Trench Fever

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Continuing Education Activity

Trench fever is an infection caused by the fastidious aerobic gram-negative rod bacterium, Bartonella quintana, formerly known as Rickettsia quintana. It can vary in symptoms and presentation, from non-specific symptoms such as fever, headache, rash, malaise, joint pain, and back pain to bacteremia, endocarditis, and bacillary angiomatosis. The disease likely has a zoonotic origin, with humans being the main host as it is now mainly transmitted by the three lice species, Pediculus humanus corporis (body louse), Pediculus humans capitis (head louse), and Pediculus humans pubis (pubic louse), with the body louse being the most common vector. This activity outlines the evaluation and management of trench fever and highlights the role of the interprofessional health team in the care of patients with this condition.

Objectives:

- Describe the epidemiology of trench fever.
- Explain the common physical exam findings associated with trench fever.
- Review the complications of trench fever in chronic or untreated patients.
- Summarize the importance of collaboration among the interprofessional team to enhance care coordination for patients with trench fever.

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Introduction

Amidst the coronavirus 2019-nCoV (COVID-19) pandemic in 2020, trench fever's emergence in Denver, Colorado, served as a reminder that we must remain ready for new and old threats. Historically, trench fever caused significant morbidity for more than 1 million soldiers during World War I and is often linked to those suffering from homelessness and/or poor hygiene. Classic trench fever typically presents with a recurrent fever pattern, "quintan fever," as well as general non-specific influenza-like symptoms like fever, headache, malaise, and a rash.

Etiology

Trench fever is caused by a fastidious aerobic gram-negative rod known as *Bartonella quintana.*[1] The disease likely has a zoonotic origin, with humans being the main host as it is now mainly transmitted by the three lice species, *Pediculus humanus corporis* (body louse)*, Pediculus humans capitis* (head louse), and *Pediculus humans pubis* (pubic louse), with the body louse being the most common vector. There has been at least one report about the possibility of transmission by bed bugs (*Cimex lectularius*) and cat fleas.[2][3][4] Transmission is likely via feces that is contaminated with the *Bartonella quintana* bacteria.

Epidemiology

Hunt and Rankin first named this disease in 1915 after noting it was distinct from typhoid, dengue, and relapsing fever.[1] The War Office Trench Fever Investigation Commission could not prove if trench fever was caused by bacteria or protozoa.[5]. In 1916, H. Topfer discovered that the lice that particularly feasted on trench fever patients had many rickettsial bodies in their gut and feces.[6] A further connection to *Rickettsia* was made in 1919 when Arkwright et al. detected that when lice fed on patients with the disease, they excreted *Rickettsia quintana*, unlike when feeding on those who were not suffering from trench fever. Finally, Arkwright et al. noted that via direct inoculation by volunteers, the rickettsial connection to lice showed increased virulence.[7] The organism was successfully cultured in 1961 by Vinson and Reed, which allowed for the first trial of specific antibiotics to treat this infection.[8] The pathogen was later reclassified from *Rickettsia quintana* to *Rochalimaea quintana* and is now known as *Bartonella quintana*.

Trench fever caused an epidemic and became a significant source of morbidity and mortality in World War I, affecting more than 1 million soldiers. It then re-emerged in World War II but did not have the same morbidity and mortality as in World War 1. Since it has caused several other outbreaks around the globe, including Ethiopia in 1964, Poland in 1949, Mexico in 1954, USSR in 1960, and Tunisia in 1961.[8] Since the 1990s, trench fever has remained in small sporadic outbreaks, mainly presenting as bacteremia, endocarditis, or bacillary angiomatosis. Recently in 2020, a small eruption was noted in Denver, Colorado, affecting many patients who suffered from homelessness.[9]

Pathophysiology

Classic trench fever is caused by *Bartonella quintana,* which is carried predominately by a vector body louse. *B. quintana* reproduces in the intestinal lumen of the louse and then transmits the disease via inoculation of contaminated feces into exposed skin or conjunctivae. The Medical Research Committee, set up by the American Red Cross, documented this transmission route in 1918.[1] Hence, expedited transmission can be detected in crowded living conditions and in those with poor hygiene, such as those suffering from homelessness.

History and Physical

The disease presentation can range from mild influenza-like illness to moderate and finally into a debilitating disease process. Patients who develop symptoms do so generally after an incubation period of seven days. The hallmark of this disease process is fever which has a somewhat comparable fever pattern to malaria. Fever can present in four common ways, with the episodic form being the most common. These include an isolated febrile episode to febrile episodes lasting four to five days, three to five recurrent febrile episodes lasting five days with asymptomatic periods in between, and persistent febrile episodes for two to six weeks.[8][10]

The febrile period recurring every five days is where the term "quintan fever" is derived, including the name of the bacteria causing the disease, *B. quintana.* Other presenting symptoms include non-specific influenza-like symptoms, which include malaise, fever, headache, dizziness, bone pain (most commonly affecting shins), nausea, vomiting, and weight loss.

Common physical examination findings include a febrile patient with temperatures generally greater than 38.4 degrees Celsius (101.1 Fahrenheit), palpable splenomegaly, and a maculopapular rash noted mainly in the truncal area.[10]

Evaluation

In the proper clinical context, *Bartonella quintana* can be diagnosed with culture, polymerase chain reaction, and histopathology. It is difficult to culture as it is a slow-growing fastidious bacterium.[11] In cases with a high likelihood of disease, it is recommended to obtain cultures with ethylenediaminetetraacetic acid (EDTA) bottles or chocolate agar under 5% carbon dioxide incubated at 35 degrees Celsius, and cultures should be held for at least 21 days. Because of its slow growth, there are other methods of diagnosis, such as the utilization of polymerase chain reaction. (PCR) According to Zeaiter et al., species-specific reverse-transcriptase polymerase chain reaction (RT PCR) was compared to serology, which helped diagnose all three *Bartonella* species.

Finally, trench fever may be diagnosed by serology by measuring antibodies to *B. quintana* with either indirect fluorescence assay (IFA) or enzyme-linked immunosorbent assay (ELISA). Using serology, acute infections can be differentiated from chronic infections based on the higher elevations of anti-*Bartonella* antibodies in those with acute infections, with titers >1:256. Serology has been recorded to be most sensitive in cases with endocarditis.[12]

Treatment / Management

The optimal management for trench fever, as well as other infections caused by *Bartonella quintana,* is sparse due to the limited published data. The recommended treatment depends on the patient's presentation and underlying comorbidities. For acute or chronic infections without endocarditis, oral doxycycline is recommended at a dose of either 100 mg or 200 mg once a day for four weeks in combination with gentamicin 3 mg/kg intravenously once daily for the first 14 days. If gentamicin is not an option due to availability, allergies, or other contraindications, rifampin 300 mg twice daily for the first 14 days can be used. This treatment was thoroughly detailed in the randomized, open-label trial conducted by Foucault et al., where complete eradication was noted per-protocol analysis in seven out of seven patients treated with combination therapy compared to two out of nine patients who received no treatment with $P = 0.003$.[13][14]

Gentamicin levels, especially in patients with renal impairment, should be monitored closely. Patients with chronic trench fever should be evaluated with an echocardiogram in order to evaluate for possible endocarditis, as this would lead to a prolonged course of antibiotic therapy.

Differential Diagnosis

Malaria

The *Plasmodium* parasite transmitted by the female *Anopheles* mosquito leads to characteristic cyclical fevers. There are five species of Plasmodium; *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Symptoms may be similar to trench fever, such as headache, malaise, weakness, gastrointestinal distress, and muscle aches. However, there may be distinguishing

traits in severe cases, including jaundice, confusion, seizures, and dark urine. If this diagnosis is recognized, the gold standard for diagnosis is a microscopic evaluation of Giemsa-stained thick and thin smears of a blood sample.[15]

Typhus

This is caused by *Salmonella typhi* and *Salmonella paratyphi*. Symptoms consist of nausea and vomiting, which may progress to diffuse abdominal pain, bloating, anorexia, and diarrhea with or without blood. This disease may also result in bacteremia. If typhoid fever is suspected, blood cultures should be obtained.

Relapsing Fever

Patients typically present with symptoms of recurrent fevers, chills, and malaise. This is caused by a spirochete known as *Borrelia recurrentis*, and diagnosis may be made via Giemsa-stained blood films, serologic analysis, or PCR.

Leptospirosis

The anicteric presentation can have similar symptoms to trench fever, such as headache, cough, non-pruritic rash, fever, rigors, muscle pain, anorexia, and diarrhea. The icteric presentation, also known as Weil's disease, may present with renal failure, jaundice, hemorrhage, and respiratory distress. This disease should be considered and diagnosed by specialized culture or microscopic agglutination test (only available at the CDC in Atlanta).[16]

Rocky Mountain Spotted Fever (RMSF)

Initial symptoms include fever, headaches, and rash, which is typically petechial but can also be maculopapular. The differentiating feature from trench fever is the rash's progression, which is usually extremities to the trunk. Other symptoms can include lymphadenopathy, and central nervous system changes, mainly confusion or nuchal rigidity, myalgias and arthralgias, hepatitis, gastrointestinal distress, and cardiovascular instability. RMSF is diagnosed by immunoglobulin M (IgM) and immunoglobulin G (IgG) serology.

Prognosis

There is limited documentation on the prognosis of trench fever, but the overall mortality is low. Some patients do not require treatment as the infection may result in a self-limited illness. However, due to increasing documentation of bacteremia, recommendation to treat the disease takes precedence. The prognosis can also differ based on the patient's immune status. More severe cases that lead to critical complications and worse outcomes are observed in patients with human immunodeficiency virus (HIV), transplantation on immunosuppressants, and alcoholism.

Complications

There are cases reported of *Bartonella quintana* causing endocarditis from chronically infected patients and bacillary angiomatosis, mainly in immunocompromised patients. Patients documented to present with endocarditis typically have chest pain, shortness of breath, weight loss, night sweats, and other non-specific symptoms of malaise, cough, and fatigue. The examination usually mimics classic endocarditis. This includes new cardiac murmurs, Janeway lesions, Osler nodes, and vascular and immunologic phenomena.[17][18]

Organisms most common for blood culture-negative endocarditis include but are not limited to *Bartonella*, *Coxiella*, *Chlamydia*, *Legionella*, *Mycoplasma*, *Aspergillus*, and *Brucella*.[18] It is very crucial to evaluate for these pathogens. In France, according to Fournier et al., *Bartonella* is the causative organism in approximately 20% of all charted cases of blood culture-negative endocarditis.[19]

Not all patients with trench fever develop bacillary angiomatosis, but it should be considered in those patients who have a cell-mediated immunodeficiency, such as HIV, and posttransplant patients on immunosuppressive therapy. *Bartonella quintana* can induce new blood vessel formation, which leads to antiproliferative tumors.[20] This occurs after a high concentration of the organism has accumulated in an immunocompromised host. According to Chiraviglio et al., *Bartonella* organisms express surface adhesins and stick easily to one another.[21]

Deterrence and Patient Education

Discussing the adverse effects of medication, such as doxycycline, with patients is essential. This includes photosensitivity with teaching on avoiding prolonged sun exposure and wearing protective garments. It is necessary to maintain sanitary environments to prevent transmission.

Pearls and Other Issues

Trench fever can present as non-specific symptoms but should be considered in patients known to live in clustered areas with inadequate hygiene. To avoid further treatment delay, it is essential to find all *Bartonella* species, including *B. quintana*, in blood culture-negative endocarditis. Consider utilizing polymerase chain reaction in addition to blood culture for diagnosis. Consider adding an aminoglycoside, especially in severely ill patients with endocarditis who are at risk for *Bartonella quintana* infection.

Enhancing Healthcare Team Outcomes

Because trench fever may result in a spectrum of diseases ranging from mild, non-specific symptoms to severe debilitating illnesses, it can help consult a specialist early in the course of the illness. These patients are best managed with an interprofessional team approach that includes clinicians (MDs, DOs, NPs, and PAs), nurses, and pharmacists, all working collaboratively to achieve optimal patient outcomes. It is important to consult an infectious disease specialist and a cardiologist if a patient is diagnosed with endocarditis or bacillary angiomatosis. Nurses can assist with patient assessment and provide patient counseling, as well as coordinate the activities of the various clinicians and serve as a communication coordinator for the team. Pharmacists will verify dosing, perform medication reconciliation, and offer patient counseling regarding drug regimens. All team members must engage in open communication with other team members and maintain accurate records, so all practitioners involved in care have the same accurate and updated data. This interprofessional approach will yield the best possible patient outcomes with the fewest adverse events. [Level 5]

Review Questions

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