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Yellow fever: laboratorial diagnosis and clinical manifestations

Febre amarela: diagnóstico laboratorial e manifestações clínicas

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ABSTRACT

Yellow fever is an infectious disease of acute evolution, initially non-contagious, transmitted by a ribonucleic acid (RNA) virus that belongs to the *Flaviviridae* family. In the period from December 2016 until March 17, 2017, 1,561 suspected cases of wild yellow fever were reported to the Ministry of Health in Brazil. Among these cases, 850 (54.8%) remain under investigation, 448 (28.7%) were confirmed and 263 (16.9%) were discarded. Out of the total cases reported, 264 died, 144 (54.5%) were confirmed for the disease, 110 (41.7%) were investigated and 10 (3.8%) were discarded. The case fatality rate among confirmed cases was 32.2%. The specific diagnosis for determining the etiology of infection can be made by demonstrating the humoral response of the antibodies, virus isolation, or histopathological study of the liver. Only through early laboratory diagnosis and epidemiological data supply can government and cooperative organizations establish public policies to combat future disease epidemics, as well as social awareness campaigns.

Key words: yellow fever; signs and symptoms; diagnosis; differential diagnosis.

INTRODUCTION

Yellow fever is an infectious disease of acute evolution, initially non-contagious, transmitted by a ribonucleic acid (RNA) virus that belongs to the *Flaviviridae* family. Man is infected by mosquito bites of the genera *Sabethes*, *Haemagogus* and/or *Aedes*[1].

This disease occurs in endemic areas of the South America and Africa, especially the wild epidemiological presentation, which requires the presence of a non-human primate for dissemination. In Brazil, it occurs especially in the Amazon region. Outbreaks and epidemics in other regions are reported sporadically, when the virus encounters a susceptible environment of unvaccinated persons. This may have a greater or lesser impact on public health, depending on the extension of the dissemination[2, 3].

In the first half of 2017, Brazil experienced a large outbreak of yellow fever, mainly in the states of the Southeast region, particularly Minas Gerais and Espírito Santo. It should be noted that all cases included residents of rural areas or people who had come into contact with wild areas for work or leisure reasons. In addition, the cases occurred in the months of December to May, seasonal period of the disease because it is the rainy season, in which the density of vector population increases, and people dedicate themselves to deforestation[1, 4, 5].

In the period from December 2016 to March 17, 2017, 1,561 suspected cases of wild yellow fever were reported to the Ministry of Health. Among these cases, 850 (54.8%) remain under investigation, 448 (28.7%) were confirmed and 263 (16.9%) were discarded. Out of the cases reported, 264 died, 144 (54.5%) were confirmed for the disease, 110 (41.7%) were investigated and 10 (3.8%) were discarded. The case fatality rate among confirmed cases was 32.2%[4].

Wild yellow fever usually affects predominantly male patients of economically active age, since these individuals are more frequently exposed to places and situations of risk when performing occupational activities. The demographic profile of confirmed

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cases in 2017 is like that observed in previous outbreaks of wild yellow fever in Brazil, as demonstrated in the field epidemiological investigations performed and portrayed in **Figure 1**[4].

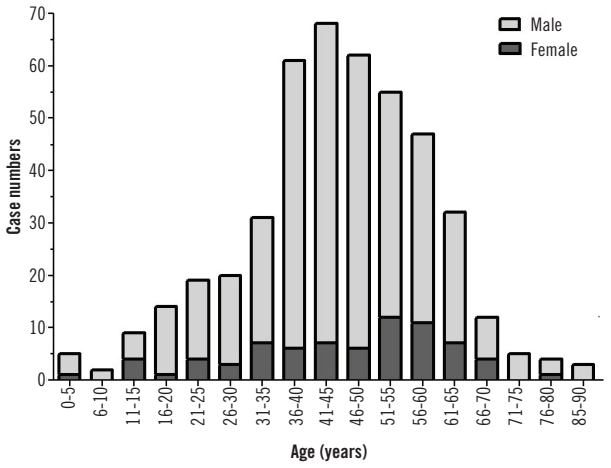

FIGURE 1 – *Gender distribution and age range of confirmed cases of yellow fever in the period from December 1, 2016 to March 17, 2017*

Source: Adapted from the Ministry of Health (2017)[4].

There are two distinct epidemiological cycles of transmission of RNA-virus that causes yellow fever: wild and urban. However, the absence of clinical, immunological and etiological differences between cycles should be emphasized. In the urban cycle, the disease is restricted to the human being (anthroponosis), and other animal reservoirs of epidemiological importance are unknown. In this cycle the transmission is made mainly by *Aedes aegypti*. In the wild cycle, the main hosts, reservoirs and amplifiers of the virus are non-human primates, particularly monkeys of the genera *Allouata* (howler monkey), *Cebus* (capuchin monkey), *Ateles* and *Callithrix*. However, some marsupials and rodents may also be reservoirs. Thus, the wild cycle is considered a zoonosis, transmitted by mosquitoes of wild habits, of the genera *Haemagogus* (*H. janthinomys* and *H. albomaculatus*) and *Sabethes* (*S. chloropterus*)[6].

The last case of urban yellow fever in Brazil was reported in 1942, in the state of Acre. The fight against mosquito vectors was one of the main aspects responsible for the disease eradication. The transmission is made between individuals through the bite of *Aedes aegypti*, without the participation of hosts or intermediate vectors. In Africa, other mosquitoes of this genus also carry out urban transmission, such as *Aedes vittatus* and *Aedes taylori*. All these mosquitoes are well adapted to urban life and use artificial collections of water as breeding grounds. The increased population of *Aedes aegypti* in Brazilian cities, and the occurrence of large epidemics of dengue, zika and chikungunya, also transmitted by this vector, are of concern to the Brazilian authorities regarding new epidemics of urban yellow fever[3, 7].

CLINICAL MANIFESTATIONS

Infection by the virus that causes yellow fever can be present in a wide and variable manner, both asymptomatic and symptomatic, and may appear even in fulminant forms. The average incubation period varies from three to six days and can take up to 10 days. Symptomatic manifestations can be classified as mild (oligosymptomatic) forms, which correspond to 90% of cases; moderate and severe, in the remaining 10%[2, 8, 9].

Asymptomatic or subclinical infections and mild forms of the disease may present changes only in specific laboratory tests. The greater number of cases with milder symptoms leads to frequent underreporting, making clinical diagnosis difficult outside an epidemic context[2, 10].

Subclinical, oligosymptomatic, and mild forms usually occur in young children with a vaccinated mother [in these cases there is transplacental transmission of maternal immunoglobulin class G (IgG) antibodies during pregnancy], indigenous people who have acquired immunity from the mother or throughout life, or adults with acquired antibodies. In these cases, the condition is restricted to asthenia, headache, fever or moderate fever, with a course of up to two days, with recovery without sequelae[8, 11, 12].

In the moderate form, in addition to the symptoms mentioned above, the patient may present nausea, myalgia and arthralgia, which do not impede their locomotion. Headache is usually more prolonged, and asthenia is more pronounced. There is at least one of the classic symptoms of the disease: oliguria/anuria, jaundice, hematemesis, but epistaxis, mild albuminuria and mild jaundice may occur. The recovery of the patient occurs in two or three days, with involution of the picture without complications or sequelae. This condition occurs in individuals who already have immunity to other Flaviviruses[6, 11].

The mild as well as the moderate forms present a set of nonspecific symptoms that could correspond to a series of diseases common in the endemic areas, such as: malaria, viral hepatitis, typhoid, infectious mononucleosis, etc.[9, 11].

In severe cases, patients may manifest the three classic symptoms of the disease: hematemesis, jaundice, oliguria/anuria. These forms have high lethality, between 30% and 70%. The evolution can occur in two phases, with a period of remission

between them, at which point the patient has sensation of improvement and imminent healing[1].

The first phase corresponds to the prodromal period or infectious phase, with high fever (reaching 39°C or 40°C), holocranial headache and generalized myalgia. Initially, the symptoms appear abruptly after five to 14 days of incubation period. There is clinical improvement after the first 48 to 72 hours, with reappearance of the clinical symptoms in sequence[1].

The second phase is the period of intoxication, toxemic or location phase. At that moment the clinical picture suddenly worsens, with worsening of all the symptoms presented and the appearance of new ones. At this stage the virus leaves the bloodstream and is found especially in the liver and spleen, and can also be found in the heart, lymph nodes and other organs. Symptomatology includes intense asthenia, conjunctival hyperemia, high fever, Faget's signal (high fever accompanied by bradycardia, i.e., a pulse-temperature dissociation), severe holocranial headache, marked and generalized myalgia (with emphasis on the back), nausea and vomiting, epigastric pain, hepatomegaly, frank jaundice (verdinic type, at the expense mainly of the increased direct fraction), elevation of total bilirubin, albuminuria and oliguria. Vomits are initially alimentary and later become hemorrhagic (in coffee grounds or frankly hemorrhagic)[2, 8, 13].

It is worth noting that it is not always possible to differentiate between the two phases, nor to identify the period of remission, which may be absent[11].

Other hemorrhagic manifestations are also present, such as uterine bleeding, epistaxis, melena, hemorrhages of the integument, gums and ear. Before or at the onset of bleeding, thrombocytopenia may occur, which, if severe, reaches less than 20,000 platelets/mm^3 of blood. However, platelet counts are not always directly associated with the severity of bleeding, so that a patient with less severe thrombocytopenia may experience exuberant bleeding. In yellow fever there are hemorrhages caused by disseminated intravascular coagulation, which is associated with the problems of complement activation, coagulation factor consumption, fibrin deposition and fibrinolysis[2, 12].

In the malignant form of the disease, hepatorenal failure is observed. There is overlapping of the liver to the renal frame, with exuberant jaundice, bilirubin and aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], and a very pronounced increase in urea and creatinine serum levels. The AST/ALT ratio (Ritis coefficient) is possibly reversed because of the cytopathic effect of the virus on liver, myocardium and skeletal muscles[8, 10, 12].

Renal insufficiency is established around the fifth to the seventh day, manifesting primarily by the reduction of urinary volume. Without treatment, the evolution is anuria and total cessation of diuresis due to acute tubular necrosis. Deaths occur more frequently in this period[1, 11].

When jaundice is severe and serum bilirubin levels are very high, encephalopathy is common, what is a sign of poor prognosis. However, most patients will die from hepatorenal failure or from bleeding. Patients who survive have a slow but complete recovery[2].

CLINICAL DIAGNOSIS

In individuals residing in endemic areas (or with recent history of travel to risk areas), with a history of sudden fever, relative bradycardia and jaundice, yellow fever should be suspected.

Clinical yellow fever diagnosis is sometimes hard, especially in isolated cases. Differences in severity degrees and manifestations of the symptoms impair the recognition of yellow fever so that slight signals are possibly ignored in diagnosis. Although classic manifestations are easily recognized, jaundice is often absent. Thus, yellow fever may be mistaken for other diseases that present headache, nausea, myalgia and fever as clinical symptoms, especially in the early stages[14].

LABORATORY DIAGNOSIS

Laboratory tests should be performed on suspected cases of yellow fever using blood, serum or viscera biopsies (liver, spleen, kidney, heart and lung samples). Associations between the results of the laboratory tests and the clinical and epidemiological data are fundamental.

NONSPECIFIC EXAMS

In asymptomatic and oligosymptomatic cases that present a benign and self-limiting clinical picture, no significant laboratory abnormalities are observed. In the early stage of the severe forms, the hemogram may present mild leukocytosis with presence of neutropenia and intense left deviation with eosinopenia. From the third or fourth day, the hematological condition is characterized by leukopenia and lymphocytosis, and the left deviation and eosinopenia are maintained. It is possible to find thrombocytopenia without direct correlation with bleeding levels. In case of bleeding, hematocrit may be decreased[1, 3].

There are also biochemical alterations characterized by a high transaminase elevation, generally exceeding 1,000 units per milliliter, reflecting the intense damage in the hepatic tissue, with necrosis, caused by the yellow fever virus[1, 3, 6].

Coagulation tests may demonstrate increased prothrombin, partial thromboplastin and coagulation times, due to the hepatic synthesis of vitamin K-dependent coagulation factors. In cases of disseminated intravascular coagulation, there is a decrease in factor VIII and fibrinogen, in addition to thrombocytopenia. Occasionally, fibrin degradation products can be detected[1, 3, 6].

In later and severe phases of the disease, hepatic and metabolic alterations can contribute to renal dysfunction, at which time urea and creatinine can rise, reaching up to five or six times the normal values. Total bilirubin may be elevated slightly or markedly, with a predominance of direct bilirubin, reaching levels higher than 30 mg/dl[1].

The urinary sediment is altered, but without diagnostic value. Among the alterations found, there may be bilirubinuria (in icteric patients), hematuria and marked proteinuria, with values above 500 mg/dl[3, 6].

It is important to emphasize that the serum levels of transaminases, urea and creatinine are important laboratory indicators of the disease severity, able to correlate with the clinical evolution of the disease, besides indicating prognosis[1].

The patient may also present hypoglycemia and cholesterolemia. Alkaline phosphatase may or may not rise. It is worth noting that these indicators, as well as bilirubin values, do not correlate with the severity of the disease[1, 3].

SPECIFIC EXAMS

The specific diagnosis can be made by demonstrating the humoral response of antibodies, virus isolation, or histopathological study of the liver.

Humoral response search is most effective from the end of the second week of infection, when there is greater detection of antibodies. This can be done using complement fixation techniques, IgM antibody capture enzyme-linked immunosorbent assay (Mac-Elisa), IgG Elisa, inhibition of hemagglutination in paired samples (with a 15-day interval between the first and the second collection) and neutralization assays. The immunoenzymatic assay for immunoglobulin class M (IgM) antibody capture, known as Mac-Elisa, may demonstrate positivity in some cases already in the first week of infection. Since positivity is demonstrated in the first week in only a few cases, two serum samples with a 14-day interval between them should be collected[5, 6, 15].

There may be cross-reactions between the various Flaviviruses. In the case of Mac-Elisa, which detects only IgM antibodies, these cross-reactions are restricted to cases in which another Flavivirus infection has occurred less than two months before, the average period in which such antibodies remain detectable, except for some cases of dengue, in which IgM antibodies may persist detectable for a year or more[3, 5, 15].

To isolate the virus from serum or detect the viral genome by the reverse transcription polymerase chain reaction (RT-PCR) technique, blood samples should be collected preferably on the first three days of disease. This serum can be maintained at 4°C for up to six hours. After this period, it should be frozen in the freezer at -70°C or preserved in liquid nitrogen. For the transport of this material the tubes must be made of plastic material with screw cap. They must be pre-sterilized, properly labeled and sealed with tape, wrapped in gauze or plastic bag. Finally, they can be placed in the cryobiological cylinder containing liquid nitrogen. In the absence of liquid nitrogen, transport can be done on dry ice (CO_2)[1, 3, 5].

As a retrospective diagnostic form, in cases of death, isolation can be obtained from fragments of the liver, kidneys, heart, spleen, lymph nodes and brain, sent for histopathological analysis. It is recommended that collection be done preferably within the first eight hours after death. Collection performed within 12 hours or more after death increases the difficulty in establishing diagnosis, however, the sample should still be sent to the laboratory, up to a maximum of 24 hours post-mortem. Two tissue samples with at least 1 cm^3 (for viral isolation) and 2 to 3 cm^3 (for histopathological and immunohistochemical studies) should be collected and placed in sterile, screw cap flasks. One of the samples should be frozen at -70°C (for viral isolation) and another larger, fixed in formalin at room temperature (for histopathological studies and/or detection of viral antigens). It is important to note that the volume of fixative is greater than 10 times the volume of tissue obtained. Samples for viral isolation should be kept at -70°C and transported in liquid nitrogen or on dry ice. Samples fixed in formaldehyde must be maintained and transported at room temperature[1].

Histopathological analysis of the liver suggestive of yellow fever usually presents centrilobular or mid-zonal necrosis and presence of Councilman acidophilic bodies. Biopsies for the diagnosis of the live patient are contraindicated due to the risks of bleeding related to the coagulation changes characteristic of the disease[3, 5, 15].

Liver biopsy could suggest the diagnosis, for example, by demonstrating the presence of the virus in the tissue, by direct immunofluorescence, *in situ* hybridization or PCR. The histopathological study could suggest diagnosis in the first days of disease, although it is not pathognomonic. Characteristic liver lesions are present only in the early stages of the disease, but later, the condition may be confused with viral hepatitis[3].

DIFFERENTIAL DIAGNOSTICS

During outbreaks, diagnosis is facilitated since the registry of previous cases directs clinical suspicion. However, outside the epidemic context, mild and moderate forms can be confused with many other infectious diseases of the respiratory, digestive and urinary systems, making diagnosis difficult. The syndromic approach serves as a guide and, in the evolution of these forms, the discreet increase in transaminases corroborates the clinical suspicion of yellow fever. In relation to severe forms, the following differential diagnoses will be discussed (**Table 1**)[1, 2, 6].

TABLE 1 – Major differential diagnoses of yellow fever

Yellow fever presentation form	Differential diagnosis with other diseases	Observations to be considered
Mild	Infectious diseases of urinary, digestive and respiratory tract Subacute hepatitis	Discreet increase in the transaminases reinforces the suspicion of yellow fever
Moderate		
Severe	Leptospirosis Malaria Viral hepatitis Septicemia with jaundice Mountain fever Viral hemorrhagic fevers Phosphorus, halothane and other intoxications	Possible diagnostic hypotheses should be corroborated by epidemiological, clinical and specific examination data

Source: Adapted from the Ministry of Health (1999)[1].

Initially, the signs and symptoms of some emergent arboviruses in Brazil will be differentiated. These diseases are extremely relevant to Brazilian health: besides having similar clinical characteristics, they present the *Aedes aegypti* mosquito as a common vector. Since this mosquito is widely distributed in the national territory, diseases such as chikungunya, dengue and zika are widespread, and such clinical manifestations are commonly observed in medical services[16, 17].

As for fever, only zika has low fever (up to 38°C when present, lasting from one to two days). Yellow fever has high fever, as well as dengue (fever that is always present, since the onset and with temperatures higher than 38°C for two to seven days) and chikungunya (almost always present, immediately following onset, 38°C and with duration of one or two days)[18, 19].

Muscle pain may occur in all these diseases, but is less frequent in chikungunya, arbovirus infection in which severe arthralgia is most prominent. Mild arthralgia may occur in cases of zika (especially in the joints of hands and feet, accompanied by periarticular edema), and mild or moderate in the case of dengue[17, 20].

Skin rash appears in the first 24 hours on zika disease. In chikungunya, it can appear from the second to the fifth day; and in dengue, it can appear from the fourth day. As for yellow fever, the cutaneous change is jaundice. Pruritus has a moderate to severe degree in zika, and mild degree in dengue and chikungunya (appears in 50%-80% of cases). Pruritus is absent in yellow fever[18-20].

Ocular hyperemia may be present in zika and chikungunya, but is not common in dengue, which, however, may be accompanied by ocular pain. In yellow fever, the sclera becomes yellowish due to jaundice. In zika, there may be intense adenomegaly[17, 20].

The differential diagnosis of viral hemorrhagic fevers can be made through epidemiological investigation, virus identification, serological studies, characteristic histopathological changes and knowledge of areas of incidence of these diseases[2].

Leptospirosis is also an acute onset disease, with fever, myalgia of the biphasic character, jaundice and renal failure. In this case, the distinction may be based in transaminases, which are low; there are milder digestive manifestations, and later bleeds on leptospirosis. In addition, with laboratory parameters such as hemosedimentation and increased mucoproteins, and presence of neutrophilia with deviation, leptospirosis should be suspected[2, 21].

As for viral hepatitis, jaundice, digestive symptoms and bleeding are common. However, in hepatitis fever is mild or absent, serum urea and creatinine values are within normal limits and albuminuria is absent. The correct diagnosis requires the detection of serum markers of viral hepatitis[22, 23].

The clinical picture of *Plasmodium falciparum* malaria at the onset of severe form development is equivalent to that of yellow fever. However, in this case anemia is precocious, there is splenomegaly, the elevation of the transaminases is discreet, and there is less propensity to the occurrence of hemorrhages. There may be overlap of the two diseases, since the epidemiological conditions of infection for both are the same. Diagnosis is confirmed by blood parasite screening[24].

In septicemia due to gram-negative microorganisms with jaundice, hemorrhages are less frequent, transaminases present

a slight increase, there are entrance doors and blood culture is positive[2].

In relation to Brazilian spotted fever, after the third day of disease, lesions of the portal of entry appear, as well as exanthematous lesions; in addition, jaundice begins late. Such aspects may guide diagnosis when there is compatible epidemiological data[12].

Other less frequent differential diagnoses are: typhoid fever, recurrent fever and Ebola. Among non-infectious diseases, it is important to highlight idiopathic thrombocytopenic purpura, some forms of poisoning (such as venomous snake bites that lead to hemorrhage), and poisoning by phosphorus, carbon tetrachloride or halothane[1, 11].

In most cases, the clinical history, the epidemiological history and the early accomplishment of some laboratory tests can solve the doubts. **Figure 2** shows in a schematic way how to approach the patient with suspected yellow fever, as well as the main exams and conducts[11].

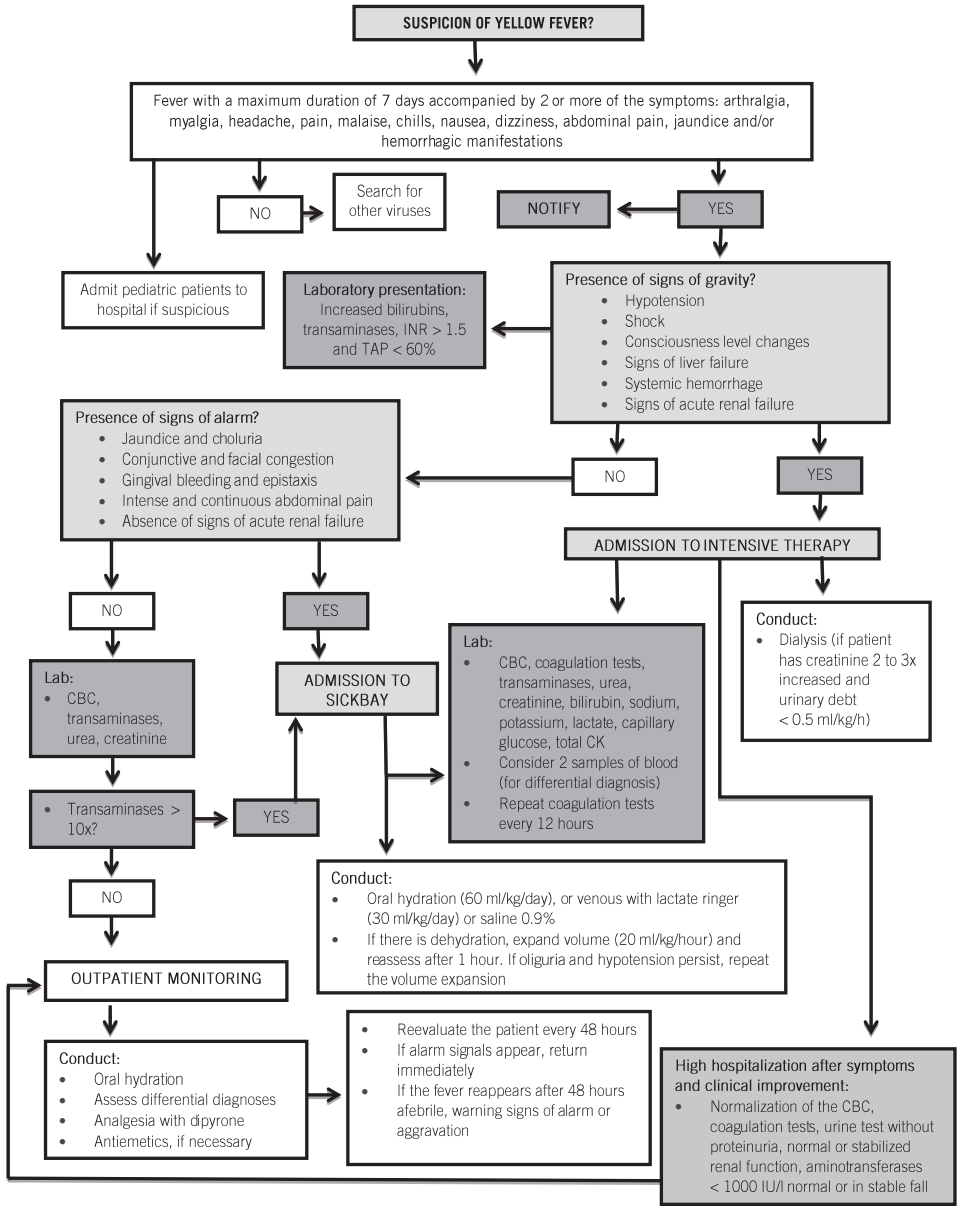

FIGURE 2 – *Initial approach of individuals suspected of yellow fever*

Source: Adapted from the State Health Secretariat of Rio de Janeiro (2018)[27].

CBC: cell blood count; TAP: prothrombin time; INR: index normatization ratio; CK: creatine kinase.

PROPHYLAXIS

In 2001, the Health Surveillance Secretariat of the Brazilian government implemented the Intensification Plan for the Prevention and Control of Yellow Fever, which aims to reduce the incidence of the wild type (it is not possible to eradicate a zoonosis) and prevent the occurrence of the urban form. The main pillars of the plan are the strengthening of epidemiological surveillance of the disease in the states and municipalities of the country and vaccination campaigns[25].

Epizootics caused by yellow fever (death of monkeys), in general precedes the occurrence of cases in humans, being defined as sentinel events. This is a signal to the need for intensified vaccination in the residents of the affected regions to avoid outbreaks and epidemics. For the objective of epidemiological surveillance to be achieved, any death of monkeys mentioned by the community and all human cases suspected of yellow fever should be reported immediately to the State Health Secretariat.

There is no indication for vector control in the wild, given the bioecological characteristics of the species involved in this cycle. It is important to emphasize that the epizootic site does not necessarily correspond to the area in which the animal was infected. Therefore, when the episode occurs, even in urban areas, one must always investigate if there are possible ecological corridors linking forests or parks from where the animal may have moved[1, 4].

Yellow fever does not have a specific treatment; however, it has an effective and safe vaccine available since the year 1930. Protection against infection occurs seven to 10 days after vaccination and is indicated for all residents of the (endemic, transitional and potential risk) areas and for travelers who will go to those areas. The vaccine is available free of charge at community health centers in all Brazilian municipalities and is indicated for use from the age of 9 months[7, 25].

The World Health Organization (WHO) has approved a new regulation for vaccination against yellow fever, which came into force in June 2016, of Annex VII of the International Health Regulations (IHR) published in 2005. The amendment in the current legislation modifies the recommendation for a booster dose every 10 years for only one lifetime dose. The amendment had the ready accession of almost all the signatory countries of the IHR. However, the Brazilian Ministry of Health has maintained the recommendation of two doses throughout life in the national territory, until more consistent studies are undertaken[26]. The current recommendations are summarized in **Table 2**.

To prevent the reoccurrence of the urban cycle, high rates of vaccination coverage must be maintained in the areas recommended by the country; strengthen vector-fighting actions against *Aedes aegypti* in municipalities (aiming to maintain infestation rates close to zero), and maintain vigorous sanitary surveillance at ports, airports, and borders to control travelers from endemic areas[6, 15].

Educational and guidance measures are essential for prophylaxis of yellow fever. Persons living in or entering enzootic or epizootic areas should be advised on the use of personal protection (suitable clothing, repellents, use of the screen at the place of residence) and disposal of artificial still water collections (such as unopened water tank, pools without chemical treatment, etc.) that act as breeding ground for mosquito larvae[6, 26].

FINAL CONSIDERATIONS

Nowadays, yellow fever has returned to be the focus of attention among the diseases that have the *Aedes aegypti* vector as the transmission route. The disease that appeared to be eradicated in many places in the Brazilian territory reappeared through wild outbreaks last year and showed high mortality rate in both animal and human hosts. The outbreak began in December 2016, involving the states of the Southeast, especially Minas Gerais and Espírito Santo. These regions were previously thought to be safe from contagion. The current easiness of moving to distant places has enabled a greater flow of people to areas at risk of the disease, what associated with a failure in vaccination coverage, is an important aspect of the outbreak.

The inclusion of the vaccine in the children's vaccination schedule throughout the country could solve the issue of vaccine coverage failure. Currently, the vaccine is only indicated for part of the population, leaving a considerable portion vulnerable to the disease. With all the inhabitants of the country vaccinated, new deaths could be avoided, regardless of the presence or absence of outbreaks and epidemics.

In addition, educational measures are necessary to guide the population as to the death of monkeys, wrongly regarded as villains. These animals are not responsible for the direct transmission of the disease, which has the mosquito as vector. It is a crime to injure or kill wild animals, and the natural death of infected monkeys is extremely important for the epidemiological surveillance of the disease, since they are considered sentinel of the virus circulation. By killing the monkeys, the population eliminates this alert, hampering the determination of new outbreaks and the definition of risk areas.

TABLE 2 – Yellow fever vaccination scheme

Age	Situation	Vaccination scheme/indication
0-6 months	-	Vaccination contraindicated
6-9 months	-	Administer a dose only on suspicion of outbreak, epizootic or confirmation of viral circulation in wild vectors. This dose will not be validated for routine coverage purposes. Revaccinate according to the scheme of children from 9 months to 5 years of age
9 months-5 years	-	Administer a dose from 9 months and a booster dose at 4 years of age, respecting a 30-day period between applications
From 5 years	With a dose administered before completing 5 years	Administer a booster dose, respecting a 30-day period between applications
	No proof of vaccination or no vaccine	Administer the first dose, and 10 years later, apply a booster dose
	With two doses of vaccine administered	Consider immunized. No other doses are required
Individuals from 60 years	No proof of vaccination or without administered vaccines	The risk/benefit ratio should be evaluated by the doctor. They are considered: the risk of the disease, the risk of adverse effects for the age range and/or arising from comorbidities
In case of trips	International trip	Comply with recommendations of the International Health Regulation
	National trip to areas in which the vaccine is recommended	Inoculation of the vaccine at least 10 days before the trip in case of an individual never vaccinated. In the case of revaccination, the minimum 10-day interval does not apply
Individuals with compromised immunity	Primary immunodeficiency In treatment with immunosuppressant drugs (corticosteroids, chemotherapy, radiotherapy, immunomodulators) History of anaphylactic reaction related to the substances present in the vaccine (chicken egg and its derivatives, bovine gelatin, for example) Former history of thymus diseases (myasthenia gravis, thymoma, cases of absence of thymus or surgical removal) With neoplasia HIV+ patients with severe immunosuppression, with CD4 cell count < 200 cells/mm^3, or less than 15% of total lymphocytes for children under 6 years old Organs transplanted	Vaccination contraindicated
Women in special situations	Pregnant (regardless of vaccination status)	There is no indication for vaccination. If vaccination cannot be postponed (an outbreak, epidemiological emergency, epidemics or trip to risk areas), the risk/benefit should be assessed by the doctor
	Breastfeeding children up to 6 months old (regardless of vaccination status)	Vaccination is not indicated and should be postponed until the child is 6 months old. If it is not possible to postpone it (situations cited above), the risk/benefit should be evaluated by the doctor. For women who have received the vaccine and are breastfeeding, breastfeeding should be interrupted for 15 to 28 days

Source: Adapted from the Ministry of Health (2015)[26].

HIV: human immunodeficiency virus.

The correct identification of cases, especially those with mild manifestations, is essential for better patient management. The disease has manifestations that can be confused with other viruses, in different stages. In these cases, the laboratory can be a great ally for the distinction between similar diseases. Non-specific exams show small but important differences in differential diagnosis. Specific tests confirm the presence of the virus or antibodies present at the different stages of the disease.

Preventive measures are of extreme importance for the control of the disease; however, treatment of infected people should also be taken into consideration. Yellow fever does not have a specific treatment. In mild and moderate forms, only the symptomatic treatment of fever, headache, myalgia and arthralgias is provided. In severe forms, patients require intensive monitoring and treatment, which is also non-specific, and it is sought to treat liver failure, renal failure, hemorrhages and metabolic alterations, as well as the most exuberant general symptoms, such as fever, headache, nausea, vomiting and restlessness. With the high number of deaths, the effectiveness of current treatment may be questioned. New researches are needed to promote proper management of the cases and reduce the mortality rate of this disease.

RESUMO

A febre amarela é uma doença infecciosa de evolução aguda, a princípio não contagiosa, transmitida por um vírus do ácido ribonucleico (RNA) que pertence à família Flaviviridae*. No período de dezembro de 2016 a 17 de março de 2017, foram notificados ao Ministério da Saúde, 1.561 casos suspeitos de febre amarela silvestre no Brasil. Destes, 850 (54,8%) permanecem em investigação; 448 (28,7%) foram confirmados e 263 (16,9%), descartados. Do total dos casos notificados, 264 evoluíram para óbito, sendo 144 (54,5%) confirmados para a doença; 110 (41,7%) em investigação e 10 (3,8%), descartados. A taxa de letalidade entre os casos confirmados foi de 32,2%. O diagnóstico específico para determinação da etiologia da infecção pode ser feito por meio da demonstração da resposta humoral dos anticorpos, do isolamento do vírus ou do estudo histopatológico do fígado. Apenas mediante o diagnóstico laboratorial precoce e o abastecimento de dados epidemiológicos é que governo e organizações cooperativas poderão estabelecer políticas públicas de combate a futuras epidemias da doença, bem como campanhas de conscientização social.*

Unitermos: *febre amarela; sinais e sintomas; diagnóstico clínico; diagnóstico diferencial.*

REFERENCES

1. Ministério da saúde. Manual de vigilância epidemiológica da febre amarela. Edição especial. Brasília: Fundação Nacional de Saúde; 1999. 60p.

2. Vasconcelos PF. Febre amarela. Rev Soc Bras Med Trop. 2003; 36(2): 275-93.

3. Setúbal S. Febre amarela [Internet]. Niterói BR: Universidade Federal Fluminense; 2012 [updated 2017]. Available at: http://www.professores.uff.br/sergiosetubal/servico/.

4. Ministério da Saúde. Informe especial febre amarela no Brasil no. 01/2017 [Internet]. Brasil: Secretaria de vigilância em saúde; 2017 [updated 2017 Mar 20]. Available at: http://portalarquivos.saude.gov.br/images/pdf/2017/marco/18/Informe-especial-COES-FA.pdf.

5. Ministério da Saúde. Orientação para profissionais de saúde sobre febre amarela silvestre nota informativa no. 02/2017 [Internet]. Brasil: Secretaria de vigilância em saúde; 2017 [updated 2017 Feb]. Available at: http://portalarquivos.saude.gov.br/images/pdf/2017/janeiro/13/NOTA-INFORMATIVA-N---02-2017-FA-FINAL.pdf.

6. Sociedade Brasileira de Infectologia. Febre amarela: informativo para profissionais de saúde [Internet]. Brasil: Associação Médica Brasileira; 2017 [updated 2017 Feb 12]. Available at: https://www.infectologia.org.br/admin/zcloud/125/2017/02/FA_-_Profissionais_13fev.pdf.

7. Smith AW, Monath TP. Responding to the threat of urban yellow fever outbreaks. Lancet Infect Dis. 2017; 17(3): 248-50.

8. Mayo Clinic. Yellow fever symptoms [Internet]. Mayo Foundation for Medical Education and Research; 2018. Available at: https://www.mayoclinic.org/diseases-conditions/yellow-fever/symptoms-causes/syc-20353045.

9. Ministério da Saúde. Febre amarela: guia para profissionais de saúde [Internet]. Brasil (DF): Secretaria de Atenção à Saúde; 2017 [updated 2017 May]. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/febre_amarela_guia_profissionais_saude.pdf.

10. Netto JCA. Aspectos clínicos e fisiopatológicos da febre amarela. Rev Patol Trop. 1991; 20(1): 43-50.

11. Vasconcelos PFC. Febre amarela: reflexões sobre a doença, as perspectivas para o século XXI e o risco da reurbanização. Rev Bras Epidemiol. 2002; 5(3): 244-58.

12. Ministério da Saúde. Guia de vigilância em saúde [Internet]. Brasil: Secretaria de vigilância em saúde; 2017. 2 ed. [updated 2017 May]. Available at: http://portalarquivos.saude.gov.br/images/pdf/2017/outubro/06/Volume-Unico-2017.pdf.

13. Ministério da Saúde. Doenças infecciosas e parasitárias [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2008. 7 ed. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/doencas_infecciosas_guia_bolso_7ed_2008.pdf.

14. Gardner CL, Ryman KD. Yellow fever: a reemerging threat. Clin Lab Med. 2010; 30(1): 237-60.

15. Monath TP, Vasconcelos PF. Yellow fever. J Clin Virol. 2015; 64(3): 160-73. doi: 10.1016/j.jcv.2014.08.030. Epub 2014 Oct 24.

16. Camara TNL. Emerging arboviruses and public health challenges in Brazil. Rev Saude Pública. 2016; 50: 36.

17. Governo do Estado de São Paulo. Orientação para atendimento de casos suspeitos de dengue, chikungunya e zika [Internet]. Brasil (DF): Centro de Vigilância Epidemiológica; 2017 [updated 2018 Oct 2]. Available at: https://www.caism.unicamp.br/PDF/orientacao_atendimento_casos_suspeitos_dengue_chikungunya_zika.pdf.

18. Ministério da Saúde. Informe: saiba conhecer os sintomas [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2017 [updated 2017 Dec 12]. Available at: http://combateaedes.saude.gov.br/pt/sintomas.

19. Ministério da Saúde. Chikungunya: manejo clínico [Internet]. Brasil: Secretaria de vigilância em saúde; 2017. 2 ed. Available at: http://http://portalarquivos.saude.gov.br/images/pdf/2016/dezembro/25/chikungunya-novo-protocolo.pdf.

20. Sociedade Brasileira de infectologia. Guia de manejo da infecção pelo vírus zika [Internet]. Brasil (DF): Associação Médica Brasileira; 2016

[updated 2016 Mar 19]. Available at: http://www.sierj.org.br/artigos/Guia_Manejo_Zika_SBI.pdf.

21. Ministério da Saúde. Leptospirose: diagnóstico e manejo clínico [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2014 [updated 2016 Sept 17]. Available at: http://portalarquivos.saude.gov.br/images/pdf/2014/dezembro/02/Miolo-manual-Leptospirose-17-9-2014.pdf.

22. Ministério da Saúde. Manual técnico para o diagnóstico das hepatites virais [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2015. Available at: http://www.cevs.rs.gov.br/upload/arquivos/201701/04162030-manual-diagnostico-das-hepatites-virais-ms-2015.pdf.

23. Ministério da saúde. Hepatites virais: o Brasil está atento [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2015. 2 ed. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/hepatites_virais_brasil_atento.pdf.

24. Ministério da saúde. Guia prático de tratamento da malária no Brasil [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2010, série A. Normas e manuais técnicos. Available at: http://portalarquivos.saude.gov.br/images/pdf/2014/maio/27/Guia-pr--tico-de-tratamento-da-mal--ria-no-Brasil.pdf.

25. Ministério da Saúde. Febre amarela: informações para profissionais da saúde [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2017. Available at: http://bvsms.saude.gov.br/bvs/febreamarela/profissionais.php.

26. Ministério da Saúde. Parecer no. 05 [Internet]. Brasil (DF): Secretaria de vigilância em saúde; 2015. Available at: http://www.anvisa.gov.br/hotsite/viajante/vacinafebreamarela.pdf.

27. Governo do Rio de Janeiro. Fluxograma de abordagem inicial de pacientes com suspeita de febre amarela. [Internet]. Brasil (RJ): Secretaria de Saúde do Rio de Janeiro; 2017. Available at: http://www.riocomsaude.rj.gov.br/Publico/MostrarArquivo.aspx?C=O6yxuk%2fyqVk%3d.

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