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Bartonellosis

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Continuing Education Activity

Bartonellosis is the term used to describe any infectious disease produced by the bacteria *Bartonella*. These include trench fever, Oroya fever, Carrion's disease cat scratch disease, peliosis hepatis, etc. This activity illustrates the evaluation and management of Bartonellosis and highlights the role of the interprofessional team in improving care for patients with this condition.

Objectives:

- Describe the role of cats and cat fleas in the transmission of Bartonellosis.
- Explain the histological, epidemiological, and bacteriological criteria used in the diagnosis of cat scratch disease (Bartonellosis).
- Identify the usefulness of a single antibiotic regimen in reducing the duration of symptoms and in treating Bartonellosis.
- Review the importance of improving care coordination among the interprofessional team in educating the patient on measures to decrease transmission of Bartonellosis.

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Introduction

Bartonella is a gram-negative intracellular facultative bacterium that is commonly implicated in causing zoonotic infections globally. Almost 20 different species of *Bartonella* have been isolated thus far among which *Bartonella henselae*, *Bartonella quintana*, and *Bartonella bacilliformis* are frequently associated with infections in humans.

Trench fever also known as the five-day fever was first reported in Europe in soldiers. Trench fever is transmitted by body louse and is known to exclusively occur in humans.

Oroya fever was first reported in 1870 when a railway line was being built from Lima to Oroya in Peru. An outbreak of fever killed several thousand workmen and was named Oroya fever after the place it was first reported. Some workers who survived the outbreak developed verruga peruana which are nodular ulcerating skin lesions. It is commonly reported in mountainous parts of Peru, Columbia, and Ecuador in South America. In 1885, a Peruvian medical student Daniel Carrion inoculated himself with material from verruga which resulted in his death from Oroya fever. Oroya fever is also known as Carrion disease for this reason.

Etiology

Cat scratch disease, caused by *Bartonella henselae* is the infection that is most commonly caused by *Bartonella* species. *Bartonella bacilliformis* causes Oroya fever and verruga peruana while *Bartonella quintana* is associated with trench fever.[1] Carrion's disease is caused by *B. angiomatosis* characterized by high-grade fever accompanied by severe anemia from the destruction of red blood cells, severe enlargement of spleen and liver, bleeding into lymph nodes, and destruction of blood vessels. Mortality is 40% without treatment.

Epidemiology

The incidence of cat-scratch disease was reported to be 6.4 cases per 100,000 population in adults and 9.4 cases per 100,000 population in children aged 5-9 years globally. The highest incidence is reported in the southeastern United States with a peak in January, late summer, and fall.[2] Epidemic and sporadic outbreaks of trench fever have been reported since the early 20 century in several countries across the globe with the largest epidemics reported during world war 1 and world war 2. The homeless population is more frequently exposed to the pathogen and has the highest risk of contracting trench fever.[3] Infections caused by *Bartonella bacilliformis* are endemic to Peru, Columbia, and Ecuador while sporadic cases have been reported in Chile, Guatemala, and Bolivia.[4]

Pathophysiology

Cat scratch disease was historically thought to be transmitted through a scratch or bite from infected cats. Cats and the cat flea, *Ctenocephalides felis* act as vectors for transmission of cat scratch disease.[5] More recent research has shown that other arthropod vectors, including ticks, lice, chiggers, and mosquitoes are also implicated in the spread of the disease among humans.[6] Human body louse, *Pediculus humanus* has been reported to be the predominant vector responsible for the transmission of trench fever caused by *Bartonella quintana*. [7] Transmission of *Bartonella bacilliformis* occurs by the bite of the female sandfly *Lutzomyia*.

Once inside the body, *Bartonella* targets CD34+ cells which are specialized white blood cells that act as precursors for endothelial cells which are cells that line blood vessels and other tissues. After its entry into the cell, it prevents the cell from self-destructing and also creates a vacuole a protective cyst around itself.

An endotoxin called lipid A which is commonly found in the outer membrane of gram-negative bacteria is the primary virulence factor for *Bartonella*. The ability of the organism to invade erythrocytes and endothelial cells plays a major role in the pathogenesis of the disease process. The organism alters the immune system in such a way that makes the host susceptible to infections by other bacterial pathogens. After this acute phase, the organism invades the endovascular, lymphatic, and other organ systems of the body contributing to multiple presentations of the disease.

History and Physical

Cat scratch disease typically presents with cutaneous manifestations at the site of inoculation. Cutaneous manifestations begin within a week to ten days of being exposed and have vesicular, erythematous, and papular phases. The lymph nodes near the site of the inoculation become enlarged. Other features such as fever, malaise, and visceral organ involvement occur, but the frequency of the symptoms is low.[8]

After the lymphatic system, the eye is the most frequently affected organ. Ocular involvement can be subclinical and visual symptoms may not be a common presenting complaint. Neuroretinitis is an optic neuropathy classically characterized by optic disc swelling in the presence of a partial or complete macular star. Its prevalence in CSD is unclear, possibly seen in 1% to 2% of cases. Typically, neuro retinitis presents unilaterally. Neuroretinitis suggests infection, whereas optic neuritis is an isolated inflammatory optic neuropathy secondary to demyelination.

Parinaud oculo-glandular syndrome that manifests as tender lymphadenopathy of pre-auricular, submandibular, and cervical lymph nodes with the infection of the conjunctiva, eyelid, and adjacent skin surface occurs in about 2-8% of affected patients. [9]

The neurological manifestation that has been reported in patients diagnosed with cat scratch disease include

encephalopathy, transverse myelitis, radiculitis, and cerebellar ataxia.[10]

Another presentation of *Bartonella* infection includes negative culture endocarditis. Even though several species have been implicated in causing endocarditis *Bartonella henselae* and *Bartonella quintana* account for about 95% of endocarditis caused by *Bartonella*.[11]

Severe, progressive, disseminated disease may occur in immunocompromised patients, especially those with HIV infection and organ transplants. Without therapy, the infection spreads systemically and can involve virtually any organ, and the outcome is sometimes fatal.

Bacillary angiomatosis is characterized by cutaneous lesions, subcutaneous masses, and bone lesions in AIDS patients.[12] It is a vascular proliferative disease most often involving the skin, but it may involve other organs. The clinical differential diagnosis includes pyogenic granuloma, hemangioma, subcutaneous tumors, and Kaposi's sarcoma. The skin lesions are very similar to those reported for verruga peruana, the chronic form of Carrion's disease. Lesions can also involve the bone marrow, liver, spleen, or lymph nodes.

Peliosis Hepatis is defined as a vascular proliferation of sinusoidal hepatic capillaries resulting in blood-filled spaces in the liver. This disease was first described in patients with tuberculosis and advanced cancers and correlated with the use of drugs such as anabolic steroids. *B. henselae* is now recognized as an infectious cause of PH in HIV-infected patients. PH has also been reported in organ transplant recipients. PH can occur simultaneously with peliosis of the spleen, and BA of the skin, in HIV-infected patients.

Trench fever caused by *Bartonella quintana* presents with clinical features of malaise, fever, headache, bone pain, and splenomegaly. The pattern of fever that occurs in trench fever is highly variable and ranges from a single episode to a persistent fever lasting for several days. [13]

The clinical manifestations of infection caused by *Bartonella bacilliformis* include an acute phase (Oroya fever) characterized by fever, malaise, headache, and a chronic phase (Verruga Peruana) characterized by eruptive cutaneous lesions that appear about 2-8 weeks after the acute phase.[14]

Chronic *Bartonella* infection can be associated with relapsing low-grade fever. Chronic eye problems include blurred vision, photophobia, and eye irritation. *Bartonella* commonly infects bone marrow with resulting bone pain, most commonly the shin bone. Another classic *Bartonella* symptom is a pain in the soles of feet upon waking in the morning. This is associated with trauma to blood vessels in the soles of the feet with walking. Anemia can occur from *Bartonella* scavenging nutrients from red blood cells. Neurological symptoms include poor balance, decreased cognition, memory impairment, insomnia, and restlessness.

Evaluation

Classical criteria for CSD diagnosis: (i) close contact with cats or a scratch or bite from a cat, (ii) typical CSD histology (granuloma with a central pyogenic abscess, with lymphoid hyperplasia not being sufficiently specific to establish a diagnosis of CSD), and (iii) positive serology by an immunofluorescence assay for antibodies against *B. henselae*.

A diagnosis of CSD must rely on the presence of a combination of epidemiological, histological, and bacteriological criteria, since no single criterion may be considered the gold standard.

The diagnostic modalities commonly used in the diagnosis of *Bartonella* infection include serological testing, culture, histopathology, and polymerase chain reaction. There are five blood tests available: Western blot, ELISA, and IFA tests, PCR DNA detection, and culture. However, it must be emphasized that *Bartonella* often is only intermittently present in the peripheral blood (bacteremia) of infected animals.

Direct Detection Methods:

1. Isolation in culture.
2. Detection of antigens of the pathogen.
3. PCR- detection of the nucleic acid (DNA).
4. Visualization by special stains.

Indirect Detection Methods:

1. Serology - detection of antibodies against the pathogen.
2. Detection of an immune cellular response against the pathogen- Bartonella skin tests. No longer used

The culture of the bacterium gives a definitive diagnosis, but it is a very time-consuming and expensive process with incubation periods as long as 21 days. *Bartonella* bacteria are very slow-growing, fastidious, and primary isolation is difficult, with the detection of colonies only after 1 to 4 weeks of incubation on blood agar plates. As *Bartonella* species are difficult to culture, culture is not routinely recommended. Serology is the best initial test and can be performed by indirect fluorescent assay or enzyme-linked immunosorbent assay.

Serological testing such as indirect fluorescence assay for *B. henselae* antibodies was the first microbiological test available but has a variable positive predictive value. It is an indirect diagnostic method that can be negative in the early stage of the disease. In some studies, the positive predictive value of the indirect immunofluorescence assay for *B. henselae* was reported to be high (=91.4%). Conversely, some studies found a lack of sensitivity of the serological test among patients with CSD. While there is variability in multiple studies of *B. henselae* IgG and IgM indirect fluorescent antibody and ELISA serology, typical sensitivity values are approximately 50% to 80%, [15] whereas specificity is 90% to 100%. Sensitivity increases when there is a higher clinical index of suspicion for CSD. An IgM titer of 1:16 or higher shows acute disease, with a 3-month duration of detection in 50% of patients. An IgG titer higher than 1:256 is considered evidence of current or past *Bartonella* infection. Unlike culture and PCR of blood, serology does not rely on *Bartonella* being present in the blood. It can be used to evaluate response to therapy.

Histopathological examination of the tissue infected by *Bartonella* species usually shows neutrophils, lymphocytes, and debris scattered throughout the lesions. Warthin-Starry silver staining will show small dark staining bacteria and electron microscopic findings include pleomorphic bacilli with a trilaminar wall. Histopathological examination for *Bartonella bacilliformis* is performed using Giemsa stain, and it shows cytoplasmic inclusions known as Rocha-Lima inclusions.[16]

Advanced diagnostic techniques such as PCR on lymph nodes or other material have been applied to the detection of *Bartonella*. PCR provides the advantages of high specificity and rapid identification, however lacking in sensitivity, ranging from 43% to 76%. The sensitivity of PCR with samples of lymph node tissue or aspirates is 30-60% for CSD. A polymerase chain reaction can detect different *Bartonella* species; specificity is high, but the sensitivity is lower than with serology.

Treatment / Management

Management of cat scratch disease depends on the clinical presentation of the disease. Patients who present with milder presentations such as lymphadenopathy and fever were usually not placed on an antimicrobial regimen because of the self-limiting nature of the disease. [17]

However, studies have shown that the use of a single antimicrobial regimen will reduce the duration of the symptoms significantly. The antimicrobial agents commonly used are azithromycin, ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, and rifampin.

For patients with extensive lymphadenopathy, oral azithromycin at 500 mg on the first day and 250 mg on days 2 to 5.

For retinitis, oral Doxycycline 100 mg twice daily for 4 to 6 weeks and oral rifampin 300 mg twice daily for 4 to 6 weeks

Trench fever or chronic bacteremia with *B. quintana* can be treated with oral Doxycycline at 200 mg once daily for 4 weeks and intravenous gentamicin 3 mg/kg for 2 weeks.[18]

Bacillary angiomatosis and Peliosis Hepatis treated with oral erythromycin 500 mg four times daily for 3 to 4 months

Documented Bartonella culture-positive endocarditis should be treated with oral Doxycycline 100 mg for 6 weeks and intravenous gentamicin at 3 mg/kg/day for 14 days.

Recommended treatment for neuroretinitis and for CNS involvement is a combination of oral doxycycline 100 mg twice daily and rifampin 300mg twice daily.[19] There are no controlled clinical trials comparing a nontreatment group with those given antibiotics. However, retrospective case series consistently associated antibiotics with hastened visual recovery and improved visual outcomes. Corticosteroid use in CSD with eye involvement has had mixed results.

The management of Oroya fever includes the use of ciprofloxacin as the primary choice with chloramphenicol, ceftriaxone being alternative choice that are very effective. Verruga peruana is managed with azithromycin primarily with rifampin, ciprofloxacin, and chloramphenicol being the preferred alternatives.

Differential Diagnosis

- Atypical mycobacterial diseases
- Coccidioidomycosis and valley fever
- Leishmaniasis
- Lyme disease
- Lymphogranuloma venereum (LGV)
- Nocardiosis
- Sarcoidosis
- Sporotrichosis
- Syphilis
- Toxoplasmosis

Deterrence and Patient Education

Prevention of *Bartonella* infections includes several common measures that will help in curtailing the transmission of the disease. For cat scratch disease taking appropriate care of the cats, avoiding being scratched, keeping them indoors as much as possible, regular treatment to eradicate cat fleas, and washing hands after playing with them will help reduce the transmission of the disease. For trench fever avoiding exposure to human lice and prompt treatment if lice are found will prevent the occurrence of the disease. Carrion's disease caused by *Bartonella bacilliformis* can be prevented by wearing clothes with long sleeves and the use of repellents to avoid being bitten by sandflies.

Pearls and Other Issues

Ongoing Research

New findings by the scientists at Beth Israel Deaconess Medical Center and the Harvard Medical School in Boston, Massachusetts, suggest that the organism can cause angiogenesis in the affected tissues. The ability of *Bartonella* to induce angiogenesis could circumvent blocked arteries in the heart, promote the formation of new blood vessels in damaged limbs, and speed up wound healing in damaged tissues. Current investigations are focused on understanding the genetic basis of the mechanisms that are involved in the causation of angiogenesis.

Enhancing Healthcare Team Outcomes

The diagnosis and management of cat scratch disease are best done with an interprofessional team that includes an infectious disease consultant, emergency department physician, primary care provider, nurse practitioner, and internist.

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Review Questions

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