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Consensus Document

Executive Summary of the Spanish Guidelines for the Diagnosis and Management of Imported Febrile Illnesses from the Spanish Society of Tropical Medicine and International Health (SEMTSI), the Imported Pathology Group of the Spanish Society of Infectious Diseases and Clinical Microbiology (GEPI-SEIMC), the Spanish Society of Family and Community Medicine (SEMFYC), the Spanish Society of Primary Care Physicians (SEMERGEN) and the Spanish Society of Emergency Medicine (SEMES)★

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A B S T R A C T

The Spanish Society of Tropical Medicine and International Health (SEMTSI), the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Emergency Medicine (SEMES), the Spanish Society of Primary Care Physicians (SEMERGEN) and the Spanish Society of Family and Community Medicine (SEMFYC) have prepared a consensus statement on the diagnosis and management of patients with imported febrile illnesses.

★ The full consensus document is available as Annex A in the additional material.

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Twenty authors with different backgrounds and representing different healthcare perspectives (ambulatory primary care, travel and tropical medicine specialists, emergency medicine, hospital care, microbiology and parasitology and public health), identified 39 relevant questions, which were organised in 7 thematic blocks. After a systematic review of the literature and a thoughtful discussion, the authors prepared 125 recommendations, as well as several tables and figures to be used as a consulting tool. The present executive summary shows a selection of some of the most relevant questions and recommendations included in the guidelines.

Palabras clave:
Enfermedades febriles importadas
Enfermedades emergentes
Medicina del viajero
Arbovirus
Malaria

Resumen ejecutivo de las Guías Españolas de Diagnóstico y Manejo de Enfermedades Febriles Importadas de la Sociedad Española de Medicina Tropical y Salud Internacional (SEMTSI), el Grupo de Patología Importada de la Sociedad Española de Enfermedades Infecciosas y microbiología clínica (GEPI-SEIMC), la Sociedad Española de Medicina de Familia y Comunitaria (SEMFYC), la Sociedad Española de Médicos de Atención Primaria (SEMERGEN) y la Sociedad Española de Medicina de Urgencias y Emergencias (SEMES)

R E S U M E N

La Sociedad Española de Medicina Tropical y Salud Internacional (SEMTSI), la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), la Sociedad Española de Medicina de Urgencias y Emergencias (SEMES), la Sociedad Española de Médicos de Atención Primaria (SEMERGEN) y la Sociedad Española de Medicina Familiar y Comunitaria (SEMFYC) han elaborado un documento de consenso sobre el diagnóstico y manejo de pacientes con enfermedades febriles importadas.
Veinte autores que representaban diferentes perspectivas de la atención médica (atención primaria ambulatoria, especialistas en medicina tropical y del viajero, urgencias, atención hospitalaria, microbiología y parasitología y salud pública), identificaron 39 preguntas clínicamente relevantes, que se organizaron en 7 bloques temáticos. Tras una revisión sistemática de la literatura, los autores elaboraron 125 recomendaciones, así como varias tablas e imágenes para ser utilizadas como herramientas de consulta. Este resumen ejecutivo muestra una selección de las preguntas y recomendaciones más relevantes incluidas en las presentes guías.

Block 1: Causes of imported fever

What are the main causes of fever in travellers?

- The main causes of imported fever are universally distributed infections, such as respiratory or gastrointestinal infections, and common tropical diseases, such as malaria and dengue fever. (**A-I**)
- Given their potential severity and non-specific signs and symptoms, from the outset causes such as malaria, dengue fever, typhoid fever, rickettsial infections and viral haemorrhagic fevers (VHF), and cosmopolitan infectious syndromes, such as sepsis and meningitis, should be considered. (**A-I**)

Block 2: Initial management of the patient with imported fever

What questions should we include when taking the history of the patient with imported fever?

- Previous medical history should include the geographical areas visited, the timing of travel and of the symptoms (incubation period), high-risk exposures during travel and preventive measures (particularly vaccination and antimalarial prophylaxis). (**A-II**)

When should we suspect and what should we do if we suspect a high-consequence infectious disease (HCID)?

- Any febrile patient who meets epidemiological and clinical criteria for HCID should be assessed for the need for management in a High Level Isolation Unit (HLIU). (**B-II**)
- VHF (such as Ebola, Marburg, Lassa, Crimean-Congo haemorrhagic fever (CCHF) should be suspected in patients with fever, haemorrhage, vomiting or diarrhoea, hypotension or shock, who have been in a VHF outbreak area, or have been in a VHF endemic area and have had a high-risk exposure (contact with sick people, animals or tick bite in the case of CCHF) within the last 21 days. (**B-II**)
- Respiratory HCID should be suspected in patients with signs or symptoms of lower respiratory tract infection who have been in a respiratory HCID-outbreak or endemic area within the last 14 days, especially if they have had a high-risk exposure (contact with sick people or camels in the case of MERS). (**B-II**)

What are the signs and/or analytical markers of alarm or severity in patients with imported fever?

- The following warning signs or severity criteria should be considered in a patient with imported fever:

(i) clinical: lethargy/obnubilation/postration; meningismus; >2 epileptic seizures in 24 h; focal neurological deficit; haemorrhagic signs; cyanosis; dyspnoea; persistent/disabling abdominal pain or peritonism; persistent vomiting/intolerance to oral intake; oliguria or anuria; signs of malperfusion; acral necrosis; shock; jaundice;
(ii) analytical: haemoconcentration; platelets $<50 \times 10^9$/l; acute kidney injury; AST, ALT or GGT > 1,000 IU/l; liver failure; lactate >2.5 mmol/l. (**A-III**)

- In the event of diagnosis or suspicion of malaria or dengue, the severity criteria and specific warning signs for these diseases should be assessed. (**A-II**)

When should a patient be referred to a hospital Accident and Emergency department?

- Referral to a hospital Accident and Emergency department is recommended for patients with imported fever with any of the following criteria:

(i) signs or analytical markers suggestive of severity or qSOFA $\geq$2
(ii) children, older adult patients, patients with comorbidities or immunosuppression,
(iii) difficulty in obtaining a rapid diagnosis of malaria (in patients returning from a malaria endemic area),
(iv) social or public health implications. (**A-III**)

Block 3: Imported febrile syndromes

What are the main causes and which additional tests should I request for a patient presenting with imported fever and haemorrhagic phenomena?

- In a patient with imported febrile syndrome and haemorrhagic phenomena, the possibility of a VHF needs to be assessed. (**A-II**)
- In the case of suspected FVH, additional tests which involve contact with blood or fluids should not be performed unless they are under HLIU measures. (**A-I**)
- After ruling out suspected VHF, tests should be performed to exclude malaria, dengue fever and leptospirosis. (**A-I**) Meningococcaemia, typhoid, rickettsial infection, viral hepatitis and yellow fever should also be included in the differential diagnosis. (**A-II**)

What are the main causes of imported exanthematous fever?

- Diseases caused by arboviruses and rickettsial diseases should be considered as a priority in imported exanthematous fever. (**A-II**)
- Differential diagnosis also includes viral (measles, rubella, mononucleoside viruses, HIV), bacterial (typhoid fever, meningococcaemia, syphilis, leptospirosis), fungal and parasitic infections (acute schistosomiasis, African trypanosomiasis), arthropod infestations and bites, and non-infectious causes (allergic and drug reactions). (**A-III**)

What are the main causes and which tests should I request in a patient presenting with imported fever and jaundice?

- The most common causes of imported fever and jaundice, once malaria has been ruled out, are viral hepatitis (especially HAV and HEV), leptospirosis and biliary tract infections. Other less common causes to consider are typhoid fever, yellow fever and dengue fever. **(A-III)**
- In the investigation of imported fever with jaundice, the need for abdominal imaging tests should be assessed. **(A-III)**
- The diagnosis of post-artemisinin delayed haemolysis should be considered in patients with signs of haemolysis and a history of malaria treated with artemisinins 1–4 weeks previously. **(A-III)**

What are the main causes of imported fever and hepato-splenomegaly?

- The main causes of imported fever and hepato-splenomegaly, once malaria has been ruled out, are mononucleosis syndromes, typhoid fever, brucellosis and visceral leishmaniasis, viral hepatitis, mycobacterial infections, Q fever, leptospirosis, schistosomiasis and non-infectious causes (mainly haematological diseases). **(A-III)**

What are the main causes of imported fever and eosinophilia?

- The most common cause of imported fever and eosinophilia is acute schistosomiasis. Other parasitic infections that may cause eosinophilic fever include disseminated strongyloidiasis, Löeffler's syndrome, filariasis and, less commonly, fascioliasis, toxocariasis and paragonimiasis. Differential diagnosis should also include non-infectious causes. **(A-II)**

What additional tests should be performed in a patient with an imported fever of no obvious cause lasting more than seven days?

- In a patient with imported fever of >7 days duration, the following additional tests should be considered: long incubation blood cultures; blood smear; malaria PCR; expanded serology and/or PCR (HIV, other mononucleoses, *Rickettsia* spp, *Leptospira* spp., *Coxiella burnetti*, *Brucella,* endemic fungi, *Leishmania* spp., *Schistosoma* spp.); and PCR and/or fungal and mycobacterial cultures; autoimmunity study and/or imaging tests (such as abdominal ultrasound, CT, echocardiography, PET). (**B-II**)

Block 4: Diagnosis and tests

Which basic tests that should be performed in the initial assessment of any case of imported fever?

- In the initial assessment of the patient with imported fever, it is recommended that priority blood tests with biochemistry including renal and hepatic profile, complete blood count and blood cultures be requested, or urgent if malaria is suspected or symptoms are severe according to qSOFA $\geq$2. (**A-I**)
- In the initial assessment of the patient with imported fever, testing for malaria (if the patient has visited an endemic area) (**A-I**) and dengue fever, in patients with incubation period <14 days (**A-II**) should be requested.
- Chest X-rays are not recommended as a routine part of the initial assessment of patients with undifferentiated fever without respiratory symptoms. (**A-III**)

Should PCR for respiratory viruses be performed on nasopharyngeal exudate samples from patients with undifferentiated imported fever?

- Given the incubation period of a few days of most respiratory viruses and their wide geographical distribution, the performance of PCR for respiratory viruses should be based on the epidemiological situation in the regions visited and in the country of return. (**A-III**)
- PCR for SARS-CoV-2 is recommended for any traveller with compatible symptoms, including undetermined fever. In the case of

return from a country during the flu season, it is also recommended. (**A-II**)
- In patients with fever and lower respiratory tract symptoms coming from the Arabian Peninsula, it is recommended to assess the need for transfer to HLIU and PCR for MERS-CoV. In the absence of clinical-radiological signs of lower respiratory tract infection, these measures are not recommended. (**A-II**)
- PCR for other respiratory viruses is recommended in high-risk patients (immunosuppressed), in situations of clinical severity or for epidemiological surveillance. (**B-III**)

What is the test of choice for malaria diagnosis and when should it be performed?

- Any patient with fever and a history of having visited a malaria-endemic area in the previous year should be tested for malaria. The absence of fever at the time of consultation should not delay the performing of such a test. (**A-II**)
- The combination of thick blood smear and PCR ensures maximum sensitivity and specificity, and both should therefore be performed in all cases of suspected malaria whenever available. If PCR is not available, thick blood smear and rapid diagnostic test (RDT) are recommended. (**A-I**)

When should a malaria diagnostic test be repeated?

- In a patient with undiagnosed imported fever, the thick blood smear should be repeated every 12−24 hours up to three times if clinical suspicion of malaria is maintained and they do not have a negative *Plasmodium* spp. PCR, especially if the patient has thrombocytopenia. (**A-II**)

When should dengue, chikungunya and Zika be suspected and what tests should be ordered for diagnosis?

- Diseases caused by arboviruses (dengue, chikungunya or Zika) should be suspected in patients with fever or rash, especially if accompanied by headache behind the eyes, leucopenia, hypertransaminasaemia or absence of respiratory symptoms, and onset of symptoms within 14 days of leaving an arbovirus endemic area. (**A-II**)
- As a first option, it is recommended that arbovirus diagnostic tests be requested in undifferentiated non-malarial fevers (NMF) with incubation period ≤14 days. (**A-II**)
- In areas not endemic for arboviruses but with the presence of *Aedes* spp. mosquitoes, diseases caused by arboviruses (dengue, chikungunya, Zika) should be suspected and assessed for in patients with compatible clinical symptoms and in the absence of an alternative diagnosis, even if they have not travelled recently. (**C-III**)
- For the diagnosis of dengue, chikungunya and Zika, it is recommended to perform a direct detection technique such as PCR in blood (during the first 7 days of symptoms), and serology paired with acute phase serum (from day 5 of symptoms) and convalescent phase serum. (**A-II**)
- In the case of dengue, RDT including NS1, IgM and IgG are recommended during the first 7 days of symptoms. (**A-II**)
- In the case of Zika, urine PCR testing is also recommended between days 5 and 15 of illness. (**A-III**)

When should typhoid fever be suspected and what tests should be ordered?

- Typhoid fever should be suspected in patients who have travelled to endemic areas, especially Asia and Southeast Asia, but also Africa and Latin America, and present with undifferentiated NMF and any of the following: abdominal pain with constipation or diarrhoea; toxic appearance; and hepato-splenomegaly. (**A-II**)
- Despite their low sensitivity, blood cultures are the diagnostic test of choice for the diagnosis of imported typhoid fever. (**A-I**)
- Although stool culture is not routinely recommended, the identification of *Salmonellatyphi/paratyphi* in stool culture allows confirmation of colonisation status and may be helpful in imported fever patients with suspected typhoid fever without microbiological identification in blood cultures. (**B-II**)
- The Widal test (**D-III**) and other RDT are not recommended for the diagnosis of typhoid fever. (**D-I**)

When should rickettsial infection be suspected and what tests should be ordered for diagnosis?

- Rickettsiosis should be suspected in patients with imported fever who have been bitten or exposed to ticks, especially if they present with: rash; eschar. However, it is recommended to also consider rickettsiosis in undifferentiated NMF despite absence of epidemiological risk and clear clinical manifestations. (**A-II**)
- For the diagnosis of *Rickettsia* spp. infection, it is recommended to collect a PCR sample from the scab if the patient has skin manifestations, and to perform serology in the acute and convalescent phase (after at least 4 weeks). (**A-III**)

When should leptospirosis be suspected and what tests should be ordered for diagnosis?

- Leptospirosis should be suspected in patients with imported fever who report contact with fresh water, who stayed in an area with flooding or had possible exposure to contaminated secretions, especially if they also report myalgias and headache or have kidney failure or jaundice. (**A-II**)
- If leptospirosis is suspected, it is recommended to ask for blood PCR in the first 10 days of symptoms, and urine PCR and serology from day 7 of symptoms. (**B-II**)

Block 5: Treatment of the patient with imported fever

When should empirical treatment for malaria be started?

- It is recommended that empirical treatment for malaria be started in patients coming from endemic areas (especially sub-Saharan Africa) with suspected malaria and severity criteria, if the diagnosis cannot be made or is going to be delayed. (**A-III**)
- Empirical antimalarial treatment would also be indicated, regardless of whether or not diagnosis is delayed, if the patient's clinical situation requires it or in cases where malaria is suspected without severity criteria, if the diagnosis is going to be delayed, especially if they have thrombocytopenia, hyperbilirubinaemia or splenomegaly. (**B-III**)

In which cases should empirical antibiotic therapy be given and which antibiotics should be included for patients with imported fever?

- In patients with clinically stable undifferentiated NMF, without severity criteria or comorbidities and in whom the cause of fever is suspected to be non-bacterial, outpatient management may be chosen without empirical antibiotic therapy, provided that close follow-up can be assured. (**B-III**)
- In patients with undifferentiated NMF (ideally after urgently ruling out dengue) who require admission, empirical antibiotic therapy with a third generation cephalosporin + doxycycline is indicated. In outpatients with undifferentiated NMF (ide-

ally after having urgently ruled out dengue), it is prudent to start empirical antibiotic therapy with an oral third generation cephalosporin + doxycycline or with azithromycin. (**A-II**)
- In the absence of an aetiological diagnosis, if the patient is doing well, it is recommended not to extend empirical antibiotic therapy beyond seven days. If the suspected diagnosis is Q fever, treatment with doxycycline should be prolonged for at least 14 days. (**A-II**)
- In the absence of clinical response 48–72 h after starting a broad-spectrum empirical antibiotic therapy, the following possibilities should be considered: bacterial infection with delayed defervescence (typhoid fever); melioidosis; infection by resistant microorganisms; non-bacterial infection (viral, parasitic or endemic mycoses); or tuberculosis. (**A-III**)

What is the most recommended antimicrobial regimen in a patient with imported fever who is critically ill or meets severity criteria?

- In a patient with imported fever who is critically ill or meets severity criteria but in whom there is no clear suspected cause (or where a rapid aetiological diagnosis cannot be obtained), it is recommended to start empirical treatment including artesunate (for people coming from malaria-endemic areas) and a broad spectrum antibiotic regimen including doxycycline 100 mg/12 h and a broad spectrum beta-lactam. (**A-III**)

Should a traveller returning with fever and requiring hospital admission be screened for multi-drug resistant microorganisms?

- Screening for colonisation with multi-drug resistant microorganisms is recommended for patients who have travelled to high prevalence areas (South and South East Asia) in the previous 12 months, required hospitalisation or antibiotic use or developed diarrhoea during travel. (**A-II**)
- Pending the results of the screening, centre logistics permitting, it is recommended that these patients be managed with contact isolation precautions. (**B-II**)

When should antibiotic coverage for multi-drug resistant microorganisms be considered empirically in the management of imported fever?

- In patients with recent travel to South Asia and Southeast Asia, XDR typhoid fever (primarily Pakistan) or cephalosporin-resistant typhoid fever should be considered and azithromycin or a carbapenem used empirically. (**A-II**)
- In patients with recent travel to South Asia[1] and Southeast Asia[2] or Northern Australia, the possibility of melioidosis should be considered (especially in case of severe sepsis/septic shock) and ceftazidime or a carbapenems should be used. (**A-II**)
- Empirical coverage of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae with carbapenems is recommended for patients with severe sepsis/septic shock who have travelled internationally in the previous 12 months, especially in the case of travel to South Asia[1], particularly India, Southeast Asia[2] or North Africa, and even more so if there is a history of hospitalisation, antibiotic use or diarrhoea during travel. (**A-II**)
- In addition, empirical MRSA coverage is recommended for patients with severe sepsis/septic shock who have had a hospitalisation during international travel in the previous 12 months. (**A-II**)

Block 6: Diagnosis and management of special populations

What are the particularities of the diagnosis and management of imported fever in pregnant women, children and immunocompromised patients?

- In pregnant women from a malaria-endemic area with fever and thick smear and/or negative rapid diagnostic test, a molecular test with PCR should be considered if diagnostic suspicion persists. (**A-II**)
- In pregnant women from arbovirus-endemic areas with fever and an incubation period $\leq$14 days, a Zika and dengue virus molecular blood test and dengue antigen should be performed (during the first 7 days of symptoms), along with Zika urine PCR (between days 5 and 15 of the illness) and serology for antibody detection (from day 5 of symptoms). (**A-II**)
- In refugee children with fever, vaccine-preventable diseases should be considered more frequently given the low vaccination coverage. (**B-II**)
- In immunocompromised patients, imported infections may present with more severe clinical forms. In an immunocompromised patient with imported febrile syndrome, malaria, leishmaniasis, strongyloidiasis, tuberculosis and endemic mycoses should be considered. (**A-II**)
- In pregnant women, children and immunosuppressed patients, early empirical antibiotic therapy should be considered for undifferentiated fevers, given their greater susceptibility to serious infectious diseases. (**B-III**)

Block 7: Public health measures

Which diseases need to be reported to the Public Health authority?

- The public health authority should be notified of any suspected or confirmed notifiable disease, including any epidemic situation or outbreak that may pose a risk to population health. Urgent reporting of notifiable diseases shall be made upon suspicion or confirmation by the quickest possible means. (**A-II**)

What public health recommendations should be considered in a patient with imported non-malarial fever?

- Health education on prevention and control measures to avoid local transmission of Zika, dengue, chikungunya and/or yellow fever is recommended, especially in patients residing in areas with an established or occasional presence of vectors competent for their transmission. (**C-III**)
- It is recommended that suspected or confirmed cases of Zika infection use condoms correctly during sexual intercourse or abstain from sexual activity for three months for men and two months for women from the onset of symptoms. If the sexual partner of the Zika-infected case is pregnant, correct use of condoms or abstinence from sex is recommended throughout the pregnancy. (**A-II**)

Ethical considerations

This consensus document does not require approval by an Independent Ethics Committee.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eimce.2024.05.011.