Tick-borne Infectious Diseases Abound

Recently, the Missouri Department of Health & Senior Services alerted physicians that tick-related infections, including ehrlichiosis, Rocky Mountain spotted fever (RMSF), & tularemia are higher than usual year-to-date for 2017. In particular, reports of RMSF & tularemia are 90% higher than previously, & ehrlichiosis reports are increased by 18%.

*Rickettsia rickettsii*, transmitted by the American dog tick, is the causative agent of RMSF. Symptoms begin with sudden onset of fever & headache 3-12 days after a tick bite. A rash occurs in 90% of RMSF cases, usually 2-4 days after fever onset. Classically, the rash begins as macules on wrists, forearms & ankles spreading to the trunk, palms, & soles. Diagnosis is by serologic testing for both IgM & IgG RMSF antibody. The antibody response may not be detected in the first 7-10 days of illness & treatment should not be delayed based on an initially negative result. PCR testing for RMSF is not reliable since the organism is predominantly found in endothelial cells & not circulating in peripheral blood.

Tularemia, caused by *Francisella tularensis*, has variable symptoms but usually manifests with fever, flu-like illness, & lymphadenopathy. Route of infection is likewise variable & may include tick bites, as well as cat bites & other animal exposures. Diagnosis is through serology (orderable as *Francisella tularensis antibody*) or by culture of blood or infected tissues, such as wounds or lymph nodes. Clinicians should notify the microbiology laboratory at the time of culture submission when tularemia is the suspected diagnosis, so that appropriate bacterial media can be utilized & precautions to avoid laboratory exposure to the organism can be taken.

Ehrlichiosis & anaplasmosis are closely related diseases caused by small, obligate intracellular bacteria, similar to rickettsia. *Ehrlichia chaffeensis* & *Anaplasma phagocytophilum* are the causative agents of ehrlichiosis & anaplasmosis, respectively. Transmission is through tick vectors *Amblyomma americanum* (Lone Star tick) or *Ixodes*, which is also associated with Lyme disease. Incubation period between tick bite & disease is generally 7 to 14 days.

Symptoms of ehrlichiosis/anaplasmosis are non-specific including fever, malaise, & headache however, secondary symptoms of anorexia, nausea, vomiting, diarrhea, & abdominal pain are more frequent in ehrlichiosis. Serious complications include hypotension, respiratory failure, meningoencephalitis, acute renal failure, & coagulopathy. Laboratory findings include leukopenia, thrombocytopenia, & elevated hepatic transaminases. CSF often shows elevated protein & pleocytosis, usually lymphocytes.

Recommended testing for ehrlichiosis/ anaplasmosis includes PCR & serology. Serology includes IgG & IgM antibody for both organisms (orderable as *Ehrlichia Antibody Panel*). Since both IgM & IgG antibodies may be negative in the first 7-14 days of infection, PCR is recommended for suspected acute disease (orderable as *Ehrlichia Detection PCR* & includes testing for both organisms). Of note, blood cultures do not detect these bacteria. Likewise, the examination of peripheral blood smears for ehrlichia/anaplasma morulae is very low yield (≤20%) & is unreliable as a diagnostic test.

Although Lyme disease, due to *Borrelia burgdorferi*, is the most common tick-transmitted disease in the United States, the reported incidence in Missouri is low (10 cases in 2016). Available testing for Lyme disease includes *Lyme total antibody*, which reflexes to Western blot confirmation when positive, as well as *Lyme PCR* for suspected acute infections.

Two new viruses, Heartland & Bourbon, have been discovered in Missouri & Kansas patients & are believed to be transmitted by tick bites. Symptoms may be non-specific including fever, anorexia & diarrhea with laboratory findings of leukopenia, thrombocytopenia & elevated liver transaminases.

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Although infections with these viruses are not thought to be widespread, both have resulted in mortality & the true incidence is unknown. Testing for Heartland & Bourbon viruses is currently investigational & available only through the CDC. The appropriate state health department must be contacted with case specifics to obtain testing (Missouri (573)526-4780 or Kansas (877)427-7317).

Specimen requirement for the orderable tests listed above is one red top tube for serology & one lavender or yellow top tube for PCR. Ticks should not be submitted for identification or testing.

**Annual Notice to Physicians for Laboratory Testing**

Saint Luke’s Regional Laboratories (SLRL) works to ensure compliance with all guidelines governing the submission of Medicare claims for laboratory services. This is to inform you that you need to be aware of the policies regarding medical necessity & Advance Beneficiary Notice (ABN) use, Medicare billing, CPT/HCPCS codes, Reflex Testing, Medicare National Limitation Amounts, & laboratory profiles that include a multichannel chemistry test or orderable multiple test results.

Medicare will only pay for tests that meet the Medicare definition of medical necessity. The Office of the Inspector General (OIG) wants to ensure that physicians order only medically necessary tests & that physicians know that the OIG may impose civil penalties on those who order otherwise. The OIG does recognize that a physician must be able to order any tests, including screening tests they believe appropriate for the treatment of their patients. Medicare may deny payment for a test that the physician believes appropriate but which does not meet the Medicare definition of medical necessity. In this case, the orders should be accompanied by a properly executed ABN.

SLRL does offer laboratory profiles that contain multichannel chemistry tests or other automated multiple test results. The individual components of these profiles & the corresponding CPT/HCPCS codes can be found in the on-line Lab Test Directory (see link information below) & on the back of the Saint Luke’s Regional Laboratories requisition. Customized panels & profiles should not be used. The Medicare Limitation Amount for each CPT/HCPCS code can be found in the Medicare National Limitation Amount reference supplied to physician’s offices by Medicare. Additional detailed information can be found with the on-line Lab Test Directory at [http://www.saintlukeshealthsystem.org/lab-test-directory](http://www.saintlukeshealthsystem.org/lab-test-directory).

**Leukocytosis and Circulating Blasts**

Leukocytosis, defined as elevated white blood cell (WBC) count >11 x 10^9/L is a relatively common finding with a wide differential diagnosis. In response to certain stressors, such as surgery, exercise, trauma, and emotional stress, leukocytosis can double within hours due to large bone marrow storage pool. Depending on the cell type contributing to leukocytosis, patient age and clinical presentation, the differential diagnosis can be benign or portend malignancy. Therefore, initial work-up of any patient with leukocytosis, must include review of WBC differential count.

Differential diagnosis of predominant neutrophilia (>7.0 x 10^9/L) includes infections, stress, chronic inflammation, and medication use. WBC count in the range of 50-100 x 10^9/L, sometimes referred to as leukemoid reaction may be seen in severe *Clostridium difficile* infection, sepsis, organ rejection, or in patients with solid organ tumors. Paradoxically some of the bacterial infections such as typhoid fever, rickettsial infection, brucellosis, and dengue may present as neutropenia. Leukocytosis >100 x 10^9/L, however are usually seen in leukemias or myeloproliferative disorders.

During the acute stage of many bacterial infections both mature and immature neutrophils, usually referred to as left-shift in maturation, may be present in the peripheral blood smear. However, presence of circulating blasts concurrent with other cell type abnormalities such as anemia and thrombocytopenia, may suggest a primary bone marrow pathology and should prompt hematology/oncology consult. In such patients, presenting clinical symptoms are usually chronic and may include fatigue, night sweats, weight loss, easy bruising, or bleeding.

Lymphocytosis (>5.0 x 10^9/L) similarly can be benign or malignant. Presence of a monomorphic lymphocytosis is usually suspicious for a neoplastic condition and requires further evaluation with a hematology/oncology consult and possibly flow cytometric analysis.

C. E. Essmyer, M.D.  •  S. Nanua, M.D., Ph.D.  •  G. Mathur, M.D., M.B.A.