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**ORIGINAL ARTICLE**

# Protocol for the correct diagnosis and treatment of dengue fever in Pediatrics

Protocolo de actuación para el correcto diagnóstico y tratamiento del dengue en Pediatría

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## ABSTRACT

**Introduction:** dengue is the most important arbovirosis worldwide, considered as an emerging infectious disease. Our country does not escape from this reality. Children are undoubtedly among the most vulnerable age groups.
**Objective:** to improve the action protocol for the correct diagnosis and treatment of dengue at the Provincial Pediatric Hospital of Pinar del Río.
**Development:** the fundamental elements of the definition of a dengue case, evolutionary course of the disease, classification according to severity, positive and differential diagnosis, with emphasis on the timely treatment for the prevention of complications and death in pediatric patients with clinical suspicion are presented.
**Conclusions:** this protocol does not replace the one approved by the National Pediatric Group, but complements and summarizes a series of aspects that are essential for the management of children with dengue fever.

**Keywords:** DENGUE/etiology; PEDIATRICS; TREATMENT; CHILD.

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**RESUMEN**

**Introducción**: el dengue es la arbovirosis más importante a nivel mundial, considerada como una enfermedad infecciosa emergente. Nuestro país no escapa de esta realidad. Los niños, sin dudas, se encuentran entre los grupos etarios más vulnerables.
**Objetivo:** perfeccionar el protocolo de actuación para el correcto diagnóstico y tratamiento del dengue en el Hospital Pediátrico Provincial de Pinar del Río.
**Desarrollo:** se presentan los elementos fundamentales de la definición de caso de dengue, curso evolutivo de la enfermedad, clasificación según gravedad, diagnóstico positivo y diferencial, con énfasis en el tratamiento oportuno para la prevención de complicaciones y muerte en pacientes pediátricos con sospecha clínica.
**Conclusiones:** este protocolo no sustituye al aprobado por el Grupo Nacional de Pediatría, pero complementa y resume una serie de aspectos que son imprescindibles para el manejo del niño con dengue.

**Palabras clave:** DENGUE/etiología; PEDIATRÍA; TRATAMIENTO; NIÑO.



## INTRODUCTION

Dengue is the arthropod-borne viral disease with the highest morbidity and mortality worldwide. Its incidence has increased in the last decades, which is why it is considered an emerging infectious disease and a global public health problem.[1,2,3,4]

In the Americas, dengue is the most important arbovirosis. The number of cases of this disease has increased exponentially, with epidemics occurring every three to five years. The most recent epidemic was reported in 2019, with more than 3,1 million cases. In September 2022, the Pan American Health Organization (PAHO) reported 2,493,414 cases of arbovirosis in the Americas region and of these, 90,2 % corresponded to dengue.[5,6,7,8]

Our country does not escape from this reality. Data from the Ministry of Public Health (MINSAP) report 3,036 cases of dengue in the first semester of 2022, with circulation of the four serotypes and high rates of vector infestation and high risk of disease for the entire population.[9]

Children are undoubtedly among the age groups most vulnerable to dengue. In pediatrics, this disease presents important particularities in its clinical course, related to the patient's age, associated comorbidities and situations that may constitute alarm signs.[10,11,12,13]

Although the disease is complex in its manifestations, treatment is relatively simple, inexpensive and very effective in saving lives, provided the correct and timely interventions are implemented. The key is early identification and understanding of clinical problems during the different phases of the disease, which allows a rational approach to case management and a good clinical response. It is significant to note how difficult it is to determine the differential diagnosis of dengue even for seasoned practitioners. [14,15,16,17]

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Taking into account the serious complications associated with dengue in pediatric patients and its incidence in the province, the present review was carried out with the aim of improving the protocol for the correct diagnosis and treatment of dengue at the Provincial Pediatric Teaching Hospital of Pinar del Río.

## DEVELOPMENT

Definition of suspected case of dengue fever

A person who lives in or has traveled in the most recent 14 days to areas with dengue transmission and initiates sudden high fever, usually lasting two to seven days, and two or more of the following manifestations:

- Nausea, vomiting.
- Rash.
- Myalgia, arthralgia.
- Headache, retro-orbital pain.
- Petechiae or positive tourniquet test.
- Leukopenia.
- Any alarm sign.
- Any criterion of severity of dengue.

Any child coming from an area with dengue transmission or residing in such an area, with acute febrile symptoms, usually lasting two to seven days and without apparent etiology, may also be considered suspicious. [18,19,20]

### Description of the disease

Dengue is a systemic and dynamic infectious disease, which may be asymptomatic or have a broad clinical spectrum that includes severe and non-severe expressions. After the incubation period (seven-14 days), the disease begins abruptly. It may have three phases: febrile phase, critical phase and recovery phase (a minority develop the critical phase). [10,19]

### Febrile phase

- Fever, generally high (39ºC to 40ºC), abrupt onset, can be biphasic and lasts from two to seven days.
- Headache, adynamia, myalgias, arthralgias and pain in the retro-orbital region may be present.
- In children under two years of age, pain symptoms manifest as intense crying, adynamia and irritability.
- Anorexia and gastrointestinal manifestations such as nausea, vomiting and diarrhea, as well as abdominal pain that becomes severe.
- Mild hemorrhagic manifestations such as petechiae and/or oral or nasal mucosal bleeding.
- Older children may have flu-like symptoms.
- Hepatomegaly that may be painful to palpation.
- Loop or tourniquet test or Rumpel-Leede test may be positive.
- Exanthema may appear during the first two days of the disease, or after the third day. It is not pathognomonic, since it can be thin (scarlatiniform or rubeoliform) or thick (morbilliform) and has a craniocaudal distribution. It is pruritic.
- Relative bradycardia is common in this phase.

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- Laboratory findings include: leukopenia, mild thrombocytopenia, and moderately increased transaminases (AST or TGO and ALT or TGP).
- Towards the end of the febrile stage -whether or not there have been skin bleedings-, and especially at the time of defervescence, when the temperature drops to 37,5-38 ºC or remains below this level, some patients show alarm signs (AS).
- Many patients recover after this phase without complications and evolve to the third phase of the disease (recovery).[19,21,22,23]

**Critical phase**

- Around the time of defervescence an increase in capillary permeability may occur in parallel with rising hematocrit levels. This marks the beginning of the critical phase of dengue. The period of clinically significant plasma leakage usually lasts 24 to 48 hours and frequently begins between the 3rd and 5th day of illness (sometimes even as early as the 2nd day alarm signs are detected in some patients).The degree of plasma extravasation is variable, it may be intermittent.
- The magnitude of the fall in Mean Arterial Pressure (MAP), the increase in hematocrit and the narrowing of Pulse Pressure (PP) accurately reflect the intensity of plasma extravasation.
- Leukopenia with neutropenia and lymphocytosis, followed by a rapid decrease in platelet count, usually precedes plasma extravasation.
- Shock is expressed mainly by hypothermia, irritability or lethargy, cold extremities and tachycardia. Subsequently, MAP tends to decline. It is almost always preceded by the appearance of alarm signs and is accompanied by a lower than normal body temperature.
- In some patients, severe organ impairment (hepatitis, encephalitis, myocarditis, major bleeding) may develop without obvious plasma extravasation or shock. There may also be involvement of other organs such as kidneys, lungs, pancreas and intestines.

If the period of shock is prolonged and recurrent, it leads to hypoperfusion and organ dysfunction, metabolic acidosis and consumption coagulopathy. [1,6,22,23]

**Recovery phase**

- In those patients who do critical phase, a gradual reabsorption of fluid from the extravascular to the intravascular compartment takes place after the critical phase, this is called the recovery phase of dengue fever. During this stage there is an improvement of the general condition, appetite returns, gastrointestinal symptoms improve, hemodynamic condition stabilizes and the patient's diuresis increases.
- Occasionally a cutaneous eruption with the appearance of "white islands in a red sea" appears.
- Bradycardia and mild electrocardiographic alterations are common in this phase.
- Hematocrit stabilizes or may be lower than initial due to the dilution effect of reabsorbed fluid and/or fluids administered. Leukocytes and neutrophils begin to rise, sometimes with a decrease in lymphocytes. Recovery of the platelet count may take several days.[1,6,22,23]

**Classification according to the severity of Dengue**

- **Dengue without alarm signs (Group A)**

A patient who meets the definition of a suspected case and has no alarm signs.

- **Dengue with alarm signs (Group B)**

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Any case of dengue fever that presents one or more of the following alarm signs close to and preferably at the onset of fever:

- ✓ Abdominal pain: progressive to continuous and severe.
- ✓ Sensory disturbance: irritability, drowsiness, lethargy.
- ✓ Mucosal bleeding: gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation or menstrual bleeding greater than usual and hematuria.
- ✓ Fluid accumulation: clinical, imaging studies or both.
- ✓ Hepatomegaly: greater than 2 cm below the rib cage and sudden onset.
- ✓ Vomiting: persistent (three or more in 1 hour or four in 6 hours).
- ✓ Progressive increase in hematocrit: in at least two consecutive measurements during the patient's follow-up. [10,24,25]

**Severe Dengue (Group C)**

The level of care for the management of this group is the pediatric intensive care unit (PICU); it includes any case of dengue that has one or more of the following manifestations:

- ➢ Shock or respiratory distress due to severe plasma extravasation demonstrated by weak pulse and at least one of the following findings:
  - ✓ Tachycardia (in the absence of fever).
  - ✓ Distal coolness.
  - ✓ Slow capillary refill (greater than two seconds).
  - ✓ Arterial hypotension :
  - ✓ Mean arterial pressure (MAP) less than 70 mmHg in adults or, in children, less than the minimum expected according to age and sex.
  - ✓ Pulse pressure (PP) equal to or less than 20 mm Hg.

- ➢ Severe life-threatening bleeding: cerebral, pulmonary, digestive, urinary or vaginal (considered clinically important by the treating physicians).
- ➢ Severe organ involvement: hepatitis (AST or ALT ≥ 1000 IU or elevation more than 6 times the normal value for age); encephalitis: altered level of consciousness and convulsions; myocarditis: with or without cardiogenic shock; glomerulitis: arterial hypertension, hematuria and acute renal failure, special attention to nephritis in pregnant women: creatinine ≥1 mg/dl; pancreatitis: elevation of pancreatic enzymes. [5,6,23,25]

**Table 1.** Clinical problems in the phases of dengue fever. [10,16,23]

| Phase | Clinical problems |
|---|---|
| Febrile | Dehydration; high fever may be associated with neurological disorders and seizures in young children. |
| Critical | Shock due to plasma extravasation; severe bleeding, serious organ involvement. |
| Recovery | Hypervolemia (if intravenous fluid therapy has been excessive). |

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## Complementary tests

Hematocrit, leukocyte and platelet counts are the recommended clinical laboratory tests on admission to the emergency department. Failure to perform these tests does not preclude initiation of the recommended treatment.

- The hematocrit determined in the early febrile phase represents the patient's baseline value.
- A decrease in the number of leukocytes makes the diagnosis of dengue more likely.

The rest of the complementary tests should be performed according to the patient's clinical picture and the treating physician's criteria.

Imaging studies (chest X-ray, ultrasound) are useful to evaluate the presence of free fluid in the abdominal cavity or in the serosa (pericardium, pleura), before they are clinically evident.

Echocardiography can be useful to evaluate pericardial effusion, in addition to assessing myocardial contractility and measuring the ejection fraction of the left ventricle, when myocarditis is suspected.[1,13,24]

## Diagnosis

Dengue is an eminently clinical disease.

- **Direct methods**

Days zero to five from the onset of symptoms (not currently available in our environment):

- ✓ Viral isolation.
- ✓ Molecular diagnosis: RT-PCR test (real-time polymerase chain reaction).
- ✓ NS1 antigen detection: immunochromatographic strips.

- **Indirect methods**

From the 6th day after the onset of symptoms (present in our environment):

For its realization it is necessary to obtain a serum sample for the determination of IgM dengue antibodies (Umelisa dengue IgM plus). This blood sample should be taken on the sixth (6th) day after the onset of symptoms. The date of onset of fever (which is the most common of all symptoms and on which the surveillance system is based) is generally taken as a reference.[1,2,16,23]

## Initial pediatric emergency assessment of a patient with suspected dengue fever

It will be performed in any of the following settings in our hospital:

- On-call corps.
- Conventional and intensive care hospital wards.
- PICU.

As expressed in the Guide for pediatric emergency assessment in Cuba, the first component of the sequence of assessments and actions is the general impression. This first phase or observational assessment should be performed using a highly efficient, prioritized and focused method called the pediatric assessment triangle (PET).

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As its name suggests, the PET is composed of three sides: the patient's appearance, his respiratory work-up and his cutaneous circulation. With them, the PET does not provide us with a diagnosis of the patient, but it does provide us with an assessment of the physiological state and the patient's urgent needs to maintain adequate homeostasis.

The involvement of one or more sides of the triangle rules out a normal physiological state, and we are faced with a situation of unstable PTE (Table 2).[26]

**Table 2.** Integration of the pediatric evaluation triangle: general impression, physiologic status

| General aspect | Respiratory work | Circulation | Physiological status | Causes |
|---|---|---|---|---|
| N | N | N | Stable | |
| A | N | N | Unstable, CNS dysfunction, general | disorder TBI, pediatric stroke, hypoglycemia, exogenous |
| N | A | N | Unstable, respiratory distress | Asthma, bronchiolitis, CAP. |
| A | A | N | Unstable, respiratory failure | Asthma, low ARF (severe), lung trauma |
| N | N | A | Inestable, shock compensado | Unstable, compensated shock |
| A | N | A | Unstable, decompensated shock | Severe diarrhea, burns, penetrating wounds, dengue fever |
| A | A | A | Critical, cardiorespiratory failure. | PCR |

A: altered, N: normal, CTE: traumatic brain injury, CAP: community-acquired pneumonia, ARI: acute respiratory infections, CRA: cardiorespiratory arrest.

Steps for the care of the pediatric patient with suspected Dengue in CG after the initial emergency pediatric assessment.

**Step no. 1**: Complete anamnesis, thorough physical examination and laboratory tests.

**Step 2:** Clinical diagnosis, disease stage and classification according to severity.

From the information obtained in Step 1, the health care provider should be able to define the following criteria in the patient with suspected dengue fever:

- Does he/she have dengue?
- What stage of dengue is he/she in (febrile/critical/recovery)?
- Does he/she have alarm signs?

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- What is the hemodynamic and hydration status? Is the patient in shock?
- Does he/she have other concomitant conditions?
- Does he/she have admission criteria?

**Differential diagnosis**

Table 3 presents the differential diagnosis to always take into account in each suspected case of Dengue, which also includes COVID-19.[6,10]

**Table 3.** Differential diagnosis of dengue fever

| **Conditions that simulate the febrile phase of Dengue Fever** | |
|---|---|
| Influenza-like syndrome: | influenza, measles, mononucleosis, seroconversion, COVID-19. |
| Diseases with exanthem: | rubella, measles, scarlet fever, meningococcal infection, drug allergy, COVID-19. |
| Acute diarrheal diseases: | Rotavirus, other enteric infections. |
| neurological manifestations: | Meningoencephalitis/febrile seizures. |
| Conditions that simulate the critical phase of Dengue fever | |
| Infectious: | acute gastroenteritis, malaria, leptospirosis, typhoid fever, viral hepatitis, acute HIV, bacterial sepsis, septic shock, COVID-19. |
| Neoplasms: | Acute leukemias and other neoplasms. |
| Other clinical conditions: | acute abdomen, acute appendicitis, acute cholecystitis, perforation of hollow viscera, diabetic ketoacidosis, lactic acidosis, leukopenia and thrombocytopenia and/or bleeding, thrombopathies, renal failure, respiratory distress, systemic lupus. |

**Admission criteria**

- Patient under 10 years of age.
- Intolerance to oral route.
- Alteration of at least 1 side of the PET.
- Comorbidities that constitute vulnerability.
- History of COVID-19 in a period of less than three months or having had the severe form of the disease.
- Not vaccinated against COVID-19 or incomplete scheme.
- Patients with poor hygienic-sanitary conditions.
- Patients living in communities with difficult access or far from health institutions. [6]

**Step 3: Treatment for intervention groups A, B and C.** [1,2,6,23]

**Group A. Dengue without alarm signs**

Management in a conventional ward if the patient meets any admission criteria. Otherwise their management is outpatient.

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**Behavior:**

- Relative bed rest, use of mosquito net in febrile phase.
- Evaluate vital signs every four hours.
- Medical evolution every eight hours.
- Keep the patient orally hydrated (breastfeeding, oral hydration salts, homemade liquids).
- Early and intense hydration.
- Paracetamol or Dipyrone if necessary.

**Group B. Dengue with alarm signs**

Admission to intensive surveillance ward.

**Behavior:**

- Relative bed rest, use of mosquito net in febrile phase.
- Diet according to tolerance.
- Hourly evaluation of vital signs (interpret them) and peripheral perfusion signs up to 4 hours after the end of the critical phase.
- Medical evolution every four hours.
- Include MAP calculation and analysis according to MAP tables by sex and age.
- Diuretic rhythm. Urine output should be evaluated every hour for the first six hours or until the patient is stabilized, then the evaluation can be determined according to the patient's condition until the critical phase is over.
- Monitor for early signs of shock.
- Parenteral hydration immediately and regardless of tolerance of the oral route according to WHO protocol.
- Hematocrit, leukocytes and platelets before hydrating the patient. However, this should not delay the initiation of hydration.
- If there is improvement, taper gradually over a maximum period of 24-48 hours and initiate the oral route progressively.
- Gradually reduce the volume of intravenous fluids, especially towards the end of the Critical Phase, at which time plasma leakage decreases.
- Serial hematocrit: before and after fluid replacement, then monitor progressive increase every 12-24 hours.
- Serial platelet counts every 24 h or earlier according to persistent moderate or severe bleeding: monitor progressive decrease.
- Look for ascites (clinical and abdominal ultrasound) and hydrothorax (chest X-ray and ultrasound of lung bases).
- On the 6th day, take a blood sample for IgM-Dengue or earlier if the patient worsens.

**Parenteral hydration schedule for Group B**

Start hydration with crystalloid solution (Ringer Lactate or 0,9 % saline): 10 mL/kg to be given in one hour in the emergency department.

Re-evaluate. If there is clinical improvement and diuresis is ≥ 1 mL/kg/h, the patient is admitted with hourly monitoring until four hours after the end of the critical phase.

Intravenous fluids may be gradually reduced to 5-7 mL/kg/h for two to four hours with hourly patient monitoring.

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Reassess the patient. If clinical improvement is evident and urine output is ≥ 1 mL/kg/h, the drip may be reduced to 3-5 mL/kg/h for two to four hours, always monitoring the patient hourly.

Re-evaluate the patient. If clinical improvement is evident and urine output is ≥ 1 mL/kg/h, reduce the drip to 2-4 mL/kg/h and continue for 24 to 48 hours.

It is necessary to provide the minimum of intravenous fluids to maintain at least a diuretic rate of 1 mL/kg/h.

Intravenous fluids are usually necessary for only 24 to 48 hours.

Clinical improvement is given by:

- Progressive disappearance of alarm signs.
- Stable vital signs.
- Normal or increased urine output.
- Decrease of hematocrit in stable patient.
- Good oral tolerance.
- Recovery of appetite.

If after the administration of the first crystalloid solution load of 10 mL/kg, to pass in one hour, the patient is reevaluated and there is no clinical improvement, the patient should continue his management in the emergency department and repeat the second crystalloid solution load of 10 mL/kg, to pass in one hour).

If in a new reevaluation after that second load there is still no clinical improvement, then a third load of crystalloid solution of 10 mL/kg in one hour can be given.

If there is no clinical improvement, the patient should be carefully reassessed and reclassified as severe dengue with shock and managed as Group C and transferred to PICU.

**Group C. Severe dengue**

- Admission to PICU.
- Oxygen therapy at 3 L/min.
- Monitor vital signs every five-30 minutes.
- Medical evolution at least every two h.
- Take blood gases, electrolytes, blood glucose, liver function tests, renal function tests, the absence of these auxiliary resources should not delay the management of shock. Ensure two venous accesses.
- Start intravenous hydration according to WHO protocol.
- We must maintain the oral route whenever possible.
- Other complementary tests according to medical criteria.
- On the 6th day Take blood sample for IgM-Dengue or before admission to PICU and repeat if necessary. Parenteral hydration regimen for Group C
- Immediate administration of a bolus of crystalloid solution 20 mL/kg in 15 to 30 minutes.
- Re-evaluate: if signs of shock disappear, then decrease the fluid volume to 10 mL/kg/h for one to two hours, with constant monitoring of the patient's hemodynamic condition.
- Re-evaluate: if the evolution is satisfactory, decrease the drip at a rate of five- seven mL/kg/h for four to six hours, with hourly monitoring of the patient.

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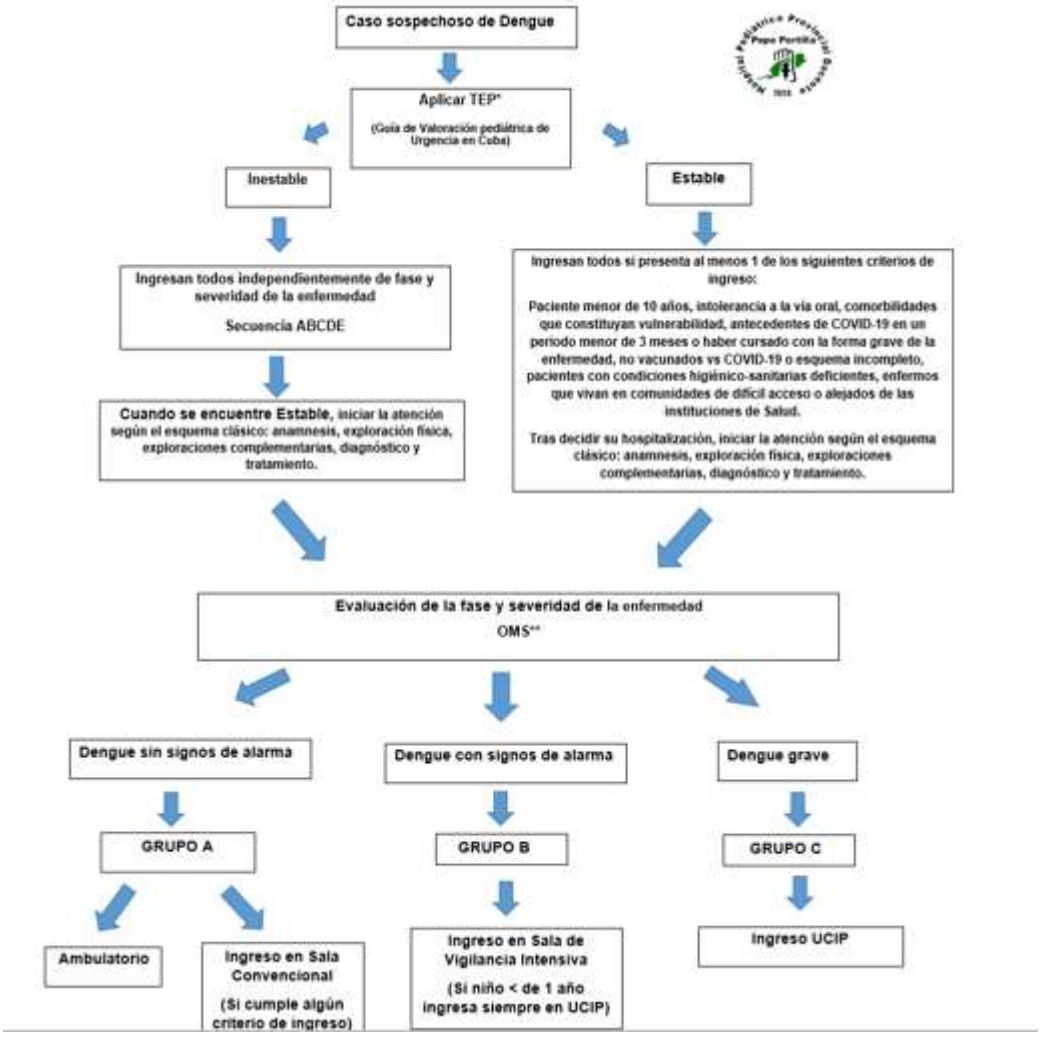
- Re-evaluate: if evolution is satisfactory, continue at a rate of 3-5 mL/kg/h for two to four h, with hourly patient monitoring.
- Re-evaluate: if evolution is satisfactory, reduce fluids to 2-4 mL/kg/h, for 24 to 48 h.
- If the patient remains in shock after the first bolus of 20 mL/kg: pass a second bolus of fluids at the rate of 20 mL/kg in 15 to 30 min.
- Re-evaluate: if signs of shock persist, and there is no evidence of fluid overload then pass a third bolus of fluids at the rate of 20 mL/kg over 15 to 30 min.
- Re-evaluate: if signs of shock persist, the possibility of management according to the intensive care protocol for patients in persistent shock should be assessed[11,27,28].

**Fig. 1** Flowchart for the management of the pediatric patient with suspected Dengue in the HPPP.



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## CONCLUSIONS

Dengue is a disease of systemic and dynamic behavior, which complicates the clinical-epidemiological scenario of the country and requires high scientific preparation for its confrontation. This protocol does not replace the one approved by the National Pediatric Group, but complements and summarizes a series of aspects that are essential for the management of the child with dengue.

### Conflict of interest
The authors declare that there is no conflict of interest.

### Authors' contribution
All authors participated in the conceptualization, formal analysis, project management, writing - original draft, writing - revision, editing and approval of the final manuscript.

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