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Open Forum Infectious Diseases

MAJOR ARTICLE

Usefulness of C-Reactive Protein in Differentiating Acute Leptospirosis and Dengue Fever in French Guiana

Paul Le Turnier,[1] Timothée Bonifay,[1,2] Emilie Mosnier,[1,3,4] Roxane Schaub,[3,5] Anne Jolivet,[6] Magalie Demar,[3,7] Pascale Bourhy,[8] Mathieu Nacher,[3,5] Félix Djossou,[1,3] and Loïc Epelboin[1,3]

[1]Unité des Maladies Infectieuses et Tropicales, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana; [2]Département de Médecine Générale, Université Antilles Guyane, Pointe-à-Pitre, Guadeloupe; [3]Ecosystèmes Amazoniens et Pathologie Tropicale, Université de la Guyane, Cayenne, French Guiana; [4]Centres Délocalisés de Prévention et de Soins, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana; [5]Centre d'Investigation Clinique Antilles Guyane, INSERM CIC 1424, Cayenne, French Guiana; [6]Service de Santé Publique, Hopital Franck Joly, Saint-Laurent du Maroni, French Guiana; [7]Laboratoire Hospitalo-Universitaire de Parasitologie Mycologie, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana; [8]Institut Pasteur, Centre National de Référence de la Leptospirose, Paris, France

Objective. Leptospirosis and dengue fever (DF) are hard-to-differentiate diseases in cocirculating areas, especially during DF epidemics. Misdiagnosis and ensuing lack of antibiotic therapy can be detrimental in leptospirosis. The objective of this study was to identify factors that help differentiate acute leptospirosis from dengue fever on admission.

Method. Patients with leptospirosis (positive serology or polymerase chain reaction) were compared with patients with DF (positive nonstructural 1 [NS1] antigen) in a case-control study with age matching. Data on admission were compared using bivariate analysis and multivariate analysis.

Results. Seventy-two patients with leptospirosis were compared to 216 patients with DF. In bivariate analysis, the factors associated with leptospirosis were male gender, cough, anemia, and elevated blood levels of C-reactive protein (CRP), leukocytes, creatinine, bilirubin, and creatine phosphokinase. Exanthema, purpura, myalgia, headache, and neutropenia were associated with DF. In multivariate analysis, elevated blood levels of leukocytes, bilirubin, and CRP were associated with leptospirosis. The CRP threshold of 50 mg/L taken alone had elevated sensitivity and specificity.

Conclusions. The CRP level, an easy-to-obtain biomarker, was a powerful tool to differentiate on admission leptospirosis and DF. Facing a dengue-like syndrome in cocirculating areas and awaiting new specific rapid diagnostic tests, CRP dosing could help the clinician to promptly consider the diagnosis of leptospirosis and initiate antibiotic therapy early.

Key words: C-reactive protein; dengue fever; diagnosis; French Guiana; leptospirosis.

INTRODUCTION

Leptospirosis is a widespread bacterial zoonosis caused by *Leptospira* spp. with potential for high lethality [1]. Leptospirosis incidence is increasing, particularly in tropical areas, because of favorable environmental and demographical conditions [2, 3]. The clinical picture of leptospirosis ranges from a nonspecific acute febrile illness to the classical Weil's disease with severe jaundice, renal failure, and hemorrhage that sometimes is associated with severe pneumonia and multiorgan failure [2, 4]. In tropical areas, many causative agents of undifferentiated acute febrile syndromes can coexist, and many studies have raised the concern of misdiagnosis in patients affected by leptospirosis. This particularly is relevant for dengue fever (DF), a mosquito-borne viral disease that can be endemic and often epidemic in those areas. Distinguishing other febrile illnesses [5, 6] and particularly leptospirosis [7–12] from DF in endemic areas, and more especially during epidemics, long has been considered a challenge. The definitive biological diagnosis of leptospirosis depends on the use of serological tests that can be negative during the early phase of the disease or the polymerase chain reaction (PCR), which is not always quickly available, notably in French Guiana [13, 14]. Overlapping clinical syndromes between the early undifferentiated phase of leptospirosis and DF may lead to its under-recognition, especially during DF epidemics, and could be associated with a worsened prognosis [15, 16]. Because an early initiation of an antibiotic regimen seems beneficial in the management of leptospirosis [17, 18] quickly discriminating leptospirosis from DF would be useful for clinicians. This study aimed to identify upon admission the clinical and biological factors associated with acute leptospirosis or DF for differentiating them.

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Correspondence: P. Le Turnier, MD, Department of Infectious and Tropical diseases, Nantes University Hospital, 1 place Alexis Ricordeau, Nantes 44000, France (paul.leturnier@gmail.com).

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METHODS

Study Design and Patient Selection

A descriptive epidemiological study previously published included leptospirosis cases diagnosed between 2007 and 2014

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in the 2 major hospitals of French Guiana (Centre Hospitalier Andrée Rosemon in Cayenne and in the Centre Hospitalier de l'Ouest Guyanais in Saint Laurent du Maroni) based on positive PCR, a positive microscopic agglutination test (MAT), or both. A confirmed leptospirosis case was defined as having 1 or any combination of the following: positive PCR in blood, urine, or cerebrospinal fluid; a MAT seroconversion with a MAT titer ≥ 200; a 4-fold increase of MAT titers on 2 consecutive sera samples; or a MAT titer ≥ 400. A probable leptospirosis case did not match the previouscriteria but had one of the following: MAT seroconversion with lowtiter (MAT = 100); a MAT titer = 200 without seroconversion;a positive MAT titer with immunoglobulin with IgM seroconversion or IgM elevated titer (IgM test performed at the French National Reference Center for Leptospirosis). Only patients aged ≥ 15 years were included [14]. An ancillary retrospective case-control study was conducted. The case group consisted of all of the leptospirosis cases of the study.

All adult patients diagnosed with DF with positive nonstructural 1 (NS1) antigen and managed in Cayenne Hospital, French Guiana, from February to August 2013 were identified. We selected among them 3 controls for each case of leptospirosis, matching them by age criteria (+/- 3 years). The 3 controls that best matched the cases by age were selected.

Data Collection and Definitions

Individual data, including socio-epidemiologic data, previous medical history, clinical symptoms, and biological results, were retrieved anonymously from the computerized medical charts. Laboratory results from the first available sample after symptom onset were used for comparison. Clinical signs and symptoms were collected from the first admission in the hospital, generally in the emergency room, and were considered absent if not mentioned in the initial medical observation. A hemorrhagic syndrome was defined by presence of any of the following: epistaxis, gum bleeding, purpura, petechial lesions, or other hemorrhagic signs.

Setting

French Guiana is a French overseas territory located on the northeastern coast of South America. About 90% of its 84 000 km^2 surface is Amazonian rain forest. The territory is inhabited by about 260 000 persons (in 2015), half of whom live in Cayenne, the capital city on the northern coast and its surroundings [19].

Statistical Methods

After primary descriptive analysis, continuous variables were categorized following the Cayenne hospital laboratory usual cut-off values or international classification [20]. The CRP cut-off value was evaluated according to a previous report [21]. The 2 groups were compared using a bivariate conditional logistic regression. The statistical significance was set at $P < .05$. Because of the unreliability of the data obtained retrospectively, variables obtained from anamnesis and clinical examination, and variables with >10% missing data were a priori excluded from the multivariate model. Remaining variables with $P < .15$ in bivariate analyses were entered into a multivariate logistic regression model using a backward stepwise procedure. Receiver operating characteristics curve analysis was used to determine the threshold of CRP value as discriminating factor. Sensitivity, specificity, positive (PPV), and negative predictive values (NPV) were calculated along with their 95% confidence intervals (CI). Data were analyzed using Stata software version 12.0 (StataCorp LP, College Station, TX).

Ethics Statement

The retrospective use of anonymous patient files on the site of patient care was authorized by the French National Commission on Informatics and Liberties (# 2068308). All the data collected retrospectively were anonymized in a standardized case report form.

RESULTS

Seventy-two patients diagnosed with leptospirosis were included as cases [14]. The median age was 39 years (interquartile, 29–50 years; range, 16–82). The ratio of males to females was 6.2. Twelve patients (16.7%) were admitted in the intensive care unit and there were 3 in-hospital deaths (4.2%). The main identified serogroup was icterohaemorrhagiae in 38.0%. All patients tested for NS1 antigen in the leptospirosis group (n = 62/72, 86%) were negative.

Between February and August 2013, 490 patients meeting DF inclusion criteria for controls were identified. Finally, 216 age-matched controls were included.

Demographic factors associated with leptospirosis were male gender, absence of medical history, and foreign-born status. Hospitalization was more common in patients with leptospirosis. At baseline, cough was more frequent in patients with leptospirosis. Anorexia, headache, muscle pain, hemorrhagic syndrome, purpura, exanthema, and pruritus were more frequent in patients with DF (Table 1).

On admission, the following blood parameters were associated in bivariate analysis with leptospirosis: hemoglobin < 10.9 g/dL, hematocrit < 38%, leukocytosis > 10 × 109/L, total bilirubin > 20 µmol/L, natremia < 135 mmol/L, creatinine > 120 µmol/L, creatinine kinase > 400 U/L, and CRP > 50 mg/L. Having leukocytes < 4 × 109/L and polymorphonuclear neutrophils < 1.5 × 109/L were more associated with DF. Platelets < 150 × 109/L, lymphocytes < 1G/L, AST > 60 U/L or ALT > 80 U/L (or both), or decreased prothrombin time < 70% were as frequent in patients with leptospirosis as in patients with DF (Table 2).

After adjustment on age and sex, the multivariate analysis revealed CRP > 50 mg/L, total bilirubinemia > 20 µmol/L,

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Table 1. Comparison of Demographical and Clinical Characteristics on Admission Between Patients With Leptospirosis and Patients With Dengue Fever (Bivariate Analysis)

Demographical or Clinical Findings on Admission	Leptospirosis, n = 72 N (%)	Dengue fever, n = 216 N (%)	Odds ratio[a]	95% CI	*P* value
Male gender	**62 (86.1)**	**136 (63.0)**	**5.3**	**2.18–12.9**	**<.001**
Born abroad	**40/66 (60.6)**	**70/203 (34.5)**	**2.76**	**1.54–4.93**	**.001**
Hospitalization	**62 (86.1)**	**85 (39.4)**	**14.6**	**5.73–37.4**	**<.001**
Hospital stay >7 days	**38/60 (63.3)**	**10/85 (11.8)**	**13.5**	**4.04–44.9**	**<.001**
Delay before consultation >72 h	32/64 (50.0)	92 (42.6)	—	—	.23
Fever	66/66 (100.0)	149/212 (70.3)	—	—	—
Asthenia	43 (59.7)	117 (54.2)	—	—	0.4
Anorexia	**19 (26.4)**	**87 (40.3)**	**0.51**	**0.28–0.94**	**.031**
Headache	**49 (68.1)**	**173 (80.1)**	**0.51**	**0.27–0.95**	**.034**
Arthralgia	19 (26.4)	39 (18.1)	—	—	.07
Muscle pain	**37 (51.4)**	**178 (82.4)**	**0.22**	**0.12–0.40**	**<.001**
Back pain	16 (22.2)	50 (23.2)	—	—	.87
Cough	**32 (44.4)**	**34 (15.7)**	**4.7**	**2.44–8.95**	**<.001**
Abdominal pain	26 (36.1)	72 (33.3)	—	—	.65
Nausea/vomiting	33 (45.8)	113 (52.3)	—	—	.5
Diarrhea	24 (33.3)	54(25.0)	—	—	.12
Malaise/dizziness	2 (2.8)	17 (7.9)	—	—	.16
Hemorrhagic syndrome[b]	**8 (11.1)**	**62 (28.7)**	**0.32**	**0.15–0.71**	**.005**
Purpura	**1 (1.4)**	**39 (18.1)**	**0.07**	**0.01–0.48**	**.007**
Rash	**3 (4.2)**	**96 (44.4)**	**0.06**	**0.02–0.18**	**<.001**

Abbrevisations: CI, confidence interval; DF, dengue fever.

[a]Variables were compared using bivariate conditional logistic regression; bold indicates significant differences ($P < .05$).

[b]Hemorrhagic syndrome was defined by the presence of epistaxis, gum bleeding, purpura, petechiae, or other hemorrhagic signs.

and leukocytes > 10 × 109/L were independently associated with the diagnosis of leptospirosis with adjusted odds ratios of 124.5 (95% CI, 37.7–411.3), 6.16 (95% CI, 1.27–29.8), and 11.7 (95% CI, 1.02–132.8), respectively (Table 2). The area under the receiver operating characteristic curve of CRP value was 0.96 (95% CI, 0.93–0.98) (see Supplementary Figure). For the 50 mg/L threshold, the sensitivity was 88.9% (95% CI, 79.3–95.1%) and specificity was 95.2% (95% CI, 91.3–97.7%). In the

Table 2. Comparison of Biological Results on Admission Blood Test Between Leptospirosis and Dengue Fever Cases (Bivariate End Multivariate Analysis)

			Bivariate Analysis[a]		Multivariate Analysis[b]	
Initial Laboratory Findings	Patients with Leptospirosis, n = 72	Patients with DF, n = 216	Odds Ratio [95% CI]	*P* value	Adjusted Odds Ratio [95% CI]	*P* value
Hemoglobin < 10.9 g/dL, n (%)	**11/70 (20.0)**	**3/195 (3.6)**	**9.9 [2.75–35.6]**	**<.001**	**—**	**—**
Hematocrit < 38%, n (%)	**21/63 (33.3)**	**21/188 (11.2)**	**3.39 [1.67–6.87]**	**.001**		
Leukocytes <4 × 109/L, n (%)	**7/70 (10.0)**	**98/195 (50.3)**	**0.13 [0.06–0.30]**	**<.001**		
>10 × 109/L, n (%)	**22/70 (31.4)**	**1/195 (0.5)**	**58.27 [7.8–432.8]**	**<.001**	**11.7 [1.02–132.8]**	**.048**
PMNs < 1.5 × 109/L, n (%)	**1/69 (1.5)**	**32/214 (15.0)**	**0.08 [0.01–0.63]**	**.016**		
Lymphocytes < 1 × 109/L, n (%)	49/60 (81.7)	133/190 (70.0)	—	.072		
Platelets <150 × 109/L, n (%)	41/71 (57.8)	102/214 (47.7)	—	.22		
Total bilirubin > 20 µmol/L, n (%)	**24/69 (34.8)**	**8/181 (4.4)**	**13.4 [4.6–39.0]**	**<.001**	**6.16 [1.27–29.8]**	**.024**
AST > 60 U/L, n (%)	23/68 (33.9)	44/188 (23.4)	—	.25		
ALT > 80 U/L, n (%)	16/70 (22.9)	31/203 (15.3)	—	.13	—	—
AST and/or ALT > 80 U/L, n (%)	25/70 (35.7)	49/191 (25.7)	—	.18		
Quick's value < 70%, n (%)	14/60 (23.3)	18/138 (13.0)	—	.12		
Natremia < 135 mmol/L, n (%)	**39/70 (55.7)**	**46/185 (24.9)**	**4.1 [2.17–7.6]**	**<.001**	**—**	**—**
CK > 400 U/L, n (%)	**15/41 (36.6)**	**14/154 (9.1)**	**6.54 [2.35–18.23]**	**<.001**		
Creatinine > 120 µmol/L, n (%)	**31/71 (43.7)**	**11/210 (5.2)**	**19.8 [6.94–56.4]**	**<.001**	**—**	**—**
CRP > 50 mg/L, n (%)	**64/72 (88.9)**	**10/207 (4.8)**	**168 [23.3–1212]**	**<.001**	**124.5 [37.7–411.3]**	**<.001**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase, CRP, C-reactive protein; DF, dengue fever; U/L, units per liter; PMNs, polymorphonuclear neutrophils.

[a]Variables were compared using bivariate conditional logistic regression. Bold indicates significant differences ($P < .05$).

[b]Analysis by unconditional multivariate logistic regression adjusted on sex and age.

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studied population, the PPV for CRP > 50 mg/L was 86.5% (95% CI, 76.5–93. 3%) and NPV was 96.1% (95% CI, 92.5–98.3%). The addition of hyperbilirubinemia or hyperbilirubinemia and hyper leukocytosis did not notably increase the diagnostic performance of the CRP threshold of 50 mg/L taken alone (data not shown).

Among the 8 patients diagnosed with leptospirosis for whom CRP value was initially < 50 mg/L, 2 had more than 3 weeks between the onset of symptoms and the first sample (CRP values were 0 and 27 mg/L, respectively); 2 gold-miner patients had taken effective antibiotics in self-medication early before the first sample and probably rapidly healed (CRP values were 39 and 5 mg/L); 2 were tested after less than 48 hours after the symptoms' onset (CRP values were 28 and 34 mg/L); 1 had no available symptom onset date, was a gold-miner, and potentially self-medicated (due to the distance of the mines from the nearest health facilities) (CRP value 11 mg/L); and 1 patient had a CRP measured at 46 mg/L after 7 days of symptoms evolution.

DISCUSSION

As leptospirosis and dengue fever have overlapping clinical symptoms, it is necessary to build tools to differentiate them to use antibiotic appropriately. This retrospective study reports the potential contribution of the CRP threshold of 50mg/L to early discriminate leptospirosis from DF in a tropical setting. Our inclusion criteria for both leptospirosis and DF were based on robust biological data to allow relevant comparison. Antibody detection assays for DF were not used as diagnostic criteria in this study. Indeed, anti-dengue virus antibodies have limited specificity in the context of DF epidemics linked to their persistence in serum, which sometimes lasts up to several months [22].

Previous studies comparing DF and leptospirosis reported heterogenous clinical symptoms associated with either leptospirosis or DF [10, 23, 24]. A brief resume of studies comparing leptospirosis and DF in adult population is presented (see Supplementary Table). Thus, serious concerns exist that using clinical symptoms only could accurately discriminate leptospirosis from DF [7, 25]. In our study, the retrospective approach may have limited the robustness and the preciseness of the collection of clinical signs and the analysis of their discriminative capacity. The most discriminating clinical symptom in favor of leptospirosis was cough and rash for DF, though their sensitivity was below 50%. Therefore, only biological factors were assessed in the multivariate analysis. The activities at risk of potential leptospiral exposure, which is an important factor that contributes to suspect leptospirosis for clinicians, was largely unknown in patients with DF and could not be analyzed.

Regarding the biological factors on admission, although elevated levels of bilirubin, leukocytosis, and CRP were associated with leptospirosis, sole use of CRP as the discriminating factor appeared adequate. To our knowledge, only 1 study (not referenced in MEDLINE database) previously assessed the CRP as a discriminating factor between DF and leptospirosis and identified the threshold of 50 mg/L. This study was conducted in 60 patients in New Caledonia (Pacific Ocean) over a period of 1 year [21]. The elevated NPV (96.1%) of the threshold of CRP < 50 mg/L found in our study seems relevant, because the main issue is not to miss the diagnosis of leptospirosis when both pathologies are suspected. Measuring the CRP level is an inexpensive and easily accessible test performed in almost all laboratories. Recently, a prospective large study conducted in Sri Lanka [26] assessed the performance of a score to differentiate leptospirosis from other etiologies of acute fever mimicking leptospirosis (mainly DF and pneumonia). Leptospiral potential exposure, creatinine > 150 µmol/L, polymorphonuclear > 80%, total bilirubin > 30 µmol/L, and platelet < 85 × 109/L were used to build the diagnostic score. The sensitivity of the score was 80%, specificity 60%, PPV 54%, and NPV 84%. CRP was not evaluated in this study [26].

In remote areas or in resource limited countries, the CRP level also could be considered through rapid diagnostic tests (RDT). In these settings, coupling CRP-RDTs with pathogen-specific RDTs could be useful to inform the correct use of antibiotics [27]. A widespread use of CRP-RTDs, with cut-offs of 40–50 mg/L, could be implemented in leptospirosis and DF guidelines of medical practices in remote areas. It also could be cost effective and contribute to substantial reductions in overuse of antimicrobials in dengue infection [28].

In French Guiana, the NS1 antigen test is widely used to diagnose DF in its early phase and is sometimes used as an RDT in remote areas. However, this test is not available for all physicians who face a patient with dengue-like syndrome. In the situation where NS1 antigen test is available and the result is quickly given to the physician, the usefulness of CRP would probably be lower to distinguish DF and leptospirosis. However, even if the NS1 antigen test is positive, an elevated level of CRP should evoke a possible bacterial coinfection, such as leptospirosis, which remains a rare situation, or malaria [5]. If the NS1 antigen is negative, a high level of CRP should evoke differential diagnoses, especially leptospirosis, because of the strong clinical similarities with dengue fever.

Naturally, an elevated value of CRP should not preclude assessing the presence of another diagnosis than leptospirosis facing a dengue-like syndrome. Because DF is already well recognized as a frequent disease in many tropical areas, it is unlikely for clinicians to overlook the diagnosis as illustrated by the high rate of NS1 antigen testing in patients with leptospirosis in our study. However, clinicians also should consider another diagnosis than leptospirosis and dengue. Indeed, because control patients were exclusively diagnosed with DF, this study did not assess the capacity of CRP to discriminate leptospirosis among undifferentiated acute tropical fevers. Therefore, one could

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argue it does not reflect the current practice in tropical settings where etiologies of an acute undifferentiated febrile illness may include a large broad and diverse group of bacteria, virus, protozoans, and even fungal agents. The discriminating performance of CRP in patients with malaria [5], Q Fever [29],or typhoid, for example, would probably be much lower. However, in certain tropical areas where these 2 pathologies have a high incidence and can overlap after severe floodings or earthquakes, in slum communities, and especially during DF epidemics, CRP appears to be a simple, sensitive, and easily available tool to discriminate leptospirosis from DF upon admission in the emergency room. CRP dosing could be proposed to avoid overlooking of leptospirosis and quickly consider antileptospirosis antibiotic treatment and specific leptospirosis laboratory diagnosis. This would be particularly interesting in mild forms of the leptospirosis where clinical suspicion is sometimes low and antibiotics are frequently prescribed with a potentially detrimental delay. In French Guiana, Q fever is the main differential bacterial diagnosis to evoke when facing a clinical picture of fever and diffuse pain. The gold standard treatment for Q fever is doxycycline, which is also active on *Leptospira* spp. In case of community-acquired pneumonia (CAP), the 2 main bacterial agents to be considered are *Coxiella burnetii* (Q fever) and *Streptococcus pneumoniae*. An association of amoxicillin (with clavulanate in patients with underlying diseases) and doxycycline is currently recommended in French Guiana [29]. In front of a severe CAP or septic shock, the empirical antibiotic regimen would consist in the association of a third generation cephalosporin with doxycycline or levofloxacin and aminoglycosides in case of shock, all of these being active against *Leptospira* spp.

To note, promising tests with potential interest for early distinction between leptospirosis and DF recently have been developed in urine [30, 31] and serum [32]. Still, they seem far from being routinely used, especially in resource-limited countries where the diagnostic dilemma remains the most problematic.

Finally, even though it yet has not been evaluated specifically in patients with DF/leptospirosis coinfection, CRP also could be a marker of interest in this situation. DF/leptospirosis coinfection is a potentially threatening condition, because it can lead to delayed or overlooked diagnosis of leptospirosis [16]. The frequency of DF/leptospirosis coinfection has been estimated to be below 5% [33, 34]. It may vary also with the magnitude of epidemics, rare in interepidemic phases and more frequent when a major proportion of the population is exposed. Factors such as hypotension, male gender [33], and deeper thrombocytopenia [35] have been associated with leptospirosis/DF coinfection. Naturally, an elevated value of CRP should not preclude considering a DF/leptospirosis coinfection.

The major limitation of the study is due to its retrospective design and to the fact that diagnostic tests for leptospirosis were not done routinely in controls. Because controls were selected during a major dengue outbreak and leptospirosis has long been neglected in French Guiana, leading to a rarely-evoked or delayed diagnosis, specific tests for leptospirosis were not done in patients with confirmed diagnosis of dengue fever by positive NS1 antigen detection. Indeed, the positive predictive value of a positive dengue fever test in an epidemic context is maximal as it increases with prevalence and can lead clinicians to stop further investigations.

Considering that all patients with a diagnosis of leptospirosis were screened in the same inclusion period as controls, it is not possible that patients diagnosed with dengue had also a proven diagnosis leptospirosis. Then, although the existence of undiagnosed leptospirosis cases among controls cannot be ruled out, coinfection remains a rare condition and only a few control patients would have been concerned (less than 5%).

Facing an undifferentiated acute fever in tropical areas where DF and leptospirosis are heavily circulating with a risk of misdiagnosis (eg, after floodings or during DF epidemics), the CRP level could help to avoid overlooking diagnosis of leptospirosis, especially when DF tests are negative, are unavailable, and lead to a beneficially early antileptospiral antibiotic regimen. Because the diagnosis of nonspecific acute tropical fever often remains challenging, especially in remote areas, high quality epidemiological studies should be encouraged to improve knowledge on local epidemiology and to help the development of more accurate cost-effective diagnostic tests for the most important diseases. Until then, simple tools like CRP could provide valuable help in some well-defined clinical circumstances.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Authors contributions. P.L.T., T.B., and L.E. performed the design conceptualization, data acquisition and analysis, and wrote the first draft of the manuscript. E.M. assisted with study design, interpretation of data, and reviewing of the manuscript. A.J. and P.B. contributed to data acquisition and interpretation. R.S and M.N. contributed to statistical analysis and review of the manuscript. M.D. and F.D. supervised and helped with the elaboration of the study.

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