



Undifferentiated tropical febrile illness in Cordoba, Colombia: Not everything is dengue



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SUMMARY

In Colombia, undifferentiated tropical febrile illness (UTFI) are frequent and of considerable concern. They also share many clinical features. Between 2012 and 2013 in an endemic tropical area of Cordoba, Colombia, we conducted a prospective study to establish an etiological diagnosis of UTFI. Using diagnostic tests for dengue, leptospirosis, hantavirus, malaria, rickettsia, brucellosis, hepatitis A and B on 100 patients recruited for the study. We identified 69 patients with presumed UTFI: leptospirosis ($n=27$), dengue ($n=26$), hantavirus infection ($n=4$), malaria ($n=4$), rickettsial infection ($n=2$), hepatitis A ($n=1$), and brucellosis ($n=1$); no hepatitis B cases were detected. Co-infections with malaria and leptospirosis ($n=1$), hepatitis A and dengue ($n=1$), hantavirus and dengue ($n=1$), hantavirus, dengue, and leptospirosis ($n=1$) were also identified. No etiologic agent was identified for 31 patients. We conclude that other etiologic agents besides dengue virus deserve greater attention by physicians and public health authorities in tropical area of Colombia.

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Introduction

During the past 20 years, there has been a dramatic emergence and re-emergence of UTFI caused by viruses, bacteria and parasites previously believed to be under control. These include dengue, Chikungunya, yellow fever, Venezuelan equine encephalitis, Saint Louis encephalitis, mayaravirus, arenavirus and hantavirus diseases, and other diseases caused by bacteria and parasites that have extended their geographic distribution, such as *Leptospira*, *Rickettsia* and *Plasmodium* [1]. The epidemiology and even the definition syndrome of many of these diseases is changing in the tropics and globally. Population growth, urbanization, unplanned human activities, displacement of people by internal violence, and even climate variability contribute, sometimes synergistically to the changing epidemiology of UTFI in the Colombian tropics.

Some UTFI, are caused by arthropod-borne agents transmitted by mosquitoes or ticks. For others, person-to-person transmission may occur through direct contact with infected blood or secretions. Animal reservoirs are often wild rodents; however, pets, domestic

livestock, urban mice, monkeys, and other primates may also serve as intermediate hosts [1].

The definition of viral hemorrhagic fevers describes a potentially fatal clinical syndrome characterized by an insidious onset of nonspecific signs followed by bleeding manifestations and shock. The hemorrhagic fever syndrome is also characterized by capillary leak and bleeding diathesis. The clinical manifestations and even histopathological findings are similar among the diseases and differential diagnosis may be difficult [1]. Because, the undifferentiated febrile illnesses can be caused by bacteria, virus and parasites and they show very similar clinical features, the definition of viral hemorrhagic fevers can be extended to them.

In Colombia endemic UTFIs are frequent and of considerable concern. Because dengue is endemic in tropical Colombia, the disease is often over-diagnosed, while other UTFIs such as leptospirosis, hantavirus and arenavirus infections, rickettsioses, Venezuelan equine encephalitis, chikungunya virus infection, Zika virus infection and malaria are misdiagnosed as dengue. Those diseases are clinically indistinguishable from dengue and other vector-borne diseases and confirmatory diagnosis requires specific laboratory tests that are often unavailable or too expensive in developing countries [2]. Consequently, many of the endemic diseases mentioned above remain mostly undiagnosed in Colombia. Recent surveillance suggests that Venezuelan equine encephalitis may represent up to 10% of the 'dengue' burden in neotropical cities,

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or tens of thousands of cases per year throughout Latin America [2]. In addition, co-infections are common in the tropics [3]. Tropical fevers diseases are defined as diseases that are prevalent in, or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation. Most often disease is transmitted by an insect “bite”, which causes transmission of the infectious agent [4].

Because, clinical manifestations and even histopathological findings are comparable and challenging to make a differential diagnosis, we conducted a study to establish the diagnosis of UTFI patients at a hospital in the Caribbean area of Colombia.

Materials and methods

Patients and data collection

Between 2012 and 2013, we conducted active surveillance at the main hospital in an endemic tropical area of Cordoba (Colombia), to establish the etiologic diagnoses of UTFI cases. The undifferentiated febrile illnesses are defined as a fever without a focus of infection on initial physical examination or in basic laboratory tests [5]. In Colombia as a tropical country, tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. Some of these occur throughout the year and some especially in rainy and post-rainy season [4]. During our study, there was no “fenomeno del niño” nor floods, distribution of rainy was normal during the year of the study. The studied area is not endemic for yellow fever and West Nile virus disease.

Patients with acute phase were admitted to the emergency ward with febrile illnesses accompanied by prodromal symptoms typical of UTFI infection, including myalgia, arthralgia, headache, asthenia, chills, icterus, dyspnea, abdominal pain, rash, and nausea. Patients were enrolled in a clinical trial for UTFI at the University of Cordoba. Serum samples were collected on admission and at discharge. Clinical data collected for each patient during their hospital stay included name, age, sex, history of illness (date of onset of disease and date of admission), symptoms, physical findings, and laboratory findings, including blood cell counts, prothrombin time, platelet counts, liver function (bilirubin, ASAT, ALAT), and renal function (creatinine). Clinical tests such as chest X-ray, electrocardiogram, and pulse oximetry were done depending on patient clinical condition. We included 100 consecutive clinically suspected UTFI cases according to the Centers for Disease Control and Prevention (CDC) case definition of viral hemorrhagic fevers [6]. For leptospira, rickettsia and malaria we followed the protocols of National Health Institute of Colombia [7,8].

Exclusion criteria

We excluded patients with upper urinary tract infections, bronchitis, tonsillitis, otitis media, tuberculosis, liver abscesses, diarrhea as initial and primary symptom, chronic liver disease, hemorrhagic syndrome of non-infectious etiology, acute poisoning, tumors, hematological diseases, autoimmune diseases, snake-bites, diseases of the biliary tract, patients under a year old, and those with possible confusion with physiological jaundice.

Sampling and diagnostic tests

From each patient we collected one acute phase and one convalescent phase (15–30 days after illness) peripheral venous blood sample. Seroconversion was defined as negative serology with becomes positive in a convalescent serum sample, hence the increase of detectable antibodies (usually four times titers increase) between the first sample and second one was used as a definition in

the present study. Diagnostic tests performed included: Duo quick test dengue NS1 Ag; ELISA IgM/IgG Ad-BIO®; Leptospirosis MAT using 19 serovars and ELISA IgM Panbio® diagnostics (Queensland, Australia); hantavirus IgG and IGM DxSelect™ (Focus Technologies, California, USA); Malaria thick smear; Rickettsia spotted fever group IgG IFI antigens from *Rickettsia rickettsii* (a strain Taiaçu) donated by M. Labruna of University of Sao Paulo (Brazil); Brucellosis Rose Bengal antigen (Pourquier Institute, Montpellier, France); hepatitis A rapid test for IgG/IgM Bio LINE Standard Diagnostics and surface antigen hepatitis B and hepatitis B anticore IgM LINE Standard Diagnostics (Republic of Korea).

Statistical analysis

The Chi-squared test to compare proportions was used, analyses were performed with EPI-INFO (Version 7.2, CDC, USA) software for Windows, with a probability (*p*) value <0.05 as statistically significant.

Ethical aspects

The research committee of the Institute of Tropical Biological Research of the University of Cordoba and hospital San Jeronimo of Monteria approved the ethics protocol, and informed consent was obtained from all patients. Patients were anonymized using a numeric code. The study incorporated procedures, management and conservation of samples, and technical-administrative procedures for health research required by resolution 8430 of the Ministry of Health of Colombia, in 1993 [9] and declaration of Helsinki for ethical and medical research in human subjects [10].

Results

Etiologic agents of undifferentiated tropical fevers

IgG or IgM seroconversion allowed the demonstration of UTFI infection in 69 of the 100 patients in the study. The pathologies diagnosed were: leptospirosis (*n* = 27), dengue (*n* = 26), hantavirus infection (*n* = 4), malaria (*n* = 4), rickettsiosis (*n* = 2), hepatitis A (*n* = 1) and brucellosis (*n* = 1). No hepatitis B cases were detected (Table 1). Co-infections of malaria and leptospira (*n* = 1), hepatitis A and dengue (*n* = 1), hantavirus and dengue (*n* = 1), hantavirus, dengue, and leptospirosis (*n* = 1) were identified. In 31 (31%) of the patients no etiology agent was identified (Table 1).

The patient's age range was 1–79 years, mean = 27 years; 40 pediatric patients (range 1–17 years, mean = 10.6 years) and 60 adults patients (>18 years, mean = 39.2 years) were included. The 30% (15/40) of pediatric patients were affected by dengue and 20% (10/40) by leptospira; 20% (17/60) of adult patients were affected by leptospira and 10% (11/60) by dengue, the majority of the population involved in the trial was male (62/100) (Table 1).

Eighteen patients died and the analysis of mortality was guided by serology, post-mortem pathological anatomy and clinical analysis. Six patients died from dengue virus infection and three died from leptospirosis (one of which had both malaria and leptospirosis), one died from hantavirus infection and one died from malaria. The remaining six patients had negative serologic results and no specific post-mortem findings (Table 1).

Clinical characteristics of patients diagnosed with UTFI

The most relevant clinical findings were: cephalgia (69%), myalgia (64%), abdominal pain (61%), arthralgia (58%) vomiting (53%), nausea (52%), and chills (36%). All of these symptoms were common to leptospirosis, dengue, hantavirus infection,

Table 1
Etiology, age, gender, co-infection and mortality distribution.

Etiologic agents	Age (years)				Gender		Mortality n (%)
	0–17	18–34	35–65	>65	M	F	
Leptospira (n = 27)	10	10	7	0	21	6	3 (10%)
Dengue (n = 26)	15	4	5	2	10	16	6 (23%)
Hantavirus (n = 4)	0	3	1	0	3	1	1 (25%)
Malaria (n = 4)	2	1	1	0	2	2	1 (25%)
Rickettsiosis (n = 2)	1	0	0	1	0	2	0%
Hepatitis A (n = 1)	0	0	1	0	1	0	0%
Brucellosis (n = 1)	0	1	0	0	1	0	0%
Malaria + leptospira (n = 1)	0	0	1	0	1	0	1 (100%)
Hepatitis A + dengue (n = 1)	0	0	0	1	0	1	0
Hantavirus + dengue (n = 1)	1	0	0	0	1	0	0
Hanta + dengue + leptospira (n = 1)	1	0	0	0	1	0	0
Negative test (n = 31)	10	10	9	2	21	10	6 (19%)

and malaria, the most frequent four diseases found in the study. Statistical analysis was carried out, between leptospira and dengue because they were the most frequent agents found in the present study. The following variables were more frequent and statistically significant in leptospira than dengue: male gender ($p=0.0083$), jaundice ($p=0.0003$), chills ($p=0.057$) and conjunctival hyperemic ($p=0.0482$). The following variables were more frequent and statistically significant in dengue than leptospira: retrocular pain ($p=0.0087$) and petechiae ($p=0.0340$).

In leptospira, icterus (48%), hepatomegaly (37%), dyspnea (25%) were others most common relevant clinical findings. Regarding hepatomegaly, although there was no statistical difference with

dengue ($p=0.0739$), is important in the differential clinical diagnoses. Bilateral palpebral edema was present in only 3% of dengue patients, in those patients retro-ocular pain was more common (30%), others relevant clinical findings in dengue patients were diarrhea (30%), dyspnea (30%). Rash was more slightly frequent in dengue (15%) than leptospirosis (11%) (Table 2), however, no statistical significant were found ($p=0.70$). There were no remarkable findings on the hemorrhagic presentations: gingival hemorrhage was more common in leptospirosis (14%) than dengue (11%), no statistical significant were found ($p=1.000$); epistaxis was more frequent in malaria (20%) than dengue (15%) and leptospirosis (3%); petechiae were seen in dengue (15%) but not leptospirosis 0% (Table 2).

Table 2
Clinical characteristics of patients with UTFI.

Clinical characteristics	Leptospirosis (N = 27)	Dengue (N = 26)	Hantavirus (N = 4)	Malaria (N = 4)	Rickettsia (N = 2)	Hepatitis A (N = 1)	Total (%)
Headache	18 (66%)	17 (65%)	3 (75%)	3 (75%)	2 (100%)	1 (100%)	69%
Myalgia	16 (60%)	20 (76%)	3 (75%)	2 (50%)	0	1 (100%)	64%
Abdominal pain	15 (55%)	18 (69%)	3 (75%)	2 (50%)	1 (50%)	1 (100%)	61%
Vomiting	17 (62%)	15 (57%)	1 (25%)	1 (25%)	1 (50%)	0	53%
Nausea	17 (62%)	12 (46%)	1 (25%)	1 (25%)	1 (50%)	1 (100%)	52%
Arthralgia	16 (60%)	15 (57%)	3 (75%)	3 (75%)	0	1 (100%)	58%
Chills	13 (48%)	6 (23%)	1 (25%)	4 (100%)	0	0	36%
Hepatomegaly	10 (37%)	4 (15%)	1 (25%)	2 (50%)	0	0	26%
Jaundice	13 (48%)	1 (3%)	2 (50%)	2 (50%)	0	1 (100%)	29%
Diarrhea	6 (22%)	8 (30%)	1 (25%)	0	0	0	23%
Dyspnea	7 (25%)	8 (30%)	2 (50%)	1 (25%)	0	0	27%
Retrocular pain	1 (3%)	8 (30%)	1 (25%)	0	0	0	15%
Pleural effusion	6 (22%)	2 (7%)	1 (25%)	0	1 (50%)	0	15%
Ascites	5 (18%)	4 (15%)	0	0	1 (50%)	0	16%
Conjunctival hyperemia	3 (11%)	3 (11%)	0	0	0	0	9%
Skin rash	3 (11%)	4 (15%)	0	0	0	0	10%
Palpebral edema	0	1 (3%)	0	0	0	0	1%
Gingival bleeding	4 (14%)	3 (11%)	1 (25%)	0	1 (50%)	0	13%
Epistaxis	1 (3%)	4 (15%)	0	1 (25%)	1 (50%)	0	10%
Haematemesis	1 (3%)	6 (23%)	0	0	0	0	10%
Petechiae	0	4 (15%)	1 (25%)	0	1 (50%)	0	9%
Melena	1 (3%)	2 (7%)	1 (25%)	0	0	0	6%
Anemia ^a	Low (6), moderate (2) severe (1).	Low (5), moderate (1), severe (1) very severe (1)	Low (1), Severe (1)	Low (1), severe (2)	0	0	35%
Leukopenia ^b	Low (5) moderate (1) severe (5)	Low (11), moderate (3), severe (4)	Low (1), moderate (1)	Low (2)	Low (1)	Moderate	55%
Leukocytosis	7 (25%)	7 (26%)	1 (25%)	0	1 (50%)	0	24%
Lymphocytosis	10 (37%)	15 (57%)	0	2 (50%)	0	1 (100%)	43%
Neutrophilia	9 (33%)	7 (26%)	2 (50%)	0	1 (50%)	0	30%
Thrombocytopenia ^c	I (8), II (2) and III (9)	I (8), II (3) III (9) and IV (1)	I (1) and II (1)	I (2) and II (1)	I (1)	0	72%

^a Low: 9.5–10.9 g/dL; moderate: 8–9.4 g/dL; severe: 6.5–7.9 g/dL; very severe: < 6.5 g/dL.

^b Low: 4000–4999 mil/mm³; moderate: 3999–3000 mil/mm³; severe: 2999–1000 mil/mm³.

^c Degree I: 150,000–75,000 mm³; Degree II: 74,900–50,000 mm³; Degree III: 49,900–25,000 mm³; Degree IV: <25,000 mm³.

Table 3
Clinical and hemorrhagic manifestations and laboratory findings in co-infected patients.

Relevant clinical finding	Leptospira+malaria (n = 1) n	Dengue + hepatitis A (n = 1) N	Dengue + hantavirus (n = 1) N	Hanta + dengue + leptospira (n = 1) n
Headache	1	1	1	0
Myalgia	0	1	1	1
Abdominal pain	1	1	0	0
Vomiting	1	0	0	0
Nausea	1	0	0	0
Arthralgia	0	1	0	1
Chills	1	0	1	1
Hepatomegaly	0	0	0	0
Jaundice	0	0	0	0
Diarrhea	1	1	0	0
Dispnea	1	1	0	0
Retrocular pain	1	0	0	0
Pleural effusion	1	0	0	0
Ascites	0	0	0	0
Conjunctival Hiperemia	0	0	1	0
Skin rash	0	0	0	0
Palpebral edema	0	0	0	0
Gingival bleeding	0	0	0	0
Epistaxis	0	0	0	0
Haematemesis	0	0	0	0
Petechiae	0	0	0	0
Melena	0	0	0	0
Anemia ^a	Low	Low	0	0
Leukopenia ^b	Low	Severe	Low	Moderate
Leukocytosis	0	0	0	0
Lymphocytosis	1	0	0	1
Neutrophilia	0	1	0	0
Thrombocytopenia ^c	II	III	I	III

^a Low: 9.5–10.9 g/dL; moderate: 8–9.4 g/dL; severe: 6.5–7.9 g/dL; very severe: <6.5 g/dL.

^b Low: 4000–4999 mil/mm³; moderate: 3999–3000 mil/mm³; severe: 2999–1000 mil/mm³.

^c Degree I: 150,000–75,000 mm³; Degree II 74,900–50,000 mm³; Degree III 49,900–25,000 mm³; Degree IV: <25,000 mm³.

Prevalence of anemia was 75% in patients suffering from malaria. Neutrophilia was seen in 33% of patients with leptospirosis and in 26% of those with dengue, statistical significant was ($p = 0.407$). Leukopenia was detected in 69% of patients with dengue and 40% of those with leptospirosis (Table 2). Fifty percent of patients with hantavirus infection had anemia, leukopenia, and trombocytopenia. One patient was diagnosed with brucellosis; he had headache, nausea, ascites, severe anemia, and leukopenia.

Four co-infections were diagnosed, one patient was affected by dengue, leptospirosis, and hantavirus infection; another had malaria and leptospirosis; one had dengue and hepatitis A; one had dengue and hantavirus disease (Table 3). Four patients had no discernable hemorrhagic manifestations.

Discussion

We diagnosed the etiology agent of infection in 69% of the 100 patients clinically suspected of UTFI (Table 1). This shows the high endemicity of UTFI in the study area. However, leptospirosis was more frequent than dengue (Table 1). It was previously believed that dengue was the most common UTFI in Colombia; but as we have demonstrated, not all UTFI could be treated as dengue, and antibiotic treatment should be established at hospital admission to avoid clinical deterioration of the patient. Although we did not make comparisons of the efficacy of various antibiotics, it is recognized that early antibiotic treatment reduces mortality of leptospirosis [11].

In Ecuador, leptospirosis was found in 13.2% of patients, malaria in 12.5%, rickettsioses in 5.9%, dengue fever in 5.3%, Q fever in 4.9%, brucellosis in 1.3%, Ilhéus virus infection in 1.0%, and Venezuelan equine encephalitis (VEE), Oropouche, and St. Louis encephalitis virus infections in less than 1% [12]. Our results were similar, however, leptospira and dengue virus were the main agents detected.

In a study of etiology of febrile syndromes in 506 patients in the north coast and the eastern jungle of Peru, the etiologic agents were identified in only 16.4%. The authors demonstrated circulation of VEE virus, detected the new DEN-3 serotype, and improved understanding of the role of arboviruses in cycle of febrile syndromes [13]. In contrast, we achieved a diagnosis for 69% of patients, but the only the arbovirus studied was dengue.

In a study of icteric hemorrhagic fever syndrome in four areas of Peru [14], the authors identified 50% of etiologic agents, including hepatitis B virus (24%), hepatitis D virus (16%), leptospira (5%), and yellow fever virus (5%). Mortality was of 16%. The authors did not screen for dengue, malaria, or hantavirus infection. In our study leptospirosis (27%), dengue (26%), hantavirus disease (6%) and malaria (5%) were the most frequent diseases found, and mortality was of 12%.

Urabá is a region on the north coast of Antioquia (Colombia) that is endemic for malaria. Investigators in the region conducted a study of febrile syndromes. All patients with malaria were excluded and the study focused on patients with acute febrile syndrome without a clear diagnosis. Approximately 42% of cases were diagnosed, including dengue (37%), leptospirosis (14%), rickettsial infections (2.7%), and arenavirus infections (0.5%). These results are similar to those from our study, perhaps because Urabá is close to our study region and has similar coepidemiological conditions [3].

Four co-infections were remarkable in our study. One patient was affected with dengue, leptospirosis, and hantavirus infection; another had malaria and leptospirosis; a third had dengue and hepatitis A; a fourth had dengue and hantavirus infection (Table 3). Similar studies also reported co-infections. Lima et al., in 2011, reported a case of dengue virus and hantavirus coinfection in Brazil similar to those reported in our study [15], we identified six hantavirus antibody-positive patients, including two coinfections with leptospira and dengue virus, respectively (Table 1). These data suggest that circulating hantaviruses

cause both mild and asymptomatic infections in Colombia [16,17].

Regarding clinical symptoms, signs, hematological alterations, and hemorrhagic presentations, there were no remarkable findings to allow us to differentiate among the diseases found. It was difficult to differentiate among leptospirosis, dengue, and malaria due to the overlap in clinical symptoms, signs, hemorrhagic presentations, and hematological alterations (Table 2). For example, thrombocytopenia was found in 80% of patients with dengue and 60% of those with leptospirosis. Epistaxis, petechiae, gingival hemorrhage, leukopenia, neutrophilia, and anemia were seen without a remarkable predominance in dengue and leptospirosis, the two principal diseases in the survey. We only studied 100 patients and some pathologies were represented by few cases (e.g., only five malaria cases) making it difficult to establish a definitive conclusion for this disease. Furthermore, the sensitivity of tests used may have been low or we may have sampled at the wrong time.

All 69 patients with diagnoses in this survey were diagnosed by IgM or IgG seroconversion, NS1 antigen (for dengue) and blood smear (for malaria). It is very difficult to make a diagnosis with a single serum sample at admission. As this study demonstrated, at least two serum samples and close patient follow-up throughout the trial are necessary.

The remaining two important conditions diagnosed were hantavirus disease and rickettsiosis. The study area is endemic for ticks and rodents [18,19]. Hantavirus disease was diagnosed for the first time in Colombia in samples obtained of this study. The patient, who survived, did not show the classical clinical presentation for hantavirus pulmonary syndrome and the disease was initially diagnosed as leptospirosis [20]. The remained four patients with hantavirus disease had hemorrhagic manifestations, 25% with gingival bleeding, petechiae and melena. No clinical signs of cardiopulmonary disease were seen; one patient who died was confirmed to be infected with a hantavirus.

Malaria due *Plasmodium vivax* was a frequent disease found in our survey, we have some endemic areas of malaria in the department of Cordoba and two cases were from the urban area of the capital, Monteria. Thus, it is clearly important to establish control measures to avoid spread of mosquito vectors into urban zones. Regarding clinical manifestations, 20% of malaria cases presented epistaxis as the only hemorrhagic manifestation, 50% had lymphocytosis, 50% had severe anemia, and 75% had thrombocytopenia (Table 2).

We did not test for flaviviruses (yellow fever), alphaviruses (Venezuelan equine encephalitis virus), or arenaviruses, but none of the patients had manifestations of these infections, which, in most cases, shown a severe course and are often fatal.

A study in India [21], established the implementation of standardized management of acute undifferentiated febrile illnesses in adults. Protocols are important for reductions in hospital admission rates, mortality rates, use of unnecessary tests, and inappropriate use of antibiotics. The Indian study identified malaria and dengue as the primary etiologies, but 51% of cases were not diagnosed, compared to the 31% of cases we failed to diagnose.

We conclude that exist other etiological agents besides dengue virus that deserve greater attention by physicians and public health authorities. Although we established the etiology of 69% of patients in our study, the fact that the agent was not identified for 31% indicates that diagnostic challenges clearly remain.

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Competing interests

None declared.

Ethical approval

Not required.

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