DENGUE

GUIDELINES FOR PATIENT CARE IN THE REGION OF THE AMERICAS

Second edition

Pan American Health Organization

World Health Organization
Regional Office for the Americas

No mosquitoes: no dengue!

Health facilities should be safe places for patients, family members, and all staff. They should also set an example for the prevention and control of mosquitoes that transmit dengue and other arboviral diseases such as chikungunya and Zika.

Health administrators and all health care workers should be committed to protecting their facilities from the transmitters of arboviral diseases. This means ensuring that:

1. All areas inside and around facilities are kept clean and there are no mosquito breeding sites or potential breeding sites.
2. All doors and windows are physically protected with screens to prevent the entry of adult mosquitoes, and all infected patients are protected by mosquito nets.
3. Patients are encouraged to control breeding sites in their homes and protect themselves against mosquito bites.

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Pan American Health Organization
Pan American Sanitary Bureau
Regional Office of the World Health Organization
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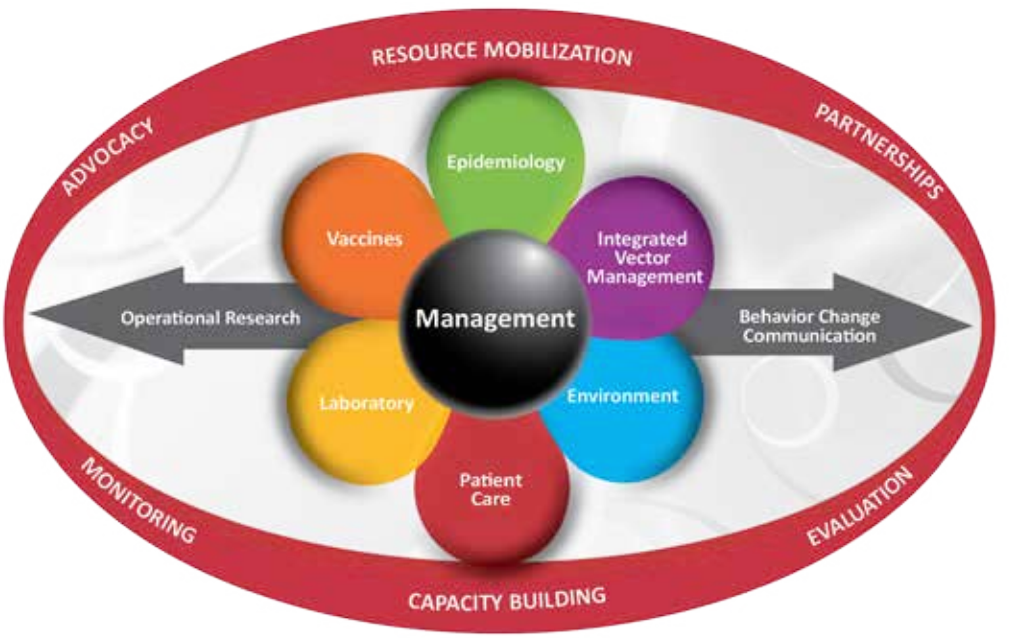
Regional Integrated Management Strategy for Dengue Prevention and Control in the Americas, 2016



FOREWORD

Faced with the complex situation caused by dengue in the Americas and around the world, in 2003 the Pan American Health Organization/World Health Organization (PAHO/WHO) developed the Integrated Management Strategy for Dengue Prevention and Control in the Americas (IMS-Dengue) in collaboration with its member countries in order to tackle the disease through these six components: laboratory, social communication, epidemiology, integrated vector management, environmental, and patient care. The Organization considers patient care to be a vital component and has made it a priority. The first edition of Dengue: guidelines for the care of patients in the Region of the Americas was published (in Spanish) in 2010, based on a WHO document published for the same purpose in 2009. Implementation of the first edition in the Americas was followed by extensive training of health care workers, specifically on timely diagnosis, classification, and case management, with an emphasis on primary care. Recent advances in diagnostic procedures and clinical management make it necessary to update the information on the care of patients with dengue.

This second edition of *Dengue: guidelines for patient care in the Region of the Americas* includes information on the clinical manifestations of the disease, care and treatment, epidemiological surveillance, and laboratory diagnosis. It also includes new information on the reorganization of health services during outbreaks and epidemics, which will be very useful to health unit managers. The guidelines consider this continent's experiences and are evidence-based at the highest scientific level.

PAHO/WHO presents this second edition to countries and territories of the Americas at a time when other arboviral diseases (chikungunya and Zika) have been introduced into the Region. Therefore, it is essential to ensure accurate and timely diagnosis of dengue cases, as well as adequate clinical monitoring. These guidelines—an essential tool for health care workers to correctly manage the dengue cases that appear daily in our countries—seek to prevent the progression to the severe forms of dengue and deaths caused by the disease.

Dr. Marcos A. Espinal

Director Enfermedades Transmisibles y Análisis de Salud

These clinical guidelines are based on *Dengue: guidelines for diagnosis, treatment, prevention, and control* (1), published in 2009 by the World Health Organization (WHO) and adapted for the Region of the Americas. New general information on important aspects of dengue that was not included in the previous edition has been added. However, this new information does not change any aspect of the treatment recommendations in the 2009 WHO guidelines.

Working groups: The International Technical Task Force on Dengue (GT-Dengue) was in charge of preparing these guidelines and the PAHO/WHO Regional Dengue Program coordinated the effort. Since the guidelines include clinical, epidemiological, laboratory, and management aspects, four working groups were created, each coordinated by a subject expert from the GT-Dengue. In 2012, the GT-Dengue met in Bolivia to review the contents of the document in detail. Technical personnel from the PAHO/WHO Regional Dengue Program were in charge of the review and final editing.

Inclusion of new scientific evidence: This edition includes the scientific evidence and recommendations contained in the 2009 WHO document (1). A literature review was essential for the new sections of the guidelines—i.e., dengue associated with other disorders or special conditions (pregnancy, newborns, young children, and older adults). Those sections do not change dengue diagnosis or treatment; they only provide information related to risk factors for dengue severity and mortality. For this reason, evidence tables were not prepared according to the methodology suggested by the GRADE group (2) and the WHO Handbook for Guideline Development (3).

The methodology used by the GT-Dengue members to prepare the document included a systematic literature search to find, update, and supplement the information in the new chapters. To this end, an advanced search was organized using associated descriptors and key words in several databases, such as PubMed, Lilacs, and Cochrane (Annex A). It is important to note that a systematic review was not done. Given that the WHO guidelines were published in 2009, the search for evidence for this second edition was restricted to the five most recent years (through April 2015). Priority was given to studies with a greater degree of evidence (meta-analyses, systematic reviews, random controlled clinical trials, cohort studies, and case-control studies). Studies included those related to dengue in older adults, pregnancy, newborns, and infants; and studies to evaluate risk factors associated with dengue severity and death in these population groups. Twenty-two studies were selected (4-25) and evaluated, and their findings were incorporated into the new chapters. The new scientific information found and evaluated did not indicate that it was necessary to change the 2009 WHO recommendations for dengue care and treatment (1). Annex A contains the search strategy and Annex B summarizes the methodology in a PRISMA flow diagram.

ACKNOWLEDGMENTS

This second edition of *Dengue: guidelines for patient care in the Region of the Americas* was prepared and reviewed by the Pan American Health Organization/ World Health Organization (PAHO/WHO) and the International Technical Task Force on Dengue (GT-Dengue), as part of processes to strengthen dengue prevention and control relevant to the Americas.

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PAHO/WHO would like to especially thank all the people who in one way or another shared their knowledge during preparation of this document. Annex C contains a detailed list of these collaborators.

ABBREVIATIONS AND ACRONYMS

ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention (United States)
DENCO	Dengue and Control Study – multi-country study
DENV	dengue virus
DF	dengue fever
DHF	dengue hemorrhagic fever
DNWS	dengue without warning signs
DP	diastolic pressure
DWWS	dengue with warning signs
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration (United States)
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GT-Dengue	International Dengue Task Force
HELLP	HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count)
HI	hemagglutination inhibition
HIV	human immunodeficiency virus
ICU	intensive care unit
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IIF	indirect immunofluorescence test
IMS-Dengue	Integrated Management Strategy for Dengue Prevention and Control

IV	Intravenous
kg	kilogram
MAC-ELISA	antibody capture ELISA
MAP	mean arterial pressure
mg	milligram
ml	milliliter
mmHg	millimeter of mercury
NS1	nonstructural protein 1
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PAHO	Pan American Health Organization
PT	prothrombin time
RELDA	Dengue Laboratory Network of the Americas
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
SD	severe dengue
SP	systolic pressure
TDR	Special Program for Research and Training in Tropical Diseases (WHO)
TT	tourniquet test
WHO	World Health Organization

REGION OF THE AMERICAS

INTRODUCTION

Dengue is a disease caused by an arbovirus, which has four related virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). It is the most important arthropod-transmitted human viral disease, and constitutes an important worldwide health problem. It is estimated that 3 billion people live in areas at risk of contracting dengue and some 390 million infections (96 million symptomatic) and 20,000 deaths from dengue occur every year (26). In the Region of the Americas, dengue is one of the main reasons for medical consultations in health units and, given that there is no specific treatment for the disease, clinical guidelines are necessary to enable adequate care of cases. Proper use of these guidelines by trained personnel has enormously reduced the dengue case-fatality rate, which is currently less than 1% in the Americas.

This second edition of the *Dengue: guidelines for patient care in the Region of the Americas* has been adapted from the clinical guidelines that the World Health Organization (WHO) published in 2009 for the same purpose. The adaptation was the responsibility of clinicians belonging to the International Technical Task Force on Dengue (GT-Dengue). The document addresses different aspects of the clinical manifestations and phases of dengue, classification of its severity, and elements of medical care and treatment of patients based on their clinical condition. It also includes new elements in the approach to the disease that were not included in the first edition, such as dengue in pregnancy, newborns, and older adults, as well as dengue and co-existing illnesses (associated infections, hypertension, diabetes mellitus, acute kidney failure, and bone and joint diseases). It also addresses elements related to epidemiological surveillance, etiologic agent, laboratory diagnosis, and reorganization of health services during outbreaks or epidemics in the different areas of medical care. This second edition provides the components of a comprehensive approach to dengue thanks to all the described elements.

This document is meant to be used by health care workers, including physicians, medical residents, nursing personnel, medical and nursing students, laboratory workers, epidemiologists, and health units managers in their practice as a tool for treating dengue cases in a more timely and accurate manner, from primary health care up to second- and third-level specialized units. The fundamental purpose of these guidelines is to prevent deaths from dengue. The primary beneficiaries will be children, pregnant women, adults, and older adults affected by the disease.

1. DENGUE: NATURAL HISTORY OF THE DISEASE

1.1. Description

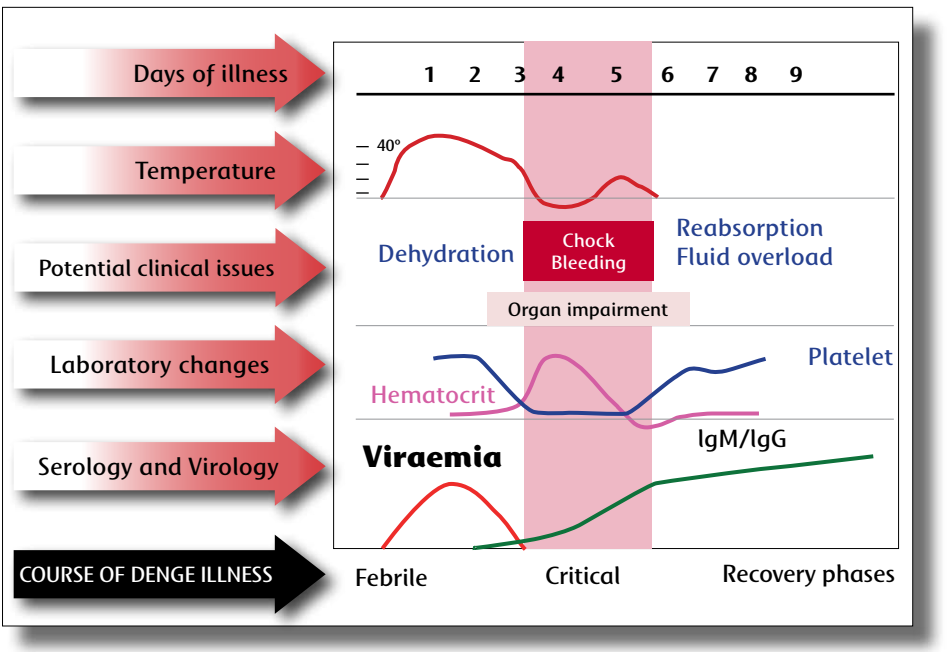
Dengue is a systemic and dynamic infectious disease. The infection may be asymptomatic or present itself with a broad clinical spectrum that includes both severe and non-severe clinical manifestations (27). After the incubation period (4 to 10 days), the illness begins abruptly and is followed by three phases—febrile, critical, and recovery (Figure 1).

For a disease as complex in its manifestations, treatment is relatively simple, inexpensive, and very effective in saving lives as long as the intervention is done in a correct and timely manner. The key is early detection and a clear understanding of the clinical problems that may arise during the different phases of the disease, in order to address cases rationally and provide a good clinical response. An overview of good and bad clinical practices is given in Annex D.

Activities (triage and management decisions) at the primary and secondary care levels (where patients are first seen and evaluated) are critical in determining the clinical outcome of dengue. Good primary care does not only reduce the number of unnecessary hospital admissions, but also saves the lives of patients with dengue. Early notification of dengue cases seen in primary and secondary care is crucial for identifying outbreaks and initiating an opportune response. To achieve this, correct differential diagnosis is important (Annexes E and F).

1.2. Course of the disease

Figure 1. The course of dengue illness



Adapted from WCL Yip, et al. 1980 (28).

1.2.1 Febrile phase

Patients typically develop sudden onset of high-grade fever, which may be biphasic. This acute febrile phase usually lasts 2 to7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, headache, and retro-orbital pain (27). Some patients may present odynophagia, and pharyngeal and conjunctival hyperemia. Gastrointestinal symptoms (anorexia, nausea, vomiting, and loose stool) are common. In the early febrile phase it can be difficult to clinically differentiate dengue from other acute febrile diseases (29). A positive tourniquet test (TT) in this phase increases the probability that the patient has dengue, even though 21% of cases with a positive tourniquet test are not confirmed as such (30, 31). Furthermore, at the beginning of the febrile stage, these clinical features are indistinguishable between dengue cases and those that later become severe dengue; the TT alone is not useful in differentiating them (31, 32). Therefore, monitoring for warning signs and other clinical parameters (Annexes G, H, and I) is crucial to recognizing progression to the critical phase.

Mild hemorrhagic manifestations like petechiae and ecchymoses on the skin may be seen a few days after onset of the illness. The liver may also be enlarged and tender (27). The earliest abnormality in the complete blood count is a progressive

decrease in total white cell count (30, 33), which should alert the physician to a high probability of dengue infection (34). Relative bradycardia is common in this phase, since fever does not substantially elevate the heart rate (35).

1.2.2 Critical phaseFase crítica

If the temperature drops and stays at 37.5 °C or less during the first 3 to 7 days, some patients may experience an increase in capillary permeability, as well as increased hematocrit levels (36). This marks the beginning of the critical phase; i.e. the phase of clinical manifestations due to plasma leakage, which usually lasts 24 to 48 hours and may be associated with bleeding of the nasal mucous membrane (epistaxis) and of the gums (gingivorrhagia), as well as transvaginal bleeding in women of childbearing age (metrorrhagia or hypermenorrhea) (36). There is no evidence that the virus infects endothelial cells (37) and only nonspecific changes have been found in microvascular histopathological studies (38, 39). The microvascular permeability phenomenon and thromboregulatory mechanisms are due to immunopathogenic causes that are not completely understood. However, available information suggests a transient interruption in the endothelial glycocalyx membrane function (40, 41).

Leukopenia with neutropenia and lymphocytosis with 15 to 20% atypical forms, followed by a rapid decrease in platelet count usually precedes plasma leakage (30). At this point, patients without a large increase in capillary permeability improve, whereas those with greater capillary permeability may worsen as a result of loss of plasmatic volume and may present warning signs. If volemia is not promptly and properly restored, "a few hours later" these patients tend to present signs of tissular hypoperfusion and hypovolemic shock. Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of administrated fluids. Chest x-ray, abdominal ultrasound, or both, are useful tools for early diagnosis of serous cavity effusions, as well as gallbladder wall thickening from the same cause (42). The intensity of the progression of plasma leakage is also reflected in progressively rising hematocrit levels, making an impact on the patient's hemodynamics. In the first stage, this could last hours and be expressed as a change in blood pressure due to the narrowing of differential blood pressure or pulse pressure, accompanied by tachycardia and other early signs of shock without a drop in blood pressure. In children, it is more important to determine changes in mental status (restlessness or lethargy) and tachypnea, in addition to tachycardia. In a second stage, the patient may present with frank hemodynamic decompensation, a drop in systolic pressure, mean arterial pressure (MAP), and shock, which in some patients can be aggravated by the presence of myocardial impairment.

Shock occurs when a critical volume of plasma is lost through leakage and is usually preceded by warning signs. The body temperature may be subnormal when shock occurs. Prolonged or recurrent shock leads to organ hypoperfusion, with hypoxia and progressive deterioration of the patient. Systemic inflammatory response syndrome

and multiple organ damage may occur, accompanied by metabolic acidosis and consumptive coagulopathy.

The aforementioned signs and symptoms may lead to severe hemorrhage causing a decrease in the hematocrit, leukocytosis, and worsening of the shock stage. Bleeding in this phase occurs mainly in the digestive system (hematemesis, melena), but can also affect the lungs, central nervous system, or any other organ. When bleeding is severe, leukocytosis may occur instead of leukopenia. Less frequently, profuse bleeding may also appear without evident plasma leakage or shock.

In some patients with dengue, several organs may be affected from the early phases of the infection due to direct action of the virus, by apoptosis and other mechanisms, which may cause encephalitis, hepatitis, myocarditis, and nephritis; previously described as atypical; these cases may present severe organ damage (43). The same cause may also damage the kidneys, lungs, and intestines, as well as the pancreas, although little information is available on the impact on this last organ (44, 45).

Patients who improve after defervescence are considered dengue cases without warning signs (DNWS). At the end of the febrile phase, some patients may progress to the critical phase of plasma leakage without abatement of fever, which will disappear some hours later. In these patients, the presence of warning signs and changes in the full blood count should be used to detect the onset of the critical phase and plasma leakage (46).

Patients who deteriorate with defervescence and manifest warning signs are dengue cases with warning signs (DWWS) (Annex G). These patients almost always recover with early intravenous rehydration. Nevertheless, some cases that do not receive timely, and adequate treatment, either because they delay seeking treatment, are not diagnosed early on, are administered inadequate solutions (in composition, volume, rate), or are not monitored by health care workers during the different stages of the disease, are those who commonly progress to severe forms of the disease (Section 2.3).

1.2.3 Recovery phase

Once patients survive the critical phase, they move on to the recovery phase, during which there is a gradual reabsorption of the leaked fluid from the extravascular to the intravascular compartment. This reabsorption period may last from 48 to 72 hours. In these cases, general well-being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes, and diuresis ensues. Some patients may have a late appearance of a rash called "white isles on a red sea" accompanied by generalized pruritus (46, 47). Sinus bradycardia and electrocardiographic changes may occur during this stage (35).

The hematocrit stabilizes or may be lower due to the dilutional effect of the reabsorbed fluid. Generally, white blood cell count starts to rise with the increase in neutrophils

and the drop in lymphocytes (34). The platelet count tends to recover after the white cell count. The circulating platelet count increases rapidly in the recovery phase and unlike other diseases, they continue to function efficiently.

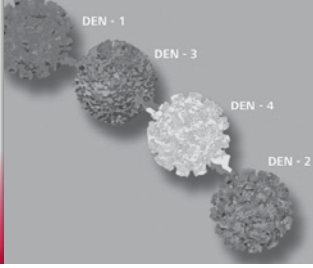
Respiratory distress, pleural effusion, and massive ascites may occur at any time during the critical or recovery phase, usually associated with very fast or excessive intravenous fluid administration, or when the administration of fluids has gone beyond the end of the plasma leakage stage or critical phase. This phenomenon may also occur in patients with renal, myocardial, or pulmonary changes from dengue or in those with prior nephropathy or myocardiopathy and it represents the leading cause of congestive heart failure, pulmonary edema, or both. In patients with hypovolemic shock of a different origin, these undesirable effects in the lungs have been associated with the use of saline solution and have not been observed with the administration of Ringer's lactate (48).

Clinical complications during the different phases of dengue are summarized in Table 1.

Table 1. Clinical problems in the febrile, critical, and recovery phases in dengue

Phase	Clinical problem
Febrile	Dehydration. High fever may be associated with neurological disturbances and seizures in children.
Critical	Shock from plasma leakage, severe hemorrhage, severe organ impairment.
Recovery	Hypervolemia (if intravenous fluid treatment has been excessive or extended into this phase).

2. DENGUE CLASSIFICATION BY SEVERITY



Dengue is a disease entity with different clinical presentations and often with unpredictable clinical evolution and outcomes (27). Classification by severity has great practical potential in a clinician's decision as to where and how intensively the patient should be observed and treated (i.e., triage, which is particularly useful in outbreaks). This will result in consistent reporting in the national and international surveillance systems, and as an end-point measure in dengue vaccine and drug trials.

The existing WHO classification (2009) uses two categories: dengue and severe dengue (Figure 2) (1). This classification arose from many criticisms and disagreements regarding the previous classification into the categories of dengue fever (DF) and dengue hemorrhagic fever (DHF) with its four grades of severity (49), because a large number of laboratory-confirmed dengue cases could not be classified. This constrained epidemiological surveillance because its name erroneously suggested that the disease's severity was related to bleeding and not to plasma leakage, which is what actually happens (32, 50, 51). That classification was also difficult, if not impossible to apply in all situations because it required laboratory support. This service is nonexistent in the majority of health care services, especially in primary care—precisely where the majority of febrile cases should be cared for during an outbreak (32).

Most times the case could only be classified when it fulfilled all the definition's criteria. As a result, the diagnosis was made when complications were already present, hence retrospectively. Furthermore, there was a widespread misconception that dengue fever (DF) is benign and that dengue hemorrhagic fever (DHF) is its severe form, which is not always the case (52). The resulting severity from organ impairment was attributed to DF and many DHF cases were not as severe as was thought nor did they need the human and material resources that its name suggested (53). This also led to errors in epidemiological surveillance of the disease (32, 54).

Figure 2. Modified dengue severity classification, PAHO/WHO

Dengue without warning signs - DNWS	Dengue with warning signs - DWWS	Severe dengue - SD
Person who lives or has traveled to areas with dengue transmission in the last 14 days and presents fever, usually of 2 to 7 days duration, and at least 2 of the following criteria: 1. Nausea/ vomiting 2. Exanthema 3. Headache/ retro-orbital pain 4. Myalgia and arthralgia 5. Petechiae or positive tourniquet test 6. Leukopenia Cases also include any child coming from or living in an area with dengue transmission, with acute febrile illness, usually of 2 to 7 days and no apparent focus.	Every dengue case that, near and preferably at defervescence, presents one or more of the following signs: 1. Intense abdominal pain or tenderness 2. Persistent vomiting 3. Fluid accumulation (ascites, pleural effusion, pericardial effusion) 4. Mucosal bleed 5. Lethargy/restlessness 6. Postural hypotension (lipothymia) 7. Liver enlargement >2 cm 8. Progressive increase in hematocrit	Every dengue case that has one or more of the following manifestations: 1. Shock or respiratory distress due to severe plasma leakage. Shock evidenced by: weak or undetectable pulse, tachycardia, cold extremities, and capillary perfusion >2 seconds, pulse pressure ≤ 20 mmHg: hypotension in late phase. 2. Severe bleeding: based on evaluation by the attending physician (e.g. hematemesis, melena, ample metrorrhagia, central nervous system [CNS] bleeding) 3. Severe organ involvement, such as liver impairment (AST or ALT ≥1000 IU), CNS (impaired mental state), heart (myocarditis), or other organs

Requiring strict observation and medical intervention

Based on the results of the multi-country Dengue and Control (DENCO) study of almost 2,000 confirmed dengue cases in eight countries and two continents, and after successive meetings of specialists from several countries (in Heidelberg, Germany; and Geneva, Switzerland), it was established that they are two clinical presentations of a single disease based on severity: dengue and severe dengue (55). Dengue with warning signs is described in detail in this document because many cases have these characteristics, which mark the beginning of the severe form of the disease and is manifested in capillary leakage. The latter is a warning sign of the real possibility of the disease progressing to severe dengue. Therefore, it enables timely intervention and prevention of cases of shock and other severe manifestations of dengue.

In 2009, the PAHO/WHO Regional Dengue Program, with support from a group of experts in the Region of the Americas, adopted the 2009 WHO classification and integrated it into the Dengue: guidelines for the care of patients in the Region of the Americas (56). Five years after it was first recommended, this dengue classification has been integrated into national guidelines of most Latin American and Caribbean countries and has been shown to be better for the clinical management of patients (52, 57). In particular, the guidelines have improved early recognition of severe cases and those that require special care, considering that they are progressing or could become more severe (warning signs). Diagnosis and treatment can be done earlier and without the dependence on the laboratory required by the 1997 classification. These advantages have been endorsed by a multicenter, 18-country study and by other studies (6, 13, 14, 52, 58, 59).

The new classification also makes epidemiological surveillance easier and more effective due to its usefulness and simplicity, since it can be used in primary health care settings and not only in technologically developed hospitals and health facilities (32, 60). It can also be used in the work of epidemiologists devoted to dengue surveillance, since it reflects the natural course of the disease from its mild to severe forms and covers all clinical manifestations without underestimating the burden of disease. The previous classification omitted up to 32% of severe cases (6, 61). At the same time, standardization of surveillance solved the old problem that arose from using different case classifications in different countries, which prevented comparisons (6, 62).

In short, the following are advantages of the new classification:

1) It is prospective and enables the attending physician to monitor a patient's clinical course (63).
2) It is complete, since it includes all severe and potentially severe cases through the recognition of warning signs (6, 52, 59).
3) It is anticipatory (64).

However, several measures are needed to overcome limitations to this classification identified by some researchers (65, 66), among them: enhance surveillance based on current concepts, to make it comprehensive, proactive, and inclusive of local, national, and regional work; expand use of the classification to all situations and areas of the health care system and not limit its use to hospitals or regional facilities equipped with more human and material resources; make primary care the main site for dengue patient care, thus decongesting the hospitalization subsystem and increasing the number of beds available for severe dengue patients; and reorganize services during epidemics (patient classification, urgent care, health care services, laboratory, medical transport, and other components) (65).

2.1. Dengue without warning signs

The clinical description of dengue without warning signs coincides with that of the febrile dengue phase (Section 1.2.1). This clinical presentation tends to be quite conspicuous and "typical" in adults, who may present many or all of the symptoms for several days (usually one week) and then move on to a convalescent phase that lasts several weeks or even months in some cases (post-dengue syndrome). In children, the clinical presentation can be oligosymptomatic and manifest itself as a nonspecific febrile syndrome (27, 67). The presence of other confirmed cases in the febrile patient's environment (epidemiological link) is a determining factor for a suspected clinical dengue diagnosis.

2.2. Dengue with warning signs

At defervescence, the dengue patient may improve and recover from the disease or present clinical deterioration and warning signs. If by that time the patient does not feel better and does not appear to improve, it should be suspected that the illness has progressed and that a more severe stage could occur. In Puerto Rico, a group of dengue deaths with confirmed diagnosis was studied. These cases presented a set of clinical signs considered warning signs, such as intense abdominal pain, persistent vomiting, sharp drop in temperature, and change in mental state, which should have alerted physicians to the severity of the patients' condition (46, 68). According to the aforementioned DENCO study, intense abdominal pain, mucosal bleeding, and lethargy were the clinical manifestations of greatest statistical significance and were presented 24 hours before the severity of dengue was established (55).

Most warning signs are the result of an increase in capillary permeability and mark the beginning of the critical phase. These signs are:

Intense and continuous abdominal pain or tenderness. Intense and continuous abdominal pain means that the patient may develop or is already developing dengue shock and its dreadful complications. Its positive predictive value (PPV)

was 90% for clinically relevant plasma leakage (ascites, pleural effusion, or both) and 82% for shock, according to a study of Salvadoran children with dengue. Something similar was observed with frequent vomiting (three or more times in 1 hour or four in 6 hours), but its PPV was not high (69).

Abdominal pain with these characteristic is not due to the more or less abrupt appearance of hepatomegaly during the critical phase of dengue or to presumed gastric mucosal erosions, as was demonstrated in a research study during the first dengue hemorrhagic fever epidemic in the Region of the Americas in Cuba in 1981 (70). The new hypothesis is that the intense pain referred to the epigastrium is reflex pain caused by the sudden presence of a large amount of fluid leaked into the pararenal and perirenal areas, which irritates the nerve plexuses of the retroperitoneal region (71). Abdominal ultrasound studies of Indonesian children with dengue shock found that 77% of them presented perirenal and pararenal liquid "masses," which did not appear in children without shock (72). This is a clear association between the accumulation of fluid in the retroperitoneal region and dengue shock, while indicating the speed with which large volumes of fluid can accumulate in that region. Furthermore, the pain, although intense, is transitory. In isolated cases, abdominal pain may correspond to hepatitis, enteritis, or pancreatitis, disorders suffered by some patients with dengue that have led to proposals to explain the symptom (73). However, in those cases, abdominal pain is not associated with plasma leakage; therefore, it should not be accepted as an explanation of the warning sign.

Additionally, it has been demonstrated that gallbladder wall thickening occurs from sudden plasma leakage in sufficient volume to produce pain in the right upper quadrant, without signs of inflammation, and constitutes a warning sign. Some have mistakenly interpreted it as acalculous cholecystitis (73), because when the gallbladder is removed in these circumstances, inflammatory cell infiltration has not been found in its wall, but instead pure liquid in the form of edema (36, 73). Leakage also occurs on the bowel wall, which forms edema and sharply increases its volume from fluid accumulated under the serous layer. This is often found during autopsy of those who have died from dengue and causes abdominal pain in any location. The pain becomes so intense that it can resemble acute abdomen conditions (cholecystitis, cholelithiasis, appendicitis, ectopic pregnancy, or bowel infarction) (74, 75).

Persistent vomiting. Defined as three or more episodes in one hour or four in six hours. This impedes proper oral rehydration and contributes to hypovolemia. Persistent vomiting has been recognized as a clinical sign of severity (76). In a study in Sinaloa, Mexico, persistent vomiting was a variable with PPV (OR = 3.04; 95% CI = 1.05 to 8.80) of a more severe disease, based on multifactorial analysis adjusted for age, sex, and local presence of dengue cases (77).

Fluid accumulation. Usually manifested by pleural effusion, ascites, or pericardial effusion and is detected by clinical methods, radiology, or ultrasound, without necessarily being associated with respiratory distress or hemodynamic compromise (78). If hemodynamic compromise is present, the patient would be classified as a severe dengue case. Presence of ascites has had a PPV for disease severity (OR = 22.12; 95% CI = 5.00 to 97.87) (77).

Active mucosal bleeding. Usually occurs in the gums and nose, but can also be vaginal (metrorrhagia and hypermenorrhea), gastrointestinal (vomiting with bloody streaks), or of the kidney (macroscopic hematuria). In the aforementioned Mexican study, gingivorrhagia and hematemesis also had a PPV of greater severity (OR = 7.35; 95% CI = 2.11 to 25.61 and OR = 7.40; 95% CI = 1.04 to 52.42, respectively) (77). Mucosal bleeding accompanied by hemodynamic impairment of the patient is considered a sign of severe dengue.

Change in mental state. Irritability (restlessness) or drowsiness (lethargy) may occur, with a Glasgow Coma Scale score of <15. It is accepted that both manifestations are expression of cerebral hypoxia induced by the hypovolemia caused by plasma leakage.

Hepatomegaly. Palpation of the liver more than 2 cm below the costal margin. This may be due to an increase in the liver's size (from a combination of congestion, intrahepatic hemorrhage, and fatty metamorphosis) or displacement of the liver from pleural effusion and other intraperitoneal (ascites) or retroperitoneal fluid accumulation (70). It has been a significant risk factor for shock in children with dengue (78).

Progressive increase in hematocrit on at least two consecutive measurements during patient monitoring

2.3. Severe dengue

Patients with severe dengue are classified as such by the attending medical group, because they: a) are at risk of imminent death; b) present signs and symptoms of a complication that, if not properly treated, could be fatal or does not respond well to conventional treatment; and c) have another disorder that determines their severity.

Severe forms of dengue are defined by one or more of the following criteria:

- shock or respiratory distress due to plasma leakage
- bleeding considered clinically important by the attending physicians
- severe organ impairment (myocarditis, hepatitis, encephalitis)

In general, if hypovolemia is not treated promptly with defervescence and increasing vascular permeability, the patient with dengue may progress to shock (36). This occurs most frequently on the fourth or fifth day of the disease (3-to-7-day range) and is almost always preceded by warning signs. During the initial stage of shock, the compensatory mechanism that maintains a normal systolic blood pressure also produces tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. The physician may measure a normal systolic pressure and underestimate the critical state of the patient. Patients in the initial stage of shock often remain conscious and lucid. If hypovolemia persists, the systolic pressure drops and the diastolic pressure rises, which results in either pulse pressure or MAP dropping or both (79). In the most advanced stage of shock, both pressures drop until disappearing abruptly. Prolonged shock and hypoxia may lead to metabolic acidosis and multi-organ failure and an extremely difficult clinical course to manage. Dengue is a viral infection in which lipopolysaccharides do not circulate, which means that it does not have a hot phase of shock as bacterial sepsis does. Shock is purely hypovolemic, at least in its initial phase.

The patient is considered to have shock if the differential pressure or pulse pressure (i.e., the difference between the systolic and diastolic pressures) is ≤20 mmHg or if the pulse is rapid and weak and at least two signs of poor capillary perfusion are present (cold limbs, delayed capillary refill >2 seconds, mottled skin); this is the same for children and adults. However, it should be kept in mind that in adults, a pulse pressure of ≤20 mmHg may indicate a more severe shock. Hypotension should be considered a late sign of shock that is usually associated with prolonged shock, often complicated by major bleeding. It is also useful to monitor MAP to determine the presence of hypotension; normal adult MAP is 70 to 95 mmHg. A MAP below 70 mmHg is considered hypotension. In children, the early sign of hypovolemia is tachycardia. MAP lower than the minimum expected for a child's age and sex may be associated with shock or lead to it (Annex I).

Shock is the most frequent form of severe dengue; it produces sudden and uncontrolled leakage of fluids from the microvasculature by affecting the endothelium, among other causes, due to the action of cytokines that induce apoptosis (80-82). This is the most relevant physiopathological characteristic of dengue, which distinguishes it from other viral infections and coincides with the progressive decrease in platelet count. Thrombocytopenia in this arbovirus results from a process that starts with the virus adhering to platelets and other megakaryocytic lineage cells and culminates in their lysis. This is an immunologically caused event due to the action of antibodies that were initially made against proteins of the viral wall and then turn into autoantibodies and cross-react with some platelet proteins, fibrinogen, and also some endothelium vascular proteins via molecular mimicry (83, 84). In patients with dengue, thrombocytopenia may be moderate (<100,000 mm3) or severe

(<10,000 mm3), but is transitory; normal levels return in a few days, because the megakaryocytopoiesis system remains intact or hyperplastic during the critical phase of the disease (70). Although thrombocytopenia does not determine shock, the progressive decline in platelet number is an excellent marker of increasing patient severity, especially when accompanied by increasing hematocrit.

Severe bleeding is multicausal, including vascular factors such as imbalance between coagulation and fibrinolysis, and thrombocytopenia, among others. In severe dengue, coagulation abnormalities may occur, although these are usually not sufficient to cause severe bleeding. When major bleeding does occur, it is almost always associated with severe shock, in combination with hypoxia and metabolic acidosis, which can lead to *multi-organ failure* and consumptive coagulopathy. Massive bleeding may occasionally occur without prolonged shock; this is a defining criterion for severe dengue. This type of bleeding may also occur as a consequence of the administration of acetylsalicylic acid (aspirin), nonsteroidal anti-inflammatory medications (9), or anticoagulants (1).

Patients may also suffer from acute liver failure, myocarditis, encephalitis, or kidney failure, even in the absence of severe plasma leakage or shock. This severe organ impairment is by itself a criterion for severe dengue. Clinical manifestations are similar to those seen when these organs are affected by other causes. Such is the case of fulminating hepatitis from dengue, in which the patient may become jaundiced—an infrequent sign in dengue in which liver function is impaired. This is expressed in an increase in aminotransferases, 10 times or more their normal maximum value; associated with elevation of prothrombin time (PT) which facilitates coagulation impairment. According to its severity, hypoglycemia, hypoalbuminemia, and altered consciousness may be observed (85, 86).

Myocarditis from dengue is mainly expressed by changes in heart rhythm (tachyarrhythmias and bradyarrhythmias), and T-wave and ST-segment inversion with ventricular dysfunction (reduction of left ventricular ejection fraction); cardiac enzymes may be elevated (87). Severe impairment of the central nervous system is mainly manifested in seizures and changes in mental state (88, 89). In dengue encephalitis, study of cerebrospinal fluid can show presence of the virus or its NS1 antigen, or the presence of IgM-specific antibodies (90). All these severe organ impairments may be of such intensity that they can lead to the patient's death. However, most deaths from dengue occur in patients with severe shock (43), sometimes complicated by pulmonary edema and often, although not always, due to fluid overload (70).

3. CLINICAL SERVICES AND CASE MANAGEMENT

3.1. Overview

Reducing dengue mortality requires an organized process that guarantees early detection of the cases, its classification, treatment, and referral when necessary. The key component of this process is the delivery of optimal clinical services at all levels of health care, from primary to tertiary. Most dengue patients recover without requiring hospital admission while some may progress to severe disease. Principles of case classification (triage) and management decisions at the primary and secondary care levels, where patients are first seen and evaluated, can help identify patients at risk of developing severe dengue and require hospital care. These decisions should be complemented with prompt and appropriate treatment of severe dengue in referral centers.

Activities at the first level of care should focus on:

- Recognizing that the febrile patient could have dengue.
- Immediately notifying the public health authorities that there is a suspected case of dengue.
- Care for the patient in the early febrile phase of dengue and provide health education to the patient or the people in charge of their care regarding bed rest and recognition of bleeding from the skin or mucosa, and any of the warning signs.
- Initiating and maintaining oral rehydration treatment on the patient's first contact with health care services.
- Recognizing early the signs of plasma leakage and beginning of the critical phase to initiate intravenous fluid therapy.
- Recognizing patients with warning signs who need intravenous fluid therapy at the same place where they were diagnosed. Intravenous fluid therapy should be initiated at the first level of care to prevent hypovolemia. Subsequently and if necessary, the patient may be referred, to continue this treatment preferably to dengue units or second and third level hospitals. The patient may be transferred once hemodynamic stability is achieved.
- Recording and monitoring vital signs (temperature, heart rate, respiration rate, blood pressure, pulse quality, and urine output).
- Managing shock, severe bleeding, organ impairment, and possible complications promptly and adequately.

3.2. Primary and secondary care

The responsibility to select patients (triage) to provide appropriate treatment lies with primary and secondary level, emergency or ambulatory health care facilities. Triage is the process of rapidly screening patients soon after their arrival in the health care facility in order to classify them in categories of severe dengue (who require immediate emergency treatment to avert death), those with warning signs (who should be given priority while waiting so they can be assessed and treated without delay), and non-urgent cases (who do not meet the criteria for severe dengue or present warning signs).

During the early febrile phase, it is often not possible to predict clinically whether a patient with dengue will progress to severe dengue. Various severe manifestations may unfold as the disease progresses to the critical phase, but the warning signs are good indicators of a higher risk of developing severe dengue. Therefore, ambulatory patients should be evaluated daily at the health care unit to monitor disease progression, warning signs and manifestations of severe dengue.

It is important to educate patients and their family members on the warning signs and disease severity, so that when these signs are recognized, they will immediately go to the nearest health care center to receive intravenous treatment with polyelectrolyte isotonic solutions.

Health care workers at the first levels of care should apply a stepwise approach, as suggested in Table 2.

Table 2. Steps for adequate treatment of dengue

Step 1. Overall assessment
I. Clinical history, including symptoms and past epidemiological, family, and personal history
II. Full physical examination, including neurological examination
III. Investigation, with current dengue-specific laboratory tests (RT-PCR, NS1, IgG/IgM, depending on availability), each one performed at the right time during the course of the disease, as well as other tests to rule out other viral or bacterial diseases. Such tests are not indispensable to initiate patient management.
Step 2. Diagnosis, assessment, and classification of disease phase
Step 3. Treatment
I. Treatment decisions. Depending on the manifestations and other circumstances, patients may: – receive outpatient treatment (group A); – be sent to dengue units for observation and oral or intravenous treatment (group B1); – be sent to dengue units or second level hospitals for intravenous treatment (group B2), or – require emergency treatment at the place of diagnosis or during transfer and urgent referral to more complex hospitals (group C).
II. Measure and interpret vital signs
III. Immediate disease notification

Section 5.2 gives treatment recommendations for the groups A, B1, B2, and C.

3.3. Referral centers

Referral centers receiving patients with severe dengue must be able to provide prompt attention to referred cases. Furthermore, beds should be made available for those patients who meet the admission criteria, even if some specific cases have to be referred to other health care centers, according to how health services are organized. For contingencies, all hospitals must have an area or unit assigned to the treatment of patients with dengue. These units should be staffed by physicians and nurses who are trained to recognize high-risk patients and adopt appropriate measures to care for them and provide adequate treatment and monitoring. They must also have supplies and appropriate diagnostic support.

Main criteria for transfer to an intensive care unit:

- patient needing respiratory or hemodynamic support or both
- plasma leakage that leads to respiratory distress
- shock that does not respond to conventional treatment
- bleeding that endangers the patient's life, according to medical criteria and evaluation of the attending physicians and the place where care is provided
- organ failure (liver failure, myocarditis, encephalopathy, encephalitis, and other severe complications)

3.4. Resources

The following is a summary of the resources required for the detection and treatment of dengue in order to deliver optimal clinical services at all levels (91):

Human resources: These are the most important resources and include trained physicians and nurses. The first level of care should have personnel trained in triage and emergency management. If possible, dengue units staffed with experienced personnel could be set up as referral centers in order to receive patients who need intravenous fluid therapy during disease outbreaks. These special services should be well equipped and have staff trained to provide immediate and transitory medical care to patients who require intravenous fluid therapy until they can be transferred or discharged.

Laboratory resources: It must be possible to do complete blood count (hematocrit, hemoglobin, platelet, and leukocyte count) in a maximum two-hour time frame.

Supplies: Isotonic crystalloid solutions and equipment for administration of intravenous solutions. Regarding medications, there should be adequate stocks of paracetamol and oral rehydration solutions (a code cart or life-support box).

Communication: Should be easily accessible among all levels of care.

Blood bank: Blood and blood products should be readily available when necessary.

Materials and equipment: Sphygmomanometers (appropriate sizes for arm circumference of adults and children of different ages), thermometers, stethoscopes, scales, and others.

3.5. Education and training

To ensure the presence of trained staff at all levels, physicians, nurses, and other health care workers need to be trained with curricula that address required content

and essential practical activities. It is mandatory to support and widely implement training and educational programs customized for the different levels of health care. These programs should develop capacities for accurate triage, clinical management, and laboratory diagnosis of dengue.

National committees should monitor and evaluate clinical management and outcomes. Review committees (e.g., state, departmental, provincial, district, hospital, and local) should review all deaths from dengue and all cases of severe dengue. They should also evaluate the health care delivery system and provide feedback to physicians and nurses on how to improve care.

In dengue endemic countries, knowledge of the disease, its vectors, and modes of transmission should be incorporated into schools curricula. The population should also be educated on dengue so that patients and their families are empowered to care for themselves, are willing to seek medical attention in a timely manner, avoid self-medication, can identify skin and mucosal bleeding, know that defervescence (and during the following 48 hours) is when complications usually occur, and are able to identify warning signs.

Mass media can make an important contribution to addressing dengue when adequately briefed. This can be achieved through workshops and other meetings with journalists, editors, artists, and executives that seek to improve the strategy for health education and communication without alarming the public.

During dengue epidemics, nursing and medical students together with community leaders can visit homes to provide health education, and detect and monitor dengue cases. These measures have been shown to be feasible, inexpensive, and effective; however, they should be coordinated with primary care units (92). It is useful to have printed information about dengue and its warning signs for distribution to the community. Health care providers (public, private, non-governmental organizations, and others) should include health education activities in their daily work in order help prevent the disease (92).

4. DENGUE ASSOCIATED WITH OTHER DISORDERS OR SPECIAL CONDITIONS (pregnancy, newborns, young children, and older adults)

4.1. Dengue and pregnancy

Pregnancy does not increase the risk of contracting dengue or predispose to a different disease course, but it is evident that dengue can affect pregnant women; so they should be treated with caution. The following are some features particular to dengue in pregnant women:

- Maternal death from dengue is infrequent (93).
- Some pregnant women may miscarry or be at risk of miscarriage or premature delivery, during or up to one month following dengue infection (94, 95).
- Fetal growth retardation occurs in a variable proportion of dengue cases (4% to 17%) in pregnant women (96).
- Clinical manifestations, management, and prognosis for dengue in pregnant women resemble those in non-pregnant women. However, there are some differences that need to be considered when caring for pregnant women with dengue (21):
  - Certain physiological characteristics of the pregnancy could make it harder to diagnose dengue (leukocytosis, thrombocytopenia, hemodilution) (97).
  - The most frequent clinical manifestations of dengue in pregnant women are fever, myalgia and arthralgia, headache, and retro-orbital pain; i.e., similar to those of the general population with dengue (98). Rash occurs in approximately half of cases (96).
  - In the first trimester of pregnancy, transvaginal bleeding related to dengue may be misdiagnosed as a miscarriage. Therefore, every pregnant woman with bleeding should be checked for fever or a history of fever in the past seven days.
  - Pregnant women with dengue without warning signs usually have a normal delivery and puerperium, from which it is inferred that the disease does not seem to affect the satisfactory progress of the mother-child dyad during pregnancy. Dengue with warning signs and severe dengue are the clinical presentations with greater association with delayed fetal growth and maternal death, although death is infrequent when the patient is treated properly. Most women who have had dengue while pregnant develop favorably to term (96).
  - Abdominal ultrasound has been predominantly interpreted as normal in pregnant women with dengue without warning signs. Gallbladder wall thickening, with or without perivesical fluid, has been a frequent finding in pregnant women who have dengue with warning signs and severe dengue.

Other disorders, such as hepatomegaly, splenomegaly, and fluid in serous cavities, are the same as those in other patients with severe dengue (96).

- A pregnant woman can continue the normal course of her pregnancy, although fetal health needs to be monitored. Fetal ultrasonography is indicated to assess the volume of amniotic fluid, since oligohydramnios may occur in some cases, requiring appropriate action. Ascites can be detected in the fetus.
- Conservative management, both clinical and obstetric, is the treatment of choice.
- For fluid administration, use Ringer's lactate, Hartmann's, or normal saline solutions in established doses, as always. Never use solutions with dextrose, in any concentration, for the recovery from shock during the critical phase.
- In most cases, dengue does not appear to affect satisfactory progress of the mother-child dyad during the course of the pregnancy (8). However, pay special attention to the pregnant woman at term (96).
- Sometimes, abdominal pain, a dengue warning sign, can simulate uterine contractions or be diagnosed as cholecystitis and rush the attending physician to perform unnecessary surgery that can cause potentially fatal complications.
- The differential diagnosis for dengue includes eclampsia, preeclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), which can also produce abdominal pain and bleeding, in this case from disseminated intravascular coagulation, whose clinical management is different than that of the patient with severe dengue leakage (99). Hemolysis does not occur in dengue, except as an exceptionally rare complication. Other diagnoses that must be ruled out are pneumonia, pulmonary embolism, multiple causes of vaginal bleeding, and other infectious causes (100).
- Pregnant women with diabetes or another underlying disease should be treated for that disease to achieve the maximum possible compensation, in addition to dengue-specific management.
- For patients with a platelet count of <50,000 per mm3 who are in labor and will undergo a caesarean section, consider administration of platelet concentrate as close to surgery as possible (19).
- The timing and route of delivery of the baby will depend on the obstetric condition.
- If a caesarean section is needed, general anesthesia is recommended. Spinal and epidural anesthesia are not recommended because they require puncture (101).
- Uterine bleeding can be a major complication during delivery if the pregnant woman has dengue, particularly if surgical procedures that can be associated with severe bleeding are performed. Some cases may be fatal, most bleeding due to surgical and postsurgical wounds is controllable (102).
- Women who had dengue while pregnant and were treated promptly do not have any more postpartum complications than other postpartum women.

- Notify the pediatric service of every baby born to a mother with dengue at the time of delivery, as the child may become ill up to 12 days after birth.
- Breastfeeding should be continuous and encouraged.
- Newborns of mothers with dengue (or a mother who had the infection up to one week before delivery) who develop thrombocytopenia, fever, hepatomegaly, or varying degrees of circulatory failure during the first week of life may be misdiagnosed with neonatal sepsis. To prevent this, the epidemiological link must be considered (7).
- Newborns whose mothers had a dengue infection before or during pregnancy receive maternal antibodies (IgG) against dengue through the placenta and are at risk of contracting severe dengue if infected by a different virus serotype (11, 15). Furthermore, newborns of mothers who contracted the disease around delivery may develop dengue and severe dengue if infected by a different virus serotype, even months later.

4.2. Dengue in newborns and infants

Children under 1 year of age infected by the dengue virus may present mild or moderate clinical manifestations or even severe disease (7, 10, 11, 15, 22, 103, 104). In this age group, mortality is higher and some show symptoms that are infrequent in dengue, such as upper respiratory tract manifestations (4), diarrhea, or seizures, which almost always are initially diagnosed as febrile seizures, but may be due to acute dengue encephalopathy (24, 105, 106).

Plasma leakage from the intravascular compartment initially manifests as palpebral and peripheral edema, although all subcutaneous cellular tissue is affected by this condition. Hydroelectrolytic disorders are relatively frequent in infants, perhaps because their bodies have a proportionately greater fluid volume than older children and adults. Hepatomegaly and splenomegaly are also up to seven times more frequent in children under one year of age than in older children (107). Shock in young children is expressed mainly as hypothermia, restlessness or lethargy, cold extremities, and tachycardia. MAP tends to decline later.

When vertical transmission of dengue infection occurs, newborns may remain asymptomatic (67) or may develop symptoms such as fever, exanthema, petechiae, thrombocytopenia, and hepatomegaly and follow an uncomplicated course (21, 24, 108). However, some develop severe symptoms that clinically resemble sepsis—which requires a differential diagnosis—with hypothermia instead of fever, pleural effusion, gastrointestinal bleeding, circulatory failure, intracranial hemorrhage, and death (15, 24, 109). Treatment of these severe cases consists of administration of balanced electrolyte solutions (Ringer's acetate, etc.) for the purpose of maintaining MAP within normal ranges for age and sex (1).

4.3. Dengue in older adults

Although age does not entail a greater risk of contracting dengue, the infection in people over 60 years of age is associated with a higher risk of complications compared to other age groups. This is mainly due to a higher incidence of co-existing diseases, unusual presentations and complications associated with dengue, and physiological and immunological characteristics of the older adult population (110).

Older adults are especially susceptible to dehydration during the febrile phase of dengue. Furthermore, many of them, because of their beliefs or customs, are reluctant to seek medical care early on and resort to traditional medicine and self-medication, thereby delaying seeking medical care. Social isolation also contributes to this delay.

Incidence of chronic degenerative diseases increases proportionately with age. For this reason, strict monitoring of hemodynamic and metabolic parameters becomes very important. Similarly, it is necessary to determine what medications these patients take, since typically at this age, they take NSAIDs, anticoagulants, steroids, antihypertensive, and hypoglycemic agents, among others.

4.4. Associated infections

There have been reports of bacterial infections associated with dengue in adults and children and of other viral infections, such as influenza H1N1 and chikungunya fever (20, 23, 111, 112). Since these infections share similar clinical manifestations, concurrency of these infectious diseases in the same patient is frequently underestimated, especially in dengue-endemic areas. In Taiwan, for example, it was reported that up to 5.5% of dengue cases have co-existing bacteremia (111). As expected, bacteremia aggravates the natural course of dengue, also demonstrated in cases of dengue with co-existing influenza. This could also occur with chronic parasitic infections, such as malaria (20, 23).

When treating dengue patients with an unusual form of the disease, concurrent infection must be suspected (20, 23). That is especially true when fever lasts more than seven days, or there are changes in mental state, renal failure, and respiratory distress or splenomegaly of some significance.

4.5. Hypertension

People older than 60 years make up the fastest growing demographic segment in the Americas and a considerable proportion of them have high blood pressure. Even people aged 55 to 65 years with normal blood pressure have over a 90% temporary risk of hypertension. At the same time, older patients have 3 to 4 times

more cardiovascular risk than younger people. These patients are more problematic for physicians. In these cases, it is recommended monitoring blood pressure more frequently and, especially, other signs of hemodynamic decompensation that can occur during dengue. If a patient's blood pressure is controlled with medications, clinical monitoring is similar to that of the population with normal blood pressure. However, a patient who, despite taking antihypertensive medications, does not have controlled blood pressure, may experience drops in blood pressure to normal values, or even below normal; secondary to capillary leakage which could be misinterpreted as "unimportant." It is reasonable to stop antihypertensive medications in all patients who present manifestations of hemodynamic decompensation during the critical phase of dengue.

Bradycardia characteristic of dengue may be aggravated or the adrenergic effect of shock may be masked in patients who use beta-adrenergic blockers. Likewise, up to 98% of patients with dengue and myocarditis may develop bradycardia. For this reason, heart rate is not a parameter for monitoring patients with dengue taking these medications. Similarly, calcium channel blockers can produce tachycardia, which should therefore be interpreted with caution.

Assessment of the hypertensive patient with dengue is further complicated, since it is always necessary to consider that hypertension is associated with impairment of various organs and may cause or contribute to renal failure, cerebral vascular events, metabolic syndrome, and other complications in the patient (113).

4.6. Diabetes mellitus

The factor that most frequently triggers diabetic ketoacidosis and hyperosmolar syndrome is infection (114). Any infection can cause decompensation. Conversely, in cases of severe and fatal dengue, it has been determined that diabetes is one of the main risk factors. Hyperglycemia leads to an increase in osmotic diuresis and dehydration and the latter, in turn, leads to metabolic acidosis (115). Since they have similar manifestations, it is not unusual to confuse dengue shock with diabetic ketoacidosis or a hyperosmolar non-ketotic state.

People who have poor oral intake due to dengue and continue to take their diabetes medications could develop hypoglycemia. This condition worsens when it is associated with disorders of the liver, pancreas, or both organs. Gastrointestinal absorption of oral hypoglycemic medications is erratic due to vomiting and diarrhea during dengue. Metformin causes lactic acidosis and hepatotoxicity (116, 117).

4.7. Acute renal failure

Older adults are more susceptible to capillary leakage, dehydration, and acute renal failure. Arterial stiffness and impaired myocardial function and pulmonary

reserve are important considerations when initiating fluid replacement. Acute pulmonary edema and congestive heart failure are frequent complications in patients with dengue.

Diuretics have a limited effect on chronic renal failure and patients who take them are more susceptible to fluid overload. Patients with chronic renal failure are at risk for metabolic acidosis and hydroelectrolytic imbalance, which could worsen during dengue shock, even to the point of requiring dialysis.

4.8. Bone and joint diseases and anticoagulant use

NSAIDs, including aspirin, are commonly used medications for rheumatoid arthritis, ankylosing spondylitis, and other bone and joint diseases. Stopping NSAIDs and replacing them with paracetamol is advisable during a dengue episode. Use of dipyrone in the first days of the disease is associated with lower platelet counts and an increase in the risk of severe dengue (16, 118). Use of aspirin in cardiovascular prevention doses will be at the discretion of the patient's attending physician, and the risk-benefit ratio needs to be considered. The use of steroids has shown no benefit in the clinical course of dengue, but there is no reason to suspend them in patients who are already taking them for an extended period of time (12).

Patients who take oral anticoagulants usually have or have had a severe thrombotic event. If that event took place in the six most recent months, suppression of anticoagulation can be considered; however, if the risk is very high, replace with low molecular weight heparins.

4.9. Electrolyte balance

Hyponatremia, hypokalemia, hyperkalemia, or hypomagnesemia may occur during dengue infection. These hydroelectrolytic disorders should be corrected according to blood electrolyte measurements and assessment of co-existing diseases.

5. RECOMMENDATIONS FOR TREATMENT (1)

5.1. Stepwise approach to the management of dengue patients

5.1.1 Step 1: Overall assessment

History. The medical history should include:

- date of onset of fever or illness
- quantity of oral intake
- assessment for warning signs (Figure 2 and Annex G)
- gastrointestinal disorders (nausea, vomiting, diarrhea, gastritis)
- change in mental state: restlessness, drowsiness, lethargy, lipothymia, dizziness, seizures, and vertigo
- urine output (frequency in last 24 hours, volume, and time of last voiding)
- relatives with dengue or within the neighborhood, or recent travel to dengue endemic areas (14 previous days)
- other patient characteristics: e.g., infant (29 days to 6 months), older adult >65 years of age, pregnant, obese, asthmatic, has diabetes or hypertension, others
- jungle trekking or swimming in contaminated rivers or reservoirs (consider differential diagnosis for leptospirosis, typhus, malaria, yellow fever, typhoid fever)
- recent unprotected sex, drug abuse (consider acute HIV seroconversion illness)
- consider differential diagnosis of chikungunya if patient has debilitating joint pain.

Physical examination

- Take and record vital signs (temperature, pulse quality, heart rate, blood pressure, pulse pressure, MAP, and respiratory rate).
- Assess mental state using Glasgow Coma Scale (Annexes J and K).
- Assess hydration status.
- Assess hemodynamic status (pulse and blood pressure, determine MAP and pulse pressure or differential pressure, capillary refill time).
- Check for pleural effusions, tachypnea, Kussmaul's breathing.
- Check for abdominal pain, ascites, and hepatomegaly.
- Examine for rash, petechiae, or Herman's (white isles in a red sea).

– Check for spontaneous or induced bleeding manifestations (tourniquet test, which is frequently negative in obese people and patients in shock).

Laboratory

Patients with fever with a potential dengue diagnosis should get the following laboratory tests.

– Initial complete blood count:
  - A hematocrit test in the early febrile phase corresponds to the patient's baseline.
  - A decreasing white blood cell count increases the probability of a dengue diagnosis (Annex F).
  - A rapid decrease in platelet counts with consecutive samples indicates active or progressing disease.
  - A rising hematocrit with consecutive samples indicates plasma leakage or dehydration and progression to severe dengue.

– Additional tests to consider:
  - liver function tests
  - blood glucose
  - albumin
  - serum electrolytes
  - serum urea and creatinine
  - arterial blood gases
  - cardiac enzymes
  - urinalysis or, if not available, urine-specific gravity

Laboratory tests to confirm a dengue diagnosis are not required to initiate treatment, except in cases with uncommon manifestations.

Once the case has been diagnosed, immediate notification of the disease to the proper authorities (epidemiology) in the country is mandatory.

5.1.2 Step 2: Diagnosis and assessment of disease phase and severity

– Determine the viral load in the first four days of fever onset (RT-PCR, NS1) if available. Perform IgM/IgG testing from the fifth day of disease onset, according to local health authority standards.

– Based on the anamnesis, physical examination, and laboratory results (complete blood count), physicians should be able to answer the following questions regarding the patient:
  - Does the patient have dengue?
  - Which phase is it in? (febrile/critical/recovery)
  - Are there warning signs?

- What is the hemodynamic and hydration status of the patient? Is the patient in shock?
- Are there any co-existing disorders?
- Is hospitalization required?

Hospital admission criteria are in Annex L and discharge criteria are in Annex M.

5.1.3 Step 3: Treatment

– Decide on clinical treatment. According to clinical manifestations and circumstances, the patients could require:

- home treatment (Group A)
- referral to dengue unit for observation and management of the infection and associated disorders (Group B1)
- referral for administration of intravenous fluids in dengue ward or secondary hospital (Group B2)
- emergency treatment, during emergency transfer and referral to a hospital with a higher level of complexity (Group C)

5.2. Treatment according to groups (A, B1, B2, and C)

5.2.1 Group A: Patients who may be treated at home

These are patients who are able to tolerate adequate volumes of oral fluids, have passed urine at least once every six hours in the last 24 hours, and do not warning signs. They have no associated clinical disorders or social risk. Ambulatory patients should be evaluated on a daily basis and should have complete blood count at least every 48 hours, to observe the evolution of the disease 24 to 48 hours after defervescence without taking antipyretics. When fever subsides, check for clinical warning signs (Annex G). Advise patients and caregivers to return immediately to the nearest health care facility if any of the warning signs develops.

What should the patient do?

– bed rest, use of mosquito net during the febrile phase, especially during the day

– regular diet plus abundant fluids

– adults: abundant oral fluids, at least five glasses (250ml each) or more a day, for an average adult weighing 70 kg (119).

– children: abundant oral fluids (milk, natural fruit juice—caution with diabetics), oral rehydration solution (ORS), or recently prepared barley or rice water or coconut water. Plain water should be given with caution, since it may cause hydroelectrolytic imbalance.

– record the prescribed amount: liters in glasses (250 ml), ounces (8.45), or liters (0.25).

- paracetamol:
  - adults: 500 to 750 mg orally every four to six hours, maximum daily dose of 4 g
  - children: 10 mg/kg every six hours.
- tepid sponging of forehead
- recommendations: look for vector (*Aedes aegypti*) breeding sites in and around the home and eliminate them. This task should be monitored by an adult trained in vector control.

What should be avoided?

- Painkillers and anti-inflammatory medications, e.g., NSAIDs (aspirin, methimazole, diclofenac, others) steroids, antibiotics, and oral anticoagulants (16). If the patient is taking any of these medications, evaluate the advisability of continuing such treatment. Intramuscular or rectal administration of medications is contraindicated.

Recommend that if any of the following signs or symptoms appear, the patient should seek medical attention immediately:

- bleeding, petechiae, epistaxis, gingivorrhagia, hematemesis, melena, metrorrhagia, or polymenorrhea
- vomiting
- abdominal pain or tenderness
- drowsiness, mental confusion, fainting, seizures
- pale, cold or moist hands or feet
- respiratory distress

Action plan: provide a card listing home-care provided and results of the monitoring (Annex N)

5.2.2 Group B1: Dengue without warning signs, but with associated disorder or social risk

Group criteria

- Patients in this group have associated diseases or conditions that may complicate dengue or its treatment such as pregnancy, age under 1 year or over 65 years, morbid obesity, hypertension, diabetes mellitus, asthma, renal failure, hemolytic diseases, chronic hepatopathy, peptic ulcer or gastritis of any etiology, use of anticoagulants, etc.
- Social risk: the patient lives alone or far from a health care facility, lacks transportation, or lives in extreme poverty.

- Manage associated conditions and treat dengue according to the protocol; also treat related compensated illnesses (e.g., hypertension, diabetes mellitus, asthma, renal damage, hemolytic diseases, chronic hepatopathy, peptic ulcer, or gastritis), according to the protocols of each country, in dengue units.
- Oral intake should be encouraged. If the patient is not drinking, drinks little, or is dehydrated, intravenous fluids should be started to rehydrate them or keep them hydrated (based on Holliday-Segar formula) with Ringer's lactate or 0.9% normal saline solution at a maintenance dose (2 to 3 ml/kg/hour). Oral treatment should be resumed as soon as possible.

Vital signs will need to be recorded and evaluated (pulse, heart rate, respiration rate, temperature, blood pressure) in addition to evaluating:

– laboratory, according to the type of associated disorder (hematocrit, platelets, leukocytes, glucose, electrolytes, others)
– thermic curve (to detect defervescence)
– volume of fluids ingested or infused, and losses
– urine output (volume, frequency, and time of last voiding)
– warning signs

5.2.3 Group B2: Dengue with warning signs

The main objective is to prevent shock.

Group criteria

This group includes patients who, close to defervescence and ideally at defervescence or in the following hours, present one or more of the following signs (beginning of the critical phase):

– intense and continuous abdominal pain or tenderness
– persistent vomiting
– fluid accumulation in serous cavities (pleural effusion, ascites, pericardial effusion) diagnosed clinically or by imaging
– mucosal bleeding
– hepatomegaly >2 cm
– lethargy, restlessness
– postural hypotension (lipothymia)
– progressively rising hematocrit

Action Plan

Response to dengue with warning signs

- Obtain a complete blood count (hematocrit, platelets and leukocytes) before hydrating the patient. The lack of a hematocrit should not delay initiation of hydration.
- Immediately administer crystalloid solution at 10 ml/kg of bodyweight in the first hour; preferably give balanced electrolyte solutions, such as Ringer's acetate or lactate or 0.9% normal saline solution.
- Strictly monitor vital signs, particularly blood pressure, pulse pressure, MAP, and heart rate.
- Re-evaluate the patient. If clinical improvement is observed and urine output is ≥1 ml/kg/h, the drip will be reduced to 5-7 ml/kg/h, and this dose will be maintained for the following 2 to 4 hours; continue tapering the drip at a rate of 3-5 ml/kg/h for 2 to 4 more hours. If improvement continues, reduce the dose to 2 to 4 ml/kg/h.
- Re-evaluate the patient's clinical and hemodynamic status and repeat hematocrit. Home care may be considered, as long as the patient has been evaluated and improvement is observed along with tolerance to oral intake for 24 hours. In cases where the patient faces some social risk or difficulty in access to health services, it is recommended that the patient remains in the hospital or a dengue unit. If vital signs deteriorate or hematocrit increases rapidly after three loads of 10 ml/kg/h, the case will be managed as if it were severe dengue with shock.

Improvement is indicated by:

- progressive disappearance of warning signs
- progressive remission of general symptoms
- stable vital signs
- normal or increased urine output
- reduction of hematocrit below baseline value in a stable patient
- good tolerance to oral intake
- improved appetite

Follow-up or monitoring by health care workers (nurses/physicians)

Patients with warning signs should be monitored until the risk has passed (48 hours after defervescence). Maintain an appropriate fluid and electrolyte balance.

Evaluate the following parameters

- vital signs (pulse, heart rate, respiration rate, temperature, blood pressure) and peripheral perfusion every hour, until the patient is out of the critical phase (for the first four hours if evolution is satisfactory, then every four hours)
- urine output every hour (for the following four to six hours) and then every four hours

Clinical assessment is critical (vital signs and urine output) as indicated. The following laboratory tests contribute to patient evaluation and monitoring; however, they should never replace clinical monitoring of the patient:

- hematocrit (before and after fluid replacement, then every 12 to 24 hours)
- glucose (before fluid replacement, then every 12 to 24 hours as needed)
- other studies, depending on the organ affected and associated disease

5.2.4 Group C: Severe dengue

In all countries with dengue, medical practice and the most recent medical literature recognize that intravenous rehydration is the most effective treatment for preventing death from plasma leakage during severe dengue (120). There is also consensus that fluid replacement should be initiated as soon as possible in these cases (9, 121).

Results of a systematic analysis of studies on this topic, published between 1999 and 2009 were compatible and consistent with the recommendations of the World Health Organization (1) and the Pan American Health Organization (56) on care of patients with severe dengue with regard to the initiation of treatment with isotonic solutions (e.g., Ringer's lactate or normal saline solution) and using colloid solutions (e.g., dextran or starch) only as a supplement to crystalloid solutions, if necessary (25, 121-130). It is also important to not over-hydrate patients (120).

Studies in this field only refer to the pediatric population and all except one were carried out in Asia. Nor was intravenous fluid therapy studied in patients with co-existing conditions, such as obesity, asthma, diabetes, heart disease, nephropathies, or others, in which the regimen might require different algorithms. More cases of adults with and without co-existing conditions need to be studied, particularly in the countries of Latin America and the Caribbean. The adverse effects of different types of solutions have also not been sufficiently studied, particularly in adults (120).

Appropriate training of medical and paramedic staff in fluid administration is possibly the key to obtaining good results. There is evidence that suggests that reorganization of services to *guarantee immediate rehydration* of patients who need it during epidemic dengue outbreaks can be decisive (131, 132).

With respect to the use of corticoids in the treatment of dengue shock syndrome, a meta-analysis was published in 2014 on eight clinical trials also done in pediatric populations (18, 133-139). It did not find a reduction in mortality (relative risk [RR] = 0.68; 95% confidence interval [CI] = 0.42–1.11), need for transfusions (RR = 1.08; 95% CI = 0.52–2.24 risk of pulmonary hemorrhage (RR = 0.97; 95% CI = 0.06–14.82), or risk of seizures (RR 6.79; CI = 95% 0.36–126.24) in patients treated with corticoids compared to those who received placebo. However, the intervention group had an average of 1.1 more inpatient days (12).

To date, no antiviral medication of demonstrated efficacy exists against dengue, although several research projects are currently underway that address this issue (16, 140).

5.2.5 Treatment of dengue shock

It is recommended to initiate intravenous rehydration with crystalloid solution at a rate of 20 ml/kg of bodyweight infused in 15 to 30 minutes. The patient's progress needs to be observed: if signs of shock disappear, reduce fluid volume to 10 ml/kg per hour, for one to two hours, constantly monitoring the patient's hemodynamic condition by repeatedly taking the abovementioned vital signs. Repeat the hematocrit. In adults, intravenous rehydration is done in accordance with hemodynamic status using MAP and heart rate, to prevent fluid overload or insufficient hydration (1, 141).

If the clinical course is satisfactory and the second hematocrit is lower than the first one, reduce the volume of hydration fluid to 5 to 7 ml/kg per hour, for 4 to 6 hours; from then on, maintain hydration, based on the patient's hemodynamic status.

- If, on the contrary, after the first rehydration bolus[1] the patient continues to show signs of shock, it will be necessary to repeat the crystalloid volume dose at a rate of 20 ml/kg, infused in 15 to 30 minutes. Reevaluate the patient's hemodynamic condition and take a new hematocrit sample. If, with this volume of fluids, the patient improves, shock disappears, and hematocrit declines, continue fluids, as previously mentioned with regard to the patient with a favorable course.
- If, after having administered two boluses of intravenous crystalloids, the patient continues to be unstable and hematocrit continues to be high compared to baseline, administer a third bolus of crystalloids at the same dose and speed as the previous one. If, with that third administration, the patient shows clinical improvement, taper IV fluid therapy volume, as previously mentioned.
- If the patient continues to have unstable vital signs (persistent shock) and hematocrit remains high compared to baseline, despite treatment with crystalloids in the abovementioned dose, it is time to weigh the exceptional

[1] A bolus is the volume administered in <30 minutes. A load is the volume administered in 30 to 60 minutes.

administration of a colloid solution at a rate of 10 to 20 ml/kg infused in 30 to 60 minutes.

- After that dose, the patient is evaluated again. If clinical improvement is observed and hematocrit drops, crystalloid solution is administered at a rate of 10 ml/kg/h, for one to two hours, and then tapering continues, based on the patient's progress.
- If the patient does not improve, a second dose of colloids is administered, at a rate of 10 to 20 ml/kg in one hour.
- If the patient does not improve, re-evaluate the patient's hemodynamic condition (vital signs and urine output), for which the following should be done:
  - Determine pumping function (myocardiopathy, myocarditis) and amine use;
  - Evaluate co-existing medical conditions (heart disease, pneumopathy, vasculopathy, nephropathy, diabetes, obesity, complicated pregnancy) and try, to the extent possible, to stabilize the baseline condition;
  - Evaluate persistent acidosis and risk of (occult) bleeding and treat them;
  - If other boluses of hydrating solution are needed during the next 24 hours, the speed and volume of each bolus will depend on the clinical response. Patients with severe dengue should be admitted, preferably, to an intensive care unit with trained physicians and nurses and where use of the dengue protocol has been accepted.

Annex O explains the choice of intravenous fluids for resuscitation. Calculation of fluids for maintenance of normal weight patients is in Annex P and calculation of fluid needs for children and adults are detailed in Annex Q. For overweight or obese patients, fluids need to be calculated on the basis of estimated ideal weight (Annexes R and S).

If a sudden drop in hematocrit is not accompanied by the patient's improvement, this indicates possible major bleeding and the need to cross-match and transfuse packed red blood cells (5 to 10 mL/kg), repeating volumes based on the patient's progress (see Section 6.2.4.2, below).

Furthermore, it is necessary to evaluate the patient's coagulation function (prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen). If fibrinogen is less than 100 mg/dl, transfusion 0.15 U/kg of cryoprecipitates (1 U/10 kg) should be prioritized. If fibrinogen is >100 mg and PT and aPTT are more than 1.5 times the standard reference values, consider transfusion of frozen fresh plasma (10 ml/kg) in 30 minutes.

Consider platelet transfusion (142) in case of:

- persistent uncontrolled bleeding after the state of shock, with corrected coagulation factors and with thrombocytopenia and prolonged bleeding time1.5 times above normal (Annex T)

– caesarean section or other emergency surgery with risk of bleeding, the platelet count should be >50,000 mm3; and in eye surgery and neurosurgery, the platelet count should be >100,000 mm3.

5.2.6 Treatment of hemorrhagic complications

Mucosal bleeding may occur in any dengue case, but if the patient remains stable with fluid resuscitation, the case should be considered low-risk bleeding. The bleeding usually improves rapidly during the recovery phase. In dengue, thrombocytopenia is not necessarily a factor in bleeding and the prophylactic use of platelets is not indicated, since the usefulness of transfusing them in these circumstances has not been proven (142-145). If bleeding has already occurred, the decision to transfuse platelets should always be based on the clinical manifestations and particular situation of each patient and not justified by a low platelet count alone. It should be recalled that bleeding in dengue is multicausal and not exclusively from thrombocytopenia (146).

Patients with profound thrombocytopenia, whose platelet count can drop to less than 10,000 mm3, must adhere to strict bed rest, and be protected from trauma and risk of bleeding. Do not administer intramuscular injections to avoid hematomas. Bear in mind that thrombocytopenia in dengue is transitory and self-limited and does not require administration of corticoids or any other medication (16). No differences have been found in platelet counts following treatment with high doses of intravenous immunoglobulin, in duration of thrombocytopenia, or in antiplatelet antibody levels (147). With frozen fresh plasma, a higher platelet count was obtained than with normal saline solution at 12 hours after treatment, but that effect was not well maintained at 24 and 48 hours (148).

If major bleeding occurs, it is usually from the gastrointestinal tract, or transvaginal in adult women. Bleeding from the upper gastrointestinal tract may not be apparent for many hours, until the first black stool or melena is passed. Pulmonary or intracranial bleeding may also occur, both with poor prognosis because they can constitute the beginning of the final phase for the patient. It should be emphasized that most of the time large hemorrhages develop during or after shock, which means that preventing shock or treating it effectively and early on prevents complications of this nature.

Patients at risk of severe bleeding are those who:

– have prolonged or refractory shock
– have hypotensive shock and renal or liver failure or severe and persistent metabolic acidosis
– are given non-steroidal anti-inflammatory agents
– have preexisting peptic-ulcer disease

– are on anticoagulant therapy
– have any form of trauma, including intramuscular injection

Dengue patients who have an underlying hemolytic condition are at risk of acute hemolysis with hemoglobinuria and may require blood transfusion. Patients with sickle-cell anemia who contract dengue may have a very slow-healing or fatal course (149).

Severe bleeding can be recognized by:

– persistent bleeding, in the presence of unstable hemodynamic status, regardless of the hematocrit level
– a decrease in hematocrit after fluid resuscitation together with unstable hemodynamic status
– refractory shock that fails to respond to consecutive fluid resuscitation of 60 ml/kg
– shock with decrease in baseline hematocrit before fluid resuscitation

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized (150, 151). However, blood transfusion must be given with care because of the risk of fluid overload. Packed red blood cells are currently recommended over whole blood (150, 151). Furthermore, do not wait for hematocrit to drop severely before transfusing blood. Note that hematocrit of <30% as a trigger for blood transfusion, as recommended by international standards for management of severe sepsis, is not applicable to severe dengue (152). The reason for this is that, in dengue, bleeding usually occurs after a period of prolonged shock that is preceded by plasma leakage, during which hematocrit levels increases before the onset of severe bleeding. When bleeding occurs, hematocrit drops and, as a result, its level may not to be as low as in the absence of plasma leakage. For this reason, it can be dangerous to wait for the hemoglobin of a dengue patient to drop to 7 g/dl before prescribing red blood cell transfusion, as some clinical researchers recommend for other situations unrelated to dengue (153).

Administration of recombinant factor VII has shown improvement in bleeding two hours after its use, but its efficacy was not statistically significant at 6, 12, and 24 hours after treatment with respect to the control group (placebo) (154).

Precautions must be taken when inserting a nasogastric tube, which may cause severe hemorrhage and block the airway; it is preferable to use an orogastric tube. If bladder catheterization is needed, a well-lubricated tube minimizes trauma during insertion. When central venous pressure evaluation is required, inserting a femoral or peripheral catheter is recommended. Insertion of subclavian or jugular catheters should be avoided as far as possible, as well as invasive procedures to drain volumes of leaked plasma.

5.2.7 Treatment of fluid overload

Fluid overload, with large pleural effusions and ascites, is a common cause of acute respiratory failure in severe dengue. Other causes include acute pulmonary edema, severe metabolic acidosis from severe shock, and acute respiratory distress syndrome.

Causes of fluid overload are:

- excessive or rapid intravenous fluids without constant evaluation of hemodynamic status, especially in adult patients
- incorrect use of hypotonic polyelectrolyte solutions rather than isotonic
- administration of large volumes of intravenous fluids in patients with unrecognized severe bleeding
- inappropriate transfusion of fresh plasma or colloidal solutions
- administration of intravenous fluids after plasma leakage has resolved (24 to 48 hours from defervescence)
- presence of co-existing diseases
- in some patients, dengue affects renal function, manifested by difficulties in fluid reabsorption in the distal tubule, glomerular function alterations, or both (155). In a study of dengue patients, it was demonstrated that the application of non-invasive methods such as bioelectrical impedance spectrometry lead to: a) an increase in the extracellular/intracellular water ratio 48 hours after defervescence, higher when the dengue clinical manifestations are more severe, and b) expansion of the extracellular space in severe dengue seems to be mainly due to the reduction in renal clearance (156).

Early clinical features of fluid overload are difficulty breathing, rapid breathing, chest wall indrawing, crackles and wheezing, large pleural effusions, tense ascites, jugular engorgement, and increasing MAP and tachycardia. Late clinical features are acute pulmonary edema and irreversible shock (heart failure, often in combination with hypovolemia).

Additional investigations: chest x-ray, electrocardiogram, arterial blood gases, echocardiogram, and cardiac enzymes.

Action plan for the treatment of fluid overload:

- Oxygen therapy should be given immediately.
- Suspension of intravenous fluid therapy during the recovery phase will allow leaked fluid to return to the intravascular compartment. This results in diuresis and resolution of pleural effusion and ascites. Recognizing when to stop administration of intravenous fluids is key to preventing fluid overload, as well as constant hemodynamic evaluation (blood pressure, pulse pressure, MAP,

heart rate) of the patient who is receiving large quantities of intravenous fluids. Intravenous fluids should be discontinued or reduced to the minimum rate if:

- plasma leakage has ceased;
- blood pressure, pulse, and peripheral perfusion are normal;
- hematocrit decreases and MAP and pulse pressure are normal;
- there has been no fever for more than 24 to 48 hours (without the use of antipyretics);
- abdominal symptoms have resolved; and
- urine output is adequate.

The management of fluid overload varies according to the phase of the disease and the patient's hemodynamic status. If the patient has stable hemodynamic status and is out of the critical phase (after 24 to 48 hours of defervescence), stop intravenous fluids and continue strict monitoring. If necessary, administer furosemide, according to the patient's condition. Monitor serum potassium and correct it if hypokalemia ensues.

If the patient has stable hemodynamic status but is still in the critical phase, reduce the intravenous fluid accordingly. Avoid diuretics during the plasma leakage phase, because they may lead to intravascular volume depletion.

Patients who remain in shock with low or normal hematocrit levels, but show signs of fluid overload may have occult hemorrhage. Further infusion of large volumes of intravenous fluids will only lead to poor outcomes.

5.2.8 Other complications of dengue

Hyperglycemia or hypoglycemia may occur in patients with dengue, even in the absence of diabetes mellitus or hypoglycemic agents (157). Electrolyte changes and acid-base imbalances are also frequently observed in severe dengue cases and are probably related to gastrointestinal losses through vomiting and diarrhea or as consequence of the incorrect use of hypotonic solutions to resuscitate the patient and correct dehydration. Hyponatremia, hypokalemia, hyperkalemia, hypomagnesemia, serum calcium imbalances, and metabolic acidosis can occur. Also be alert for co-infections and nosocomial infections.

5.3. Supportive care and adjuvant therapy

Supportive care and adjuvant therapy may be necessary in severe dengue cases. This may include:

– treatment with inotropic and vasopress medications (Annex U)

– dialysis, preferably hemodialysis, since peritoneal dialysis has a risk of bleeding. If this is not possible, some specialists consider that peritoneal dialysis should be started, preferable at the end of the critical phase.

– particular and specific treatment of organ impairment as established for each of these complications, such as severe liver failure, encephalopathy, or encephalitis; cardiac abnormalities, such as conduction disorders; and contractility disorders from myocarditis or myocardiopathy, among others. Trials involving corticoid use in the initial stages of dengue complications have been performed, but conclusive results of their efficacy are not yet available (12, 17), along with the use of chloroquine and other immunomodulatory medications, such as statins.

5.4. Dengue intervention and care algorithm

The following figure illustrates the algorithm for the care of clinical cases of dengue, based on severity classification.

Dengue: clinical definitions, categories for case intervention and management

Clinical definitions

Suspected dengue case: a person who lives in or has traveled to areas with dengue transmission in the last 14 days and presents acute fever, usually from 2 to 7 days duration, and two or more of the following manifestations: nausea/vomiting, rash, headache/retro-orbital pain, myalgia and arthralgia, petechiae or positive tourniquet test (+), leukopenia, with or without any warning sign or sign of severity.

Any child who resides or has traveled in the last 14 days to an area with dengue transmission that presents acute fever, usually from 2 to 7 days duration, with signs of a neurological focus is also considered a suspected case.

Ask: Does the patient have any warning sign or sign of severity?

- **No** → Dengue without warning signs (DNWS)
  - Ask: Are there co-existing conditions or social risk?
    - **No** → **Intervention Category A**: Minimal care at home by the family, evaluation every 24-48 hours by health care workers in dengue units in the primary care level.
    - **Yes** → **Intervention Category B1**: Minimal care supervised by health care workers. Admit to dengue units in the first and second levels of care during the morning shift, while fever lasts and up to 48 hours after defervescence.
- **Yes** → Dengue with warning signs (DWWS) → **Intervention Category B2**: Intermediate care and hourly evaluation by qualified health care workers in dengue units located in the three levels of care, preferably in basic and second level hospitals.
- **Yes** → Severe dengue (SD) → **Intervention Category C**: Minute-by-minute evaluation by highly qualified personnel. Stabilize where diagnosis is made and continue treatment during transfer to a hospital of higher complexity.

Intervention categories

Every patient classified as DWWS or SD requires strict observation and immediate medical treatment.

Intervention category A - DNWS	
Case management	**Group criteria** – patient without warning signs – no co-existing conditions – no social risk – fully able to tolerate oral route – normal urination in the last 6 hours
	Laboratory tests – complete blood count at least every 48 hours (hematocrit, platelets, and leukocytes) – IgM five days or more after the onset of the illness
	Treatment – bed rest – strict use of mosquito net during febrile phase – adequate fluid intake **adults: five glasses of ≥250 ml** **children: abundant oral fluids** – paracetamol **adults: 500 mg/dose every 6 hours; maximum dose daily: 4 g** **children: 10mg/kg/dose every 6 hours** – do not give aspirin or NSAIDs – do not give corticoids – do not give antibiotics – intramuscular or rectal administration contraindicated – always accompanied by an adult trained in dengue management – patients with stable hematocrit can continue home care
	Monitoring appointments **Evaluate immediately if:** – a warning or shock sign develops – hospitalization criteria develop (see Annex F) – patient does not urinate for 6 or more hours – patient or patient's attendant indicates that patient feels worse **Evaluate every 48 hours in the absence of the above points** **What needs to be evaluated at each monitoring appointment** – course of the disease – hematocrit, as soon as report is available (observe whether it is progressively increasing) – if illness continues to be active (platelets continue to drop) – leukopenia – recognize warning signs, if any **Monitoring appointments should also:** – emphasize to the patient or the person in charge of patient's care to return urgently to the dengue unit or hospital if one or more of warning signs develop – provide a written list of the care the patient needs at home **Notify epidemiology within 24 hours.**

Intervention category B1 - DNWS and associated conditions	
Case management	**Associated conditions:** pregnancy, children <1 year of age, older adult >65 years of age, morbid obesity, hypertension, diabetes mellitus, renal damage, hemolytic diseases, chronic hepatopathy, patient receiving anticoagulant therapy, among others. **Social risk:** lives alone or far from a health care facility, lacks transportation, or lives in extreme poverty.
	Laboratory tests – complete blood count within three days of onset of illness – IgM five days or more after onset of illness
	Treatment – Keep patient hydrated orally. In case of intolerance to oral route, start intravenous therapy with crystalloid (Ringer's lactate or saline solution (0.9%) at dose maintenance: (2 to 4 mL/kg/hour) and restart oral route as soon as possible. – Treat symptoms the same as in Group A. **The patient will also:** – make strict use of mosquito net during febrile phase – receive the same information as Group A **Provide specific supervised care for associated conditions** **Monitor/evaluate** – vital signs: pulse, heart rate, respiration rate, temperature, blood pressure – thermic curve – fluid balance: intake and output (report how often patient urinates) – warning signs (mainly on day of defervescence) – laboratory: according to the type of associated condition (hematocrit, leukocytes, glucose, electrolytes, among others). – hematocrit, platelets, and leukocyte count every 24 at 48 hours – education on warning signs **Monitoring appointments** – See Group A.
	Hospital referral criteria (see more details in Annex F) – presence of any warning sign – presence of any sign or symptom related to plasma leakage (possible hypotension) – spontaneous bleeding – any proof of organ impairment – presence of co-existing illness (complicated pregnancy, co-existing infection) **Notify epidemiology within 24 hours.**

Intervention category B2 - DWWS	
Case management	**Group criteria** Every dengue case that develops one or more of the following signs or symptoms near or preferably at defervescence: – intense abdominal pain or tenderness – persistent vomiting – fluid accumulation (ascites, pleural or pericardial effusion) – mucosal bleeding – lethargy/restlessness/irritability – postural hypotension (lipothymia) – hepatomegaly >2 cm – progressive increase in hematocrit
	Laboratory tests – complete blood count before hydrating patient – specimen for RT-PCR, NS1, IgM, and IgG at first contact. Repeat IgM, IgG from 10 to 14 days after first specimen, if none of the viral tests were positive
	Treatment **Lack of a hematocrit should not delay start of hydration.** – Administer Ringer's lactate or Hartmann's or 0.9% saline solution: 10 ml/kg in 1 hr. – Reevaluate: if warning signs persist and urine output is <1 mL/kg/h, repeat load with isotonic crystalloids once or twice. – Reevaluate: if clinical improvement is observed and urine output is ≥1 mL/kg/hr, reduce drip to 5-7 mL/kg/hr and continue for 2 to 4 hrs. If clinical improvement continues, reduce to 3-5 mL/kg/hr for 2 to 4 hrs. Then continue the drip at a rate of 2-4 mL/kg/hr for 2 to 4 hrs according to the patient's needs. – Reevaluate patient's clinical status. Repeat hematocrit and, if it continues unchanged or increases minimally, continue the drip at a rate of 2-4 mL/kg/hr for 2 to 4 hrs. – If vital signs deteriorate or hematocrit increases rapidly: treat as Group C and refer to the next level of care. – Reevaluate patient's clinical status, repeat hematocrit, and change fluid infusion velocity. – Gradually reduce fluid velocity when the volume of plasma leakage drops or critical phase ends. **Criteria for clinical improvement** – progressive disappearance of warning signs – progressive remission of overall symptoms – stable vital signs – normal or increased urine output – reduction of hematocrit to less than baseline value in a stable patient – good tolerance of oral route – recovery of appetite **Hourly evaluation of:** – vital signs and peripheral perfusion up to 4 hrs after critical phase ends – urine output up to 4 to 6 hrs after critical phase ends – hematocrit before and after fluid resuscitation, then every 12 to 24 hrs – blood glucose every 12 or 24 hrs – other tests (according to affected organ and associated disease) **Notify epidemiology within 24 hours.**

Intervention category C - SD

Case management

Group criteria

Every dengue case that has one or more of the following manifestations:

1) Shock or respiratory distress due to severe plasma leakage. Evident shock by: weak or undetectable pulse, tachycardia, cold extremities, and capillary refill time >2 seconds, pulse pressure ≤20 mmHg: hypotension in late phase.
2) Severe bleeding: according to the evaluation by the attending physician (e.g., hematemesis, melena, ample metrorrhagia, and central nervous system bleeding).
3) Severe organ impairment: such as liver damage (AST or ALT ≥1000 IU), central nervous system (change in mental state), heart (myocarditis), or other organs

Laboratory tests

Complete blood count, RT-PCR or NS1 (first four days of illness) and IgM/IgG (five days or more after the onset of illness). If RT-PCR or NS1 test results are negative, repeat IgM and IgG 14 to 21 days after first test. Other tests according to affected organ; e.g., transaminases, arterial blood gases, electrolytes, blood glucose, blood urea nitrogen and creatinine, cardiac enzymes, cultures, chest x-ray, chest or abdominal ultrasonography or both, echocardiogram, electrocardiogram

Treatment of shock

Obtain a hematocrit before hydrating patient; lack of hematocrit should not delay start of hydration.

- monitor ABC and vital signs every 5 to 30 min
- oxygen therapy
- initiate intravenous fluid therapy with crystalloids (Ringer's lactate or 0.9%saline solution) at 20 mL/kg in 15 to 30 min (in pregnant women and older adults >65 years of age boluses are administered at 10 mL/kg in 15 to 30 min).
- If signs of shock disappear, decrease fluid volume to 10 mL/kg/hr; continue for 1 to 2 hrs. Repeat hematocrit.
- If progress is satisfactory, decrease drip to a rate of 5-7 mL/kg/hr, for 4 to 6 hrs; continue at a rate of 3-5 mL/kg/hr for 2 to 4 hrs, then maintain at 2-4 mL/kg/hr, for 24 to 48 hrs.
- If there is no improvement, administer a second bolus with Ringer's lactate or 0.9% saline solution at 20 mL/kg in 15 to 30 min (in pregnant woman and older adults >65 years of age, 10 mL/kg). If there is improvement, decrease drip to 10 mL/kg/hr and continue for 1 to 2 hrs. If improvement continues, decrease drip to 5-7 mL/kg/hr, for 4 to 6 hrs and continue hydration as mentioned above.
- If there is no improvement, repeat a third bolus with Ringer's lactate or 0.9% saline solution at 20 mL/kg in 15 to 30 min.
- If there is improvement, decrease drip to 10 mL/kg/hr and continue drip for 1 to 2 hrs. If improvement continues, decrease drip to 5-7 mL/kg/hr, for 4 to 6 hrs and continue hydration as mentioned above.
- Repeat hematocrit. If it continues high compared to baseline, crystalloids can be continued, or change IV solution to colloid. Reevaluate after resuscitation. If improvement is observed, change to crystalloid solution 10 mL/kg/hr, for 1 to 2 hrs and continue tapering drip as mentioned above.
- If patient continues in shock, give colloid for the second time in the same dose for the abovementioned time. Continue with crystalloids, as previously indicated.
- If patient continues to be unstable, review hematocrit taken after any previous bolus. Hematocrit that has declined abruptly and hemodynamic instability suggest bleeding and the urgent need for cross-matching and transfusion of blood or blood products immediately.

Intervention category C - SD (Continued)	
Case management	Treatment of bleeding: red blood cells 5-10 ml/kg or fresh blood at 10-20 ml/kg. – If patient does not improve, evaluate hemodynamic status again. – Evaluate pump function (myocardiopathy, myocarditis) determine use of amines. – Evaluate concomitant medical conditions (heart disease, pneumopathy, vasculopathy, nephropathy, diabetes, obesity, pregnancy). Stabilize underlying disorder. – Assess persistent acidosis and risk of occult bleeding and treat them. **Notify epidemiology within 24 hours.**

Discharge criteria for categories B1, B2, and C (Annex G)

All these criteria should be met at the same time:

- absence of fever for 48 hours, without administration of antipyretics
- improvement of clinical status
  - general well-being
  - good appetite
  - normal hemodynamic status
  - normal or increased urine output
  - no respiratory distress
  - no evidence of bleeding
- increasing trend for platelet count
- stable hematocrit without administration of intravenous fluids

6. GUIDELINES FOR ORGANIZATION OF HEALTH SERVICES IN A DENGUE OUTBREAK OR EPIDEMIC

Introduction

Each country, region, or city should have developed and be in the process of implementing a dengue prevention and control program that includes each of the components in the Integrated Management Strategy for Dengue Prevention and Control (IMS-Dengue) (158). Its main objectives are to prevent the transmission of the disease; achieve epidemiological surveillance in which other types of surveillance come together harmoniously (virological, serological, clinical, entomological, and environmental); train human resources; and have contingency plans to reorganize health systems in each location that can be put into place as soon as an epidemic outbreak begins (159). The contingency plan should include medical care, laboratories, availability of funds to purchase equipment and reagents and contract supplementary resources, agreements with other institutions that provide medical care to increase the number of inpatient beds, if necessary. In general, everything that is needed to reach the main goal: prevent deaths from dengue (160).

This chapter is about the reorganization of health services during emergencies. It is based to a great extent on the document "*Diretrizes para a organização dos serviços de atenção à saúde em situação de aumento de casos ou de epidemia de dengue–2011*" (161), which was adapted to generalize it and make it applicable in the countries of Latin America, with changes tailored to each location.

Dengue is a complex problem that demands human, financial, and infrastructure resources in the main urban health care centers. The main objective of the guidelines for the prevention and control of dengue epidemics are to prevent deaths, as well as to prevent and control epidemics. To achieve these results, it is necessary to promote timely and proper patient care, organize the prevention and control functions, and strengthen coordination among different areas and services.

To reduce dengue mortality, early recognition of suspected cases is required and the correct management of patients according to the clinical protocol recommended in the PAHO guidelines for the care of patients with dengue in the Region of the Americas (56).

A recent evaluation by the Ministry of Health of Brazil with the support of state and municipal health departments, attempted to determine the factors related to dengue mortality, as well as patient access to the health care services network, the quality of care given to patients with suspected dengue, and the organization of patient care services. With regard to the organization of health services, it was confirmed that inputs, equipment, medications, and tests did not constitute a problem for the quality of care. However, wait times and logistical support for

obtaining laboratory test results, bed availability, lack of accuracy in the flow of patients to referral and counter-referral units, and limited use of the monitoring card for patients with suspected dengue may have contributed to negative outcomes in such cases (162).

These observations emphasize the need for organizing the services network in all areas of care, as well as providing ongoing training for health care professionals, working on the relevant ongoing accreditation, and integrating dengue surveillance into primary health care. According to Dr. Eric Martínez, "preparing health services to adequately take care of patients and prevent deaths is as important as preventing dengue transmission. We should aspire to not have epidemics, but if they do occur, it is necessary to prevent deaths. A good health manager is capable of saving more lives during a dengue epidemic than physicians" (91).

With the publication of these guidelines for the organization of health services in dengue epidemic situations, PAHO aspires to help countries organize those services and reduce dengue mortality.

Background

In most cases, caring for dengue patients does not require highly complex and costly technology or facilities. However, an opportune approach, correct case classification, and case management are critical elements of care to prevent deaths of severe cases.

To that end, the health care team should be sensitized and trained to adopt measures for patient surveillance at home, detect cases through home visits, and provide health care services as part of primary care, in dengue units, emergency services, hospital wards, and intensive care units (ICUs). Therefore, patient intake and classification according to the risk of severity should be undertaken at all the first points of contact the patients have with health care services. These will also have to conduct triage to reduce wait times and improve the quality of care. This approach to patients and their classification requires techniques for care and clinical and laboratory investigation that are accessible to all points of care.

Access to flow charts (widely distributed by health services directors), supplies, clinical and laboratory tests, early hydration, and patient support are essential components to the successful evolution of cases. Furthermore, they guarantee good care for patients classified into groups A (dengue without warning signs) and B2 (dengue with warning signs). Cases classified into group C (severe dengue) require more complex and costly services; however, if diagnosis is done early and timely, complications of dengue will be less frequent and burdensome. Up to 90% of cases can be resolved in primary care services, in coordination with other care settings, including private services. In this regard, management capacity is essential to link services in a single network, with guaranteed access, monitoring, and quality of

care. The regulatory function should be present in health centers, either through the central adjustment device or as defined in the emergency protocol for this purpose. The protocol includes competencies and the classification of risk for cases and ensures timely referral of patients (to dengue units at the first level of care, emergency units, hospital wards, or ICU beds).

Service management and organization should ensure information, records, and proper notification of all cases treated. In addition to serving other purposes, the information provides data to estimate the need for equipment, materials, and medications, and for gauging work services. Proper records also facilitate monitoring of suspected dengue cases in different care settings. The foregoing also applies to private health care services, which will have to adopt measures to ensure the use of official care guidelines provided by the ministries of health.

Health teams should ensure participation of their members in training and implementation of official protocols. Dengue contingency plans should be developed in advance to face situations efficiently and effectively. Lack of planning leads to exceptional situations which, in most cases, will require new ways of organizing services to solve problems involving the timeframes and legalities required by procurement and contracting. Consequently, it is necessary to have a legal and management structure that establishes measures that ensure the care of users. The process of organizing services for crisis situations—in a planned manner—requires the coordinated management of health care services. It also requires collaboration among the people in charge of the health services in different areas of the health care system (primary care, specialized care, emergency care, hospital care, and regulation). As a result, there will have to be a coordinator, appointed by the respective director, who has the required skills and delegation of power that the role requires.

6.1. Primary care

6.1.1 Organization of work

If no professional is assigned, it is recommended that a professional who knows all the organization's processes for care and support is delegated to coordinate the activities. This professional would also be the focal point for the team and maintain relations with other services.

In epidemic situations, expansion of access to primary care is essential, since this will make it possible to have higher-level units available for referred patients in need of closer observation and hospitalization. To this end, the following should be taken into account:

– proximity to involved areas and predictions of greater demand, depending on what the epidemiological situation indicates

- working hours and performance
- physical space and availability of materials
- existing and needed equipment
- characteristics of the demand
- patient monitoring and support

To ensure timely care, it may be necessary to suspend regularly scheduled activities, for which it is recommended to:

- Redefine the organization of services in relation to care for acute cases.
- Receive, classify, and attend patients, according to the dengue flow chart.
- Assign health professionals to the waiting room who can, beyond offering early hydration, observe patients to detect warning signs or signs of severity and recognize those who are worsening.
- Expand and strengthen the team with general practitioners, internists, pediatricians, nursing staff, and other health professionals.
- Extend the unit's hours of operation (to 12 to 24 hours, if possible), including weekends and holidays, to prevent overcrowding in hospital emergency units.
- Estimate the number of necessary units and their location, in accordance with local conditions and the risk situation.
- Strictly follow the guidelines for diagnosis, treatment, prevention, and control approved by the corresponding national health authority, based on PAHO and WHO recommendations.
- Report every suspected case to authorities in charge of surveillance.
- Provide all health care professionals with the flow chart for classification and management of patients with suspected dengue and monitoring cards for outpatients with suspected dengue.
- Schedule the patient's follow-up visits during the first visit.
- Carry out an active search for people with an epidemiological link to the unit's catchment area (look for new cases and patients who miss their scheduled appointments).
- Ensure appropriate transportation of patients during the hours that primary care units are open.
- Ensure direct communication with the spokesperson to clarify specific situations and discuss cases (hospitals, dengue units).
- Set up a situation room for reporting suspected dengue cases and establish a daily flow of information for epidemiological surveillance. Severe cases must be immediately reported (telephone, fax, spreadsheets).

6.1.2 Service structure

a) Setting (according to local conditions)

- patient intake and registration
- patient classification, adequate space
- waiting room
- examining room(s)
- room for oral rehydration (or appropriate space)
- additional physical space for observation
- bathrooms

b) Supplies

- chairs
- recliners (if the unit provides hydration over a longer period)
- water fountains (drinking water)
- availability of hydration fluid
- stretchers (only for patients awaiting transfer)
- oxygen cylinders
- glucometer
- telephone, fax
- scales (adult and pediatric)
- oxygen masks
- negatoscope (if possible)
- thermometers
- sphygmomanometer for adults and children (with age-appropriate cuffs)
- covered containers for waste or refuse
- paper towels
- pitchers and glasses to administer electrolytic hydration solutions available in the waiting room and oral rehydration room
- appointment cards for follow-up appointments for patients with dengue
- intravenous infusion supplies (stands, hydration fluids, needles in several gauges, disposables, syringes, cotton, adhesive tape, alcohol)
- gowns, gloves, masks, caps

– hygiene and cleaning supplies
– office supplies

c) Medications

– oral rehydration salts
– paracetamol (drops, syrup, and tablets)
– isotonic solutions for intravenous administration (Hartmann's, Ringer's lactate, 0.9% saline) for immediate replenishment while patient is transferred to a unit of higher complexity

6.1.3 Diagnostic support

a) Essential tests (misnamed "routine"): complete blood count (platelet and leukocyte count, hematocrit, hemoglobin). Aim to have these results delivered in a maximum of two hours. Other tests: according to patient's clinical condition and the health care unit's potential. If needed and not available in the unit, ensure appropriate transportation to the location where they can be performed.

b) Receive test results by fax, e-mail or other online means.

c) Guarantee the collection and shipment of serology samples (IgM/IgG) as established in the epidemiological surveillance guidelines (collect samples at the right time, six days or more after the onset of symptoms) and according to the epidemiological situation and criteria established by the health authorities from:

- 100% of cases hospitalized with first and second samples
- 100% of deaths from dengue
- 10% of suspected cases with 6 to 21 days duration, during the outbreak in affected localities[2]
- 100% of first suspected cases in places where circulation of the dengue virus has not been confirmed, until outbreak has been documented

Furthermore, aim to:

– Test samples from a number of suspected cases with 1 to 4 days duration (by RT-PCR, following coordination with the laboratory that has the capability to perform this test) in places with outbreaks to document the circulating dengue virus serotype and alert to the entry of a new serotype.
– Process samples and communicate results using established channels.
– Include ongoing participation of the laboratory in national, regional, and local commissions for continuous analysis of information that guides timely decision-making.

[2] This percentage will be adjusted based on analysis of the epidemiological situation and availability of resources.

– Carry out appropriate national and international coordination for additional tests to support differential diagnosis, when necessary.

6.2. Emergency units

6.2.1 Organization of care

Care provided in this type of unit should not be a risk factor for patients. On the contrary, it must ensure their observation, from first contact with the service until discharge; due to the potential for rapid progression to severe disease and complications from dengue, particularly at the end of the febrile phase or defervescence. In this regard, patient intake and care in emergency units should be differentiated and include mechanisms to ensure minimal wait times, immediate hydration (availability of oral fluids in the waiting room) and constant monitoring before and after being evaluated by medical or nursing personnel. Change-of-shift reporting should include a thorough description of the case and be done in-person between clinicians; this description must also be documented in the medical record.

The following are recommendations for emergency units:

– See the patient and classify overall and dengue risk: presence of a clinician in the waiting room, who, in addition to offering early hydration, knows the warning signs or signs of severity and can detect them while waiting.

– Reinforce and strengthen the medical and nursing team.

– Expand the physical waiting areas, before and after care.

– Strictly follow the guidelines for organization of services during epidemic dengue outbreaks and patient care: "Dengue: diagnosis and clinical handling: Adult and Child" (up-to-date).

– Establish a specific patient flow of first consultation and subsequent visits to ensure necessary return and follow-up visits (maintain direct communication with the primary care unit to orient patients and those responsible for their care).

– Increase the number of beds for temporary admission or observation and ensure medical and nursing observation to detect warning signs or signs of severity in time and initiate treatment.

– Ensure adequate transportation of patients.

– Provide all health care service providers with a flow chart for risk classification and management of suspected dengue cases, as well as a reporting form for suspected dengue case (and place posters in places with good visibility within the unit).

– Ensure direct communication with the healthcare unit that has been previously assigned to receive referred patients or with the central control unit indicated

in the regulations of the corresponding level.

– Ensure direct communication with the receiving clinician to clarify specific issues and discuss cases.

– Establish a situation room or join one online.

6.2.2 Organization of work

Beyond its existing structure, the emergency unit should have oral rehydration fluids, solutions for intravenous replacement of plasma volume, and epidemiological forms to monitor patients with dengue. Recliners or other furniture will be necessary for intravenous fluid therapy of patients.

6.2.3 Diagnostic support

a) Essential ("routine") tests: complete blood count (platelet and leukocyte count, hematocrit, and hemoglobin). Aim to have these results delivered in a maximum of two hours.

Other tests: according to patient's clinical condition and the potential of the healthcare unit. If needed and not available in the unit, ensure transportation to the location where they can be performed.

b) Specific tests:

- Collection and shipment of serology samples (IgM/IgG) as stablished in the epidemiological surveillance guidelines (collect samples at the right time, six days or more after the onset of symptoms) and according to the epidemiological situation and criteria established by the health authorities.
- Process samples and communicate results using established channels.
- Ongoing participation of the laboratory in national, regional, and local commissions for continuous analysis of information that guides timely decision-making.

6.3. Dengue units

6.3.1 Features of care

These are *provisional facilities* that can be set up in any physical space with adequate conditions for providing care and ensuring patient and staff safety (an already existing unit or service, now repurposed). These will be the referral units designated for patient hydration, particularly patients needing intravenous administration (maximum of 24 hours): time necessary for hemodynamic stabilization or referral to a unit of higher complexity. The decision to refer should take no longer than the absolute minimum time to recognize that the patient needs care from a unit of higher complexity.

Care recommendations for emergency units apply to these provisional units, because patients require greater observation of their clinical course. A coordinated effort is also required here for proper functioning.

6.3.2 Service organization and support

- hospital medical supplies, medications, and resources for the diagnosis and care of patients with associated disorders
- supplies and equipment for emergency care (emergency cart, intubation supplies, specific medications, others)
- communications infrastructure, transportation, and meals; administrative assistance, clothing, office supplies, hygiene and cleaning supplies, sterilization service, and laundry service
- referral to hospital emergency rooms guaranteed through immediate transport, given the greater possibility that patients in these units will develop complications

It is recommended that this service be set up inside, next to, or close to another health care facility that can provide supplies, support services, and consultations.

6.3.3 Human resources

The unit must be staffed 24 hours a day. If it is open for only 12 hours, referral should be ensured for patients who, due to their condition, should not return home.

The complexity of the teams and supplies will depend on the size of the unit and on the number of cases that remain in the facility each day. Health professionals (physicians, nursing professionals and technicians, biochemists and laboratory technicians, if testing is done in the unit) and support personnel (cleaning, security) are required. In the case of a unit set up on a temporary basis, where professionals from other units or hired specifically for these situations are working, it is essential to provide training to the entire team.

6.4. Hospital care

Efficient primary care, the creation of dengue units for patient rehydration during short periods (less than 24 hours) in already existing health units, and those set up in new locations will greatly reduce the need for hospital care.

According to a study in Brazil, approximately 7% of all reported cases required admission to dengue units or hospitals from 2001 to 2010,[3] of the total admitted, 10% required intensive care. The average stay was from three to four days for general hospitalization and five days for intensive care. This information was used to calculate that a bed with its respective nursing care can receive an average of seven admissions in 30 days, with 90% occupancy; and an ICU bed, an average of six admissions in 30 days.

[3] Source: Information and Statistics System of the Unified Health System of Brazil.

This data can be used to calculate the resources needed in a city or region, based on a hypothetical number of clinical cases of dengue, as such:

- estimated dengue cases
  - 2% of the high-risk population, 1% of the medium- and low-risk population
- patients who will be cared for in dengue units (primary care)
  - 90% of estimated dengue cases
- Percentage of patients who will require medical and nursing interventions and care: oral or intravenous rehydration in dengue units at the primary and secondary levels of care
  - of that total, 10% will require medical interventions and care in ICUs
- Complete blood count for the estimated number of dengue patients
  - number of estimated dengue cases multiplied by two

Since dengue is an acute illness that develops quickly and has a short duration, access to pediatric, internal medicine, and ICU beds should be guaranteed immediately.

If beds are not immediately available, the supply could be expanded through contracting from the public and private networks or by agreement (e.g., short-term, four months).

Teams of hospital clinicians should also have to receive training in management of dengue patients or suspected dengue patients, focusing on warning signs, severe dengue patients, management of hypovolemic shock—with characteristics specific to dengue—and in aspects described in the procedures for care in emergency units and dengue wards (rehydration wards).

6.4.1 Recommendations

- Reinforce and strengthen the medical team (general practitioners, pediatricians, internists, nursing personnel, among others).
- Strictly follow the guidelines for organization of services during epidemic dengue outbreaks and patient care: " Dengue: diagnosis and clinical handling: Adult and Child" (up-to-date).
- Establish a specific patient flow of first consultation and subsequent visits.
- Ensure direct communication with the primary care unit to ensure necessary return and follow-up visits, to guide patients and those responsible for their care. Provide all medical and nursing service providers with a flow chart for risk classification and management of suspected dengue patients, as well as a reporting form for suspected dengue case.
- Ensure direct communication with the healthcare unit that has been previously designated to receive referred patients (another hospital of higher complexity, if the patient needs it) or with the central control unit indicated in the regulations of the corresponding level.

– Establish a situation room or join one online.

6.4.2 Needs for hospitalization services

Hospital units that care for dengue patients must have equipment, inputs, and laboratory supplies to carry out specialized procedures, according to patient severity and their complications.

6.4.3 Diagnostic support

Clinical laboratory tests and diagnostic imaging:

– complete blood count (platelet and leukocytes count, hematocrit, and hemoglobin)

– other laboratory tests, according to the treatment protocol for dengue patients, severity and type of complication, and associated disorders

– strategies to ensure that lab tests and delivery of results are done quickly (aim for delivery in a maximum of two hours)

– provide ultrasonography and X-rays

Specific tests

– Collect serology samples (IgM/IgG) starting on the fifth day after the onset of illness, based on the epidemiological situation and as established by the health authorities for the location.

– Collect samples for viral studies from all severe dengue patients: carry out RT-PCR in the first three days from onset of illness or to determine the viral antigen (NS1 protein) in the first four days from onset of illness. A previously determined number of samples from suspected cases are needed from places with outbreaks to document the circulating dengue virus serotype and alert to the entry of a new serotype.[4]

– Process samples and immediately communicate results using established channels.

– Include ongoing participation of the laboratory in national, regional, and local commissions for continuous analysis of information that guides timely decision-making.

– Carry out appropriate national and international coordination for additional tests to support differential diagnosis, when necessary.

6.5. Hospital contingency plan

The hospital contingency plan is a document that defines the responsibilities of an organization to respond to emergency situations. It also contains detailed information

[4] This number of samples or percentage of total cases will be adjusted based on analysis of the epidemiological situation and availability of resources.

on the characteristics of the affected area. Its objective is to describe measures that should be taken in response to the emergency. This requires preparation of a joint, integrated document that considers the different situations in which transmission occurs, the strength of the outbreak, the activities that need to be done, the way to do them, and their monitoring.

It is important to prepare contingency plans for the different levels of management and care (national, regional, municipal, and health units).

To cope with dengue epidemics, the strengthening of strategic actions for the care and support of the patients with suspected illness is recommended. Those strategies should be included in the contingency plans and be evaluated by those in charge of management and care. Strategic measures include the following:

- Improve patient access to health care units (hospitalized and ambulatory patients).
- Implement a single clinical protocol in all health facilities that has been approved by national and regional health authorities, based on PAHO and WHO recommendations.
- Implement risk classification in all health facilities.
- Establish a flow for the management of monitoring and support of cases, which spells out the activities planned in each unit.
- Establish the flow for notification to epidemiological surveillance services.
- Train the team for patient care and service organization.
- Ensure that supplies, equipment, and printed forms are available to meet demands and ensure a strategic reserve based on existing risk.
- Have clinical laboratory services available for essential diagnostic tests.
- Inform the public about the organization of patient care services.
- Explain to the public the importance of early oral hydration, warning signs, and seeking medical care.
- Mobilize representatives from professional associations, civil society, nongovernmental organizations, and managers from the mass media communications and private institutions to provide the support needed to disseminate the guidelines.

7. EPIDEMIOLOGICAL SURVEILLANCE

Dengue is a notifiable disease/mandatory reporting.

The person in charge of reporting each case is the medical or nursing staff member attending the case at the time of clinical diagnosis. This responsibility is part of national standards and the International Health Regulations. Notification initiates the epidemiological surveillance process and triggers prevention and control measures. Early detection and reporting are essential to improving the effectiveness of the warning and response system.

The clinician will assume responsibility for filling out the notification form properly and in a timely manner. This is as an essential contribution to dengue control and should be considered an important part of their daily work. Table 3 provides the case definition of dengue for epidemiological surveillance purposes.

Table 3. Dengue case definition for epidemiological surveillance

Type of case	Characteristics of the classification
Suspected dengue case	**Dengue:** person who lives or has traveled to areas with dengue transmission in the last 14 days and presents acute fever, usually of 2 to 7 days duration, and **two or more** of the following manifestations: – nausea, vomiting – exanthema – myalgia and arthralgia – headache, retro-orbital pain – petechiae or positive tourniquet testleukopenia Any child coming from or living in an area with dengue transmission, with acute febrile illness, usually of 2 to 7 days duration and no apparent etiology, can also be considered a suspected case.
	Dengue with warning signs: every dengue case that presents near or at defervescence or in the following hours one or more of the following signs: – intense and continuous abdominal pain or tenderness – persistent vomiting – fluid accumulation (ascites, pleural effusion, pericardial effusion) – mucosal bleeding – lethargy, restlessness/irritability – postural hypotension (lipothymia) – liver enlargement >2 cm – steady increase in hematocrit
	Severe dengue: every dengue case that has one or more of the following manifestations: – shock or respiratory distress due to severe plasma leakage – shock evident from tachycardia, cold extremities, and capillary refill time equal to or greater than three seconds, weak or undetectable pulse, convergent/ differential blood pressure ≤20 mmHg; arterial hypotension in late phase. **Severe bleeding,** based on evaluation by the attending physician (e.g. hematemesis, melena, ample metrorrhagia, and central nervous system bleeding). **Severe organ involvement,** such as major liver impairment (AST or ALT >1000 IU)[5], central nervous system (change in mental state), heart (myocarditis), or other organs. **Note:** Every severe case should be confirmed by laboratory tests specific for dengue.

[5] AST- aspartate aminotransferase; ALT- alanine aminotransferase

Type of case	Characteristics of the classification
Probable dengue case	Every suspected dengue case that has a positive IgM or NS1 result or clinical-epidemiological link.[6] **Note:** During outbreaks, reported cases that could not be investigated are also considered probable dengue cases, since it is considered that all have a clinical-epidemiological link.[7]
Confirmed dengue case	Every laboratory-confirmed dengue case (molecular techniques, such as conventional RT-PCR, real-time RT-PCR, or others; viral isolation, IgM or IgG seroconversion in paired sera or a fourfold IgG titer increase).[8] **Note:** Laboratory diagnosis should include differential diagnosis for other diseases, according to the epidemiological characteristics of each country. Serological diagnosis should include an evaluation of cross-reactivity with other flaviviruses.
Death from dengue	Every patient who meets the definition for suspected, probable, or confirmed case who dies as a consequence of dengue. **Note:** It is recommended that in every death from dengue, specific laboratory tests be performed. Similarly, all deaths from dengue should be analyzed by an interdisciplinary committee.
Ruled out case	Every suspected dengue case that meets one or more of the following criteria: – has a negative laboratory diagnosis. (Confirm that samples were obtained within the adequate time frame) – does not have a clinical-epidemiological link, – has a laboratory diagnosis of another clinical disorder, – is a case without laboratory testing whose clinical and epidemiological investigations are compatible with suspicion of other disorders

[6] Case with an epidemiological link is understood as every person who lives or has been in the same area as a confirmed dengue case within 30 days.

[7] At the end of each epidemiological year countries should make adjustments to the final case classification, subtracting cases ruled out from suspected cases.

[8] WHO definitions adjusted by dengue experts in the International Task Force (GT-Dengue international of PAHO/WHO).

8. LABORATORY

Given the increasing importance of dengue worldwide and regionally, and the need to keep the countries of the Region up to date on the progress, advantages, disadvantages, and challenges of laboratory diagnosis and surveillance, the Dengue Laboratory Network of the Americas (RELDA), led by the Pan American Health Organization (56), summarizes the methods used today for dengue diagnosis in the context of clinical case management and laboratory surveillance (18).

8.1. The agent

The four dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), like other flaviviruses, are spherical enveloped viruses that contain a single-stranded, positive RNA genome that encodes three structural proteins (capsid C, membrane M, and envelope E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). The E protein has an important function in the development of antibodies and the protective immune response, as well as in the viral immuno-amplification phenomenon. The NS1 protein appears in association with the infected cell on its surface and extracellularly and can be detected in the early stages of infection and mark virus replication (163).

8.2. Types of Infection

After an incubation period of 4 to 10 days, infection by any of the four DENV serotypes can be asymptomatic or symptomatic. The disease can occur as dengue fever (with or without warning signs) or severe dengue, according to the current clinical classification (1).

Since infection by a given DENV serotype confers prolonged immunity only against that serotype, an individual can contract up to four dengue virus infections throughout their lifetime (164). Furthermore, an individual can be naturally infected by other flaviviruses present in the Region (e.g., Zika virus, West Nile Virus, vaccinal or natural yellow fever virus, Saint Louis encephalitis virus, and other less common ones).

Primary dengue infection affects the individual without prior flavivirus exposure. Secondary infection occurs mainly in individuals previously infected by any of the remaining virus serotypes, but also individuals immune to another flavivirus (165).

Viremia (presence of virus in blood) is generally concurrent with the onset of symptoms and is not detectable at defervescence. Detection of IgM antibodies against dengue is concurrent with the disappearance of viremia and fever (28).

Primary infection is characterized by detectable levels of IgM antibodies by days five or six after onset of fever; levels peak at about 14 to 15 days and can remain high up to 30 to 60 days later, and then decline gradually over time. IgG antibodies against dengue are elevated after the eighth or ninth day of the onset of fever and are detectable for life (49, 166, 167).

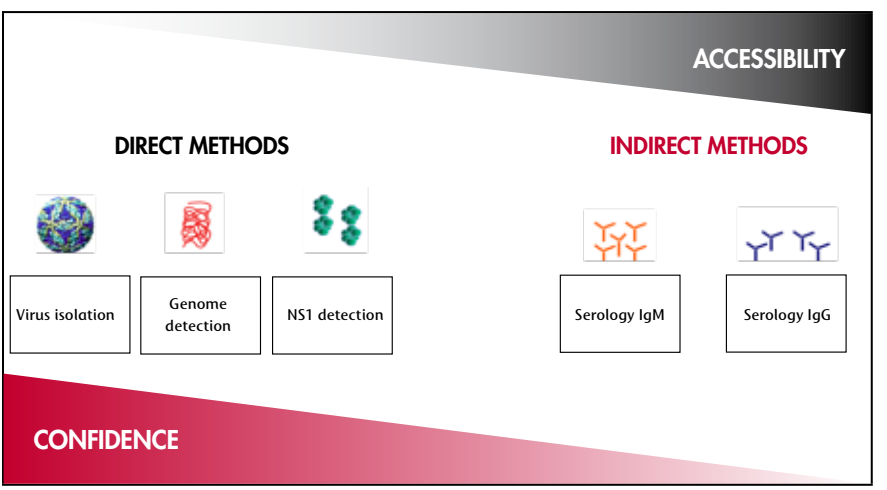
In secondary infection, very high levels of IgG antibodies against dengue are observed from the second or third day of fever. IgM antibody levels can be less elevated in secondary infections and are sometimes not detectable (168).

8.3. Diagnostic methods: direct and indirect

Dengue infection can be diagnosed by viral isolation, viral genome detection (through RT-PCR or real-time RT-PCR), and detection of a dengue antigen, as well as the study of serological response (Figure 3) (169).

Clinical specimens. The specimen to be collected and the diagnostic method depend on which clinical phase of the disease the patient is in. Serum is the specimen of choice for dengue diagnosis, although plasma can also be obtained (Table 4). Attempts may be made to collect specimens to test tissues from liver, spleen, lymph nodes, and others from patients who died with a clinical suspicion of dengue, using viral isolation, molecular diagnosis, and viral antigen detection (170). All specimens should be accompanied by the patient's general information as well as their clinical and epidemiological data.

Figure 3. Dengue diagnostic methods



Adapted from Peeling, RW et al 2010 (175).

Virus isolation: The most commonly used diagnostic method for isolation of the agent is inoculation of C6/36 *Aedes albopictus* mosquito cells accompanied by viral identification through indirect immunofluorescence (171), which uses monoclonal antibodies specific to each virus serotype. Intrathoracic mosquito inoculation and inoculation of mosquito larvae are the most sensitive methods for isolation of this agent, although they are not the ones most commonly used in daily practice. Virus isolation is considered the "gold standard," because, if positive, it constitutes a specific and unequivocal test of virus presence and viability. However, these techniques are laborious and not sufficiently sensitive to be used widely or for clinical case management. RT-PCR can also be used for virus identification in the place of IIF.

Molecular diagnosis: Since it is highly sensitive, RT-PCR has become the method of choice for detection of the dengue virus in patient serum obtained in the acute stage of the disease (0 to 5 days after the onset of symptoms). Tests based on DENV genome detection and visualization in gels, such as "nested RT-PCR" are sensitive and specific with respect to dengue detection and serotyping, but are not sufficiently automated for use in surveillance (169). Real-time RT-PCR has become a widely used technique for diagnosis of RNA viruses, and several protocols have already demonstrated 80% to 90% sensitivity with serum samples obtained in the first five days of the disease, and their specificity is approximately 100% (does not produce false positive results).

Table 4. Characteristics and usefulness of clinical samples to be obtained and studied

Disease phase	Clinical specimen	When to collect specimen	Conditions for specimen taking, transfer, and storage	Usefulness
Acute stage	Serum	1 to 4 days after the onset of fever	Collect in sterile conditions. Transport immediately at 4 °C or storage at 4 °C for no more than 48 hours. Storage at -80 °C for longer periods.	Detección del virus, de alguno de sus componentes o producto de la replicación viral.
Early convalescent stage		Days 5 to 6 of fever	Collect in sterile conditions. Transport immediately at 4 °C or storage at 4 °C for no more than 48 hours. Storage at -20 °C for longer periods.	Serological tests
Late convalescent stage	Serum pair	Second serum obtained 21 days after the first		
Deceased	Liver, spleen, lymph node, and other tissues.[9]		Obtain as soon as possible after death. Store in individual sterile bottles with PBS (phosphate buffered saline) or 0.9%saline solution; label them. Transport immediately at 4 °C. Storage preferably at -80 °C for longer periods.	Detection of the virus, of one of its components, or of the product of viral replication.

[9] A portion of the tissues can be sent for histopathological and immunohistochemical testing and should be kept at room temperature and set in buffered formalin or in paraffin (for immunohistochemical stain). Tissues can remain in buffered formalin for up to 24 hours. If being sent to the laboratory later, they should be moved to 70º alcohol.

8.3.1 Direct diagnostic methods

Some real-time RT-PCR assays do not differentiate between serotypes, although they can detect any of the four dengue virus serotypes in a relatively simple reaction. Today, the majority of tests normally confirm the serotype of the virus in question. Although determination of the serotype does not have an immediate medical application, it does have epidemiological importance; therefore, public health laboratories prefer tests that indicate serotype. The US Food and Drug Administration (FDA) recently approved a real-time RT-PCR assay (CDC DENV-1, DENV-2, DENV-3, and DENV-4 Real-Time RT-PCR Assay) that makes it possible, in one test, to detect the four dengue virus serotypes in serum and plasma (with sodium citrate) obtained in the first five days of the disease. This test detects a high proportion of cases (>90% of cases with serological confirmation) and can be run in two modalities (singleplex and multiplex), with the same sensitivity and high specificity for the four virus serotypes (172).

Antigen detection: Methods that enable early diagnosis with high sensitivity and specificity are a support to clinical management of patients. Furthermore, early diagnosis is useful for rapidly adopting vector control measures to decrease transmission. Taking advantage of the fact that NS1 protein is a marker for viral replication that is detected in serum and plasma during the acute stage of the disease, several commercial ELISA kits and immunochromatographic strips have recently been produced. This method provides a potential opportunity to make an early and specific diagnosis of dengue, because it can detect viral replication before the development of IgM antibodies. Variable sensitivity (48-93%) has been reported in several studies, which can be influenced by the virus serotype, the type of infection (primary or secondary), the day the sample is collected, the gold standard used in evaluations, and the affinity of the monoclonal antibodies used in the tests, among others (173). The quality of the results of these kits depends on the manufacturer, the geographical origin of the samples, and the composition of the serum panels analyzed, as well as the expertise of the people analyzing the tests. In general, ELISA test kits are more sensitive than rapid tests. Several countries in the Region of the Americas have begun to use NS1 detection kits for the purpose of facilitating and decentralizing diagnosis into lower complexity laboratories. Negative results using this test on samples from patients in the acute phase (zero to five days from the onset of disease) can be confirmed by RT-PCR.

The increasing development and use of direct methods (nested RT-PCR and NS1) have helped accelerate case confirmation and decrease the need for paired samples for diagnostic confirmation. However, it should be clarified that negative results do not rule out a dengue infection, for which serological tests are required. These samples can be used to attempt IgM antibody detection (it has been reported that in the first four days of fever, determination of both parameters—NS1 and IgM antibodies— enables case diagnosis in more than 80% of samples). If

results are negative, a new sample taken several days later should be tested by serology before ruling out dengue infection.

The immunohistochemistry method detects dengue antigens in tissues. A combination of polyclonal and monoclonal antibodies has made it possible to confirm the diagnosis in tissue samples from suspected dengue cases who died (170).

8.3.2 Indirect diagnostic methods

Serological methods are widely used in routine dengue diagnosis, but are more useful when the sample is obtained three or four days after onset of symptoms or on samples subsequent to those with negative results with the direct techniques described above. In general, dengue IgM antibody analysis is recommended in samples obtained five or six days after the onset of disease or later (1, 168).

These methods are used to confirm infection or to suspect that there has been a recent infection. Although several studies have suggested the usefulness of detecting dengue IgA and IgE antibodies, detection of IgM antibodies is the most frequently used marker of recent infection (168, 174, 175). IgM antibodies can normally be detected in the early convalescent phase of the disease, although in some cases they can be detected during the acute phase. IgM antibody capture ELISA (MAC-ELISA) is a fast and simple test used for the detection of IgM antibodies. It only requires one serum sample and is widely used in dengue diagnosis and serological surveillance. A protocol was recently developed to use ELISA for rapid detection of IgM antibodies, which demonstrated sensitivity and specificity similar to those of the classical protocol (176). That protocol is being used in Brazil's public health laboratory network.

The presence of IgG antibodies in serum indicates past infection. However, the presence of high IgG antibody titers in a serum sample or the seroconversion, or a fourfold or greater increase in the antibody titer in paired serum samples obtained from a case of clinically suspected dengue, indicates recent infection or confirmed infection, respectively. This approach could be very useful in cases of secondary infection that show no detectable levels of IgM antibodies (171).

Even though the hemoagglutination inhibition technique (126) is the gold standard for IgG antibody detection, IgG ELISA is the most commonly used test that detects the presence of IgG antibodies and even determines its titer. Currently, a large number of commercial kits offer differing degrees of sensitivity and specificity for both ELISA and immunochromatographic tests using rapid test strips that detect IgM and IgG antibodies.

Antibodies detected through HI and ELISA show cross-reactivity among flaviviruses, an important aspect to be considered in both patient diagnosis and laboratory surveillance. When the presence of a flavivirus that is not dengue is suspected, a virus neutralization assay should be performed on paired serum against the

suspected flaviviruses, this being the only serological method to determine the etiologic agent with certainty. Situations like this can occur in areas where, in addition to dengue, other flaviviruses such as West Nile or yellow fever circulate; and in patients whose clinical signs lead to suspicion of these infections. Despite the neutralization technique's high specificity, it has limitations and in some cases cannot determine the causal flavivirus, mainly because of the presence of secondary infections where serological crossover increases and the phenomenon of "original antigenic sin"[10] is seen (*177, 178*). Table 5 summarizes methods currently used for virological, molecular, antigenic, and serological diagnosis.

[10] When an adaptive immune response is generated against a given antigen, upon a second exposure to a cognate antigen, antibody production is directed more strongly toward epitopes common to both antigens.

Table 5. Current methods for virological, molecular, antigenic, and serological diagnosis of dengue

Type of diagnostic	Method	Comments
Detection of the virus, any of its components, or a product of viral replication		
Aislamiento viral	*Aedes albopictus* mosquito cell culture, C6/36	Indirect immunofluorescence with specific monoclonal antibodies for each virus serotype and RT-PCR can be used for virus identification.
Diagnóstico molecular	RT-PCR and real-time RT-PCR	Different protocols show 80% to 90% sensitivity, with close to 100% specificity.
Diagnóstico antigénico	ELISA and rapid tests for detection of NS1 protein	NS1 is a marker of viral replication present in the patient's serum and on the surface of the infected cell. There are different commercial kits that require further evaluation.
	Immunohistochemistry technique in tissues	Through a combination of polyclonal and monoclonal dengue antibodies, viral antigens can be detected in tissues.
Serological diagnosis		
IgM antibody detection	IgM ELISA antibody apture (MAC ELISA) and rapid tests	It is the most frequently used marker of recent infection. It uses a single serum sample. Several commercial ELISA kits have shown adequate sensitivity and specificity.
IgG antibody detection	IgG ELISA Hemoagglutination inhibition (126) Rapid tests	The presence of IgG antibodies in serum is indicative of a prior flavivirus infection. However, presence of high titers in a serum sample or the seroconversion or fourfold increase in the antibody titer in paired serum samples obtained from a case of clinically suspected dengue indicates recent infection or confirmed infection, respectively.

8.4. Laboratory diagnosis for clinical case management

Early and accurate diagnosis of dengue is important for medical care of the patient, detection of severe cases, confirmation of infection, and differential diagnosis of other infectious diseases. However, when dengue is suspected, do not wait for laboratory diagnosis to start treatment. The abovementioned diagnostic methods are also useful for clinical diagnosis, although molecular and antigen detection methods are preferred because their response time is quicker. In daily practice, if the hospital is not fully equipped (laboratory infrastructure, equipment, reagents, trained staff) or if it takes a long time for specimens to reach the reference laboratory, results are not going to be readily available to provide the best clinical care for the patient. In such cases, NS1 protein detection tests, mainly rapid strips, could become the early diagnostic method of choice. Nevertheless, better evaluation of available commercial kits is needed, along with more sensitive tests. Currently, these kits are being introduced for routine diagnosis in several countries; therefore, it must be kept in mind that a negative test result does not rule out dengue infection in the patient (*5*, *179*).

8.5. Dengue surveillance in the laboratory

IMS-Dengue states the need for integrated surveillance, in which clinical and epidemiological surveillance with laboratory support, coupled with entomological and environmental surveillance, has a primary role. Such integration should be able to determine environmental and entomological risk factors in order to develop plans to reverse or minimize such risks. It should also be able to detect dengue transmission early and facilitate a rapid and effective response.

In dengue-endemic countries, monitoring the incidence and prevalence of dengue over time establishes a baseline that will facilitate the early detection of an increase in the number of cases, including severe cases, provided that there is adequate and sustained clinical-epidemiological and laboratory surveillance. This also facilitates the process of recognizing the introduction of a new virus serotype or genotype and taking prevention and control measures that interrupt or decrease transmission. In countries where dengue is not endemic but where the risk of transmission exists due to the presence of the vector, surveillance should have the capacity to determine early on that the virus has been introduced.

Samples that should be studied: Each country, depending on its capacity and epidemiological situation, must define the total amount of samples that will need to be processed as part of laboratory surveillance. In outbreaks and epidemics, a smaller percentage of samples may be tested, primarily in areas where transmission has been confirmed. It is recommended that some countries temporarily monitore the duration of the outbreak through the study of a percentage of samples to determine IgM antibodies and the circulating virus serotype (in samples of cases

in the acute phase). This, in turn, includes surveillance of the potential spread of transmission to new geographical areas and the study of all atypical, severe, or fatal cases, using the available methods.

Furthermore, each country should determine the need to establish laboratory networks to strengthen dengue diagnosis and surveillance. Table 6 shows the model proposed by the World Health Organization for the organization of dengue laboratory diagnostic services as part of primary care, district-regional care, and reference centers. Reference center functions include training, supervision, and quality control; surveillance and investigation activities; testing of samples that are problematic or of interest; and differential diagnosis of other flaviviruses. Important primary care center functions include quality assurance and referral of problematic samples. In turn, district-regional health care centers have to be prepared for training, supervision, and quality control; surveillance activities; and referral of problematic samples.

Table 6. Proposed model for the organization of dengue diagnostic services

Diagnostic tests	Primary care	District-regional care	Reference centers
Virus isolation			X
Viral genome detection			X
Antigen detection	X	X	X
– ELISA	X	X	X
– Rapit strips	X	X	X
Serology	X	X	X
– ELISA	X	X	X
– Rapit strips	X	X	X

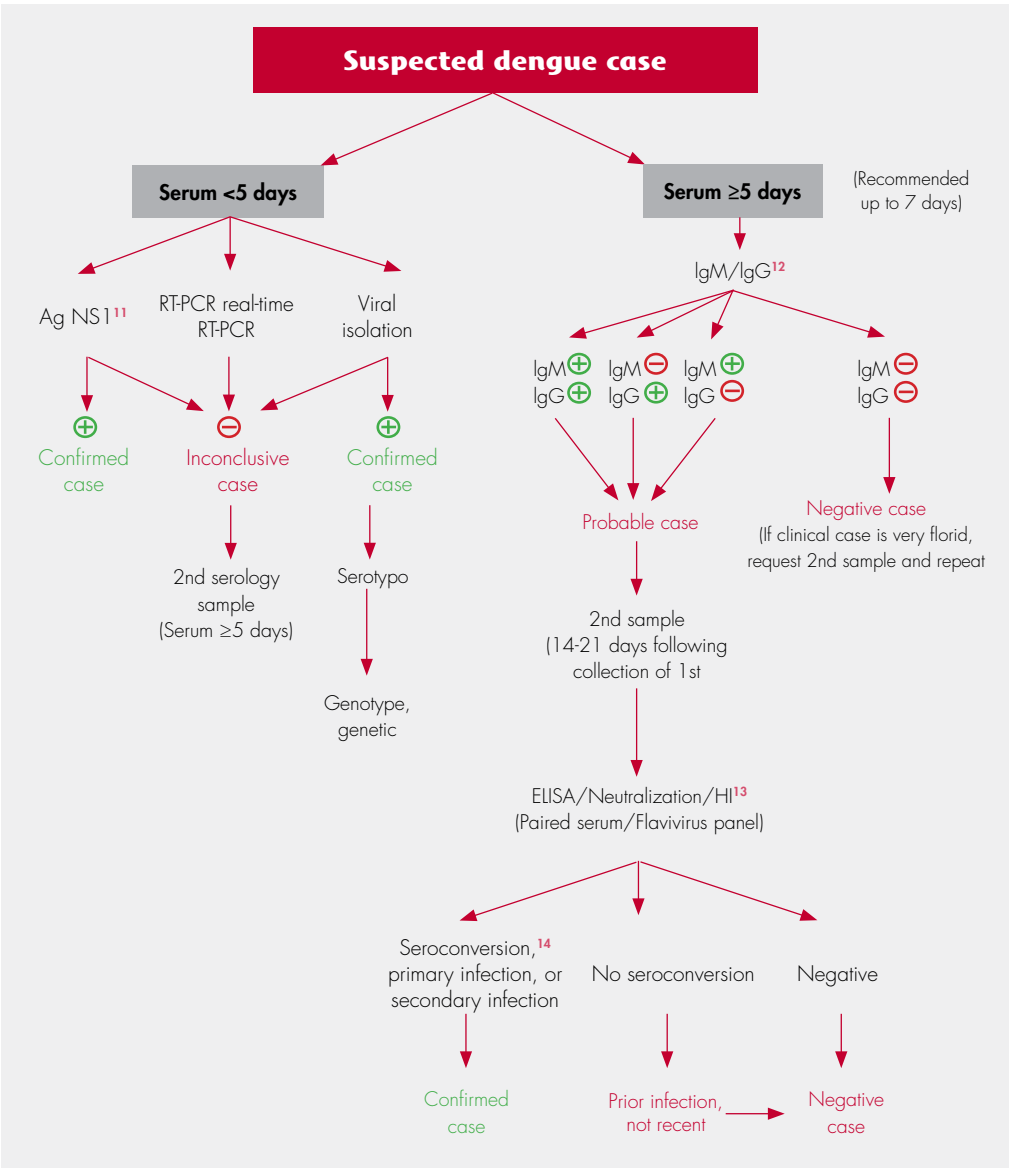
8.5.1 Diagnostic algorithm in laboratory surveillance

Laboratory surveillance is intended to detect an increase in transmission early, the introduction of a new serotype or genotype in a given location, confirmation of severe dengue cases, and follow-up and support the characterization of an epidemic. Integrated surveillance does not require laboratory confirmation of all probable cases. However, a percentage of them need to be studied to evaluate as quickly and accurately as possible the epidemiological situation at a given time and place to be able to take immediate action.

Each country will need to establish a dengue diagnostic algorithm as part of integrated surveillance; this may vary according to national capacity, the epidemiological situation of dengue, and even the presence of other arboviral diseases.

Figure 4 is only a model or guide for each country to establish its own diagnostic algorithm; it takes into consideration which day the sample is collected, and the differential diagnosis of other flaviviruses, for those countries where more than one of these microorganisms circulates.

Figure 4. Proposed algorithm for laboratory diagnosis of dengue



[11] NS1 has a sensitivity of 34-76% and specificity of 100% (173).

[12] IgG positive is an ELISA IgG with titers ≥1280, or a rapid strip positive for IgG.

[13] A neutralization test is recommended when there are cases with doubtful clinical manifestations and in those countries or places where other flaviviruses circulate.

[14] Seroconversion: negative IgM test that becomes positive on the second sample, or an IgG that increases titers fourfold in the second sample compared to the first sample.

Viral isolation, nested RT-PCR or real-time RT-PCR, and NS1 protein detection can be attempted on the samples collected in the first four days after onset of fever. It is not necessary to test all the samples or test them at the same time. Each laboratory will decide on its test of choice, according to its capacity and availability of diagnostic supplies. IgM antibody testing can be an option for samples collected during the acute stage of the disease when the virus and its viral markers cannot be detected, although those antibodies might not be detectable in that phase of the disease.

Whenever possible, carry out IgG antibody detection in paired sera. If seroconversion is determined, it is indicative of a recent flavivirus infection. If the patient's clinical and epidemiological manifestations support these results, it can be considered to be a case of dengue. When circulation of another flavivirus is suspected, infection should be confirmed through a neutralization test. In these cases, an attempt will be made to reach etiological diagnosis through viral isolation and nested RT-PCR, with specific primers for the suspected virus.

Criteria for a confirmed or probable case. Notification. Table 7 summarizes laboratory criteria for cases that are confirmed or highly suggestive of dengue according to WHO (1). As part of surveillance, all cases (probable and confirmed) must be reported to the health authorities. In countries where only a percentage of suspected cases is tested, those that have not been tested in the laboratory, but meet clinical and epidemiological criteria for dengue, will also have to be reported as probable cases.

Table 7. Highly suggestive and confirmed dengue case criteria (1, 180)

Highly suggestive of dengue	Confirmed dengue case
One of the following: – IgM positive in a single serum sample – IgG positive in a single serum sample with an antibody titer of 1280 or greater – NS1 positive	**One of the following:** – RT-PCR positive – Viral culture positive – IgM antibody seroconversion in paired sera – IgG antibody seroconversion or fourfold IgG titer increase in paired sera

Integration of laboratory surveillance into clinical-epidemiological surveillance. Laboratory surveillance is an inseparable component of integrated surveillance and, primarily, of clinical-epidemiological surveillance. The success and impact of dengue surveillance lies in the proper integration of these components.

The participation of laboratory specialists in the design, development, and establishment of surveillance, as well as in integrated situation analysis, will enable better real-time knowledge of the epidemiological situation. This, in turn, will help determine the incidence of dengue and severe dengue; hospitalization, mortality, and case-fatality rates by age group and sex; and the relationship to a given virus serotype. Seasonality, age distribution, patterns of transmission, and risk factors, among other characteristics, can also be determined properly (1).

8.6. Principal difficulties and challenges in laboratory surveillance

The main challenges of laboratory surveillance include:

- the need to improve the availability of diagnostic and reference reagents
- periodic staff training
- standardization and evaluation of technical protocols
- evaluation of commercial diagnostic kits
- periodic proficiency tests
- greater integration of laboratory staff into national epidemiological analysis
- the need to boost country investigation capability to conduct studies of molecular and seroepidemiological characterization, among others, in support of dengue surveillance
- strengthening diagnostic capacity of national laboratories for dengue and other medically-important arboviral diseases
- improvement of country collection, transportation, and storage systems
- standardization and integration (national and regional) of clinical-epidemiological, entomological, environmental, and laboratory information to create a single optimal information system for more integrated and timely surveillance
- strengthening of good laboratory practices and biosafety

8.7. The role of national laboratories, national laboratory networks, and PAHO/WHO collaborating centers in the Region

Faced with the dengue situation in the Region, countries have gradually instituted laboratory diagnosis and surveillance of the infection. Today, most of the Region's countries have a national laboratory, many of them capable of performing serological, virological, and molecular studies, in addition to being able to analyze the epidemiological situation and molecular characterization of circulating viruses. An example of this is the recent molecular characterization of DENV-4 in Brazil, which made it possible to determine that the identified genotypes (I and II) had

been frequently introduced into the country before their spread. Furthermore, several countries have created laboratory networks with serological diagnostic capability, for the purpose of improving patient access to diagnosis and improving surveillance. In addition, the Region has six PAHO/WHO collaborating centers devoted to regional reference activities; development, evaluation, and introduction of new diagnostic instruments that countries can implement; preparation of reagents and reference antigens; development of performance tests; evaluation of technical protocols; continuing training and research; and addressing dengue and other arbovirus emergencies. Along those lines, RELDA brings the Region's laboratories together for the purpose of strengthening dengue surveillance and diagnosis, to better respond to the regional situation and emergencies (181).

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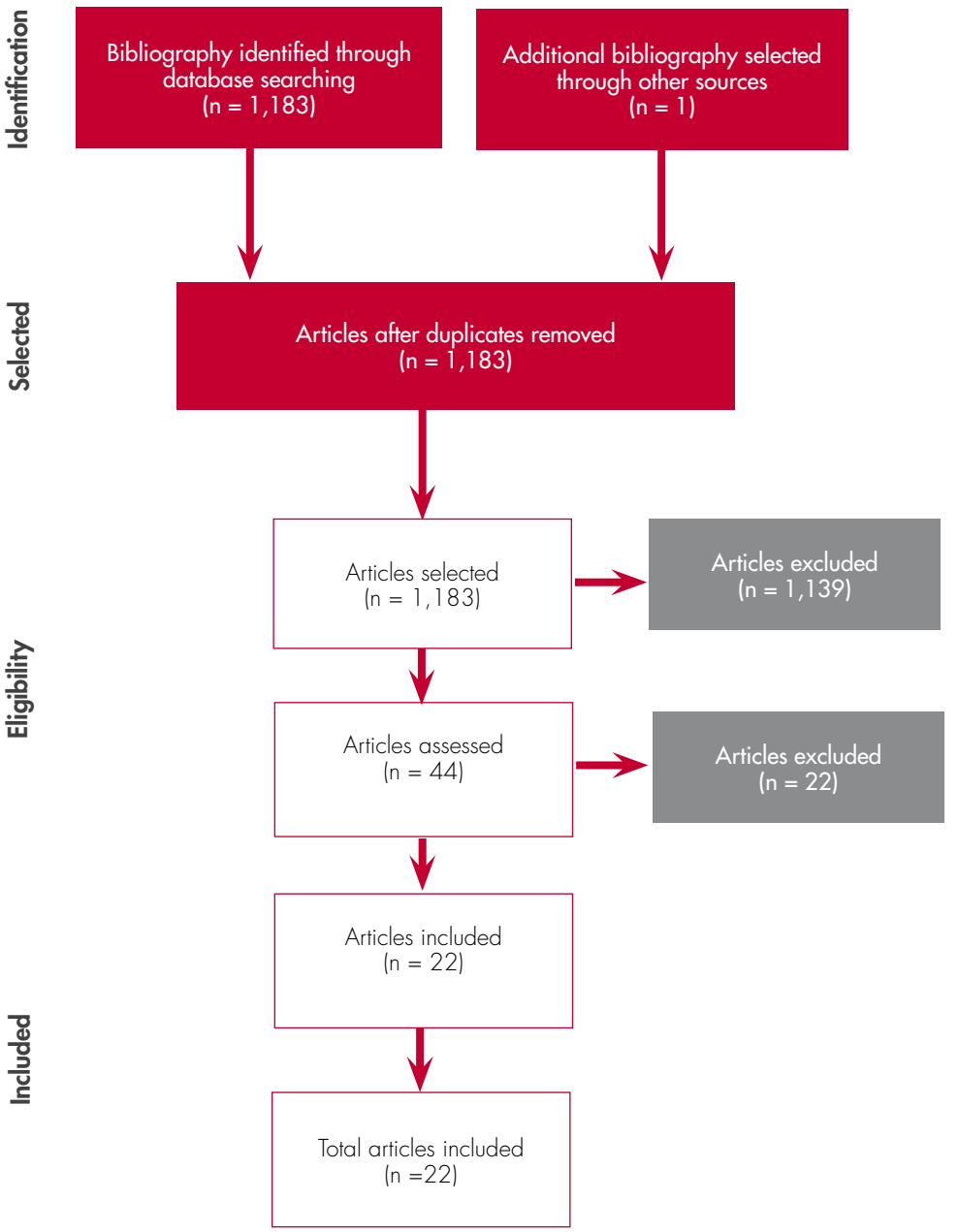
10. ANNEXES

Annex A. Literature search algorithm

(dengue [mh] OR dengue [tw]) AND ((Pregnancy [mh] OR Pregnant Women [mh] OR Pregnan* OR abortion OR pre-natal OR Prenatal Care [mh] OR antenatal* OR Prenatal OR antenatal OR (maternal mortality) OR Maternal Mortality [mh] OR (maternal survival) OR contracept* OR Contraception [mh] OR labour OR labor OR Labor, Obstetric [mh] OR Obstetric Labor Complications [mh] OR Obstetric Surgical Procedures [mh] OR Delivery, Obstetric [mh] OR postpartum OR Postpartum Period [mh] OR postnatal Care [mh] OR Postpartum Hemorrhage [mh] OR obstetric OR eclampsia OR Eclampsia [mh] OR Pre-Eclampsia [mh] OR miscarriage OR Placenta Previa [mh] OR prelabor OR prelabour OR preeclampsia OR antepartum OR cesarean OR hellp syndrome [mh] OR ("hellp syndrome") OR Diabetes, Gestational [mh] OR Hypertension, Pregnancy-Induced [mh] OR Chorioamnionitis OR Puerperal) OR (Infant[MeSH] OR Infant* OR infancy OR Newborn* OR Baby* OR Babies OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child[MeSH] OR Child* OR kid OR kids OR Pediatrics[MeSH] OR Paediatric* OR Paediatric* OR Peadiatric*) OR (Elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab]OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR Adl [tiab] OR Frailty [tiab] OR Gds [tiab] OR Ageing [tiab] OR elders [tiab] OR Frail [tiab] OR Mci [tiab] OR Demented [tiab] OR Psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR Comorbidities [tiab] OR geriatric assessment [mh] OR Nursing homes [mh] OR frail elderly [mh] OR cognition disorders/diagnosis [mh] OR cognition disorders/epidemiology [mh] OR homes for the aged [mh] OR Alzheimer disease [mh] OR dementia [tiab]) OR (Hypertension [mh] OR Hypertension [tiab] OR hypertensive [tiab] OR (High Blood Pressures)) OR (Diabetes Mellitus [mh] OR Diabetes [tiab] OR prediabetic [tiab]) OR (Kidney Diseases [mh] OR Renal Dialysis [mh]) OR hemodialysis OR dialysis OR ((Renal [tiab] OR kidney [tiab]) AND (Insufficiency [tiab] OR failure [tiab] OR disease)) OR (Arthritis [mh] OR Arthritis [tiab] OR Osteoarthritis [mh] OR Osteoarthritis) OR (Anticoagulants [mh] OR Anticoagulan* [tiab]) OR (Water-Electrolyte Imbalance [mh] OR (WATER-ELECTROLYTE IMBALANCE [tiab])))

Annex B. PRISMA 2009, flow diagram



Adapted from: Moher D, Liberati A, et al., The PRISMA Group (2009) (182).

Annex C. Professionals involved in the preparation of the clinical guidelines

Anabelle Alfaro, Arleta Añez, Maria Elena Calderón, Yadira Carrera, Nayda Cossio Alba, Orlando Cuellar, María García de Luna Orosco, Rosmery Gross, Gamaliel Gutiérrez, Maria Guadalupe Guzmán, Franklin Hernández, Ana Gabriela Herrera, Carlos la Fuente, Eric Martinez, José Guadalupe Martínez, David Fernando Ortiz, Daniel Pizarro, Ernesto Pleités, Arturo Quiñonez, Jhony Rada, Ludovic Reveiz, Frank Bernardo Reyes, Freddy Rivera, Doris Salgado, José Luis San Martín, Carlos Alberto Suárez, Fernando Terrazas, Osmin Tovar, Eliana Vega and Rivaldo Venancio.

Annex D. Good and bad clinical practices

	Good practices (recommended)	Bad practices (not recommended)
1	Assessment and follow-up of patients with dengue and instructions to carefully monitor warning signs and how to identify them.	Discharging patients with dengue with no follow-up or inadequate instructions.
2	Administration of paracetamol to the patient with fever and pain.	Administration of aspirin or NSAIDs.
3	Obtaining a hematocrit level before and after each fluid bolus.	Ignoring the relationship between hematocrit levels and fluid therapy.
4	Clinical assessment of the patient's hemodynamic status before and after each fluid bolus.	Not monitoring patient response to fluid therapy.
5	Interpretation of hematocrit levels in the context of fluid administration hemodynamic monitoring.	Interpretation of hematocrit levels independent of patient's clinical status.
6	Administration of intravenous fluids for persistent vomiting or a rapid elevation of hematocrit.	Administration of intravenous fluids to any patient with dengue.
7	Use of isotonic solutions in cases with severe dengue or dengue with warning signs.	Use of hypotonic solutions in cases with severe dengue or dengue with warning signs.
8	Administration of sufficient intravenous fluid volume in order to maintain effective circulation during the period of plasma leakage in cases with severe dengue.	Excessive or prolonged intravenous fluid administration in cases with severe dengue or dengue with warning signs.
9	Avoiding intramuscular injections to patients.	Administration of intramuscular injections to patients.
10	Adjusting intravenous fluid therapy according to monitoring of vital signs, patient's hemodynamic condition, and hematocrit measurement.	Maintaining a fixed rate of intravenous fluid infusions in patients with severe dengue without changing its frequency according to patient monitoring and hematocrit measurements during hospitalization.
11	Strict monitoring of blood glucose (glycemic control).	No controlar la glucosa sanguínea y desatender los efectos hiperglucémico y de la diuresis osmótica que complican la hipovolemia.
12	Discontinuation or reduction of intravenous fluid therapy once hemodynamic condition stabilizes.	Not modifying intravenous fluid therapy once hemodynamic condition stabilizes or at the end of the critical phase.

Annex E. Differential diagnosis of dengue

Condition	Differential diagnosis
Conditions that mimic the febrile phase of dengue infection	
Influenza-like illnesses	Influenza, measles, chikungunya, infectious mononucleosis, HIV seroconversion illness
Illnesses with a rash	Rubella, measles, scarlet fever, meningococcal infection, chikungunya, toxicoderma, rickettsiosis, ehrlichiosis, Zika infection
Diarrheal diseases	Rotavirus, other enteric infections
Illnesses with neurological manifestations	Meningo/encephalitis, febrile seizures
Conditions that mimic the critical phase of dengue infection	
Infections	Acute gastroenteritis, malaria, leptospirosis, typhoid fever, typhus, viral hepatitis, acute HIV seroconversion illness, severe sepsis, septic shock, hantavirus infection, visceral leishmaniasis, yellow fever
Hemorrhagic fevers	Leptospirosis, Brazilian hemorrhagic fever, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, Mayaro, others
Malignant neoplasms	Leukemias, lymphomas, and other neoplasms
Other clinical manifestations	Acute abdomen (appendicitis, cholecystitis), diabetic ketoacidosis, lactic acidosis, leukopenia and thrombocytopenia with and without bleeding, platelet disorders (purpura), renal failure, respiratory distress (Kussmaul's breathing), systemic lupus erythematosus, hemolytic anemias

Annex F. Differential diagnosis of dengue fever and chikungunya fever *

Clinical and laboratory features	Dengue	Chikungunya
Fever (> 39 °C or 102 °F)	++	+++
Myalgia	++	+
Arthralgia	+/-	+++
Headache	++**	++
Exanthema	+	++
Pruritus	++	+++
Bleeding	++	+/-
Shock	+	-
Leukopenia	+++	++
Neutropenia	+++	+
Lymphopenia	++	+++
Elevated hematocrit	++	-
Thrombocytopenia	+++	+
C-reactive protein	-	++
Erythrosedimentation (ESR)	-	++

* Mean frequency of symptoms from studies where the two diseases were directly compared among patients seeking care. Table modified from Staples et al. (+++) = 70-100% of patients; (++) = 40-69%; (+) = 10-39%; (+/-) = <10%; - = 0%

** Often retro-orbital.

Table modified from: Pan American Health Organization, Preparedness and Response for Chikungunya Virus Introduction in the Americas. Washington, DC. PAHO, 2011. (183)

Annex G. Warning signs

	Signs
Clinical	– Intense and continuous abdominal pain or tenderness – Persistent vomiting (three or more episodes in one hour or four in six hours) – Fluid accumulation (ascites, pleural effusion, pericardial effusion) – Active mucosal bleeding – Lethargy/restlessness – Postural hypotension (lipothymia) – Hepatomegaly >2 cm
Laboratory	– Steady increase of the hematocrit

Annex H. Hemodynamic assessment: continuum of hemodynamic changes

Parameters	Stable circulation	Compensated shock	Hypotensive shock
Conscious level	Clear and lucid	Clear and lucid (shock can be missed if you do not touch the patient)	Change of mental state - restless, combative
Capillary refill time	Normal ≤ 2 seconds	Prolonged (from 3 to 5 seconds)	Very prolonged >5 seconds, mottled skin
Extremities	Warm and pink	Cold	Cold, clammy extremities
Peripheral pulse volume	Normal pulse	Weak and thready pulse	Feeble or absent pulse
Heart rate	Normal for age	Tachycardia	Initial tachycardia and bradycardia in late shock
Blood pressure	Normal for age	Normal systolic pressure, but rising diastolic pressure	Hypotension (see note below)
Mean arterial pressure (adults)	Normal pulse pressure for age	Narrowing pulse pressure (≤20 mmHg), postural hypotension	Pulse pressure <10 mmHg Unrecordable blood pressure Decreased
Respiration rate	Normal for age	Tachypnea	Metabolic acidosis, polypnea, or Kussmaul's breathing

Definition of hypotension: systolic blood pressure of <90 mmHg or mean arterial pressure <70 mmHg in adults or a systolic blood pressure decrease of >40 mmHg or <2 SD below normal for age. Pulse pressure ≤20 mmHg.

In adults, the decrease in MAP associated with tachycardia is very significant.

In children up to 10 years of age, the 5th percentile for systolic blood pressure can be determined by the formula: 70 + (age in years x 2) mmHg.

Annex I. Table of mean arterial pressure in females and males aged 1 week to 18 years old

Blood pressure in females aged 1 week to 18 years old						
AGE	Systolic/diastolic blood pressure			Mean arterial pressure		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum
<7 days	62,5 / 42,1	71,8 / 50,5	81,1 / 58,9	48,9	57,6	66,3
8-30 days	69,7/ 39,2	81,7 / 50,7	93,7 / 62,2	49,4	61,1	72,7
1-5 months	79,8 / 38,9	92,0 / 49,5	104,2 / 60,1	52,5	63,7	74,8
6-11 months	79,9 / 42,9	94,5 / 52,5	109,1 / 62,1	55,2	66,5	77,8
1 year	80,2 / 43,2	93,0 / 52,4	105,8 / 61,6	55,5	65,9	76,3
2 years	83,7 / 48,2	94,6 / 57,0	105,5 / 65,8	60,1	69,5	79,1
3 years	79,9 / 45,3	92,6 / 55,1	105,3 / 64,9	56,8	67,6	78,4
4 years	77,6 / 45,3	90,7 / 54,5	103,8 / 63,7	56,1	66,6	77,1
5 years	83,5 / 47,4	94,1 / 57,3	104,7 / 67,2	59,4	69,6	79,7
6 years	84,9 / 49,1	95,5 / 59,3	106,1 / 69,5	61,1	71,4	81,7
7 years	86,1 / 49,4	96,4 / 59,7	106,7 / 70,0	61,6	71,9	82,2
8 years	88,0 / 50,9	98,3 / 61,0	108,6 / 71,1	63,3	73,4	83,6
9 years	89,4 / 52,5	100,2 / 62,7	111,0 / 72,9	64,8	75,2	85,6
10 years	90,9 / 53,2	101,8 / 63,1	112,7 / 73,0	65,8	76,1	86,2
11 years	93,5 / 54,4	104,6 / 64,5	115,7 / 74,6	67,4	77,9	88,3
12 years	96,0 / 57,4	107,5 / 67,1	119,0 / 76,8	70,3	80,6	90,7
13 years	95,1 / 56,7	107,2 / 67,4	119,3 / 78,1	69,5	80,7	91,8
14 years	96,0 / 57,0	107,8 / 67,6	119,6 / 78,2	70,1	81,1	92,1
15 years	96,1 / 56,0	107,5 / 66,2	118,9 / 76,4	69,4	80,1	90,6
16 years	97,9 / 56,3	109,1 / 67,0	120,3 / 77,7	70,2	81,1	91,9
17 years	98,8 / 57,5	109,9 / 67,6	121,0 / 77,7	71,3	81,7	92,1
18 años	99,1 / 57,0	110,0 / 67,4	120,9 / 77,8	71,1	81,6	92,2

Mean arterial pressure = (diastolic pressure) + (systolic pressure – diastolic pressure)/ 3 or MAP = DP + (PP/3)
MAP = DP ([SP-DP])/3
MAP = (SP + [2DP])/3

Blood pressure in males aged 1 week to 18 years old

AGE	Systolic/diastolic blood pressure			Mean arterial pressure		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum
<7 days	63,1 / 42,2	72,5 / 51,1	82,3 / 60,0	49,2	58,3	67,4
8-30 days	79,9 / 39,1	82,0 / 50,3	93,1 / 61,5	52,7	60,9	72,1
1-5 months	81,8 / 36,6	93,0 / 47,8	105,9 / 59,0	51,1	62,9	74,6
6-11 months	80,6 / 43,3	95,4 / 53,3	110,2 / 63,2	55,8	67,3	78,9
1 year	81,4 / 44,0	93,6 / 53,0	105,8 / 62,0	56,5	66,5	76,6
2 years	84,2 / 47,9	95,0 / 56,5	105,8 / 65,1	60,1	69,3	78,7
3 years	80,8 / 44,9	93,5 / 54,3	106,2 / 63,7	56,9	67,4	77,9
4 years	78,7 / 44,5	90,8 / 53,9	102,9 / 63,3	55,9	66,2	76,5
5 years	83,4 / 47,7	94,3 / 57,4	105,2 / 67,1	59,6	69,7	79,8
6 years	86,1 / 48,5	96,2/ 58,5	106,3 / 68,5	61,1	71,1	81,1
7 years	87,4 / 50,5	97,8 / 60,7	108,2 / 70,9	62,8	73,1	83,3
8 years	88,7 / 51,6	98,7 / 61,6	108,7 / 71,6	64,1	74,1	84,1
9 years	90,6 / 52,6	100,7 / 62,6	110,1 / 72,6	65,3	75,3	85,1
10 years	91,4 / 54,1	101,9 / 63,6	112,4 / 73,1	66,5	76,4	86,2
11 years	92,4 / 53,6	103,2 / 63,4	114,0 / 73,2	66,5	76,7	86,8
12 years	95,0 / 55,8	105,8 / 65,6	116,6 / 75,4	68,9	79,1	88,9
13 years	95,2 / 54,7	107,8 / 65,5	120,4 / 76,3	68,2	79,6	91,1
14 years	97,2 / 55,3	110,1 / 66,2	123,0 / 77,1	69,3	80,8	92,4
15 years	100,5 / 55,2	113,0 / 66,2	125,5 / 77,2	70,3	81,8	93,3
16 years	102,4 / 56,3	114,7 / 67,4	127,0 / 78,5	71,7	83,2	94,7
17 years	105,4 / 59,8	117,6 / 70,2	129,8 / 80,6	75,1	86,1	97,1
18 años	106,3 / 61,8	118,7 / 71,9	131,1 / 82,0	76,6	87,5	98,4

Note: Scheduled interval for taking MAP is based on patient's conditions, from every 15 minutes for severe cases to every 4 hours for stable cases. When MAP drops below the minimum value, start infusion of crystalloids, according to protocol. When MAP starts rising above the normal maximum, stop fluid infusion to prevent fluid overload.

Annex J. Glasgow Coma Scale

Glasgow Coma Scale					
Eye response		**Verbal response**		**Motor response**	
	Points		**Points**		**Points**
Spontaneous	4	Oriented	5	Obeys commands	6
To verbal command	3	Confused	4	Localizes painful stimuli	5
To painful stimuli	2	Inappropriate words	3	Flexion/Withdrawal to painful stimuli	4
No eye opening	1	Incomprehensible sounds	2	Abnormal flexion to painful stimuli	3
		No verbal response	1	Extension to painful stimuli	2
				No motor response	1

Annex K. Blantyre Coma Scale (for children)

Blantyre Coma Scale		
Response	**Findings**	**Points**
Best motor response	Localizes painful stimulus	2
	Withdraws limb from painful stimulus	1
	No response or inappropriate response	0
Best verbal response	Cries appropriately with pain, or, if verbal, speaks	2
	Moan or abnormal cry with pain	1
	No vocal response to pain	0
Eye movement	Watches or follows	1
	Fails to watch or follow	0

Annex L. Hospitalization and observation criteria

Criteria for hospitalization/admission to dengue ward	
Warning signs	Any of the warning signs (Annex G)
Signs and symptoms related to plasma leakage or shock	Weak pulse Tachycardia Narrowing pulse pressure Dehydration, oral intolerance. Dizziness or postural hypotension (lipothymia) Profuse perspiration, syncope, prostration during defervescence Hypotension or cold extremities Pleural effusion, ascites, or both
Bleeding	Spontaneous bleeding, independent of the platelet count
Organ impairment	Renal, hepatic, neurological, or cardiac Enlarged, tender liver, although not yet in shock Chest pain or respiratory distress, cyanosis
Laboratory findings and auxiliary diagnostic methods	Rising hematocrit in at least two consecutive samples (hemoconcentration) Pleural effusion, ascites, pericardial effusion, or symptomatic gallbladder-wall thickening
Co-existing conditions or disorders	Complicated pregnancy Co-existing infection
Criteria for admission exclusively to dengue ward[15]	
Co-existing conditions	Uncomplicated pregnancy Diseases such as diabetes, hypertension, peptic ulcer, hemolytic anemia, and others, stable Pneumopathy (asthma, chronic obstructive pulmonary disease, others) Obese or overweight Infancy <1 year of age or older age
Social circumstances	Living alone Living far from a health facility Without reliable means of transportation

[15] Each country's authorities determine the place of admission or type of monitoring that ensures differentiated care, according to the structure of its health system.

Annex M. Discharge criteria (all of the following conditions must be present)

Criteria	
Clinical	– No fever for 48 hours without administration of antipyretics – Improvement in clinical status (general well-being, good appetite, normal hemodynamic status, normal or increased urine output, no respiratory distress, and no evidence of bleeding)
Laboratory	– Increasing trend of platelet count – Stable hematocrit without intravenous fluids

Annex N. Assessment card for dengue patients receiving home care and report on findings for follow-up visits

Date, time each symptom appears (dd/mm/yyyy. tt)	Day						
	1	2	3	4	5	6	≥7
Bleeding							
Vomiting							
Abdominal pain							
Drowsiness or fainting							
Hematocrit							
Platelets							
Leukocytes							
Urine output/time of last voiding							
Defervescence							
Oral intake amount							
Hemodynamic status							
Temperature							
Pulse (normal, weak, or strong)							
Blood pressure							
Respiration rate							
Heart rate							

Annex O. Choice of intravenous fluids for resuscitation

Based on three randomized controlled trials comparing the different types of fluid resuscitation regimes in dengue shock in children, there is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. As a result, crystalloid solutions (0.9% saline solution or Ringer's lactate) are the choice for resuscitation of a dengue patient.

However, colloids may be the preferred choice if blood pressure has to be restored urgently, i.e. in those with pulse pressure less than 10 mm Hg. Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock (121, 122, 125).

An ideal physiological fluid is one that resembles the extracellular and intracellular fluids compartments closely. However, the available fluids have their own limitations when used in large quantities. Therefore, it is necessary to understand the limitations of these solutions to avoid their respective complications.

Crystalloid solutions

0.9% saline solution. 0.9% saline solution (normal saline solution) has an osmolarity of 308 mOsmol/L and contains a high sodium and chlorine level (154 mmol/L, each).

Normal plasma chloride ranges from 95–105 mmol/L. 0.9% saline is a suitable option for initial fluid resuscitation; however, administration of large volumes of 0.9% saline may lead to hyperchloremic acidosis, which may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels will help to identify this problem.

When the patient's serum chloride level exceeds the normal range, it is advisable to change to other alternatives such as Ringer's lactate.

Ringer's lactate/acetate. This has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolarity of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatremia. However, it is a suitable option to complete the treatment after 0.9% saline has been administered and the patient's serum chloride level has exceeded the normal range. Many specialists recommend Ringer's lactate/acetate solution for the treatment of hypovolemic shock.

Colloid solutions

Colloids are gelatin-, dextran-, or starch-based solutions. The reason not to administer colloids to dengue patients or to do so only exceptionally is that whichever colloid solution is used, it will filter into the extravascular space and increase the oncotic pressure in that space. This can perpetuate shock and make it irreversible. Another major concern regarding their use is their impact on coagulation. Dextrans have an antithrombotic activity when acting on primary hemostasis (decrease platelet aggregation) and coagulation factors (facilitate lysis of the thrombus). These effects appear four to six hours following their administration and last about 24 hours.

Of all the colloids, gelatin has the least effect on coagulation, but the highest risk of allergic reactions. Allergic reactions such as fever and chills have also been observed with Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolemic patients.

Annex P. Calculations for intravenous fluid infusion maintenance

Volume	Normal maintenance fluids per hour can be calculated based on the following formula* (equivalent to Holliday-Segar formula): 4 ml/kg/hr for the first 10 kg of body weight + 2 ml/kg/hr for the next 10 kg of body weight + 1 ml/kg/hr for every additional kg of body weight *For overweight/obese patients calculate normal maintenance fluid based on ideal body weight, (Adapted from WHO, 1997) (49).
Weight	Ideal weight for overweight or obese adults can be calculated on the basis of the following formula: female: 45.5 kg + 0.91 (height –152.4 cm); male: 50.0 kg + 0.91 (height –152.4 cm) (184).

Annex Q. Calculations for fluid needs

Fluid needs include both baseline and additional needs due to:

- diarrhea, vomiting, fistula
- perspiration
- fever: needs increase 13% for every degree Celsius
- dehydration

Several methods exist to calculate baseline fluid needs:

Adults

- 1,500 ml/m2
- 1,500 ml for the first 20 kg + 20 ml for each additional kg
- 30-35 ml/kg (ages18 to 65 years), 25 ml/kg (aged >65 years)
- 1 ml/kcal

Children

Bodyweight (kg)	Daily baseline fluid needs
1-10	100-150 ml/kg according to age
11-20	1,000 ml + 50 ml per kg above 10 kg
>20	1,500 ml + 20 ml per kg above 20 kg

Table adapted from: Food and Nutrition Board (185) and Zeman FJ (186).

Annex R. Hourly maintenance fluid regime for obese or overweight patients

Estimated ideal bodyweight (kg)	Normal maintenance fluid (ml/h) based on Holliday-Segar formula	Fluid regime based on 2-3 ml/kg/h (ml/h)	Fluid regime based on 1.5-2 ml/kg/h (ml/h)
5	10	10-15	
10	20	20-30	
15	30	30-45	
20	60	40-60	
25	65	50-75	
30	70	60-90	
35	75	70-105	
40	80	80-120	
50	90	100-150	
60	100		90-120
70	110		105-140
80	120		120-150

Annex S. Estimated ideal bodyweight for obese or overweight patients

Height (cm)	Estimated ideal bodyweight (kg) for adult males	Estimated ideal bodyweight (kg) for adult females
150	50	45.5
160	57	52
170	66	61.5
180	75	70

Annex T. Classification of bleeding risk from thrombocytopenia

Risk	
Normal	150 – 450 x 103 µL
Mild	149 – 101 x 103 µL
Moderate	100 – 50 x 103 µL
Severe	49 – 11 x 103 µL
Very severe	≤ 10 x 103 µL

Annex U. Table of inotropic and vasoactive medications

Medication	Dosage (µg/kg/min)	Comments
Adrenaline	0,01 – 3,0 (µg/kg/min)	Predominant beta effect to 0.3 µg/kg/min; increasing alpha effect with dosage >0.5 µg/kg/min. Excellent choice in post-cardiopulmonary arrest status and in patients who do not respond to dopamine. Its use requires very close EKG and hemodynamic monitoring.
Amrinone	5,0 – 20 (µg/kg/min)	Inotropic and vasodilator. Requires loading dose (3 mg/kg, rapid loading, monitoring blood pressure). May cause platelet dysfunction.
Dobutamine	5,0 – 20 (µg/kg/min)	Beta inotropic effect, virtually pure. Doses >20 µg/kg/min may be needed.
Dopamine	0,5 – 5,0 (µg/kg/min) 5,0 – 10,0 >10 (µg/kg/min)	Delta effect: renal, splanchnic, and cerebral vasodilatation (in the absence of effective self-regulation). Inotropic effect predominates (beta1). Vasopressive effect predominates (alfa1). First choice in most cases of septic shock. Dose limits are approximations. There may be individual variations in the patient's cardiovascular response, especially in newborns.
Phenylephrine	0,2 – 40 (µg/kg/min)	Vasoconstrictor (alfa1) with few or no direct effects on the heart. Good combination with beta1 inotropes.
Isoproterenol	0,05 – 1,0	Nonspecific beta effect (beta1 and beta2). Produces reflex tachycardia and vasodilatation. Favors arterial hypotension. No direct application in management of shock.
Nitroprusside	1,0 – 10	Vasodilator that can be used in septic shock as adjuvant therapy in pump failure associated with increased vascular resistance (reduces afterload). Often requires simultaneous fluid loads. Prolonged use (>72 hours) may be linked to toxicity. During shock, it can only be used under close invasive hemodynamic monitoring (Swan-Ganz catheter).
Norepinephrine	0,05 – 5,0	Causes vasoconstriction and increases cardiac output (alpha and beta agonist). Useful in some cases of dopamine and adrenaline ineffectiveness. Good combination with dobutamine (beta1).

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