. This organism takes 9 to 45 days to grow. PCR can differentiate *B. henselae* from *B. quintana*, the other cause of bacillary angiomatosis. Serologic assays include an indirect immunofluorescence assay and enzyme-linked immunosorbent assay (ELISA). Cross-reactions occur with other species of *Bartonella*. Cross-reactions have also been reported with other organisms including *Chlamydia* spp. and *Coxiella burnetti*. A rise in titer or the presence of IgM suggests a recent infection. Histopathology of the lymph nodes, and sometimes liver or spleen, is suggestive but not diagnostic.

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Treatment

- Disease usually self-limiting
- Treatment options
  - Supportive care
  - Lymph node excision
  - Antibiotics
    - Not consistently effective for CSD
    - Useful for treatment of bacillary angiomatosis caused by *B. henselae*

Most cases of cat scratch disease in immunocompetent individuals are self-limiting. Treatment is usually supportive and symptomatic. Severely affected lymph nodes are
occasionally excised. Although *B. henselae* is sensitive to a number of antimicrobials *in vitro*, antibiotics are not consistently effective for cat scratch disease. They may be recommended by some authorities, particularly if the lymph nodes are severely affected, the course of disease is prolonged, or organs other than the lymph nodes have become involved. In contrast, bacillary angiomatosis caused by *B. henselae* usually responds well to antibiotics. Numerous antibiotics, including erythromycin, doxycycline, rifampin, aminoglycosides, cefoxitin, cefotaxime, mezlocillin, trimethoprim sulfamethoxazole and ciprofloxacin may be effective.

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DISEASE IN ANIMALS

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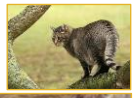
Species Affected

- Cats, felids are reservoir hosts
- Experimental infection
  - Dog
  - Armadillo
  - Mice



Cats and other felids are thought to be the only reservoir hosts for *B. henselae*. Organisms have been isolated from domestic cats, cheetahs and mountain lions. Antibodies have been found in domestic cats, Florida panthers, mountain lions, bobcats and cougars. Symptomatic infections have been reported only in some experimentally infected cats. However, there have been suggestions that *B. henselae* may be involved in some chronic feline diseases. *B. henselae* has not, to date, been isolated from naturally infected animals other than the Felidae. *B. henselae* DNA was recently found in liver lesions (peliosis hepatis) in a dog, but bacterial isolation was not done. Armadillos are susceptible to experimental infection. Mice can also be infected under some conditions.

[Photos: (Top) Coon cat. Source: Umberto Salvagnin/Flickr-Creative Commons; (Bottom) Mountain lion. Source: USDA National Wildlife Research Center]

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Disease in Cats

- Often asymptomatic
- Possible clinical manifestations
  - Lymphadenopathy
  - Kidney disease
  - Ocular disease
- Experimental infections
  - Equivocal

Naturally-infected bacteremic cats are asymptomatic. Some studies have suggested that *B. henselae* might be pathogenic under some circumstances: In one study, there was a significant increase in the incidence of lymphadenopathy and gingivitis in cats that were seropositive for both feline immunodeficiency virus (FIV) and *B. henselae*, compared to cats with antibodies only to FIV. Another study found a correlation between the presence of antibodies to *B. henselae* and stomatitis or kidney disease. An association between *B. henselae* and uveitis has been proposed. Experimental infections have been equivocal: In some experimental infections, all inoculated cats remained asymptomatic. In others, clinical signs such as transient fever, lethargy, anorexia, myalgia and lymphadenopathy have been reported. Mild transient anemia, eosinophilia, delayed conceptions and reproductive failures have also been seen. Both type I and types II *B. henselae* have caused clinical signs.

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Disease in Other Animals

- Experimental infections
  - Dogs
    - No bacteremia
  - Rodents
    - Asymptomatic
    - Granulomatous hepatitis
  - Non-human primates
    - Asymptomatic
    - Fever
    - Subcutaneous skin lesions at inoculation site

B. henselae has not been isolated from dogs, and experimentally infected dogs do not become bacteremic. In some studies, experimentally infected rodents have
remained asymptomatic. In rodents inoculated with large numbers of bacteria, the only lesion was granulomatous hepatitis. In one experiment, simian immunodeficiency virus (SIV)-infected macaques inoculated with *B. henselae* remained asymptomatic. These monkeys did not become bacteremic or seroconvert. In another experiment, two macaques became febrile and developed subcutaneous purple-red spots at the inoculation site. The significance of this finding is unclear, as *B. henselae* was not recovered from the regional lymph nodes and the animals did not seroconvert.

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Post Mortem Lesions

- Lymphadenomegaly
- Multiple histopathologic lesions
- Blood-filled cysts and cavities in the liver
  - Peliosis hepatitis
- Granulomatous hepatitis

Lymphadenomegaly, and histopathologic lesions in a variety of tissues, have been reported in cats experimentally infected with *B. henselae* or *B. clarridgeiae*. The histopathologic lesions included lymph node hyperplasia, splenic follicular hyperplasia, lymphocytic cholangitis, lymphocytic hepatitis, lymphocytic plasmacytic myocarditis and lymphocytic interstitial nephritis. *B. henselae* DNA has been found in blood-filled cysts and cavities (peliosis hepatis) in the liver of a dog. The significance of this finding is unknown. Granulomatous hepatitis has been reported in experimentally infected rodents.

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Diagnosis and Treatment

- Diagnosis
  - Culture
    - Time consuming, used mainly in research
  - Serology
    - Cross reactions possible
  - PCR
- Treatment
  - Tetracycline

B. henselae can be isolated from the blood and tissues of infected cats, as well as from cat fleas. Isolation of *B. henselae* is difficult, requires specialized media, and has mainly been used in research. The organism takes 9 to 45 days to grow. Serologic assays (indirect immunofluorescence, ELISA, immunoblotting), polymerase chain reaction (PCR) assays, transmission electron microscopy and confocal microscopy have also been used in research. There can be cross-reactions between *Bartonella* species in serologic assays. Some cats do not have antibodies at the time of bacteremia. Preliminary data suggest that tetracycline can be used to treat asymptomatic *B. henselae* bacteremia in cats; however, it is not known whether these cats are susceptible to reinfection or recrudescence.

[Photo: Diagnostic test tubes. Source: Danelle Bickett-Weddle, Iowa State University/CFSPH]

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PREVENTION AND CONTROL

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Prevention

- Avoid bites and scratches
  - Kittens
- Wash wounds immediately
- Flea control?
- Clip nails
- Keep cats indoors
- Antimicrobials?

Prevention depends on avoiding bites and scratches from cats, particularly kittens. Rough play with kittens should be discouraged, and any bites or scratches should immediately be washed with soap and water. Allowing the cat to lick the skin, particularly open wounds, should also be discouraged. Hand washing after contact with a cat may be helpful. Flea control may also be a preventative measure, but this is not certain. Declawing does not appear to affect transmission but keeping the nails clipped is suggested by some sources. Some authorities suggest that keeping cats indoors may also be beneficial. Preliminary data suggest antimicrobials may be able to clear the bacteremia in cats; however, it is not known whether these cats are susceptible to reinfection or recrudescence.

[Photo: Cat on examination table. Source: AVMA Press Room Photo Gallery]

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Disinfection

- Susceptibility of *B. henselae* not specifically known
  - Closely related organism *B. bacilliformis*
- Susceptible to:
  - 70% ethanol
  - 1% sodium hypochlorite
  - 2% formaldehyde

The disinfectant susceptibility of *B. henselae* does not seem to have been published; however, the closely related organism *Bartonella bacilliformis* is susceptible to common disinfectants including 70% ethanol, 1% sodium hypochlorite and 2% formaldehyde.

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Additional Resources

- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- CDC Healthy Pets Healthy People: Cat Scratch Disease
  - http://www.cdc.gov/healthypets/diseases/catscratch.htm

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Acknowledgments

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