A Farmer's Fear: Ehrlichiosis, a Tick-borne Disease

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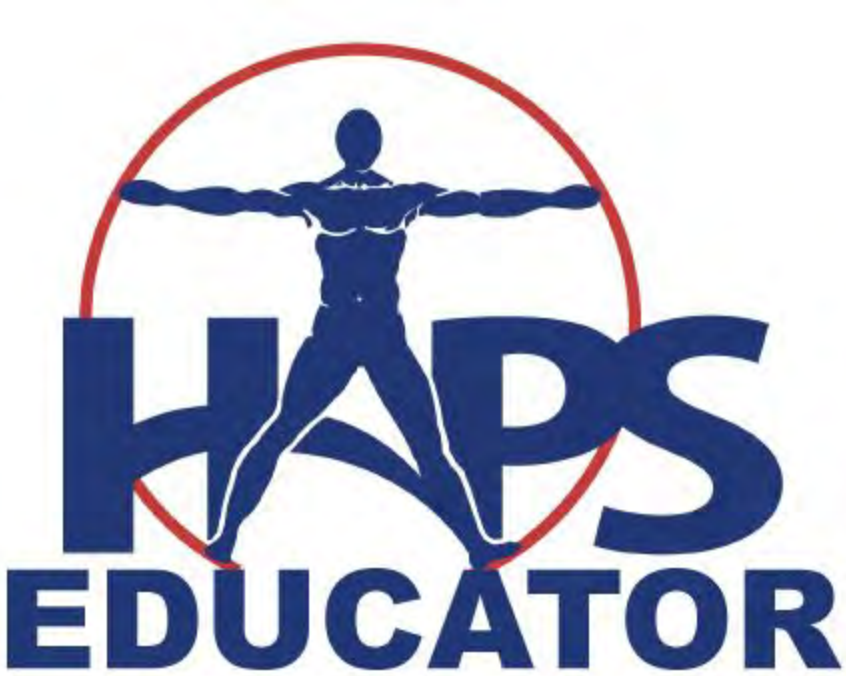

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Abstract
Ehrlichiosis (*Ehrlichia chaffeensis*), a bacterial infection transmitted by ticks, and its complications are examined here in a case-based learning approach. This case scenario describes a person who was bitten by a tick while farming and the complications they experienced. Students are presented with a patient case scenario that entails a detailed assessment of the patient's physical status, medical history, vital signs, laboratory values, and treatment methods so as to provide a complete picture of the pathophysiology of ehrlichiosis. This case scenario can be used to teach physiology or pathophysiology of infection and inflammation topics in clinical courses such as nursing, physician assistant, pharmacy, and other allied health programs.
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Key words: *Ehrlichia chaffeensis*, ehrlichiosis, pathophysiology, inflammation, infection, case-based learning

Introduction/Background
Teaching physiology to health professional students using lecture alone is not the most effective approach because students may find the subject vast, dry, and challenging due to innumerable factual details and complex mechanisms (Miller et al. 2013; Alaagib et al. 2019). Case-based learning (CBL), which utilizes clinical case scenarios to teach underlying physiological concepts, is a student-centered learning method that allows open-ended exploration of topics, encourages discussion, and offers a structured approach to clinical problem-solving (Srinivasan et al. 2007; Gade and Chari 2013). Compared to traditional lecture-based learning, CBL allows students to engage in learning activities, helps boost their confidence as well as test scores, and improves long-term memory (Latif 2014; McFee et al. 2018). The CBL method described here utilizes a team-based learning (TBL) strategy in order to promote peer interaction at multiple levels and enrich the students' learning experience (Gopalan and Kist 2018).

The development of ehrlichiosis, a tick-borne disease, was written for the advanced physiology course offered in professional year I of the pharmacy curriculum at the St. Louis College of Pharmacy. This course was a five-credit course that consisted of three components: lecture (3 credits), laboratory (1 credit), and case discussion (1 credit). The lectures were 50-minute meetings, three times per week, with approximately 250 students. The laboratory sections were limited to 20 to 24 students in a two-hour block, once a week, where students performed hands-on physiology experiments. The case discussion sections involved 24 students (subdivided into groups of four) for a weekly two-hour session. Each case discussion session focused on one key physiology topic that was addressed in the lecture. For example, during pulmonary physiology lectures, the clinical case scenario would pertain to a lung-focused pathophysiology such as asthma, chronic bronchitis, or pneumothorax.

The use of a clinical scenario during the case discussion session of the course allowed students to apply their knowledge for a better understanding of a selected physiology topic. The ehrlichiosis case study served as an example of the CBL method in teaching infection and inflammation topics. Before this case study discussion, students received a lecture on inflammation that covered the causes of inflammation, the characteristics of acute and chronic inflammation, cellular and chemical components associated with inflammation, and step-by-step details of events during inflammation (Hall and Hall 2021). In preparation for the case discussion, students in their respective groups were expected to complete a set of homework questions over a few days following the lecture. The homework questions allowed students to not only apply knowledge from the lecture but also to access resources they found helpful in answering these questions. An individual assessment (individual readiness assessment test) was administered immediately prior to the case discussion.

The following ehrlichiosis case scenario would be an excellent resource for immunology, microbiology, or pathology classes in a biomedical science program or in medicine, nursing, or other health-related professions. In conclusion, the ehrlichiosis case could serve as a resource and an example of CBL while teaching infection and inflammation topics in a student-centered teaching method.

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Objectives

At the end of ehrlichiosis case study session, students would be able to:

- differentiate ehrlichiosis and other tick-borne diseases such as Lyme disease and Rocky Mountain Spotted Fever.
- characterize the vectors responsible for the transmission of mentioned diseases, including the distribution and natural reservoir.
- list the methods utilized to diagnose ehrlichiosis.
- describe clinical manifestations of ehrlichiosis, including immune response and morbidity and mortality rate.
- differentiate the treatment choices for ehrlichiosis and, in particular, the first-choice antibiotics.

Classroom Management

The students learned the basics of tick-borne diseases in multiple forms: 1) during class, 2) while answering the questions for the homework portion of the CBL, and 3) when applying their knowledge by discussing and solving a clinical case scenario on the topic. The lecture on inflammation included discussing the types of inflammation, causes of inflammation and their consequences, cellular and molecular components associated with inflammation, signs and symptoms, diagnosis, and treatment options (Hall and Hall 2021).

The steps to be completed by instructors and students in preparation for and during a typical case-based discussion session are described below and summarized in Table 1.

Timeline	Instructor Activities	Student Activities
Preparatory Session a. Reading(s) b. Lecture(s) c. Homework assignment	a. Assign reading(s) b. Three 50-minute lecture sessions per week c. Release homework questions with a due date by the start of the case discussion session d. Create an individual quiz over homework questions	a. Complete reading assignment b. Attend lecture session c. Submit answers to homework questions before the start of the case discussion session d. Prepare for the homework-based quiz
In-class Case-Discussion Session a. An individual quiz	a. Review of quiz b. Release of case c. Review of case d. Case questions released	a. Complete an individual quiz b. Answer questions as teams and submit answers c. Engage in review of the case d. As groups, engage in organizing answers by discussing, using resources
Post-case Session	a. Grading of homework b. Assessment of team member participation in completing homework questions c. Grading of teams' answers pertaining to the case using a rubric	Receive graded answers with comments

Table 1. *Summary of Student and Instructor Roles in a Case Discussion Session*

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Homework

To prepare for the case discussion session, the instructor assigned homework questions (Appendix 1) as a group activity. These questions were designed to help review the background knowledge to complete the case study (quiz and in-class group questions). Students were given one week to complete homework questions and were expected to provide citations for the information submitted. The participation of all group members was expected. The students were expected to submit the completed assignment on the day of the case discussion before the scheduled session.

Case Session

To assess each student's readiness level, a five-question quiz (individual readiness assessment test; Table 2) was given before the case was presented. Subsequently, questions and answers were reviewed with the students. Upon reviewing the quiz questions, students assembled in their respective groups. Each group of four students was formed early in the semester and remained unchanged for the entire course (Gopalan et al. 2013). The groups were formed utilizing multiple factors such as GPA, gender, and ethnicity to create the most heterogeneous groups possible (Gopalan et al. 2013).

1. _____ Ehrlichiosis is a
   a. viral infection.
   b. bacterial infection.
   c. fungal infection.
   d. none of the above.

2. Match the disease with the common tick species vector:

_____ Rocky Mountain spotted fever	a. American dog tick
_____ Ehrlichiosis	b. Lone star tick
_____ Lyme disease	c. Black-legged tick

3. _____ Which test or physical sign might help the health professional to most quickly diagnose ehrlichiosis?
   a. Polymerase chain reaction
   b. Blood smear
   c. Complete blood count
   d. Wide-spread skin rash

4. _____ The first-choice antibiotic for the treatment of ehrlichiosis is?
   a. tetracycline
   b. penicillin
   c. amoxicillin
   d. amphotericin B
   e. doxycycline

5. _____ Which lab values pertaining to blood cells or components are frequently elevated or depressed in ehrlichiosis?
   a. Leukopenia
   b. Thrombocytopenia
   c. Anemia (decreased hemoglobin and hematocrit)
   d. All choices are correct

Quiz answers 1. B; 2. A, B, and C respectively; 3. B; 4. E; and 5. D.

Table 2. *Individual Readiness Assessment Test and Answers*

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A copy of the case was distributed, and the instructor provided a brief introduction to the case scenario. Once students reviewed the case, the in-class discussion questions were released to the students one at a time. The students were encouraged to discuss the questions, look up the answers using available resources (textbooks, homework, peer-reviewed journals), and provide answers in essay form. During this period, the instructor was available to answer any questions and provide guidance. Approximately 20 to 30 minutes was allocated to each in-class question. One student from each group was expected to submit their group's answers by the end of the case session, including citations used to complete this assignment (team readiness assessment test).

Background Information Related to the Case

Before solving the ehrlichiosis case, students were expected to be familiar with white blood cells, types of white blood cells, and their functions.

Pathophysiology of Ehrlichiosis

Ehrlichiosis is a tick-borne disease predominately found in the Midwest and Southern USA, especially during the summer season (Dumler and Bakken 1995; Dumler et al. 2007; Gangulya and Mukhopadhayay 2008). It is caused by *Ehrlichia chaffeensis*, a gram-negative, obligatory intracellular, cholesterol-dependent bacterium that is incapable of aerobic metabolism (Dumler and Bakken 1995; Gangulya and Mukhopadhayay 2008; Rikihisa 2015). This bacterium causes damage to the host's defense system and there are two types of ehrlichiosis based on the leukocyte type that is affected (Rikihisa 2015). If the bacterium invades monocytes (a non-granular leukocyte), the disease is called human monocytic ehrlichiosis (HME), and if the bacterium invades a neutrophil (granular leukocyte), the disease is human granulocytic ehrlichiosis (HGE) (Dumler et al. 2007; Gangulya and Mukhopadhayay 2008).

Although the exact mechanism by which *E. chaffeensis* causes the disease in the human host is not fully understood, it appears that binding of *E. chaffeensis* to the cell membrane of monocytes triggers remodeling of cytoskeletal structures in order to promote engulfment. Once they are within the cell, they alter vesicular trafficking to avoid delivery to lysosomes. Furthermore, it appears that *E. chaffeensis* uses mechanisms to prevent damage to itself and to host cells (Rikihisa 2015).

Clinical Manifestations

Clinical manifestations of this disease include gastrointestinal disturbances (nausea, vomiting, diarrhea), fever, myalgia, headache, malaise, and a wide-spread rash (~30% of cases, but the rash is a late finding); other findings include leukopenia (low leukocyte count), thrombocytopenia (low platelets), and elevated liver enzymes (Paddock and Childs 2003; Dumler et al. 2007). To be noted, the liver is frequently (~80%) involved in the disease, but other organs such as the heart, lungs, brain, pancreas, gastrointestinal tract, or kidneys may also be affected (Paddock and Childs 2003). Destruction in immunologic tissues such as the liver and the spleen results in low levels of leukocytes and platelets (Paddock and Childs 2003; Kumar et al. 2015; Abbas et al. 2018). Cardiovascular, respiratory, and central nervous system complications can be severe; especially, with HME, which carries higher morbidity and fatality rates (Dumler et al. 2007).

Because of the risk of severe consequences from waiting for the definitive diagnosis, treatment should not be delayed (Dumler et al. 2007; Huntington et al. 2016). When presenting this case, it should be emphasized that many tick-borne diseases have similar presentations, including influenza-like and nonspecific signs and symptoms such as fever, headache, malaise, and myalgias (Bratton and Corey 2005; Huntington et al. 2016). Ehrlichiosis can be diagnosed via blood smear testing (Schotthoefer et al. 2013; Bakken and Dumler 2015).

The Case Study

In July, Bill, a 60-year-old farmer in Missouri, went to the emergency department (ED) of a city hospital after being referred by a walk-in medical clinic's physician. An 18-gauge IV (intravenous) catheter was placed in his left forearm. A medical history was taken along with a physical examination and blood tests, as described below.

Bill's Medical History

- Childhood infections of measles and mumps.
- Immunizations are up to date, including tetanus shots.
- Arthritis.
- Patient reported frequent tick bites despite using preventive measures, such as protective clothing and repellents.
- Used to smoke about one pack of cigarettes for a period of 5 years. He quit smoking 30 years ago.
- Family history:

  Father died of lung cancer with a history of cigarette smoking.
- Medication

  Meloxicam 15 mg once a day

  Prednisone 5 mg once a day as needed

  Sulfasalazine 1000 mg once a day

  Simponi injection monthly

  Melatonin 5 mg every night as needed for insomnia.
- Allergies: No known drug allergies.

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Vital Signs

Objective Data	Vital Signs	Normal Values
Blood Pressure	**105/80** mm Hg	**120/80** mm Hg
Pulse Pressure	**25** mm Hg	**40** mm Hg
Heart Rate	**130** beats/minute	**60-100** beats/minute
Respiratory Rate	**36** breaths/minute	**12-18** breaths/minute
O_2 Saturation	**94%**	**95%** on room air (21% FiO_2)
Body Temperature	**39.4^0** C	**36.1^0 - 37.2^0** C
Body Mass Index	**33.1** kg/m^2	**18.5 - 24.9** kg/m^2
Height	**5' 10"**	5' 8" – 6'
Weight	**200 lb**	165 lb - 180 lb

Physical Assessment

Bill was alert, awake, and oriented to time, place, and location. Pupils were equal, round, and reactive to light and accommodation at 4 mm bilaterally. Pulses were present in all four extremities but were weak and rapid with a delayed capillary refill of three seconds. He was found to be febrile, dehydrated, and experiencing chills, malaise, and myalgia. He complained of anxiety, weakness, and headache but showed no signs of a rash. Breath sounds with some rales were noted. No heart murmurs were auscultated. Blood samples were obtained and sent to the laboratory.

Laboratory Data

Arterial blood gas (ABG) laboratory values

ABG values	Lab Results	Normal Values
ABG pH	Within normal limit	7.35-7.45
$PaCO_2$	Within normal limit	35-45 mm Hg
PaO_2	Within normal limit	80-100 mm Hg (21% FiO_2)
FiO_2	Within normal limit	21% FiO_2 (Room Air)

Venous blood laboratory values

Venous Values	Lab Results	Normal Values
Electrolytes: K^+, Cl^-, Na^+	K^+ **5.6** mEq/L Cl^- **97** mEq/L Na^+ **128** mEq/L	K^+ (3.5-5.0 mEq/L), Cl^- (95-105 mEq/L) Na^+ (135-145 mEq/L)
Troponin-I Level	**0.017** ng/L	**0.000-0.049** ng/L
Liver Function Test	ALT/SGPT **84** U/L AST/SGOT **111** U/L	ALT/SGPT (13-61 U/L) AST/SGOT (5-40 U/L)
Complete Blood Count (Hemoglobin, Hematorcrit, Platelets, WBC's with differential)	Hemoglobin **12.4** gm/dL Hematocrit **34.4**% Platelets cells/mcL **73,000** WBC cells/mcL **6700** Neutrophils **80**% Lymphocytes **1**%	Hemoglobin (13-18 gm/dL) Hematocrit (35.2-51.7%) Platelets (150,000-350,000 cells/mcL) WBC (5,000 -10,000 cells/mcL) Neutrophils (44-73%) Lymphocytes (2-8%)

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Diagnostic Data

12-Lead EKG	Sinus tachycardia 130 beats per minute
Chest X-Ray	Perihilar infiltrates per anterior posterior and lateral chest films
Blood Smear with Staining (Wright's)	Demonstrated no bacteremia per microscope slides
Blood Cultures	Pending
Antibody Titers for a Variety of Tick-borne Diseases	Pending

Diagnosis

The ED physician suspected that Bill had contracted a tick-borne disease. Titers for Rocky Mountain spotted fever, ehrlichiosis, and Lyme disease were drawn and were pending.

Care Plan

Supportive measures to reduce fever was initiated along with regular patient monitoring. Started gentle fluid hydration with continuous 0.9% normal saline at 125 mL/hr. Began doxycycline administration, a treatment of choice for ehrlichiosis and all other tick-borne rickettsial diseases. Doxycycline is most effective at preventing severe complications if started within the first week of illness. Transferred to the medical ward for close observation until the patient's condition stabilized. After discharge, continued doxycycline treatment and recommended follow-up with primary care physician.

Case Study Questions with Answers

1. Which symptoms, signs, and laboratory values are consistent with the diagnosis of ehrlichiosis and which ones are not?

Possible symptoms include generally feeling poor, a marked fever, headache, chills, weakness, gastrointestinal disturbances such as nausea, diarrhea, and rash (non-itchy). Also, the symptoms develop slowly over one to two weeks, but once the infection is established, it progresses quickly. To be noted, many of the tick-borne diseases have similar presentations. A tick-borne disease should be considered in an individual during the warmer months of the year when that person is manifesting nonspecific, influenza-like signs and symptoms such as fever, headache, malaise, and myalgias.

Thrombocytopenia, leukopenia (especially monocytes), and/or elevated liver enzyme levels are helpful predictors of ehrlichiosis, but may not be present in all patients depending on the course of the disease. After a diagnosis is made on clinical suspicion and treatment has begun, specialized laboratory testing should be used to confirm the diagnosis of ehrlichiosis. The PCR-based test results were positive for antibodies, which manifested later and confirmed the diagnosis in Bill.

Treatment should begin immediately based upon suspicion of a tick-borne illness. Early treatment with doxycycline (or tetracycline) may substantially lower morbidity and mortality, and many of the tick-borne diseases (Rocky Mountain Spotted Fever, Lyme disease, tularemia, etc.) are sensitive to this antibiotic as the first line of treatment. With regard to the current case, the physical exam ruled out myocardial infarction (no murmurs, normal 12-lead, and normal Troponin I). The fever was related not only to interleukins and/or immune response but also to the fact that this organism behaves like mitochondria, producing excessive ATP (adenosine triphosphate). The elevated fever drives the metabolic rate, which is readily supported with excessive ATP. Electrolytes and dehydration status need to be maintained within normal limits to avoid cell membrane potential disturbances. To be noted, while perihilar lung infiltrates are consistent with the diagnosis, the patient has normal arterial blood gases and pH. Thus, at this point, the infiltrates have not caused a ventilation-perfusion mismatch to the degree needed to make the values abnormal.

2. Which values of a complete blood count and differential are typically elevated or depressed with a tick-borne illness?

Although it varies from one tick-borne disease to another, the most common findings are decreased hematocrit due to hemolytic anemia, thrombocytopenia, leukopenia, elevated serum creatinine, and blood urea nitrogen values, and mildly elevated hepatic transaminase values.

3. What is the first choice of antibiotic for a tick-borne disease?

Doxycycline and tetracycline are the treatments of choice for anaplasmosis, ehrlichiosis, and spotted fever group rickettsioses. Treatment may begin as soon as they are clinically confirmed because any delay may result in severe illness and even death.

4. What is the probable cause of the elevated liver enzymes?

The liver is involved in >80% of all infected patients in ehrlichiosis. The underlying hepatic pathology is incompletely described and includes a variety of lesions ranging from focal hepatic necrosis to ring granulomas identical with those described in fever and cholestatic hepatitis. These findings suggest the induction of nonspecific mononuclear

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phagocyte activity and the potential for immunopathologic or cytokine-mediated hepatic injury as potential pathogenetic mechanisms. A few studies have described the microscopic pathological lesions and implied that the most dramatically involved organs are those of the mononuclear phagocyte system, especially the spleen, liver, bone marrow, and lymph nodes. Many other organs have perivascular lymphohistiocytic infiltrate, reflecting the systemic distribution of the infection, immune and inflammatory responses of the host, or a response to tissue injury due to the variable hemodynamics sometimes seen with ehrlichiosis (Ismail et al 2012). Immunohistologic studies have demonstrated that *E. chaffeensis* can establish infection in many organs and tissues; this characteristic is determined only by the presence of an appropriate phagocytic host cell. The lung is also a frequent target demonstrating interstitial pneumonitis, pulmonary hemorrhage, and diffuse alveolar damage with organizing pneumonia.

Conclusions

In summary, this case study can teach physiological and pathological concepts associated with bacterial infections transmitted by ticks. Students would be able to connect this case with what they have learned about inflammation, such as causes of inflammation and specific signs and symptoms associated with it. While becoming familiar with clinical terminology, students would be able to apply their knowledge of infection and inflammation by working on an ehrlichiosis case study with their group members.

About the Authors

Dr. Chaya Gopalan is a professor in the departments of Applied Health and Nurse Anesthesia at Southern Illinois University Edwardsville. She received her Ph.D. from the University of Glasgow, Scotland. She has been teaching anatomy, physiology, and pathophysiology at graduate and undergraduate levels. Dr. Gopalan practices evidence-based teaching using team-based learning, case-based learning, and the flipped classroom methods. She has received many teaching awards, including the Arthur C. Guyton Educator of the Year award from the American Physiological Society and the Outstanding Two-Year College Teaching award by the National Association of Biology Teachers.

Nhan Nguyen, RN, BSN is a candidate for Doctor of Nursing Practice specializing in Nurse Anesthesia at Southern Illinois University Edwardsville. He has served as a teaching assistant for the students in the Advanced Human Physiology course for the Doctor of Nursing Practice specializing in Nurse Practitioner program and the Biology of Cardiovascular and Metabolic Diseases course in the Exercise Science program.

Dr. William Kist is a physiology professor with strong clinical skills in respiratory physiology. He has written and published several cases as a way to teach physiology to students in the healthcare professions.

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APPENDIX: Homework Questions and Answers

1. Compare and contrast the diseases Rocky Mountain spotted fever, Lyme disease, and ehrlichiosis in adults on signs, laboratory values, and symptoms. (reference for answers is Bratton and Corey 2005: 2325)

Tickborne Disease	Signs and Symptoms	Lab tests
Rocky Mountain spotted fever	Fever, headache, nausea, vomiting, nonproductive cough, sore throat, pleuritic chest pain (sudden sharp pain), abdominal pain, and petechial rash (small purple or red rash) affecting pads and soles of feet, malaise (uneasiness), and myalgias (muscle soreness)	Skin biopsy of rash (60 percent sensitive); routine findings include thrombocytopenia (less than normal number of thrombocytes) and hyponatremia (less than normal sodium ion in the blood)
Lyme disease	**Stage 1** (early localized): erythema migrans rash (expanding rash) at the site of the bite, flu-like symptoms, fever, fatigue, arthralgias (joint pain), headache, cough, lymphadenopathy **Stage 2** (early disseminated): secondary cutaneous annular lesions, fever, adenopathy, central nervous system symptoms; possible cough and pharyngitis **Stage 3** (late chronic): arthritis, central nervous system impairment, dermatitis, keratitis, neurologic, and myocardial abnormalities	Not helpful
Ehrlichiosis	Flu-like symptoms, fever, chills, cough, malaise, headache, and myalgia; macular, maculopapular, or petechial rash (rare with human granulocytic ehrlichiosis)	Leukopenia, thrombocytopenia, and elevated serum transaminase levels; diagnosis made during the gradual recovery

2. Characterize and explain the tick vectors that are responsible for the transmission of these above diseases. What is the natural reservoir throughout the Midwest for these above diseases/organisms?

Children five to nine years of age have the highest incidence of Rocky Mountain spotted fever. A tick bite is recalled in 50 to 70 percent of patients. Rocky Mountain spotted fever is the most common rickettsial disease caused by *Rickettsia rickettsii* in the Midwest. Its reservoirs include small mammals such as rodents and rabbits, and dogs. Lyme disease is the most common vector-borne infectious disease in the United States. It is caused by the spirochete *Borrelia burgdorferi*. Vectors for this disease are black-legged or deer tick (*Ixodes scapularis*). The main reservoir for *B. burgdorferi* in the Midwest is the white-footed mouse. The larvae and nymphs of the tick feed on the white-footed mouse and become infected. Adult ticks or, more commonly, nymphs may then infect humans.

Human ehrlichiosis has been reported in the United States with two identifiable subtypes. Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis*, and human granulocytic ehrlichiosis (HGE) is caused by Anaplasma phagocytophilum (formerly called *Ehrlichia equi* or *Ehrlichia phagocytophila*). The two subtypes are clinically indistinguishable but epidemiologically distinct. HME occurs most frequently in the south-central and southeastern United States. It occurs year-round, with the highest incidence in June and July. In contrast to Lyme disease and Rocky Mountain spotted fever, HME typically affects adults. *E. chaffeensis* is found in *Amblyomma americanum* (lone star tick) and *D. variabilis* (dog tick). The white-tailed deer is the principal animal reservoir.

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3. Describe the general immune response to a bacterial invasion including the inflammatory response.

The immune response defends the host from bacterial invasion by using both innate and adaptive immune mechanisms. The innate immune response is the immediate response to infection. Pathogen-associated molecular patterns include bacterial lipopolysaccharides that bind to pattern recognition receptors on special immune cells such as macrophages and dendritic cells and turn on the inflammatory response.

In response to infection, one of the first groups of cells to respond are mast cells that release histamine. Histamine and other chemical agents released by the cells at the site of infection act on endothelial cells to increase capillary permeability so that more phagocytic leukocytes and plasma proteins crucial to the defense are recruited to the site of infection. Almost immediately, arterioles and capillaries within the area dilate, increasing blood flow to the site of infection. Local (resident) macrophages immediately begin to phagocytose foreign microbes, defending against infection during the first hour. Resident macrophages also secrete chemical mediators, which help recruit more leukocytes to the area. The recruited leukocytes are now activated by local chemical mediators, and these activated leukocytes tend to remove infectious agents and cellular debris by phagocytosis.

The leaked plasma proteins include clotting factors. On exposure to tissue thromboplastin in the injured tissue, fibrinogen, the final factor in the clotting system, is converted into fibrin. Fibrin forms clots in the spaces around the bacterial invaders and damaged cells. The walling off of the injured region from the surrounding tissues prevents or at least delays the spread of pathogens and their toxic products. The activation of the innate immune system ultimately turns on the adaptive immune system.

Dendritic cells process the antigen and present it to the helper T cells. Naïve B lymphocytes may also process the pathogen and receive secondary signals from the helper T cells to differentiate into plasma cells and secrete antibodies. Acute-phase proteins such as complement proteins are activated by innate and adaptive immune mechanisms, which help promote opsonization and phagocytosis. The production of antibodies by the antibody-mediated immune system also uses opsonization and phagocytosis in addition to neutralization, precipitation, and other mechanisms to combat infection. Opsonized bacteria are engulfed and destroyed by phagocytes using mechanisms turned on by both antibody-mediated and cell-mediated immunity.

4. What is the physiological connection between some tick-borne infections and mitochondria?

Studies have shown that the host's immune cells will generate reactive oxygen species (ROS) in response to some tick-borne infections. The predominant generator of ROS within the cells are the mitochondria. High levels of ROS create a toxic environment that can lead to damage of DNA, protein, and lipid and turn on the NF-kB pathway, which triggers the production of pro-inflammatory cytokines resulting in excessive inflammation and tissue injury (Peacock et al. 2015).

5. How is the diagnosis of tick-borne illness confirmed? That is, which molecular biology technique is most useful in the differential diagnosis? Briefly describe the crux of how the technique works.

Diagnostic tests include (a) examination of peripheral blood smears; (b) immunohistochemical staining of an organism from the skin, tissue, or bone marrow biopsies and (c) detection of DNA by PCR of whole blood. The PCR method uses specific oligonucleotide PCR primers based on nucleotide sequences of the pathogen and is very sensitive during the first week of illness. Sensitivity may decrease after tetracycline-class antibiotics treatment. Presence of morulae in the cytoplasm of granulocytes during the examination of blood smears is highly suggestive of a diagnosis.

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6. Explain the general process of infection by ticks.

Ticks transmit pathogens that cause disease through the process of feeding. Depending on the tick species and their stage of life, preparing to feed can take ten minutes to two hours. When the tick finds a feeding spot, it grasps the skin and cuts into the surface. The tick then inserts its feeding tube. Many species also secrete a cement-like substance that keeps them firmly attached during the meal. The feeding tube can have barbs that help keep the tick in place. Ticks can also secrete small amounts of saliva with anesthetic properties so that the animal or person cannot feel that the tick has attached itself.

If the tick is in a sheltered spot (e.g., pubic region and hair) on the body, it can go unnoticed. A tick will feed on the blood slowly for several days. Small amounts of saliva from the tick may also enter the skin of the host animal during the feeding process. If the tick contains a pathogen, the organism may be transmitted to the host animal in this fashion. After feeding, most ticks will drop off and prepare for the next life stage. *Ehrlichia chaffeensis*, whose natural reservoir is the white-tailed deer, is generally transmitted to humans by the lone star tick (common in the state of Missouri).

7. Are different stages of the life cycle of ticks important/relevant to the infection process?

Most ticks go through four life stages: egg, six-legged larva, eight-legged nymph, and adult. After hatching from the eggs, ticks must ingest blood from a host body at every stage to survive. Thus, ticks can take up to three years and require several host bodies to become adults and complete their full life cycle; most die because they do not find a host for their next feed.

8. What is the morbidity and mortality rate of untreated tick-borne illnesses?

Certain types of tick-borne illnesses can cause deadly complications. Rocky Mountain spotted fever is the deadliest tick-borne disease in the world. Untreated Rocky Mountain spotted fever can cause damage to blood vessels, leading to organ and tissue injury (Centers for Disease Control and Prevention 2018).

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