EDUCATIONAL COMMENTARY – TICK-BORNE PATHOGENS

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- describe at least three tick-borne infections found in the United States.
- discuss the clinical manifestations and geographic distribution of selected tick-borne diseases.
- describe appropriate laboratory testing strategies in selected tick-borne diseases.

Ticks are found across the United States and throughout the world. To survive, these organisms require a blood meal from a host. During the blood meal, disease can spread through exchange of tick saliva and host blood. Although most tick species do not transmit disease to humans, a fraction carry significant pathogens such as *Borrelia*, *Babesia*, *Anaplasma*, and *Rickettsia*. This commentary will discuss and describe ticks and select tick-borne diseases that occur in the United States, and their clinical manifestations, geographic distribution, and diagnosis.

Ticks

As with other arachnids, ticks begin as eggs and ascend through characteristic life phases. Eggs hatch into six-legged larvae, which are extremely small: typically a fraction of a millimeter in size. The larva transition to eight-legged nymphs, and although nymphs gain size, they remain extremely small and can be difficult to see. After two to three years of development, an eight-legged adult phase is reached. Adults gain significant size, making them readily visible. Typically, their distinctive characteristics allow easy sex identification.¹

Ticks are referred to as *ectoparasites* because of their ability to acquire a blood meal from the external surface of the host. Host blood meals are taken seasonally and are necessary for the tick to survive and ascend through the life phases described above. To obtain a blood meal, ticks have developed a variety of clever adaptations to identify hosts, attach, and feed without being detected.

Ticks spend significant time in a position known as *questing*, in which they sneakily cling to a blade of grass or leaf with their back two pairs of legs and hold the front two pairs outstretched waiting for an unsuspecting host. During questing, ticks have specialized senses to identify their host: they can detect
body odors, body heat, moisture, and vibrations, and possibly recognize shadows. Once the tick climbs aboard the host, it searches for a feeding spot. The tick’s saliva has anesthetic properties which allow it to break the skin surface and insert a feeding tube without alerting the host of its presence. During this blood meal, which typically takes several days, pathogens may be transferred from tick to host or from host to tick.

Different ticks are adapted to live under different environmental conditions and preferentially feed on different host organisms. The geographic distribution of various tick species is based on climate and preferred host availability. Since specific ticks carry specific pathogens, tick-borne diseases localize with the geographic distribution of the tick.

*Dermacentor variabilis*, also known as the *American dog tick* or *wood tick*, and *Dermacentor andersoni*, also known as the Rocky Mountain wood tick, may transmit Rocky Mountain spotted fever, Colorado tick fever, and tularemia. *Dermacentor variabilis* is found ubiquitously east of the Rocky Mountains and *Dermacentor andersoni* is found in the region of the Rocky Mountains. Both have similar morphologic characteristics, with both female and male adults being reddish brown. They are easy to sex: the female has a cream colored scutum and uniform reddish brown body, and males have variably patterned cream-colored markings contrasting their reddish brown dorsum.

*Amblyomma americanum*, also known as the *Lone Star tick*, is primarily found in the southeastern United States, where it may transmit the pathogens *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Francisella tularensis* and STARI (southern tick-associated rash illness). These ticks are found in wooded areas and the adult females are easily identified by a white spot on the center of their reddish brown dorsum. The adult males also have a reddish brown body, but instead of a central white spot, scattered white streaks are noted at the margin of the dorsum. This contrasts with *Amblyomma maculatum*, also known as the *Gulf Coast tick*, which closely resembles the previously described *Dermacentor* ticks. The Gulf Coast tick can transmit *Rickettsia parkeri* and is found, as its name indicates, along the Gulf of Mexico.

*Ixodes scapularis* is found throughout deciduous forests in the eastern United States. The northeastern and midwestern United States are hotspots for Lyme disease, babesiosis, and anaplasmosis, as well as lesser-known illnesses such as Powassan disease and *Borrelia miyamotoi* infection. *Ixodes scapularis* is more commonly known as the *deer tick*, and although it is not uncommon for adults to take blood meals from deer, nymphs prefer rodent hosts, such as the white footed mouse. Adult females of *Ixodes scapularis* and its close relative found on the pacific coast, *Ixodes pacificus*, are easily identified by their orange-red dorsum and dark brown-black scutum. The adult males have a dark brown-black scutum and dorsum with a lighter colored peripheral margin.
EDUCATIONAL COMMENTARY – TICK-BORNE PATHOGENS (cont.)

Tick-borne Diseases

Tick-borne diseases may be parasitic, bacterial, or viral. Their clinical presentations vary and there is considerable overlap between different tick-borne diseases and other infectious and noninfectious disease states. Some tick-borne illnesses, such as Lyme disease and STARI, may produce a fairly characteristic rash, allowing rapid clinical diagnosis. However, because most tick-borne diseases present with nonspecific symptoms such as fever, muscle aches, fatigue, and headache, and identified tick bites frequently go unreported, their diagnosis can be difficult. Therefore, laboratory diagnosis, geographic considerations, and a good clinical history are crucial.

Babesiosis

*Babesia microti* is a red blood cell parasite associated with babesiosis, a malaria-like illness. This organism is most commonly transmitted by a bite from the tick *Ixodes scapularis*, although cases of transfusion-related and congenital transmission have been reported. The geographic distribution of disease reporting correlates with the geographic range of *Ixodes scapularis*, which has a strong presence in the Northeast and Midwest. In the northern climates, peaks in transmission occur in the warmer months of the year, when ticks actively seek blood meals. Statistics from the Centers for Disease Control and Prevention (CDC) show that in 2012, 72% of cases were reported from June to August, and 96% of cases occurred in just seven states in the Northeast and Midwest: Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin.3

Multiple organisms play host to *Babesia microti*, with the two most important being the definitive host, *Ixodes scapularis*, and the white-footed mouse. *Babesia* organisms concentrate in the saliva of the ticks and enter the blood stream of the next host during the blood meal. On entering the blood stream, parasites enter red blood cells, divide asexually, and ultimately damage the infected red blood cell membrane, causing hemolysis.4 Humans do not play a significant role in the perpetuation of the parasite but do become infected as innocent bystanders.

The clinical disease state of a *Babesia microti* infection, babesiosis, is quite variable, nonspecific, and dependent on host factors. Many healthy patients are asymptomatic or have fairly mild nonspecific symptoms, such as fever, chills, malaise, dark urine, sweats, headache, body aches, loss of appetite, nausea, or fatigue.4 However, in some patients, including those who are asplenic, immunocompromised, elderly, or who have other significant comorbidities, the disease can be severe. While death is uncommon, severe organ dysfunction, disseminated intravascular coagulation, acute respiratory distress syndrome, shock, and severe anemia can occur, especially in at-risk individuals.3
EDUCATIONAL COMMENTARY – TICK-BORNE PATHOGENS (cont.)

Even without a documented history of tick exposure, suspicion for babesiosis should be raised in patients from endemic areas who experience nonspecific malaria-like symptoms in the summer months. In 2012, the CDC reported that only 43% of patients diagnosed with babesiosis noted a history of tick exposure within eight weeks before symptom onset. Because the constellation of symptoms and physical examination findings of babesiosis are not specific and a clinical history of tick exposure is not reliable, laboratory diagnosis is crucial.

A Giemsa-stained peripheral blood smear is recommended to diagnose babesiosis. Babesia parasites appear as intraerythrocytic, 2×1.5-µm rings with central clearing. These rings show significant morphologic overlap with Plasmodium falciparum, and errors in interpretation can occur. However, a few morphologic features aid in the distinction. Babesia parasites lack brown pigment deposits, various organism stages (schizonts, gametocytes, etc.) are not seen, and Babesia occasionally demonstrate tetrads resembling a Maltese cross, which if seen are pathognomonic. If definitive organisms are seen, the diagnosis is made. However, the organisms may be missed when there is a low level of parasitemia or an inexperienced reviewer.

Given the difficulty of morphologically detecting these organisms, especially in the setting of low-level parasitemia, additional testing methodologies may be needed. Multiple serologic platforms are available, and they can provide additional diagnostic information. As with other serology-based tests for infection, there are limitations. Patients may be serologically negative in the early phase of disease, and serologic tests do not provide information in monitoring therapy. Recent polymerase chain reaction (PCR)-based methods are sensitive and specific and can be extremely helpful in settings where organisms are not identified morphologically owing to low-level parasitemia.

Lyme Disease

The most commonly reported vector-borne disease in the United States is Lyme disease. Initially described in 1977 as “Lyme arthritis” in children from Connecticut who were believed to have juvenile arthritis due to Borrelia burgdorferi.
rheumatoid arthritis, Lyme disease is a heterogeneous disease involving multiple organ systems. Lyme disease is caused by a spirochete, *Borrelia burgdorferi*, and the body's own immune response to infection. Although in 2012, 95% of cases were transmitted in the Northeast and Midwest by *Ixodes scapularis*, on the Pacific Coast a few cases were likely transmitted by another black-legged tick, *Ixodes pacificus*.

Lyme disease may be divided into three overlapping clinical stages. In the early phase of disease, patients typically present with symptoms of a nonspecific viral syndrome, with or without a history of a tick bite. In most cases, a clinical history of a tick bite is not reported, and the differential diagnosis can be quite broad. Thankfully, the characteristic rash, erythema migrans, develops in approximately 70% to 80% of patients. This expanding “bulls-eye” rash with central clearing occurs initially at the tick feeding site, typically within seven to fourteen days of exposure. It is not characteristically painful, but in some cases may burn or itch and with progression of disease, additional lesions may occur throughout the body. This rash is diagnostic of Lyme disease in the proper clinical and geographic setting, especially because serologic studies are frequently negative in the acute presentation and cultures are not highly successful.

Given the nonspecific nature of early Lyme disease symptoms and that not all patients develop the characteristic rash, patients may not seek medical attention and receive appropriate antibiotic therapy. Without prompt treatment, Lyme disease may become disseminated within weeks to years following tick exposure. Early disseminated disease may show significant pathologic features, including inflammation involving the heart, cranial nerves, spinal cord, meninges, and brain resulting in conditions such as Lyme carditis, Bell palsy, myelitis, meningitis, and encephalitis, respectively. Ocular involvement may also occur and include conjunctivitis, keratitis, vasculitis, and uveitis. If early disseminated disease is not identified and treated, Lyme disease can persist for years. In patients with persistent disease, arthritis is the most common clinical symptom, although neurologic and cutaneous manifestations may occur.

While PCR-based platforms are becoming more readily available, serologic diagnosis remains the standard for diagnosing early and late disseminated disease. The CDC recommends a two-step serologic testing process beginning with an enzyme linked-immunosorbent assay (ELISA) performed as a screen. Given the possibility of false-positive results, a follow-up Western blot is recommended to confirm positive results in ELISA studies. Although follow-up evaluation with Western blot increases specificity, the clinical manifestations and exposure to an endemic region must be well-matched to confirm the diagnosis.
Anaplasmosis

*Anaplasma phagocytophilum* is the causative organism of human granulocytic anaplasmosis. Like babesiosis and Lyme disease, anaplasmosis is transmitted by a bite from the *Ixodes scapularis* tick; hence, the geographic distribution of cases is similar, with most cases occurring in the Midwest and Northeast. Symptoms typically present seven to fourteen days following exposure and can be variable. Many patients have subclinical disease, but significant infections can occur and severe infections are more likely in patients with significant comorbidities.

The acute presentation is fairly non-specific with vague symptoms such as fatigue, fever, headache, and arthralgias. In some cases a rash may occur but unlike in Lyme disease or STARI, the rash is not characteristic and is variably described as macular, maculopapular or even petechial. In the absence of treatment, symptoms may persist for months and, in a small fraction of healthy patients, critical illness and even death may occur.

Although a peripheral blood smear may reveal intra-white blood cell bacterial clusters, these morulae are only variably seen in 20% to 80% of patients with anaplasmosis. This lack of sensitivity has led to the development of improved techniques. While serologic studies can be performed, they have limitations, including suboptimal specificity and false-negative results early in the course of disease. Cultures are also not optimal as they are not timely, sensitive, or readily available. PCR testing has come to the forefront and is the most sensitive method of detecting *Anaplasma phagocytophilum*.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by a gram-negative, obligate intracellular bacterium that induces direct vascular injury, *Rickettsia rickettsia*. Infections can be transmitted by several tick species, including *Dermacentor variabilis*, *Dermacentor andersoni*, and *Rhipicephalus sanguineus* and have been
EDUCATIONAL COMMENTARY – TICK-BORNE PATHOGENS (cont.)

reported in nearly all U.S. states. The majority of cases occur in the south central and southeastern United States, with North Carolina and Oklahoma reporting the highest number of cases.

Although many tick-borne diseases can be difficult to diagnose given their nonspecific symptom profiles, Rocky Mountain spotted fever is a notorious mimic, often referred to as a "wolf in sheep’s clothing" and "the great imitator." The initial symptoms are nonspecific and classically include rash, fever, and headache within two to fourteen days following tick exposure. Unlike many tick-borne diseases with a fairly insidious onset of symptoms, Rocky Mountain spotted fever can develop suddenly and, if left untreated, may be extremely serious. Fatalities can occur within eight days of symptom onset.

Therefore, early diagnosis is crucial to limit complications and fatalities. Because a truly reliable and rapid test is not available, diagnosis is most dependent on the clinical symptom profile and exposure history. Although Rickettsia may be cultured in blood, few laboratories perform this testing, testing takes time, and sensitivity is low in most cases. PCR and immunohistochemistry are available and can provide a more rapid and reliable result if performed on a biopsy specimen from the rash. However, not all patients have a rash, and sensitivity is compromised if therapy has been started. Serologic studies remain the criterion standard for confirming diagnosis, but the information is of value only retrospectively as it takes over a week to develop detectable antibodies in 85% of patients, and ideally Rocky Mountain Spotted fever should be treated within five days.

Other Tick-Borne Diseases in the United States

There are several other tick-borne diseases which have been reported in the United States including Borrelia miyamotoi infection, Colorado tick fever, ehrlichiosis, Heartland virus, Powassan disease, Rickettsia parkeri, STARI, tick-borne relapsing fever, tularemia, and 364D rickettsiosis. For additional information and discussion of these diseases, the reader is referred to the CDC website.

References


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