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DENGUE FEVER IN EMERGENCY MEDICINE PRACTICE

Abstract

Due to the increasing number of Russian citizen's visits to the tropics, the number of cases of imported endemic infectious diseases, mostly dengue fever (DF), also has increased. Dengue fever is an acute viral vector transmitted disease characterized by fever and intoxication, with the possible development of hemorrhagic syndrome and shock, in which survival depends on the time of the onset of intensive care. The greatest incidence of DF in Moscow is associated with travelling to the tropics during the Christmas holidays, which coincides with the seasonal rise in the incidence of influenza and other ARVIs. However, emergency medical technicians mostly (except for cases of calling the ambulance to the medical institution during the working hours of the laboratory) are not able to carry out and assess even minimal hematological parameters. Therefore, when diagnosis and determining the phase of the disease and its severity, the emergency medical technician can rely only on epidemiological and clinical data. In this regard, a group of authors proposed an algorithm for early diagnosis and treatment of patients with suspected dengue fever at the prehospital stage, taking into account clinical symptoms and standard tourniquet test.

Key words: *dengue fever, emergency medicine, tourniquet test, dengue shock syndrome, classification*

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DF — dengue fever, CDF — classical dengue fever, DHF — dengue hemorrhagic fever

Fever is one of the most common causes of seeking emergency medical care. It is also the most common reason for calling an ambulance in up to 30% of cases, and a house-call pediatrician in 8 of 10 calls [1]. The number of calls for ambulance and emergency medical care due to high body temperature has a pronounced seasonality with a maximum in March (up to 600 calls every day) and a minimum in June (up to 150).

Dengue fever (DF) is an acute viral vector transmitted zooanthroponosis characterized by fever, severe myalgia and arthralgia, exanthema, lymphadenopathy, and leukopenia [2]. According to the World Health Organization (WHO), there are now more than 2.5 billion people living in areas where DF is spread, which makes DF the second most common transmissible infection in the world after malaria.

The DF pathogen is the dengue virus belonging to the Flaviviridae family, which has 4 genotypes, and the immune response is type-specific and life-long, which allows for recurrent disease when infected with heterologous genotype. At the same time, it is

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believed that re-infection can lead to the development of more severe forms of the disease due to the phenomenon of antibody-dependent enhancement of the infection [3, 4].

The spread of DF is closely related to natural area of vectors — mosquitoes of Aedes genus, primarily, Ae. aegypti. The disease is common in both hemispheres throughout the tropical and partly subtropical zone limited to the winter isotherm equal to 10 °C, which prevents the reproduction of mosquitoes [4]. Cases of local transmission in Southern Europe associated with an alternative, more cold-resistant vector, Ae. albopictus, are reported regularly. On the territory of the Krasnodar Krai there are stable populations of Ae. aegypti, which may predetermine local transmission within the Russian Federation.

On the basis of sanitary rules, DF is included in the list of diseases requiring measures for sanitary control of Moscow [1, 2, 5, 6]. Official registration of DF in the Russian Federation began in 2012. During this time more than 800 cases of the disease were registered [7], while after the recession associated with the economic crisis in 2013–2014, the number of DF cases has continued to grow in recent years (Figure 1). An increase in the number of DF cases inevitably leads to severe forms of the disease. A case of hemorrhagic DF with severe liver damage secondary to Wilson's disease was described in 2013 [8]. A case of acute myocardial infarction secondary to severe DF was described in 2018 [9], and in 2014 the first case of fatal dengue shock syndrome was registered in Russia, in a woman who had visited an endemic region for the first time [10]. Currently, the International Classification of Diseases, X revision (ICD-10) has been adopted as a single classifier in Russia [11]. In this classification, dengue fever has two codes: A90 is dengue fever or classical dengue fever (CDF), and A91 is hemorrhagic fever caused by dengue virus (HDF) [12].

According to the 10-year observation conducted at the State Budgetary Healthcare Institution of Infectious Clinical Hospital No. 1 of the Department of Health of Moscow, more than 90% of cases of DF are imported from the Asian region, with more than 50% from Thailand.

In the analysis of referral diagnoses in patients with DF hospitalized in 2009–2018, diagnosis of fever of unknown etiology was the most commonly reported for referral (Table 1).

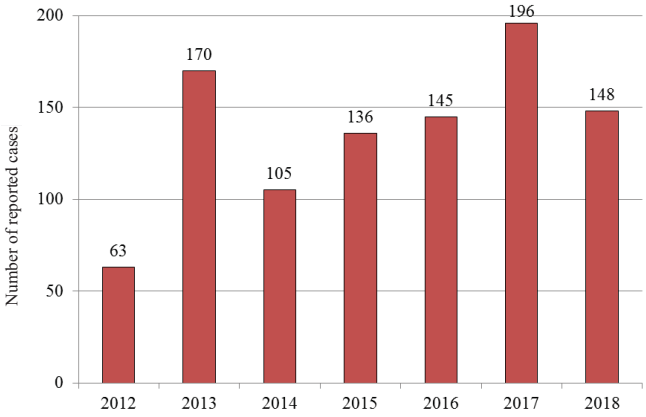

Figure 1. *Incidence of dengue fever in the Russian Federation from 2012 till June 2018 (according to the data of the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, Rospotrebnadzor)*

Table 1. *Referral diagnoses of patients with dengue fever (n = 257)*

Referral diagnosis	Number of cases	%
Fever of unknown etiology	168	65.4
Dengue fever	40	15.6
ARVI	36	14.0
Influenza	8	3.1
Rubella	2	0.8
Meningitis	1	0.4
Paratonsillar abscess	1	0.4
Hepatitis A	1	0.4

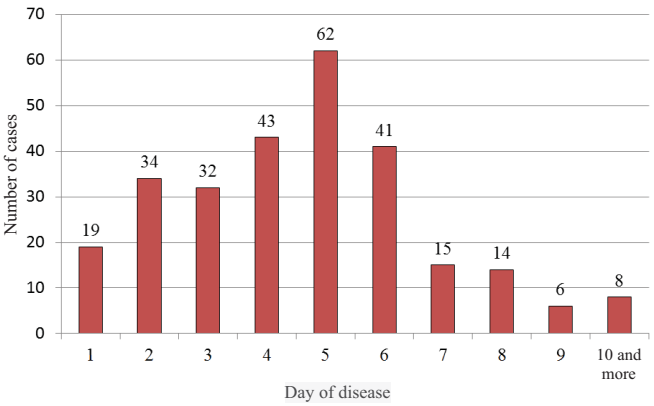

Figure 2. *Days from disease onset to admittance (according to data of Infectious Clinical Hospital No. 1, Moscow)*

Among hospitalized patients, 31% was hospitalized during the first 3 days of the disease, 58% — in 4 to 7 days, and 11% — during the second week of the disease (Figure 2), which was associated with both late seeking of medical care and incorrect interpretation of the fever by primary care physicians, which in turn led to delayed laboratory examination and unjustified prescription of treatment. Among the interviewed patients, 17.8% received antibiotics, and no tests for malaria were performed in an outpatient setting in any case, which is mandatory in febrile patients arriving from endemic regions.

Classification and Diagnosis of Dengue Fever

Currently, two classifications of DF are used in the world. The WHO classification dated 1997 provides for the division of dengue fever into classical and hemorrhagic (Table 2), with differentiation of HDF by 4 degrees of severity, of which 3 and 4 were attributed to shock syndrome [13].

Experience has shown that, in practice, this grading did not always correspond to the severity of the disease, and in 2009, WHO experts proposed a new interpretation (Table 3), which includes the following categories: probable dengue fever, dengue fever with severe signs and severe dengue fever [4]. In examination of patients admitted to intensive care units (ICUs), it was found that the 2009 classification has the advantage that it includes the definition of dysfunction of any system as a criterion of severe dengue fever, while the 1997 WHO classification takes into account only hemodynamic disorders as a criterion for hemorrhagic fever of III and IV degrees [14, 15]. However, according to Brazilian researchers, APACHE II scale was more sensitive than both WHO classifications of patient survival at ICU admission [15]. In addition, the study conducted in 2018 showed that mortality in patients with DF who were in ICU correlated with a low score on the Glasgow coma scale, platelet count, and multiple organ dysfunction syndrome severity [16].

It should be noted that all three classifications provide for the assessment of laboratory parameters (hematocrit, platelet count, electrolyte composition), which can be done only when calling an

Table 2. *Grading the severity of dengue fever (WHO, 1997)*

Form	Severity	Clinical symptoms	Laboratory criteria
CDF		Fever and 2 or more symptoms: headache, retroorbital pain, myalgia, arthralgia	Leukopenia (not in all cases). Thrombocytopenia may exist. No signs of plasma loss
HDF	I	The same symptoms + positive tourniquet test	The same parameters + thrombocytopenia less than 100,000/μl Hematocrit ≥ 20% of normal range
HDF	II	The same symptoms and occurrence of spontaneous bleeding	
HDF	III	The same symptoms with hemodynamic disorders	
HDF	IV	Shock with undetectable pulse and blood pressure	

Table 3. *Suggested dengue fever classification and levels of severity (WHO, 2009)*

Probable dengue fever	Dengue fever with severe signs	Severe dengue fever
Accommodation or travel to an endemic area, fever, and two or more of the following symptoms: - nausea, vomiting; - exanthema; - retroorbital pain; - positive tourniquet test; - leucopenia; - any grave symptom.	Abdominal pain Repeated vomiting Signs of fluid accumulation (swelling, ascites, etc.) Bleeding of mucous membranes Lethargy or anxiety Hepatomegaly > 2 cm Increased hematocrit Rapid reduction of platelet count	Signs of plasma loss (shock, fluid accumulation in the cavities, respiratory distress syndrome) Acute bleeding Multiple organ dysfunction syndrome Increased AST or ALT ≥ 1000 Impairment of consciousness

ambulance to a medical institution during laboratory working hours. In this regard, for assessment of the severity of the disease and choice of strategy of therapy and medical evacuation, the medical worker can only rely on clinical symptoms.

According to the general opinion of leading specialists in infectious diseases, due to pronounced clinical polymorphism, the final diagnosis of dengue fever should be confirmed by specific laboratory methods [3]. In this regard, there is a controversial question on the possibility of dengue fever diagnosis at the pre-hospital stage. The WHO classification makes it possible to establish the diagnosis of probable dengue fever (see Table 2) [4]. A similar recommendation for diagnosis is presented in the clinical guidelines on dengue fever in adults of the National society of infectious diseases [3]. Such a diagnostic approach has been approved by the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing for a number of infectious diseases [17, 18]. Thus, the presence of fever that has developed after a visit to countries in South and South-East Asia, combined with two or more symptoms from the following: nausea, vomiting, exanthema, eye pain, positive tourniquet test, abdominal pain, bleeding of mucous membranes, lethargy or anxiety, hepatomegaly more than 2 cm from the costal margin, gives reason to diagnose suspicion of dengue fever by an emergency medical technician.

Therapeutic Strategy in Different Timing of the Disease

When examining a patient with fever, it is especially necessary to pay attention to their social history. When gathering anamnestic data, the fact of the patient staying in an endemic area (risk area) during the seasonal rise of morbidity (risk time) within the incubation period of the disease, the presence of contact with a patient suffering from a similar disease, or contact with infectious material, the patient having mosquito, lice, fleas, tick bites (risk factors), as well as for other possible risks of infection, including the patient's attitude to the contingents at risk, are clarified [19]. At the same time, as shown by our observations, severe forms of DF can develop in primary infection, and therefore the lack of data on previous DF does not allow excluding the development of hemorrhagic or shocking syndrome.

Currently, during DF it is customary to distinguish three phases of the disease: febrile phase, critical phase, and recovery or convalescence phase. The division of the disease by stages is determined not only by the clinical symptoms typical for each of them, but also directly reflects the pathogenetic chain, and allows to choose the necessary therapeutic strategy based on the timing of the disease (Figure 3).

The febrile phase lasts up to 3–4 days from the moment of the sudden onset of the disease and is accompanied by high fever with chills, headache, eye pain, and myalgia of varying intensity. During physical examination of the patient, moderate skin hyperemia can be detected; although, with underlying sunburn obtained in the endemic region, the skin color can be difficult to assess. Oropharyngeal mucosal hyperemia quite often occurs in patients, which can lead to an erroneous diagnosis of ARVI. But the absence of sore throat, rhinitis, cough, and, first of all, patient's social history, do not give grounds to diagnose respiratory infection. It should be noted that in the first 3 days in patients with dengue fever, complications do not develop, and in this regard, oral hydration, paracetamol (drugs containing acetylsalicylic acid are excluded) and control of platelet and hematocrit parameters are recommended. In addition, based on SanPiN 3.2.3215-14, all patients with high body temperature, who came from tropical regions, should be examined for malaria [20]. In this regard, if it is impossible to perform examination on an outpatient basis, hospitalization in an infectious disease hospital is indicated.

The critical phase (4 to 7 days of the disease) is caused by damage to the capillary vessel wall with the development of endothelial dysfunction syndrome common to all hemorrhagic fevers. In these terms, hemorrhagic syndrome and/or plasma leakage from the blood stream to the interstitial space may develop. Typical complaints: occurrence of pruritus or paresthesia of the hands and feet, petechial rash (most often on the shins), dizziness, dry mouth, reduced diuresis, the occurrence of previously unusual bleeding of the mucous membranes,

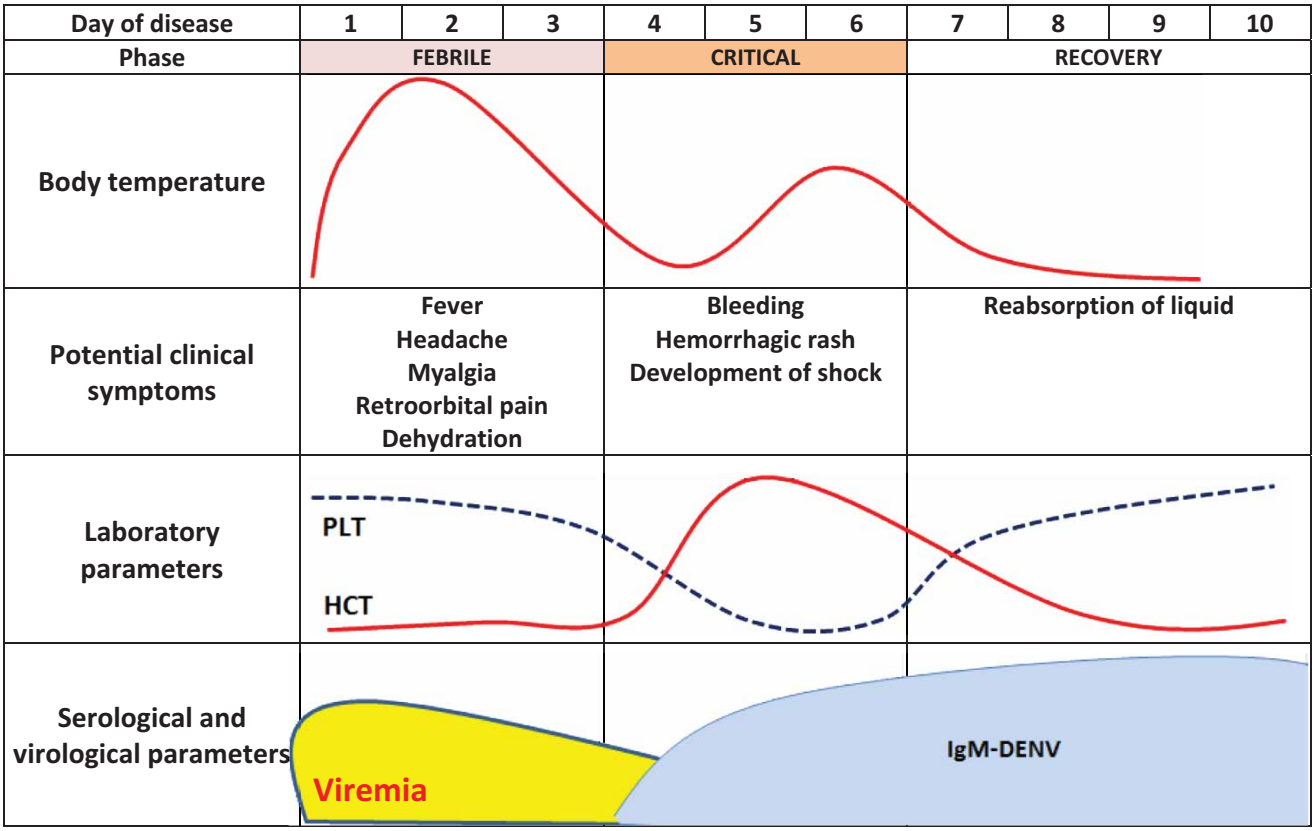

Figure 3. *Dengue fever phases (scheme)*

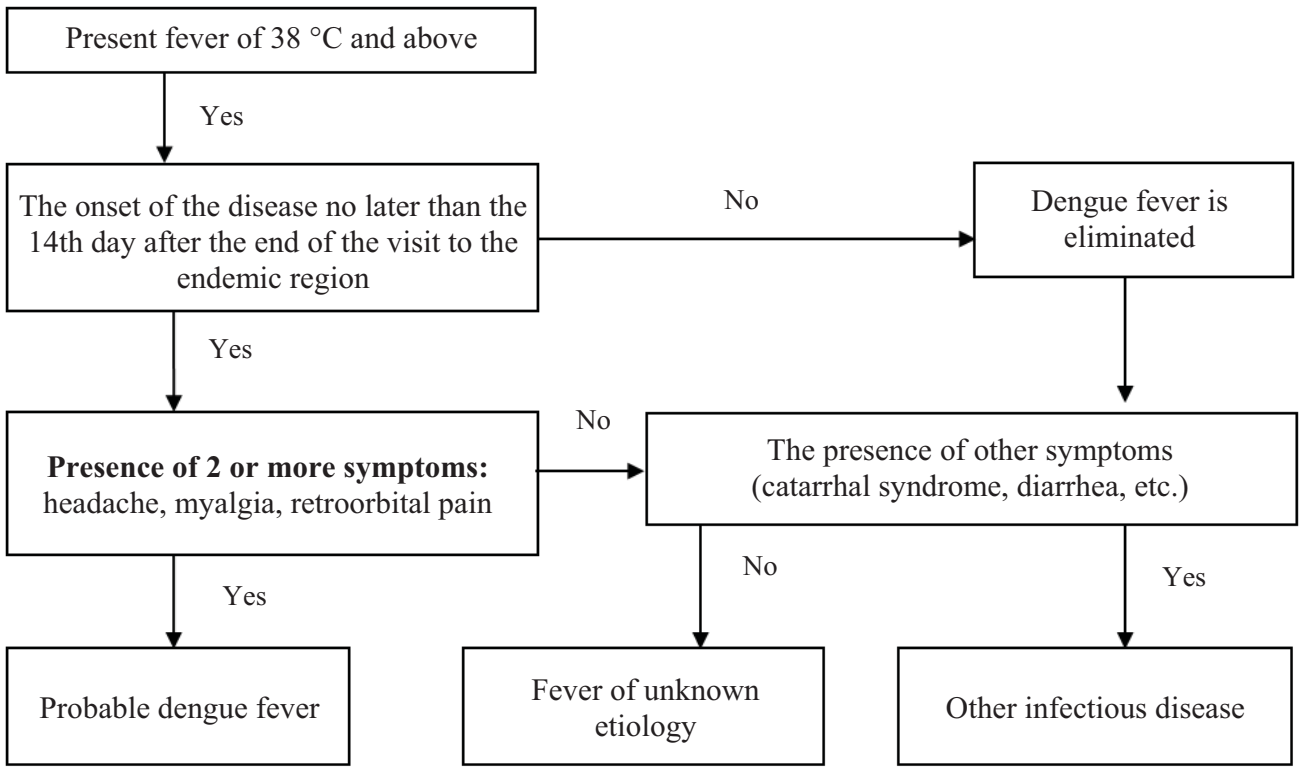

Figure 4. *Dengue fever diagnosis algorithm*

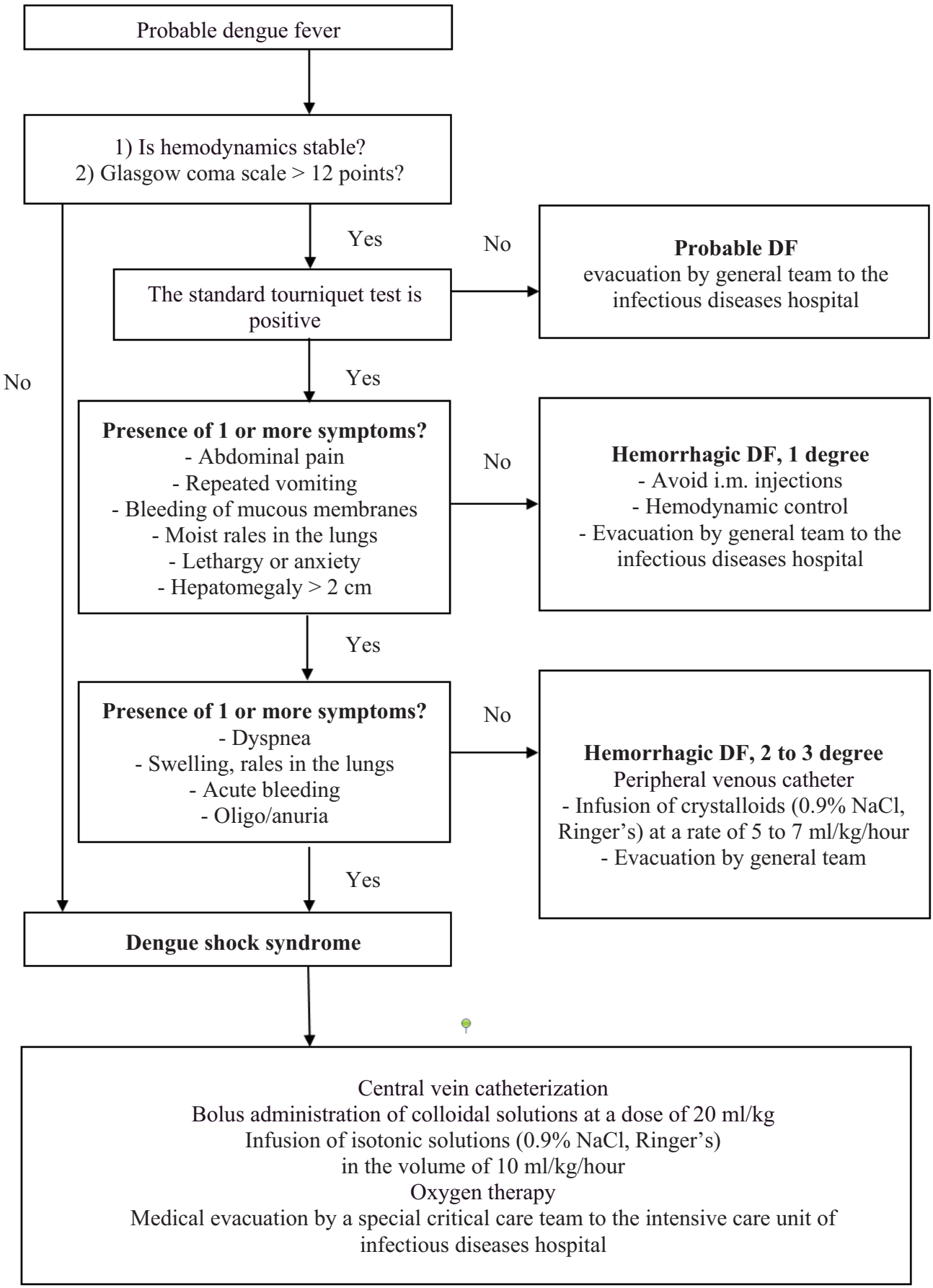

Figure 5. *Algorithm of therapy and medical evacuation of a patient with probable dengue fever*

premature and/or more abundant vaginal discharge. Assessment of hemorrhagic syndrome is carried out on the basis of the patient's complaints (the presence of nasal bleeding, bleeding gums, bleeding from the genital tract, not peculiar to the patient). Even in the absence of such complaints, the patient on Day 4 to 7 of the disease is required to take a standard tourniquet test, with a positive result of which it is necessary to diagnose hemorrhagic dengue fever. With stable hemodynamics and no signs of internal bleeding, the patient is hospitalized in the isolation unit of the infectious disease hospital.

With the development of dengue fever with emergency signs, the administration of isotonic saline solutions (0.9% sodium chloride, Ringer's, Hartmann's solutions) in an amount of 5 to 7 ml/kg per hour for 1–2 hours, and then 3 to 5 ml/kg for 2–4 hours is indicated, after which the volume of infusion is reduced to 2–3 ml/kg per hour. In the absence of improvement and increase in hematocrit, the infusion rate is increased to 10 ml/kg per hour.

The problem of the use of crystalloid solutions is associated with a rapid redistribution of the injected volume from the bloodstream to the interstitial fluid. The existing experience of therapeutic use of colloidal solutions indicates the advisability of their administration in the case of development of hemodynamic disorders associated with endothelial dysfunction [21]. With the development of hypotension and shock syndrome, WHO recommends bolus administration of colloidal solutions in the volume of 20 ml/kg followed by administration of crystalloids at a rate of 10 ml/kg per hour [4].

The recovery phase (the second week of the disease) is accompanied by stabilization of body temperature, blood pressure, resorption of fluid from tissues into the bloodstream. Within 1–2 months, patients may complain of weakness, sweating, hair loss, and work decrement. These symptoms are not specific to DF, but are inherent in all viral fevers accompanied by damage to the endothelium. At this stage of the disease, hospitalization is not required; outpatient follow-up with hematological control and serological examination for mosquito fevers is indicated taking into account the region of stay.

Standard Tourniquet Test

The procedure for carrying out a standard tourniquet test (for its conduction it is necessary to have a mechanical tonometer and a stopwatch, a ruler or a sheet of paper with a cut circle with a diameter of 3 cm)

1. Measure blood pressure.
2. Create a compression of shoulder using tonometer cuff at the level of pulse pressure for 5 minutes.
3. Release air and remove the cuff.
4. Estimate the number of petechial elements appearing on the forearm. Make a calculation in the area of the maximum number of elements.

If there are 20 or more elements per square inch, the tourniquet test is considered as positive.

Thus, the diagnosis, as well as the first aid and medical evacuation strategy can be represented as the following algorithm (Figure 4, 5):

Conflict of Interests

The authors declare no conflict of interests.

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