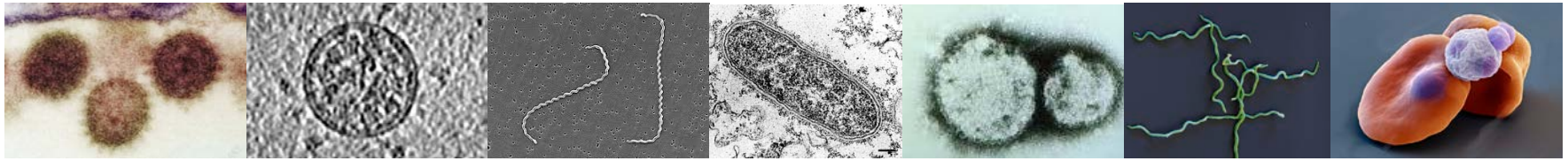

CCHFV | SARS-CoV-2 | Leptospira | Rickettsia | Hantavirus | Borrelia | Babesia

Zoonotic febrile illnesses misdiagnosed as COVID-19

Silva Ramos Carlos Ramiro *et al*., 2023 Le Infezioni in Medicina (IF 4.5 H-Index 33, Q2)

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Brief Introduction

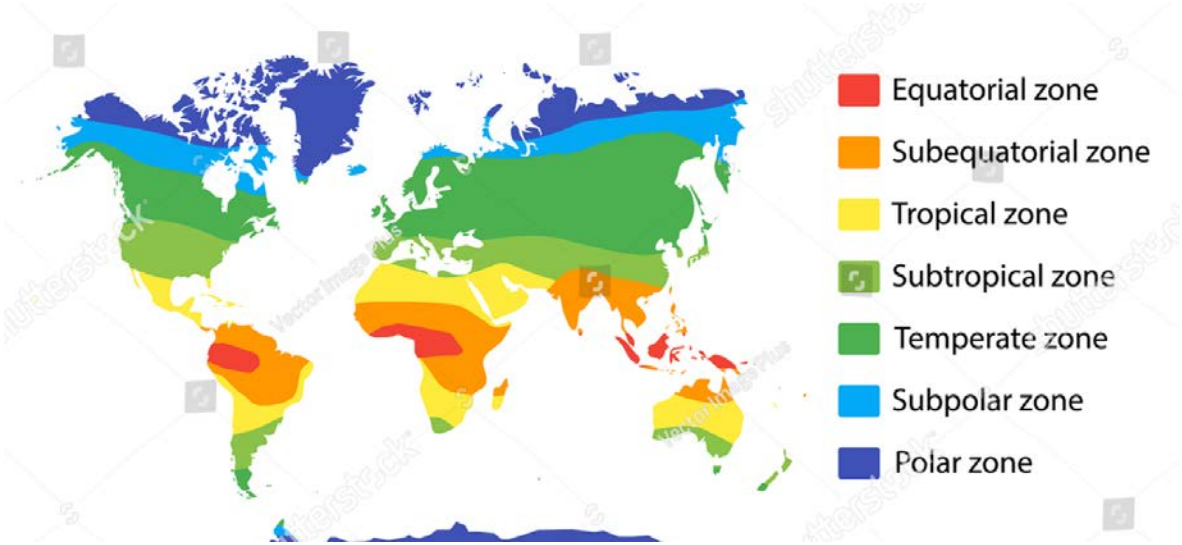
The article is a review of eighteen reported clinical cases where the initial suspected disease was SARS-CoV-2 but as the supportive therapy did not improve the patient's condition and the laboratory tests were negative, the doctors had to rethink the etiology.

Brief Introduction

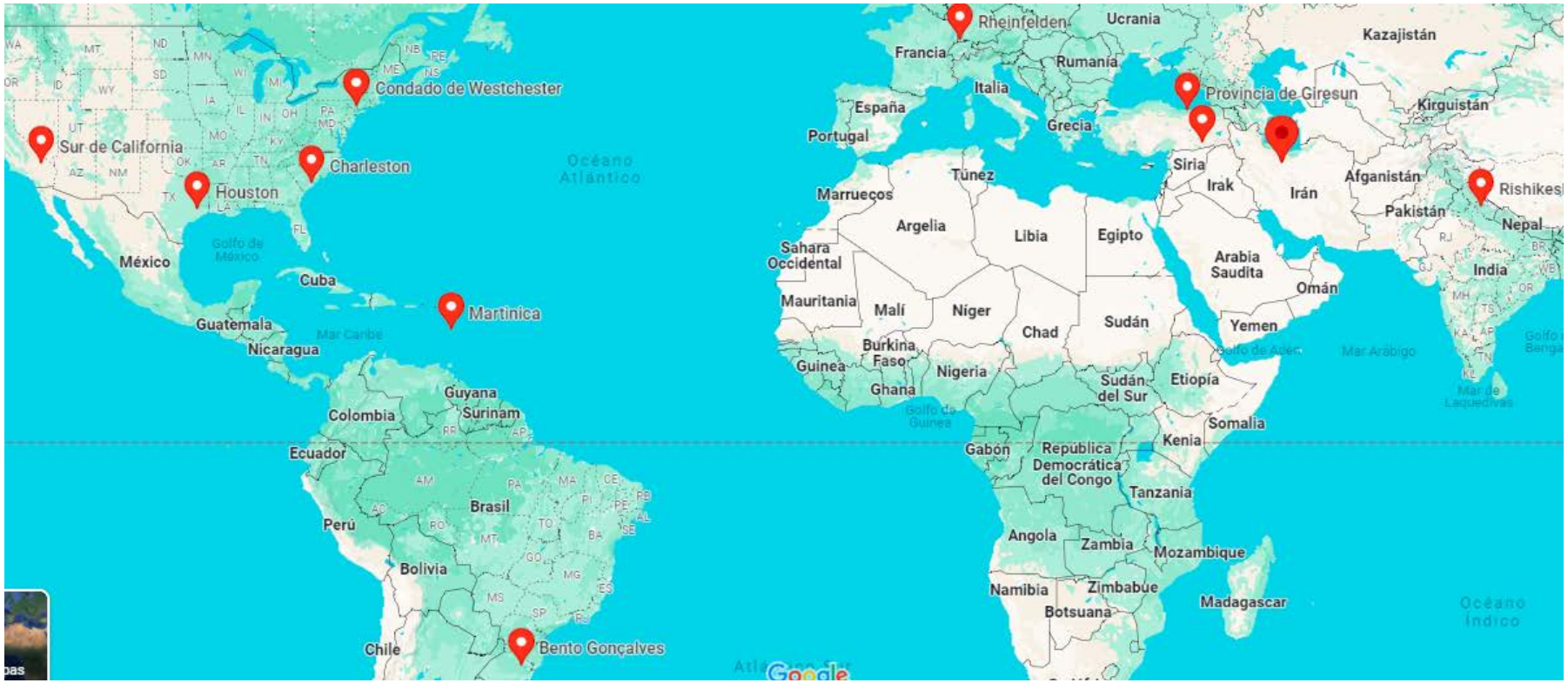
General concepts:

- Acute undifferentiated febrile illness (**AUFI**):
  sudden onset of fever (≥38°C or ≥ 100.4°F) that lasts for less than 2 weeks and cannot be attributed to a specific cause after a thorough clinical evaluation and appropriate laboratory testing (Shrestha et al. 2020).

- Tropical regions.



Brief Introduction



Map that shows the location of the cases mentioned in the article.

Materials and Methods

- The authors searched for information in PubMed, MEDLINE, EMBASE, Scopus and BVS.
- Used terms “misdiagnosis”, “COVID-19” and “febrile”.
- Case reports from January 1, 2020 to December 31, 2022.

SARS-CoV-2 (COVID-19)

- SARS-CoV-2 is a positive single-stranded RNA virus and the causative agent of coronavirus disease of 2019 (COVID-19).
- The 80% of patients experience a mild, self-limited disease involving only the upper respiratory tract.
- In 20% of patients, the virus infects alveolar cells, causing pneumonia that rapidly progresses to severe acute respiratory distress syndrome.
- COVID-19 has no pathognomonic symptom.

SARS-CoV-2 (COVID-19)

July 22, 2022 COVID-19 case definition according to WHO.

Suspected case of SARS-CoV-2 infection (3 options)

A A person who meets the clinical **OR** epidemiological criteria:

Clinical criteria:

- acute onset of fever AND cough (ILI)

OR

- acute onset of **ANY THREE OR MORE** of the following signs or symptoms: fever, cough, general weakness/fatigue[1], headache, myalgia, sore throat, coryza, dyspnoea, nausea/diarrhoea/anorexia

OR

Epidemiological criteria [2]:

- contact of a probable or confirmed case, or linked to a **COVID-19 cluster.**[3]

B A patient with **severe acute respiratory illness**
(SARI: acute respiratory infection with history of fever or measured fever of ≥38 °C; and cough; with onset within the last 10 days; and requires hospitalization)

C A person
with no clinical signs or symptoms **OR** meeting epidemiologic criteria
with a **positive professional-use or self-test** SARS-CoV-2 Antigen-RDT.[4]

Leptospira spp.

Case 1 (Leptospira)

- Rheinfelden, Germany
- 35 years old
- Nurse,
- Chronic smoker,
- Gardening practice.
- AUFI with severe myalgia and jaundice
- Intrahepatic cholestasis.
- Leptospira Serology positive outcomes; Tx Hydration and Ceftriaxona.

Clinical manifestations	*Laboratory parameters*	*Treatment*	*Outcome*
Fever, cough, sore throat, body ache, tachycardia, jaundice, myalgia	Thrombocytopenia, leukocytosis, hypoalbuminemia, ↑Cr, ↑Urea, ↑uric acid, ↑AST, ↑ALT, ↑GGT; ↑TBil, ↑DBil,	Hydration, ceftriaxone	Recovered

Leptospira spp.

Case 12 (Leptospira)

- Rishikesh, India.
- 23 years old
- Chronic smoker
- Farming activity.
- AUFI with loose stools, SpO2 62%, hyperbilirubinemia and yellow-wish expectoration.
- ELISA IgM to Leptospira (+).
- Doxycycline was administered; patient died during the hospital stay.

Fever, shortness of breath, yellowish expectoration, loose stools, tachypnea, respiratory failure	Leukocytosis, neutrophilia, lymphopenia, ↑Urea, ↑Cr, ↑TBil, ↑DBil, ↑AST, ↑ALT, ↑ALP, ↑GGT	Doxycycline	Deceased

Leptospira spp.

Case 16 (Leptospira)

- Martinique island
- 83 years old
- **AUFI** with myalgia, arthralgia, **diarrhea**, SpO2 88% wich evolved to respiratory failure.
- Due **endemicity on the island**, leptospirosis was suspected.
- Amoxicillin and steroid therapy.

Fever, dyspnea, myalgia, arthralgia, diarrhea	Lymphopenia, thrombocytopenia, ↑Cr, ↑BUN, ↑CRP, ↑AST, ↑ALT	Amoxycilin, steroid therapy	Recovered

Leptospira spp.

Case 17 (Leptospira)

- Mardin, Turkey
- 3 years old
- Domestic contact with COVID 19
- **The patient´s family worked as farmers.**
- AUFI and **abdominal pain.**
- Leptospira PCR (+), Tx: Doxycycline.

Fever, cough, weakness, abdominal pain, tachycardia, tachypnea	Thrombocytopenia, ↑CRP	Hydration, cefotaxime, doxycycline	Recovered

Leptospira spp.

Weil syndrome (icteric leptospirosis).

Kidneys and liver are primary injured tissues, other organs like lungs can be affected (20-70%).

Jaundice, kidney failure, liver damage and thrombocytopenia.

Contact with rodent excreta.

Rickettsia spp.

Case 2

- Southern California, USA
- 25 years old
- **Dog trainer.**
- AUFI, headache, back pain.
- Serology titers above 1:256 (+)
- Diagnosis: murine typhus. Doxycycline was administered.

United States	Murine typhus	Fever, headache, myalgia, chills, vomiting, diarrhea, cough, congestion, fatigue, dizziness, back pain, tachycardia, body aches	Bandemia, lymphopenia, ↑ESR	Doxycycline

Rickettsia spp.

Case 3 to 8

- Houston, USA
- 6 pediatric cases,
- All had previous **exposure to dogs**
- Two cases reported canine **flea** infestation.
- AUFI, **rash**, **mialgia** and digestive manifestations
- Elevated liver enzymes.
- Anti-R. typhi IgM (+) in all cases, only four received doxycycline, but all improved.

United States (6/6)	Murine typhus (6/6)	Fever (6/6), tachycardia (6/6), tachypnea (6/6), rash (6/6), myalgia (5/6), cough (5/6), abdominal pain (5/6), sore throat (4/6), vomiting (4/6), diarrhea (1/6), fatigue (1/6)	↑AST (6/6), ↑ALT (6/6), ↑LDH (6/6), ↑Ferritin (6/6), ↑D-dimer (6/6), ↑CRP (6/6), ↑Procalcitonin (6/6), leucopenia (3/6), neutrophilia (3/6), thrombocytopenia (3/6), lymphopenia (2/6)	Doxycycline (4/6) None (2/6)

Rickettsia spp.

Case 18

- Charleston City, South Carolina, USA
- 72 years old.
- IgG and IgM antibodies to spotted fever group (SFG) rickettsiae antigens (+).
- Two weeks after the onset of symptoms, the patient experienced mental fogginess, myodesopsia, and blurry vision, which were compatible with **retinal vasculitis** due to SFG Rickettsia infection.

Spotted fever group rickettsiosis	Fever, myalgia, fatigue, dry cough, nausea, hyporexia, headache, oral lesions, non-pruritic rash, arthralgia, mental fogginess, myodesopsia, blurry vision	Hyponatremia, ↑AST, ↑ALT, ↑CRP,	Doxycycline

Borrelia burgdorferi

Case 9

- Westchester Country, NY
- 36 years old
- **Erythematous skin lesión** (misdiagnosed as cellulitis)
- AUFI with bradycardia and partial heart block (**Lyme carditis**).
- IgM and IgG inmunoblot against BB (+); Tx ceftriaxone and doxycycline.
- *Babesia microti* PCR (+) but was not treated.

Lyme disease rash

Celulitis

Borrelia burgdorferi

Case 9

Lyme disease rash

Celulitis

Babesia spp.

Case 9

- Coinfeccion with *Borrelia burgdorferi*, same reservoir *Ixodes* spp.

Case 10

- Westchester Country, NY
- 69 years old
- **History of tick bites** –was initially evaluated for COVID 19.
- Febrile, weakness, anorexia.
- Babesia microti PCR (+); Tx: Azithromycin and atovaquone
- No lab test.

Anaplasma phagocytophilum

Case 11

- Westchester Country, NY.
- 56 years old
- **Tick bite history.**
- Fever, rigors, headaches and joint pains
- Anaplasma phagocytophilum PCR (+); Dx human granulocytic anaplasmosis.
- No antibiotic treatment was administered, but the patient improved and resolved the disease.
- No lab test.

Orthohantavirus

Case 13

- In Giresun, Turkey
- 57 years old
- Contact with a COVID 19 case.
- Fever, fatigue, hyporexya, myalgia, arthralgia, tachycardia; decreased urine output over time.
- Considering the **geographic region**, realized Hantavirus IgM and IgG IFA(+).

Fever, fatigue, hyporexia, myalgia, arthralgia, tachycardia, oliguria	Leukocytosis, thrombocytopenia, ↑Urea, ↑Cr, ↑CRP, ↑D-dimer, ↑Ferritin, ↑AST	Hydration, Supportive therapy	Recovered

Orthohantavirus

Case 14

- In Bento Gonçalves, Brazil
- 24 years old
- Two weeks after travel to Paraná and **visit an abandoned warehouse.**
- Fever, headache, dry cough, diarrhea, and hyporexia
- Later dry cough with blood, prostration, vomiting
- Dyspnea were developed, with an oxygen saturation of 90%.
- Patient developed respiratory failure, died.
- Hantavirus RT-PCR postmortem (+).

Fever, headache, dry cough, diarrhea, hyporexia, respiratory discomfort, dry cough, hemoptysis, tachycardia, prostration,	Normal WBC with left shift, bandemia, thrombocytopenia, ↑AST, ↑ALT	Oxygen therapy, amoxicillin/ clavulanic acid, oseltamivir	Deceased

CCHF orthonairovirus

- **Case 15**
  - In Tehran, Iran
  - 41-year-old man
  - **Recent travel to Karbala**, Iraq.
  - Fever, myalgia, malaise, **coffee ground vomitus**, and melena
  - Hepatitis virus and CMV (-).
  - Both ELISA IgG/ IgM antibodies and PCR against the CCHF virus were positive.
  - Dx: Crimean-Congo hemorrhagic fever.

Fever, myalgia, malaise, coffee ground vomitus, melena,	Thrombocytopenia, ↑PTT, ↑AST, ↑ALT, ↑Ferritin, ↑LDH, ↑D-dimer, ↑CRP	Ribavirin	Recovered

Conclusion

- “When you hear hoofbeats, think of horses, not zebras.”- Dr Theodore Woodward

- Probable cause? It depends on the **patient's history.**

- Although COVID-19 has become one of the etiologies of tropical febrile illnesses, it should not represent the first cause of fever in tropical regions.

RVPVE

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