DIAGNOSIS AND TREATMENT OF BARTONELLA HENSELAE INFECTIONS

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There are four Bartonella species known to be pathogenic for humans (Table 1).\(^1\) Carrion’s disease (Bartonella bacilliformis) is endemic to certain areas of South America and has a clinical course that varies widely. It may occur as a subclinical latent disease, an acute fulminant and fatal febrile illness, or an insidious disease of the skin. Trench fever (Bartonella quintana) is transmitted by the human louse and appears to be endemic in Poland, Eastern Europe, North Africa, and Russia. Patients usually have a single acute febrile illness that lasts 3–6 days, but prolonged or relapsing fevers may also occur.

Bartonella elizabethae has caused endocarditis in at least one patient. The most important of these species, however, is Bartonella henselae. As more information is obtained about this species of Bartonella, it becomes necessary for the clinician to have a working knowledge of the typical and atypical presentations of clinical disease, methods of diagnosis, and acceptable treatment options for this organism.

Epidemiology

B. henselae is the causative agent for the well-recognized, benign, and self-limited cause of lymphadenitis in children referred to as cat-scratch disease (CSD). Cat-scratch disease is usually transmitted from infected kittens to humans by means of a scratch or bite that is often recalled only in retrospect. Seroprevalence studies of cats from geographically diverse regions of the United States have revealed higher prevalence of B. henselae antibodies in the warmer, more humid climates that would be ideal for the cat flea, Ctenocephalides felis.\(^2\) This flea is thought to be the major vector by which the cat becomes infected. The precise mechanism by which transmission to humans occurs still remains somewhat unclear.

Clinical illness

Typical CSD consists of chronic solitary or regional lymphadenopathy in a patient with cat or kitten contact. Fever and mild systemic symptoms may occur in up to one-third of patients. A history of a papule or pustule at a scratch/bite site which preceded the lymphadenopathy by as much as 1–2 weeks may also be obtained. The lymphadenopathy usually involves the nodes that drain the site of inoculation such as cervical, axillary, epitrochlear, or inguinal nodes. The area around the nodes may be non-inflamed but is often warm, tender, erythematous, and indurated, and as many as 30% of the affected nodes will suppurate spontaneously.

Although typical CSD manifests with chronic lymphadenopathy, fever, and a self-limited clinical course, many atypical presentations of infection with B. henselae are now recognized. Atypical CSD...
occurs in the minority of cases. In most of these patients severe systemic symptoms persist and evidence of disseminated infection occurs. Prolonged fever and fever of unknown origin, vertebral osteomyelitis, and new onset status epilepticus have recently been described. Besides these presentations, other well-recognized atypical clinical syndromes include conjunctivitis with preauricular adenopathy (Parinaud’s ocularoglandular syndrome), encephalopathy or encephalitis, osteolytic bone lesions, granulomatous hepatitis, and ocular lesions such as optic neuritis and chorioretinitis.

Manifestations of atypical cat scratch in immunocompromised patients include a rare vasoproliferative disorder termed bacillary angiomatosis. Patients with bacillary angiomatosis gradually develop numerous brown to violaceous or colorless vascular tumors of the skin and subcutaneous tissues which may number from a few to several hundred. Bacillary peliosis is another vasoproliferative condition that affects solid internal organs with reticuloendothelial elements (e.g. liver, spleen) of immunocompromised patients. Bacillary angiomatosis and bacillary peliosis can be caused by B. henselae or B. quintana.

Diagnosis

Until recently a cat-scratch skin test was used in patients to aid in the diagnosis but due to the current availability of specific laboratory tests the cat-scratch skin test should no longer be used. Most adenopathy does not require surgical intervention, but if a node is removed a presumptive diagnosis of CSD can be made on histologic examination by demonstrating the cat-scratch bacilli with the use of Warthin-Starry silver impregnation staining. Bartonella can be cultured from blood, lymph nodes, and other tissue but grows slowly, usually taking from 9 to 40 days, and therefore requires a 6-week incubation period. Imaging studies of patients with typical CSD is usually not warranted but in patients with atypical or disseminated disease these studies may demonstrate granulomata in the liver and spleen which might help establish the diagnosis.

Serologic testing for the presence of antibodies to B. henselae is the most widely used test to confirm the diagnosis of CSD in a patient with signs and symptoms consistent with the illness. The indirect fluorescent antibody (IFA) test and the enzyme immunoassay (EIA) for detection of serum antibody to antigens of B. henselae are the currently available methods of detection in most commercial and reference laboratories. Such testing can be challenging because the timing of IgG and IgM B. henselae antibody responses is variable. Some patients produce high levels of both antibodies, while others produce only high levels of IgM, and a few produce only low levels of antibody. Additionally, with the IFA or EIA, there is cross-reaction with antibodies to B. quintana. Polymerase chain reaction assays are available in some commercial laboratories but on a limited basis.

Therapy

Previous studies have shown a significant discordance between the in vitro activity of antimicrobial agents and their effectiveness in the treatment of CSD. This is important because in immunocompetent hosts the illness is generally self-limited and usually unresponsive to antimicrobial agents while in immunocompromised hosts the infection can be progressive and fatal unless treated. If antimicrobial agents are used for the treatment of acutely or severely ill patients with systemic symptoms, it is clear that β-lactam agents are ineffective despite favorable in vitro susceptibility testing. It would appear that trimethoprim-sulfamethoxazole, rifampin, erythromycin, clarithromycin, azithromycin, doxycycline, ciprofloxacin, and gentamicin are among the best agents to choose from.

The majority of data on antimicrobial therapy have been obtained from small case reports or retrospective reviews. There has been one prospective randomized double blind placebo-controlled study for the treatment of CSD. Fourteen patients were treated with azithromycin and 15 were given placebo for typical cat-scratch adenopathy. During the first 30 days of observation, there was an 80% decrease of the initial lymph node volume in 7 of 14 azithromycin-treated patients as compared with 1 of 15 placebo-treated controls. After 30 days there was no significant difference in rate or degree of resolution of the adenopathy between the two groups. The authors concluded that treatment of patients with typical CSD with oral azithromycin for 5 days demonstrates some clinical benefit as measured by total decrease in lymph node size but only during the first 30 days of the illness.

For the atypical presentations of CSD, there are no data regarding the benefit of specific antimicrobial therapy for the immunocompetent patient. Even for the neurologic complications of illness such as status epilepticus, encephalopathy, or encephalitis a favorable prognosis should be anticipated in spite of the presenting symptoms without specific antimicrobial therapy. For immunocompromised patients with atypical CSD, most of the data concerning therapy has been for patients with bacillary angiomatosis and peliosis. Studies indicate that these patients should be treated with erythromycin, erythromycin plus rifampin, or doxycycline for at least 6 weeks. Patients that relapse should receive 4–6 months of therapy and those with repeated relapses should receive suppressive therapy indefinitely.

Further studies will help elucidate the reasons for the variety of clinical presentations with B. henselae infection and if antimicrobial therapy is effective. Until then, clinicians should be encouraged by the fact that in most circumstances
antimicrobial therapy is not required and the long-term outcome for the patient is favorable.

References

HEPATITIS A VACCINE
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Hepatitis A is one of the most frequently reported vaccine-preventable diseases in the US.1 The ability to propagate hepatitis A virus (HAV) in cell culture allowed for the development of hepatitis A vaccines.

HAV infection
HAV infection is acquired primarily by the fecal-oral route. After an average incubation period of 28 days, HAV produces either asymptomatic or symptomatic infection. The likelihood of having symptoms is related to age. In children <6 years old, most infections (70%) are asymptomatic or characterized by nonspecific symptoms.2 Among older children and adults, infection is usually symptomatic, with jaundice occurring in >70% of adult patients.3 Chronic infection does not occur.

Among reported cases in the US, the highest disease incidence rates occur among children 5–14 years old, and almost 30% of cases occur among children <15 years old.1 Higher disease incidence rates occur in the West and Southwest compared to other regions of the country.1

The most common source for infection is household or sexual contact with a person who has hepatitis A. However, 40–50% of reported cases do not have an identified source.1

Most hepatitis A occurs in the context of community-wide epidemics, by person-to-person transmission in households and extended family settings. Children likely play an important role in transmission during these outbreaks. In studies in which household contacts of adult cases without an identified infection source were tested, 25–40% of their contacts <6 years old had serologic evidence of acute HAV infection.4

Hepatitis A vaccines
Both inactivated and live, attenuated hepatitis A vaccines have been developed using defined isolates from infected cell lines, but only inactivated vaccines have been evaluated for efficacy in controlled clinical trials.5, 6 The two inactivated vaccines currently licensed in the US are HAVRIX (SmithKline Beecham Biologicals) and VAQTA (Merck & Co., Inc.). Both vaccines are licensed for children ≥2 years old and for adults, and are available in pediatric and adult formulations given intramuscularly in a two dose schedule. The pediatric formulation of HAVRIX is licensed for persons <19 years old, and that of VAQTA for persons <18 years old.

Immunogenicity
In extensive studies among children and adults, both vaccines were highly immunogenic when administered according to a variety of schedules. In general, >97% of children ≥2 years old develop levels of antibody considered to be protective by four weeks after one dose. Large boosts in antibody levels occur after a second dose given at least 6 months later.7, 8 This second dose is felt to be necessary for long term protection. Studies among children <2 years old indicate a favorable safety profile and high rates of seroconversion. However, among infants with passively transferred maternal antibody, final antibody concentrations have been one-third to one-tenth those of vaccine recipients without maternal antibody.9, 10 Studies to determine the optimum dosage and schedule to overcome this interference are underway.

Efficacy
Inactivated hepatitis A vaccines have been shown to be highly efficacious. In large studies conducted among children 2–16 years old, hepatitis A vaccines were 94–100% efficacious in preventing clinically apparent disease when administered before exposure.5, 6 Hepatitis A vaccines are not recommended for postexposure prophylaxis because no trials have been conducted comparing vaccine to immune globulin (IG). IG, administered within two weeks of exposure, is highly efficacious and continues to be recommended to prevent hepatitis A in this setting.1

Levels of antibody considered protective have been shown to persist for at least 6 years in adults vaccinated according to the recommended schedule.11 Estimates based on kinetic models of antibody decline suggest that the duration of protection could be longer than 20 years.12

Limited data from studies conducted among adults indicate that hepatitis A vaccine can be administered with other vaccines commonly given to international travelers13 and concurrently with IG.14

Safety
In total, >65 million doses of hepatitis A vaccine have been administered worldwide.1 In prelicensure trials, soreness at the injection site was reported for 9–15% of vaccinated children. Reviews of data regarding adverse events have not identified any serious adverse events among children or adults that could be attributed to the vaccine.1

Recommendations
Recommendations for the use of hepatitis A vaccine have been developed by the ACIP and AAP.1, 15 Because of the marked geographic

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variations in hepatitis A rates, areas can be identified in which rates have been consistently elevated and that contribute the majority of cases to the national disease burden. Routine vaccination is recommended for children living in states, counties and communities where the average annual reported hepatitis A incidence during 1987–1997 was at least twice the national average of approximately 10 cases/100,000 population (Table). In these areas, routine vaccination of children is being implemented using a variety of strategies, including vaccination of single age cohorts and vaccination of children in settings such as child care centers. In addition, consideration of routine vaccination is recommended for children living in states, counties and communities where reported hepatitis A rates were less than twice, but at least the national average during this time (Table).

In populations that have high rates of HAV infection, prevaccination testing may be considered to reduce costs. However, in most instances testing of children is not necessary, because of their expected low prevalence of infection. Postvaccination testing is not indicated because of the high rate of vaccine response. In addition, response to vaccination cannot be determined using the commercially available assay because it is not sensitive enough to detect the low, but protective, anti-HAV concentrations induced by vaccination.

Persons from developed countries who travel to developing countries are at substantial risk for acquiring hepatitis A (Table). Children account for approximately 36% of reported hepatitis A cases among returning international travelers. Children visiting in their parents’ country of origin may be at particular risk because their need for preexposure prophylaxis often is not recognized. Hepatitis A vaccine is also recommended for other persons in identified groups at increased risk of infection or its adverse consequences (Table).

There has been considerable interest in using hepatitis A vaccine to control ongoing community-wide epidemics. Although individuals who receive a single dose of vaccine during outbreaks did not develop hepatitis A, the success of vaccination programs in interrupting an epidemic has been variable. Efforts are probably better focused on sustained, routine childhood vaccination to prevent future epidemics.

Outbreaks in childcare centers have been recognized since the 1970s, often only when adult contacts become ill. Outbreaks rarely occur in childcare centers that do not include diapered children. Until more data become available, IG, which has proven effective in limiting transmission, should continue to be used in this setting. In communities where vaccination of childcare attendees is being used as a way to implement routine hepatitis A vaccination, previously unvaccinated children receiving IG can also receive hepatitis A vaccine.

**Summary**

Inactivated hepatitis A vaccines are highly immunogenic and efficacious. Because of their high disease rates and importance as a reservoir of transmission to others, children should be the primary focus of vaccination. A long-term strategy of sustained routine vaccination of children living in areas with consistently elevated hepatitis A rates has been adopted. Ultimately, elimination of HAV transmission will require vaccination of all children in the US. This effort would be facilitated by the availability of vaccine formulations or schedules for use in infants or children in the second year of life, and combination vaccines that include hepatitis A.

**References**

1. CDC. MMWR. 1999;48:RR-12.