Use of Routine Complete Blood Count Results to Rule Out Anaplasmosis Without the Need for Specific Diagnostic Testing

Sarah E. Turbett,^{1,2,a} Melis N. Anahtar,^{1,a} Vikram Pattanayak,¹ Marwan M. Azar,³ K. C. Coffey,⁴ George Eng,¹ Joseph W. Rudolf,⁵ Kent B. Lewandrowski,¹ Jason Baron,¹ Eric S. Rosenberg,¹ and John A. Branda¹

Departments of ¹Pathology and ²Medicine, Massachusetts General Hospital and Harvard Medical School, Boston; ³Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut; ⁴Section of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; and ⁵Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis

Background. Anaplasmosis presents with fever, headache, and laboratory abnormalities including leukopenia and thrombocytopenia. Polymerase chain reaction (PCR) is the preferred diagnostic but is overutilized. We determined if routine laboratory tests could exclude anaplasmosis, improving PCR utilization.

Methods. *Anaplasma* PCR results from a 3-year period, with associated complete blood count (CBC) and liver function test results, were retrospectively reviewed. PCR rejection criteria, based on white blood cell (WBC) and platelet (PLT) counts, were developed and prospectively applied in a mock stewardship program. If rejection criteria were met, a committee mock-refused PCR unless the patient was clinically unstable or immunocompromised.

Results. WBC and PLT counts were the most actionable routine tests for excluding anaplasmosis. Retrospective review demonstrated that rejection criteria of WBC $\geq 11\,000$ cells/ μL or PLT $\geq 300\,000$ cells/ μL would have led to PCR refusal in 428 of 1685 true-negative cases (25%) and 3 of 66 true-positive cases (5%) involving clinically unstable or immunocompromised patients. In the prospective phase, 155 of 663 PCR requests (23%) met rejection criteria and were reviewed by committee, which endorsed refusal in 110 of 155 cases (71%) and approval in 45 (29%), based on clinical criteria. PCR was negative in all 45 committee-approved cases. Only 1 of 110 mock-refused requests yielded a positive PCR result; this patient was already receiving doxycycline at the time of testing.

Conclusions. A CBC-based stewardship algorithm would reduce unnecessary *Anaplasma* PCR testing, without missing active cases. Although the prospectively evaluated screening approach involved medical record review, this was unnecessary to prevent errors and could be replaced by a rejection comment specifying clinical situations that might warrant overriding the algorithm.

Keywords. *Anaplasma phagocytophilum*; diagnosis; stewardship; utilization management; PCR.

Human granulocytic anaplasmosis (HGA) is an emerging tick-borne infection caused by the bacterium *Anaplasma phagocytophilum*. First described in 1990 in a patient from Wisconsin, most cases occur in the upper midwest and north-eastern regions of the United States [1]. The incidence of anaplasmosis is increasing in the United States, with 4151 cases of confirmed or probable *A. phagocytophilum* infection reported in 2016, a >4-fold increase from the prior decade [1]. Patients typically present with fever, headache, myalgias, and malaise, and 70% of patients have leukopenia, thrombocytopenia, or transaminitis at the time of initial presentation [2–4].

Severe complications, including hospitalization, occur in up to one-third of patients [2, 5].

The diagnosis of HGA can be made by peripheral blood smear examination, serologic testing, culture, or blood polymerase chain reaction (PCR). The sensitivity of peripheral blood smear examination for the detection of anaplasmosis ranges from 20% to 80%, and performance of this procedure is labor intensive and requires significant expertise, limiting its use in clinical laboratories [6–8]. Serology is insensitive during the acute phase of infection, burdensome to perform, and requires documentation of a 4-fold rise in titer between the acute and convalescent phases of infection for confirmation of the diagnosis [6, 9]. Culture requires specific cell culture lines for isolation and can require several weeks of incubation, precluding its use outside research settings [4]. Of all of the available diagnostic modalities, PCR is the most sensitive when used within the first week of illness, with a diagnostic sensitivity and specificity approaching 100% [9, 10]. At our institution, PCR is the preferred diagnostic method for *A. phagocytophilum* infection

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^aS. E. T. and M. N. A. contributed equally to this work.

Correspondence: S. E. Turbett, Massachusetts General Hospital, Gray Bldg 526, 55 Fruit St, Boston, MA 02114 (turbett.sarah@mgh.harvard.edu).

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and is a send-out test to a commercial diagnostic reference laboratory.

Internal review of *Anaplasma* PCR testing has revealed the assay is overutilized, with a positive rate of only 3%. Improving utilization would reduce healthcare costs, allow for redistribution of resources, and reduce unnecessary testing and treatment in the rare event of a false-positive result. Bakken et al demonstrated an inverse correlation between mean white blood cell (WBC) and platelet (PLT) counts in patients with anaplasmosis, suggesting these values could potentially be used to identify patients with active infection [8]. To improve utilization, a 2-phase study was performed to assess the value of these routinely ordered tests in the diagnosis of anaplasmosis.

METHODS

The study was conducted in 2 phases. In phase 1, a retrospective data analysis was performed to determine if either complete blood count (CBC) or liver function test (LFT) laboratory values, or both, could exclude *Anaplasma* infection without the need for PCR. In phase 2, rejection criteria based on routine test results were developed and applied prospectively, in a mock stewardship program, to determine the potential impact on PCR utilization.

Retrospective Phase Overview

Massachusetts General Hospital (MGH) is an urban, primarily adult, quaternary care hospital in Boston, Massachusetts. All *Anaplasma* PCR test results from samples referred from the MGH between March 2013 and August 2016 were reviewed. Thirty-six duplicate tests, defined as repeat tests ordered within 1 week on the same patient, were excluded from further analysis. Associated CBC and LFT values measured within 2 days of *Anaplasma* PCR testing were obtained from the laboratory information system, when available. If multiple WBC or PLT values were available, the values most proximate to the PCR sample collection date were used, and 89% were from the same day. *Anaplasma* PCR tests with no available CBC and LFT results within 2 days of testing were excluded. Receiver operating characteristic (ROC) curves were generated for each CBC and LFT component, illustrating the sensitivity and specificity of the analyte at various cutoffs to predict *Anaplasma* PCR results. Laboratory screening criteria were determined by reviewing each ROC curve to select potential cutoff values for each analyte that could achieve maximum sensitivity without overly compromising specificity. This study was approved by the MGH Institutional Review Board.

Prospective Phase Overview

To determine the safety and efficacy of potential *Anaplasma* PCR rejection criteria developed during the retrospective phase, mock stewardship of all *Anaplasma* PCR tests was performed prospectively during a 6-month period (end of April through

October 2017). WBC and PLT values measured within 2 days of *Anaplasma* PCR testing were used to determine initial test approval or rejection. If a corresponding CBC was not available, one was performed on a sterilely decanted aliquot of the same sample collected for *Anaplasma* PCR testing, for study purposes only. If a sample met the WBC and PLT rejection criteria, medical record review of the case was performed by a clinical committee comprised of infectious diseases specialists, microbiologists, and clinical pathologists. Approval was mock-granted if the subject was critically ill (requiring intensive care level of support) or had one of the following conditions resulting in a high degree of immunosuppression: solid organ transplantation, hematopoietic stem cell transplantation, leukemia, lymphoma, asplenia, or the use of high-dose immunosuppressive therapy. If none of these clinical features was present, the request was mock-rejected, meaning that although all requested *Anaplasma* PCR tests were performed during the study period, the committee's recommendation to reject was recorded in real time before PCR results became available. Once mock stewardship was complete, an infectious diseases specialist reviewed the medical records of any patients with positive *Anaplasma* PCR results, for whom PCR was mock-rejected by the algorithm or the committee, to determine the clinical implications of the missed test result.

Laboratory Testing

Anaplasma PCR testing was performed at the Mayo Medical reference laboratory using real-time PCR followed by hybridization to DNA probes that differentiate among *A. phagocytophilum*, *Ehrlichia chaffeensis*, *Ehrlichia muris* subspecies *euclairensis*, and *Ehrlichia ewingii/canis*. CBC and WBC differentials were determined using an automated cell counter (XN-9000, Sysmex, Norderstedt, Germany). LFT values (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and direct bilirubin) were determined with an automated enzymatic assay (Cobas c501, Roche, Indianapolis, Indiana).

Statistical Analysis

Two-tailed Mann-Whitney *U* tests were used to compare laboratory test values, as the data were not normally distributed (RStudio version 1.1.442). *P* values < .05 were considered statistically significant.

RESULTS

Characterization of Laboratory Abnormalities Associated With *Anaplasma* Infection (Phase 1a)

During the 41-month period of the retrospective study (phase 1), 2165 specimens from 2080 patients were tested by *Anaplasma* PCR (on average, 634 tests per year), of which only 69 (3.2%) were positive. The monthly incidence rate peaked in June, with 81% of test orders and 84% of positive test results occurring between May and October (Supplementary Table 1). There were no positive cases identified in February or March.

Among these, 66 positive PCR results (96%) had an associated CBC, differential, and LFTs obtained within 2 days of the PCR test. Additionally, of the 2096 negative PCR results, 1685 (80%) had an associated CBC, 1668 (80%) had an associated WBC differential, and 1541 (74%) had associated LFTs obtained within 2 days of the PCR test.

When CBC values were reviewed, the median total WBC count associated with positive *Anaplasma* PCR results was significantly lower than the WBC count associated with negative PCR results ($P < .0001$; Table 1). The median PLT count associated with positive *Anaplasma* PCR results was also significantly lower than the median PLT count associated with negative PCR results ($P < .0001$; Table 1). Moreover, positive *Anaplasma* PCR test results were associated with significantly lower absolute lymphocyte ($P < .0001$), monocyte ($P < .0001$), neutrophil ($P = .005$), and eosinophil ($P < .0001$) counts, compared with values obtained in the context of negative *Anaplasma* PCR results (Table 1). There was a small but significant difference in the hematocrit level ($P = .014$) and no significant difference in the absolute basophil count between the groups.

When LFT values were reviewed, the median AST, ALT, and total bilirubin values associated with positive *Anaplasma* PCR results were significantly higher compared to those associated with negative PCR results ($P < .0001$, $P < .001$, and $P = .0064$, respectively; Table 1).

Defining Rejection Criteria Using WBC and PLT Parameters (Phase 1b)

Results from the retrospective study were further analyzed to design a highly conservative and practical screening algorithm. Although AST, ALT, total bilirubin, and absolute cell count values were all informative in differentiating between

Anaplasma PCR-positive and -negative cases, these values were not included in the algorithm for the following practical considerations. These tests are (1) less frequently ordered in association with *Anaplasma* PCR, compared with the basic CBC and (2) not amenable to add-ons due to different specimen collection container requirements. In contrast, both the CBC and *Anaplasma* PCR tests are performed on blood collected in an ethylenediaminetetraacetic acid tube, which enables the laboratory to perform off-line CBC testing for screening purposes in cases where the *Anaplasma* PCR test is ordered without a concurrent CBC. PCR rejection criteria were therefore based on only 2 parameters: the total WBC count and the PLT count.

Next, specific WBC and PLT cutoff values were modeled as potential rejection criteria, to optimize the screening algorithm's accuracy in rejecting true-negative cases for PCR while allowing for PCR in true-positive cases (Supplementary Table 2). Implementing a cutoff WBC count of 11 000 cells/ μ L, the upper limit of normal at our institution, 5% (3/66) of patients with a positive *Anaplasma* PCR and 15% (253/1685) of patients with a negative PCR had a WBC count greater than or equal to this threshold (Figure 1A). Using a cutoff PLT count of 300 000 cells/ μ L, 1.5% (1/66) of patients with a positive *Anaplasma* PCR and 15% (248/1685) of patients with a negative PCR had PLT counts greater than or equal to this threshold (Figure 1B). By combining these thresholds, such that *Anaplasma* PCR testing is rejected if a patient has a WBC count ≥ 11 000 cells/ μ L or a PLT count ≥ 300 000 cells/ μ L, 5% of true-positive cases (3/66) would be rejected for *Anaplasma* PCR, along with 25% of true-negative cases (428/1685).

The 3 *Anaplasma* PCR-positive patients whose laboratory values were above the WBC and PLT thresholds were further examined. The first patient had a WBC count of 33 430 cells/ μ L,

Table 1. Complete Blood Count, Differential, and Liver Function Testing Results Associated With *Anaplasma* Infection in Phase 1

Test Name	Reference Range ^a	Negative <i>Anaplasma</i> PCR, Median (IQR)	Positive <i>Anaplasma</i> PCR, Median (IQR)	Univariate Analysis <i>P</i> Value ^b
Complete blood count				
WBC count, K/ μ L	4.5–11.0	6.54 (4.57–8.96)	4.92 (3.31–6.93)	< .0001
Platelet count, K/ μ L	150–400	198 (134–257)	91 (54–150)	< .0001
Hematocrit, %	36.0–46.0	38.4 (33.0–42.1)	40.4 (36.7–42.9)	.014
Differential				
Absolute neutrophil count, K/ μ L	1.8–7.7	4.04 (2.64–6.10)	3.21 (2.05–4.68)	.005
Absolute lymphocyte count, K/ μ L	1–4.8	1.38 (0.83–1.91)	0.79 (0.44–1.56)	< .0001
Absolute monocyte count, K/ μ L	0.2–1.2	0.53 (0.36–0.75)	0.33 (0.23–0.50)	< .0001
Absolute eosinophil count, K/ μ L	0–0.9	0.085 (0.03–0.16)	0.00 (0.00–0.01)	< .0001
Absolute basophil count, K/ μ L	0–0.3	0.02 (0.01–0.04)	0.02 (0.01–0.04)	.75
Liver function testing				
ALT, U/L	7–33	25 (17–50)	54 (32–94)	< .0001
AST, U/L	9–32	28 (21–50)	64 (39–120)	< .0001
Total bilirubin, mg/dL	0–1.0	0.5 (0.3–0.8)	0.6 (0.5–1.0)	.0064
Direct bilirubin, mg/dL	0–0.4	0.1 (0.1–0.2)	0.2 (0.1–0.2)	.15

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PCR, polymerase chain reaction; WBC, white blood cell.

^aReference ranges used at Massachusetts General Hospital for adults.

^bSignificance levels determined by the Mann-Whitney *U* test.

Figure 1. White blood cell (WBC) count (A) and platelet (PLT) count (B) in patients with positive and negative *Anaplasma* polymerase chain reaction test results in phase 1 of the study. The shaded area represents the normal reference range, the black horizontal line represents the median, and the dotted horizontal line represents the threshold criteria. The open circles indicate 3 patients who tested positive for *Anaplasma phagocytophilum* but had WBC and/or PLT values above the thresholds. *P* values were determined with the Mann-Whitney *U* test.

due to chronic lymphocytic leukemia. Closer analysis revealed that the patient developed a relative leukopenia and thrombocytopenia during his *A. phagocytophilum* infection, which resolved with treatment (Supplementary Figure 1). The second patient had a history of type 1 diabetes mellitus and presented with refractory hyperglycemia and confusion. He required intensive care unit (ICU) support due to septic shock and was found to have coinfection with *Borrelia burgdorferi*. The third patient had a history of autoimmune hemolytic anemia, and had previously undergone splenectomy, resulting in chronically elevated WBC and PLT counts.

Based on the review of these 3 subjects, the additional step of a focused medical record review was added to the proposed screening algorithm (Figure 2A). If the WBC count was $\geq 11\,000$ cells/ μL or the PLT count was $\geq 300\,000$ cells/ μL , approval for PCR was nevertheless granted if the subject was critically ill (admitted to an ICU) or had one of the following conditions resulting in a high degree of immunosuppression or elevation of WBC or PLT counts: solid organ transplantation, hematopoietic stem cell transplantation, leukemia, lymphoma, asplenia, or the use of high-dose immunosuppressive therapy. In patients with these conditions, the risks associated with a delayed or missed diagnosis [2] outweigh the benefits of improved test utilization. If these clinical features were not present, the *Anaplasma* PCR request was rejected in accordance with the algorithm.

Prospective Mock Implementation of the Screening Algorithm (Phase 2)

The proposed algorithm was evaluated prospectively in mock fashion over a 6-month period, covering peak season for anaplasmosis in our region (Supplementary Table 1). During

the prospective evaluation, the screening algorithm was internally applied to PCR requests and the outcome (a recommendation to proceed with *Anaplasma* PCR testing or to reject the request) was recorded for subsequent analysis, even though recommendations to reject PCR were not implemented. During the 6-month mock stewardship period, 681 *Anaplasma* PCR tests were ordered. Among these, 18 (2.6%) were excluded from the study because CBC laboratory values could not be performed within 2 days of testing ($n = 14$), were cancelled or refused for other reasons ($n = 3$), or key information was missing from the medical record ($n = 1$). Thus, 663 cases were included for mock stewardship; the results are shown in Table 2. When the screening algorithm was mock-applied, 155 of 663 cases (23%) met the proposed CBC laboratory rejection criteria and were reviewed by the clinical committee, whereas 508 of 663 cases (77%) did not meet rejection criteria and would have been accepted for PCR according to the algorithm. Of the 508 cases that did not meet rejection criteria, 24 (5%) were positive for anaplasmosis. Among the 155 cases meeting PCR rejection criteria based on CBC results, 110 (71%) were mock-refused after medical record review, and 45 (29%) were mock-accepted for *Anaplasma* PCR based on clinical criteria. One of the 110 cases that were mock-refused was ultimately positive by *Anaplasma* PCR (0.9%). This case involved an immunocompetent patient who developed fevers, myalgias, and rash after an insect bite on her leg. She had been seen at an urgent care clinic and prescribed doxycycline for presumed cellulitis. No CBC was performed at the time of initial clinical presentation. *Anaplasma* PCR and CBC testing were subsequently performed, over a week after initiation of doxycycline, at which

Figure 2. Screening algorithm for *Anaplasma* polymerase chain reaction testing used during phase 2 (A) and the proposed implementation of a “soft stop” (B). Abbreviations: PCR, polymerase chain reaction; PLT, platelet count; WBC, white blood cell count. *Measured within the last 2 days. **Requiring intensive care level of support or one of the following conditions resulting in a high degree of immunosuppression: solid organ transplantation, hemopoietic stem cell transplantation, leukemia, lymphoma, asplenia, or the use of high-dose immunosuppressive therapy.

point the patient’s symptoms had improved. The remaining 24 *Anaplasma* PCR-positive cases (96%) had not met the screening rejection criteria and therefore would have been accepted for PCR without committee review.

DISCUSSION

Creating a laboratory stewardship algorithm for *Anaplasma* PCR testing has the potential to improve healthcare utilization by eliminating low-yield testing. Here, we provide both retrospective and prospective evidence that a simple laboratory screening algorithm using WBC and PLT count thresholds can be used to improve the pretest probability of *Anaplasma* infection and reduce unnecessary testing. Using a WBC cutoff value of $\geq 11\,000$ cells/ μL or a PLT cutoff value of $\geq 300\,000$ cells/ μL would have reduced *Anaplasma* PCR testing by 23% over a 6-month period. To our knowledge, this is the first description of a set of rejection criteria for *Anaplasma* PCR.

During the study’s 6-month prospective phase, there was only 1 patient with a positive *Anaplasma* PCR result whose PCR request would have been rejected according to the proposed algorithm. The case involved an immunocompetent patient

in whom the *Anaplasma* PCR and CBC had been performed over a week after the initiation of empiric doxycycline for presumed cellulitis, at which point the patient was minimally symptomatic. As the patient’s symptoms were resolving and she was completing appropriate therapy for *Anaplasma* infection, the positive PCR result was not needed to inform healthcare decisions. The proposed screening algorithm was intentionally designed to be conservative, with minimal risk of rejecting PCR in active (untreated) cases of acute anaplasmosis, and in this sense there were no errors.

Implementation of this laboratory algorithm would require the addition of a corresponding CBC to every *Anaplasma* PCR test request. In our retrospective review, the majority of *Anaplasma* PCR tests (81%) had a corresponding CBC performed within ± 2 days of *Anaplasma* PCR specimen collection, limiting the number of tests that would need to be added on for screening purposes. During the prospective phase of the study, these tests were added on manually; however, if the algorithm were to be applied in the clinical setting, a CBC could be automatically added whenever *Anaplasma* PCR is requested. As a CBC can be performed from an aliquot of the same sample collected for *Anaplasma* PCR testing and is performed in many clinical laboratories on a routine basis with minimal

Table 2. Results of *Anaplasma* Polymerase Chain Reaction Mock Stewardship Over a 6-Month Period

Total Cases, No.	<i>Anaplasma</i> Polymerase Chain Reaction Tests, no. (%)			
	Positive		Negative	
	Mock-rejected	Mock-accepted	Mock-rejected	Mock-accepted
663	1 (4)	24 (96)	110 (17)	528 (83)

turnaround time, adding this test could easily be done without the need for further sample collection, and the results would be available quickly for screening purposes. This would ensure the timely application of the algorithm and provide feedback to the ordering providers on a real-time basis. Although a formal cost calculation of the additional CBCs was not performed, the cost associated with them would likely be minimal in comparison to the cost of unnecessary *Anaplasma* PCR tests.

During the prospective phase of our study, we adopted a step involving a focused medical record review for those cases meeting CBC-based rejection criteria. This step was added to avoid rejecting PCR requests in true positive cases, based on 3 errors that occurred during the study's retrospective phase. Interestingly, this measure provided no additional benefit (ie, did not avert any potential errors) during the prospective phase of the study. This step is the most labor-intensive portion of the algorithm, requiring manual medical record review to obtain the necessary information for *Anaplasma* PCR approval or rejection. Considering its minimal benefit, a new algorithm could be considered, in which the medical record review step is replaced with a carefully crafted "soft stop" rejection comment, to be added when *Anaplasma* PCR is rejected based on CBC rejection criteria (Figure 2B). The comment would alert the ordering clinician of specific clinical attributes that might warrant an override of the PCR rejection. This approach would allow for full automation of the screening algorithm within the laboratory but would still permit PCR testing in the correct clinical setting. Combined with focused provider education on the clinical features of anaplasmosis that would warrant testing, this algorithm would have the potential to significantly improve test utilization. Regardless of the approach taken, clinical judgment remains important in the decision to perform *Anaplasma* PCR and should not be superseded by the algorithm. All rejected specimens should be held for a minimum of 7 days, so that samples are available should PCR testing be requested based on clinical features after initial rejection.

There are several limitations to this study. First, our data were collected from a single academic center, in an area with a relatively high prevalence of *A. phagocytophilum* infection, which limits the generalizability of our findings to other institutions in areas with lower *A. phagocytophilum* prevalence. However, in theory our proposed screening algorithm should perform even better in low-incidence areas, since in such settings there are fewer opportunities for error by rejecting PCR in true-positive cases. Nonendemic areas may also gain additional stewardship value by adding a "hard stop" for orders in January or February, as these months typically have a very low incidence rate [11]. Second, although a prospective mock stewardship of *Anaplasma* PCR was performed, real-time (nontheoretical) implementation of this algorithm was not carried out. It was necessary to perform all requested PCR tests, whether or not they would have been rejected

according to the algorithm, to determine the clinical safety of the algorithm. A prospective study evaluating the real-time use of these laboratory rejection criteria would better assess the feasibility of executing the algorithm and would better measure the potential reduction in unnecessary PCR tests; plans are currently under way to implement this algorithm at our institution. Finally, no formal cost analysis was performed to determine the overall cost savings associated with the stewardship algorithm. The list price for *Anaplasma* PCR at the commercial reference laboratory we use is approximately \$400.00 per test, although this cost is higher than the actual cost to our institution. Given the relatively high cost associated with this test as compared to the cost of the additional CBCs needed to execute the algorithm, one can assume net savings although the exact degree of savings is unknown and likely institution specific. A formal cost analysis at each institution would need to be done to determine if there is sufficient benefit to implementing this protocol in the clinical setting.

In conclusion, we provide evidence that WBC and PLT counts can be used to safely improve utilization of *Anaplasma* PCR testing in an area with relatively high prevalence of *A. phagocytophilum* infection. The proposed algorithm outlined in Figure 2B, in which *Anaplasma* PCR test requests are screened and either accepted or rejected based solely on WBC and PLT counts, without medical record review, has been approved for clinical laboratory use by the medical policy committee at MGH with plans for implementation in the spring of 2019. Enhanced provider education on the clinical features of anaplasmosis targeting high-volume test users will also be performed at the time of implementation to improve overall test utilization. The "real-life" utility and cost-effectiveness of the algorithm will be further studied at that time.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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