Acute Febrile Syndrome in an endemic region of Colombia: What is there beyond Dengue?

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ARTICLE INFORMATION

ABSTRACT

Objective: Evaluate the presence of alternative diagnoses in patients presenting with Acute Febrile Syndrome (AFS) and a negative Dengue IgM test.

Methods: A retrospective descriptive study of the clinical records of patients who presented to the emergency department of ESE Hospital Universitario San Jorge from Pereira, Colombia with Dengue-like Acute Febrile Syndrome between January 2014 and December 2017.

Results: 561 patients attending to the emergency department of a third level care and referral center in Pereira, Colombia with a Dengue-like Acute Febrile Syndrome. One hundred thirty three (23.7%) patients were included in the analysis. The three most common alternative diagnoses were leptospirosis (7.5%), malaria (3.8%) and bacterial bloodstream infection (2.3%). The main AFS presentations were hemorrhagic (34.6%), exanthematic (21.1%) and undifferentiated (21.1%). A statistically significant proportion were from rural origin and coursed with anemia, leukocytosis, hyperbilirrubinemia, icterohemorrhagic and icteric AFS. Acute kidney injury with serum creatinine >2 mg/dl and blood urea nitrogen >25 mg/dl were associated with the finding of an alternative diagnosis.

Conclusions: The low rate of definitive diagnosis, the low request of tests to exclude Malaria, and the significant proportion of Dengue IgM tests requested within the first 4 days of fever, suggests the need to evaluate clinical practice. Training the Emergency Department personnel in the recognition of Acute Febrile Syndrome, as well as the development of prospective investigations, could lead to improvement in the quality of attention, the outcomes, and higher rates of diagnosis.

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Síndrome Febril Agudo en una región endémica de Colombia: ¿Qué hay más allá del Dengue?

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INFORMACIÓN ARTÍCULO

RESUMEN

Objetivo: evaluar la presencia de diagnósticos alternativos en pacientes con Síndrome Febril Agudo y prueba IgM negativa para Dengue.

Métodos: estudio descriptivo retrospectivo de las historias clínicas de los pacientes que se presentaron al servicio de urgencias de la ESE Hospital Universitario San Jorge de Pereira con Síndrome Febril Agudo similar al Dengue entre enero de 2014 y diciembre de 2017.

Resultados: 561 pacientes acudieron al servicio de urgencias con un Síndrome Febril Agudo similar a Dengue. 133 (23,7 %) pacientes fueron analizados. Las tres causas más comunes fueron Leptospirosis (7,5 %), Malaria (3,8 %) y Bacteremia (2,3 %). Las tres presentaciones clínicas más frecuentes de Síndrome Febril Agudo fueron: hemorrágico (34,6 %), exantemático (21,1 %) e indiferenciado (21,1 %). Una proporción significativa fue de procedencia rural y cursó con anemia, leucocitosis, hiperbilirrubinemia y síndromes icterohemorrágico e ictérico. La presencia de falla renal aguda con creatinina mayor a 2 mg/dl y nitrógeno ureico en sangre mayor a 25 mg/dl se asociaron con el hallazgo de un diagnóstico alternativo.

Conclusiones: la baja tasa de diagnóstico definitivo, la baja solicitud de pruebas para excluir malaria, y la gran proporción de pacientes con solicitud de prueba para Dengue dentro de los primeros cinco días de fiebre demuestra la necesidad de revisar la práctica clínica. El entrenamiento del personal del servicio de urgencias en el reconocimiento del Síndrome Febril Agudo, al igual que la realización de investigaciones prospectivas pueden llevar a mejorar la calidad de atención, los desenlaces y mayores tasas de diagnóstico.

Introduction

More than 60 infectious/contagious diseases known in Colombia share a clinical presentation known as Acute Febrile Syndrome (AFS) (1). AFS refers to sudden onset of fever of less than 7 days, in patients between 5 to 65 years of age, without an apparent infectious source/focus (1). Dengue Fever (DF) is the main cause of AFS in Colombia, ranging from 37 to 43.6% of the cases, followed by Rickettsiosis and Leptospirosis (1). Knowing the differential diagnosis of the main causes of this syndrome is key to any physician who comes upon this scenario. Wise choices of tests may confirm the most common causes, and less probable diagnoses may be ruled out based solely on the clinical examination.

In the first 26 epidemiological weeks of 2019, 1,297,632 cases of DF were reported in Latin American countries with the confirmation of 46.7% of them (2). According to Colombia's National Institute of Health, the cumulative cases of DF up to the 23rd week of 2020 are 56,923, pointing Risaralda as a territory with alarming behavior for this disease (3). The diagnosis of DF is essentially made through clinical evaluation (4). Case confirmation requires testing serum for detection of IgM antibodies against Dengue, in which flaws have been evidenced due to the request of the test within the first 5 days of fever onset, a sign of inadequate clinical practice which could lead to false negative cases (5).

There is an underestimation of pathogens that are known to be the cause of AFS but are not tested for, therefore underreported (6). Among these are: Leptospirosis, Rickettsiosis, Bartonellosis, Q fever, Hantavirus, Chagas disease, and endemic invasive mycosis (7). Missing these diagnoses could lead to increased morbidity and mortality among this group of patients. A syndromic approximation of patients with AFS is recommended, separating them in categories according to their associated symptoms such as jaundice (e.g. Hepatitis A/B, Malaria, Leptospirosis, and Yellow Fever), hemorrhagic signs (e.g. Dengue), exanthema (e.g. Dengue, Rickettsiosis, Chikungunya, HIV), adenopathy (e.g. Toxoplasmosis) or unspecific febrile syndrome (e.g. Rickettsiosis, Typhoid Fever) (1).

As fever is one of the most common patient complaints in the Emergency Department (ED) (8), the objective of this paper is to determine the current state of clinical practice and to identify alternative diagnoses among those patients with clinical suspicion of DF, who had negative IgM serum testing, presenting to a referral center of Pereira, Colombia.

Methods

Study design

A descriptive retrospective study.

Setting

The hospital is in Pereira, Risaralda, Colombia (4°48′53″N, 75°41′40″O), at 1411 meters above sea level (MASL) with an annual mean temperature of 22°C, a relative humidity varying between 74% and 79%, and a total area of 702 square kilometers. The estimated population is of 443,554 people according to the National Administrative Department of Statistics (DANE). This institution is a third level care and referral center for people from all the 14 municipalities in Risaralda, as well as some near municipalities of two neighboring departments: Caldas and the north of Valle del Cauca.

Subject of study/Population

Clinical records were obtained for this study from patients who were five years and older that attended the ED of ESE Hospital Universitario San Jorge de Pereira, Colombia between January 2014

and December 2017, and had a Dengue IgM test requested. The first step was the identification of those who tested negative and positive. Inclusion criteria were: patients with a negative IgM test presenting with AFS to the emergency department, who had suspicion of DF. AFS was defined as sudden onset of fever (temperature of 37.6 ºC or higher at admission or during hospitalization) of less than 7 days, in patients who were 5 years or older, without an apparent infectious source/focus. Exclusion criteria used were: first, patients that did not have fever during the period of analysis; and, second, patients with incomplete data for the variables included in the study. Clinical records of patients that tested negative for Dengue IgM test were individually analyzed by all the authors to determine if patients fit the definition of AFS, to apply the remaining exclusion criteria, and to collect all the necessary information to fill out the excel data base. Sample size was not calculated because all patients that presented to the ED during the period of analysis and fulfill the inclusion/exclusion criteria were included. There was not any direct intervention over clinical practice regarding the attention of the patients included in this study, as well as any practice of laboratory or physical evaluation from the authors.

Variables

The presence of fever was defined as an axillary body temperature registered at admission or during hospitalization of 37.6 ºC or more. Cases were classified according to the syndromic approximation suggested by Cortés JA et al (1). Jaundice was defined as a yellowish discoloration of the skin or mucous membranes with total bilirubin of 1.3 mg/dL or more. Hemorrhagic signs were defined as the presence of any of the following: spontaneous bleeding, petechiae, ecchymoses, hematomas, easy bruising, or a platelet count of less than 120.000/µL.

Exanthema was defined as the presence of red discoloration of the skin or rash recorded during the physical examination. Adenopathy was defined as the presence of enlargement of any lymph nodes registered in the clinical findings. Hepatomegaly was defined as the presence of craniocaudal span of 13 cm or more in ultrasonography or palpation of liver below costal margin. Splenomegaly was defined as the largest dimension of the spleen measuring 13 cm or more in ultrasonography or palpation of the spleen. Anemia was defined as hemoglobin levels of 13 or less for men and 12 or less for women.

Leukocytosis was defined as more than 10,000 WBC/µL. Unspecific febrile syndrome was defined as the presence of fever lacking any group of symptoms that lead towards any specific febrile syndrome (e.g. hemorrhagic, icteric, exanthematic).

Definite diagnoses were stablished based on positivity of the following tests by etiology: Dengue (Dengue IgM), Leptospirosis (*Leptospira* spp. IgM), Malaria (Malaria Blood Smear), Hepatitis B (Hepatitis B Surface Antigen – HbsAG), Hepatitis C (Antibodies against Hepatitis C), HIV (ELISA), bloodstream infection (Blood culture), Syphilis (VDRL/RPR), Toxoplasmosis (*Toxoplasma gondii* IgM), and *Parvovirus B19* (Blood Marrow Biopsy). Given the recognition in the literature of composite syndromes of AFS, two additional groups were created: exanthematic-hemorrhagic and ictero-hemorrhagic. These were defined as the simultaneous presence of the manifestations of these syndromes in the same patient. Furthermore, patients were classified in two groups, whether they have a definitive diagnosis or not.

Data collection and source

To describe sociodemographic characteristics, clinical records information was registered in a formulary designed and approved by the research group for that purpose. Variables related to the patients were collected, such as: 1. Age and sex, 2. housing municipality, and 3. clinical manifestations at admission and during the length of stay. The main and only sources of information were the patients' clinical records.

Statistical methods

Continuous variables were described with medians and interquartile ranges (IQR). Categorical variables were described as proportions. A bivariate analysis was made according to clinical and sociodemographic characteristics among each category. Statistical significance among groups was evaluated using Chi-Square test or Fisher's exact test for categorical variables and Mann-Whitney U Test for comparing medians. The data were analyzed using Microsoft Excel software and STATA 16.0.

Ethics statement

This descriptive study was approved by the Institutional Research Board of the ESE Hospital Universitario San Jorge from Pereira and the Ethics Committee of the Universidad Tecnológica de Pereira, Colombia. It waived the need for informed consent of the subjects, given that this was a historical review of patient records, and no interventions were done. This was classified as an investigation without risk according to national and international guidelines. The data collection was made following the recommendations of good clinical practice guidelines and the declaration of Helsinki.

Results

Throughout 2014 until 2017, 561 patients that attended the ED of ESE Hospital Universitario San Jorge had Dengue IgM test requested (Figure 1). DF diagnosis was confirmed in 312 cases (55.6%). 95 patients (16.9%) had Dengue IgM requested but it was not practiced. 154 cases (27.4%) tested negative for Dengue IgM (Table 1). Among these patients, 3 cases (2%) had no fever during observation and 18 patients were under the age of 5, therefore were excluded, leaving 133 (23.7%) patients for analysis. 54.9% (n=61) of analyzed patients were females, the median age was 26 years (IQR 18-47), with 22% coming from rural areas, a median of 4 days of fever at admission (IQR 3-6) and a median of 5 days (IQR 3-7) from fever onset to DF IgM testing. 81 cases (60.9%) had IgM test for DF done before the sixth day of illness.
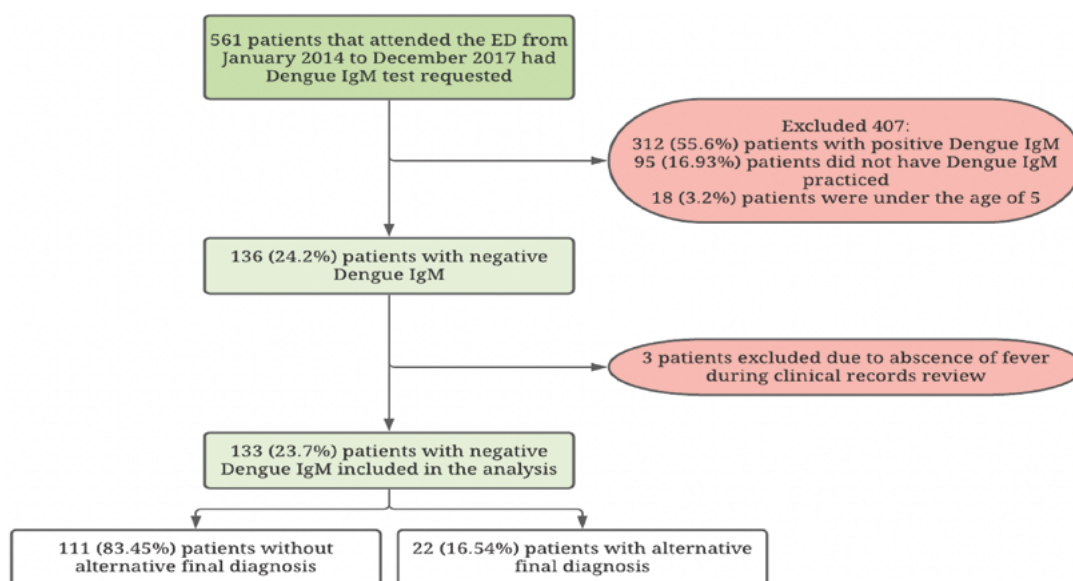
Figure 1. Flow of cases in the study
Source: own creation

Table 1. Patient characteristics of unconfirmed dengue cases according to final diagnosis status

Variables	No Alternative diagnosis Total (%) n=111	Alternative diagnosis Total (%) n=22	p
Female	61 (54.9)	10 (45,5)	0.414[6]
Age (IQR)	26 (18-47)	36.5 (22-52)	0.229[7]
5 to 14 y	15 (13.5)	3 (13.6)	
15 to 65 y	87 (78.4)	17 (77.3)	1.000[8]
More than 65 y	9 (8.1)	2 (9.1)	
Procedence			
Rural	22 (19.8)	9 (40.9)	0.033[6]
Insurance status			
Subsidiated	44 (39.6)	8 (36.6)	
Contributors	51 (45.9)	8 (36.6)	
Indigenous	0 (0)	1 (4.5)	0.216[6]
Vinculated	13 (11.7)	4 (18.2)	
Military forces	3 (2.7)	1 (4.55)	
Days of fever at admission (IQR)	4 (3-6)	5.5 (4-8)	0.008[7]
Days of fever at Dengue IgM test	5 (3-7)	5.5 (4-10)	0.066[7]
Headache	70 (63.1)	14 (63.6)	0.959[6]
Myalgia	79 (71.2)	16 (72.3)	0.883[6]
Respiratory manifestations	4 (3.6)	3 (13.6)	0.089[8]
Hepatosplenomegaly	10 (9.0)	5 (22.7)	0.075[8]
Thrombocytopenia[1]	47 (42.3)	13 (59.1)	0.149[6]
Leukocytosis[2]	14 (12.6)	7 (31.8)	0.048[8]
Anemia[3]	37 (33.3)	18 (81.8)	<0.001[6]
Hyperbilirrubinemia[4] (n=71)	5/52 (9.6)	7/19 (36.8)	0.012
BUN > 25 mg/dL	3 (2.7)	6 (27.3)	<0.001[8]
Creatinine > 2 mg/dL	0 (0)	2 (9.1)	0.016[8]
Hospital stay (IQR)	3 (1-4)	4 (2-8)	0.035[7]
Death as outcome[5]	3 (2.5)	2 (6.7)	0.032[8]

Abbreviations: n: sample number, p: probability, IQR: interquartile range, mg: milligrams, dL: deciliter, IgM: immunoglobulin M. [1]Platelets < 100.000/μL. [2]Leukocites >10.000/μL. [3]Hemoblogin < 13 g/dL in males and < 12 g/dL in females. [4]Total bilirubin > 1.2 mg/dL. [5]Status at discharge. [6]Pearson chi². [7]Mann-Whitney. [8]Fisher's exact test. Source: own creation

The three main alternative diagnoses were leptospirosis (7.5%, n=10), malaria (3.8%, n=5) and bacterial bloodstream infection (2.3%, n=3) (Table 2). Only 22 patients (16.54%) without DF confirmation had a final confirmed alternative diagnosis. Of these patients, a statistically significant proportion were from rural origin and coursed with anemia, leukocytosis, hyperbilirrubinemia, icterohemorrhagic and icteric AFS. The three most common AFS presentations were hemorrhagic (34.6%, n=46), exanthematic (21.1%, n=28) and undifferentiated (21.1%, n=28) (Table 3). Myalgia (71.2%, n=79) and headache (63.1%, n=70) were the most common clinical manifestations.

Table 2. Diagnostic test results distribution

n=133	Positive Total (%)	Negative Total (%)	Not Done Total (%)
IgM *Leptospira*	10 (7.5)	32 (24.1)	91 (68.4)
Malaria blood smear	5 (3.8)	44 (33.1)	84 (63.2)
Blood cultures[1]	3 (2.3)	10 (7.5)	120 (90.2)
HIV ELISA	2 (1.5)	54 (40.6)	77 (57.9)
HBsAg	0 (0)	42 (31.6)	91 (68.4)
HCV Ab	0 (0)	18 (13.5)	115 (86.5)
VDRL/RPR	2 (1.5)	39 (29.3)	92 (69.2)
IgM *Toxoplasma gondii*	2 (1.5)	3 (2.3)	128 (96.3)
BMB for PVB19	1 (0.7)	0 (0)	132 (99.3)

Abbreviations: MBS: malaria blood smear, HIV: human immunodeficiency virus, ELISA: Enzyme-Linked Immunosorbent Assay, IgM: immunoglobulin M, HBsAg: hepatitis B surface antigen, HCV: hepatitis C, Ab: antibody, VDRL: Venereal Disease Research Laboratory, RPR: Rapid Plasma Reagin, BMB: Bone Marrow Biopsy. [1]3 for gram negative bacilli (2 *Escherichia coli* and 1 *Klebsiella pneumoniae*). Source: own creation

Table 3. Syndromic presentation of unconfirmed dengue cases according to final diagnosis status[1]

Variables	No Alternative diagnosis Total (%) n=111	Alternative diagnosis Total (%) n=22	Total (%) n=133
Undiferentiated	24 (85.7)	4 (14.9)	28 (21.1)
Hemorrhagic	38 (82.6)	8 (17.4)	46 (34.6)
Exanthematic	27 (96.4)	1 (3.6)	28 (21.1)
Exanthematic-hemorrhagic	15 (88.2)	2 (11.7)	17 (12.8)
Icterohemorrhagic	6 (54.5)	5 (45.5)	11 (8.3)
Icteric	1 (33.3)	2 (66.7)	3 (2.3)

[1]Fisher's exact test p=0.010. Source: own creation

In 84 patients (63.2%) with dengue-like AFS, no tests for malaria (Blood Smear) were performed. HIV testing (ELISA) was only carried in 56 cases (37.08%), IgM for leptospirosis in 42 cases (31.57%), and blood cultures were drawn in only 13 cases (9.77%). Coinfections were detected: 2 (1.3%) patients tested positive for VIH (ELISA test), one of them also had a positive test for Syphilis (Positive VDRL) and the other one for *Toxoplasma gondii* (IgM test); and 1 patient (0.66%, n=1) tested positive for both malaria (Malaria Blood Smear) and leptospirosis (IgM test).

Patients with a definitive diagnosis had a statistically significant longer hospital stay (3 (IQR 1-4) vs 4 (IQR 2-8) days, p=0.035) and greater mortality (3/111 (2.5%) vs 2/22 (6.7%), p=0.032). On the other hand, among patients without a definitive diagnosis and an undifferentiated or icterohemorrhagic presentation of AFS, blood cultures and Hepatitis C antibodies were the most used tests. In general, the use of malaria (29.7%, n=33), HIV (42.3%, n=47) and leptospirosis (20.7%, n=23) testing was low in all subgroups of AFS without a definitive diagnosis (Table 4), and these patients did not have any specific clinical presentation favoring its utilization.

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Table 4. Tests ordered in the patients without alternative diagnosis according to febrile syndrome

Test ordered	Undife-rentiated Total (%)	Hemo-rrhagic Total (%)	Exanthe-matic Total (%)	Exanthe-matic-Hemo-rrhagic Total (%)	Icterohe-morrha-gic Total (%)	Icteric Total (%)	All Total (%)	p[1]
	n= 24	n= 38	n= 27	n= 15	n= 6	n= 1	n=111	
MBS	10 (41.7)	14 (36.8)	4 (14.8)	3 (20)	2 (33.3)	0	33 (29.7)	0.218
Blood cultures	3 (12.5)	1 (2.6)	0	0	2 (33.3)	1 (100)	7 (6.3)	0.001
HIV ELISA	11 (45.8)	16 (42.1)	11 (40.7)	6 (40)	2 (33.3)	1 (100)	47 (42.3)	0.947
IgM *Leptospira* spp.	6 (25)	8 (21.1)	3 (11.1)	2 (13.3)	3 (50)	1 (100)	23 (20.7)	0.120
HBsAg	8 (33.3)	11 (28.9)	6 (22.2)	5 (33.3)	2 (33.3)	1 (100)	33 (29.7)	0.672
HCV Ab	3 (12.5)	4 (10.5)	0	2 (13.3)	2 (33.3)	1 (100)	12 (10.8)	0.018
VDRL/RPR	7 (29.2)	10 (26.3)	8 (29.6)	3 (20)	1 (16.7)	1 (100)	30 (27)	0.716
IgM CMV	0	2 (5.3)	1 (3.7)	2 (13.3)	1 (16.7)	0	6 (5.4)	0.249

Abbreviations: MBS: malaria blood smear, HIV: human immunodeficiency virus, ELISA: Enzyme-Linked Immunosorbent Assay, IgM: immunoglobulin M, HBsAg: hepatitis B surface antigen, HCV: hepatitis C, Ab: antibody, VDRL: Venereal Disease Research Laboratory, RPR: Rapid Plasma Reagin. [1]Fisher's exact test. Source: own creation

Discussion

The findings from this study highlight the need of reinforcing clinical practice concerning the approach to patients presenting with AFS to the emergency department. The most common etiologies for AFS were, in a considerable proportion, not properly addressed according to the number of tests done for these (malaria, leptospirosis, rickettsiosis, etc.). The use of diagnostic test in patients not meeting clinical case definitions was common. Regardless, our findings suggest that the three main detected causes of Dengue-like AFS were: leptospirosis, malaria, and bloodstream infection.

Risaralda is a department, in average, under 1516 MASL, what makes it the perfect place for any cause of AFS to occur. 21.8% (n=74,596) of the population in Risaralda lives in rural areas (9), which have sanitary deficits such as inappropriate waste disposal and water drains; cultural/educational factors that condition poor hygiene, inappropriate living conditions, unsafe sex, and unhealthy food source that could also play a determinant role in the incidence of AFS (10).

These conditions are relevant since a significant proportion of patients with alternative diagnosis were from rural origin, a population characterized for having the highest incidence of malaria and leptospirosis in Risaralda, the two main alternative diagnoses in this study. Consistently, 22% of the analyzed patients were from rural origin. The association of anemia, leukocytosis, hyperbilirubinemia, and acute kidney injury with final alternative diagnosis can be explained by their occurrence in the clinical course of any of the three main alternative causes of Dengue-like AFS identified in our study. Regarding alternative diagnosis to Dengue, the underutilization of tests to diagnose leptospirosis and malaria, which are among the three main etiologies of AFS and AUFI in Colombia, is of concern (11,12). Exanthematic, hemorrhagic, and undifferentiated AFS favored having a final diagnosis at discharge, which is related to our findings of leptospirosis and malaria being the two main alternative diagnoses, as both can cause any of these three clinical profiles. We were not able to rule out DF in 60.9% of the cases, as IgM test was drawn within the first 5 days of fever, leading to

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a large potential of undiagnosed DF cases (13,14). In a referral center of a South American country, over 80% of cases with DF-like AFS were ruled out without an etiological diagnosis (2).

Despite being an endemic area for malaria and having a high frequency of leptospirosis, rickettsiosis and HIV, the active search of these entities is not taken into account during the study of undifferentiated and icterohemorrhagic AFS (2). Interestingly, among our patients without a definite diagnosis, whose main syndromic presentation was icterohemorrhagic and undifferentiated fever, there were no significant number of tests to identify leptospirosis or rickettsiosis, the latter due to no availability of Indirect Immunofluorescence (IIF) test. Overall, testing for leptospirosis was low, even in patients with alternative diagnoses.

This reinforces the concept of leptospirosis as a neglected disease. Faccini-Martínez et al. reported comparable proportions of patients who ended up having no confirmed alternative diagnoses (86.6% vs 83.4%) (15), where our findings of bloodstream and HIV infection become relevant as they could explain the clinical profile of some patients presenting with AFS.

Other studies have approached our objective from a different point of view. Arroyave et al. (12) analyzed 220 cases with non-malaria AFS, finding DF (37.3%) as the main cause followed by Leptospirosis (14.1%), and Rickettsiosis (2.7%). Leptospirosis represented 8.2% of cases with alternative diagnosis among patients that did not have Dengue, which is comparable to our rate of diagnosis (7.5%). The difference between our study and Arroyave's lies in that they practiced tests for leptospirosis, dengue, rickettsiosis, arenavirus, and hantavirus in all the patients included in their study. 68.4% of our patients did not have tests performed for Leptospirosis and Arroyave's sample is small as ours, therefore both of our rates of isolation are not a true reflection of what we could encounter in clinical practice.

Only one study in Brazil during 2008 evaluated other causes of AFS in patients with a negative IgM for dengue, finding a definitive diagnosis in 27.1% of the cases. The results were limited because investigators restricted testing to Dengue, Rubella, Leptospirosis and Hantavirus, showing an 11.8% seroconversion for dengue and leptospirosis as the main cause (13.9%) (16).

Two other studies were conducted in Colombia, one on non-malarial AFS (12) and one on AUFI (11), those studies have shown that there is an increase in the rate of final diagnosis (between 42.7% to 69% of cases) if routine testing for hantavirus, leptospirosis, dengue, malaria and rickettsiosis are systematically done. Also, these studies showed that, although there is a widespread idea that certain manifestations could help to clinically differentiate patients with these infections, it is frequent to find coinfections and there are no statistically significant differences between manifestations among these etiologies. Clinical case definition for dengue, leptospirosis, and malaria in Colombian guidelines overlap in several manifestations. Hence, the clinical picture could lack specificity and can be even misleading, which can explain why we had 3 patients with coinfections as they were tested to narrow down diagnostic possibilities, findings also reported in other studies (12).

Since this was a retrospective study of clinical records, it has several limitations. First, information collected was limited to what was written by the attending physician. Therefore, clinical data necessary to specify the syndromic profile and the remaining variables were not widely available. Second, there was a scarce availability of the laboratory tests needed to rule out *Rickettsia* spp. (IIF), typhoid fever (PCR), *Leptospira* spp (PCR and microagglutination) and arboviral infections besides DF. Third, the high proportion of DF IgM tests taken before the 6th day of fever could have led to a higher proportion of negative DF cases because of misdiagnosis. Fourth, this study was conducted on a small sample over a short period of time. Fifth, laboratory tests practiced in the differential diagnosis lacked complementary tests (e.g Hepatitis B virus anti core IgM and IgG), context (e.g *Toxoplasma gondii* IgM positivity lasting beyond 1 year), appropriateness (e.g Parvovirus B19 IgM serology instead of Bone Marrow Aspiration) or were not available (e.g Viral panels for Zika, Chikungunya, and IIF

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for Rickettsiosis). Sixth, with the available data, it was not possible to know the exact prevalence of AFS that is caused by leptospirosis, typhoid fever, rickettsiosis, malaria, or acute retroviral syndrome. Hence, it reflects rates of isolation.

Overall, we found that there is an increasing need of reinforcement of clinical practice when approaching to patients with AFS. Differential diagnosis should take in account local epidemiology and clinical presentations that favor specific laboratory testing, two main items we intended to contribute to with our results. Further research is needed to determine the impact of training the ED personnel in the recognition of AFS with respect to improvement in quality of attention, and rates of diagnosis. Results from these types of investigations might improve the capacity and availability of tests for neglected and underreported causes like rickettsiosis and leptospirosis. Once this is accomplished, the real impact of these zoonotic AFS in Colombia could be known. Local common causes of AFS should be recognized to ensue provisional adequate treatment and targeted laboratory evaluation.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could represent a conflict of interest.

Acknowledgments

References

1. Cortés JA, Romero Moreno LF, Aguirre León CA, Pinzón Lozano L, Cuervo SI. Enfoque clínico del síndrome febril agudo en Colombia. Infectio. 2017;21:39–50. https://doi.org/10.22354/in.v21i1.640

2. Zambrano LI, Rodriguez E, Espinoza-Salvado IA, Rodríguez-Morales AJ. Dengue in Honduras and the Americas: The epidemics are back! Travel Med Infect Dis. 2019;31:101456. https://doi.org/10.1016/j.tmaid.2019.07.012

3. Intituto Nacional de Salud [internet]. Bogotá: Instituto Nacional de Salud; 2020 [cited June 11 2021]. Qué debe saber del Dengue [5 screens aprox.]. Available in: https://www.ins.gov.co/Noticias/Paginas/Dengue.aspx

4. Clemen G, Angel J, Montes C, Tovar J, Osorio L. Contribución de la prueba rápida NS1 e IgM al diagnóstico de dengue en Colombia en el periodo pre-zika. Infectio. 2019;23:259. https://doi.org/10.22354/in.v23i3.790

5. Torres EM. La prevención de la mortalidad por dengue: un espacio y un reto para la atención primaria de salud. Rev Panam Salud Pública. 2006;20:60–74. https://doi.org/10.1590/S1020- 49892006000700013

6. Rhee C, Kharod GA, Schaad N, Furukawa NW, Vora NM, Blaney DD, et al. Global knowledge gaps in acute febrile illness etiologic investigations: A scoping review. PLoS Negl Trop Dis. 2019;13:1–16. https://doi.org/10.1371/journal.pntd.0007792

7. Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. Clin Microbiol Infect. 2018;24:827–35. https://doi.org/10.1016/j.cmi.2018.05.001

8. DeWitt S, Chavez SA, Perkins J, Long B, Koyfman A. Evaluation of fever in the emergency department. Am J Emerg Med. 2017;35:1755–8. https://doi.org/10.1016/j.ajem.2017.08.030

9. Departamento Administrativo Nacional de Estadística (DANE). Resultados Censo Nacional de Población y Vivienda 2018. In: Condición de Ocupación de la Vivienda – Risaralda y Pereira. Pereira, Risaralda, Colombia: DANE; 2019. p. 30.

10. Secretaría Departamental de Risaralda. Análisis de Situación de Salud con el modelo de los Determinantes Sociales en Salud. In: Capítulo III. Priorización de los efectos de salud. 3.2 Priorización de los problemas de salud. Tabla 44. Risaralda, Colombia: Secretaría Departamental; 2020. p. 145

11. Mattar S, Tique V, Miranda J, Montes E, Garzon D. Undifferentiated tropical febrile illness in Cordoba, Colombia: Not everything is dengue. J Infect Public Health. 2017;10:507–12. https://doi.org/10.1016/j.jiph.2016.09.014

12. Arroyave E, Londoño AF, Quintero JC, Agudelo-Florez P, Arboleda M, Díaz FJ, et al. Etiología y caracterización epidemiológica del síndrome febril no malárico en tres municipios del Urabá antioqueño, Colombia. Biomédica. 2012;33:99–107. https://doi.org/10.7705/biomedica.v33i0.734

13. Instituto Nacional de Salud (Colombia). Guía para la atención clínica integral del paciente con dengue. In: Confirmación por Laboratorio. Bogotá, Colombia: El Instituto; 2010. p. 34

14. Carvajal venus ZM, Martinez CND, Vergara JMA. Memorias © 2012 - 2013. Bogotá: Minist Prot Soc. 2013;7–46.

15. Faccini-Martínez ÁA, Ramírez-Hernández A, Barreto C, Forero-Becerra E, Millán D, Valbuena E, et al. Epidemiology of spotted fever group rickettsioses and acute undifferentiated Febrile Illness in Villeta, Colombia. Am J Trop Med Hyg. 2017;97:782–8. https://doi.org/10.4269/ajtmh.16-0442

16. da Silva AD, Evangelista M do SN. Syndromic surveillance: Etiologic study of acute febrile illness in dengue suspicious cases with negative serology. Brazil, Federal district, 2008. Rev Inst Med Trop Sao Paulo. 2010;52:237–42. https://doi.org/10.1590/S0036-46652010000500003