CLINICAL MANAGEMENT OF YELLOW FEVER IN THE REGION OF THE AMERICAS

EXPERIENCES AND RECOMMENDATIONS FOR HEALTH SERVICES

PAHO
Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas

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"(...) "I have a funny bit of information. A nurse who had been working with the Department but had married an oil worker in southern Trinidad several years ago, came to see me two or three days ago and asked me for a job. I asked why, thinking that she had been taken care of, but she said her husband had died the week before and that she had to start to work again. I inquired what her husband had died of, and she responded, 'Typhoid fever with jaundice.'" (...)"

Wilbur G. Downs, Yellow Fever Conference, Washington, D.C., 1954

Yellow fever conference, 21-22 December 1954. Am J Trop Med Hyg. 1955 Jul;4(4):571-661.

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ABBREVIATIONS AND ACRONYMS

ALT	alanine aminotransferase
APACHE II	acute physiology and chronic health evaluation II
AST	aspartate aminotransferase
CI	confidence interval
INR	international normalized ratio
NHPs	nonhuman primates
PAHO	Pan American Health Organization
SOFA	sequential organ failure assessment
ULN	upper limit of normal
WHO	World Health Organization
YF	yellow fever

ABSTRACT

Yellow fever (YF) is a serious viral hemorrhagic disease that poses a challenge for the health professional. It requires early recognition of signs and symptoms, which are often nonspecific, and it can mimic other acute febrile syndromes. Classic studies of the natural history of YF show that the disease is clinically characterized by three phases: 1) infection phase, with elevated body temperature; 2) remission phase, with the presence of albuminuria; and 3) toxic phase, with hemorrhagic manifestations and signs and symptoms of acute liver failure, such as jaundice and hepatic encephalopathy.

There is still no specific treatment for YF. Therefore, early detection of suspected or confirmed cases, monitoring of vital signs, life support measures, and management of acute liver failure continue to be the recommended strategies for case management. In this context, the goal of the present publication is to systematize the experience of specialists in the Region of the Americas who have worked in the clinical management of YF patients, especially during outbreaks and epidemics, contextualizing this experience within the current body of medical and scientific evidence and taking into account the technical guidelines already available in the countries of the Region, and to propose regional recommendations for the laboratory and clinical management of suspected and confirmed cases of YF. Flowcharts are included, with steps for initially addressing the patient with clinically suspected YF, along with a minimum package of laboratory tests that may be useful in situations where material and human resources are limited. The report also includes reviews of current medical and scientific evidence on the clinical, laboratory, and therapeutic management of YF and identifies aspects of the health system organization for dealing with YF outbreaks and epidemics. Thus, it fills a historical gap by recognizing YF as a unique disease entity that requires early case detection, proper management of complications, and, above all, efficient organization of the health services network in order to reduce the morbidity and mortality associated with the disease.

Keywords: yellow fever, emerging and reemerging diseases, outbreak/epidemic, clinical management, consensus, clinical guidelines

INTRODUCTION

Yellow fever (YF) is an endemic arbovirus disease in the tropical regions of Africa and South America caused by a virus of the genus Flavivirus. Humans may become infected when bitten by mosquitoes either previously infected from feeding on monkey carriers of the virus (jungle cycle)—mainly mosquitoes of the genera Haemagogus or Sabethes—or acting as a viremic host in person-to-person transmission (urban cycle)—in the latter case, mainly by *Aedes aegypti* mosquitoes (*1*).

YF poses a challenge for the health professional: it is a serious viral hemorrhagic disease that requires early recognition, yet its signs and symptoms are often nonspecific and can mimic other acute febrile syndromes. Classic studies of the natural history of YF show that, clinically, the disease is characterized by three phases: 1) infection phase, with elevated body temperature; 2) remission phase, with the presence of albuminuria; and 3) toxic phase, with hemorrhagic manifestations and signs and symptoms of acute liver failure, such as jaundice and hepatic encephalopathy. However, according to a study by Monath et al. (*2*), nearly 50% of YF patients present with an inapparent clinical picture, while 20% have minor symptoms and 30% have fulminating forms.

To date, there is no specific treatment for YF. Therefore, early detection of suspected or confirmed cases, monitoring of vital signs, life support measures, and therapeutic management of acute liver failure continue to be the recommended strategies for case management.

GOALS

This publication has the following goals:

1. Systematize the experience of specialists in the Region of the Americas who have worked in the clinical management of YF patients, especially during outbreaks and epidemics, contextualizing this experience within the current body of medical and scientific evidence and taking into account the technical guidelines already available in the countries of the Region;
2. Propose regional recommendations for initial patient management, including clinical and laboratory aspects and the organization of health services.

Preparation of this document by the Infectious Hazard Management Unit in the Health Emergencies Department of the Pan American Health Organization (IHM/PHE/PAHO) began in 2017, motivated by the need to generate responses to the Member States regarding the management of YF cases in the health services, particularly in primary care, and by YF outbreaks and ultimately the epidemic in the Region starting in 2016. The process involved three stages: review of the medical and scientific literature, review of existing regional guidelines, and consultation with an advisory group of specialists from the countries of the Region of the Americas who have worked in the management of YF cases.

MEDICAL AND SCIENTIFIC EVIDENCE

A review was conducted of the available medical and scientific literature on the clinical management of YF, including the use of antiviral agents and other therapies in the treatment of cases. Following the World Health Organization's methods for preparing recommended standard and rapid guidelines (*3*), a search and objective assessment of the evidence was conducted using PICO questions related to population(s), intervention(s), comparator(s), and outcome(s).

Three PICO questions were formulated for consultation in the SciELO, LILACS, MEDLINE/ PubMed, and Epistemonikos databases:

1. In patients with YF, does the use of antiviral agents reduce deaths, days with fever, or length of hospital stay compared with non-use of antiviral agents?
2. In patients with YF, does liver transplantation result in better survival rates than nonintervention?
3. In patients with YF, does plasma exchange/apheresis result in better survival rates than nonintervention?

The search strategy for each PICO question appears in Annex 2. The review of the medical and scientific literature revealed an absence of robust systematic evidence on the clinical management of YF. Nevertheless, summary results of this search have been used throughout this document to support the advisory group's discussion.

DOCUMENTARY REVIEW

The review of the literature looked for guidelines, directives, or protocols on epidemiological surveillance, laboratory performance, clinical management, and health service organization relating to YF in the Member States of the Region of the Americas published in the last 15 years.

The review of national documents was initially conducted in November 2018 and updated on 16 October 2021 during epidemiological week 41 of 2021. The update involved reviewing official technical documents to study the components of the response to YF outbreaks (surveillance in humans, surveillance of epizootics, specific laboratory diagnosis, clinical management, and immunization) in the 12 countries that had experienced YF outbreaks in the Region of the Americas: Argentina, Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, Guyana, Panama, Paraguay, Peru, Suriname, Trinidad and Tobago, and Venezuela (Bolivarian Republic of). Nine of these countries had at least one technical document on one of the following components: surveillance in humans (eight countries), surveillance of epizootics (seven), laboratory analyses (seven), clinical management (five), and immunization (eight). Technical documents were identified in the following countries with confirmed reported cases of YF during the two most recent waves of YF transmission in the Region in 2016–2018 (Box 1): Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, and Peru. Annex 1 lists the technical documents from the countries with their respective links. No technical documentation was available for two additional countries that reported confirmed cases: French Guiana and Suriname.

At the time the documentary review was updated, the specialists recognized that Brazil was the country in the Region that had made the most progress in the area of clinical management. As of 2017, both the national Ministry of Health[1] (*4*) and the Minas Gerais State Secretariat of Health (*5*) had published specific documents on the clinical

1 Brasil, Ministério da Saúde, Secretaria de Atenção à Saúde. Febre amarela: guia para profissionais de saúde. Brasília: Ministério da Saúde; 2017. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/febre_amarela_guia_profissionais_saude.pdf. This document was expanded in 2020. For further information, see: Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Imunização e Doenças Transmissíveis. Manual de manejo clínico da febre amarela [Internet] / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Imunização e Doenças Transmissíveis. Brasília: Ministério da Saúde; 2020. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/manual_manejo_clinico_febre_amarela.pdf. ISBN 978-85-334-2818-8

management of YF. In 2018 (*6*), the Brazilian Society of Infectious Diseases added to the literature with a report on the experiences of health professionals with the clinical management of YF in areas with limited resources for patient management. In the states of Minas Gerais, São Paulo, and Rio de Janeiro, which reported the most cases of YF during the 2016–2018 epidemic, there was already an effort under way to validate complex issues in YF management, such as the use of antiviral agents, liver transplantation, and reorganization of health services.

At the start of the epidemic in Brazil, clinical management was influenced by past experience with the clinical management of dengue and most of the patients were hospitalized, overloading the health services network and its human and financial resources. However, the severity of the YF cases made it necessary to change the procedures and address the disease differently, adopting many new approaches at the hospital level. Also, obtaining timely laboratory results became a very important aspect of initial case management at the primary care level.

Box 1. Transmission waves in the Region of the Americas, 2016–2021

The transmission waves in the Region of the Americas during 2016–2018 produced the largest number of human and epizootic YF cases reported in several decades. During this period, seven countries and territories reported cases: Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, French Guiana, Peru, and Suriname (*7*, *8*). Brazil contributed the most reported cases: 778 confirmed human cases, including 262 deaths (*9*), during the 2016–2017 seasonal period, and 1376 cases and 483 deaths between July 2017 and July 2018. The state of Minas Gerais reported the largest number, with 520 confirmed cases and 177 deaths, followed by São Paulo, with 516 cases and 163 deaths, and Rio de Janeiro, with 223 cases and 73 deaths. As a result, Brazil extended the recommended vaccination area to the entire country (*10*). During 2019–2020, three countries in the Region reported confirmed cases of YF: Bolivia (Plurinational State of), with one confirmed case; Brazil, with 19 confirmed cases (*10*); and Peru, with nine probable cases (*11*, *12*). During this same period, Brazil also reported 976 suspected human cases, 19 of which were confirmed. Sporadic cases continued to be reported in the Brazilian Amazon region, where the disease is considered endemic, with 17 confirmed cases in the state of Santa Catarina. In the country's Northern region, cases were recorded in the states of Pará (one case) and Acre (one case) during the monitoring period. However, no YF epizootics in nonhuman primates (NHPs) were documented in that region. Outside the Amazon region, transmission started again during the July–October 2019 season, with cases detected in São Paulo, Paraná, and Santa Catarina. Beginning in November 2019, the frequency of confirmations in primates increased, with spread of the virus in the southern and western areas of Paraná and along the coast of Santa Catarina. In January 2020, the first human cases were detected in Santa Catarina, the only state outside the Amazon region to report cases during the period (*13*, *14*).

In 2021, confirmed YF cases were reported in four countries: Bolivia (Plurinational State of), with one confirmed case; Peru, with 10 confirmed cases, including seven deaths; Venezuela, with 11 confirmed cases; and Brazil, with nine confirmed cases, including three deaths. In Venezuela (Bolivarian Republic of), 11 confirmed cases included five patients who were asymptomatic and six who developed signs and symptoms of the disease. The probable infection sites were the municipality of Maturín for 10 of the confirmed cases and the municipality of Punceres for the one remaining confirmed case. Also in 2021, between epidemiological weeks 32 and 49, a total of 13 epizootics of YF were reported in NHPs in Venezuela (Bolivarian Republic of), 10 of them in the state of Monagas and three in the state of Anzoátegui (*15*). During the 2020–2021 seasonal period, between July 2020 and June 2021, Brazil reported 527 suspected human cases of YF, nine of which (1.7%) were confirmed, 13 (2.5%) were still under study, and 500 (94.9%) were ruled out. All the confirmed cases, including three fatal cases, were reported in the state of Santa Catarina. In addition, between 1 July and 28 December 2021, a total of 276 suspected epizootic cases were reported, 13 of which were confirmed to be YF and 10 remained under study. Epizootic cases were confirmed in the states of Minas Gerais and Santa Catarina (*15*).

EXPERIENCE OF COUNTRIES OF THE REGION OF THE AMERICAS IN THE MANAGEMENT OF YELLOW FEVER CASES

During 2018, the Infectious Hazard Management Unit IHM/PHE/PAHO organized two regional consultations[2] with members of academic and scientific organizations, epidemiologists, health managers, and medical health professionals and nurses from primary care and high-complexity facilities in the Region of the Americas (Box 2). The participants in these consultations (the advisory group) had experience in the clinical management of YF and had been involved in responding to YF outbreaks over the last 15 years. At these meetings, the specialists shared their experiences with the challenges of clinical management of YF, proposed a package of minimum laboratory tests for initial management and monitoring of cases, agreed on a flowchart for the initial management of suspected and confirmed cases of YF, and proposed an organization chart at different levels of the health system for dealing with YF during outbreaks or epidemics. Each participant signed a commitment and confidentiality agreement.

Box 2. Discussion Topics for Consultations on the Management of Yellow Fever

- Guidelines for the clinical management of YF – Regional perspectives
- Initial measures for patients with clinical suspicion of YF
- Severity criteria for patients with clinical suspicion of YF
- Hospitalization criteria for patients with clinical suspicion of YF
- Clinical management of YF patients – General and specific behaviors and flowchart
- Minimum requirements for laboratory testing of YF patients
- Management of acute liver failure in YF patients – Special characteristics?
- Use of antiviral agents in YF patients – Preliminary results of studies
- Other therapeutic approaches in YF management – Liver transplantation, plasma exchange/apheresis
- Criteria for hospital discharge of YF patients
- Ambulatory follow-up of YF patients – Proposed schedule of consultations

YF = yellow fever

Three questions guided the discussion coordinated by the moderators, aimed at producing compelling and specific information to elicit pertinent and appropriate measures in the health services of the countries of the Region:

1. When faced with a suspected case of YF, what should be the initial clinical approach?
2. When faced with a suspected case of YF, what laboratory tests should be ordered to initially assess cases and evaluate the progression of more serious forms?
3. When faced with an outbreak or epidemic of YF, how should the health services organize to address the increased number of cases?

2 The first consultation was held in Brazil during the 54th Congress of the Brazilian Society of Tropical Medicine (1–4 September 2018). The second consultation was held in Peru as part of the Workshop on Recent Developments in Yellow Fever in the Americas (13–15 November 2018).

With a view to using the resulting material as a basis for preparation of this publication, the recordings were transcribed and validated by the group of specialists.

Laboratory Management of the Patient with Clinical Suspicion or a Confirmed Diagnosis of Yellow Fever

Even when YF patients are stable and clinically asymptomatic, they can present laboratory results that are suggestive of liver injury.[3] The advisory group concluded that it was essential to identify a minimum package of laboratory tests for initial assessment of patients with clinical suspicion of YF. The suggested minimum package is listed in Table 1.

Table 1. Suggested laboratory tests for the initial assessment of patients with clinical suspicion of yellow fever

Category	Test	Remarks
Biochemistry	Alkaline phosphatase	– Assessment of obstructive hepatobiliary disease
	Alanine aminotransferase (ALT)	– Diagnosis of acute viral hepatitis, especially when ALT > AST – Differential diagnosis of bile duct obstruction vs. alcoholic liver disease
	Aspartate aminotransferase (AST)	– Predictive of evolution of encephalopathy and serious disease
	Serum creatinine	– Elevated in serious forms of the disease – Prognosis of acute liver failure
	Blood glucose	– Glycemic alterations can be a result of liver dysfunction and may also be seen in patients with comorbidities such as systemic hypertension, diabetes mellitus, bronchial asthma, and other conditions
	Total bilirubin	– Hyperbilirubinemia (with predominance of direct over indirect bilirubin) is indicative of acute hepatic dysfunction and may be regarded as a prognostic factor for evolution to severe forms
Hematology	Hemogram including platelet count	– The blood platelet count is useful for assessing bleeding risk and monitoring liver injury from YF virus infection – Assessment of hemoconcentration and thrombocytopenia – Leukocytosis with neutrophilia and left shift may be present in the initial phases of the disease – Leukopenia with lymphocytosis and left shift may be observed on day 3 or 4 of the disease, with eosinopenia
	Prothrombin time/INR	– Coagulogram for case-fatality indicators – High prothrombin time: marker of liver injury
Hormone panel	Pregnancy test	– For women at high obstetric risk

3 The subject of a specific laboratory diagnosis for YF was not discussed during the meetings with the specialists. For further information, see: Organización Panamericana de la Salud. Diagnóstico por laboratorio de la infección por virus de la fiebre amarilla, 2018. Washington, DC: OPS; 2018. Available from: https://www.paho.org/es/documentos/diagnostico-por-laboratorio-infeccion-por-virus-fiebre-amarilla-2018.

Category	Test	Remarks
Microbiology	Hemoculture/urine culture	– Collect paired samples for antibiogram when available – Patients may present secondary infectious signs and evolution to sepsis
Urinalysis	Urine sediment analysis	– Assessment of urine density and proteinuria, indicative of serious forms of the disease
Diagnostic imaging	Electrocardiogram	– Not a routine examination, to be used when there are alterations in the heart rate (sinus bradycardia without conduction defects, ST-T abnormalities, or extrasystole)
	Chest X-ray	– Depending on the initial clinical assessment, to rule out diagnosis of other infections

INR = international normalized ratio.

In the process of drafting the list of tests for initial assessment of a patient with clinical suspicion of YF, consideration was given to the complexity of the tests taking into account existing resources and the level of care, as well as the possibility of identifying specific packages for each level of care and for differential diagnosis. The list of tests may vary depending on their availability and the organization of the local health services network. It should always be updated as new knowledge becomes available and lessons are learned during YF outbreaks and epidemics. Meanwhile, for the management of patients in this context, the health professional should always consider requesting transaminase (AST/ALT) levels and a hemogram with platelet count.[4] During the Brazilian experience with the 2016–2018 epidemic, the hemogram with platelet count was considered an important parameter when there was suspicion of the disease. In addition, thrombocytopenia and jaundice were considered indicative in the differential diagnosis of YF.

The advisory group cited a study by Wamala et al. (*16*) on the epidemiological characterization and laboratory diagnosis of a 2011 YF outbreak in Uganda, in which 50.8% (n = 32/63) of the patients presented low hemoglobin levels and 46% (n = 29/63) had thrombocytopenia, which further underscores the importance of a hemogram with platelet count in the initial assessment of cases.

Creatinine and bicarbonate levels are also useful for reaching a diagnosis. However, according to the advisory group, high serum creatinine levels are not always seen. Both tests were considered difficult to perform at the primary care level, although venous serum bicarbonate can be tested with portable equipment, which could facilitate its use. In any case, only transaminase tests were recommended for primary care settings since they can be administered in the health services context at feasible associated costs.

Additional suggested laboratory tests for research purposes and for monitoring patients with clinical suspicion of YF are listed in Table 2.

4 ***Note:*** "Hemogram with platelet count" is equivalent to "complete blood count (CBC)."

Table 2. Additional laboratory tests for use in research and clinical monitoring of patients with clinical suspicion of yellow fever

Category (*)	Additional tests	Initial and prognostic assessment
Biochemistry	Albumin	– May be low due to compromised liver
	Creatine phosphokinase	– For differential diagnosis with other arbovirus diseases
	Gamma-glutamyl transferase	– Useful for differential diagnosis with acute jaundice in chronic alcoholic patients
	Urea	– Useful for assessing indication for dialysis in patients who develop kidney failure
	Ammonia	– Arterial, if available
	Amylase	– Level may be high; test is especially useful for differential diagnosis with acute pancreatitis
	Arterial blood gas and arterial lactic acid	– For assessment of hypoperfusion or severe disease. There may be metabolic alkalosis in the early phases of the disease, which can exacerbate liver encephalopathy. In later phases, metabolic acidosis may be present due to kidney failure and elevated arterial lactate
	Serum bicarbonate	– Useful for assessing metabolic acidosis but not always available in primary care settings
	Serum minerals (calcium, chlorine, phosphate, magnesium, potassium, sodium)	– The following conditions may be present: hyponatremia, hyper/hypokalemia, hypomagnesemia, hyper/hypophosphatemia, hyper/hypocalcemia
	C-reactive protein/blood sedimentation rate	– These tests are not very sensitive, but they are useful for assessing acute inflammatory and infectious conditions
	Serum lipase	– For differential diagnosis with acute pancreatitis
Hematology	Malaria (blood smear)	– For differential diagnosis with acute hemorrhagic fevers, especially in endemic and mining areas
Immunology	Immunological test for dengue	– For differential diagnosis with acute hemorrhagic fevers
	Immunological tests for viral hepatitis: anti-HAV IgM, anti-HCV, HCV RNA, HBsAg, anti-HBc IgM, herpes simplex virus, and herpes zoster virus	– Indicated when serum transaminase levels are high and a YF diagnosis has been ruled out. Consider epidemiological link and risk factors
	Leptospirosis	– For differential diagnosis with acute hemorrhagic fevers. Consider epidemiological link and risk factors to decide on treatment when specific laboratory tests are not available
	HIV	– To assess the presence of comorbidities and the patient's immune status

Category (*)	Additional tests	Initial and prognostic assessment
Diagnostic imaging	Abdominal ultrasonography	– Abdominal ultrasonography only for patients with significantly high laboratory alterations or complications during evolution of the disease

(*) Tests for toxicology, ceruloplasmin blood level, and autoimmune disease markers are expensive. They are usually available in high-complexity services and should only be considered if it is desired to rule out a yellow fever diagnosis.

In the hospital management of patients with a confirmed YF diagnosis, health professionals should consider using liver transaminase tests (AST/ALT), hemogram with platelet count, and coagulogram. The advisory group made the following observations about these tests:

- **Liver transaminase (AST and ALT) tests:** The YF virus is viscerotropic (*1*, *17*) and some degree of liver injury can be expected in patients with a confirmed YF diagnosis. Thus, it is recommended to test for AST and ALT at the outset. Levels five times higher than the upper limit of normal should be considered a warning sign. During the initial days, the requesting interval should be every 24 hours, or every 12 hours when there are signs of severity. The signs of severity should arise starting on day 4 since the appearance of symptoms, or in other words, on day 2 or 3 from arrival at the health service, when the patient presents toxemia. Stable transaminase levels of 500 U/L or lower without significant variations are a sign of mild YF.
- **Hemogram with platelet count:** This test is easily available and the result can be obtained quickly. The advisory group pointed out that it was important to watch the curve in the blood platelet tests, since worsening levels precede worsening of the disease. This clinical pattern should always be kept in mind. In mild cases, the test should be repeated every 24 hours to monitor the hematocrit level and the platelet count. The purpose of regularly repeating the hemogram is to watch for a drop in platelet count, which is considered one of the first warning signs of severity of the disease, and to help differentiate a mild case from a moderate or severe one. The alterations expected in the hemogram of a YF patient are a falling platelet count and leukopenia. A low hematocrit level indicates bleeding; the health care provider should look for the source of previously unseen or unidentified bleeding. Platelet levels below 50 000/mm^3 should be regarded as a sign of progression of the disease. The patient should be admitted to the health facility for clinical monitoring. Leukocytosis and a high level of C-reactive protein are not characteristic of YF; these results are useful in triage to exclude a diagnosis of YF and should be regarded as a sign to seek a differential diagnosis. Laboratory results should always be considered together with the clinical picture. In the event of toxemia, the patient should be referred to the hospital level or an intensive care unit, depending on the severity of the condition. When a patient is referred from primary care to a higher level, the frequency for requesting the hemogram should be increased to every 12 hours in a hospital of average complexity and every six hours in an intensive care unit.
- **Coagulogram:** Patients with YF present variable coagulation rates due to liver compromise. Often both activated partial thromboplastin clotting time and prothrombin time/INR (international normalized ratio) are increased, the latter being the most important criterion of severity, since high levels of this index are associated with increased case fatality.

A patient with signs of severity but low liver transaminase levels should be cause for concern. A lack of parallel between the clinical and laboratory signs may be caused by a transaminase dilution error. In such cases, the test should be repeated. It has been noted that the most helpful test for detecting AST dilution problems is prothrombin/INR time, which reinforces the importance of requesting this test during the initial assessment.

Systematization of Signs and Symptoms and Stratification by Level of Care

The advisory group emphasized the nature of YF as a dynamic broad-spectrum systemic disease with a clinical picture marked by phases:

- Infection phase, with elevated body temperature;
- Remission phase, with presence of albuminuria; and
- Toxic phase, with hemorrhagic manifestations and signs of acute liver failure, such as jaundice and liver encephalopathy.

Since the disease can rapidly evolve into more serious forms, it is essential to systematize the clinical signs and symptoms in order to support health professionals at the basic, average, and higher complexity levels in quickly detecting those individuals who might present complications or need to be transferred to a service with more treatment resources.

Three types of health facilities/levels of care should be considered in the management of YF patients:

- Basic (primary care) health units: For the management of mild cases or for patients without a confirmed diagnosis of the disease—usually those in day 2 or 3 since the onset of symptoms (Group A).
- Secondary level of care: For patients in the remission phase of the disease, those with a diagnosis or suspicion of YF, and those in day 3 or 4 since the onset of symptoms (Group B).
- Intensive care units: For the management of serious cases with liver and kidney complications (Group C).

Table 3 shows warning and severity signs and symptoms; clinical and laboratory findings; and stratification of patients with a confirmed YF diagnosis by corresponding level of care.

Table 3. Clinical manifestations and laboratory findings in patients with a confirmed diagnosis of yellow fever

	Clinical findings	Laboratory findings	Level of care
Warning signs and symptoms Infection phase	Dehydration, vomiting, diarrhea, abdominal pain, mild bleeding (epistaxis, bleeding gums, petechiae)	AST > 5 ULN Platelet count < 50 000/mm^3 Proteinuria	– Primary care (Group A)
Signs and symptoms of severity Remission/toxic phases	Jaundice, oliguria, mental confusion, convulsions, hemorrhagic phenomena,* tachypnea, hypotension, signs of poor blood perfusion	AST > 2000 U/L Serum creatinine > 2.0 mg/dL INR > 1.5	– Secondary level of care (Group B) – Intensive care unit (Group C)

AST = aspartate aminotransferase; ULN = upper limit of normal; INR = international normalized ratio.

*Hemorrhagic phenomena defined as epistaxis, bleeding at a puncture site, hematemesis, hematuria, melena, conjunctival hemorrhage, hypermenorrhagia, hemoptoic sputum, and hemoptysis.

Supportive Treatment of Yellow Fever Patients

The advisory group agreed that a set of factors should be considered to identify practices related to evolution of the disease. These include rate of disease progression and availability of in-service health laboratory tests.

Patient-related practices during the infection phase of the disease – Group A (primary care)

Patients in this group present **fever, pain, and nausea**. From the laboratory standpoint, the findings are nonspecific. The patient may have bleeding without any evidence of it. Difficulty eating may lead to dehydration, which should be managed with intravenous and oral rehydration to replace the losses.

Reclassification to "Group B": The advisory group recommended oral replacement to hydrate and replace the losses, starting with initial volume expansion of 20 ml/kg. Dehydration can be expected to be resolved within 24 hours. If there is no favorable evolution, it is recommended to reclassify the patient as "Group B." The health professional should monitor the patient's level of consciousness.

For **pain** and **control of fever**, it was suggested to use dipyrone (maximum 8 g/day) and paracetamol (maximum 2 g/day), with attention to the status of the liver and avoiding non-steroidal anti-inflammatory drugs.

Patient-related practices during the remission phase – Group B (hospitalization)

Patients in this group present **dehydration, repeated episodes of vomiting, nausea, diarrhea, decreased urinary output, and an altered hemodynamic pattern**. These are patients who may evolve to a state of hypovolemic shock, requiring hospitalization and frequent monitoring of cardiac, renal, hepatic, and metabolic parameters. The advisory group recommended not to delay the use of vasoactive drugs.

Reclassification to "Group C": After the second volume expansion, the patient should be referred to the intensive care unit. The health professional should also monitor the level of consciousness, the intensity of abdominal pain, and the presence of new hemorrhagic phenomena[5] for new reclassification.

Patient-related practices during the toxic phase – Group C (intensive care unit)

Patients in this group present typical signs and symptoms of acute liver failure, including jaundice, altered liver function tests, acute kidney failure, and liver encephalopathy. These patients should be referred to more complex services that provide specific treatment along with continuous monitoring and supportive treatment such as the use of vasoactive drugs, ventilation, and dialysis. The advisory group did not discuss specific protocols for managing these complications. Health services should base their treatment on local protocols.

Criteria for Hospital Discharge and Management of Delayed-onset Hepatitis Associated with Yellow Fever

The advisory group agreed that the following criteria should be considered for hospital discharge:

- Afebrile for the last 48–72 hours
- Clinical stability without evidence of bleeding for the last 7 days
- Normal laboratory tests, with transaminases <1000 U/L and an independent drop in bilirubin.

The group noted that during the YF convalescent phase, some patients continue to present high transaminase levels or even symptoms of the disease. During the 2016–2018 YF epidemic in Brazil, a few cases of delayed-onset hepatitis were reported in patients with a specific diagnosis of YF (*18–20*) within six months after normalization

5 The following hemorrhagic phenomena are included in the clinical picture of YF: epistaxis, bleeding at a puncture site, hematemesis, hematuria, melena, conjunctival hemorrhage, hypermenorrhagia, hemoptoic sputum, and hemoptysis.

or improved liver function following an acute YF infection. Casadio et al. (*20*) have characterized this event as a new inflammatory liver process with new alterations in transaminase and bilirubin levels. The authors described the phenomenon in 26 (37%) of patients being followed post-discharge in in-service referral monitoring. Of all the patients studied, 58% did not present symptoms. Among the clinical cases, the most frequently mentioned symptoms were abdominal pain, malaise, and nausea. All the patients presented clinical recovery with normalization of liver enzymes. Denis et al. (*18*) described the phenomenon in two French travelers who had been in an area where YF was circulating in Brazil. Also, Rezende et al. (*19*) described the case of a patient with loss of appetite, weakness, jaundice, and increased liver transaminase and bilirubin levels 2 months after a YF diagnosis. These examples underscore the need for ambulatory monitoring of patients with awareness of this phenomenon. Casadio et al. (*20*) suggest that a pro-inflammatory process resulting from the presence of virus particles remaining from the acute phase of the disease may be involved in these cases of delayed onset hepatitis.

Severity Criteria for Predicting Mortality

According to Johansson et al. (*21*), in their study estimating the incidence of YF cases based on the number of severe cases, 55% (confidence interval [CI] 95% 0.37–0.74) of the cases are asymptomatic, 33% (CI 95% 0.13–0.52) presented mild disease, and 12% (CI 95% 0.05–0.26) were severe forms. In the severe forms, the probability of death was 47% (CI 95% 0.31–0.62).

So far, there is no model that offers criteria for predicting severity of YF for mortality. After the 2016–2018 YF epidemic in Brazil, four studies (*22–25*) presented results that may eventually provide support for defining and validating criteria for mortality in YF patients. Kallas et al. (*22*) conducted an observational cohort study based on data from 76 cases with a laboratory-confirmed YF diagnosis in referral hospitals in the city of São Paulo, Brazil. The authors propose the following factors for predicting mortality: age (with each additional five years, the risk ratio increases by 1.28 [CI 95% 1.7–1.55]), neutrophil level (with each rise of 1000 cells/µL, the risk ratio increases by 1.21 [CI 95% 1.09–1.34]), AST (with each rise of 100 U/L, the risk ratio increases by 1.01 [CI 95% 1.00–1.02]), indirect bilirubin (with each rise of 1 mg/dL, the risk ratio increases by 1.41 [CI 95% 0.98–2.06]), creatinine level (with each rise of 1 mg/dL, the risk ratio increases by 1.07 [CI 95% 0.88–1.32]), and YF viral load (with each rise of 1 log10 copies/ml, the risk ratio increases by 1.27 [CI 95% 1.42–2.0]).

Similar results were found by Ribeiro et al. (*23*) in a logistic regression model of a retrospective cohort of 72 YF patients admitted to another referral hospital of the city of São Paulo, Brazil. In their study, the independent associated risk factors for mortality were AST > 1841 IU/L (adjusted risk ratio 12.92 [CI 95% 1.50–111.37]) and creatinine level > 1.2 mg/dL (adjusted risk ratio 81.47 [CI 95% 11.33–585.71]).

In a descriptive cohort study of 79 patients admitted to a high-complexity hospital in the city of São Paulo (*24*), patients with a history of diabetes mellitus had a higher case-fatality rate than non-diabetic patients. Finally, study of a longitudinal cohort of 114 patients admitted to an intensive care unit in a tertiary referral hospital for infectious diseases in the state of Minas Gerais, Brazil (*25*) revealed the following factors associated with mortality: INR > 1.5 (risk ratio 1.32 [CI 95% 1.04–1.67]), acute physiology and chronic health evaluation II (APACHE II) score (risk ratio 1.08 [CI 95% 1.04–1.12]) and stage IV hepatic encephalopathy (risk ratio 2.01 [CI 95% 1.06–3.84]).

Flowcharts for the Management of Patients with Clinical Suspicion of Yellow Fever and Convalescents

The experts' experience is reflected in a flowchart they developed for the initial management of a patient with clinical suspicion of YF (Figure 1). The assessment of a patient with clinical suspicion of YF starts with the following steps:

1. Assessment of the patient's YF vaccination status to determine the type of vaccine administered (standard or fractional dose)[6] and rule out viscerotropic disease.
2. Assessment of any epidemiological link to YF, especially in areas with prior circulation of the virus or rumors or occurrence of epizootics.

This flowchart can be adapted to different contexts or expanded to include other aspects of initial patient management, depending on how the health services are organized and the availability of human and financial resources. The experts agreed that it was important not to rely on only one criterion to determine severity. Two criteria should be considered—for example, a clinical criterion plus laboratory tests, or two clinical criteria and a laboratory test—because of the dynamic characteristics of the disease and also, in some situations, difficulty for the health professional to recognize the early clinical picture of YF. Thus, it is extremely important for the health service to have access to the minimum set of recommended tests and for the results to be available as quickly as possible, within 4–6 hours.

6 Viscerotropic disease associated with YF vaccination was not discussed at the meetings with the specialists. For further information, see: Pan American Health Organization. Enfermedad viscerotropica asociada a la vacunación contra la fiebre amarilla: Casos de estudio. Facilitator's version. Washington, DC: OPS; 2013. Available from: https://iris.paho.org/handle/10665.2/53870.

Figure 1. Flowchart for the initial management of patients with clinical suspicion of yellow fever

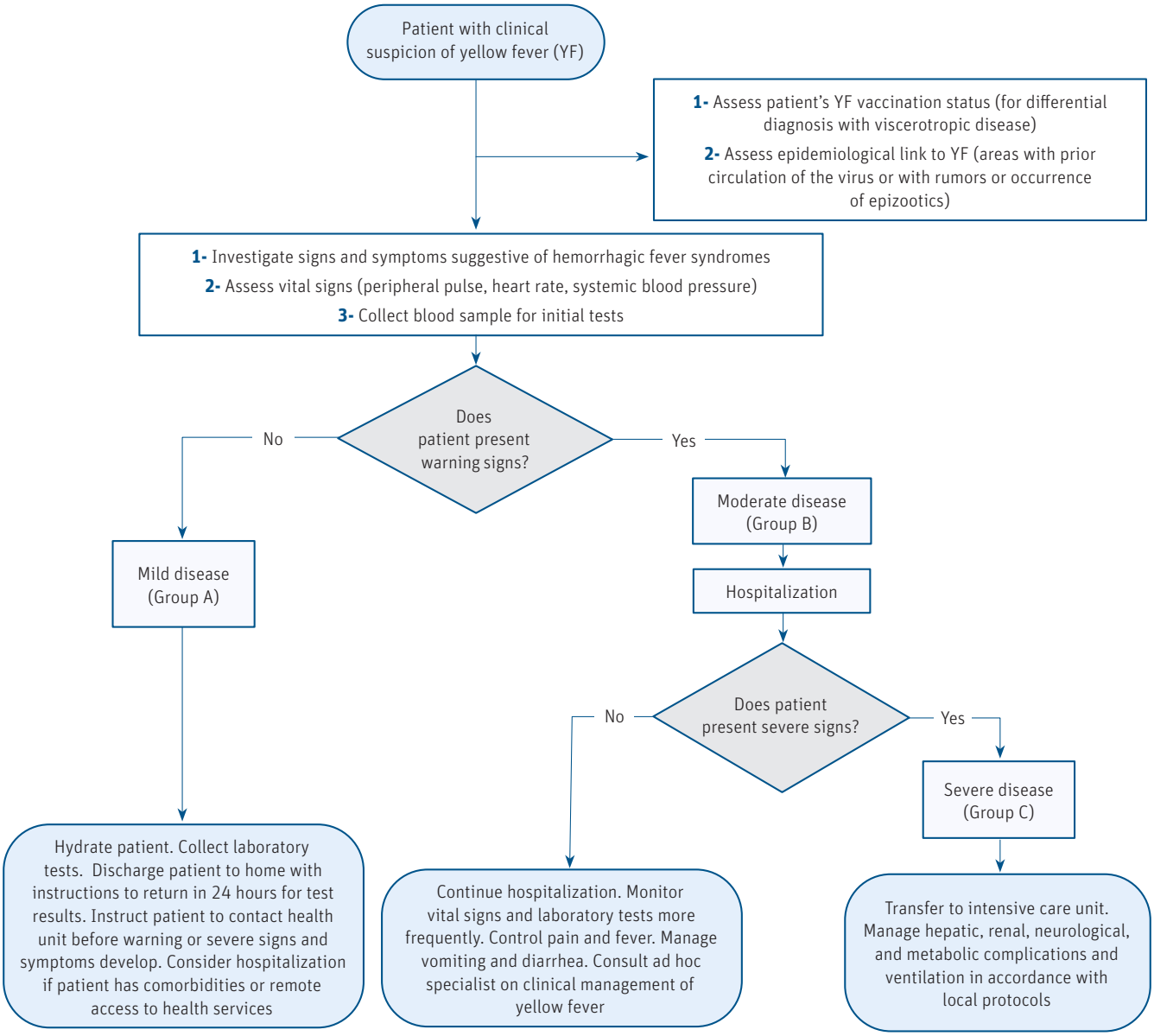
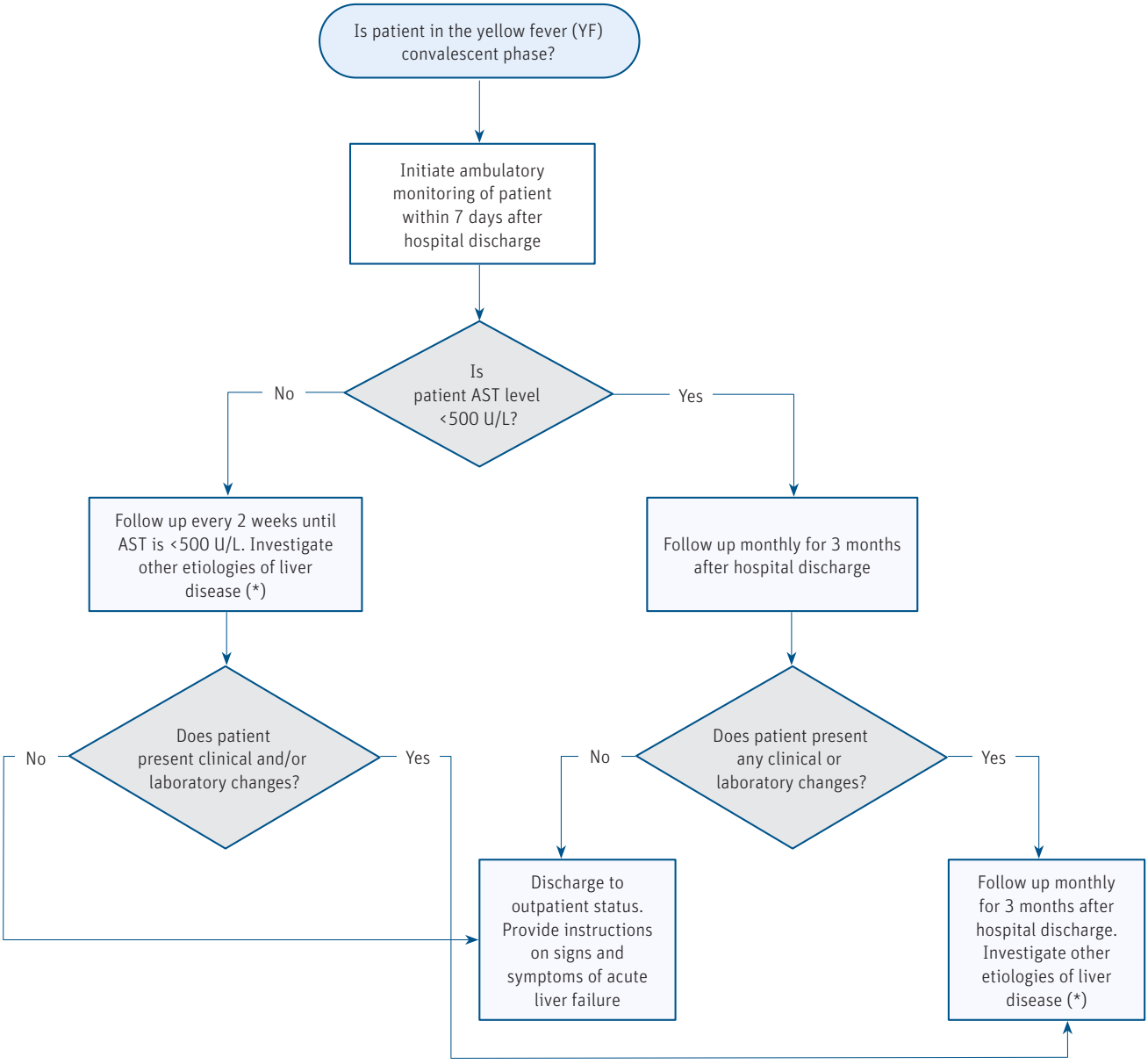


Figure 2 is a flowchart for ambulatory monitoring of YF patients during the convalescent phase. The algorithm uses the initial AST level as the baseline for defining the interval for ambulatory monitoring and the need for additional research on other etiologies to account for liver disease.

Figure 2. Flowchart for ambulatory monitoring of patients with yellow fever during the convalescent phase



(*) Liver diseases: serological tests for viral hepatitis B and C, serology for HIV, abdominal ultrasonography
AST = aspartate aminotransferase.

Specific Treatments for the Clinical Management of Yellow Fever

Specific treatments for the clinical management of YF, such as the use of antiviral agents and other drugs, plasma exchange/apheresis, and liver transplantation, have not been proven to be beneficial and therefore are not currently indicated.[7]

7 For further information on the availability of evidence on the clinical management of YF, see Annex 2.

Antiviral agents, sofosbuvir, and other drugs

The specialists understand that there is still no robust scientific evidence for recommending antiviral agents such as ribavirin or sofosbuvir, immune-modulating drugs, or interferon alpha as treatment options for the management of YF. Studies establishing the effectiveness, benefit, and safety of these agents in the treatment of YF are still lacking (*26*, *27*).

Sofosbuvir is a direct-action antiviral agent approved for the treatment of viral hepatitis C (*28*). When it was recently identified as an agent capable of inhibiting the in vitro activity of Zika virus (*29*), researchers postulated that the same virucidal action could be effective in the treatment of YF. Investigators in Brazil proposed a randomized clinical trial (SOFFA study) (*30*) to evaluate the effects of sofosbuvir in a daily oral dose of 400 mg compared with the standard treatment of hospitalized patients with a YF diagnosis (*30*). The outcomes to be analyzed included: severity that meets criteria for admission to intensive care unit, viral burden levels at 72 hours after inclusion in the research protocol, need for a liver transplant, and mortality within 60 days.

Ivermectin, a parasiticide, has been shown to inhibit in vitro replication of the YF virus (*31*). However, there have been no randomized clinical trials to assess its clinical effectiveness. Its use is not recommended for the treatment of YF.

Plasma exchange/apheresis

Apheresis is a medical procedure in which certain blood components are replaced with blood derivatives or albumin. Its modalities include plasmapheresis or high-volume plasma exchange. The objective is to remove antibodies and other inflammatory components that may be involved in pathogenesis of the disease (*32*). Patients with acute liver failure frequently develop hemodynamic instability and shock, together with tissue hypoperfusion and multiple organ failure.

Larsen et al. (*33*) led a randomized clinical trial to assess the effectiveness of high-volume plasma exchange (defined as the exchange of 8% to 15% of bodyweight with fresh frozen plasma) in patients with acute liver failure following liver transplantation. The results showed increased survival; a reduction in serious adverse events such as systemic inflammatory response syndrome; and improvement in systemic, cerebral, and splanchnic parameters (improvement in the sequential organ failure assessment—SOFA). During the 2016–2018 YF epidemic in Brazil, modified plasmapheresis was performed in fourth-level hospitals as adjuvant therapy in patients with acute liver failure due to YF (*24*, *34*). However, this procedure is not practicable from the public health standpoint, given the absence of randomized clinical trials, the unavailability of supplies and trained human resources to carry it out, and the possibility of complications such as bleeding and anaphylactic shock. For these reasons, the experts agreed not to recommend it for patients with acute liver failure due to YF, except experimentally in the context of clinical studies.

Liver transplantation

Liver transplantation is a complex, high-cost medical procedure with risks for complications during the peri- and postoperative periods. During the 2016–2018 YF epidemic in Brazil, fourth-level hospitals in the country's Southeastern region performed liver transplants on 23 patients, six of whom (26%) survived (*35*). The high cost of the procedure and the need for specialized professionals to perform it are limitations to its implementation as a public health policy. At the time of the 2016–2018 YF epidemic, the Brazilian Ministry of Health established a strategy

for emergency assistance in cases of hyperacute liver failure associated with YF under a specific decree defining patients with criteria for liver transplantation and specialized services for the management of these cases (*36*, *37*). The incidence of YF in large cities with adequate infrastructure was the factor that permitted access to the procedure. However, the expert group understands that liver transplantation is currently not a treatment option in cases of liver failure due to YF and does not recommend it for case management. Future studies will determine the role of transplantation in the management of patients with severe YF. Annex 3 summarizes the experience with liver transplantation in YF patients based on published reports of cases (*35*, *38–40*).

Organization of the Health Systems for the Management of Yellow Fever in the Context of Outbreaks and Epidemics

Health services should be prepared to meet the demand of suspected and confirmed cases of YF and be able to refer cases to a higher level of care that are likely to evolve into more serious forms or that need more frequent monitoring at the highest level of complexity.

The expert group recognized that primary care services are not prepared to handle suspected cases of YF. In the context of an epidemic, there should be sufficient primary care capacity to at least order a hemogram including platelet count and measure transaminase levels. The focal point managing the epidemic situation should be alerted and the services should be prepared to meet the demand, either transferring the patient to another level or creating a compact assessment structure to ensure receipt of the test results within the desired period.

To support health decision makers and managers in organizing health services to manage YF cases during outbreaks and epidemics, the advisory group suggested creating a matrix showing the respective responsibilities and how health systems should be organized to fulfill them. The proposed matrix should cover: 1) organization of the response, 2) management of cases (protocol and clinical guidelines, establishment of advisory groups, and training of health professionals), and 3) organization of health services (service network, supplies, and laboratory services) at the national, subnational (or departmental) and municipal (or district) level. This matrix of responsibilities is illustrated in Table 4.

Table 4. Organization of health services for the management of yellow fever cases during outbreaks and epidemics

Responsibilities and organization of health systems to address yellow fever outbreaks and epidemics			
Components of the response	**National level**	**Subnational or departmental level**	**Municipal or district level**
Organization of the response	– Create committee to investigate and respond to outbreak or epidemic. – Manage and coordinate technical areas at all levels. – Manage resources for prevention and control activities at all levels. – Assess the quality, effectiveness, and cost of response to the outbreak or epidemic.	– Articulate response with other levels while respecting protocols and guidelines established at the national level. – Coordinate intersectoral planning of surveillance and control activities with involvement of the community – Manage subnational distribution of resources for prevention and control.	– Coordinate response with the local technical team. – Coordinate the intersectoral response with participation by the community and the population at risk. – Manage timely distribution of local prevention resources and facilitate local prevention and control activities.
Case management			
Protocols and clinical guidelines	– Develop a national protocol or adapt existing protocols for the management of YF cases.	– Disseminate, oversee, and evaluate use of the current national protocol in health units and train health workers in case management according to this protocol.	– Ensure the availability of specialized case management in health units. – Provide training and assess case management in the local health units.
Creation of advisory group	– Create ad hoc advisory group to support management of cases that exceed capacity at the subnational level.	– Identify specialists to form an ad hoc advisory group that can be enlisted if the event exceeds local capacity.	– Identify specialists in the municipality/district capable of leading the response to the outbreak or epidemic at the local level.
Training of health professionals	– Ensure the availability of resources to train health professionals in surveillance, control of outbreaks, and case management.	– Organize training for health professionals in the management of cases in municipalities/ districts under their jurisdiction.	– Train primary care professionals in the early recognition of suspected cases, referral to specialized services, epidemiological surveillance, and control of outbreaks.

Responsibilities and organization of health systems to address yellow fever outbreaks and epidemics			
Components of the response	**National level**	**Subnational or departmental level**	**Municipal or district level**
Organization of the health services			
Services network	– Establish standards and manage resources for the referral and counter-referral network. – Identify and set up specialized treatment units, including intensive care units.	– Form a referral and counter-referral network of health services and show them on a map. – Ensure the operation of specialized treatment units, including intensive care units.	– Ensure the availability of adequate patient triage for suspicion of YF at the primary care level. – Ensure adequate outpatient follow-up of suspected cases with warning signs. – Ensure the hospitalization of suspected cases with signs of severity.
Inputs	– Ensure the availability of supplies and equipment, including blood products and derivatives, drugs, and infrastructure.	– Ensure the allocation and distribution of inputs, including blood products and derivatives, medicines, and infrastructure.	– Maintain stocks and distribute supplies, including vaccines, blood products and derivatives, and medicines.
Laboratory	– Ensure the availability of resources and the operation of a national reference laboratory or laboratories for the diagnosis of YF.	– Ensure the shipment of laboratory samples to reference laboratories for specific diagnosis of YF.	– Ensure proper shipment of samples to reference laboratories for diagnostic confirmation. – Ensure availability of minimum set of laboratory tests for initial assessment and monitoring of cases.

Source: Based on Pan American Health Organization. Control of yellow fever: field guide. Washington, DC: PAHO; 2005. (Scientific and Technical Publication 603). Available from: https://iris.paho.org/handle/10665.2/722.

FINAL CONSIDERATIONS

Yellow fever is a disease that evolves very rapidly in seven days. It is highly lethal and requires prompt and carefully targeted interventions on the part of health services. However, the disease is difficult to diagnose and treat. To date, there is no specific drug for treatment and only scant evidence regarding the clinical management of severe cases. Given these concerns, it is important to prepare guidelines for clinical management with descriptions of clinical and laboratory procedures (decided on by consensus) that will be useful for orienting the services, especially at the primary care level, and for managers at the decision-making level.

For development of the present publication, the recent experience of countries that faced outbreaks in 2016–2018 was an important resource, given weak scientific evidence, scant literature on clinical management of the disease, absence of standardized clinical data, and lack of emphasis on good practices and clinical management in areas with limited resources.

The network of health system complexity, which is different in each country, needs to be taken into account in preparing a guide, specifying the care of patients with clinical suspicion of YF in the health services, or developing recommendations on the clinical management of YF. The consultations leading up to the present document focused on developing a systematic set of recommendations for clinical management that could be adapted to real situations and the needs of public health institutions in terms of human, technical, and physical resources. In this way, it was possible to produce a document that can support health professionals in meeting the daily challenges that they face during an epidemic.

A clinical guide for countries with limited human and material resources needs to bear in mind the pressure that will face the services in an epidemic situation. Physicians are not usually trained to deal with YF. Primary care services are not prepared to provide a rapid response. In an epidemic situation, experience has shown that the capacity to identify serious cases that require hospitalization is fundamental. Primary care personnel need to be trained to perform triage and to treat outpatients who do not need to be hospitalized. It is also essential to be able to ensure that test results will be received on a timely basis, which means that managers will also need to organize a network to deliver those services.

FUTURE OUTLOOK

The document resulting from this effort is a synthesis of many discussions, constructed from the perspective of public health and incorporating positive, practical recommendations for decision-making by health managers and by health professionals directly involved in the care of YF patients. Both managers and health professionals will find technical and scientific information on the clinical and laboratory detection of YF based on signs and symptoms, on criteria of severity, on laboratory testing for outpatients with suspicion of YF, on differential diagnosis, on triage, and on the steps that need to be taken. The best laboratory recommendations and information on the safest and most effective treatments will be used to guide health teams and decision makers. Mention of the controversies and

dilemmas faced by these health professionals during past YF outbreaks have also been included. It was considered appropriate to share the experiences, challenges, and limitations that this health situation imposes on the health professional as part of the collective building of knowledge.

Yellow fever has been a subject of concern and action by PAHO since its inception. The present synthesis of discussions in the context of the 2016–2018 YF epidemic now fills a historical gap by treating it as a separate disease entity that requires early detection of cases, proper management of complications, and, especially, organization of the health services network to reduce morbidity associated with the disease. In 1954, PAHO's Director, Dr. Fred L. Soper, convened a regional conference with various public health agencies and decision makers to discuss progress with YF in the Region of the Americas in the context of outbreaks in Trinidad (1953–1954) and Panama and Costa Rica (1948–1953) (*41*). The conference called attention to gaps in knowledge about the origins of the disease, its persistence in certain jungle areas, and the application of control measures. Of special interest is the contribution of Dr. Wilbur G. Downs of the Rockefeller Foundation, whose quote from the rural doctor in Trinidad opens this publication. In the report of that meeting, YF was considered a hemorrhagic fever syndrome typically found in jungle settings. More than 50 years later, the subject of the clinical management of YF is still timely and raises questions that need to be answered.

REFERENCES

1. Kerr JA. The clinical aspects and diagnosis of yellow fever. In: Strode GK, ed. Yellow fever. New York: McGraw-Hill; 1951. 629-40.
2. Monath TP, Vasconcelos PF. Yellow fever. J Clin Virol. 2015;64:160-73.
3. World Health Organization. WHO handbook for guideline development. 2nd ed. Geneva: WHO; 2014. Available from: https://apps.who.int/iris/handle/10665/145714. Accessed January 2022.
4. Brasil, Ministério da Saúde, Secretaria de Atenção à Saúde. Febre amarela: guia para profissionais de saúde. Brasília: Ministério da Saúde; 2017. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/febre_amarela_guia_profissionais_saude.pdf. Accessed January 2022.
5. Brasil, Minas Gerais, Secretaria de Estado de Saúde. Manejo clínico febre amarela. Belo Horizonte: SES/MG; 2017. Available from: https://www.saude.mg.gov.br/images/documentos/Manejo%20Clinico%20Febre%20Amarela%20SES-MG_03-02-2017.pdf. Accessed January 2022.
6. Sociedade Brasileira de Infectologia. Febre Amarela em pacientes adultos: manejo imediato das formas clínicas. 2018. Available from: https://ameci.org.br/manejo-imediato-das-formas-clinicas-em-pacientes-adultos-com-febre-amarela/. Accessed January 2022.
7. Pan American Health Organization. Epidemiological update: yellow fever. 12 January 2018. Washington, DC: PAHO; 2018. Available from: https://www.paho.org/en/documents/12-january-2018-yellow-fever-epidemiological-update. Accessed January 2022.
8. Pan American Health Organization. Epidemiological update: yellow fever. 25 January 2019. Washington, DC: PAHO; 2019. Available from: https://www.paho.org/en/documents/25-january-2019-yellow-fever-epidemiological-update. Accessed January 2022.
9. Pan American Health Organization. Epidemiological update: yellow fever. 20 March 2018. Washington, DC: PAHO; 2018. Available from: https://www.paho.org/en/documents/20-march-2018-yellow-fever-epidemiological-update-0. Accessed March 2022.
10. Brasil, Ministério da Saúde. Informes de febre amarela. Brasília: Ministério da Saúde; 2020. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/edicoes/2020/boletim-epidemiologico-vol-51-no-01. Accessed January 2022.
11. Perú, Ministerio de Salud. Salas de situación semanal. Lima: Centro Nacional de Epidemiología, Prevención y Control de Enfermedades; 2021. Available from: https://bit.ly/3FMwNSi. Accessed January 2022.
12. Perú, Ministério de Salud. Salas de situación de salud; Perú a la SE 53-2020. 2020. Available from: https://www.dge.gob.pe/epipublic/uploads/asis-sala/asis-sala_202053.pdf. Accessed January 2022.

13. Brasil, Ministério da Saúde. Violência interpessoal contra pessoas com deficiência/transtorno no Brasil; situação epidemiológica da febre amarela no monitoramento 2019/2020. Boletim Epidemiológico. 2019;51(46). Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/boletins-epidemiologicos/edicoes/2020/boletim_epidemiologico_svs_46.pdf/view). Accessed January 2022.

14. Pan American Health Organization. Epidemiological update: yellow fever. 6 March 2019. Washington, DC: PAHO; 2019. Available from: https://www.paho.org/en/documents/epidemiological-update-yellow-fever-6-march-2019. Accessed January 2022.

15. Pan American Health Organization. Epidemiological update: yellow fever. 28 December 2021. Washington, DC: PAHO; 2021. Available from: https://www.paho.org/en/documents/epidemiological-update-yellow-fever-28-december-2021. Accessed January 2022.

16. Wamala JF, Malimbo M, Okot CL, Atai-Omoruto AD, Tenywa E, Miller JR, et al. Epidemiological and laboratory characterization of a yellow fever outbreak in northern Uganda, October 2010–January 2011. Int J Infect Dis. 2012;16(7):e536-42.

17. Thomas SJ, Endy TP, Rothman AL. Flaviviruses (dengue, yellow fever, Japanese encephalitis, West Nile encephalitis, St. Louis encephalitis, tick-borne encephalitis, Kyasanur Forest disease, Alkhurma hemorrhagic fever, Zika). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Volume 2. 8th ed. Philadelphia: Elsevier/Saunders; 2015. chap 155, 1881-1903.

18. Denis B, Chirio D, Ponscarme D, Brichler S, de Verdiere NC, Simon F, et al. Hepatitis rebound after infection with yellow fever virus. Emerg Infect Dis. 2019;25(6):1248-9.

19. Rezende IM, Pereira LS, Fradico JRB, Pascoal Xavier MA, Alves PA, Campi-Azevedo AC, et al. Late-relapsing hepatitis after yellow fever. Viruses. 2020;12(2):222.

20. Casadio L, Nastri AC, Malta FM, Araujo J, Silva JB, Solomon J, et al. Late-onset relapsing hepatitis associated with yellow fever. N Engl J Med. 2020;382(21):2059-61.

21. Johansson MA, Vasconcelos PF, Staples JE. The whole iceberg: estimating the incidence of yellow fever virus infection from the number of severe cases. Trans R Soc Trop Med Hyg. 2014;108(8):482-7.

22. Kallas EG, D'Elia Zanella L, Moreira GLH, Buccheri R, Diniz GBF, Castiñeiras ACP, et al. Predictors of mortality in patients with yellow fever: an observational cohort study. Lancet Infect Dis. 2019;19(7):750-8.

23. Ribeiro AF, Cavalin RF, Suleiman JMAH, Costa JA, Vasconcelos MJ, Sant'Ana Málaque CM, et al. Yellow fever: factors associated with death in a hospital of reference in infectious diseases, São Paulo, Brazil, 2018. Am J Trop Med Hyg. 2019;101(1):180-8.

24. Ho YL, Joelsons D, Leite GFC, Malbouisson LMS, Song ATW, Perondi B, et al. Severe yellow fever in Brazil: clinical characteristics and management. J Travel Med. 2019;26(5):taz040.

25. de Ávila RE, Fernandes HJ, Barbosa GM, Araújo AL, Gomes TCC, Barros TG, et al. Clinical profiles and factors associated with mortality in adults with yellow fever admitted to an intensive care unit in Minas Gerais, Brazil. Int J Infect Dis. 2020;93:90-7.

26. Julander JG. Experimental therapies for yellow fever. Antiviral Res. 2013;97(2):169-79.

27. Monath TP. Treatment of yellow fever. Antiviral Res. 2008;78(1):116-24.

28. Poordad F, Dieterich D. Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. J Viral Hepat. 2012;19(7):449-64.

29. Sacramento CQ, de Melo GR, de Freitas CS, Rocha N, Hoelz LV, Miranda M, et al. The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication. Sci Rep. 2017;7:40920.

30. Figueiredo-Mello C, Casadio LVB, Avelino-Silva VI, Yeh-Li H, Sztajnbok J, Joelsons D, et al. Efficacy of sofosbuvir as treatment for yellow fever: protocol for a randomised controlled trial in Brazil (SOFFA study). BMJ Open. 2019;9(11):e027207.

31. Mastrangelo E, Pezzullo M, de Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother. 2012;67(8):1884-94.

32. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice; evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. J Clin Apher. 2019;34(3):171-354.

33. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol. 2016;64(1):69-78.

34. Melo RCB, Read HY, Tatsui NH, Nakamura MM, Inowe EK, Oak HB, et al. Papel da troca plasmática na insuficiência hepática aguda pós-infecção pelo vírus da febre amarela; descrição da experiência de um serviço quaternário. Hematology, Transfusion, and Cell Therapy; 2018. Poster presentation at the Brazilian Congress of Hematology, Hemotherapy, and Cellular Therapy – HEMO, 31 October–3 November 2018.

35. Song ATW, D'Albuquerque LAC. Yellow fever: prevention in transplant candidates and emerging treatment data for liver transplant. In: Morris MI, Kotton CN, Wolfe C, eds. Emerging transplant infections: clinical challenges and implications. Cham: Springer International Publishing; 2020. 1–16.

36. Brasil, Ministério da Saúde, Secretaria de Atenção à Saúde. Portaria Nº 2.117, de 11 de Julho de 2018. Institui, no âmbito do Sistema Único de Saúde - SUS, a estratégia para assistência emergencial em casos de Insuficiência Hepática Hiperaguda relacionada à febre amarela (IHHFA) por meio da análise e acompanhamento específicos dos transplantes de fígado. Brasília: Diário Oficial da União; 2018. Available from: https://www.in.gov.br/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/31548007/DiarioOficialdaUniao. Accessed January 2022.

37. Brasil, Ministério da Saúde, Secretaria de Atenção à Saúde. Portaria Nº 1.232, de 6 de Agosto de 2018. Concede habilitação a estabelecimentos de saúde para transplante de fígado em febre amarela. Brasília: Diário Oficial da União; 2018. Available from: https://www.in.gov.br/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/35901350/do1-2018-08-08-portaria-n-1-232-de-6-de-agosto-de-2018-35901341. Accessed January 2022.

38. Song ATW, Abdala E, de Martino RB, Malbouisson LMS, Tanigawa RY, Andrade GM, et al. Liver transplantation for fulminant hepatitis attributed to yellow fever. Hepatology. 2019;69(3):1349-52.

39. Vieira V, Pacheco L, Demetrio L, Balbi E, Bellinha T, Toledo R, et al. Liver transplantation for acute liver failure due to yellow fever: a case report. Transplant Proc. 2019;51(5):1625-8.

40. Duarte-Neto AN, Cunha MDP, Marcilio I, Song ATW, de Martino RB, Ho YL, et al. Yellow fever and orthotopic liver transplantation: new insights from the autopsy room for an old but re-emerging disease. Histopathology. 2019;75(5):638-48.

41. Yellow Fever Conference: 21–22 December, 1954. Am J Trop Med Hyg. 1955;4(4):571-661.

ANNEXES

ANNEX 1. TECHNICAL DOCUMENTS ON YELLOW FEVER AVAILABLE FROM THE COUNTRIES IN THE REGION OF THE AMERICAS

Official documents, guidelines, and/or published protocols available online with content on the response to YF outbreaks in 12 countries dealing with YF in the Region of the Americas (list reviewed as of epidemiological week 3 of 2022, 20 January 2022).

Country	Authoritative norm	Document	Subject
Argentina	Ministry of Health https://www.argentina.gob.ar/salud; https://www.argentina.gob.ar/salud/fiebreamarilla	– Intensificación de la vigilancia de fiebre amarilla ante la presencia de epizootias en Brasil cercanas a la frontera con Argentina	– Surveillance/humans – Surveillance/epizootics – Laboratory – Immunization
		– Diagnóstico de fiebre Amarilla – Guía para el equipo de salud	– Clinical management
		– Vigilancia de epizootias de monos por amarilla fiebre	– Surveillance/epizootics
Bolivia (Plurinational State of)	Ministry of Health and Sports https://www.minsalud.gob.bo https://pai.minsalud.gob.bo/ver_vigilancia_famarilla	– Manual de Vigilancia de Enfermedades Inmunoprevenibles	– Surveillance/humans – Surveillance/epizootics – Laboratory – Immunization
		– Vacuna contra la Fiebre Amarilla	– Immunization

Country	Authoritative norm	Document	Subject
Brazil	Ministry of Health https://www.gov.br/saude/pt-br https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/f/febre-amarela	– Plano de Contingência para Resposta às Emergências em Saúde Pública - Febre Amarela - 2ª Edição	– Surveillance/humans – Surveillance/epizootics
		– Manual de manejo clínico da Febre Amarela	– Clinical management
		– Ministério da Saúde – Febre Amarela – Guia de Vigilância em Saúde: volume único	– Surveillance/humans – Surveillance/epizootics – Laboratory – Immunization
		– Guia de Vigilância de Epizootias em Primatas Não Humanos e Entomologia aplicada à Vigilância da Febre Amarela	– Surveillance/epizootics
Colombia	Ministry of Health and Social Protection https://www.minsalud.gov.co/Paginas/default.aspx	– Plan nacional para la prevención y control de la fiebre amarilla en Colombia 2017 – 2022 – Protocolo de Vigilancia en Salud Pública – Fiebre Amarilla	– Surveillance/humans – Surveillance/epizootics – Laboratory – Immunization
		– Guía de atención de la Fiebre amarilla	– Clinical management
Ecuador	Ministry of Public Health https://www.salud.gob.ec/	– Manual de procedimientos del subsistema alerta acción SIVE-Alerta	– Surveillance/humans – Surveillance/epizootics – Laboratory
		– Manual de vacunas para enfermedades inmunoprevenibles	– Immunization
Guyana	Ministry of Health https://www.health.gov.gy	– No documents on the topics under consideration	
Panama	Ministry of Health http://www.minsa.gob.pa/ http://www.minsa.gob.pa/informacion-salud/epidemiologia	– Guia Nacional de Epidemiologia 2018	– Surveillance/humans
		– Esquema nacional de vacunación	– Immunization

Country	Authoritative norm	Document	Subject
Paraguay	Ministry of Public Health and Social Welfare http://www.mspbs.gov.py/build/index.php	– Fiebre Amarilla: Riesgo de importación a través de los viajeros y aparición de epizootias 2019	– Surveillance/humans – Surveillance/epizootics – Laboratory – Clinical management – Immunization
		– Guía de vigilancia de epizootias en primates no humanos, con sospecha de fiebre amarilla. 2019	– Surveillance/epizootics
		– Normas nacionales de vacunación, técnico administrativas y de vigilancia del Programa Nacional de Enfermedades Inmunoprevenibles y PAI. 2016	– Immunization
Peru	Ministry of Health https://www.gob.pe/minsa/	– Protocolos de vigilância epidemiológica – Parte I – Herramientas para la vigilancia epidemiológica	– Surveillance/humans – Surveillance/epizootics – Laboratory – Immunization
		– Protocolo sanitário de urgência Para el diagnóstico y tratamiento de pacientes con fiebre Amarilla. 2016.	– Surveillance/humans – Clinical management
Suriname	Ministry of Health https://gov.sr/ministerie-van-volksgezondheid/	– No documents on the topics under consideration	
Trinidad and Tobago	Ministry of Health http://www.health.gov.tt/	– No documents on the topics under consideration	
Venezuela (Bolivarian Republic of)	Ministry of Popular Power for Health http://www.mpps.gob.ve/	– No documents on the topics under consideration	

ANNEX 2. PICO QUESTIONS ON THE CLINICAL MANAGEMENT OF YELLOW FEVER

To support the advisory group's discussions on specific aspects of the clinical management of YF, three PICO questions were developed:

1. In patients with YF, does the use of antiviral agents reduce deaths, days with fever, or length of hospital stays compared with non-use of antiviral agents?
2. In patients with YF, does liver transplantation result in better survival rates than nonintervention?
3. In patients with YF, does plasma exchange/apheresis result in better survival rates than nonintervention?

The search, which was initiated on 16 October 2019, included the following databases:

- SciELO (https://search.scielo.org/)
- LILACS (https://bvsalud.org/es/)
- MEDLINE/PubMed (https://pubmed.ncbi.nlm.nih.gov/)
- Epistemonikos (https://www.epistemonikos.org/)

No language restrictions were applied.

Box A2.1 lists the inclusion and exclusion criteria for the studies that were evaluated on the clinical management of YF.

Box A2.1. Inclusion and exclusion criteria for the studies evaluated on the clinical management of yellow fever

Inclusion criteria

- Clinical trials in humans
- Studies on YF patients using any of the following interventions: antiviral agents (sofosbuvir or ribavirin), liver transplantation, or plasma exchange/apheresis
- Studies that show any of the following outcomes: death, days of fever, length of hospital stay
- Prospective or retrospective cohort studies, case-control studies
- No language restriction

Exclusion criteria

- Commentary on studies
- Phase 1 of a clinical trial
- In vitro study
- Preclinical study
- Protocol for a clinical trial
- Protocol in progress
- Narrative review
- Full text unavailable

Finally, Figure A2.1 shows the stages in the process of selecting the studies. For evaluation of the studies, Clarivate Analytics Endnote® 2021 software and PRISMA directives[1] were used. During the study identification stage, 31 studies were initially identified (Q1, 30 studies; Q2, 0 studies; and Q3, 1 study). After the elimination of 12 duplicate

1 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Available from: https://doi.org/10.1136/bmj.n71

studies, 19 were evaluated. Of these, the following were excluded: commentaries (n = 3), phase 1 of a clinical trial (n = 1), in vitro study (n = 1), preclinical study (n = 7), protocol for a clinical trial (n = 2), narrative review (n = 4), full text unavailable (n = 1). Table A2.1 shows the reasons for excluding the studies that were initially retrieved.

Question 1: In patients with YF, does the use of antiviral agents reduce deaths, days with fever, or hospital stays compared with non-use of antiviral agents?

P Yellow fever patients

I Use of antiviral agents (sofosbuvir, ribavirin)

C Placebo/nonintervention

O Death, days of fever, length of stay

Search terms

"Yellow Fever"[mh]

"Antiviral Agents"[mh]

"Ribavirin"[mh]

"Sofosbuvir"[mh]

Strategy

Database	#	Query	Hits
MEDLINE/PubMed	1	"Yellow Fever"[MeSH Terms]	2,847
	2	"Antiviral Agents"[MeSH Terms] OR "Ribavirin"[MeSH Terms] OR "Sofosbuvir"[MeSH Terms]	142,711
	3	#1 AND #2	20
LILACS	1	"Febre Amarela" AND db:("LILACS")	701
	2	"Antivirais" AND db:("LILACS")	1,472
	3	"Ribavirina" AND db:("LILACS")	1,575
	4	"Sofosbuvir" AND db:("LILACS")	1,581
	5	#1 AND (#2 OR #3 OR #4)	2
SciELO	1	“febre amarela” (all indexes)	211
	2	antivirais (all indexes)	81
	3	ribavirina (all indexes)	113
	4	sofosbuvir (all indexes)	30
	5	#1 AND (#2 OR #3 OR #4)	0
Epistemonikos	1	"yellow fever"	171
	2	antiviral OR ribavirin OR sofosbuvir	8,769
	3	#1 AND #2	8

Question 2: In patients with YF, does liver transplantation result in better survival rates than nonintervention?

P Yellow fever patients

I Liver transplantation

C Nonintervention

O Survival

Search terms

"Yellow Fever"[mh]

"Liver Transplantation"[mh]

Strategy

Database	#	Query	Hits
MEDLINE/PubMed	1	“Yellow Fever”[MeSH Terms]	2,847
	2	“Liver Transplantation”[MeSH Terms]	59,936
	3	#1 AND #2	0
LILACS	1	mh:(“Febre Amarela”) AND db:(“LILACS”)	701
	2	mh:(“Transplante de Fígado”) AND db:(“LILACS”)	1,036
	3	#1 AND #2	0
SciELO	1	“febre amarela” (all indexes)	211
	2	“transplante de fígado” (all indexes)	282
	3	#1 AND #2	0
Epistemonikos	1	“yellow fever”	171
	2	“liver transplantation”	3,259
	3	#1 AND #2	0

Question 3: In patients with YF, does plasma exchange/apheresis result in better survival rates than nonintervention?

P Yellow fever patients

I Plasma exchange/plasmapheresis

C Nonintervention

O Survival

Search terms

"Yellow Fever"[mh]

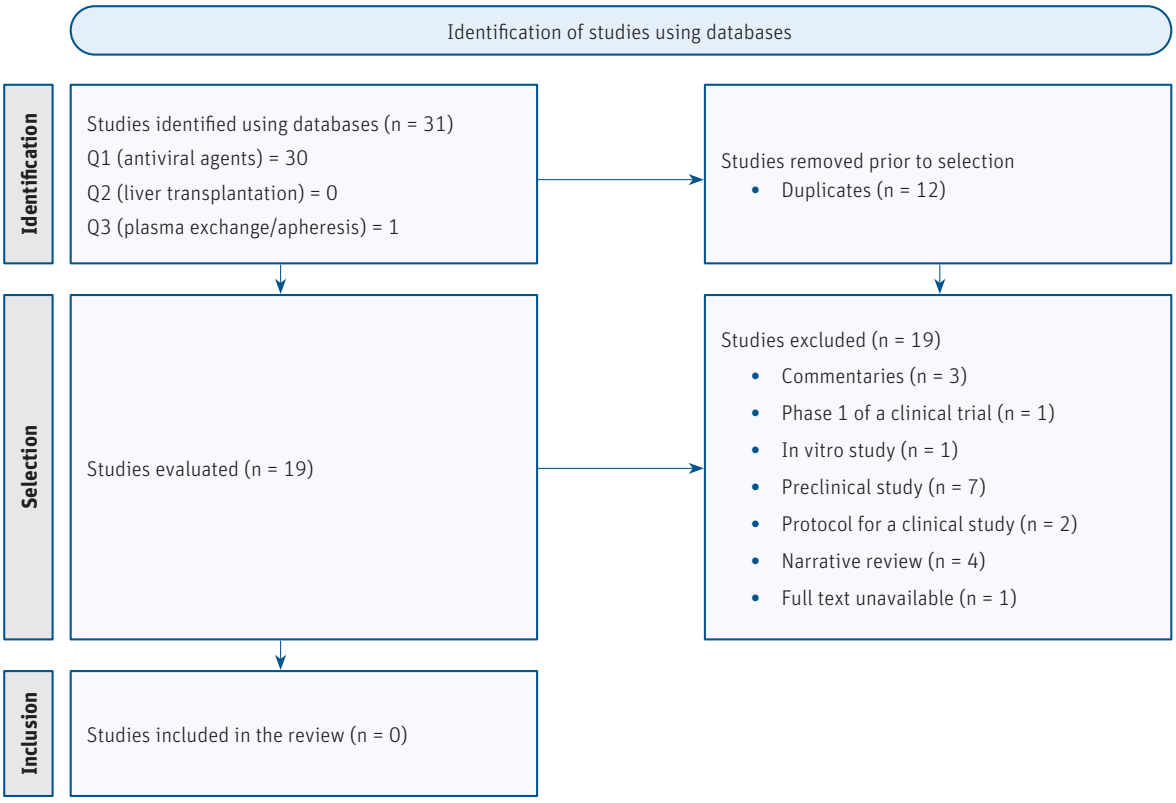
"Plasma Exchange"[mh]

"Plasmapheresis"[mh]

Strategy

Database	#	Query	Hits
MEDLINE/PubMed	1	"Yellow Fever"[MeSH Terms]	2,847
	2	"Plasma Exchange"[Mesh]) OR "Plasmapheresis"[Mesh]	14,996
	3	#1 AND #2	1
LILACS	1	mh:("Febre Amarela") AND db:("LILACS")	701
	2	mh:("Troca Plasmática") AND db:("LILACS")	28
	3	mh:("Plasmaferese") AND db:("LILACS")	239
	4	#1 AND #2	0
SciELO	1	"febre amarela" (all indexes)	211
	2	"troca plasmática" (all indexes)	81
	3	"plasmaferese" (all indexes)	36
	4	#1 AND (#2 OR #3)	0
Epistemonikos	1	"yellow fever"	171
	2	"plasma exchange" OR plasmapheresis	945
	3	#1 AND #2	0

Figure A2. 1. Flowchart showing the study selection process



Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Available from: https://doi.org/10.1136/bmj.n71.

Table A2.1. Reasons for excluding studies identified in the literature under review

#	Reference	Reason for exclusion
1	Siqueira-Batista R, de Souza Bayao T, do Carmo Cupertino M, Alfred Joseph Mayers N, Patrícia Gomes A. Sofosbuvir use for yellow fever: a new perspective treatment. Pathog Global Health [Internet]. 2019;113(5):207-8. Available from: http://www.tandfonline.com/loi/ypgh#.VwHiPU1f1Qs	Commentary
2	Avelino-Silva VI, Figueiredo-Mello C, Casadio LVB, Nastri ACSS, Marcilio I, Ribeiro AF, et al. Perspective piece confronting the multidimensional challenges of research in the context of emerging infectious diseases in Brazil: the example of yellow fever. Am J Trop Med Hyg [Internet]. 2020;103(1):38-40. Available from: http://www.ajtmh.org/content/journals/10.4269/ajtmh.19-0559	Commentary
3	Grossi PA. Urban Spread of flaviviruses: a new challenge in solid-organ transplant recipients. Clin Infect Dis. 1 Jan 2020;70(1):149-51.	Commentary
4	Low JG, Ng JHJ, Ong EZ, Kalimuddin S, Wijaya L, Chan YFZ, et al. Phase 1 trial of a therapeutic anti-yellow fever virus human antibody. New Engl J Med [Internet]. 2020;383(5):452-9. Available from: http://www.nejm.org/medical-index	Phase 1 of a clinical trial
5	Faddy HM, Fryk JJ, Hall RA, Young PR, Reichenberg S, Tolksdorf F, et al. Inactivation of yellow fever virus in plasma after treatment with methylene blue and visible light and in platelet concentrates following treatment with ultraviolet C light. Transfusion [Internet]. 2019;59(7):2223-7. Available from: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1537-2995	In vitro study
6	Alavala RR, Kulandaivelu U, Bonagiri P, Boyapati S, Jayaprakash V, Subramaniam AT. Synthesis and antiviral activity of dihydropyrimidines-ciprofloxacin mannich bases against various viral strains. Anti-Infect Agents [Internet]. 2015;13(2):154-65. Available from: http://www.eurekaselect.com/article/71421	Preclinical study
7	Cannalire R, Tarantino D, Piorkowski G, Carletti T, Massari S, Felicetti T, et al. Broad spectrum anti-flavivirus pyridobenzothiazolones leading to less infective virions. Antiviral Res [Internet]. 2019;167 (Cannalire, Massari, Felicetti, Barreca, Sabatini, Tabarrini, Cecchetti, Manfroni) Dipartimento di Scienze Farmaceutiche, Universita degli Studi di Perugia, Via del Liceo, Perugia 1-06123, Italy):6-12. Available from: http://www.elsevier.com/locate/antiviral	Preclinical study
8	de Freitas CS, Higa LM, Sacramento CQ, Ferreira AC, Reis PA, Delvecchio R, et al. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. PLoS Negl Trop Dis [Internet]. 2019;13(1):e0007072. Available from: https://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0007072&type=printable	Preclinical study
9	Gupta AK, Raushan R, Singh J, Roy PP. Exploring the QSAR analysis of imidazole-4, 5- and pyrazine-2,3-dicarboxamides derivatives using online available resources. Lett Drug Des Discov [Internet]. 2016;13(10):1047-54. Available from: https://www.eurekaselect.com/article/77076	Preclinical study
10	Gwon Y-D, Strand M, Lindqvist R, Nilsson E, Saleeb M, Elofsson M, et al. Antiviral activity of benzavir-2 against emerging flaviviruses. Viruses [Internet]. 2020;12(3):351. Available from: https://www.mdpi.com/1999-4915/12/3/351	Preclinical study
11	Lu X, Xiao H, Li S, Pang X, Song J, Liu S, et al. Double lock of a human neutralizing and protective monoclonal antibody targeting the yellow fever virus envelope. Cell Rep [Internet]. 2019;26(2):438. Available from: http://www.sciencedirect.com/science/journal/22111247	Preclinical study

#	Reference	Reason for exclusion
12	Zandi K, Amblard F, Amichai S, Bassit L, Tao S, Jiang Y, et al. Nucleoside analogs with antiviral activity against yellow fever virus. Antimicrob Agents Chemother [Internet]. 2019;63(9):e00889-19. Available from: https://aac.asm.org/content/aac/63/9/e00889-19.full.pdf	Preclinical study
13	Tysana Pte Ltd. Safety and tolerability of an antibody against yellow fever virus (TY014) in humans. clinicaltrials.gov [Internet]. 2018; Available from: http://www.epistemonikos.org/documents/86e05da20e19d01915b43e9b519f2327a8774518	Protocol for a clinical trial
14	BioCryst Pharmaceuticals. A study to evaluate the safety, pharmacokinetics and antiviral effects of galidesivir in yellow fever. clinicaltrials.gov [Internet]. 2020; Available from: http://www.epistemonikos.org/documents/a60bf4889697e0afbe34bef9bc024240ffcbc63e	Protocol for a clinical trial
15	Figueiredo-Mello C, Casadio LVB, Avelino-Silva VI, Yeh-Li H, Sztajnbok J, Joelsons D, et al. Efficacy of sofosbuvir as treatment for yellow fever: protocol for a randomised controlled trial in Brazil (SOFFA study). BMJ Open [Internet]. 2019;9(11):e027207. Available from: http://bmjopen.bmj.com/content/early/by/section	Narrative review
16	Julander JG Experimental therapies for yellow fever. Antiviral Res. 2013;97(2):169-79.	Narrative review
17	Andrei G, De Clercq E. Molecular approaches for the treatment of hemorrhagic fever virus infections. Antiviral Res. 1993;22(1):45-75.	Narrative review
18	Winch P, Kendall C, Gubler D. Effectiveness of community participation in vector-borne disease control. Health Policy Plann. 1992;7(4):342-51.	Narrative review
19	Organización Panamericana de la Salud. División de Vacunas e Inmunización. Programa Ampliado de Inmunización. Brote de fiebre amarilla selvática en Minas Gerais, Brasil. OPS Boletin Informativo PAI [Internet]. abril de 2002;24(2):5-6. Available from: http://www.paho.org/Spanish/HVP/HVI/sns2402.pdf	Full text not available

ANNEX 3. CHARACTERIZATION OF YELLOW FEVER CANDIDATES FOR LIVER TRANSPLANTATION

Reference, location of case	Case	Sex and age (years)	Symptoms	Duration (days)				Outcome
				Jaundice	Symptoms at time of hospital admission	Symptoms until liver transplant	Hospital days	
Song et al. (*38*), Rio de Janeiro, Brazil	1	Male, 54	Fever, headache, myalgia, jaundice	3	3	14	19	Survival
Vieira et al. (*39*), São Paulo, Brazil	2	Female, 27	Fever, headache, myalgia, jaundice, convulsions, AKF	NR	3	10	41	Survival
Song et al. (*38*), São Paulo, Brazil	3	Male, 25	Fever, headache, myalgia, jaundice, abdominal pain, gastrointestinal bleeding, liver encephalopathy, shock, AKF	NR	4	6	10	Death
Duarte-Neto *et al.* (*40*), São Paulo, Brazil	4	Female, 16	Fever, headache, vomit, myalgia, jaundiced, abdominal pain, gastrointestinal bleeding, liver encephalopathy, shock, AKF	NR	9	11	18	Death
	5	Male, 28	Fever, headache, myalgia, jaundice, abdominal pain, gastrointestinal bleeding, liver encephalopathy, shock, AKF	NR	6	7	5	Death
	6	Male, 40	Fever, headache, myalgia, jaundice, abdominal pain, gastrointestinal bleeding, liver encephalopathy, shock, AKF	NR	6	7	5	Death
	7	NR	NR	NR	NR	NR		Survival
	8	NR	NR	NR	NR	NR		Survival
	9	NR	NR	NR	NR	NR		Survival
Song *et al.* (*35*), São Paulo, Brazil	10–75	59 males (median age 39)	NR	NR	NR	NR		12 deaths; 53 survivals

AKF = Acute kidney failure; NR = Not reported

The waves of yellow fever (YF) transmission in the Region of the Americas in 2016–2018 involved the largest number of human and epizootic cases to be reported in several decades. Yellow fever is a serious viral hemorrhagic disease which poses a challenge for health professionals. It requires early recognition of signs and symptoms, which are often nonspecific, and it can mimic other acute febrile syndromes. Early detection of suspected or confirmed cases, monitoring of vital signs, life support measures, and treatment of acute kidney failure continue to be the recommended strategies for case management.

This report is the result of discussions among experienced specialists in the Americas on the clinical management of yellow fever patients, especially during outbreaks and epidemics, in the context of current medical and scientific evidence and taking into account the technical guidelines already available in the countries of the Region. It includes flowcharts for initially addressing patients with clinical suspicion of yellow fever and proposes a minimum package of laboratory tests that may be useful in contexts where resources are limited. In addition, it considers aspects of health system organization for dealing with yellow fever outbreaks and epidemics.

PAHO Pan American Health Organization World Health Organization Regional Office for the Americas