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Spectrum and Treatment of Cat-Scratch Disease

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Cat-scratch disease (CSD) was first identified in 1931. In 1992, Regnery et al[1] reported isolation of the causative agent, *Bartonella henselae,* from the blood of a domestic cat and demonstrated antibodies to *B. henselae* in patients with CSD.[1] Now, CSD has been recognized worldwide as a zoonosis with a wide clinical spectrum. Because CSD is not reportable, its true incidence is unknown; serologic studies performed over the last 10 years suggest that it is emerging, particularly in immunocompromised patients.

Epidemiology. Zangwill et al[2] in 1993 noted that individuals with kittens <12 months old were 15 times more likely to develop CSD than owners of adult cats. The organism is transmitted to humans by a kitten scratch, bite, lick or other intimate contact. Demers et al[3] further demonstrated that antibodies to *B. henselae* are detected by indirect immunofluorescence assay (IFA) in 84% of initial sera of patients with clinical CSD and in 29% of exposed symptom-free family members. Matched controls with no cat exposure lacked such antibodies. Older cats had evidence of past infection but were less likely to be bacteremic or to transmit disease. The cat flea transmits *B. henselae* from one kitten to another[4] and is hypothesized to be responsible for direct transmission to humans.

B. henselae is endemic in warm humid climates. Cats living in U.S. regions with high annual precipitation and high average daily temperatures, such as the Southeast, Hawaii, coastal California, Pacific Northwest and South-Central Plains have an elevated seroprevalence of *B. henselae* antibodies.[5] Drier, cool environs that do not support high flea density have the lowest seroprevalences.

Clinical Manifestations. CSD may present in a typical or atypical fashion in both immunocompetent and immunocompromised patients. Typical disease in immunocompetent persons includes a scratch, bite, lick or other contact with a kitten followed in 3–10 days by a round, red-brown, nontender papule within the scratch line. Regional, unilateral lymphadenopathy occurs 1–3 weeks later with gradual nodal enlargement. Unlike pyogenic lymphadenopathy, CSD does not progress rapidly, and patients are usually well-appearing with mild nonspecific symptoms such as anorexia, malaise, headache, arthralgia, myalgia or abdominal pain. Lymph nodes usually enlarge over 2–3 weeks, stabilize for 2–3 weeks and then resolve over 2–3 weeks. Any stage may be more prolonged; symptoms rarely exceed 6 months. Histologic examination reveals granulomas with central necrosis and multiple microabscesses. Up to 10% of lesions may suppurate and require needle or open drainage. CSD lymphadenopathy does not produce chronic draining fistulous tracts when incised and drained.

The most common atypical manifestation is Parinaud's oculoglandular syndrome (POGS) consisting of unilateral preauricular lymphadenopathy and conjunctivitis. Palpebral conjunctivas demonstrate a 2- to 3-mm red-yellow nodule or nodules, the equivalent of the inoculation papule seen with a scratch. Although POGS can be caused by other infections, *B. henselae* is the most common etiology. POGS is a predictable, self-limited infection with full recovery regardless of treatment in most cases.

Fever of unknown origin (FUO) and hepatosplenic CSD represent dissemination that may present in immunocompetent patients as daily spiking fevers lasting weeks to months. Frequently patients have an elevated erythrocyte sedimenta-

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tion rate, but abdominal pain and lymphadenopathy are seen in less than one-half of cases.[6] The diagnosis is likely with a history of kitten contact, dermal scratch scars and lytic lesions in the liver and/or spleen on ultrasound or computerized tomography (CT) scan and is suspect in patients who do not have these findings. CSD accounts for 5% of FUO in some populations.[7]

In immunocompetent patients, insidious back pain is frequently the presenting sign of *B. henselae* vertebral osteomyelitis,[8] with or without a paravertebral mass. Clinical and radiographic resolution appears to occur over months without intervention.

CSD causes many cases of endocarditis.[9] Surgical intervention, including valve replacement, followed by months of antibiotics, is necessary in both pediatric and adult patients with *Bartonella* endocarditis.

Neurologic complications of CSD include Leber's stellate neuroretinitis, characterized by painless, unilateral loss of vision with a macular star visible on retinal examination. Visual loss occurs abruptly over hours to days. Recovery occurs in weeks to months, with or without treatment. CSD encephalopathy is a severe complication frequently requiring admission to an intensive care facility and respiratory support.[10] Progression from headache to coma typically develops within hours, often followed by rapid recovery. Cerebrospinal fluid and blood studies, as well as head CT scans, are often normal or nonspecific. Focal seizures or prolonged coma portend neurologic sequelae. Most immunocompetent patients recover fully without therapy.

Immunocompromised hosts may develop bacillary angiomatosis and peliosis.[11] *Bartonella* stimulates endothelial vasoproliferation that can develop into large, pedunculated and painful tumors in skin, soft tissue, bone, bone marrow, respiratory or gastrointestinal tract, lymph nodes or brain. Severely immunosuppressed patients can form large blood-filled cysts in the liver and spleen. *Bartonella* bacilli can be demonstrated in these lesions by Warthin-Starry staining. Patients may present with gastrointestinal symptoms and malaise, but prolonged fever is the most common complaint.

Diagnosis. A history of kitten contact supports the diagnosis of CSD. Fever and/or adenopathy should be prolonged. It is essential to examine the skin for scratches, bites, inoculation papules and adenopathy. A careful history and examination, along with serologic testing, can obviate the need for tissue diagnosis in immunocompetent patients with typical CSD. Atypical disease should be confirmed by serology or, if necessary, culture, by polymerase chain reaction (PCR) or by histology. Ultrasound or abdominal CT scan may be helpful in cases of FUO.

The IFA to detect IgG and IgM antibodies to *Bartonella*, first described by Regnery et al,[1] remains the most widely used and reliable serologic test, reported sensitivity 88% and specificity 94% and performs well in recent comparison studies with enzyme immunoassay.

There is wide variation in the *Bartonella* antibody responses in immunocompetent hosts. Although a *Bartonella* titer $>1/64$ is considered positive, some individuals with past disease may maintain this titer for long periods. One result of $\geq 1/512$, or a 4-fold rise over 2–4 weeks, has been proposed as diagnostic for acute CSD.[12] PCR of infected tissues is far superior to histology or culture for detection of *B. henselae*. PCR is also capable of identifying distinct genotypes within the species *B. henselae* and may explain geographic differences in the sensitivity of serologic tests.[13] IFA and PCR tests are widely available commercially.

Treatment. Typical CSD is self-limited in immunocompetent individuals; resolution occurs in 1–3 months with or without treatment. Bass et al[14] showed a modest hastening in resolution of lymphadenopathy (as measured by ultrasound) with azithromycin. Management strategies for atypical disease are limited to retrospective reviews given that most patients are treated with antimicrobials before confirmation of the diagnosis. Macrolides, rifampin, doxycycline, gentamicin, trimethoprim-sulfamethoxazole and ciprofloxacin may be effective alone or in combination.[6,8,11,15]

Immunocompromised hosts with atypical disease clearly require prolonged antimicrobial therapy to reduce morbidity and mortality.[11]

B. henselae bacteremia persists for weeks to months in kittens, despite the presence of specific antibodies. Most adult cats possess *Bartonella* antibodies but are not bacteremic. It is unknown when or how cats form protective immunity or whether vaccination induces immunity. Treatment of cats is impractical and routine culture or serologic testing of pets is not recommended.

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