Human Granulocytic Anaplasmosis

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KEYWORDS
- Anaplasmosis • Ixodes • Deer tick • Tick-borne • Leukopenia • Thrombocytopenia
- Doxycycline

KEY POINTS
- Anaplasmosis is transmitted by the bite of Ixodes ricinus complex ticks, which includes the black-legged or deer tick (Ixodes scapularis) in north central and eastern North America, and the western black-legged tick (Ixodes pacificus) in western North America.
- Symptoms of anaplasmosis include fever, headache, malaise, loss of appetite, and aches.
- Illness can be mild and self-limited or progress to severe illness and death, particularly in older individuals and those with comorbid conditions.
- Laboratory findings may include leukopenia, thrombocytopenia, and elevated hepatic transaminases.
- The probability of anaplasmosis increases with a history of Ixodes tick/habitat exposure and the presence of typical symptoms and can be confirmed with polymerase chain reaction testing.
- A patient with compatible illness and epidemiologic exposures should be treated with doxycycline. Continue treatment if they improve while on doxycycline, regardless of confirmatory test results.

INTRODUCTION

Human granulocytic anaplasmosis (HGA) is a vector-borne bacterial infection caused by Anaplasma phagocytophilum. It has one of the most rapidly increasing incidences of tick-borne infections in the United States.1 It is transmitted to humans when infected nymphal or adult Ixodes ricinus complex (black-legged or deer) ticks take a blood meal.2 These ticks are found in north central and eastern North America and the West coast of North America. Related I ricinus complex ticks transmit HGA in much of Eurasia and eastern Asia. In the United States, HGA was first described in 1994 in the upper Midwest3,4 and then in multiple areas of the Northeast.5,6 The illness was initially known as human granulocytic ehrlichiosis because the pathogen was named Ehrlichia phagocytophilum at the time. Subsequent work involving 16s rRNA
gene sequences led to realignment of families in the order Rickettsiales and renaming of the bacteria as Anaplasma phagocytophilum. Members of the genera Anaplasma cause infections in humans and animals. In addition to HGA, A phagocytophilum causes canine and equine granulocytic anaplasmosis, and tick-borne fever in cattle and sheep.

BACKGROUND

A phagocytophilum is an obligate intracellular gram-negative bacterium in the order Rickettsiales, family Anaplasmataceae. It multiplies in vacuoles called morulae in the cytoplasm of mammalian host neutrophils. In tick vectors, the organism initially lives in cells of the midgut and then migrates to salivary glands where it develops. A phagocytophilum has been found in the salivary glands of infected ticks that have yet to begin a blood meal, suggesting the possibility of faster transmission than occurs with other organisms, such as Borrelia burgdorferi.

A phagocytophilum is able to interfere with molecular pathways in both tick and host cells to evade the immune response in each. This allows the organism to infect tick midgut cells, evade mammalian host cell defenses, and cause infection.

There are distinct genetic variants of A phagocytophilum that have specificity for the host in which they are maintained, and for the type of host in which they cause infection. In North America, genetic variant Ap-ha, which causes HGA in humans, is maintained in a white-footed mouse (Peromyscus leucopus) and Eastern chipmunk (Tamias striatus) reservoir. Ap-V1, which is found in white-tailed deer (Odocoileus virginianus), is not pathogenic to humans. An abundance of Ap-ha–infected host-seeking ticks in the environment is predictive of human anaplasmosis case distribution and incidence based on data from New York State (Melissa Prusinski, personal communication, January 5, 2022) and other parts of eastern North America.

VECTOR-BORNE TRANSMISSION

A phagocytophilum is transmitted primarily by the bite of I ricinus complex ticks. It is important to be familiar with the range of these ticks in order to assess a patient’s risk for acquiring HGA. In the eastern and Midwest United States and south central and south eastern Canada, the vector is Ixodes scapularis, commonly called the black-legged (deer) tick. In the western United States and Canada, it is Ixodes pacificus. Throughout much of the United Kingdom and Eurasia, I ricinus is the vector I persulcatus is the vector in Japan, Korea, and eastern portions of Russia and China.

I ricinus complex ticks are not infected as larvae by transovarial transmission. Instead, larval and nymph forms of these ticks may acquire A phagocytophilum when they take a blood meal from an infected host. These ticks feed and acquire a blood meal over the course of several days during the same “bite.” Mammalian models suggest that 24 hours or more of tick attachment is needed to transmit enough A phagocytophilum to cause an infection in hosts. I ricinus complex ticks required at least 2 days of feeding to cause symptomatic tick-borne fever owing to A phagocytophilum in sheep. Infected I ricinus ticks that fed on dogs began transmission of A phagocytophilum within hours, but more than 48 hours of feeding was needed to transmit a sufficient inoculum of the organism to cause infection. Depending on the study, nymphal I scapularis ticks that fed on mice typically required 24 to 48 hours to transmit A phagocytophilum to the mouse. Some models showed the presence of A phagocytophilum DNA in hosts after feeding by infected ticks in less than 24 hours, but those hosts did not develop antibodies against A
phagocytophilum. This suggests that insufficient inoculum had been transmitted to cause infection during more brief feeding periods.

**BLOOD TRANSFUSION AND ORGAN TRANSPLANT–RELATED TRANSMISSION**

HGA can be transmitted by both red blood cell and platelet transfusion as well as organ transplantation. Several transfusion–related cases have been reported, including some that were fatal. A review of the cases that occurred between 1997 and 2020 identified 10 transfusion–related cases of HGA and 7 solid organ transplant–related cases. The blood supply is not screened for HGA. Leukoreduced blood units may reduce, but not eliminate, the risk of transfusion–related HGA.

**EPIDEMIOLOGY**

HGA is an emerging disease in parts of North America, East Asia, and Eurasia. The geographic range of HGA and overall incidence are increasing. The rate of increase is higher than has been seen with other tick–borne infections, and it is estimated that the actual number of cases may be 11 times higher than is reported by public health departments. Seroprevalence of antibodies against *A phagocytophilum* in asymptomatic humans varies by region and exposure type. They were found in 36% of forest workers in Poland, 14.9% of northwestern Wisconsin residents with no known preceding tick bite, and 23% of potential organ donors in Manitoba, where the presence of *I scapularis* had only recently been described.

This increase in HGA cases is multifactorial. Elias and colleagues postulated that case recognition and testing for HGA in individuals with compatible illnesses have increased because of better public and clinician awareness of HGA as well as widespread availability of accurate molecular testing. Other factors include the increased population density and range of *I ricinus* complex ticks, and new areas in that range that questing ticks carry *A phagocytophilum*. For example, in New York State, the percentage of adult *I scapularis* (black-legged or deer) ticks that were positive for *A phagocytophilum* increased from 4.0% to 9.2% (P<.01%) between 2010 and 2018. In eastern New York State, adjacent to HGA endemic areas of New England, the proportion of ticks carrying *A phagocytophilum* increased fourfold during that time. *I scapularis* has been present in many of those areas for years but did not previously transmit *A phagocytophilum*. A similar lag was seen between the time when *I scapularis* populations were established on coastal Maine islands and when *B burgdorferi* was detected in those ticks.

There is a temporal pattern of infection related to timing of tick exposure. Infec-
tion is most common in ticks and subsequently in humans in late spring and early summer when nymphal *I scapularis* and *I pacificus* ticks are most active (Fig. 1). Most reported cases in New York State that occurred between 2010 and 2018 were reported in May, June, and July. This coincides with peak abundance and activity of *I scapularis* nymphs, which cause most human infection. However, HGA should be considered whenever *I ricinus* complex ticks are active. Adults may be present in early spring and fall and during the winter if there is not heavy snow cover and temperatures climb above freezing. Cases of HGA that present outside of peak tick season may be more likely to have a delay in diagnosis.

Older white men are at highest risk of infection, possibly because of behavioral factors that increase risk of exposure. More problematic symptoms are common in older age, and infection may be unrecognized in young and otherwise healthy individuals. Russell and colleagues reported that 63% of reported cases in New York State were in those over age 50 years.
More severe cases have been associated with age over 75 years, higher neutrophil count, lower lymphocyte count, anemia, detection of morulae in neutrophils, immunosuppression, chronic inflammatory illnesses, and underlying malignancy.57–59

**HUMAN INFECTION**

The incubation period of HGA is 5 to 14 days after a tick bite.1 HGA symptoms range from minimally symptomatic to fulminant, including sepsis and death.60 The illness is often mild and self-limited,1 which makes it difficult to know the true prevalence of infection. Most case series included a preponderance of cases that were severe enough to require hospitalization, so the available data may represent symptoms and complications seen in more severe cases.

**SYMPTOMS**

The symptoms and presentation of HGA are nonspecific and may not differentiate it from other infections. Symptoms include fever (92%–100%), malaise (97%), myalgia (77%), headache (82%), and anorexia61 (Table 1). The headache can be severe enough to lead to lumbar puncture, but cerebrospinal fluid is normal. In patients unable to give a history, caregivers may report malaise or loss of interest in usual activities and decreased appetite.

One series reported that 76% of patients in a mix of inpatients and outpatients with HGA also had respiratory or gastrointestinal symptoms.62 When focal symptoms are prominent in HGA, the correct diagnosis may be delayed. For example, several cases...
of HGA with respiratory symptoms, hypoxia, and imaging findings of interstitial pneumonitis have been reported. A case in France presented as acute respiratory distress syndrome. Others have presented with prominent abdominal pain. If gastrointestinal symptoms are prominent, the initial diagnostic focus may be on an underlying abdominal disorder. As an example, a patient with abdominal pain, transaminitis, and fever underwent cholecystectomy for presumed acute cholecystitis before HGA was diagnosed (Robert Smith, personal communication, January 1, 2022).

Most reported cases of HGA in the literature have been in adults. Children are commonly infected as well, but case reports are few. Pediatric infection may be asymptomatic or cause a mild, self-limited illness in younger people. Symptoms in children are similar to those in adults but may be more likely to include abdominal pain.

**PHYSICAL EXAMINATION**

There are no physical examination findings that help make the diagnosis of HGA. Fever and muscle or joint tenderness without synovitis may be present. Rash is uncommon, present in 6% of patients who were diagnosed by polymerase chain reaction (PCR). A description of the rashes seen in HGA are not readily available. However, a 14-year-old patient in Slovenia with HGA had a maculopapular rash on the trunk and neck. Rash may be an epiphenomenon related to systemic infection and inflammation.

**EVALUATION**

When evaluating a patient for HGA, it is important to ask about outdoor exposure or contact with outdoor companion animals to gauge their probability for tick exposure. The lack of a known tick bite does not rule out HGA, as the bite often goes unnoticed. In one case series, less than two-thirds recalled a bite. In nonendemic areas,
consider HGA in people who become ill after traveling to an area where it is endemic or emerging. Complete blood count may reveal leukopenia and thrombocytopenia with occasional anemia. Depending on the case series, leukopenia was present in 47% to 71% of cases, thrombocytopenia in 61% to 91%, and anemia in 6% to 44%. Metabolic panels may show elevated hepatic transaminases in 63% to 98% of cases. These abnormalities may not be present at the same time and not always at the time of initial evaluation. Bakken and colleagues described a fluctuating course of leukopenia, anemia, and thrombocytopenia that varied during the course of illness and resolved with effective antibiotic treatment. They observed that leukocytosis or thrombocytosis in a patient with symptoms for less than a week was unlikely to have HGA. Blood cell and platelet level changes in HGA are due to increases in specific proinflammatory cytokine levels that impact hematopoiesis. Elevated C-reactive protein is typically seen during this and many febrile illnesses.

These blood findings are nonspecific and occur in many viral and bacterial processes. They support the possibility of HGA in a patient with a compatible illness and epidemiologic exposure. They may also resolve spontaneously during the course of illness so if they are absent and symptoms are present for more than a week, HGA remains on the differential diagnosis.

Children with HGA are less likely to have telltale laboratory findings. In children with confirmed or probable HGA, 33% had elevated hepatic transaminases, 24% had leukopenia, and 17% had thrombocytopenia.

Confirmatory blood testing is best accomplished with PCR for the presence of *A. phagocytophilum* nucleic acid. PCR was found to have 74% sensitivity and 100% specificity, whereas antibody seroconversion had a sensitivity of 32% and specificity of 97% in a series in France. PCR may have a delayed turnaround time in locations where it is a send-out test.

Empiric coverage of HGA is appropriate in ill patients whereby the diagnosis is suggested while awaiting confirmatory results. A rapid symptomatic response is expected and can be a helpful clue to the cause of illness even before a PCR result has returned.

A Wright-Giemsa–stained blood smear can also be used to detect morulae in neutrophils. Reports in severely ill patients showed diagnostic blood smears in only 25% to 60% of cases, so it is not useful in ruling out HGA. It is also labor intensive and requires expertise in staining and smear preparation. A group of pathologists determined that one would need to review 200 granulocytes to detect morulae in their series of 14 hospitalized patients with confirmed HGA.

Acute and convalescent titers that show a fourfold increase are also confirmatory if PCR is not available. Serology may miss some mild cases and overdiagnose others because of cross-reactivity of antibodies. Immunoglobulin G antibodies will persist for years after HGA infection, so they are not helpful to recheck after treatment as proof of cure.

Turbett and colleagues used a complete blood count–based strategy to rule out HGA without PCR testing during acute illness. When they combined a white blood cell count greater than 11,000 and a platelet count greater than 300,000, they rejected performing PCR testing for 25% of true negative (by PCR) HGA cases and 3 (5%) of true positive cases. In the true positive group of 3 patients, 1 patient had a history of splenectomy and another patient had chronic lymphocytic leukemia with a baseline leukocytosis. They implemented a testing stewardship criterion to reject PCR testing for HGA if the white blood cell count was greater than 11,000, the platelet count was greater than 300,000, and the patient was not critically ill or immunocompromised. In the outpatient setting, consider obtaining a complete blood count before proceeding...
to PCR testing. This would be particularly safe if empiric treatment of HGA was used concomitantly.

In those with HGA, it is worth considering coinfection with Lyme or babesiosis. Black-legged ticks transmit *B burgdorferi*, which causes Lyme infection, and *Babesia microti*, which causes babesiosis. In a group of patients in New York State who presented with erythema migrans rash owing to *B burgdorferi* infection, between 2.3% and 10% also met diagnostic criteria for HGA, depending on the criteria used.78

**OUTCOMES**

Early literature suggests that 36% of HGA infections required hospitalization,59 and 17% of admitted patients needed critical care.57 Deaths occurred in less than 1% of patients.59,79 In patients with HGA in the United States reported to the Centers for Disease Control and Prevention between 2008 and 2012, the fatality rate was 0.3% and the hospitalization rate was 31%.80

More recently, a series of 33 patients diagnosed by PCR in Massachusetts showed that 42% were hospitalized, one required critical care, and none died.62 In this series, the average age of admitted patients was 64 years, whereas the mean age for those who did not need admission was 53 years (P = .04). The severity of thrombocytopenia was associated with need for admission, whereas the degree of leukopenia was not. Thirty-five percent of patients in a series of all HGA cases reported in New York State between 2010 and 2018 were hospitalized, and 0.5% died.51 Delay in diagnosis is correlated with increased length of stay in hospitalized patients with HGA.56

In a small case series of pediatric cases with probable or confirmed HGA, 7% of patients required hospital admission, and there were no fatalities.72 Data in pregnancies complicated by HGA infection also suggest excellent outcomes. There was only 1 case of perinatal transmission in a case series of 6 pregnant women who were diagnosed by PCR and treated with doxycycline or rifampin. There were no adverse outcomes for the pregnancies or for those women and their children in the following 21 months.81

There are no reports of relapse or longstanding infection after HGA treatment.

**COMPLICATIONS**

Evidence of end-organ damage may be present in severe cases, including acute kidney injury, rhabdomyolysis, and multiorgan failure.82,83 There are 2 reports of nontraumatic splenic rupture in patients with HGA.84,85 There are reports of pancreatitis86 and secondary hemophagocytic lymphohistiocytosis that complicate the infection.87

Focal neurologic manifestations are rare and should lead to consideration of another diagnosis or coinfection. There is 1 report of meningoencephalitis (and a facial nerve diplegia) putatively owing to *A phagocytophilum*.88 This is in contrast to human monocytic ehrlichiosis owing to *Ehrlichia chaffeensis*, which more commonly causes central nervous system infection.89 There are cases of HGA that presented with stroke symptoms that did not have evidence of CNS infection or imaging suggestive of stroke.56 One patient with stroke symptoms and HGA had brain imaging that showed basal ganglia infarct (but no evidence of CNS infection)90 and one with bilateral subarachnoid hemorrhage but no evidence of CNS infection.91 Other neurologic manifestations are reported rarely, including postinfectious brachial plexopathy.92 In severe cases involving the elderly or compromised hosts, transient encephalopathy from HGA is common.
TREATMENT

Doxycycline is the treatment of choice for HGA in all patients (Table 2). Empiric treatment for seriously ill patients with suspected HGA should be initiated while pending confirmatory testing. Doxycycline is also appropriate for treatment of HGA in children. The 2021 Report of the Committee on Infectious Diseases of the American Academy of Pediatrics (Red Book) now recommends doxycycline for the treatment of children of all ages with HGA.93 Tetracycline has been associated with discoloration of teeth and enamel hypoplasia in children under 8 years of age, but this is not seen with short courses of doxycycline.94 Doxycycline is taken at a dose of 2.2 mg/kg every 12 hours by mouth. The maximum dose is 100 mg every 12 hours, as in adults. There is a liquid formulation of doxycycline available for those who cannot swallow pills.

As with treatment in children, doxycycline is the treatment of choice during pregnancy. This has evolved with more safety data in young children, recognition of potential severe outcomes with suboptimal treatment of HGA in pregnancy, and a systemic review that did not show adverse effects with doxycycline use during pregnancy.95 High-dose tetracycline therapy had been associated with acute fatty liver in pregnancy,96 but this has not been reported with doxycycline treatment.1

In children, treatment is continued for a minimum of 72 hours after resolution of fever, although the standard course in children is 5 to 7 days and in adults is 7 to 10 days.1 If there is a strong suspicion for HGA, based on potential *Ixodes* complex tick exposure and a compatible illness that improves with doxycycline, and no alternative diagnosis made, a full course of doxycycline should be completed per CDC recommendations.1 In those who have allergic reaction or severe intolerance to doxycycline, rifampin is the treatment for HGA. Krause and colleagues97 reported successful treatment of HGA in children with rifampin for 5 to 7 days. Dhand and colleagues81 reported success in using rifampin to treat pregnant women with HGA. In children, rifampin is taken at a dose of 10 mg/kg every 12 hours up to a maximum of 300 mg per dose. This is the adult dose as well. Like doxycycline, it is taken by mouth. Intravenous formulations are available if medications cannot be taken by mouth or absorbed via the gastrointestinal tract.

In vitro data show favorable minimal inhibitory concentrations attained against *A phagocytophilum* for doxycycline and rifampin but not ampicillin, ceftriaxone, azithromycin, or trimethoprim-sulfamethoxazole.98–100 In vitro susceptibility to levofloxacin and ciprofloxacin has been demonstrated. However, there are reports of relapse

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<td>Doxycycline</td>
<td>Adults</td>
<td>100 mg twice a day</td>
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<td>Doxycycline</td>
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<td>100 mg twice a day</td>
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<td>Doxycycline</td>
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<td>2.2 mg/kg every 12 h</td>
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<td>Rifampin</td>
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Data from Refs.1,81,93,97
and possible inducible resistance when levofloxacin was used to treat HGA.\textsuperscript{101} Fluoroquinolones are not recommended treatment options for HGA.

If rifampin or courses of doxycycline are limited to less than 7 days, closer symptom monitoring during and after treatment should be undertaken. Rifampin is not active against \textit{B burgdorferi}. If it is used for HGA and coinfection with Lyme is suspected, a second agent should be added to treat Lyme.

Doxycycline can cause side effects, including profound anorexia and nausea, which is not an allergic reaction but can lead to poor compliance. These symptoms can be mitigated by eating a small meal before taking each dose of the medication. Doubly positive cations, such as calcium and magnesium, decrease its absorption. Separate its use by 2 hours from dairy products and vitamins that contain them. Doxycycline can also cause severe photosensitivity reactions, including a blistering rash, and therefore, direct sunlight should be avoided and sunscreen used along with sun-protective clothing to prevent this reaction. Rifampin has several drug-drug interactions that should be checked before it is used.

PREVENTION

There has not been a study of antibiotics after tick bite to demonstrate efficacy to prevent HGA. There is not a vaccine to prevent HGA in humans. Given an expected 24 hours’ time from bite to transmission, development of an “anti-tick” vaccine could theoretically become a tool to prevent HGA.\textsuperscript{102}

Preventing tick attachment and removing attached ticks after spending time in black-legged tick habitat are key to preventing tick-borne infections. This includes brief exposure to wooded or brushy areas with leaf litter on the ground and can include yards in urban and suburban settings. Prevention of attachment can be accomplished by tick repellents such as DEET or permethrin,\textsuperscript{103} use of long sleeves and long pants while outdoors, and modification of habitat around high-use areas.

As previously discussed, \textit{A phagocytophilum} transmission occurs more rapidly from tick vector to host than \textit{B burgdorferi} transmission. However, daily tick check and removal after outdoor exposure are probably sufficient. The bigger issue is remembering to do the tick check, particularly when outdoor exposure has been minimal. An equally challenging issue is finding minuscule immature ticks during a tick check. Carefully explore the whole anatomy and consider using a magnifying glass. Tick removal is best carried out with either a twisting device or a tweezer at the base of the tick where it attaches to the skin and applying slow gentle pressure over 1 to 2 minutes until the tick releases.\textsuperscript{104}

Testing black-legged ticks removed from patients for human pathogens could yield misleading results and is not recommended. Nonhuman disease-causing genetic variants of \textit{A phagocytophilum} have been identified in \textit{I ricinus} complex ticks removed from humans\textsuperscript{105} and could return a false positive result. The presence of pathogenic bacterial genetic material in a tick does not mean the organism was transmitted to the human host from which it was removed. In addition, a negative test may lead people to stop monitoring for symptoms of infection after exposure. A more prudent approach is to monitor for symptoms of tick-borne infection in the weeks after exposure to tick habitat.

SUMMARY

HGA is a bacterial infection caused by \textit{A phagocytophilum}. It is transmitted by the bite of the \textit{I ricinus} complex (black-legged) ticks, which include \textit{I scapularis} and \textit{I pacificus}. These ticks are present on the west coast of North America, north central and eastern
North America (where they are known as deer ticks), Eurasia, and eastern Asia. The incidence of HGA is increasing steadily throughout an expanding geographic range. *A phagocytophilum* can be transmitted to humans after 24 hours, and more often after 48 hours, of tick attachment. The incubation period is 5 to 14 days after a tick bite. Many people will not be aware of their tick bite, so ask about exposure to black-legged (deer) tick habitat to assess their risk for HGA. Symptoms vary in severity and include fever, chills, headache, and body aches. HGA is often self-limited in younger and healthy people. Complications of infection include shock, organ dysfunction, and death. Mortality is less than 1%. Blood test findings include leukopenia, thrombocytopenia, and elevated hepatic transaminases. PCR is the confirmatory test of choice. Doxycycline is first-line treatment for all patients, regardless of age. Start it empirically in patients with a compatible illness who have spent time in black-legged tick habitat. Complete a 7- to 10-day course if symptoms resolve with treatment, regardless of confirmatory test results. The keys to preventing HGA are preventing tick bites with repellants and checking for ticks frequently while in tick habitat.

**CLINICS CARE POINTS**

- To assess for risk of human granulocytic anaplasmosis, inquire as to time spent in black-legged (deer) tick habitat as opposed to presence of recent tick bites.
- Blood test findings may include leukopenia, thrombocytopenia, and elevated hepatic transaminases, sometimes alone or in combination.
- Polymerase chain reaction testing for *A phagocytophilum* is the most sensitive and specific test to confirm human granulocytic anaplasmosis.
- Doxycycline for 7 days in children and 7 to 10 days in adults is the treatment of choice for human granulocytic anaplasmosis.
- Human granulocytic anaplasmosis is a life-threatening infection. If it is deemed a possible cause of a patient’s symptoms, start doxycycline while awaiting confirmatory test results.
- Complete a 7- to 10-day course if symptoms resolve with treatment, regardless of confirmatory test results.

**DISCLOSURE**

Neither author has any commercial or financial conflict of interest. There are no funding sources for either author.

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