HANDBOOK FOR CLINICAL MANAGEMENT OF DENGUE

Handbook for clinical management of dengue

Contents

Foreword

Since publication of the new edition of *Dengue: Guidelines for diagnosis, treatment, prevention and control* by the World Health Organization (WHO) in 2009[1], the need to provide more training to health-care workers in this area has become increasingly evident. Existing training materials need to include more detail to help clinicians recognize the evolution of the course of dengue disease in its various forms of severity, and to enable them to apply the knowledge and principles of management accordingly.

With this aim in mind and following previous successful collaborations, the WHO Department of Control of Neglected Tropical Diseases (WHO/NTD) and the Special Programme for Research and Training in Tropical Diseases (WHO/TDR), set out to develop new training materials.

This handbook has been produced to be made widely available to health-care practitioners at all levels. Aspects of managing severe cases of dengue are also described for practitioners at higher levels of health care. Additional and more specific guidance on the various areas related to clinical management of dengue (from other sources in WHO and elsewhere) are cited in the reference sections.

Contributions and reviews, by many experts both within and outside WHO, have facilitated the preparation of this publication through consultative and peer review processes. We are most grateful to all contributors who are listed in the acknowledgements section.

This handbook is not intended to replace national treatment training materials and guidelines but it aims to assist in the development of such materials produced at a local, national or regional level. All information is up-to-date at the time of writing, to the best knowledge of the authors.

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[1] Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf, last accessed July 2012.

Methodology

This handbook was developed as outlined below:

Writing team
Each chapter was allocated to one lead writer who received a small fee for their work. Declarations of interest were obtained from all lead writers and no conflicting interests were declared as a result. The lead writers were chosen because of their expertise in the field and their willingness to undertake the work.

Peer review
All the chapters were submitted for peer review. The group of peer reviewers was determined by the coordinator and lead writers in consensus, not excluding any potential peer reviewer for a particular view. The peer reviewers were not paid for their work. Declarations of interest were obtained from all peer reviewers and no conflicting interests were declared.
For each chapter, resolution of disputed issues arising from the comments of the peer reviewers was achieved by electronic mail discussion within the group of lead writers.

Acknowledgements

Abbreviations

ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BP	BP
°C	Degree Celsius
CBC	Complete blood count
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRF	Chronic renal failure
CRT	Capillary refill time
CT	Computer tomography
CVP	Central venous pressure
CVVH	Continuous veno-venous haemodialysis
DEN	Dengue
DEN-1	Dengue virus serotype 1
DEN-2	Dengue virus serotype 2
DEN-3	Dengue virus serotype 3
DEN-4	Dengue virus serotype 4
DF	Dengue fever
DHF	Dengue haemorrhagic fever
DIVC	Disseminated intravascular coagulopathy
DSS	Dengue shock syndrome
DPG	Diphosphoglycerate
ECG	Electrocardiogram
ED	Emergency department
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
FFP	Fresh frozen plasma
FWB	Fresh whole blood
G6PD	Glucose-6-phosphate dehydrogenase
GCS	Glasgow Coma Scale
GP	General practitioner
Hb	Haemoglobulin
HCO_3	Bicarbonate
HCT	Haematocrit
HF	Haemorrhagic fever
HELLP	Haemolysis, elevated liver enzymes and low platelet count
HI	Haemagglutinin inhibition test
HIA	Haemagglutination inhibition assay
HIV	Human immunodeficiency virus
HPS	Hantavirus pulmonary syndrome
HR	Heart rate
IBW	Ideal body weight
ICU	Intensive care unit
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IHA	Indirect haemagglutination
IMCI	Integrated management of childhood illness
INR	International normalized ratio
JVP	Jugular venous pressure

LVEDD	Left ventricular end-diastolic diameters
MAP	Mean arterial pressure
NS1 Ag	Non-structural protein 1 antigen
NSAID	Non-steroidal anti-inflammatory agent
NT	Neutralization test
ORS	Oral rehydration solution
PaCO$_2$	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PICU	Paediatric intensive care unit
PLT	Platelets
PR	Pulse rate
PT	Prothrombin time
PTT	Partial thromboplastin time
RA	Ringer's acetate
RBC	Red blood cell
RL	Ringer's lactate
RR	Respiratory rate
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SpO$_2$	Oxygen saturation
TWBC	Total white blood count
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization
WHO/TDR	Special Programme for Research and Training in Tropical Diseases
WHO/NTD	Department of Control of Neglected Tropical Diseases
YF	Yellow fever

1. Overview, differential diagnosis and dengue diagnostics

1.1 Overview and course of dengue illness

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations (1). After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases – febrile, critical and recovery (Figure 1). Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence i.e. during the transition of the febrile to the afebrile phase, which often coincides with the onset of the critical phase.

For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives, so long as correct and timely interventions are instituted. The key to a good clinical outcome is understanding and being alert to the clinical problems that arise during the different phases of the disease, leading to a rational approach in case management. An overview of good and bad clinical practices is given in Textbox A.

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. A well-managed front-line response not only reduces the number of unnecessary hospital admissions but also saves the lives of dengue patients. Early notification of dengue cases seen in primary and secondary care is crucial for identifying outbreaks and initiating an early response. Differential diagnosis needs to be considered (Textbox B).

Fig. 1. The course of dengue illness
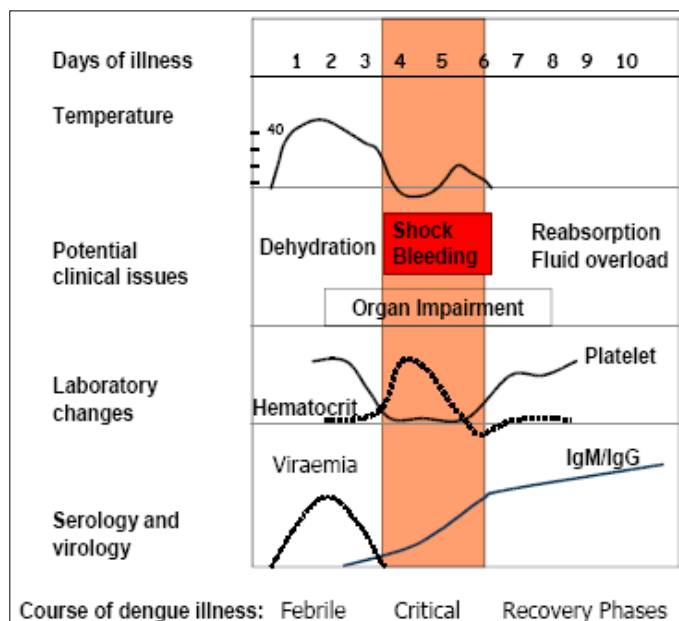
IgM = immunoglobulin M; IgG = immunoglobulin G. Temperature is given in degrees Celsius (°C)
Source: adapted from Yip, 1980 (2) by authors.

1.1.1   Febrile phase

Patients typically develop a high-grade fever suddenly. This acute febrile phase usually lasts 2−7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, retro-orbital eye pain, photophobia, rubeliform exanthema and headache (1). Some patients may have a sore throat, an injected pharynx, and conjunctival injection. Anorexia, nausea and vomiting are common.

It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early febrile phase. A positive tourniquet test in this phase indicates an increased probability of dengue (3, 4). However, these clinical features do not predict the severity of disease. Therefore it is crucial to monitor for warning signs and other clinical parameters (Textbox C) in order to recognize progression to the critical phase.

Mild haemorrhagic manifestations such as petechiae and mucosal membrane bleeding (e.g. of the nose and gums) may be seen (3, 5). Easy bruising and bleeding at venepuncture sites is present in some cases. Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase although this is not common (5). The liver may be enlarged and tender after a few days of fever (3). The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue (3). In addition to these somatic symptoms, with the onset of fever patients may suffer an acute and progressive loss in their ability to perform their daily functions such as schooling, work and interpersonal relations (6).

1.1.2   Critical phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. Instead of improving with the subsidence of high fever; patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage.

The warning signs (summarized in Textbox C) mark the beginning of the critical phase. These patients become worse around the time of defervescence, when the temperature drops to 37.5−38°C or less and remains below this level, usually on days 3–8 of illness. Progressive leukopenia (3) followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing haematocrit above the baseline may be one of the earliest additional signs (7, 8). The period of clinically significant plasma leakage usually lasts 24−48 hours. The degree of plasma leakage varies. A rising haematocrit precedes changes in blood pressure (BP) and pulse volume.

The degree of haemoconcentration above the baseline haematocrit reflects the severity of plasma leakage; however, this may be reduced by early intravenous fluid therapy. Hence, frequent haematocrit determinations are essential because they signal the need for possible adjustments to intravenous fluid therapy. Pleural effusion and ascites are usually only clinically detectable after intravenous fluid therapy, unless plasma leakage is significant. A right lateral decubitus chest radiograph, ultrasound detection of free fluid in the chest or abdomen, or gall bladder wall oedema may precede clinical detection. In addition to the plasma leakage, haemorrhagic manifestations such as easy bruising and bleeding at venepuncture sites occur frequently.

If shock occurs when a critical volume of plasma is lost through leakage, it is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With profound and/or prolonged shock, hypoperfusion results in metabolic acidosis, progressive organ impairment, and disseminated intravascular coagulation. This in turn can lead to severe haemorrhage causing the haematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response in patients with severe bleeding. In addition, severe organ involvement may develop such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding, without obvious plasma leakage or shock (9).

Some patients progress to the critical phase of plasma leakage and shock before defervescence; in these patients a rising haematocrit and rapid onset of thrombocytopenia or the warning signs, indicate the onset of plasma leakage. Cases of dengue with warning signs will usually recover with intravenous rehydration. Some cases will deteriorate to severe dengue (see Section 1.1.4).

Warning signs of dengue

Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between days 3–7 of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. The patient becomes increasingly lethargic but usually remains mentally alert. These symptoms may persist into the shock stage. Weakness, dizziness or postural hypotension occur during the shock state. Spontaneous mucosal bleeding or bleeding at previous venepuncture sites are important haemorrhagic manifestations. Increasing liver size and a tender liver is frequently observed. However, clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids. A rapid and progressive decrease in platelet count to about 100 000 cells/mm^3 and a rising haematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia ($\leq$ 5000 cells/mm^3) (4).

1.1.3 Recovery phase

As the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes, and diuresis ensues. Some patients have a confluent erythematous or petechial rash with small areas of normal skin, described as "isles of white in the sea of red" (10). Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage. The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure will occur during the critical and/or recovery phases if excessive intravenous fluids have been administered. Clinical problems during the different phases of dengue are summarized in Table 1.

Table 1. Medical complications seen in the febrile, critical and recovery phases of dengue

1	Febrile phase	Dehydration: high fever may cause neurological disturbances and febrile seizures in young children
2	Critical phase	Shock from plasma leakage: severe haemorrhage; organ impairment
3	Recovery phase	Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema

1.1.4 Severe dengue

A case of severe dengue is defined as a suspected dengue patient with one or more of the following (see Section 1.2, Figure 2):

(i)   severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress;

(ii)   severe bleeding;

(iii)   severe organ impairment.

1.1.4.1 Severe plasma leakage and dengue shock

Dengue shock syndrome (DSS) is a form of hypovolaemic shock and results from continued vascular permeability and plasma leakage. This usually takes place around defervescence, i.e. on days 4–5 of illness (range of days 3–8), and is often preceded by warning signs. From this point onwards, patients who do not receive prompt intravenous fluid therapy progress rapidly to a state of shock.

Dengue shock presents as a physiologic continuum, progressing from asymptomatic capillary leakage to compensated shock to hypotensive shock and ultimately to cardiac arrest (Textbox D).

Tachycardia (without fever during defervescence), is an early cardiac response to hypovolaemia. It is important to note that some patients, particularly adolescents and adults do not develop tachycardia even when in shock.

During **the initial stage of shock**, the compensatory mechanism that maintains a normal systolic BP produces tachycardia, quiet tachypnoea (tachypnoea without increased effort) (11), and peripheral vasoconstriction with reduced skin perfusion (manifested as cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses). As peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure (the difference between the systolic and diastolic pressures) narrows. The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure is ≤ 20 mmHg in children (e.g. 100/85 mmHg) or if they have signs of poor capillary perfusion (cold extremities, delayed capillary refill, or tachycardia). In adults, a pulse pressure of ≤ 20 mmHg may indicate more severe shock. Compensated metabolic acidosis is observed when the pH is normal with low carbon dioxide tension and a low bicarbonate level.

Patients who have dengue and are in compensated shock often remain conscious and lucid. The inexperienced physician may measure a normal systolic pressure and a normal pulse oximetry (SpO$_2$ 95–100%) in a conscious patient and underestimate the critical state of the patient.

Worsening hypovolaemic shock manifests as increasing tachycardia and peripheral vasoconstriction. Not only are the extremities cold and cyanosed but the limbs become mottled, cold and clammy. By this stage the breathing becomes more rapid and increases in depth − a compensation for the metabolic acidosis (Kussmaul's breathing). Finally, there is decompensation, both systolic and diastolic BPs disappear suddenly and dramatically, and the patient is said to have hypotensive or decompensated shock.

At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective. One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. Adults have been known to be able to work until the stage of profound shock is reached. The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypoperfusion, as is the failure to respond to painful stimuli such as venepuncture. Parents may be the first to recognize these signs − but they may be unable to describe them, other than to say something is wrong. Listen to parents! Hypotension is a late finding and signals an imminent total cardiorespiratory collapse.

Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis, multiple organ failure and an extremely difficult clinical course (12) (Textbox D). It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes for hypotensive shock to progress to cardiorespiratory collapse and cardiac arrest.

Hypotension is associated with prolonged shock which is often complicated by major bleeding (12). Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding (13). When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation.

Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen, or corticosteroids have been taken. Bleeding may occur in patients with previous peptic or duodenal ulcers (14, 15). Acute liver and renal failure and encephalopathy may be present in severe shock; these have been described even in the absence of severe plasma leakage or shock (16–21). Cardiomyopathy and encephalitis have also been reported in a few dengue case series (22–25). However, most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid overload.

Patients with severe plasma leakage may not have shock if prompt fluid replacement has been carried out. Instead, they manifest with respiratory distress due to massive pleural effusion and ascites, which can also be exacerbated by unguided intravenous fluid therapy.

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1.2 Dengue case classification

Changes in the epidemiology of dengue, especially with an increasing number of cases in adults (with and without co-morbidities) and the expansion of dengue into other regions of the world, has led to problems with the use of the existing WHO classification.

This clinical guide uses three categories for case management (A, B, C), based on the model of case classification that follows (Figure 2) after a patient has fulfilled the criteria for probable dengue.

Fig. 2. Dengue case classification by severity

Dengue case classification by severity

Dengue ± warning signs   **Severe dengue**

Without   **with warning signs**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

Criteria for dengue ± warning signs

Probable dengue
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:
• Nausea, vomiting
• Rash
• Aches and pains
• Tourniquet test positive
• Leucopenia
• Any warning sign
Laboratory confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy; restlessness
• Liver enlargement >2cm
• *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

* *Requiring strict observation and medical intervention*

Criteria for severe dengue

1. Severe plasma leakage
leading to:
• Shock (DSS)
• Fluid accumulation with respiratory distress

2. Severe bleeding
as evaluated by clinician

3. Severe organ involvement
• Liver: AST or ALT>=1000
• CNS: Impaired consciousness
• Heart and other organs

WHO/TDR 2009

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; DSS = dengue shock syndrome; HCT = haematocrit

1.2.1 Development of the revised dengue case classification

The development of the revised dengue case classification into dengue (with or without warning signs), and severe dengue, is based on several different steps and studies:

1. There have been many reports of difficulties in the use of the previous classification (1–3), which were summarized in a systematic literature review (4). Difficulties in applying the criteria for dengue haemorrhagic fever in the clinical situation, together with the increase in clinically severe dengue cases which did not fulfil the strict criteria, led to the request for the classification to be reconsidered.

2. A further set of studies (5), comparing existing national, regional and international guidelines for dengue prevention and control, concluded that the dengue case

classification existing at the time was being used inconsistently. Many countries report dengue according to locally-adapted case classification schemes and there was a perceived need to revise the case classification into levels of severity.

3. A prospective clinical multicentre study across dengue-endemic regions was set up to collect evidence about criteria for classifying dengue into levels of severity. This was supported by WHO/TDR and funded by the European Union. The study findings confirmed that by using a set of clinical and/or laboratory parameters, one sees a clear-cut difference between patients with severe and non-severe dengue. However, for practical reasons it was desirable to split the large group of patients with non-severe dengue into two subgroups – patients with warning signs and those without. The criteria for diagnosing dengue are presented in Figure 2. It must be kept in mind that even dengue patients without warning signs may develop severe dengue.

4. Expert consensus groups meeting in Latin America (Havana, Cuba, 2007), South-East Asia (Kuala Lumpur, Malaysia, 2007) and at WHO headquarters (Geneva, Switzerland, 2008) agreed that "dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome".

5. The updated model for classifying dengue has been suggested by the Geneva-based expert group and a set of studies has been initiated comparing this model to the previous case classification in terms of applicability and user-friendliness.

6. Based on current experience it can be concluded that classification into levels of severity is highly likely to be of practical use. First, to aid the clinicians' decisions about where, and how intensively, the patient should be observed and treated (i.e. for triage, which is particularly useful in outbreaks). Second, for more consistent reporting in national and international surveillance systems, and as an end-point measure in dengue vaccine and drug trials.

7. Since many countries have started to use the newly suggested model, this handbook adopts the distinction between dengue and severe dengue.

1.2.2   References

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1.2.3 Differential diagnoses of dengue

A number of infectious and non infectious diseases mimic dengue and severe dengue. It is thus necessary for clinicians to be familiar with the epidemiological characteristics of febrile diseases in the locality. Clinical manifestations associated with fever, epidemiological information and virological tests (if available) are particularly useful in patients with acute undifferentiated fever (1, 2).

Conditions that present with an influenza-like syndrome, such as influenza itself, measles, chikungunya, infectious mononucleosis and human immunodeficiency virus (HIV) seroconversion illness, may mimic the febrile phase of dengue (Textbox B). Upper respiratory symptoms such as rhinitis and cough are always present in influenza, in addition to fever, headache and body pains which are also commonly seen in dengue. Patients with dengue usually have gastrointestinal symptoms (i.e. abdominal discomfort, vomiting and sometimes diarrhoea) during the febrile phase. Coinfections with both dengue and influenza viruses make the differential diagnosis more difficult. Only rhinitis and/or nasal congestion are frankly prominent in influenza cases (3).

Infection with adenoviruses may cause fever associated with rash, abdominal pain, leukopenia, lymphopenia and organ impairment (liver, heart). Bleeding can occur, but is not frequent. Rhinitis or pharyngitis, cough and other respiratory symptoms are present, associated with cervical adenopathies in most patients (4). The diagnosis of severe acute respiratory syndrome (SARS) is difficult early in the illness. When large SARS outbreaks occurred in dengue-endemic countries, laboratory features that were highly predictive of dengue diagnosis were leukopenia and low platelet count (5).

While fever, arthralgia, rash, malaise and leukopenia are common in both chikungunya and dengue, symmetric arthritis of small joints is pathognomonic of the former. A bleeding tendency and pronounced thrombocytopenia are more frequent in dengue (6, 7).

Primary infection with HIV may mimic dengue with high fever, malaise, rash and generalized adenopathies (8). Splenomegaly and prolonged fever should prompt the consideration of malaria and typhoid in the differential diagnoses. Fever, malaise, vomiting, liver enlargement and elevated liver enzymes may be misdiagnosed as infectious hepatitis, and vice-versa (9). Evidence of plasma leakage during defervescence and thrombocytopenia are more in keeping with dengue.

The rash associated with measles and rubella has a particular distribution from the head to the trunk and extremities, but in dengue the rash usually first appears on the trunk and later extends to the face and extremities (10). Although both diseases may have common signs and symptoms, including myalgia and arthralgia, measles patients always have a cough, rhinitis and conjunctivitis. Fever, rash and adenopathies may be seen in dengue, rubella, erythema infectiosum caused by parvovirus B19 (11), and herpes virus type 6 (12). Other exanthems such as enteroviruses, infectious mononucleosis, scarlet fever and Kawasaki disease are associated with particular characteristics.

Sepsis and meningococcal disease should be considered in shock patients because of the need for urgent treatment with specific antibiotics. Common symptoms and signs with dengue cases are fever, rash, petechiae, bleedings and shock associated with leukopenia (particularly in severe gram-negative sepsis and poor prognosis meningococcaemia) and thrombocytopenia (13). In septic shock, the temperature is usually high, although it could be subnormal in the late stages. Bounding pulses with warm extremities are present in

early septic shock. In dengue patients, shock usually occurs after defervescence; hence the temperature is often subnormal or normal, pulse volume is small, and pulse pressure is narrowed with the patient having cold extremities. Clinical and radiographic signs of plasma leakage and progressive haemoconcentration in severe dengue cases are useful distinguishing features. Another helpful tool to differentiate dengue from these other diseases is to determine the sequence of signs and symptoms, including warning signs during defervescence that frequently announce severe dengue.

Clinical distinction between leptospirosis and dengue may be challenging, particularly when both epidemics are concurrent (14). Delayed antibiotic therapy is associated with mortality in leptospirosis. Jaundice is more often associated with leptospirosis, but ocular pain, arthralgia and diarrhoea could be present as well (15). Leptospirosis is frequently associated with professional activity (e.g. working with garbage or in agriculture) or with a history of certain pastimes (e.g. trekking to waterfalls or playing water sports). Pulmonary haemorrhage is a particular form of leptospirosis without jaundice that has some common signs and symptoms with severe dengue; these include fever, thrombocytopenia, shock and massive bleeding in the lungs (16). Pulmonary haemorrhage is uncommon in dengue; evidence of plasma leak such as pleural effusion or ascites would suggest the diagnosis of dengue.

Leukopenia and thrombocytopenia, with or without bleeding, may be clinical manifestations of infectious diseases such as malaria, leptospirosis, typhoid, typhus, bacterial sepsis and acute HIV-seroconversion illness. Leukopenia and thrombocytopenia may be present in non-infectious diseases such as systemic lupus and other systemic auto-immune diseases; acute leukaemia (17) and other haematological disorders such as Henoch-Schönlein purpura and thrombocytopenic purpuric syndromes, mainly thrombotic thrombocytopenic purpura and immunological thrombocytopenic purpura.

During the critical phase of dengue, patients with plasma leakage or shock may present with severe abdominal pain when the fever subsides. The severe abdominal pain may mimic an acute abdominal condition such as in acute appendicitis. Ultrasound studies in these patients have shown fluid collection around the appendix. Other abdominal signs such as right iliac fossa tenderness and rebound tenderness disappear after a few days of conservative management (18).

Another misdiagnosis is acute (alithiasis) cholecystitis, with the abdominal ultrasonograph showing thickening/oedema of the wall of the gallbladder. This is associated with pain in the subhepatic region, mainly during defervescence. Plasma leakage, not inflammation, is responsible for these clinical features. Patients who underwent surgery as a result of misdiagnosis with an acute surgical abdominal condition have been found to have life-threatening bleedings; some went on to die. Failure to recognize severe abdominal pain as a warning sign that heralds severe dengue has led to the misdiagnosis of renal lithiasis and delayed intravenous fluid treatment for dengue shock. A differentiating feature of an acute surgical abdomen and the severe abdominal pain of dengue shock is that the abdomen in dengue shock is soft and the pain subsides with fluid resuscitation. Other medical emergencies presenting with intense and continuous abdominal pain include diabetic ketoacidosis, renal failure and lactic acidosis. Again, evidence of plasma leakage (especially after intravenous fluid therapy), thrombocytopenia and bleeding tendencies help to distinguish dengue from other medical or surgical conditions.

The group of viral haemorrhagic fever diseases have bleeding, thrombocytopenia and shock in common. All have the monocyte/macrophage as the target cell (19). These diseases are present in different geographic areas, have different vectors (Table 2), have causative agents that belong to different viral families (20–22), and have different means of transmission. The main pathogenic difference is that the severity of dengue disease is mediated by an immunological disorder that enhances viral infection, causing patients to have complications after the viraemic (febrile) phase, during defervescence or 24 hours later. An analysis of the particular clinical, epidemiological and vectoral information will lead to the respective diagnosis.

Yellow fever (YF) is now considered a re-emergent disease in Africa and the Americas. *Aedes aegypti* is the common vector of YF and dengue and some clinical features are common to both diseases. The classic description of YF covers two phases: the febrile phase and the toxic phase. During the toxic phase, liver damage causing jaundice, renal insufficiency and central nervous system impairment are life-threatening characteristics. The disease in adults has been associated with high mortality, a relatively short duration, symptoms such as headache, back pain, fever, vomiting and nausea, jaundice, haemorrhages and unconsciousness (23).

Severe dengue with noncardiogenic pulmonary oedema (fluid overload) and pulmonary distress has clinical signs common to the Hantavirus pulmonary syndrome (HPS). In severe dengue, and not in HPS, the pulmonary oedema is usually preceded by prolonged or recurrent shock, associated with bleedings in the lung and other sites, together with signs of plasma leakage and fluid overload. The initial picture of HPS is very similar to that of influenza, with fever, myalgia, vomiting and cough associated with dyspnoea at the end of the first week, and leukocytosis, neutrophilia, thrombocytopenia and elevated haematocrits (24). Children with HPS may have severe abdominal pain and liver enlargement, but bleeding is not frequent and they do not present with pulmonary haemorrhage, but with interstitial and alveolar oedema (25).

Table 2. Viral haemorrhagic fevers

Disease	Virus (family)	Geographic area	Vector
Argentinian HF	Junin (*Arenaviridae*)	Argentina	Rodents
Bolivian HF	Machupo (*Arenaviridae*)	Plurinational state of Bolivia	Rodents
Lassa fever	Lassa (*Arenaviridae*)	Africa	Rodents
Dengue	Dengue (*Flaviviridae*)	America/Africa/Asia	Mosquitoes
Yellow fever	Yellow Fever (*Flaviviridae*)	South America/Asia	Mosquito
Haemorrhagic fever with renal syndrome	Hantaan and related (*Bunyaviridae*)	Europe/Asia/America and Africa	Rodents
Rift valley fever	Rift Valley fever (*Bunyaviridae*)	Africa	Mosquito
Crimean-Congo haemorrhagic fever	Crimean/Congo haemorrhagic fever virus (*Crimea Bunyaviridae*)	Africa/Europe/Asia	Ticks
Ebola fever	Ebola (*Filoviridae*)	Africa	Unknown
Marburg fever	Marburg (*Filoviridae*)	Africa	Unknown
Kyasanur forest fever	Kyasanur HF (*Flaviviridae*)	India	Ticks
Omsk haemorrhagic fever	Omsk HF (*Flaviviridae*)	Russia-Romania	Ticks
Venezuelan haemorrhagic fever	Guanarito (*Arenaviridae*)	Venezuela (state of Portuguesa)	Rodents

HF = haemorrhagic fever

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1.3 Dengue diagnostics for clinicians

The objectives of dengue laboratory diagnosis are (i) to confirm the clinical diagnosis and (ii) to provide information for epidemiological surveillance. Laboratory diagnosis is not necessary for clinical management except in atypical cases or when carrying out differential diagnosis with other infectious diseases.

Laboratory diagnosis of dengue is made by detecting the virus and/or any of its components (infective virus, virus genome, dengue antigen) or by investigating the serological responses present after infection (specifically IgM and IgG levels) (Table 3) (1–4).

Table 3. Dengue diagnostics and sample characteristics

	Clinical sample	Diagnostic method	Methodology	Time to results
Virus detection and its components	Acute serum (1–5 days of fever) and necropsy tissues	Viral isolation	Mosquito or mosquito cell culture inoculation	One week or more
		Nucleic acid detection	RT-PCR and real time RT-PCR	1 or 2 days
		Antigen detection	NS1 Ag rapid tests	Minutes
			NS1 Ag ELISA	1 day
			Immuno-histochemistry	2–5 days
Serological response	Paired sera (acute serum from 1–5 days and second serum 15–21 days after)	IgM or IgG seroconversion	ELISA HIA	1–2 days
			Neutralization Test	Minimum 7 days
	Serum after day 5 of fever	IgM detection (recent infection)	ELISA	1 or 2 days
			Rapid tests	Minutes
		IgG detection	IgG ELISA HIA	1 or 2 days

ELISA = enzyme-linked immunosorbent assay; HIA = haemagglutination inhibition assay; IgG = immunoglobulin G; IgM = immunoglobulin M; NS1 Ag = non-structural protein 1 antigen; RT-PCR = reverse transcriptase polymerase chain reaction

Dengue viruses are RNA viruses belonging to the family *flaviviridae*, genus *flavivirus*. The four dengue viruses (DEN-[1–4]) are serologically related but antigenically and genetically distinctive (5–7).

Three main aspects should be considered for an adequate dengue diagnosis:

• virological and serological markers in relation to the time of dengue infection;

• type of diagnostic method in relation to clinical illness;

• characteristics of the clinical samples.

Virological and serological markers in relation to time of dengue infection (Figure 3)

An incubation period of 4–10 days occurs after the mosquito bites, resulting in an asymptomatic or symptomatic dengue infection. During this period the virus replicates and an antibody response is developed. In general, viraemia is detectable in most dengue cases at the same time that symptoms appear, and is no longer detectable at the time of defervescence. The development of IgM antibody is coincident with the disappearance of fever and viraemia (8). Virological and serological markers differ in time evolution and titre response and according to whether the infection is primary or secondary.

In a primary infection (i.e. when an individual is infected for the first time with a flavivirus), viraemia develops from 1–2 days before the onset of fever until 4–5 days after. Accordingly, anti-dengue IgM specific antibodies can be detected 3−6 days after fever onset. On average, IgM is detected in 50% of cases by days 3–5 after the onset of illness, this figure increasing to 95–98% for days 6−10. Low levels of IgM are still detectable around one to three months after fever. In addition, the primary infection is characterized by slowly increasing but low levels of dengue-specific IgG, becoming elevated at days 9−10. Low IgG levels persist for decades, an indication of a past dengue infection (1–4, 9, 10).

A totally different picture is observed during a secondary infection, with a rapid and higher increase of anti-dengue specific IgG antibodies and slower and lower levels of IgM. High IgG levels remain for 30–40 days. A short-lasting but higher viraemia level characterizes the secondary infection compared to the primary infection (1–4, 9, 10).

Fig. 3. Virological and serological markers of dengue infection according to time of illness
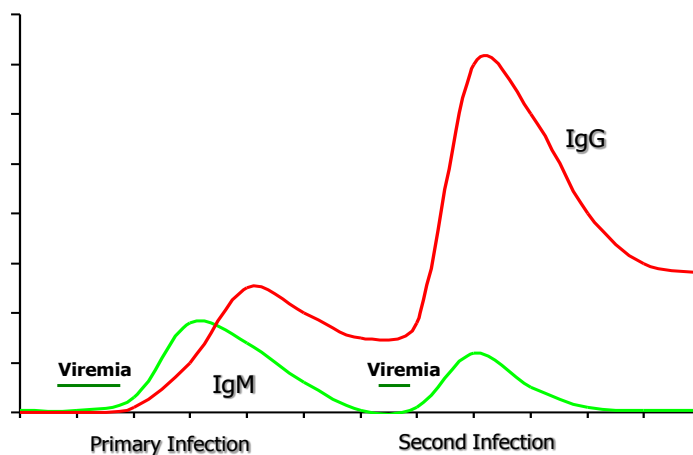
IgG = immunoglobulin G; IgM = immunoglobulin M

Type of dengue diagnostic method in relation to time of clinical illness

The diagnostic method to confirm an acute infection depends on the time of clinical illness: the febrile phase is coincident with the presence of viraemia, some viral components and replication products in blood; the critical and convalescent phases coincide with the development of antibodies, as summarized in Table 3.

Febrile phase (day 1 to days 4–5 of fever)

The infective virus can be isolated in serum by inoculation in tissue culture (mosquito cell cultures) and mosquitoes. This method allows for identification of the viral serotype.

Virus genome detection using reverse transcriptase polymerase chain reaction (RT-PCR) and real-time RT-PCR confirms an acute dengue infection. Both methods have a high sensitivity and allow serotype identification and quantification of genome copies (1–4, 11–13). Some studies suggest the presence of a higher number of copies in severe dengue cases (14–16).

NS1 Ag is a marker of acute dengue infection. Both enzyme-linked immunosorbent assay (ELISA) and rapid commercial tests are available for NS1 Ag detection. The sensitivity and specificity of commercial kits in different serotype infections and days of illness are being evaluated (17–19).

Critical and convalescent phases (after days 4–5 of illness)

Specific IgM is the best marker of a recent dengue infection. MAC-ELISA and rapid tests are the most frequent methods for IgM detection; however a recent evaluation of four rapid tests demonstrated a low sensitivity (20, 21). In addition to IgM, high levels of specific IgG in sera collected early after fever onset as detected by ELISA and haemagglutination inhibition assay (HIA) also suggest a recent dengue infection (1–4, 9).

Primary infections are characterized by high levels of IgM and low levels of IgG, while low levels of IgM with high levels of IgG characterize secondary infections.

A single serum sample collected after day 5 of fever onset is useful for IgM determination. Depending on the IgG level in the sample, classification into primary or secondary infection can also be determined using the IgM/IgG optical density ratio. Ratios greater than 1.2 (using the patient's sera at 1/100 serum dilution) or 1.4 (using serum dilution of 1/20) suggest a primary infection (1). In addition, IgG titres higher than 1/1280 by HIA or ELISA are also suggestive of a secondary infection (1–4, 9, 10).

As IgM antibodies persist for almost three months after fever onset, the detection in samples collected late after the acute phase of illness suggests a recent infection. In dengue endemic countries, acute clinical cases with a positive IgM are classified as probable dengue cases.

The study of paired sera (acute and convalescent serum samples with the second sample being collected 15–21 days after the first sample), allows for serological confirmation of dengue infection. The diagnosis depends upon the demonstration of rising titres of dengue antibodies between acute and convalescent sera (1–4, 9, 22).

A broad cross-reactivity of ELISA and HIA with other flaviviruses has been observed. Neutralization Test is the method of choice for determination of specific serotype (1–4, 9, 10, 23).

Characteristics of the clinical sample

Similar to other enveloped viruses, dengue virus is labile and readily inactivated at temperatures above 30°C, so care should be taken during transportation and storage of samples. Serum samples collected during the first 4 days of fever are useful for virus, genome and dengue antigen detection, thus confirming a dengue infection. Samples should be rapidly transported at 4°C to the laboratory and be processed as soon as possible. Sterile serum without anticoagulant is useful. If specimen delivery cannot be performed in the first 24–48 hours, freezing at –70°C is recommended.

Sera for serological studies should be stored at 4°C for short time periods and at –20°C for a longer time periods. When serum collection or transportation is not possible, blood collected on filter papers represents an opportunity for IgM and IgG determination and also for RNA detection (24, 25).

Tissue specimens collected from fatal cases are useful for virus, genome and antigen detection. Liver, spleen and lymph nodes are the tissues of choice (26, 27). Tissue samples should be collected immediately after death and be immediately frozen at –70°C, or rapidly transported at 4°C to the laboratory for sample processing. Fresh tissues are also suitable for virus isolation (26–29).

Besides general patient information a summary of clinical and epidemiological data, such as the date of fever onset, method of sample collection and the type of sample, should accompany clinical samples (1).

The usefulness of available diagnostic tests depends on the level of health care (see Table 4). At primary-care level, rapid tests for NS1 Ag detection (suggestive of an acute dengue infection) as well as rapid tests for IgM determination (suggestive of a recent infection), are useful. As patients access care independent of the period of infection suffered – some early, some late – a combination of both NS1 Ag and IgM markers is advisable. At district health centres, both antigen-based tests and serology can be performed using ELISA and rapid tests. All diagnostic methods should be available at reference centres, including virus isolation, nucleic acid detection, diagnostics for tissues samples and all serological techniques (1–4, 30).

Laboratory confirmation of a dengue case

A diagnosis of dengue infection is confirmed by the detection of the virus, the viral genome or NS1 Ag, or seroconversion of IgM or IgG (from negative to positive IgM/IgG or four-fold increase in the specific antibody titre) in paired sera (see Table 5).

A positive IgM serology or a haemagglutinin inhibition test (HIA) antibody titre of 1280 or higher (or comparable figures by ELISA in a single specimen), are all diagnostic criteria of a probable dengue infection. Both probable and confirmed dengue cases should be notified to health authorities (1–4, 9, 30).

Table 4. Recommended diagnostic tool according to laboratory service level

		Primary health-care centres	District health centres	Reference centres
Virus isolation				Yes
Genome detection				Yes
NS1 Ag detection	Rapid tests	Yes	Yes	Yes
	ELISA		Yes	Yes
IgM detection	Rapid tests	Yes	Yes	Yes
	ELISA		Yes	Yes
IgG detection	ELISA			Yes
	IHA			Yes
	Neutralization assay			Yes

ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IgM = immunoglobulin M; IHA = indirect haemagglutination; NS1 Ag = non-structural protein 1 antigen

Table 5. Confirmed and probable dengue diagnosis, interpretation of results and sample characteristics

	Method	Interpretation	Sample characteristics
Confirmed dengue infection	Viral isolation	Virus isolated	Serum (collected at 1–5 days of fever) Necropsy tissues
	Genome detection	Positive RT-PCR or positive real-time RT-PCR	
	Antigen detection	Positive NS1 Ag	
		Positive immunohistochemical	Necropsy tissues
	IgM seroconversion	From negative IgM to positive IgM in paired sera	Acute serum (days 1–5) and convalescent serum (15–21 days after first serum)
	IgG seroconversion	From negative IgG to positive IgG in paired sera or 4-fold increase IgG levels among paired sera	
Probable dengue infection	Positive IgM	Positive IgM	Single serum collected after day 5
	High IgG levels	High IgG levels by ELISA or HI (≥ 1280)	

ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IgM = immunoglobulin M; NS1 Ag = non-structural protein 1 antigen; RT-PCR = reverse transcriptase polymerase chain reaction

1.3.1 References

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2.   Recommendations for clinical management

2.1   *A stepwise approach to the management of dengue*

Health-care workers at the first levels of care should apply a stepwise approach as suggested in Table 6.

Table 6. A stepwise approach to the management of dengue

Step I − Overall assessment	
I.1	History, including symptoms, past medical and family history
I.2	Physical examination, including full physical and mental assessment
I.3	Investigation, including routine laboratory tests and dengue-specific laboratory tests
Step II − Diagnosis, assessment of disease phase and severity	
Step III − Management	
III.1	Disease notification
III.2	Management decisions. Depending on the clinical manifestations and other circumstances, patients may (1): - be sent home (Group A) - be referred for in-hospital management (Group B) - require emergency treatment and urgent referral (Group C)

2.1.1   *Step I – Overall assessment*

The **history** should include:

- date of onset of fever/illness;
- quantity of oral fluid intake;
- diarrhoea;
- urine output (frequency, volume and time of last voiding);
- assessment of warning signs (Textbox C);
- change in mental state/seizure/dizziness;
- other important relevant history, such as family or neighbourhood dengue, travel to dengue-endemic areas, co-existing conditions (e.g. infancy, pregnancy, obesity, diabetes mellitus, hypertension), jungle trekking and swimming in waterfalls (consider leptospirosis, typhus, malaria), recent unprotected sex or drug abuse (consider acute HIV-seroconversion illness).

The **physical examination** should include:

- assessment of mental state;
- assessment of hydration status;
- assessment of haemodynamic status (Textbox D);
- checking for quiet tachypnoea/acidotic breathing/pleural effusion;
- checking for abdominal tenderness/hepatomegaly/ascites;
- examination for rash and bleeding manifestations;
- tourniquet test (repeat if previously negative or if there is no bleeding manifestation).

The **investigation** (refer also to Section 1.3)

If facilities are available, a full blood count should be done at the first visit (it may be normal); and this should be repeated daily until the critical phase is over. The haematocrit in the early febrile phase could be used as the patient's own baseline. Decreasing white blood cell and platelet counts make the diagnosis of dengue very likely. Leukopenia usually precedes the onset of the critical phase and has been associated with severe disease. A rapid decrease in platelet count, concomitant with a rising haematocrit compared to the baseline, is suggestive of progress to the plasma leakage/critical phase of the disease. These changes are usually preceded by leukopenia ($\leq$ 5000 cells/mm^3). In the absence of the patient's baseline, age-specific population haematocrit levels could be used as a surrogate during the critical phase.

If facilities for a full blood count are not available or if resources are limited, such as in outbreak settings, a full blood count or microhaematocrit should be done at the first visit to establish the baseline. This should be repeated after the 3rd day of illness and in those with warning signs and risk factors for severe disease.

Dengue-specific laboratory tests should be performed to confirm the diagnosis. However, it is not necessary for the acute management of patients, except in cases with unusual manifestations.

Additional tests should be considered in patients with co-morbidities and severe disease as indicated. These may include tests of liver function, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine-specific gravity.

2.1.2 Step II – Diagnosis, assessment of disease phase and severity

On the basis of evaluations of the history, physical examination and/or full blood count and haematocrit, clinicians should determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and haemodynamic state of the patient, and whether the patient requires admission (Textboxes E and F).

2.1.3 Step III – Disease notification and management decision (Groups A–C)

Disease notification

In dengue-endemic countries, cases of suspected, probable and confirmed dengue should be notified early so that appropriate public-health measures can be initiated. Laboratory confirmation is not necessary before notification, but it should be obtained. In non-endemic countries, usually only confirmed cases will be notified.

Management decisions

Depending on the clinical manifestations and other circumstances, patients may either be sent home (Group A); be referred for in-hospital management (Group B); or require emergency treatment and urgent referral (Group C). Figure 4 shows a summary of management decisions.

Fig. 4 Dengue case management algorithm (2)

Dengue Case Management

Assessment

Presumptive Diagnosis:
Live in / travel to endemic area plus
Fever and two of the following:
• Anorexia and nausea
• Rash
• Aches and pains
• Warning signs
• Leucopenia
• Tourniquet test positive

Lab.confirmed dengue
(important when no sign of plasma leakage)

Warning signs:
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy; restlessness
• Liver enlargement >2cm
• Laboratory: Increase in HCT concurrent with rapid decrease of platelet count

Classification

negative

positive

Co-existing conditions
Social circumstances → positive

negative

Dengue without warning signs

Dengue with warning signs

Severe Dengue

Management

Group A	Group B		Group C
May be sent home	**Referred for in-hospital care**		**Require emergency treatment**
Group criteria	**Group criteria**	**OR**	**Group criteria**
Patients who do not have warning signs **AND** who are able: ○ T o tolerate adequate volumes of oral fluids ○ T o pass urine at least once every 6 hours	Patients with any of the following features: ○ C o-existing conditions such as pregnancy, infancy, old age, diabetes mellitus ○ S o cial circumstances such as living alone, living far from hospital	Existing warning signs: ○ A b d o minal pain or tenderness ○ P ersistent vomiting ○ C l i nical fluid accumulation ○ M u c o sal bleeding ○ L ethargy/ restlessness ○ L i ver enlargement >2cm ○ L a b oratory: increase in Hct	Patients with any of the following features. ○ S e v ere plasma leakage with shock and/or fluid accumulation with respiratory distress ○ S e v ere bleeding ○ S e v ere organ impairment
Laboratory tests ○ F ull blood Count (FBC) ○ H a e matocrit (Hct)	**Laboratory tests** ○ F ull blood Count (FBC) ○ H a e matocrit (Hct)		**Laboratory tests** ○ F ull blood Count (FBC) ○ O t h er organ function tests as ○ H a e matocrit (Hct) indicated
Treatment Advice for: ○ A d e quate bed rest ○ A d e quate fluid intake ○ P a r a c etamol, 4 gram max. per day in adults and accordingly in children Patients with stable Hct can be sent home	**Treatment** ○ E n c ouragement for oral fluids ○ I f not tolerated, start intravenous fluid therapy 0,9% saline or Ringer Lactate at maintenance rate	**Treatment** ○ O btain reference Hct before fluid therapy ○ G i v e isotonic solutions such as 5-7 ml/kg/hr for 1-2 hours, then reduce to 3-5 ml/kg/hr for 2-4 hr, and then reduce to 2-3 ml/kg/hr or less according to clinical response **Reassess clinical status and repeat Hct** ○ I f Hct remains the same or rises only minimally -> continue with 2-3 ml/kg/hr for another 2-4 hours ○ I f worsening of vital signs and rapidly rising Hct -> increase rate to 5-10 ml/kg/hr for 1-2 hours **Reassess clinical status, repeat Hct and review fluid infusion rates accordingly** ○ R e duce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase. **This is indicated by:** ○ A d e quate urine output and/or fluid intake ○ H c t decreases below the baseline value in a stable patient	**Treatment of compensated shock:** ○ Start I.V. fluid resuscitation with isotonic crystalloid solutions at 5-10 ml/kg/hr over 1 hr ○ R eassess patient's condition, **If patient improves:** ○ I . V. fluids should be reduced gradually to 5-7 ml/kg/hr for 1-2 hr, then to 3-5 ml/kg/hr for 2-4 hr, then to 2-3 ml/kg/hr for 2-4 hr and then reduced further depending on haemodynamic status ○ I . V. fluids can be maintained for up to 24 - 48 hours **If patient still unstable:** ○ C h eck Hct after first bolus ○ **If Hct increases**/ still high (>50%), repeat a second bolus of crystalloid solution at 10-20 ml/kg/hr for 1 hr. ○ I f improvement after second bolus, reduce rate to 7-10 ml/kg/hr for 1-2 hr, continue to reduce as above. ○ **If Hct decreases,** this indicates bleeding and need to cross-match and transfuse blood as soon as possible **Treatment of hypotensive shock** ○ I nitiate I.V. fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus for 15 min **If patient improves** ○ G i v e a crystalloid / colloid solution of 10 ml/kg/hr for 1 hr, then reduce gradually as above **If patient still unstable** ○ R e view the Hct taken before the first bolus ○ **If Hct was low** (<40% in children and adult females, < 45% in adult males) this indicates bleeding, the need to crossmatch and transfuse (see above) ○ **If HCT was high** compared to the baseline value, change to I.V. colloids at 10-20 ml/kg as a second bolus over ½to 1 hour; reassess after second bolus ○ **If improving** reduce the rate to 7-10 ml/kgt/hr for 1-2 hours, then back to I.V. crystalloids and reduce rates as above ○ I f condition still unstable, repeat Hct after second bolus ○ **If Hct decreases,** this indicates bleeding, see above ○ **If Hct increases/** remains high (> 50%), continue colloid infusion at 10-20 ml/kg as athird bolus over 1 hr, then reduce to 7-10 ml /kg /hr for 1-2 hours, then change back to crystalloid solution and reduce rate as above **Treatment of haemorrhagic complications:** ○ G i v e 5-10 ml/kg of fresh packed red cells or 10-20 ml/kg fresh whole blood
Monitoring ○ D a i l y review for disease progression: ▪ D e creasing WBC ▪ D e f ervescence ▪ W a r ning signs (until out of critical period) ○ A d vice for immediate return to hospital if development of any warning signs ○ W r i tten advice of management (e.g. home care card for dengue)	**Monitoring** ○ T emperature pattern ○ V olume of fluid intake and losses ○ U rine output – volume and frequency ○ W a r ning signs ○ H ct, white blood cell and platelet counts	**Monitoring** ○ V ital signs and peripheral perfusion (1-4 hourly until patient is out of critical phase ○ U rine output (4-6 hourly) ○ H ct (before and after fluid replacement, then 6-12 hourly) ○ B l o o d glucose ○ O t h er organ functions (renal profile, liver profile, coagulation profile, as indicated)	

Discharge criteria:
-> all of the following criteria must be present

○ **No fever for 48 hours**
○ **Improvement in clinical picture**

○ **I n c r e asing trend of platelet count**
○ **No respiratory distress**

○ **S t able haematocrit without intravenous fluids**

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2.2 Treatment according to Groups A–C (1)

2.2.1 Group A

These are patients who may be sent home (see the home-care card for dengue in Textbox G).

These patients are able to tolerate adequate volumes of oral fluids, pass urine at least once every six hours and do not have any of the warning signs (particularly when fever subsides).

The key to the success of ambulatory (outpatient) management is to give clear, definitive advice on the care that the patient needs to receive at home: i.e. bed rest and frequent oral fluids. Patients with ≥ 3 days of illness should be reviewed daily for disease progression (indicated by decreasing white blood cell and platelet counts and increasing haematocrit, defervescence and warning signs) until they are out of the critical period. Those with stable haematocrit can be sent home but should be advised to return to the nearest hospital immediately if they develop any of the warning signs and to adhere to the following action plan:

- Adequate oral fluid intake may reduce the number of hospitalizations (3). Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. The choice of fluids should be based on the local culture: coconut water in some countries, in others rice water or barley water. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance. Commercial carbonated drinks that exceed the isotonic level (5% sugar) should be avoided. They may exacerbate hyperglycaemia related to physiological stress from dengue and diabetes mellitus. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. A record of oral fluid and urine output could be maintained and reviewed daily in the ambulatory setting.

- Give paracetamol for high fever if the patient is uncomfortable. The recommended dose is 10 mg/kg/dose, not more than 3−4 times in 24 hours in children and not more than 3 g/day in adults). Sponge with tepid water if the patient still has a high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding.

- Instruct caregivers that the patient should be brought to hospital immediately if any of the following occur: no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffee-ground vomiting), shortness of breath, not passing urine for more than 4−6 hours.

Admission during the febrile period should be reserved for those who are unable to manage adequate oral hydration at home, infants, and those with co-existing conditions. Refer to Textbox C and Section 1.1.2 for a description of the warning signs.

Ambulatory patients should be monitored daily for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding and complete blood counts.

2.2.2   Group B

These are patients who should be admitted for in-hospital management for close observation as they approach the critical phase. These include patients with warning signs, those with co-existing conditions that may make dengue or its management more complicated (such as pregnancy, infancy, old age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic haemolytic diseases such as sickle-cell disease and autoimmune diseases), and those with certain social circumstances (such as living alone, or living far from a health facility without reliable means of transport). Rapid fluid replacement in patients with warning signs is the key to prevent progression to the shock state.

If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy from this early stage may modify the course and the severity of disease. The action plan should be as follows and applies to infants, children and adults:

- Obtain a reference haematocrit before intravenous fluid therapy begins. Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution. Start with 5–7 ml/kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hour for 2–4 hours, and then reduce to 2–3 ml/kg/hour or less according to the clinical response (see Textboxes H, J and K).

- Reassess the clinical status and repeat the haematocrit. If the haematocrit remains the same or rises only minimally, continue at the same rate (2–3 ml/kg/hour) for another 2–4 hours. If the vital signs are worsening and the haematocrit is rising rapidly, increase the rate to 5–10 ml/kg/hour for 1–2 hours. Reassess the clinical status, repeat the haematocrit and review fluid infusion rates accordingly.

- Give the minimum intravenous fluid volume required to maintain good perfusion and an urine output of about 0.5 ml/kg/hour. Intravenous fluids are usually needed for only 24–48 hours. Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase. This is indicated by urine output and/or oral fluid intake improving, or the haematocrit decreasing below the baseline value in a stable patient.

- Patients with warning signs should be monitored by health-care providers until the period of risk is over. A detailed fluid balance should be maintained. Parameters that should be monitored include vital signs and peripheral perfusion (1–4 hourly until the patient is out of the critical phase), urine output (4–6 hourly), haematocrit (before and after fluid replacement, then 6–12 hourly), blood glucose and other organ functions (such as renal profile, liver profile, coagulation profile, as indicated).

If the patient has dengue with co-existing conditions but without warning signs, the action plan should be as follows:

- Encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% saline or Ringer's lactate with or without glucose at the appropriate maintenance rate (Textbox H). Use the ideal body weight for calculation of fluid infusion for obese and overweight patients (Textboxes J and K). Patients may be able to take oral fluids after

a few hours of intravenous fluid therapy. Thus, it is necessary to revise the fluid infusion frequently. Give the minimum volume required to maintain good perfusion and urine output. Intravenous fluids are usually needed only for 24−48 hours.

Patients should be monitored by health-care providers for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, haematocrit, white blood cell and platelet counts (Textbox K). Depending on the clinical picture and the facilities of the hospital or health centre, other laboratory tests (such as liver and renal functions tests) can also be carried out.

2.2.3 Group C

These are patients with severe dengue who require emergency treatment and urgent referral because they are in the critical phase of the disease and have:

- severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress;

- severe haemorrhages;

- severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

All patients with severe dengue should be admitted to a hospital with access to blood transfusion facilities. Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. The crystalloid solution should be isotonic and the volume just sufficient to maintain an effective circulation during the period of plasma leakage. Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution: in the case of hypotensive shock, colloid solution is preferred (Textbox L). If possible, obtain haematocrit levels before and after fluid resuscitation.

Continue replacement of further plasma losses to maintain effective circulation for 24−48 hours. For overweight or obese patients, the ideal body weight should be used for calculating fluid infusion rates (see Textboxes J and K). All shock patients should have their blood group taken and a cross-match carried out. Blood transfusion should be given only in cases with established severe bleeding, or suspected severe bleeding in combination with otherwise unexplained hypotension.

Fluid resuscitation must be clearly separated from simple fluid administration. This is a strategy in which larger volumes of fluids (e.g. 10−20 ml/kg boluses) are administered for a limited period of time under close supervision, to evaluate the patient's response and to avoid the development of pulmonary oedema. These fluids should not contain glucose. The degree of intravascular volume deficit in dengue shock varies. Input is typically much greater than output, and the input/output ratio is of no help in judging fluid resuscitation needs during this period.

The goals of fluid resuscitation include:

- improving central and peripheral circulation – i.e. decreasing tachycardia, improving BP and pulse volume, warm and pink extremities, a capillary refill time < 2 seconds;

- improving end-organ perfusion – i.e. achieving a stable conscious level (more alert or less restless), and urine output ≥ 0.5 ml/kg/hour or decreasing metabolic acidosis.

2.2.3.1 Treatment of shock (4–8)

The action plan for treating patients with **compensated shock** is as follows (see algorithms in Figures 5 and 6):

- Obtain a reference haematocrit before starting intravenous fluid therapy. Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour in adults and 10–20 ml/kg/hour over one hour in infants and children. Then reassess the patient's condition (vital signs, capillary refill time, haematocrit, urine output).

- If the **adult** patient's condition improves, intravenous fluids should be gradually reduced to 5–7 ml/kg/hour for 1–2 hours; then 3–5 ml/kg/hour for 2–4 hours and finally 2–3 ml/kg/hour which can be maintained up to 24–48 hours. Consider reducing intravenous fluid earlier if oral fluid intake improves. The total duration of intravenous fluid therapy should not exceed 48 hours.

- If the condition in the **infant or child** improves, intravenous fluids should be reduced to 10 ml/kg/hour for 1–2 hours; then to 7 ml/kg/hour for 2 hours; 5 ml/kg/hour for 4 hours and then to 3 ml/kg/hour, which can be maintained for up to 24–48 hours. Consider reducing intravenous fluid earlier if oral fluid intake improves. The total duration of intravenous fluid therapy should not exceed 48 hours.

- (See Textboxes H and J for a more appropriate estimate of the normal maintenance requirement based on ideal body weight).

- If **vital signs are still unstable (i.e. shock persists)**, check the haematocrit after the first bolus.

    - **In adults:**

        If the haematocrit increases or is still high (e.g. haematocrit > 50%), repeat a second bolus of crystalloid/colloid solution at 10–20 ml/kg/hour for one hour. After this second bolus, if there is improvement continue with crystalloid solution and reduce the rate to 7–10 ml/kg/hour for 1–2 hours, then continue to reduce as above.

        If haematocrit decreases compared to the initial reference haematocrit (especially if the repeat haematocrit is below the baseline, for example < 35–40% in adult females, < 40–45% in adult males), **and** the patient still has **unstable vital signs**, this may indicate bleeding. Look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding, If there is no bleeding, give a bolus of 10–20 ml of colloid, repeat clinical assessment and determine the haematocrit level. A senior staff member should carry out a review to consider blood transfusion (see Section 2.2.3.3, Treatment for haemorrhagic complications).

   - **In infants and children:**

        If the haematocrit increases or is still high, change to colloid solution at 10–20 ml/kg/hour. After the initial dose, reduce the rate to 10 ml/kg/hour for 1 hour, then reduce to 7 ml/kg/hour. As mentioned above, change to crystalloid when the patient's condition improves.

        If the haematocrit decreases compared to the initial reference haematocrit (especially if the repeat haematocrit is below the baseline, for example,

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< 35−40%), **and** the patient still has **unstable vital signs**, this may indicate bleeding. Look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding. If there is no bleeding, give a bolus of 10−20 ml/kg of colloid over 1 hour, repeat clinical assessment and determine the haematocrit level. A senior staff member should carry out a review to consider blood transfusion.

- Further boluses of crystalloid or colloidal solutions may need to be given during the next 24−48 hours.

- Please refer to Section 2.4.7 for an outline of dengue in infants and children.

Fig. 5. Algorithm for fluid management of compensated shock: in adults
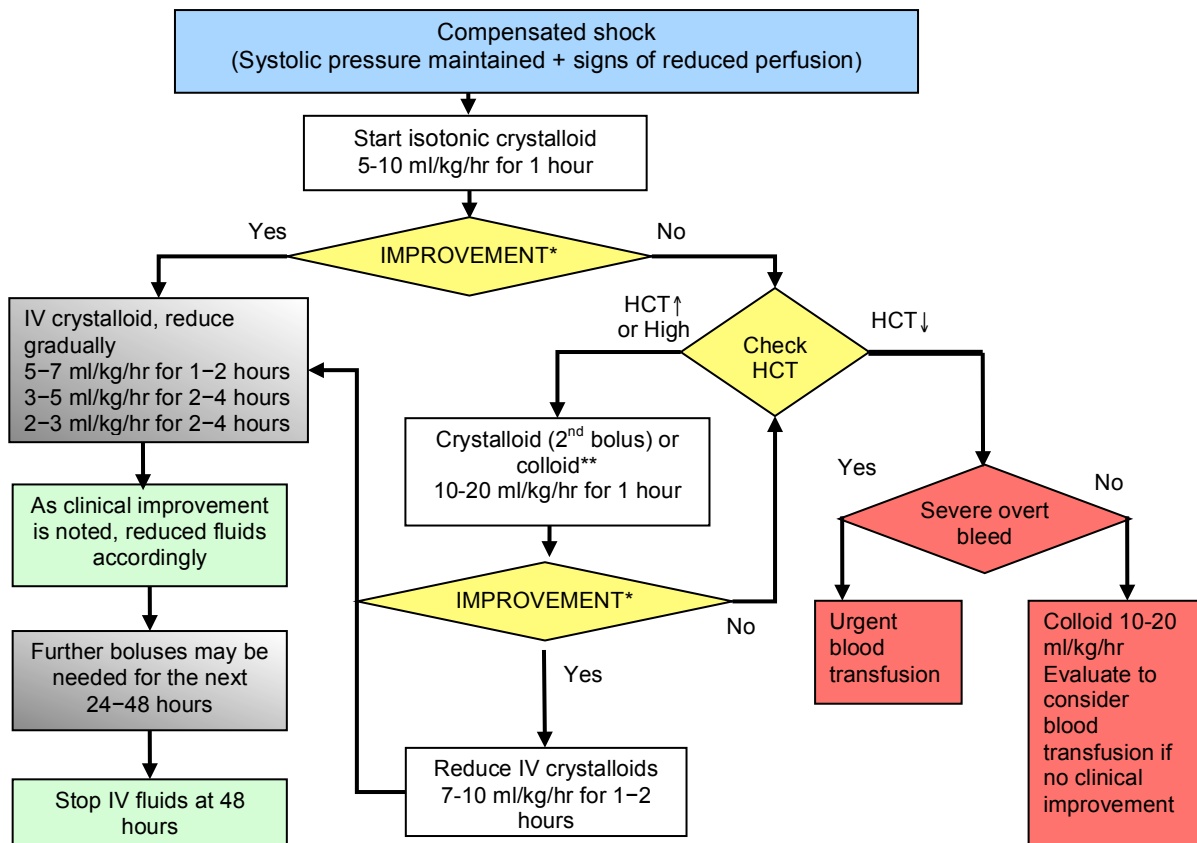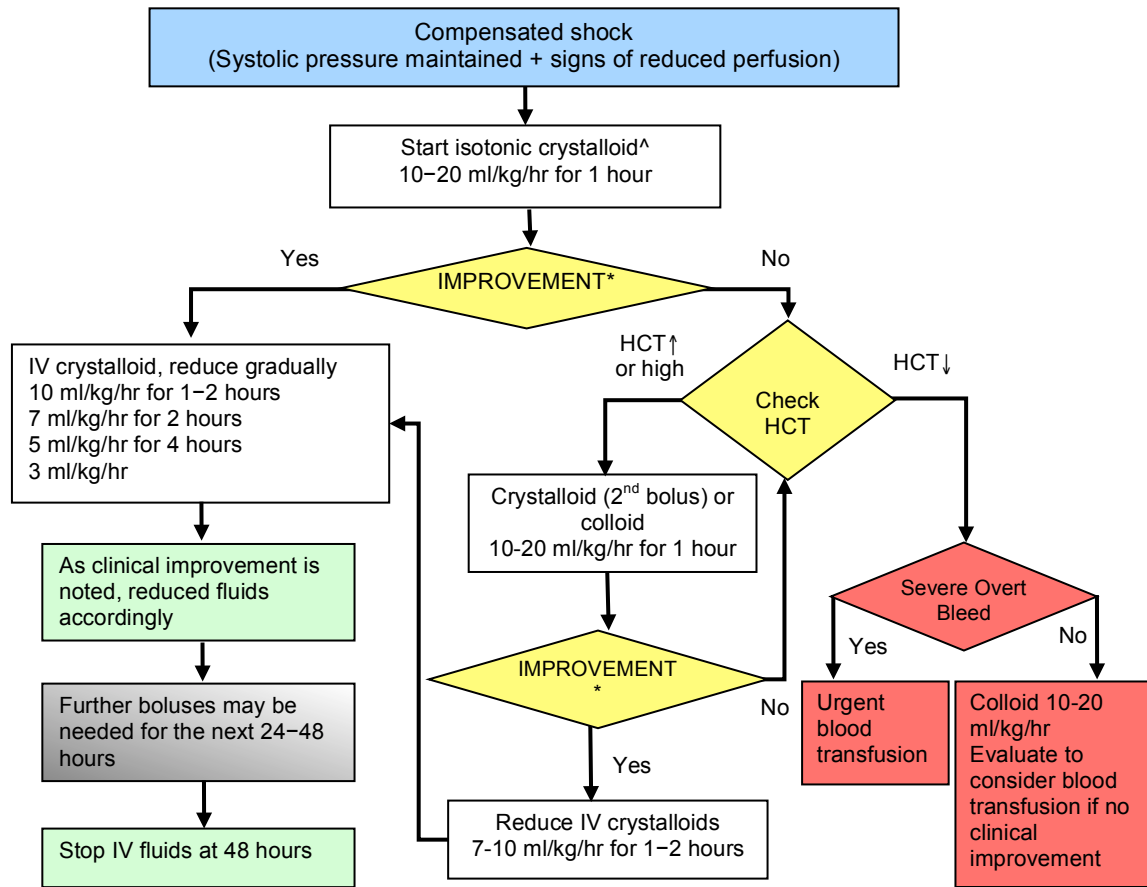

*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
**Colloid is preferable if the patient has already received previous boluses of crystalloid
-IV: intravenous, HCT: haematocrit, ↑: increased, ↓: decreased.

Fig. 6. Algorithm for fluid management of compensated shock: in infants and children

^Colloid is preferable if the patient has already received previous boluses of crystalloid
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased

Treatment of profound shock (hypotensive; undetectable pulse and BP)

All patients (infants, children and adults) with **hypotensive shock** should be managed more vigorously. The action plan for treating patients with hypotensive shock is outlined below (also see Textbox D and Figure 7).

For all patients (infants, children and adults), initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus given over 15−30 minutes to bring the patient out of shock as quickly as possible. Colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock (4−6). The intra-osseous route should be attempted if peripheral venous access cannot be obtained.

- If the patient's condition improves:
  - In **adults**, give a crystalloid/colloid infusion of 10 ml/kg/hour for 1 hour. Then continue with crystalloid infusion and gradually reduce to 5−7 ml/kg/hour for 1−2 hours, then to 3−5 ml/kg/hour for 2−4 hours, and finally to 2−3 ml/kg/hour (or less), which can be maintained for up to 24−48 hours (Textbox H). Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve. The total duration of intravenous fluid therapy should not exceed 48 hours.
  - In **infants and children**, give colloid infusion of 10 ml/kg/hour for 1 hour. Then continue with crystalloid 10 ml/kg/hour for 1 hour, then to 7.5 ml/kg/hour for 2 hours, to 5 ml/kg/hour for 4 hours and to 3 ml/kg/hour, which can be maintained for up to 24−48 hours. Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve. The total duration of intravenous fluid therapy should not exceed 48 hours.

- For all patients, if vital signs are **still unstable** (i.e. shock persists), review the haematocrit obtained before the first bolus.
  - If the haematocrit was normal or low (< 30–35% in infants, < 35–40% in children and adult females, < 40–45% in adult males), this may indicate bleeding. Look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding. If there is no bleeding, give a second bolus of 10–20 ml/kg of colloid over 30 minutes to 1 hour, repeat clinical assessment and haematocrit level plus a review by senior staff to consider blood transfusion (see treatment for haemorrhagic complications).
  - If the haematocrit was high compared to the baseline value (if not available, use population baseline), change intravenous fluids to colloid solutions at 10−20 ml/kg as a second bolus over 30 minutes to 1 hour. After the second bolus, reassess the patient. If the condition improves, reduce the rate to 7−10 ml/kg/hour for 1−2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above.

- If the condition is **still unstable**, repeat the haematocrit after the second bolus.
  - If the haematocrit decreases compared to the previous value (< 35% in infants, < 40% in children and adult females, < 45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible (see 2.2.3.3 for haemorrhagic complications).
  - If the haematocrit increases compared to the previous value or remains very high (> 50%), continue colloid solutions at 10−20 ml/kg as a third bolus over 1 hour. After this dose, reduce the rate to 7−10 ml/kg/hour for 1−2 hours, then change back to

crystalloid solution and reduce the rate of infusion as mentioned above when the patient's condition improves. If the condition is still unstable, repeat the haematocrit after the third bolus.

- Further boluses of fluids may need to be given during the next 24 hours. The rate and volume of each bolus infusion should be titrated to the clinical response. Patients with severe dengue should be admitted to the high-dependency or intensive care area and be managed by senior staff.

   o Clinicians who take care of dengue shock infants should remember that an infant with a low baseline haematocrit of 30%, presenting with dengue shock and a haematocrit of 40%, is relatively more haemoconcentrated than another child with a baseline value of 42% and haematocrit of 50% at the time of shock.

Fig. 7. Algorithm for fluid management in hypotensive shock – infants, children and adults
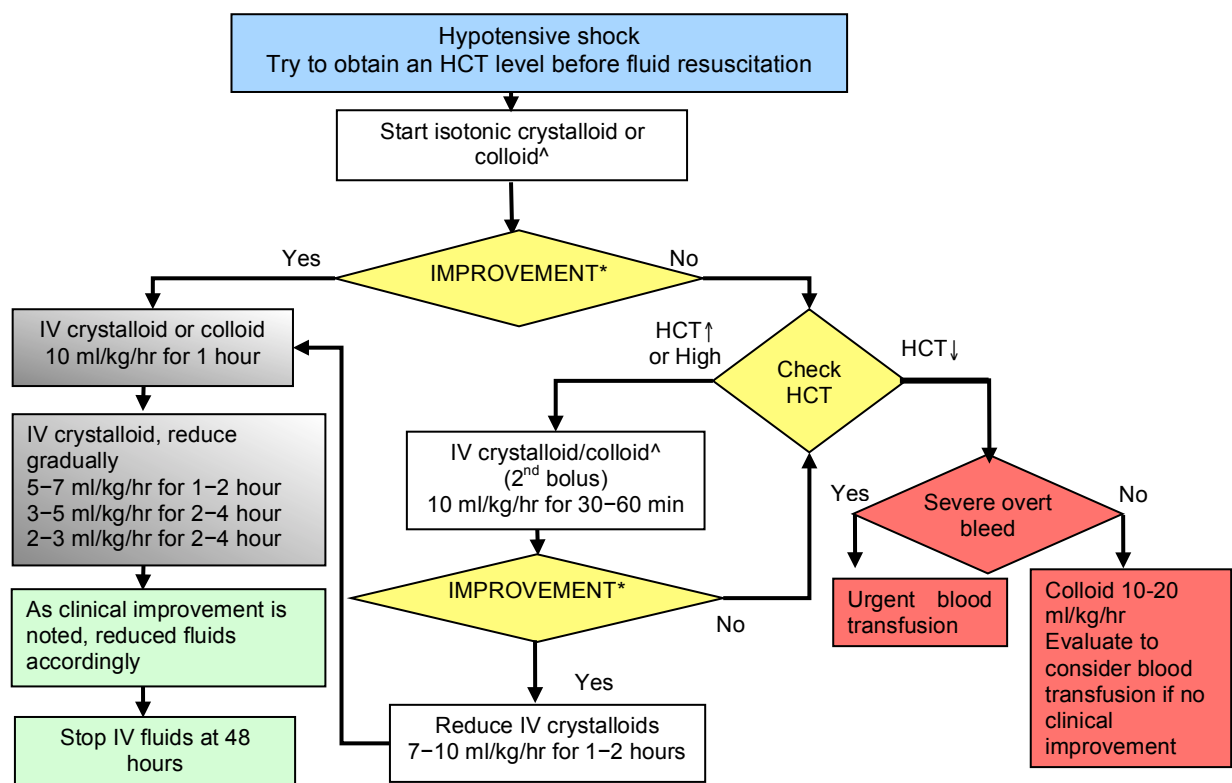
^Colloid is preferable if the patient has already received previous boluses of crystalloid
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased

Patients with dengue shock should be monitored frequently until the danger period is over. A detailed fluid balance of all inputs and outputs should be maintained.

Parameters to be monitored include: alertness and comfort levels, vital signs and peripheral perfusion (every 15–30 minutes until the patient is out of shock then 1–2 hourly). In general, the higher the fluid infusion rate, the more frequently the patient should be

monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement. If previously not detectable, pleural effusion and ascites should be detectable after fluid boluses. Monitor their effects on breathing.

If resources are available for blood gas and/or lactate analysis, capillary or venous blood should be sampled for repeated analysis to monitor changes in the circulation during fluid replacement. An arterial line has certain advantages but its placement is hazardous because of the attendant bleeding from failed attempts. The advantage of an arterial line is that in shock states, estimation of BP using a cuff is commonly inaccurate. The use of an indwelling arterial catheter allows for continuous and reproducible BP measurements and frequent blood sampling to base decisions regarding therapy. Monitoring of ECG and pulse oximetry should be available in the intensive care unit.

Urine output should be checked regularly (each hour until the patient is out of shock, then every 1−2 hours). A continuous bladder catheter enables close monitoring of urine output. The first urine volume after bladder catheterization should be discarded because the duration in the bladder is unknown. Thereafter, an acceptable urine output would be about 0.5 ml/kg/hour. Haematocrit should be monitored (before and after fluid boluses until stable, then 4−6 hourly). In addition, there should be monitoring of: blood glucose (before fluid resuscitation and repeat as indicated); arterial or venous or capillary blood gases; lactate; total carbon dioxide/bicarbonate (every 30 minutes to 1 hour until stable, then as indicated); and other organ functions (such as renal profile, liver profile, coagulation profile) before resuscitation and as indicated.

Interpretation of haematocrit

The patient's baseline haematocrit on the first three days of illness is a useful reference point. It is important to note that during fluid therapy, blood samples for haematocrit should be timed such that they are taken before or after the infusion of a known volume of intravenous fluid. The interpretation will be most meaningful if the corresponding haemodynamic state, or response to fluid therapy and the acid-base balance, are known at the time of blood sampling. Used in this "3-dimensional" way, changes in the haematocrit are the most useful guide to decision-making about fluid therapy. Random haematocrit levels, such as random blood glucose in diabetes mellitus, may not be meaningful for interpretation of the real-time clinical situation.

A rising or persistently high haematocrit together with unstable vital signs (such as narrowed pulse pressure) indicates active plasma leakage and the need for a further bolus of fluid replacement. However, a rising or persistently high haematocrit together with stable haemodynamic status and adequate urine output does not require extra intravenous fluid. In the latter case, continue to monitor closely and it is likely that the haematocrit will start to fall within the next 24 hours as plasma leakage stops.

A decrease in haematocrit (for example from 50% to 40% or below the patient's known baseline) **together with unstable vital signs** (narrowed pulse pressure, tachycardia, metabolic acidosis and poor urine output), may indicate major haemorrhage. If there is severe haemorrhage, urgent blood transfusion should be given. If there is no clinical sign of bleeding, then a further bolus of 10–20 ml/kg of colloid should be given, followed by repeat clinical assessment and haematocrit level determination plus a review by senior staff to consider blood transfusion. Concealed bleeding may take several hours to become

apparent and the patient's haematocrit will continue to decrease **without** achieving haemodynamic stability.

On the other hand, a decrease in haematocrit **together with stable haemodynamic status** and adequate urine output, indicates haemodilution and/or reabsorption of extravasated fluids In this case intravenous fluids must be discontinued immediately to avoid pulmonary oedema.

2.2.3.2   *When to stop intravenous fluid therapy*

Recognizing when to decrease or stop intravenous fluids as part of the treatment of severe dengue is crucial to prevent fluid overload**.** When any of the following signs are present, intravenous fluids should be reduced or discontinued:

- signs of cessation of plasma leakage;
- stable BP, pulse and peripheral perfusion;
- haematocrit decreases in the presence of a good pulse volume;
- apyrexia (without the use of antipyretics) for more than 24–48 hours;
- resolving bowel/abdominal symptoms;
- improving urine output.

Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary oedema and other complications such as thrombophlebitis.

2.2.3.3   *Treatment of haemorrhagic complications*

Mucosal bleeding may occur in any patient with dengue but if the patient remains stable with fluid resuscitation/replacement, this should be considered as a minor issue. The bleeding usually improves rapidly during the recovery phase. In patients with profound thrombocytopenia, ensure strict bed rest and protection from trauma. Do not give intramuscular injections. No evidence exists (from observational studies) that prophylactic platelet transfusions are beneficial in haemodynamically stable patients.

If major bleeding occurs it is usually from the gastrointestinal tract, and/or hypermenorrhoea. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of severe bleeding are those who:

- have profound/prolonged/refractory shock;
- have hypotensive shock and multi-organ failure or severe and persistent metabolic acidosis;
- are given non-steroidal anti-inflammatory agents;
- have pre-existing peptic ulcer disease;
- are on anticoagulant therapy;

- have any form of trauma, including intramuscular injection.

Patients with haemolytic conditions are at risk of acute haemolysis with haemoglobinuria and may require blood transfusion (see Section 2.4.3).

Severe and occult bleeding is the most common cause of profound/refractory/prolonged shock, but can be difficult to recognize. This is because bleeding usually occurs after a period of prolonged shock in dengue (9). The preceding plasma leakage causes the haematocrit to rise to very high levels. When bleeding occurs the haematocrit will then drop from this high level and as a result haematocrit levels may not be as low as in the absence of plasma leakage. Even in severe bleeding, the haematocrit remains above the baseline and only drops to normal or low levels after several fluid boluses.

Severe bleeding should be recognized in the following situations:

- persistent and/or severe overt bleeding in the presence of unstable haemodynamic status, regardless of the haematocrit level;

- a decrease in haematocrit after boluses of fluid resuscitation **together with unstable** haemodynamic status;

- refractory shock that fails to respond to consecutive fluid resuscitation of 40–60 ml/kg;

- hypotensive shock with inappropriately low/normal haematocrit;

- persistent or worsening metabolic acidosis in patients with a well-maintained systolic BP, especially in those with severe abdominal tenderness and distension.

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Do not wait for the haematocrit to drop too low before deciding on blood transfusion. Note that for the reasons stated above a haematocrit of < 30% as a trigger for blood transfusion, as recommended in the Surviving Sepsis Campaign Guideline (10), is **not** applicable to dengue.

The action plan for the treatment of haemorrhagic complications is as follows:

- If possible, attempts should be made to stop bleeding if the source of bleeding is identified e.g. severe epistaxis may be controlled by nasal adrenaline packing.

- If blood loss can be quantified, this should be replaced. If not, give aliquots of 5–10 ml/kg of fresh -packed red cells or 10–20 ml/kg of fresh or fairly fresh whole blood (FWB) at an appropriate rate and observe the clinical response. It is important that fresh whole blood or fresh red cells are given. Oxygen delivery at tissue level is optimal with high levels of 2,3 diphosphoglycerate (2,3 DPG). Stored erythrocytes lose 2,3 DPG, low levels of which impede the oxygen-releasing capacity of haemoglobin, resulting in functional tissue hypoxia. A good clinical response includes improving haemodynamic status and acid-base balance.

- Consider repeating the blood transfusion if there is further overt blood loss or no appropriate rise in haematocrit after blood transfusion in an unstable patient.

- There is no evidence that supports the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding in dengue (11). Observational studies

show that transfusions of platelet concentrates and fresh frozen plasma in dengue were not able to sustain the platelet counts and coagulation profile. However, in the case of massive bleeding, they often exacerbate the fluid overload.

- Nevertheless, in certain situations such as obstetrical deliveries or other surgeries, transfusions of platelet concentrates with or without fresh frozen plasma should be considered in anticipation of severe bleeding.

- In gastrointestinal bleeding, H-2 antagonist and proton pump inhibitors have been used, but their efficacy have not been studied.

- Great care should be taken when inserting a nasogastric tube or bladder catheters which may cause severe haemorrhage. A lubricated orogastric tube may minimize the trauma during insertion. Insertion of central venous catheters should be done with ultra-sound guidance or by an experienced person.

- It is essential to remember that blood transfusion is only indicated in dengue patients with severe bleeding. Unnecessary blood transfusions cause the haematocrit to rise sharply, thus giving a false impression of haemoconcentration and severe plasma leakage leading to unwarranted fluid therapy (see Chapter 3, pitfall 30).

2.2.3.4   *Glucose control*

Hyperglycaemia and hypoglycaemia may occur in the same patient at different times during the critical phase through the following mechanisms. Hyperglycaemia is the result of a neuroendocrine stress response, occurs in diabetes mellitus and results from large quantities of glucose-fluids administered in resuscitation. Starvation in young children, diabetic patients on oral hypoglycaemic agents and severe liver involvement can cause hypoglycaemia. Hyperglycaemia causes osmotic diuresis which worsens the hypovolaemic shock. Osmotic diuresis also gives a false impression of a "good urine output". Hyperglycaemia is associated with increased morbidity and mortality in critically ill adult and paediatric patients. Hypoglycaemia may cause seizures, mental confusion and unexplained tachycardia.

Most cases of hyperglycaemia will resolve with appropriate (isotonic, non-glucose) and adequate fluid resuscitation. When the haemodynamic state improves, normal blood glucose levels should be maintained with a glucose-isotonic fluid, such as dextrose 5%– 0.9% sodium chloride, at 1–3 ml/kg/hour, included as part of fluid replacement according to the algorithms in Figures 6 and 7. In infants and children, blood glucose should be monitored frequently during the critical phase and into the recovery phase if the oral intake is still reduced. However, if hyperglycemia is persistent, undiagnosed diabetes mellitus or impaired glucose tolerance should be considered and intravenous insulin therapy initiated. Subcutaneous insulin should be avoided as absorption is unreliable in the shock state (see Section 2.4.3).

Hypoglycaemia should be treated as an emergency with 0.1−0.5 g/kg of glucose, rather than with a glucose-containing resuscitation fluid. Frequent glucose monitoring should be carried out and euglycaemia should then be maintained with a fixed rate of glucose-isotonic solution and enteral feeding if possible.

2.2.3.5 Electrolyte and acid-base imbalances

Hyponatraemia is a common observation in severe dengue; the underlying mechanism is not fully understood. It could be related to gastrointestinal losses through vomiting and diarrhoea or the use of hypotonic solutions for resuscitation and correction of dehydration. The use of isotonic solutions for resuscitation will prevent and correct this condition.

Hyperkalaemia is observed in association with severe metabolic acidosis or acute renal injury. Appropriate volume resuscitation will reverse the metabolic acidosis and the associated hyperkalaemia. Life-threatening hyperkalaemia, in the setting of acute renal failure should be managed with Resonium A and infusions of calcium gluconate and/or insulin-dextrose. Renal support therapy may have to be considered.

Hypokalaemia is often associated with gastrointestinal fluid losses and the stress-induced hypercortisol state; it is usually encountered towards the later part of the critical phase. It should be corrected with potassium supplements in the parenteral fluids.

Serum calcium levels should be monitored and corrected when large quantities of blood have been transfused or if sodium bicarbonate has been used.

2.2.3.6 Metabolic acidosis

Compensated metabolic acidosis is an early sign of hypovolaemia and shock. Lactic acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock. Correction of shock and adequate fluid replacement will correct the metabolic acidosis. If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding and check the haematocrit. Transfuse fresh whole blood or fresh packed red cells urgently (see Section 2.2.3.3).

Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH ≥ 7.10. Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO_2 and a decrease in serum ionized calcium. A left shift in the oxy– haemoglobin dissociation curve may aggravate the tissue hypoxia.

Hyperchloraemia, caused by the administration of large volumes of 0.9% sodium chloride solution (chloride concentration of 154 mmol/L), may cause metabolic acidosis with normal lactate levels (12). If serum chloride levels increase, use Hartmann's solution or Ringer's lactate as crystalloid. These do not increase the lactic acidosis.

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2.3 Complications and intensive care management

Many of the complications seen in dengue are preventable if clinical team members are alert to the physiological problems of the three different phases. When hypovolaemic shock is adequately managed, patients appear to "sail out" of the critical phase with mere parenteral fluids. But that belies the effort that has been invested in the monitoring and careful titration of intravenous fluid therapy, guided by frequent clinical and haematocrit evaluation.

Causes of complications in dengue include:

- missed diagnosis at the frontline;

- inadequate monitoring and misinterpretation of vital signs;

- inadequate monitoring of fluid intake and urine output;

- late recognition of shock leading to profound and/or prolonged shock;

- late recognition of severe bleeding;

- too much or too little intravenous fluids i.e. not following/understanding the treatment guidelines;

- careless attitude towards aseptic techniques.

Outcome: These lead to a life-threatening situation characterized by one or a combination of the following:

- prolonged and/or profound shock;

- severe bleeding with severe disseminated intravascular coagulopathy;

- fluid overload;

- respiratory distress and failure;

- multi-organ dysfunction of liver, kidneys and neurological system;

- irreversible shock and death.

This group of patients should be referred to a hospital with intensive care facilities wherever possible.

The **clinical evaluation** of these patients should include:

A **general inspection** of the mental state: remember that shock patients remain quiet but alert until hypotension sets in. An irritable combative dengue patient indicates severe shock with declining cortical perfusion. Confusion, lethargy, seizures and coma will set in very quickly. Other possible causes of change in mental state are fulminant hepatic failure (1, 2), hypoglycaemia, electrolyte abnormalities and rarely, intracranial bleeding and encephalitis (3−5).

Airway and breathing: There is usually no problem with the airway. Breathing should be assessed carefully. The patient in early compensated shock has quiet tachypnoea (the lungs are clear). As shock progresses, metabolic acidosis sets in; the breathing then becomes deeper and faster. The lungs remain clear with good air entry. There might be clinically detectable pleural effusion but the question should be: Is this enough to cause the tachypnoea? If no, then this could be Kussmaul's breathing. Patients with Kussmaul's

breathing will prefer to lie horizontal because of hypovolaemia, whereas patients with true respiratory distress from pulmonary causes will most probably be sitting up for optimal chest wall mechanics.

For **pleural effusion** to be the cause of the respiratory distress, it should be substantial and easily detectable. The diaphragm may be splinted by tense ascites. This scenario occurs after unrestrained intravenous fluid therapy, not before. Wheezing and rhonchi indicate pulmonary oedema and hypervolaemia, not the presence of asthma. Fine crepitations of pulmonary oedema may not be audible if the breathing effort is poor. Again, this occurs after aggressive or unguided intravenous fluid therapy.

Occasionally a combination of metabolic acidosis and fluid overload may be seen in patients who have received inappropriate fluid therapy. Thus they remain in severe shock and have fluid overload at the same time. These patients cannot get comfortable lying down or sitting up and are very restless. The clinical evaluation should be corroborated with radiological findings and blood gas analysis. Diminished air entry in a drowsy patient indicates impending respiratory failure. Cyanosis and gasping respiration is seen in an imminent respiratory arrest.

Circulation: The peripheral perfusion should be assessed by examination and palpation of the extremities and the radial pulse – pulse volume, capillary refill time, temperature, colour of extremities and pulse pressure (see Section 1.1.4).

Examine for bleeding (orogastric tube insertion, if indicated), jaundice, evidence of plasma leakage and abdominal tenderness and distension.

Monitoring: Continuous heart rate (ECG), respiration and pulse oximetry should be monitored. With the latter it may be difficult to get a signal in severe shock. Intermittent BP (measured every 5−30 minutes), peripheral perfusion and four-hourly temperature checks should be maintained for these critically ill patients. Finger-on-the-pulse may be necessary in patients with feeble pulses.

Insert a bladder catheter for continuous bladder drainage and hourly urine output measurements.

An arterial line may be inserted (if available) when the radial pulse is stronger, but in the meantime use venous or capillary samples for intermittent blood gas and lactate analysis, and frequent haematocrit timed to before or/and after fluid boluses. Lactate levels are higher in venous and capillary samples rather than arterial ones. A micro-haematocrit centrifuge in the ward facilitates the management of severe dengue.

Evaluate the history and prior treatment:

• What was the date of onset of fever?

• Which phase of dengue illness is the patient in? Is the patient in the critical phase? The countdown may begin from the time of defervescence (temperature below 38°C), or appearance of warning signs, or increase in haematocrit, or sudden decrease in platelet count. For those patients who present with shock, the beginning of the critical period could be a few hours before presentation to the hospital. The period of intravenous therapy should therefore be less than 48 hours in those who present to the hospital with shock.

- Is there evidence of plasma leakage? How many more hours of plasma leakage do you envisage? These timelines may be approximations but will help guide your decision about stopping intravenous fluid therapy.

- Review the fluid intake, output and balance since the start of parenteral fluid therapy. What types of fluids have been administered – hypotonic, glucose solutions, isotonic crystalloids (0.9% sodium chloride solution or Ringer's lactate or Hartman's solution), colloids, blood, and blood products? When was the last urine output? What is the amount of urine? Is the urine volume appropriate to the haemodynamic state? How much is the positive fluid balance? A large positive balance of fluid is reflected in large pleural effusions, ascites, respiratory distress and generalized oedema.

- Review the haemodynamic response to the volume and type of intravenous fluid therapy, and the corresponding trends of haematocrit. You will obtain a better understanding of the clinical situation and the dynamics if you view the process in a "3-dimensional" way.

Additional investigations:

- Full blood count, haematocrit, blood glucose, blood gas analysis and lactate should be done for patients with tachypnoea and shock. Serum electrolytes and calcium, liver function tests, blood urea and creatinine is indicated in all cases of severe dengue shock. Coagulation profile – prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen degradation products and fibrinogen level is indicated in severe bleeding.

- Chest radiography – a small heart shadow indicates intravascular depletion. A large heart (cardiothoracic ratio > 0.55) together with prominent pulmonary vascular markings, "bat's wings" appearance ± Kerley B lines are suggestive of intravascular hypervolaemia and pulmonary oedema. The lung volume may be reduced by the pleural effusion and upward displacement of the diaphragm by gross ascites.

- Determine blood group and match for fresh whole blood or fresh packed cells, at least 10−20 ml/kg aliquot.

- Blood culture and sensitivity (if indicated)

- Dengue diagnostic tests (see Section 1.4)

Key questions to answer:

- Is the patient alert and cooperative or restless, combative or drowsy?

- Is the patient in respiratory distress or failure?

- Does the patient have stable haemodynamics? The arterial, venous or capillary blood gases and lactate levels will complement the clinical information about the hemodynamic stability. As shock progresses, carbon dioxide tension reduces together with a reduced bicarbonate level. A rising lactate level is a sign of worsening tissue perfusion.

- Has the fluid therapy been adequate to maintain the circulation and tissue organ perfusion?

- Is the patient in the beginning or nearing the end of the critical phase or in the recovery phase?

- Does the patient have intravascular and extravascular fluid overload?

- Is the shock prolonged? Has it been missed? You could track shock by the tachypnoea, tachycardia and/or the period of anuria/oliguria and/or metabolic acidosis.

- Is there multi-organ dysfunction? This is seen in prolonged shock.

- Is there hyperglycaemia? If there is, is it related to stress, inappropriate fluids or undiagnosed or uncontrolled diabetes mellitus? Please refer to the information on hyperglycaemia in Section 2.2.3.4.

- Is there electrolyte disturbances? Please refer to section on electrolyte disturbances in Section 2.2.3.5.

- Does the patient have severe overt bleeding? An orogastric tube may reveal fresh bleeding or coffee grounds.

- Does the patient have severe internal/occult bleeding? There are several ways to answer this question. The most direct method: Is the patient's baseline haematocrit known i.e. the haematocrit on days 1−3 of fever? If yes, then it is valuable information. If not, the population haematocrit may be used, although this will not be as precise as the patient's own baseline. Many conditions such as iron deficiency, mild haemolytic disease, chronic smoking, and chronic obstructive sleep apnoea will affect the patient's baseline haematocrit.

  o For other ways to answer this very important question, refer to Section 2.2.3.3 on the recognition of severe bleeding.

  o The earlier this critical condition is recognized, the earlier definitive treatment can be given, saving the patient from receiving several ineffective bolus fluids, most of which will be redistributed to the third spaces.

Prolonged/profound shock:

Prolonged/profound shock is characterized by severe metabolic acidosis ± multi-organ failure.

Scenario 1

If the patient is quietly alert and cooperative, an urgent haematocrit will guide further fluid therapy. If the analysis indicates severe bleeding and matched fresh whole blood (FWB) is available, blood transfusion should be started as soon as possible. However, the following applies if blood is not available:

- If the patient has received < 2 boluses of resuscitation fluid, a colloid solution of 10−20 ml/kg over 15−30 minutes should be used (refer to the algorithm in Figures 5–7). If the patient has received more than 2 boluses of resuscitation fluid, fluids should be switched to a colloid solution of 10−20 ml/kg over 30 minutes for hypotensive shock, and over 1−2 hours for compensated shock.

If severe overt bleeding is apparent (haematemesis, malaena or hypermenorrhoea), the colloid bolus should be followed urgently by transfusion of 10−20 ml/kg FWB, regardless of

the haematocrit level. After transfusion of FWB, some degree of haemodynamic stability is usually achieved together with improvement of metabolic acidosis. Further colloid infusions may be necessary if the haematocrit rises again. A repeat transfusion of FWB will be required if bleeding continues. Bleeding will usually slow down towards the end of the critical phase.

There is no evidence that transfusion of platelet concentrates or the disseminated intravascular coagulopathy (DIVC) regime is effective. This practice will contribute to third space losses and expose the patient to multiple blood donors. Prolonged stay in the intensive care unit (ICU) is also expected.

If no overt bleeding is seen after the colloid bolus, a repeat clinical evaluation and haematocrit level should be performed. A decrease in haematocrit together with clinical improvement means there is restoration of circulatory volume with colloids. However, a decrease in haematocrit, not accompanied by clinical improvement should prompt the suspicion of severe internal/occult bleeding.

Scenario 2

The patient is restless and combative. This patient has prolonged severe shock and is at high risk of dying soon. This scenario is often associated with severe bleeding. In addition to the management as in scenario 1, one should make preparations for tracheal intubation and mechanical ventilation. The patient should be given a high flow oxygen mask, or the airway and breathing should be supported with mask ventilation. Fresh, safe, group "O" blood should be considered if cross-matched blood will take > 1 hour to become available. Refer to mechanical ventilation later in Chapter 2.

Scenario 3

If the patient does not respond to the above measures, a concomitant nosocomial infection should be suspected and appropriate antibiotics started.

2.3.1   *Acute respiratory distress and failure*

Causes of acute respiratory distress and failure are:

- severe metabolic acidosis from severe shock

- fluid overload – large pleural effusions and ascites

- acute pulmonary oedema

- acute respiratory distress syndrome (ARDS)

Severe metabolic acidosis from severe shock:

Kussmaul's breathing will be observed in addition to tachycardia and other signs of shock. Tracheal intubation should not be the first treatment. Instead, these patients should be given treatment as for hypotension shock i.e. prompt resuscitation with fluid boluses after sampling blood for haematocrit determination (refer to algorithm, Figure 7). After fluid resuscitation, evaluate to ensure that the respiratory effort has subsided and that other parameters of adequate circulation are present. Otherwise the haematocrit needs repeating and the question of severe bleeding needs to be considered. A chest radiograph may

indicate that the intravascular volume is depleted but it is the haematocrit that will guide whether transfusion with FWB is required (refer to interpretation of haematocrit and Section 2.2.3.1, Treatment of shock).

2.3.2   Fluid overload

Some degree of fluid overload is inevitable in patients with severe plasma leakage. The skill is in giving them just enough intravenous fluid to maintain adequate perfusion to keep them alive, while waiting it out until the plasma leakage process spontaneously reverses, and at the same time avoiding excessive fluid overload.

Causes of excessive fluid overload are:

- excessive and/or too rapid intravenous fluids during the critical phase;

- incorrect use of hypotonic crystalloid solutions e.g. 0.45% sodium chloride solutions;

- inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding;

- inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates;

- prolonged intravenous fluid therapy, i.e., continuation of intravenous fluids after plasma leakage has resolved (> 48 hours from the start of plasma leakage);

- co-morbid conditions such as congenital or ischaemic heart disease, heart failure, chronic lung and renal diseases.

Early clinical features of fluid overload are:

- sapid breathing;

- suprasternal in-drawing and intercostal recession (in children);

- respiratory distress, difficulty in breathing;

- wheezing, crepitations;

- large pleural effusions;

- tense ascites, persistent abdominal discomfort/pain/tenderness (this should not be interpreted as warning signs of shock);

- increased jugular venous pressure (JVP).

Late clinical features are:

- pulmonary oedema (cough with pink or frothy sputum, wheezing and crepitations, cyanosis) - this may be mistaken as pulmonary haemorrhage;

- irreversible shock (heart failure, often in combination with ongoing hypovolaemia).

Additional investigations are:

- blood gas and lactate analysis;

- the chest X-ray which shows cardiomegaly, pleural effusion, upward displacement of the diaphragm by the ascites and varying degrees of "bat's wings" appearance ± Kerley B lines, suggestive of fluid overload and pulmonary oedema;

- ECG to exclude ischaemic changes and arrhythmia;

- echocardiogram for assessment of left ventricular function and left ventricular end-diastolic diameters (LVEDD) and regional wall dyskinesia that may suggest underlying ischaemic heart disease. The LVEDD is a reliable measure of the filling volume of the left ventricle and is increased in hypervolaemia. Other indirect measures of the intravascular compartment status are the sizes of internal jugular vein and inferior vena cava;

- cardiac enzymes.

Action plan:

- Oxygen therapy should be given immediately.

- The further action plan for the treatment of fluid overload is dependent on the patient's haemodynamic stability, intravascular volume status and the timing of this event with respect to the timeline of the critical phase.

Scenario 1

Strong pulses with warm extremities are positive indications to stop (if ≥ 48 hours of plasma leakage) or reduce (if ≤ 48 hours of plasma leakage) intravenous fluids. The haematocrit is typically low; however it may remain elevated in some patients. The acid-base balance and lactate level are almost normal. If the patient has difficulty in breathing because of excessive third space fluid accumulation, it is all the more imperative to stop fluid therapy. Small doses of furosemide 0.1−0.5 mg/kg/dose twice or thrice daily or a continuous infusion of furosemide 0.1 mg/kg/hour may be indicated for patients who are out of the critical phase. Monitor serum potassium and correct the ensuing hypokalaemia. A high creatinine level suggests that the kidneys may only respond to higher doses of furosemide. Watch out for hypertension and treat during the recovery phase otherwise hypertensive encephalopathy may occur. Respiratory support may be indicated depending on the severity of respiratory distress. Recognizing when to decrease or stop intravenous fluids is crucial to preventing fluid overload (see Section 2.2.3.2).

Scenario 2

The patient has stable haemodynamic status but is still within the critical phase, < 48 hours of plasma leakage. The acid-base balance and lactate level are almost normal. Reduce the intravenous fluid accordingly or change to a colloid solution at 1–2 ml/kg/hour and reduce accordingly. Avoid diuretics during the plasma leakage phase because they may precipitate intravascular volume depletion. Refer to scenario 1 when the patient is out of the critical period.

Scenario 3

Patients who remain in shock with elevated haematocrit levels but show excessive fluid accumulation are likely to have received rapid infusions of crystalloid or hypotonic solutions or blood products. In these patients a carefully titrated bolus of colloid solution at 5−10 ml/kg/hour for 1–2 hours may be helpful; reduce accordingly. All fluids should be

stopped at or before the 48 hours of the critical period. Furosemide therapy may be required as in scenario 1.

Scenario 4

Patients who remain in shock with low or normal haematocrit levels but have excessive fluid accumulation, are most likely to have severe occult bleeding (see Section 2.2.3.3). If the BP is low, a dopamine infusion should be started. Further infusion of large volumes of intravenous fluids will lead to a poor outcome. Careful transfusion of FWB, at least 10 ml/kg, should be initiated as soon as possible at a rate titrated to a clinical response, blood gases and lactate. Respiratory support may be required; refer to section on mechanical ventilation.

Scenario 5

A combination of scenarios 3 and 4 may play out in some cases. Patients with both intravascular and extravascular fluid overload remain in shock with metabolic acidosis because the severe bleeding has been replaced with non-fresh whole blood. Refer to Chapter 3, pitfall 28. A combination of FWB or fresh packed red cells transfusion and careful colloid infusion may help the patient out of the plasma leakage phase with minimal worsening of the respiratory condition. Dopamine should be commenced for hypotension and the patient should be monitored carefully for respiratory failure.

Pulmonary oedema and acute respiratory distress syndrome (ARDS)

These two conditions will cause life-threatening hypoxaemia. Pulmonary oedema is more common than ARDS. Both are aggravated by rapid infusion of large volumes of fluid during the critical phase.

The goals of therapy are to optimize oxygenation and ventilation with respiratory support and stabilize the haemodynamic situation.

- Apart from increasing the fractional inspired oxygen, positive end-expiratory pressure (PEEP) is essential to maintain adequate oxygenation and reduce the work of breathing. PEEP can be delivered through non-invasive ventilation such as continuous positive airway pressure (CPAP) and mechanical ventilation.

- Patients who are alert, cooperative and haemodynamically stable with no, or mild, metabolic acidosis may benefit from non-invasive ventilation (6).

- If the patient is out of the plasma leakage phase and has stable haemodynamics, intravenous fluid therapy should be discontinued and diuretic therapy can be commenced cautiously. Please refer to Section 2.3.2.

- Indications for mechanical ventilation include:
  o patients who have shock and are restless, combative or confused;
  o respiratory failure from acute pulmonary oedema/ARDS ± shock;
  o patients who fail to respond to non-invasive ventilation.

Undertaking a tracheal intubation in a dengue shock patient is a risky procedure for the following reasons:

- Sedation and induction agents will precipitate hypotension and cardiac arrest in a hypovolaemic patient.

- Unless the tidal volume and respiratory rate (RR) are increased to match those of the patient's own respiratory effort, muscle relaxants will worsen the metabolic acidosis by removing the respiratory compensation. This will further precipitate hypotension and cardiac arrest.

- The compliance of the respiratory system will be diminished by the pleural effusion and ascites, so higher pressures will be required to achieve adequate ventilation and oxygenation.

- Trauma to the airway will cause bleeding which will block the tracheal tube.

Possible **benefits of sedation and mechanical ventilation** are:

- easier monitoring of the haemodynamic status;

- adequate respiratory support will decrease the oxygen demand of the body.

The first step in carrying out this procedure is to inform the caregiver and the patient (if still cognizant). Explain the risks and take measures to ensure the patient's safety. These include full monitoring of the ECG, pulse oximetry and BP, careful choice of sedation and induction agents, and the availability of 500 ml of colloidal fluid and FWB if the patient is evaluated to have hypovolaemia or have severe bleeding. A syringe of dilute dopamine should be ready to be started if needed. An adequate size cuffed tracheal tube should be selected in anticipation of decreased compliance of the respiratory system.

The role of each team member should be rehearsed. Intubation should be undertaken by experienced personnel. Pre-oxygenation will be necessary with mask-bag ventilation, synchronized to the patient's breathing effort. Before administration of sedation, ensure that the BP is within the normal range. The BP will decrease after sedation. You may start the colloid infusion/blood transfusion and/or dopamine if the BP before sedation is on the low side. Sedate the patient with midazolam or fentanyl or ketamine which may help increase the BP. A fraction of the usual dose may be all that is required to put the patient to sleep, so titrate to the conscious level so that the BP does not crash. The BP should be monitored continuously. If appropriate equipment is not available, finger-on-radial/femoral pulse will indicate when fluids and inotropes will be required to support the BP. Even mild hypotension should be treated.

When the patient is sedated and their breathing becomes shallow, you should try to take over their breathing by simulating the pre-sleep breathing pattern. This will prevent worsening of metabolic acidosis. Cricoid pressure and a PEEP should be applied. A muscle relaxant such as succinyl choline should be used if there is no hyperkalaemia, otherwise use agents such as atracurium or rocuronium. Atropine should be used to prevent bradycardia. Oral-tracheal intubation should be performed with minimal trauma to the airway. Once the position of the tracheal tube has been verified, the cuff should be inflated and cricoid pressure released. An orogastric tube should be inserted to remove stomach contents.

Manual ventilation breaths should simulate the patient's pre-sleep breathing pattern to enable respiratory compensation of metabolic acidosis, thus maintaining the pH within the normal range. **It is essential to remember this principle**: the immediate goal is to achieve adequate oxygenation and ventilation to a near-normal pH of about 7.35 rather than a normal partial pressure of carbon dioxide ($PaCO_2$). In metabolic acidosis, the $PaCO_2$ level has to be low to maintain a normal pH. Ventilator settings should be adjusted to attain this

goal. As the patient's circulation improves with blood transfusion and other fluids, the metabolic acidosis will subside. Likewise, ventilator settings have to be scaled back; otherwise the pH will increase to the alkalosis range.

PEEP will be required to restore lung volume compressed by pleural effusion and ascites. Remember that PEEP will decrease venous return: this may be desired in intravascular hypervolaemia, but may precipitate hypotension in intravascular hypovolaemia. However, it is best to maintain PEEP ≤ 10 cm H_2O to avoid increasing intra-abdominal pressure that will in turn reduce urine output. Adjust the fractional inspired oxygen accordingly. If large pleural effusions or ascites interfere with ventilation and oxygenation, a careful aspiration of the thorax with a small bore needle may be performed, but there is a high risk of bleeding from the procedure.

The next immediate task is to stabilize the haemodynamic state. Refer to the key questions again. Verify the state of the intravascular volume by clinical examination, jugular venous pressure, chest radiography or echocardiography and blood gases. The central venous pressure may not accurately predict the intravascular volume, particularly if PEEP is used. Arterial blood gas analysis and serial lactate will add valuable information. Lactic acidosis and a low/normal haematocrit indicate severe bleeding and the need for urgent transfusion of FWB. The haemodynamic state and urine output should be evaluated frequently throughout the process of blood transfusion. Any inotropes that have been used to support the BP during tracheal intubation should be decreased to the minimum possible level. If this is not possible, there could be unrecognized hypovolaemia and/or unrecognized severe bleeding and/or myocarditis, verified with echocardiography.

Once the haemodynamic state has been stabilized, intravenous fluid therapy should be reduced accordingly and stopped when the point of 48 hours of plasma leakage has been reached. A low infusion of glucose-isotonic fluid may be required to maintain euglycaemia in young children with liver impairment. The urine output should gradually increase. A urine volume of ~0.5 ml/kg/hour is adequate. Furosemide may be indicated in those with massive positive fluid balances and those with increased creatinine levels.

The urine volume is a reliable indicator of end-organ perfusion as fluid repletion gets underway. Urine output should not be used as an indicator of organ perfusion under the circumstances listed below:

• blood glucose exceeds the renal threshold of 10 mmol/L;

• there is acute kidney injury, as manifested by elevated serum creatinine levels;

• there is underlying chronic renal failure, or uncontrolled hypertension or diabetes mellitus;

• moderately high PEEP is used;

• intra-abdominal pressure is elevated;

• administration of furosemide or hyperoncotic fluids.

2.3.3   Co-infections and nosocomial infections

Co-infections with gram-negative bacteria have been reported in patients with diabetes mellitus and renal failure. Other tropical diseases such as leptospirosis, typhus, malaria, chikungunya and enteric fever may occur concomitantly. A high index of suspicion is necessary to recognize this, especially in those with atypical presentations such as prolonged fever, pulmonary haemorrhage, unexplained renal failure or liver failure in the absence of shock.

It is not uncommon for patients to acquire a nosocomial infection, especially those with severe dengue and when intravenous therapy has been prolonged. Careful attention to aseptic techniques is necessary in procuring and accessing intravascular devices. Prompt and appropriate antibiotic therapy will be crucial to prevent morbidity and mortality.

2.3.4   Haemophagocytic syndrome

Evidence of haemophagocytosis in dengue was alluded to by the presence of numerous macrophages that have phagocytosed erythrocytes and lymphocyte phagocytosis in the spleen (7, 8). The unusual incidence of phagocytic reticulum cells which phagocytosed all blood elements has been reported (9−11).

The clinical significance of reactive haemophagocytosis in dengue has not been studied. However, case reports of prolonged fever in dengue patients have been attributed to this phenomenon. The clinical picture is characterized by persistent high fever, variable cytopenia and multi-organ failure associated with macrophage activation, haemophagocytosis and hypercytokinaemia. Serum ferritin levels are markedly elevated. Definitive diagnosis is made by bone marrow biopsy which demonstrates haemophagocytic activity. Response to methyl-prednisolone and immunoglobulin has been reported to be dramatic (12). However, supportive treatment leading to spontaneous recovery has also been reported (13 and 14).

2.3.5   Supportive care and adjuvant therapy

Supportive care and adjuvant therapy may be necessary in severe dengue and includes:

Vasopressor and inotropic therapy

The use of vasopressor and inotropic therapy should be limited to the following clinical situations:

- As a temporary measure to prevent life-threatening hypotension in dengue shock and during induction for intubation, while correction of intravascular volume is being vigorously carried out. The recommended choice of vasopressor is dopamine which should be titrated to maintain mean arterial BP of 65 mmHg in adults. Vasopressor therapy should be weaned off as intravascular volume is restored and end-organ perfusion re-established.

- Evidence of cardiogenic shock due to myocarditis or ischemic heart disease. Dobutamine is the recommended choice.

In concomitant septic shock, dopamine or norepinephrine are the vasopressors of choice.

Vasopressor therapy should be carefully monitored since dengue shock is primarily a hypovolaemic shock caused by plasma leakage ± haemorrhage. The most essential and effective strategy is the correction of intravascular volume with the appropriate types of

fluids. Vasopressors, by further increasing the peripheral vascular resistance, may be able to maintain the central BP but without improving end-organ perfusion. Paradoxically, vasopressors exacerbate tissue hypoxia and lactic acidosis when the intravascular volume has not been restored. The correct use of vasopressor therapy is reflected in an increased BP concomitant with a decreased tachycardia. If both the BP and tachycardia increase, then repletion of intravascular volume should be considered as the urgent alternative strategy.

Central venous pressure monitoring

The use of central venous pressure (CVP) to guide fluid therapy in severe dengue with profound or prolonged shock has been described (15). Although the CVP provides an additional parameter to gauge the intravascular volume, its reliability in predicting left ventricular filling volume and hemodynamic response to fluid challenge has been contested (16, 17). The risks of severe bleeding and pneumothorax due to placement of the central venous line could be minimized with the use of ultrasound guidance. A more reliable method to evaluate the intravascular volume status in patients with severe dengue is echocardiography.

Renal replacement therapy

Renal replacement therapy may be indicated in acute kidney injury. It should be commenced after haemodynamic stability has been achieved and maintained without further fluid resuscitation, usually after the critical period of plasma leakage. The preferred choice of renal replacement therapy is continuous veno-venous haemodialysis (CVVH). Peritoneal dialysis may be considered if CVVH is not available, but there is a risk of bleeding. However, commencement of CVVH during the critical phase when hypovolaemia has not been corrected will lead to technical problems. The placement of a large dialysis catheter in a hypovolaemic patient may cause unnecessary trauma and severe bleeding. CVVH is not possible in the hypovolaemic and hypotensive state. When renal replacement therapy is not available or cannot be performed yet, the ensuing hyperuricaemia, hyperkalaemia and hyperphosphataemia should be managed with allopurinol, Resonium A and calcium carbonate respectively.

Other organ impairment

Drug toxicity resulting from the use of paracetamol or acetaminophen should be suspected if liver enzymes have increased disproportionate to the severity of shock (18). Paracetamol should be discontinued in patients with liver enlargement or raised liver enzymes. Further treatment of organ impairment, such as severe hepatic involvement, encephalopathy or encephalitis may be needed − otherwise cardiac abnormalities, such as conduction abnormalities, may occur (the latter usually not requiring interventions). The most critical issue for recovery is stabilization of the haemodynamic state; without this there can be no recovery of any organ. Once the critical period is over and stability of the haemodynamic state attained, it is essential to stop or reduce intravenous fluids to the minimum and to maintain euglycaemia. The body will heal itself remarkably over the next few days to weeks. Excessive fluid is cleared by the kidneys and normal liver function returns gradually, coagulation abnormalities and platelet counts return to normal. During this period any suspected nosocomial sepsis should be treated vigorously, but without adding further insults to the kidneys or liver. Supportive treatment (for the liver and kidneys) and enteral nutrition is all that is required in most cases.

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2.4 Treatment of dengue in specific risk groups

The rapid increase in extent of dengue infections around the globe has resulted in a shift in dengue disease burden to older children and adults. Age-related differences in dengue disease and its severity have been observed.

2.4.1 Dengue in adults – some specific issues

While there are many similarities in the disease course, there are minor but significant differences in clinical manifestations and laboratory findings between adults and children with dengue.

Clinical manifestations and laboratory findings

Some clinical manifestations such as petechiae, melaena, headache, retro-orbital pain, joint pain, myalgia, nausea and vomiting may be more common in adults, while epistaxis, oliguria and liver enlargement are more common among children (1). Adults have higher baseline haematocrit levels than children. Among adults, males have a higher baseline haematocrit than females. Among the bleeding manifestations, haematuria and menorrhagia may be more prevalent in adults whereas haematemesis and melaena are more often seen in children (2). Infants, followed by children and then adults are most susceptible to plasma leakage and thrombocytopenia.

Issues in management

• Recognition of plasma leakage

Due to its name "dengue haemorrhagic fever", a general clinician may become overly concerned about the risks of bleeding. The name "dengue haemorrhagic fever" may also create panic in some doctors and the general public. The critical phenomenon of plasma leakage that leads dengue patients to the initial shock is often overlooked. Refer to Chapter 3, pitfall 13. Clinicians should familiarize themselves with the warning signs of severe dengue and early signs of shock.

• Recognition of shock

Young adult patients with normal cardiorespiratory function can compensate for hypovolaemic shock for several hours. As with children, their mental status is clear and they may even be able to work until the stage of profound shock. Other manifestations of shock such as tachycardia, tachypnoea, cold peripheries, delayed capillary refill, reduced urine output (with concentrated urine), are subtle but very important parameters that should alert the physician to the early recognition of shock and prompt fluid correction. A pulse pressure of ≤ 20 mmHg that defines shock in children often indicates a far more advanced state of shock in adults.

Patients self-medicate with analgesics such as paracetamol, NSAIDs, anti-emetics and other drugs that worsen liver and platelet functions. Adult patients should be advised to take no more than 3 g per day of paracetamol (3). In addition, some adult patients may not even be aware of the fever themselves and hence may delay seeking medical attention.

- The impact of increased co-morbidities

Refer to Section 2.4.3).

- Dual-infection

Concurrent bacteraemia or dual-infections have been reported in adult dengue. Due to the overlapping clinical manifestations, concurrent bacteraemia can be overlooked in a dengue endemic setting. Prolonged fever (> 5 days) and acute renal failure may predict the presence of dual infection (4). Failure to make a timely diagnosis of dual infection and to start timely and appropriate antibiotic therapy will lead to increased morbidity and mortality.

2.4.2 Dengue in the elderly

Clinical manifestations

Little is known about dengue in the elderly. A surveillance study (5) showed that clinical manifestations of dengue in the elderly are similar to those of younger adults. However, rash, hepatomegaly and mucocutaneous haemorrhage are less frequent but gastrointestinal tract bleeding and microhaematuria are more common.

The elderly have significantly lower incidences of fever, abdominal pain, bone pain and rashes but higher frequencies of concurrent bacteraemia, gastrointestinal bleeding, acute renal failure, and pleural effusion, higher incidence of prolonged prothrombin time and lower mean haemoglobin levels than younger adult patients (6).

Risk of severe dengue and death

A higher incidence of plasma leakage and case fatalities has been reported in the elderly (5–9) compared to young adult dengue patients.

Issues in management

- Non-febrile elderly with dengue

About 10% of elderly dengue patients may have no complaints of fever (6). This observation highlights the importance of a diligent search for other manifestations of plasma leakage and haemorrhage in suspected afebrile elderly patients in a dengue-endemic setting.

- Higher rate of acute renal failure

The effects of ageing on the kidneys render them more susceptible to the hypovolemic effects of plasma leakage and acute renal failure (6).

- The impact of increased co-morbidities (refer to Section 2.4.3).

Ageing-related decline in cardiopulmonary function is another important consideration during fluid replacement and/or resuscitation in dengue illness. Complications such as congestive heart failure and acute pulmonary oedema may occur. Frequent assessments and adjustments of the fluid regime are required to avoid or to minimize such complications.

2.4.3 *Dengue in cases with co-morbidities*

Co-morbidities such as diabetes mellitus (see Table 8), hypertension (see Table 7) and renal insufficiency are significantly associated with severe dengue and higher fatality rates (6).

Haemolytic anaemias – sickle-cell anaemia, thalassaemias, hereditary spherocytosis, glucose-6-phosphate dehydrogenase (G6PD) deficiency and other haemoglobinopathies (10, 11 and 12)

Acute dengue illness may precipitate intravascular or extravascular haemolysis in patients with haemolytic anaemias. The patient appears pale and jaundiced. Reticulocytosis, a normal response of the bone marrow to haemolysis may be absent in these dengue patients because of bone marrow suppression.

Other markers for haemolysis should be checked. Haemoglobinuria (black urine) is an indicator of severe intravascular haemolysis while plasma haptoglobin will be low or absent if significant intravascular or extravascular haemolysis has occurred.

Low baseline heamatocrit in thalassaemias and other chronic haemolytic anaemias

Without knowledge of the low baseline haematocrit, haemoconcentration (raised haematocrit) during plasma leakage will be missed in anaemic patients with dengue. Despite severe plasma leakage the haematocrit may seem to be normal. Hypochromic and microcytic red blood cells may alert the clinician to the underlying baseline anaemia. Clinicians should interpret the haematocrit data in the light of the patients' clinical status and make reference to the baseline haematocrit level whenever available, particularly during the plasma leakage phase. Transfusion with fresh packed red cells or fresh whole blood should be given if significant haemolysis is suspected.

Haemoglobinuria and acute renal injury

Haemoglobinuria following intravascular haemolysis may cause rapid deterioration of renal function resulting in acute renal injury. The renal hypoperfusion of dengue shock exacerbates this organ impairment.

Adequate hydration is essential to prevent acute renal injury from haemoglobinuria. Prompt and appropriate blood transfusion is necessary if there is evidence of significant haemolysis. Diuretics and alkalinization normally used to counter the effects of haemoglobinuria have to be instituted carefully and in a timely way. Diuretics should be avoided during the plasma leakage phase when hypovolaemia has yet to be corrected.

Hypertension

Table 7. Challenges when managing dengue patients with pre-existing hypertension

Interpretation of BP	Hypotension is a late sign of shock. However, in patients with uncontrolled hypertension a BP reading that is considered normal for age may, in reality, be low for patients with uncontrolled hypertension. Similarly, what is considered as "mild" hypotension may in fact be profound. Patients with chronic hypertension should be considered to be hypotensive when the mean arterial pressure (MAP) declines by 40 mmHg from the baseline, even if it still exceeds 60 mmHg. (For example, if the baseline MAP is 110 mmHg, a MAP reading of 65 mmHg should be considered as significant hypotension.) Look for other manifestations of shock (see Section 2.2.3.1).
The heart rate response: Bradycardia:	It is essential to know the specific antihypertensive agent a patient is taking for the following reasons. ß-blockers, a common antihypertensive medication, cause bradycardia and may block the tachycardic response in shock. The heart rate should not be used as an assessment of perfusion in patients on ß-blockers.
Tachycardia:	Antihypertensive agents such as calcium channel blockers may cause tachycardia. Tachycardia in these patients may not indicate hypovolemia. Knowing the baseline heart rate before the dengue illness is helpful in the haemodynamic assessment.
The impact on hypotension:	The continuation of antihypertensive agents during the acute dengue illness should be evaluated carefully during the plasma leaking phase. The BP lowering effects of these agents and diuretic therapy may exacerbate the hypotension and hypoperfusion of intravascular volume depletion.
End-organ damage from chronic hypertension:	Heart failure and renal failure are common complications of chronic uncontrolled hypertension. Clinicians should be aware if there is pre-existing or new onset of end-organ damage. Interpretation of urine output as a marker of renal perfusion has to be revoked in these situations.

Table 8. Challenges when managing dengue patients with pre-existing diabetes mellitus

Hyperglycaemia	Just like other acute infections, dengue can precipitate diabetic ketoacidosis or hyperosmolar hyperglycaemia, the two major acute metabolic complications in diabetics.
Osmotic diuresis:	Hyperglycaemia results in osmotic diuresis and worsens intravascular hypovolaemia. Not correcting the hyperglycaemic state exacerbates the shock state (see Section 2.2.3.4).
Increased risk of concomitant sepsis:	Hyperglycaemia also puts patients at risk of bacterial infection.
Diabetic ketoacidosis and hyperosmolar hyperglycaemia:	Clinical manifestations of diabetic ketoacidosis and hyperosmolar hyperglycaemia (nausea, vomiting and abdominal pain) are similar to the warning signs of severe dengue. It is not uncommon for dengue shock to be misdiagnosed as diabetic ketoacidosis.
Hypoglycaemia:	Hypoglycaemia may occur in those patients taking oral hypoglycaemic agents (e.g. long-acting sulphonylurea), but who had poor oral intake. Hypoglycaemia could be aggravated by severe hepatitis from dengue.
Oral hypoglycaemic agents:	Gastrointestinal absorption of oral hypoglycaemic agents is unreliable because of vomiting and diarrhoea during the dengue illness. Some hypoglycaemic agents such as metformin may aggravate lactic acidosis, particularly in dengue shock. These agents should be avoided or discontinued during dengue shock and also in those with severe hepatitis.

Management

Dengue patients with known diabetes mellitus should be admitted for closer monitoring of the diabetic as well as dengue states. If the patient has gastrointestinal disturbances, blood glucose should be controlled with intravenous short-acting insulin during the dengue illness.

A validated protocol for insulin dose adjustments to a target glucose level of < 150 mg/dl (8.3 mmol/L) should be used. A source of glucose may be maintained once the target is achieved while receiving intravenous insulin. Blood glucose should be monitored every 1–2 hours until glucose values and insulin rates are stable and then every 4 hours thereafter.

Electrolyte imbalances

Hyponatraemia, hypokaleamia, hyperkalaemia or hypomagnesaemia are common electrolyte imbalances observed during dengue illness. These imbalances may be more severe and require prompt attention and appropriate actions.

Chronic renal failure

Dengue patients with chronic renal failure (CRF) have a significantly higher risk of severe dengue and mortality. The outcome correlates with the renal function (13, 14).

Warning signs in severe dengue versus the presentation of uraemia:

The warning signs of severe dengue are similar to those of uraemia in CRF. Ascites and/or pleural effusion, and signs of plasma leakage in dengue, are not uncommon findings in patients with CRF and fluid retention. The ambiguity of these symptoms and signs could delay the recognition of plasma leakage and severe dengue.

Low baseline haematocrit and platelet count:

Patients with CRF have a low baseline haematocrit. Refer to 2.4.3 above: Low baseline haematocrit in thalassaemias

A low baseline platelet count is not an uncommon finding in dialysis patients. This could be another challenge in the early recognition of dengue infection.

Challenges in fluid management:

- Narrow window of fluid tolerance.

    Patients with CRF have limited fluid tolerance. Frequent assessments of the haemodynamic state and frequent fluid regime adjustments are mandatory to avoid fluid overload or under-fill. Adequate fluid replacement is necessary to prevent worsening of renal function during the critical phase.

- Urine output

    The urine output should not be used as an indicator of the intravascular volume status because patients with CRF can have either low or high urine-output renal failure. Low urine output in CRF contributes to the risk of fluid overload whereas high urine output may aggravate hypovolaemia.

- Limited effect of diuretics

    Diuretics have a limited effect in CRF, making patients more susceptible to fluid overload. Dialysis may be required.

Acid base balance and electrolyte balance

Patients with CRF are at risk of metabolic acidosis and electrolyte imbalance which will become worse during dengue shock. If these persist after adequate fluid replacement, dialysis may be considered after haemodynamic stability is achieved (see Section 2.3.5).

Platelet dysfunction

Platelet dysfunction, well recognized in CRF together with severe thrombocytopenia ± coagulopathy, predispose the dengue patient to severe bleeding that may be difficult to control.

Chronic heart disease with or without heart failure

Congenital or acquired cardiac lesions such as valvular heart disease or ischaemic heart disease, especially the latter, are common co-morbidities in adults or the elderly. Patients may be well compensated under normal circumstances. However, an infection such as dengue that causes high fever, tachycardia and increased metabolic demands may precipitate decompensation of cardiac functions. Such patients have limited ability to compensate for hypovolaemia or hypervolaemia. Therefore, fluid therapy should be guided by frequent clinical assessments, haematocrit and blood gas determinations. Patients with cyanotic heart diseases have polycythemia and a high baseline haematocrit.

- Positive pressure ventilation

  Non-invasive positive pressure ventilation should be considered to support patients with cardiac decompensation. Failing this, mechanical ventilation should be instituted.

- The use of loop diuretics

  Loop diuretics should be used cautiously and in a timely way: after achieving haemodynamic stability when intravenous fluid therapy has been discontinued or reduced and in patients with fluid overload.

2.4.4 References

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2.4.5 Dengue in pregnancy

Introduction

In the recent decade more cases of dengue in pregnancy are being reported. The clinical manifestations, treatment and outcome of dengue in pregnant women are similar to those of non-pregnant women but with some important differences (1, 2).

Misdiagnosis or delayed diagnosis are not uncommon due to some of the overlapping clinical and/or laboratory features with the better recognized conditions of pregnancy. These include eclampsia or pre-eclampsia, haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, pneumonia, pulmonary embolism, various obstetric causes of per-vaginal bleeding and other infectious diseases (Table 9).

Table 9. Similarities and differences between dengue, pregnancy and HELLP syndrome

	Normal Pregnancy	Dengue	HELLP
Fever	Blunted febrile response	+	-
Bleeding	Bleeding can be due to obstetrical cause	+ (mild to severe)	- (DIVC in severe disease)
Abdominal pain	+/-	+/-	+/-
Ascites, pleural effusion	-	+ in plasma leakage	-
WBC	Elevated	Leukopenia	No specific changes
Thrombocytopenia	+	+ unique FBC changes	+
Haematocrit	↓ (haemodilution after the second trimester)	↑ in plasma leakage	Maybe normal / ↓
Haemolysis	-	-	+
Liver enzymes	Mild ↑	Mild to severe ↑	Mild to moderate ↑

DIVC = disseminated intravascular coagulopathy; FBC = full blood count; HELLP = haemolysis, elevated liver enzymes and low platelet count; WBC = white blood cell

In order to recognize and diagnose dengue disease early in pregnancy, clinicians need to maintain a high index of suspicion when dealing with pregnant women who present with febrile illness after travelling to, or living in dengue-endemic areas.

Impact of dengue on pregnancy:

- Adverse pregnancy outcome (2–6)

  It is still uncertain whether dengue is a significant factor for adverse pregnancy outcomes such as preterm birth, low-birth weight and caesarean deliveries, as most of the published data were based on hospitalized patients.

- Risk of vertical transmission (2, 6–10)

  The risk of vertical transmission is well established among women with dengue during the perinatal period (see Section 2.4.5).

- Significant impact of dengue at parturition (5,11)

  Severe bleeding may complicate delivery and/or surgical procedures performed on pregnant patients with dengue during the critical phase, i.e. the period coinciding with marked thrombocytopenia with or without coagulopathy and vasculopathy.

Management of dengue during pregnancy:

- Early admission for close monitoring is recommended, especially for women close to full-term/labour.

- Conservative medical and obstetrical management is the treatment of choice (12).

Challenges in recognition of dengue disease and plasma leakage in pregnancy

- Symptoms of hyperemesis during the first trimester of pregnancy resemble the warning signs of severe dengue and this may delay the recognition of severe dengue.

- After the second trimester of pregnancy it is normal to see an increase in circulating blood volume with generalized vasodilatation, resulting in an increased baseline heart rate and lower baseline BP, as well as a lower baseline haematocrit. This can confuse the diagnosis of dengue and therefore clinicians need to be alert to the following:

  o The lower BP and tachycardia of normal pregnancy could be misinterpreted as hypotensive shock.
  o The lower baseline haematocrit after the second trimester of pregnancy should be noted. Establishing the baseline haematocrit during the first 2–3 days of fever is essential for early recognition of plasma leakage.
  o Clinical signs of plasma leakage such as pleural effusion and ascites could be difficult to elicit in the presence of a gravid uterus.

- Please refer to Section 2.2 for treatment

Challenges in monitoring and management

- Close observation and monitoring, prompt, adequate and appropriate replacement therapy during the pre-, intra- and post-delivery periods are essential.

- Failure to recognize plasma leakage and/or shock early will lead to prolonged shock and eventually massive bleeding and multi-organ failure.

- There is no difference in fluid therapy compared with the non-pregnant state (see section on fluid management in Section 2.2). However it is important to note that the growing gravid uterus may result in narrower tolerance of fluid accumulation in the peritoneal and pleural cavity from plasma leakage. Hence excessive fluid replacement should be avoided.

- The increased baseline heart rate and a lower baseline BP are normal physiological changes in late pregnancy. Targeting an inappropriate heart rate and "normal" levels of BP could result in fluid overload and respiratory distress.

- The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, coagulopathy and vasculopathy creates a substantial risk of severe haemorrhage.

- If severe haemorrhage occurs, replacement with transfusion of fresh whole blood/fresh packed red cells should be promptly instituted (see Section 2.2.3.3).

- Prophylactic platelet transfusion is not recommended unless obstetrically indicated.

- Delivery should take place in a hospital where blood/blood components and a team of skilled obstetricians and a neonatologist are available.

- Tocolytic agents and measures to postpone labour to a suitable time may be considered during the critical phase of dengue illness. However there is currently a lack of evidence on this practice.

Inevitable delivery during critical phase

- If delivery is inevitable, bleeding should be anticipated and closely monitored.

- Blood and blood products should be cross-matched and saved in preparation for delivery.

- Trauma or injury should be kept to the minimum if possible.

- It is essential to check for complete removal of the placenta after delivery.

- Transfusion of platelet concentrates should be initiated during or at delivery but not too far ahead of delivery, as the platelet count is sustained by platelet transfusion for only a few hours during the critical phase.

- Fresh whole blood/fresh packed red cells transfusion should be administered as soon as possible if significant bleeding occurs. If blood loss can be quantified, it should be replaced immediately. Do not wait for blood loss to exceed 500 ml before replacement, as in postpartum haemorrhage. Do not wait for the haematocrit to decrease to low levels.

- Ergotamine and or oxytocin infusion as per standard obstetrical practice should be commenced to contract the uterus after delivery to prevent postpartum haemorrhage.

- Refer to Section 2.2.3.3 for management of severe bleeding.

Post-delivery

- Newborns with mothers who had dengue just before or at delivery, should be closely monitored in hospital after birth in view of the risk of vertical transmission (7, 8), see Section 2.4.5.

- o At or near-term/delivery, severe foetal or neonatal dengue illness and death may occur when there is insufficient time for the production of protective maternal antibodies.
  - o Clinicians should be aware that presentation in either maternal or neonatal disease may be atypical and confound diagnosis.

- Congenital infection could eventually be suspected on clinical grounds and then confirmed in the laboratory.

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2.4.7   *Dengue in paediatric cases*

Dengue virus infections affect human populations of all age groups worldwide. In some parts of the world, dengue is mainly a paediatric health problem. The vast majority of dengue cases occur in children < 15 years of age and around 5% of all severe dengue cases occur in infants (1–4). In one dengue-endemic area, the incidence of dengue infection exceeded 10% in infants aged 2–15 months (5). Most infants acquire primary dengue virus infections (1, 5–6). Clinical manifestations, the course of dengue illness and management of dengue in older children and adults are well documented in the previous sections of this handbook. In this section clinical manifestations and management of dengue in infants will be addressed and compared to clinical manifestations and management of dengue in older children and adults. Vertical transmission and dengue in neonates are also covered briefly.

Manifestations of dengue in infants

As in older children and adults, dengue virus can cause a spectrum of outcomes in infants, ranging from asymptomatic infection to mild or clinically significant, severe disease (5). The burden of severe dengue lies predominantly in infants 4–9 months of age (1, 4, 6).

Infants with dengue typically have high fever that usually lasts 2–7 days; the same as in older children. Upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnoea), gastrointestinal symptoms (vomiting, diarrhoea), and febrile convulsions are more common in infants with dengue compared to older children (3, 5, 6). Differentiation between dengue and other common infections in infants (such as pneumonia, bacterial sepsis, meningoencephalitis, hand foot and mouth disease, measles, rotavirus infections, etc.) is often not possible at the febrile stage. The presence of a febrile seizure, macular rash, petechiae and lower platelet counts early in the illness are significantly associated with dengue among infants with acute undifferentiated febrile illness (5).

In the majority of dengue infants, an increase in capillary permeability, in parallel with increasing haematocrit levels, becomes apparent around the time of defervescence (which usually falls on days 3–6 of illness). The period of clinical plasma leakage lasts 24–48 hours (3, 6, 7). During this critical phase, clinical features and laboratory findings of infant dengue become more prominent. Skin bleeding such as petechiae, mucosal membrane bleeding (e.g. of the nose and gums), and gastrointestinal bleeding may occur. Hepatomegaly is usually noted (2, 6, 7, 8). Splenomegaly is seen in almost 10% of dengue infants, seven times more frequently than in older children (2, 6, 8).

Shock occurs when a critical volume of plasma is lost through leakage. As with older children, it is often preceded by warning signs. The body temperature may be subnormal when shock occurs. However, some infants may still have fever at the onset of shock; in these patients a differential diagnosis of septic shock should be kept in mind (6). With prolonged shock, the consequent organ hypoperfusion results in multiple organ dysfunction, metabolic acidosis and disseminated intravascular coagulation.

The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. Haemoconcentration, manifested by an increase in haematocrit of ≥ 20% above the baseline haematocrit may be seen (6, 9). The normal value of haematocrit in infants 2–12 months of age is relatively low (28–42%) (10) and may be even lower in iron-deficiency anaemia. The mean maximal haematocrit values in dengue infants vary from 31.1−40.8% (range = 30–60%) (2, 6, 11). Thrombocytopenia and leukopenia are often

observed in this phase. Liver involvement and/or dysfunctions, as indicated by mean aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation and prolonged prothrombin time compared to children, are found more frequently in infants (3).

During the recovery phase, progression of infants with dengue is the same as that of children and adults (see Section 1.1.3).

Management of dengue in infants

Severe dengue is less common in infancy but when it does occur the risk of dying is higher than in older children and adults (3, 6, 11). Infants with dengue should be referred for in-hospital management.

Management of dengue infants without warning signs

Treatment is supportive. Oral rehydration should be encouraged with oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar, together with breastfeeding or formula feeding and/or solid food. Febrile seizures are more frequent in infants and young children with dengue than in older patients. Parents or caregivers should be instructed about fever control with antipyretics and tepid sponging. Advise the parent or caregiver to bring the infant back to the nearest hospital immediately if the infant has any of the warning signs.

Management of dengue infants with warning signs (see Section 2.2.2 for more details)

Intravenous fluid therapy is indicated when the infant has dengue with warning signs. Judicious volume replacement of lost plasma by intravenous fluid therapy from this early stage may modify the course and severity of the disease. Only isotonic crystalloid solutions such as Ringer's lactate (RL), Ringer's acetate (RA), or 0.9% saline solution should be used. Start with 5–7 ml/kg/hour for 1–2 hours and then adjust the rate according to the patient's clinical response. A recent study indicates that 79.6% of non-shock dengue infants require intravenous fluid therapy with the mean volume of 102.1 ml/kg over a mean time of 25.9 hours (11). The percentage of dengue infants requiring parenteral fluid therapy (79.6%) is higher than that of non-shock dengue children older than 1 year of age (25–33%) (11). Parenteral fluid therapy is only required for 24–48 hours in most infant patients since the capillary leak resolves spontaneously after this time (3, 11).

Management of infants with severe dengue

Treatment of shock (see Section 2.2.3.1 for more details)

Volume replacement in infants with dengue shock is a challenging management problem. The strategy for fluid resuscitation in infants is similar to that in children and adults. The recommended regimen for the treatment of infants with dengue shock is as follows:

- Immediate and rapid replacement of the plasma loss with isotonic crystalloid solutions or, in the case of profound shock, colloid solutions.

- Continued replacement of further plasma losses to maintain effective circulation for 24–48 hours.

- Correction of metabolic and electrolyte disturbances.

- Blood transfusion – only to cases with severe bleeding.

Treatment of compensated shock in infants: Please refer to Section 2.2.3.1

Treatment of profound shock (hypotensive; undetectable pulse and BP) in infants: Please refer to Section 2.2.3.1

Clinicians who take care of dengue-shock infants should remember that an infant with a low baseline haematocrit of 30%, presenting with dengue shock and a haematocrit of 40%, is relatively more haemoconcentrated than another child with a baseline value of 42% and a haematocrit of 50% at the time of shock.

In patients with profound, recurrent or prolonged shock, a central venous catheter may be inserted through the antecubital basilic vein or internal jugular vein to guide intravenous fluid therapy. This should be done by an experienced member of staff using ultrasound to guide the insertion (if available).

In infants intravenous fluids must be administered with special care to avoid fluid overload. Fluids account for a greater proportion of body weight in infants than children and minimum daily requirements are correspondingly higher. Infants have less intracellular fluid reserve than older children and adults. Moreover, capillary beds are intrinsically more permeable than those of older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely if capillary leaks occur in these circumstances (12).

Monitoring dengue-shock infants

Dengue-shock infants should be under close observation around the clock until it is certain that danger has passed. Generally, the duration of intravenous therapy should not exceed 24−48 hours after the infant is out of shock. Stop intravenous fluid therapy when the infant's condition has been stable for more than 24 hours or if there is any sign or symptom of fluid overload (1, 6−8); see Sections 2.2.3.2 and 2.3.2.

Treatment of haemorrhagic complications, hyponatraemia, and metabolic acidosis

Blood transfusion is only indicated in dengue infants with severe bleeding (see Section 2.2.3.3). Hyponatraemia and metabolic acidosis can occur in severe cases. Electrolyte levels and blood gases should be determined periodically in severe cases. Early volume replacement will usually correct the metabolic acidosis and generally result in a favourable outcome. Sodium bicarbonate may be considered in severe metabolic acidosis.

Although dengue in infants comprises around 5% of all paediatric cases, mortality rates are higher in infants than in older children (3, 6, 13). Fluid replacement in infants with severe dengue is a challenge to good clinical management. This involves following established procedures for use of colloid solutions and blood transfusions. To further reduce case fatalities, special emphasis needs to be given to dengue infants who have severe complications or who go on to develop them.

Vertical transmission and neonatal dengue

Pregnant women with dengue virus infection can transmit the virus to their foetus and vertical dengue transmission has been described. Questions about dengue in pregnant women relate to the effect of the pregnancy on the disease process; the effect of the disease on the pregnancy; possible effects on the foetus and the neonate; and how the pregnant woman and the newborn might best be managed (14). Answers to questions about the effect of the disease on the pregnancy are discussed in Section 2.4.5 of this

handbook. Here follows a review of the effects of dengue on the neonate, clinical manifestations and management of neonatal dengue.

Dengue virus can be vertically transmitted to the foetus in utero or to the infant at parturition. Results of a recent systematic review indicate 16 cases of vertical transmission among 25 (64.0%) neonates reported from 12 case reports, and vertical transmission occurring in 4 of the 10 case series, in 18 of 143 (12.6%) of cases (15). One comparative study that tested 64 umbilical cord serum samples for dengue IgM from 63 women who were found to be IgM positive at the time of delivery, found a vertical transmission rate of 1.6% (16).

In the vertical transmission cases, some newborns may be asymptomatic (16). Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with clinical sepsis, pleural effusion, gastric bleeding, circulatory failure, massive intracerebral haemorrhage and death (17−24). Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status, or mode of delivery (19, 24, 25). However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. A review of 17 mother–infant pairs with dengue infection found that the time intervals between the mothers' onset of fever and that of their neonates, were 5–13 days (median, 7 days); fever in neonates occurred at 1–11 days of life (median, 4 days), and the duration of fever in neonates was 1–5 days (median, 3 days) (24).

Passive transfer of maternal dengue antibodies to the foetus influences the occurrence of a severe development of the disease (9). Antibodies to the dengue virus in the dengue-infected mother can cross the placenta and can cause severe dengue in newborn infants (1, 26).

Management of neonatal dengue

When a pregnant or parturient woman develops signs consistent with dengue, the diagnosis of dengue should be considered in her neonate even if the neonate appears well in the first several days of life. Remember that some neonates have become ill as long as 11 days after birth (24). The diagnosis of neonatal dengue could eventually be suspected on clinical grounds and then confirmed in the laboratory, but initial presentation may be confused with bacterial sepsis, birth trauma and other causes of neonatal illness. Symptomatic and supportive treatment under close observation is the mainstay of treatment (14, 20, and 24).

2.4.8   References

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3.   Pitfalls in the management of dengue and solutions

The clinical management of dengue is more fraught than that of most other infectious tropical diseases. The uninitiated physician who has managed uncomplicated dengue cases may be lulled into believing that dengue is a "mild disease of thrombocytopenia" that requires no more than intravenous fluid therapy and platelet transfusions for a couple of days. When faced with severe dengue, these same physicians may be unprepared for the changing clinical, biochemical and haematological profiles that accelerate after the first few days of fever and therefore will not step up their vigilance during the critical period.

In this chapter we identify some of the common pitfalls in dengue management and include some explanations for the misconceptions together with suggested solutions.

3.1   *Frontline physicians*

Pitfall 1: Recognition of dengue at the frontline

The frontline physician does not recognize dengue when the patient presents as a febrile illness in the first few days, and no follow-up is given.

A cursory history and physical examination in a busy out-patient practice will not identify the early dengue patient. The diagnoses of upper respiratory tract infection or viral fever are usually assigned. These febrile patients are more ill and may not be able to attend school or work, but these questions are seldom asked by the busy physician.

Solution:

The only way to recognize dengue in the early febrile phase is to suspect it in every febrile patient. Direct questioning may reveal the patient lives in a dengue endemic locality or has recently travelled there. Physicians at the frontline should take a detailed history and perform the step-wise evaluation as in Section 2.1

A positive tourniquet test may be useful to differentiate dengue from non-dengue viral illness; however a negative test does not exclude it. Even if dengue is suspected, it will be difficult to predict the clinical course of illness. Therefore, if the patient fulfils the criteria for probable dengue, the physician should inform the patient about the suspected disease and schedule daily follow-up and advice with immediate medical attention should warning signs occur.

Pitfall 2: Missed opportunity for FBC in early febrile period

Full blood count (FBC) not determined until day 4 of illness.

It is a common practice not to do the FBC until day 4 of illness, to detect the falling platelet count, by which time changes in haematocrit levels are also expected.

Solution: A full blood count should be done at the first visit when dengue is suspected. See below for more explanation.

Pitfall 3: Not understanding the evolving FBC

Full blood count is "normal" and the physician excludes the diagnosis of dengue.

The earlier the FBC is done, the more likely it is that the result will seem normal. An uninitiated physician may misinterpret this and rule out dengue.

Solution: The purpose of an early FBC is to establish the patient's baseline haematocrit. The baseline haematocrit will become useful to guide clinical management when haematocrit levels increase during the critical phase. The early and progressive decrease in white cell and platelet counts during the febrile period is a useful indicator of dengue.

Pitfall 4: Surge of hospital admissions during a dengue outbreak

During a dengue outbreak there may be a surge in hospital admissions because of fear and panic among patients and frontline physicians, or institutional directives to admit all suspected dengue patients.

Explanation: In a small group of dengue patients the disease could progress very rapidly during the critical phase resulting in severe shock and death. However, admission of all suspected dengue cases will overwhelm the hospital system with many uncomplicated dengue cases that could be taken care of in the ambulatory system.

Solution: Clear guidelines for admissions need to be available. Integrating an out-patient management protocol within the hospital system can ensure effective gate-keeping in a dengue outbreak (1, 2). Please refer to Section 2.2.1 and Integrated Management of Childhood Illness (IMCI) guidelines (3, 4, 5).

Admission during the febrile period should be for those who are unable to manage adequate oral hydration at home, infants and those with co-morbid conditions. Refer to Textbox C for warning signs.

The chart presented in Table 10 is to assist frontline physicians in the early recognition and management of dengue patients, and is in accordance with IMCI guidelines.

Table 10. Chart for case management of dengue for frontline physicians*

Assessment	Classification	Management
Indicators of shock: • Cold, clammy extremities *and* • Prolonged capillary refill time *and* • Weak pulse • Severe bleeding • Impaired consciousness	Severe dengue	• Give intravenous crystalloid fluids if the patient has shock • Refer URGENTLY to hospital
• Abdominal pain or tenderness • Persistent vomiting *or* • Lethargy or restlessness *or* • Bleeding from nose or gum *or* • Blood in vomit or stool *or* • Petechiae on the skin	Dengue with warning signs	• Refer URGENTLY to hospital
None of the above signs and no other infectious causes of fever, able to drink enough (refer section 5.7, Textbox G)	Dengue	Instructions for: - home care - follow-up - warning signs

*for a patient from a dengue endemic locality, with fever, or history of fever, which lasts 2–7 days, and fulfils criteria for probable dengue (refer to Figure 2: Dengue classification)

The frontline physicians (health-centre staff, private doctors and primary health-care workers), should use the chart (Table 10), to assess, identify, classify and manage patients with fever or history of fever which lasts 2–7 days. The chart can also be used by staff at the hospital outpatient clinic with some modifications, e.g. direct hospitalization of patients with severe dengue or dengue with warning signs.

How to use the chart:

1. The patient comes from a dengue endemic locality and fulfils criteria for probable dengue. Start with the top row. Assess the patient to discern whether they have signs of shock (cold, clammy extremities, prolonged capillary refill time and weak pulse), or signs of severe bleeding or impaired consciousness.

1.1. If the answer is **YES**, classify the case as **severe dengue** and **refer** the patient **URGENTLY** to hospital.

For those patients with signs of shock, treat urgently as follows:

- If it is possible to give intravenous fluid immediately, start with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour in adults and 10–20 ml/kg/hour over one hour in infants and children at the health centre. Then arrange to **refer** the patient **URGENTLY** to hospital.

- If it is not possible to give intravenous fluid immediately, **refer URGENTLY** to the nearest hospital for intravenous fluid therapy.

1.2. If the answer is **NO**, proceed to the next row of the chart.

2. Assess whether the patient has any of the following signs:

- abdominal pain or tenderness

- persistent vomiting

- lethargy or restlessness

- bleeding from the nose or gum

- blood in vomit or stool

- petechiae on the skin.

2.1. If the answer is **YES**, classify the case as **dengue with warning signs** and treat the patient as follows:

- **Refer** the patient **URGENTLY** to hospital.

- Give one dose of paracetamol 10 mg/kg orally for high fever if the patient is uncomfortable.

- Provide as much oral fluid as the patient can drink during transportation to hospital.

2.2. If the answer is **NO**, proceed to the last row of the chart.

3. If the patient has none of the above signs and no other identified infectious causes of fever, classify as **dengue**, and manage as follows:

- Give paracetamol for high fever if the patient is uncomfortable. The recommended dose is 10 mg/kg/dose, not more than 3−4 times in 24 hours in children and not more than 3 g/day in adults.

- Advise mothers to continue feeding and giving fluids to a child patient.

- Instruct caregivers that the patient should be brought to hospital immediately if any of the following occur: no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffee-ground vomiting), shortness of breath, not passing urine for more than 4−6 hours.

- According to the guidelines in the chart, follow-up and reassess the patient every day until the patient has no fever on two consecutive days without the use of paracetamol.

- If fever has been present for more than 7 days, perhaps fever is attributable to other causes such as bacterial infections, and therefore the patient should be referred to the hospital for further evaluation.

Pitfall 5: Warning signs

Patients who develop warning signs at night usually wait until their next scheduled morning appointment to seek medical attention. This waiting period will allow the plasma leakage to deteriorate to hypovolaemic shock.

Solution: Ambulatory patients should receive explicit advice about the warning signs and the urgency of seeking immediate medical attention.

3.2   At the emergency department

Pitfall 6: Triage based on fever

The afebrile dengue patient gets a non-urgent triage and has to wait for medical attention or be sent home.

Explanation: A subnormal temperature is seen in patients with established plasma leakage or dengue shock. At this stage the clinical outcome is extremely time-sensitive; any delay in fluid resuscitation will lead to profound, prolonged shock and a stormy course for the disease.

Solution: Triage personnel should be taught assessment of perfusion (refer to Pitfall 8), especially when the BP is measured by a digital machine (see Textbox D). Additionally, a quick targeted history for nausea, vomiting and lethargy will indicate the severity of illness.

Pitfall 7: Waiting for full blood count results (for thrombocytopenia)

Waiting for FBC results to make decisions about admission and intravenous fluid therapy will cause further delay in recognition and treatment of dengue shock.

Solution:

Intravenous fluid therapy should be initiated when warning signs or clinical evidence of shock are present. However, it is useful to sample blood for FBC and haematocrit before commencement of intravenous fluid therapy.

3.3   Shock and its many manifestations

Pitfall 8: Vital signs are "stable"

Explanation: This phrase means that the patient is alert and has BP within the normal range. These two conditions are present in compensated shock. With respect to the "ABC" of resuscitation, patients with airway and breathing problems are "visible" – in other words they are sitting up and struggling to breathe noisily. The patient who is in shock is initially quietly tachypnoaeic; alert but lying down. This is more difficult to recognize. Unless you touch the patient, you will not be able to detect the cold extremities, feeble peripheral pulses and prolonged capillary refill time that are the earliest changes in shock. The patient in shock remains in this quiet alert state until cerebral perfusion diminishes, and then develops a "sudden" shortness of breath and restlessness or seizures followed quickly by a "sudden" collapse.

Solution: Make it a habit to touch and assess the peripheral perfusion of every patient, not only dengue patients. It takes less than 30 seconds to assess the four parameters that inform you whether the patient's life may be in danger: pulse volume, capillary refill time, colour and temperature of the extremities. Only trained humans can perform this vital function, no machine can do it.

Pitfall 9: Symptomatic treatment with antispasmodic agents or antacid is being given to patients with abdominal pain

Abdominal pain is an early sign of plasma leakage and becomes more severe as hypovolaemia progresses. The pain could be in the epigastrium and, together with vomiting, may be misinterpreted as gastritis. The patient will progress into full-blown shock if definitive treatment for shock is not given promptly.

Solution: A history of transitioning from fever to no-fever and the development of gastrointestinal symptoms such as nausea, vomiting or diarrhoea, should suggest dengue with warning signs or dengue shock. Patients with these symptoms should be carefully assessed for signs of dehydration and hypovolaemic shock.

Pitfall 10: Patients who present with severe abdominal pain are referred to the surgical team or for ultrasound studies.

Explanation: Plasma leakage is associated with abdominal pain that may occur anywhere in the abdomen. Guarding and rebound tenderness in the right iliac fossa have been described. This may be due to serosal oedema and lymphoid hyperplasia (6) of the intestines. The abdominal pain becomes more severe in the shock state due to splanchnic vasoconstriction. Referrals or ultrasound studies further delay initiating fluid resuscitation and may compound the morbidity and clinical outcome.

Solution: Evaluate the patient's history for fever that preceded the onset of abdominal pain. Assess the patient for signs of shock. Haemoconcentration and thrombocytopenia should raise the suspicion of dengue diagnosis. A bolus of intravenous fluid (5−10 ml/kg over 1 hour) may lead to resolution of abdominal pain, making the diagnosis of a surgical abdomen unlikely.

Pitfall 11: Shortness of breath misinterpreted as fluid overload or due to pleural effusion or pneumonia.

As plasma leakage progresses undetected and untreated, the patient develops metabolic acidosis (lactic acidosis) that initially appears as quiet tachypnoea. This represents the respiratory compensation to maintain the acid-base balance. With further deterioration to the shock state, the breathing becomes deeper and gives the impression of shortness of breath. (See Section 2.3.1, Acute respiratory distress and failure).

Solution: It is essential to be familiar with this breathing pattern, which is seen in dengue shock as well as diabetic ketoacidosis. Do not be distracted by the patient's dramatic breathing pattern. Look for features of shock: if unsure, a blood gas (+ lactate) analysis should be done. Start intravenous fluid resuscitation immediately after sampling blood for haematocrit determination.

Pitfall 12: Seizures or altered sensorium – diagnosed as meningitis or meningoencephalitis.

Seizures could occur during the febrile phase and during the critical phase. The first group will usually affect young children who present as febrile seizures during the viraemic febrile phase of dengue. At this time the full blood count may suggest a viraemic illness. The child should be treated as for febrile seizures with vigilance for warning signs and plasma leakage during the transition from the febrile to the afebrile phase.

The second group of patients present during the critical phase with no fever, or low-grade fever, but who are in severe shock. The brain is one of the last organs compromised by perfusion in hypovolaemic shock. When seizures or loss of consciousness occur during the critical phase, it is associated with prolonged and profound shock that causes acute cerebral ischaemia. At this stage the clinical outcome is extremely time-dependent; any delay in fluid resuscitation such as a detour to the computer tomography (CT) scan will lead to cardiorespiratory collapse and irreversible shock.

Solution: A targeted history is essential to confirm that the patient had fever preceding the seizures and might not be febrile at the time of seizures. The evidence of shock, such as narrowed pulse pressure and tachycardia, should alert the physician that urgent fluid resuscitation should be initiated, regardless of diagnosis. A CT scan is not necessary if the patient's neurological state recovers together with a stable haemodynamic state.

Pitfall 13: Bleeding versus plasma leakage

The physician who is overly concerned about the risks of bleeding, focuses on monitoring the trend of platelet counts alone to the exclusion of the bigger picture of plasma leakage. These physicians may administer platelet transfusions in addition to the maintenance of intravenous fluid. Fluid overload or inadequate fluid replacement may ensue, depending on the severity of the plasma leakage and the phase of disease at the time of platelet transfusion. Inadequate fluid replacement leads to prolonged and profound shock characterized by bleeding, the very phenomenon that these physicians are trying to prevent. It is important to note that the platelet count may remain low/very low during the first one or two days of recovery and that platelet transfusion during this time will cause fluid overload (7, 8).

Solution: The physician should be alert to the onset of this unique syndrome of dengue vasculopathy that causes plasma leakage and hypovolaemic shock when the fever subsides. Monitoring should be focused on manifestations of plasma leakage, bleeding and shock. The trend of haematocrit level together with haemodynamic status is the main guide to fluid management.

The usefulness of trending of the platelet count during the febrile phase is to identify its rapid decrease, which marks the beginning of plasma leakage. Beyond this phase, trending of platelet counts has no bearing on fluid management.

Pitfall 14: Pulse rate and systolic and diastolic pressures

Physicians frequently focus on the systolic BP and ignore the rising diastolic pressure and pulse rate (PR). (See Section 1.1.4, Severe dengue).

Solution: Patients with compensated shock may be critically ill despite being alert and having a "normal" systolic BP. Furthermore, automated BP devices can provide normal BP readings (i.e. falsely high BP results) in severe shock and hypotension. In general, if you cannot palpate the radial or brachial pulse and the central (femoral) pulses are weak or absent, assume that the patient is hypotensive. Do not rely on automated BP devices in patients with clinical signs of shock.

3.4 Parenteral fluid therapy

Pitfall 15: During the febrile stage the tachycardia and cold extremities could be misinterpreted as shock and fluid resuscitation commenced.

Vasoconstriction resulting in cold extremities is part of the body's normal mechanism to conserve heat to increase core body temperature.

Solution: The assessment of the intravascular volume of a patient should not be based on one or two parameters only. During the early febrile phase in addition to the high body temperature, the haematocrit and platelet count, pulse volume and urine output will be normal. Some patients may continue to have fever during the plasma leakage phase. In these patients, there may be tachycardia and cool peripheries despite a good pulse

volume. Other parameters of intravascular volume should be sought, e.g. capillary refill time, pulse pressure, urine output and/or acid-base balance.

Pitfall 16: Starting intravenous fluids in the febrile phase (because NS1 Ag is positive)

This practice should not be routine. Studies have shown that plasma leakage is detectable as early as day 2 of fever onset (9). Early intravenous fluid therapy will exacerbate accumulation of third space losses before the critical phase when plasma leakage increases significantly.

Solution: During the febrile phase hydration should be maintained by the oral route (see Section 2.2.1). Only in exceptional cases should intravenous infusion be used and then it should be kept at a minimal infusion rate and be discontinued as soon as the patient can take oral fluids.

Pitfall 17: Administering intravenous fluid at high rates for several hours without review of the clinical state.

The management of dengue shock is centred on intravenous fluid management. In dengue, unlike acute gastroenteritis, there is no loss of fluid from the body. Instead, fluid is merely lost from the intravascular to the extravascular compartments through leaky capillary endothelium. This state will continue for 24−48 hours during the critical phase of illness.

Solution: Thus it is important to consider that in a "leaky" capillary state, beyond a certain hydrostatic pressure, the more fluids are infused, the more they will leak into the "third space"; also that all fluids administered will be reabsorbed and fluid overload may result. Massive pleural effusion and ascites are the consequences of unrestrained intravenous fluid administration that leads to respiratory distress 12−48 hours later. Thus, it is essential to administer the minimum intravenous fluid necessary to maintain a "just-enough" circulation. Placing a micro- haematocrit centrifuge on the ward for use by trained staff facilitates the use of haematocrit determinations to manage fluid requirements. Titration of intravenous fluid as in the algorithm is recommended to avoid such situations (see Section 2.2.3.1, Treatment of shock).

Pitfall 18: Increased fluid therapy in a well perfused patient with persistently elevated haematocrit.

The haematocrit may remain elevated towards the end of the critical phase (24−48 hours of plasma leakage) despite adequate fluid therapy. A patient who remains well perfused i.e. with warm extremities, stable BP, PR and pulse volume as well as urine output, is compensating well for the ongoing plasma leakage.

An attempt to correct the haematocrit level by increasing intravenous fluid therapy in this scenario will often lead to fluid overload.

Solution: Continue close monitoring of this patient. Do not increase the intravenous fluid therapy; if the patient continues to be well perfused in the next 2–3 hours then intravenous fluids should be gradually reduced and even stopped, regardless of the haematocrit level. The haematocrit will gradually reduce even when intravenous fluid is discontinued signifying the re-absorption phase. This is illustrated in case study 2 (see Section 4).

Pitfall 19: Intravenous fluid therapy is continued into the recovery phase because the patient is not drinking.

A careful examination of the patient and the fluid intake and output chart should convince the physician that the patient has a big, positive balance of fluid accumulated in the third spaces over the past 48 hours of intravenous therapy. The only way for the pleural effusion and ascites to be reabsorbed into the circulation is to stop intravenous therapy. The patient's own thirst mechanism will kick in after the diuresis.

3.5 Urine output

Pitfall 20: During the febrile phase the urine output is often ignored and not factored into the evaluation of adequate oral fluids.

The urine output is a useful marker of the hydration state during the febrile phase.

Solution: Adequate oral intake of fluids should result in a urinary output frequency of 4−6 times per day.

Pitfall 21: During the critical phase the urine output of 1 ml/kg/hour is used as a criterion of adequate intravenous therapy or might not be monitored at all.

During the critical phase the urine output is a useful indicator of the intravascular volume state but should not be used as the sole criterion.

Solution: In severe shock, urine output should be monitored hourly using an indwelling catheter. The expectation of what constitutes an adequate urine output should be scaled down to ~ 0.5 ml/kg/hour to avoid fluid overload. On the other hand, a urine output exceeding that may be an indication to reduce intravenous fluid therapy.

Pitfall 22: Use of furosemide for oliguria during the critical phase.

Oliguria in this phase is due to "pre-renal", i.e. inadequate tissue-organ perfusion. The use of loop diuretics such as furosemide will produce some urine but will exacerbate the shock state.

Solution: Adequate peripheral perfusion should be the main end-point of intravenous fluid therapy. Patients with oliguria should continue to receive intravenous fluid therapy until peripheral perfusion is established.

Pitfall 23: The practice of a fluid bolus challenge followed by furosemide may produce urine; the physician may think they have averted an oliguric renal failure.

This practice may be detrimental in dengue with plasma leakage. During the infusion of a large fluid bolus, fluid will inevitably be redistributed to the "third space". However with furosemide administration fluid can only be drawn out of intravascular compartment. The net effect is that the "third space" gains fluids while the intravascular compartment remains depleted and the patient loses electrolytes such as potassium.

Solution: Urine will be produced by the kidneys when there is adequate renal perfusion. However, if established acute kidney injury sets in, as manifested in anuria and high serum creatinine levels, volume infusion should continue until the circulation is established. The physician should recognize that urine output as a parameter of adequate perfusion is very limited in this situation.

Pitfall 24: Worsening or persistent abdominal pain/tenderness appearing after 24 hours of large volumes of fluid replacement, misinterpreted as "warning sign for shock".

After more than 24 hours' administration of large volumes of fluid, tense ascites would have developed in patients with severe plasma leakage. These patients often complain of abdominal discomfort or pain. This may be due to tense ascites and/or enlarged and congested liver from the fluid overload.

Solution: This symptom and sign should be interpreted cautiously. The intravascular volume should be thoroughly assessed based on peripheral perfusion, pulse pressure and volume, urine output (~0.5 ml/kg/hour) and acid-base balance; not just by abdominal symptoms and signs alone. Intravenous fluid should be changed to colloids or be reduced and discontinued. Further fluid replacement will not only increase the abdominal symptoms but also aggravate the respiratory distress.

Pitfall 25: Abdominal compartment syndrome.

Abdominal compartment syndrome is the result of massive ascites accumulated in a short time, and hence is under tension. It may be precipitated by using moderately high PEEP during mechanical ventilation of dengue patients. Pressure on the retroperitoneal structures such as the kidneys, renal veins and inferior vena cava, will cause reduced renal perfusion with consequent oliguria even though peripheral perfusion may have been adequate.

Solution: The physician should realize this and be cautious about using urine output as a parameter of adequate perfusion. (See Textbox D). If it is possible, the patient may be put in a reclining or lateral position to relieve pressure on the retroperitoneal structures. However with time and especially when intravenous fluid therapy is discontinued at the end of the critical period, the intra-abdominal tension will ease and urine may start flowing gradually, spontaneously or with the help of an infusion of furosemide. The use of furosemide should be commenced in the recovery period when the patient is stable without intravenous fluid infusion. Premature use of furosemide may precipitate a shock state (10).

Pitfall 26: Use of renal replacement therapy such as continuous venous haemodialysis during the critical phase when the patient has severe metabolic acidosis and oliguria.

There is a misconception that lactic acidosis can be "washed out" by using lactate-free solutions in dialysis. Severe metabolic acidosis and oliguria are the consequences of uncorrected and prolonged shock. The haemodialysis machine will face technical problems with drawing blood from the hypovolaemic patient. Invariably your attention will be diverted to sorting out the machine rather than the patient.

Solution: Renal replacement should be reserved for patients who are already in the recovery phase, who are haemodynamically stable, are fluid overloaded and have oliguria not responding to furosemide therapy. In this situation the haemodialysis machine works very well and is effective in preventing life threatening pulmonary oedema.

Pitfall 27: Large volumes of dilute urine in a patient with unstable haemodynamics could mislead a physician into judging that the patient is stable.

Not correcting the hyperglycaemic state would exacerbate the shock state. (See Section 2.2.3.4.)

3.6 Blood transfusions for severe bleeding

Pitfall 28: Not transfusing blood until the haematocrit has decreased to low levels in unstable patients.

Severe but occult bleeding can be difficult to recognize (see Section 2.2.3.3, Treatment of haemorrhagic complications).

The haematocrit will only decrease to low levels after several boluses of fluid resuscitation (especially with colloids), or if the bleeding has been very severe. Throughout the period of fluid resuscitation the patient remains unstable while the "third space" fluid accumulation increases.

Solution: It is critical to recognize that the lower the haematocrit in dengue shock (8, 9), the more likely the significant bleeding, and therefore it is vital to change strategy from crystalloid/colloid infusion to blood transfusion. This change in strategy will prevent excessive infusion of non-blood fluids and accumulation of "third space" fluid. Bleeding should always be considered as a possible cause of prolonged/profound shock. Some authors have stated that "haematocrit is not useful in bleeding patients" (10). On the contrary, haematocrit is very useful in recognizing severe bleeding, provided that it is interpreted together with other clinical parameters. Please refer to interpretation of haematocrit Section 2.2.3.1.

Pitfall 29: DIVC regime for severe bleeding.

The causes of severe bleeding in dengue are not well understood. These patients have thrombocytopenia, deranged coagulation and disseminated intravascular coagulopathy. It is inevitable that these laboratory parameters become the targets of therapy with multiple transfusions of fresh frozen plasma, platelet concentrates and cryoprecipitate. Unfortunately, the clinical and laboratory responses are poor (7); meanwhile bleeding and plasma leakage continue unabated. Unless transfusion with fresh whole blood is given urgently, the patient will succumb to haemorrhagic shock with massive third space accumulation.

Solution: See Section 2.2.3.3. It may not be possible to arrest the bleeding or correct the thrombocytopenia or coagulopathy during the critical phase, but it is essential to keep abreast of blood loss with repeated blood transfusions if necessary. This should be guided by clinical assessment, haematocrit levels, blood gas and lactate analysis. Bleeding will usually decrease once the critical phase is over, as manifested by decreasing tachycardia and improved peripheral perfusion.

It is important to request fresh whole blood, otherwise nearly expired blood may be issued by the blood bank. Stored blood does not have the same properties as fresh whole blood and may not reverse the clinical situation.

Pitfall 30: Blood transfusion when the haematocrit is on the rise in a shocked patient.

Fluid boluses that are administered aggressively in unwarranted situations, such as in compensated shock (refer to Figure 6), may give the impression of refractory shock and prompt the physician into changing treatment from crystalloid fluid to blood transfusion. The subsequent haematocrit will rise even more sharply after the blood transfusion and prompt

the physician to give more crystalloids even though the haemodynamic situation is stable. The patient will become fluid overloaded with such an approach.

Solution: If haematocrit continues to rise despite fluid resuscitation, the physician should consider using a colloid bolus at 10 to 20 ml/kg. If the shock patient has a normal systolic BP, there is no need to rush the fluid resuscitation. Aggressive fluid resuscitation over 15 minutes should be reserved for those with hypotension (see Figure 7).

Pitfall 31: Blood transfusion in a stable patient with low haematocrit.

This usually occurs during the recovery period when re-absorption causes haemodilution. A blood transfusion at this stage may precipitate life-threatening pulmonary oedema.

Solution: If the patient has a stable circulation they do not need blood transfusion. The haematocrit will increase after the excess fluid has been diuresed.

Pitfall 32: Severe shock and inotropes.

Physicians who have administered 40−60 ml/kg of fluid and have failed to reverse the shock state will usually start inotropes such as dobutamine or dopamine and norepinephrine to support the BP (10).

Refractory shock is the most common cause of death within 24−48 hours of admission. There is usually a combination of plasma leakage and bleeding following prolonged uncorrected shock and this is accompanied by renal and liver impairment.

Solution: After every bolus infusion of 10−20 ml/kg, there should be a re-evaluation of the haemodynamic state. If there is no clinical improvement, a repeat haematocrit should be done. (see Figure 7). A rising haematocrit or an haematocrit that is still high, would suggest ongoing plasma leakage. This should prompt a change to colloid solution. A decrease in haematocrit suggests significant bleeding and the physician should proceed to transfuse matched fresh whole blood as soon as possible (see Section 2.2.3.3). Colloids and inotropes should be used as a temporary measure.

Pitfall 33: Liver enzymes and multi-organ involvement may prompt multi-specialty referrals that result in several "single organ" treatments.

There are many parameters that can be deranged in severe dengue – raised liver transaminases, muscle enzymes, e.g., creatine kinase, high blood creatinine levels, hyperglycaemia, thrombocytopenia, coagulopathy – all serving to distract the physician's attention. The multi-organ involvement is mainly due to shock with tissue hypoperfusion and diminished oxygen delivery.

Solution: Specialty consultations must not distract the physician from prioritizing achievement of haemodynamic stability and improved tissue oxygenation by fluid, colloid, or blood administration until the patient is out of the critical period. All other outstanding clinical issues (except hypoglycaemia and electrolyte imbalances) should await achievement of haemodynamic stability.

Pitfall 34: Last but not least, dengue shock treated "aggressively" as in septic shock

The main haemodynamic elements of septic shock are maldistribution of blood volume resulting from an increased vascular capacitance and myocardial suppression, while dengue shock is hypovolaemia with decreased vascular capacitance resulting from plasma leakage. The increased diastolic pressure in compensated shock preserves myocardial

perfusion. The clinical picture is dissimilar; septic shock is characterized by warm flushed extremities, decreased diastolic pressure and increased pulse pressure; the latter on the other hand is by cold vasoconstricted extremities, increased diastolic pressure with decreased pulse pressure (see Textbox D). Thus, the strategy of aggressive fluid resuscitation of septic shock is not applicable to severe dengue with plasma leakage.

Aggressive fluid resuscitation may indeed be harmful and should be limited to dengue shock with hypotension. Once the peripheral pulses are established the rate of parenteral fluid replacement should be reduced, as per frequent and simultaneous haemodynamic and haematocrit assessment.

In summary, training in the clinical management of dengue is essential if the clinician is to be able to navigate the patient through the three phases of the illness. Training is needed, first, to understand the disease course and second, to be alert to the physiological problems.

Intravenous fluid therapy is life-saving in dengue shock. However, there is a "narrow therapeutic index". In other words, fluids have to be given timely, at the appropriate volume, rate, of the appropriate type (crystalloids, colloid and/or blood) and for the appropriate duration. Therein lies the challenge to physicians who are not familiar with the important practice of fluid titration through frequent and meticulous assessment. Progression of the disease through the critical phase should be tracked in hours of plasma leakage. Recognizing the cues to discontinue intravenous fluid therapy is just as important as knowing when to start it. Given time and haemodynamic stability, other issues such as thrombocytopenia, coagulopathy and raised liver enzymes will recover spontaneously or with supportive care.

3.7 **References**

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4. Case studies

4.1 Case study one

15 May A previously well 32-year-old male had a history of high fever since 10 May, associated with vomiting and diarrhoea over the last three days. He presented to the emergency department (ED) in a poor condition at 18:30 on 15 May. Because of his poor general condition he was immediately sent to the red zone of the ED.

18:30 He was moderately dehydrated, had shallow breathing and a Glasgow Coma Scale (GCS) of 13 E4V4M5. His pupils were 3 mm reactive bilaterally. His temperature was 37.1°C, PR 165/min, BP 110/95 mmHg, RR 24/min and oxygen saturation (SpO$_2$) 100 %.

While he was being attended to by the ED physician the patient had generalized tonic-clonic seizures which were aborted with diazepam. After the seizures, he had shallow, laboured breathing and neck-stiffness. No abnormalities were detected in the cardiovascular system and abdomen. Due to his reduced breathing effort he was intubated in the ED and 5 ml/kg of 0.9% saline solution was given rapidly. By this time the GCS was E1V1M2, PR 120/min, BP 150/60mmHg, SpO$_2$ 100%, and bedside glucose 8.9 mmol/L. His reflexes were depressed and mild clonus was elicited.

The provisional diagnosis was meningoencephalitis with a differential diagnosis of sepsis with acute gastroenteritis. A full maintenance fluid regime was prescribed (2 ml/kg/hour). The estimated ideal body weight was 60 kg. A septic work-up and leptospira IgM, CT scan of the brain and chest radiograph were ordered. He was started on ceftriazone, acyclovir and ranitidine.

Table 11. Routine laboratory case 1

Complete blood counts and biochemistry results at 19:00	
Hb	184 g/L
HCT	57.1%
Platelet	22 x10^9/L
WBC	13.6 x10^9/L (neutrophil 79%)
Total bilirubin	41.8 μmol/L
ALT	543 IU/L
Blood urea	5.5 mmol/L
Serum sodium	130 mmol/L
Serum potassium	5.7 mmol/L
Creatinine	254 μmol/L

ALT = alanine aminotransferase; HCT = haematocrit; WBC = white blood cell

23:00 He was admitted to the ICU after the CT scan of the brain which showed no intracranial bleed or oedema. He had spontaneous breathing but was deeply sedated. The lung fields were noted to be clear. His BP was 85/50 mmHg, PR 116/min, RR 27/min and

SpO$_2$ 100%. The arterial blood pH was 6.97, bicarbonate 7.3 mmol/L, base excess -23.7 and lactate 18.50 mmol/L. Refer to Table 11 for other investigations. A central venous catheter was inserted and a pressure of 6 cm H$_2$O was obtained. He was given 5 ml/kg of colloid over 1 hour, followed by 3 ml/kg/hour of crystalloids. Dopamine was administered at 5 μg/kg/min.

16 May

03:00 The patient was unresponsive except to pain. By then he had received 500 ml of fluid and a second 500 ml was in progress. His BP was 88/46 mmHg, PR 110/min. His urine output was minimal. Refer to Table 12 for serial blood results.

07:00 The patient's abdomen was distended, soft and tender. His BP was 87/52 mmHg with PR 105/min and SpO$_2$ 100%. Dopamine was administered at 10 μg/kg/min,

Investigations carried out at 03:00 were reviewed (Table 12). One unit of DIVC regime was ordered − 4 units of cryoprecipitate, 4 units platelet concentrates, 4 units FFP (fresh frozen plasma). Dopamine was increased to 20 μg/kg/min and noradrenaline was added. The patient was referred to the nephrology and surgical team.

08:00 A nephrology assessment showed the labile BPs, systolic pressure 70−80 mmHg, diastolic pressure 50−60 mmHg, double inotropes, CVP 12−15 cm H$_2$O, heart rate (HR) 106/min, SpO$_2$ 100% on ventilation, RR 18/min; auscultation showed bi-basal crepitations in the lungs, his abdomen was distended but soft and non tender. Bowel sounds were present. The total fluid balance by this time was intake/output: 3207/95 ml.

The problems identified were:

1.   Septic shock with possible perforation of viscus or ischaemic gut.

2.   Coagulopathy with thrombocytopenia – to transfuse one cycle DIVC regime.

3.   Acute renal failure with severe metabolic acidosis and hyperkalaemia for renal replacement therapy.

4.   Meningoencephalitis.

Noradrenaline was increased and titrated to maintain the MAP (mean arterial pressure)> 65 mmHg. A second cycle of DIVC regime transfusion was initiated.

10:00 Surgical review noted unstable BPs, tachycardia and distended but soft abdomen with no guarding. Per-rectal examination showed fresh blood. The nasogastric tube did not yield any blood.

10:00 to 18:00 The patient's condition continued to deteriorate despite increasing inotropes infusions and transfusions of FFP, platelets and cryoprecipitates. Sodium bicarbonate infusions were started for metabolic acidosis, calcium gluconate infusions for hyperkalaemia. The CVP continued to increase from 12 cm to 20 cm H$_2$O. His BP was 120/80 mmHg and his SpO$_2$ 100%.

Ultrasound study of abdomen showed that the liver was mildly enlarged with normal liver echogenicity. No focal liver lesions were noted. The biliary tree was not dilated. The gall bladder was distended with thickened walls and no calculus within. There was pericholecystic fluid. There were no focal lesions within the normal-sized spleen. The pancreas was obscured by bowel gas. Both kidneys were normal in echogenicity and size

with no focal lesion. The urinary bladder was empty. Generalized ascites and a right pleural effusion were noted.

18:00 Investigations done at 15:00 (Table 12) were reviewed. He was started on continuous renal replacement therapy and one unit of packed cells was transfused together with a third cycle of DIVC regime.

Despite all these treatments, the general condition continued to deteriorate and blood lactate continued to increase as the BP remained low. The patient died on 17 May at 14:00.

The results of laboratory diagnostic tests were as follows:

- dengue serology: positive for IgG and IgM;

- leptospira serology: negative;

- blood culture and sensitivity: no growth

Post-mortem examination:

Head & neck:

The brain was normal, weighing 1240 g. No oedema was noted.

Thorax:

Both lungs were congested and there were bilateral pleural effusions. There was no pericardial effusion.

Abdomen:

There was ascites. Patchy ecchymoses were present all over the surface of the liver and of the large and small bowels. No perforations were noted. The spleen, kidneys, gall bladder, ureter and bladder were congested.

Table 12. Summary of serial laboratory results: fever began 10 May

	15 May 19:00	23:00	16 May 03:00	15:00
Hb (g/L)	184		111	83
HCT (%)	57		35	26
PLT (x 10^9/L)	22		17	48
WBC (x 10^9/L)	13.6		8.2	6.8
Urea/Sodium/Potassium mmol/l	L15.5/130/5.7	15.2/127/6.1	15.6/132/7.2	
Creatinine (μmol/L)	254		288	
ALT (IU/L)	543		>942	
AST (IU/L)		2429	3846	
Lactate (mmol/L)	18.5		12.0	
pH	6.972		6.906	
HCO$_3$	7.3		11.1	
PT ratio/ PTT (sec)			43/ >120	30.9/>200
INR			3.47	2.4

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = haemoglobulin; HCO$_3$ = bicarbonate; HCT = haematocrit; INR = international normalized ratio; PLT = platelets; PT = prothrombin time; PTT = partial thromboplastin time; sec = seconds; WBC = white blood cell

Learning points and pitfalls

The most outstanding pitfall in the clinical management was the missed diagnosis of shock at presentation to the ED at 18:30 on 15 May. Although the BP was seemingly normal, the pulse pressure was less than 20 mmHg, accompanied by severe tachycardia in the absence of fever. This is a typical picture of dengue shock. The high haematocrit of 57% suggesting plasma leakage and thrombocytopenia should also alert the physician to the possible diagnosis of severe dengue. Generalized tonic-clonic seizures could mislead physicians into thinking of an intracranial pathology. As shown in the CT scan, the brain was structurally normal.

Although it may not be easy to be certain about the underlying diagnosis of either severe sepsis or dengue shock, what is important is the recognition of shock. Not once was peripheral perfusion assessed. Fluid resuscitation should still be the primary action, whether due to sepsis, dengue or some other cause, as compromised hemodynamic status is recognized.

The severity of the compromised hemodynamic status was also underestimated. Rapid and shallow breathing in a young patient with the absence of significant lung findings and adequate SpO$_2$ without O$_2$ supplement should prompt the suspicion of possible acidotic

breathing; i.e. metabolic acidosis, and hence strengthen the suspicion of profound and/or prolonged shock. Similarly, the poor urine output and seizures are all pointing towards the same conclusion. Inotropes have limited value in the management of hypovolaemic shock although they make actual BP readings appear better,

Significant bleeding was recognized late. By 03:00 on 16 May, the haematocrit had decreased to 35% while the pH and lactate remained in severe acidosis. In the context of dengue, this signifies severe haemorrhage and the need for urgent transfusion with fresh whole blood. The main pitfall here was that the clinicians looked only at the Hb/ haematocrit level to determine the possibility of bleeding and to decide on blood transfusion. This practice would result in no, or late, recognition of severe bleeding and no, or delayed, blood transfusion. It is also important to note that overt bleeding may not be present at the beginning. In practice, the patient's poor hemodynamic status and the need for large volumes of fluid resuscitation, with or without oliguria and/or metabolic acidosis, are important clues to the possibility of significant bleeding. Given the missed diagnosis of shock at presentation in this patient and the progression to prolonged and profound shock, severe bleeding should have been anticipated.

The other main pitfall is the practice of following a DIVC transfusion regime in managing bleeding in dengue. Red cell transfusion is always the last to be given in this scenario. By the time transfusion of other blood products has been completed, much time has been lost and Hb/ haematocrit would have dropped even further. Hence it was not surprising that this patient continued to deteriorate and bleed even though the abnormal coagulation profile or platelet count level were partially corrected with aggressive transfusion of blood products. This is because adequate tissue oxygen delivery needs sufficient levels of red cells, particularly fresh red cells.

Another lesson is that if a patient continues to deteriorate while undergoing treatment, the provisional diagnosis should be re-visited and the patient re-evaluated, perhaps by a fresh team of clinicians who may be able to see the real picture. This case study demonstrated the inability of clinicians to re-evaluate the clinical diagnosis even when the patient was not responding to the prescribed therapy.

4.2   *Case study two*

24 July A previously well 7-year-old girl was referred by a general practitioner. She had a temperature of 40°C at 17:00. On arrival at the ED, at 19:00, her vital signs were recorded at the triage counter; these were a BP of 107/82 mmHg, a PR of 103/min, an RR of 22/min, and a temperature of 37°C.

20:00   The child was seen by an ED physician. The onset of fever was on 21 July and she had a cough and running nose. Throughout her illness she had poor oral intake and was less active but her urine output was normal and she was able to attend school on the first two days. However, she did not go to school on the third and fourth day of illness. On 24 July she had two episodes of vomiting and one episode of loose stools. She had no abdominal pain, rash or bleeding. Physical examination showed an alert child who appeared weak. Her extremities were warm, capillary refill time (CRT) was <2 seconds and a small volume pulse was detected. Her throat was injected, lungs and abdominal examination were normal. A diagnosis of upper respiratory tract infection (URTI) with dehydration was made and her blood was sampled for complete blood count (CBC) and

renal profile. An infusion of 3 ml/kg/hour of 0.9% saline was given for 2 hours. The estimated body weight was 16 kg.

22:00 A review by the paediatric doctor noted the lethargy, good peripheral perfusion with good pulse volume, BP 92/68 mmHg and PR 131/min. The liver was 2 cm enlarged and tender. CBC (taken at 20:00, before intravenous infusion) showed Hb 17 gm/L, haematocrit 46%, WBC 7.3 x 10^9/L, platelets 100 x 10^9/L, serum sodium 121 mmol/L, potassium 3.9 mmol/L, creatinine 59 μmol/L, blood urea 4.5 mmol/L.

The diagnosis was revised to dengue with warning signs in the critical phase and she was admitted to hospital; the estimated defervescence time was 18:00 to 19:00. An order was made for 0.9% normal saline at 5ml/kg/hour for 2 hours then to be reduced to 3 ml/kg/hour.

24:00 Upon arrival in the ward she was noted to have lethargy, warm extremities and a good pulse volume. Her BP was 104/78 mmHg, PR 125/min and temperature 36.4°C. A repeat CBC was ordered.

25 July

02:00 A review of the haematocrit sampled 2 hours ago was 46%. The intravenous fluid therapy was increased to 5 ml/kg/hour.

04:00 At this point the child had a BP of 98/64 mmHg, a PR of 136/min, and a temperature of 37°C. The intravenous therapy was increased to 6 ml/kg/hour and a CBC repeated.

06:00 A repeat assessment showed warm extremities and a fair pulse volume, clear lung fields and tenderness at the right hypochondrium. The 04:00 haematocrit was 50%. Intravenous therapy was increased to 8 ml/kg/hour. The repeat haematocrit at 07:00 was 51%.

08:15 She was lethargic, drowsy and complained of severe abdominal pain. She had cold extremities, a feeble pulse, and a CRT of 4–5 sec. Her BP was 68/51 mmHg, PR 130/min, temperature 36°C, and RR 36/min (with reduced breath sounds in both lung bases). The abdomen was mildly distended and tender. A diagnosis of dengue with severe plasma leakage and hypotensive shock was made. She was quickly given 20 ml/kg of 0.9% normal saline. Subsequent evaluation showed perfusion and pulses remained poor. While waiting for colloid solution, another 10 ml/kg of 0.9% normal saline was given. After 30 ml of 0.9% normal saline boluses, the BP was 114/70 mmHg, PR 118/min and the pulse volume improved. A colloid (hydroxyethyl starch) infusion of 10 ml/kg over 1 hour followed and she was transferred to the paediatric intensive care unit (PICU).

10:30 About 16 hours post defervescence, she was alert, with fair pulse volume, cold peripheries, a CRT of 3 sec, a BP of 105/78 mmHg, a PR of 100/min. Her lungs had reduced breath sound at bases (R > L) and her urine output was 144 ml since admission (continuous bladder drainage). The intravenous therapy was reduced to 8 ml/kg/hour. An arterial line was inserted for continuous BP monitoring and blood sampling.

Between 11:00 and 16:00, her extremities became warm, her pulse volume improved, and she had a systolic BP of 90–98 mmHg, a diastolic BP of 64–70 mmHg, a PR of 100–120/min (mildly tachypnoeic) and a SpO_2 of 100% in air. Periorbital oedema and increasing right pleural effusion (up to mid-zone) were noted. Her urine output was 2–5 ml/kg/hour. At 12:00 her haematocrit was 41%. A dextrose-saline infusion was added. The total intravenous fluid was reduced every 1–2 hours from 8–6–5–4–3 ml/kg/hour.

16:00 (22 hours post defervescence), she complained of abdominal pain and vomited about 200 ml of coffee ground fluid. Her PR was 140–150/min, her peripheries were cold and there was a small pulse volume. The systolic BP was 96–100 mmHg while the diastolic BP was 78–88 mmHg and pulse pressure 15–20 mmHg (refer to clinical chart, page 95).

The bedside microcentrifuge showed an haematocrit of 53% and a blood glucose level of 8.8 mmol/L. Intravenous fluid was increased to 7 ml/kg/hour and she was started on intravenous ranitidine (H-2 blocker) and cross-matched for fresh whole blood. (She was not given the blood transfusion.)

18:00 She had no more abdominal pain or vomiting but clinically she had not improved; her pulse volume was still small, her PR 140–145/min, and CRT 3–4 sec. Her pulse pressure was narrow (10–15 mmHg). The bedside haematocrit was 48% (laboratory haematocrit 50%). Fluid therapy was changed to colloid solution at 10 ml/kg/hour for one hour.

19:00–24:00 Progressive clinical improvement was observed, refer to clinical chart: HR 120–130/min, pulse volume improved, BP 100/80 mmHg, pulse pressure 20–25 mmHg, urine output 1–2 ml/kg/hour. Colloid infusion was reduced every hour from 8–7–6 ml/kg/hour then changed to crystalloid at 5 ml/kg/hour. At 24:00 total fluid intake/output since admission was 3466/1077 ml (positive balance of 2389 ml).

26 July

00:00–07:00 (30–37 hours post-defervescence), she showed improvement in the haemodynamic state. Intravenous fluid therapy was reduced from 5–4–3–2–1 ml/kg/hour, every 1–2 hours. By 07:00 she had warm peripheries and a good pulse volume, moderately severe periorbital oedema, bilateral pleural effusion and ascites. The BP systolic was 100–108, diastolic was 82–86 mmHg, HR 110–120/min, RR 40–45/min, SpO_2 > 95% on air. Her urine output was 1–1.5 ml/kg/hour. Her haematocrit remained about 49−48%. Intravenous fluid therapy was discontinued at 07:00 on 26 July. At 16:00 her haematocrit was 43%. Spontaneous diuresis ensued and her appetite improved. She was discharged from the PICU on 27 July. Dengue IgM was positive. Table 13 shows a summary of serial CBC and intravenous fluid therapy.

Lessons learnt and analysis of disease course:

At the ED medical consultation, a patient with fever, cough and running nose will usually be given a diagnosis of URTI. However, the reduced oral intake, absence from school and weakness and dehydration should prompt a more serious diagnosis. If one is unsure, a CBC should be done. Another clue to the diagnosis of dengue is that the patient's condition worsened at a time when the temperature was becoming normal.

She presented to the hospital on the fourth day of illness, just after defervescence (her temperature decreased from 40°C at 17:00 to 37°C at 19:00 on 24 July) with warning signs of poor oral intake, vomiting, lethargy, high haematocrit and enlarged tender liver. (Her baseline haematocrit was estimated to be <35%). Although she had evidence of plasma leak, pleural effusion was not clinically detectable and peripheral circulation was assessed to be normal at presentation to the ED.

Despite intravenous fluid therapy between admission and 07:00 on 25 July, she had tachycardia and increasing haematocrit levels. These suggest inadequate replacement of ongoing plasma leak.

At 08:15 on 25 July, about 14 hours after defervescence, she developed severe abdominal pain and hypotensive shock. Pleural effusion had become detectable by this time. The tachypnoea could be related to metabolic acidosis. She was resuscitated with 30 ml/kg of crystalloid; the ideal fluid would have been colloids. Intravenous fluid therapy was gradually reduced upon transfer to the PICU.

However, at about 17:00 on 25 July she developed compensated shock, having a BP of 100/90 mmHg with rising heart and respiratory rates. Although she had gastrointestinal bleeding, her elevated haematocrit of 48−53% suggested that the main cause of shock was plasma leak. Hence a colloid solution of 10 ml/kg was given. Clinical improvement after the colloid infusion supported the decision to withhold blood transfusion. From admission to 18:00 on 25 July the cumulative fluid balance was positive (1381 ml) and this was reflected in the moderately severe right pleural effusion and ascites.

Her haemodynamic status stabilized thereafter and intravenous therapy was discontinued at 07:00 on 26 July, about 36 hours after defervescence (with a cumulative positive fluid balance > 2000 ml). Note that the haematocrit was elevated to 48% at this time but her peripheral perfusion was good, suggesting that she could compensate well for the plasma leak. She was already in respiratory distress which would become worse if intravenous fluid therapy were continued. A decrease in haematocrit at 16:00 was evidence of the re-absorption phase of the disease. It is therefore important to consider the patient's haemodynamic state rather than the laboratory value exclusively, particularly when there is already a big positive fluid balance. No blood products or antibiotics were given. The haematocrit was 32% at hospital discharge on 29 July.

Table 13. Summary of serial CBC and intravenous fluid therapy: fever began on 21 July

Date Time	HCT (lab)%	Bedside HCT %	IV fluid therapy	WBC (x 10^9/L)	PLT (x 10^9/L)
24 July					
20:00 (at ED)	46		NS 3 ml//kg/hour for 2 hr, 5 ml//kg/hour for 2 hours, then 3 ml//kg/hour	7.3	100
25 July					
00:30 (ward)	47		NS 3 ml//kg/hour	9.0	82
02:00			NS 5 ml//kg/hour		
04:00	50		NS 6 ml//kg/hour	10.4	59
06:00	51		NS 8 ml//kg/hour	10.6	44
08:15 10:30			NS 20 + 10 ml/kg bolus Then colloids 10 ml//kg/hour Then 8 ml//kg/hour		
11:00	41		6 ml//kg/hour	8.5	30
13:00		48	5 ml//kg/hour		
15:00			3 ml//kg/hour		
16:00	53	56	7 ml//kg/hour (colloid)	20.1	18
18:00	50	48	10 ml//kg/hour (colloid)		
19:00			8 ml//kg/hour (colloid)		
20:00			7 ml//kg/hour (colloid)		
22:00			5 ml//kg/hour (Hartmann's solution)		
23:00	44	48	4 ml//kg/hour (Hartmann's solution)	19.3	17
26 July					
00:00	49	48	3 ml//kg/hour (Hartmann's solution)		
02:00	49	54	2 ml//kg/hour (Hartmann's solution)	30.3	6
06:00	48	52	1 ml//kg/hour for 1 hour then stopped	30.6	10
16:00	43		No IV, oral fluids	36.0	10
21:00	38		No IV, oral fluids		
27 July	34		Oral fluids	32.1	27
28 July	31		Oral fluids	16.0	Clump
29 July	32		Discharge		

CBC = complete blood count; ED = emergency department; HCT = haematocrit; IV = intravenous; NS = normal saline or 0.9% sodium chloride solution; PLT =platelets, WBC = white blood cell

Clinical chart
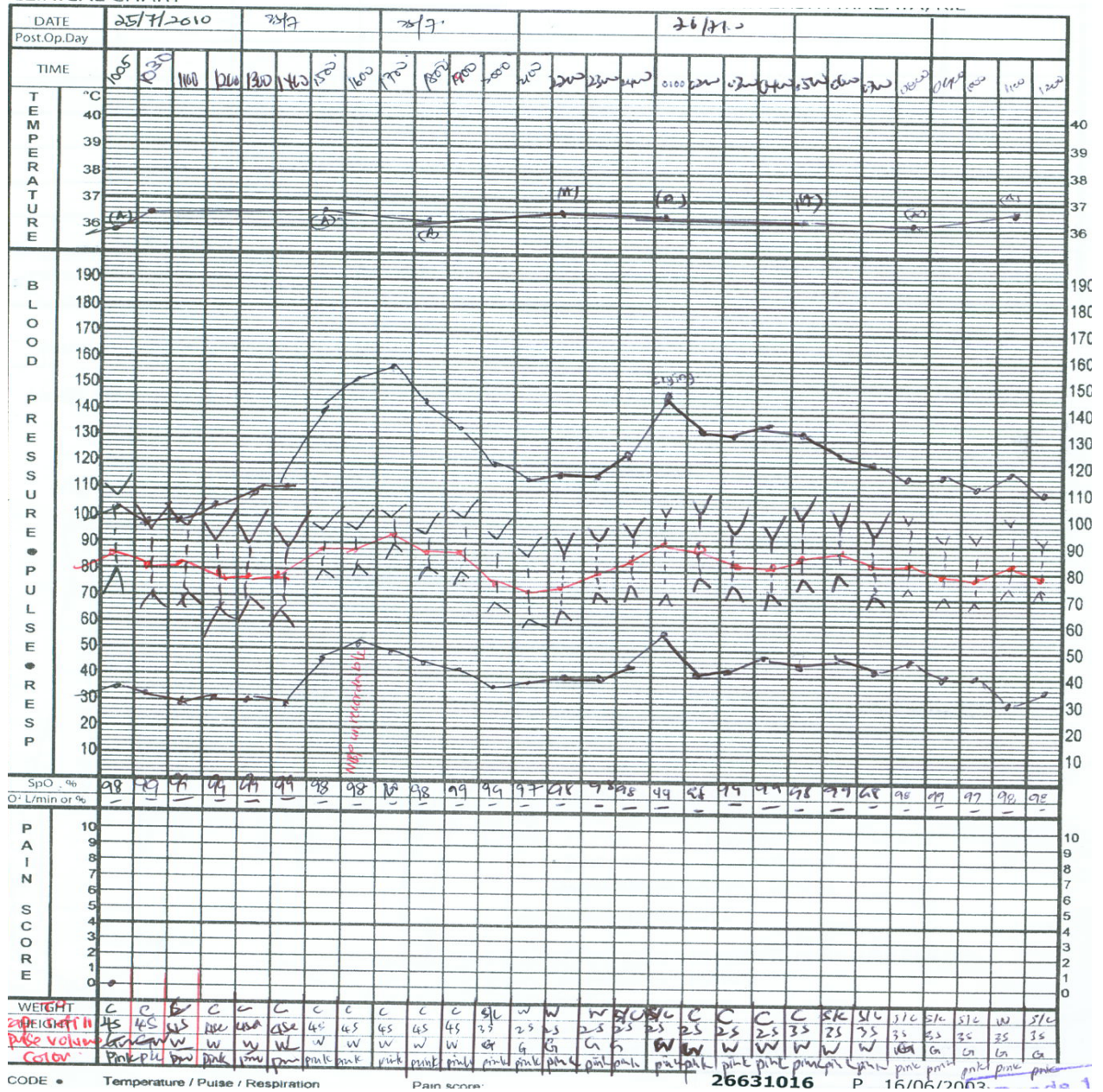
Clinical chart in the paediatric intensive care unit showing temperature, BP, heart rate (upper black line) mean arterial BP (red line), RR (lower black line) and peripheral perfusion records (First row, temperature of extremities: c = cold; w = warm; s/c = slightly cold. Second row, capillary refill time in seconds. Third row, pulse volume: w = weak; g = good. Fourth row, colour of extremities. Note the increasing diastolic pressure and narrowing pulse pressure and tachycardia between 15:00 and 18:00 on 25 July and the improving pulse pressure and reducing heart rate after colloid infusion between 16:00 and 20:00 on 25 July.

4.3 *Case study three*

First section

A previously well 10-month-old girl was brought to the ED on 31 October with generalized seizures during the preceding 30 minutes.

She had had a high fever since 27 October (5 days duration); this was associated with poor oral intake of fluids (water and a total of 90–120 ml of milk per day). She was less active than usual.

On 28 October she had a generalized rash and was brought to the health clinic where a blood test was said to be normal. The rash subsided on the 29 October; however the fever persisted and she developed vomiting and diarrhoea twice a day while her fluid intake continued to be poor. She had passed urine but her mother was unsure of the volume.

On 31 October she was lethargic and at 11:00 she became limp with up-rolling eyeballs. This was followed by generalized tonic-clonic seizures. She was then brought to the ED.

31 October

12:00 On arrival at the ED her vital signs were: temperature 35.5°C (axilla), PR 162/minute, BP 110/50 mmHg, SpO_2 100% in room air. She was unresponsive and had jerking of the limbs. Her pupils were about 2–3 mm equal. She showed neck stiffness, a depressed anterior fontanelle, and a dry coated tongue. Feeble pulses with cold extremities and prolonged capillary refill time were present. Her breathing was labored, but air entry was clear bilaterally. A soft abdomen with a 4 cm firm liver was palpated. Her estimated body weight was 7 kg.

The following investigations were carried out:

Complete blood count, renal function test, liver function test, random blood glucose, venous blood gases, blood culture and sensitivity, blood group and screen and dengue serology.

She was administered with high flow oxygen, diazepam 3 mg intravenously followed by 200 ml of 0.9% saline fluid bolus. Intravenous ceftriaxone was given.

Another 100 ml of 0.9% saline and intravenous infusion of phenytoin was given for the status epilepticus. She was then referred to the PICU.

Interpret the clinical history and physical signs at the ED (answers are to be found after third section).

Second section

The following were the results of investigations in ED, before fluid resuscitation.

Table 14. Laboratory findings, case study 3, day 5 of illness, 31 October

pH	6.949
PCO_2	84.6 mmHg
PO_2	72.8 mmHg
Bicarbonate	12.1 mmol/L
Base excess	-12.9 mmol/L
Random blood glucose	14.8 mmol/L
Sodium	124 mmol/L
Potassium	5.2 mmol/L
Urea	10 mmol/L
Creatinine	52 µmol/L
Albumin	28 g/L
Aspartate aminotransferase	958 IU/L
Alanine aminotransferase	299 IU/L
Prothrombin time ratio	1.77
Partial thromboplastine time	> 200 sec

Table 15. Complete blood counts on day 2 (28 October) and day 5 of illness (31 October)

	Day 2, 28 October (Health centre)	Day 5, 31 October, ED of hospital
Haemoglobin (g/L)	113	108
Haematocrit (%)	36	33
White blood cell (x 10^9/L)	4.0	15.2 (63% lymphocytes, 24% neutrophils)
Platelet count (x 10^9/L)	340	24

Interpret the blood investigations, Tables 14 and 15 on day 2 and day 5 of illness (see answers after following section).

Third section

31 October

15:00 On arrival in the PICU the patient was pale, unconscious with occasional decerebrate posturing, and her pupils were equal in size, about 1–2 mm. She responded only to pain. Her heart rate was 130/min and she had a normal breathing effort, an axillary temperature of 36.5°C and cold extremities with feeble radial pulses, prolonged capillary refill time and a BP of 115/62 mmHg. The anterior fontanelle was sunken and petechial hemorrhages and bleeding from venepuncture sites were noted. A nasogastric tube yielded about 70 ml of coffee-ground aspirates. A right pleural effusion was detected.

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Investigation results in PICU (after resuscitation in ED):

Repeat blood glucose   6.8 mmol/L

Repeat haematocrit after 300 ml saline   0.26

Haemoglobin   86 gm/L

Interpret the clinical picture and blood investigations on arrival in PICU.

What is the definitive management?

ANSWERS

First section

Interpret the clinical history and physical signs at the emergency department

The history was that of an acute febrile illness associated with decreased fluid intake and increased fluid loss resulting in dehydration. Clinical signs of shock included tachycardia in the absence of fever, and decreased peripheral perfusion.

Seizures could indicate acute ischemia to the brain or meningitis/encephalitis or electrolyte imbalance. Although seizures with neck stiffness were suggestive of meningitis, the subnormal temperature made this diagnosis less likely. The sub-normal temperature meant defervescence and the critical phase of dengue marked by increased vascular permeability, plasma leakage and hypovolaemic shock. The patient most probably had dengue shock syndrome.

Second section

Interpret the blood investigations on days 2 and 5 of illness, Tables 14 and 15

The CBC on day 2 of illness showed that the baseline haematocrit was 36%; the total white cell count suggested a viral infection. The platelet count is expected to be normal on day 2 of dengue illness.

On the day of admission, the venous blood gas showed severe metabolic acidosis, consistent with shock. Hyperglycemia was part of the stress response. A lower haematocrit (33%) than the baseline (36%) at the time of shock presentation suggested significant bleeding. The low platelet count indicated the critical phase of dengue. Although the total white count was elevated, this was predominantly due to lymphocytes; hence it was less likely that the patient had a bacterial infection. The coagulation disorder (with prolonged prothrombin time and activated partial thromboplastin time) together with raised liver enzymes, were consistent with severe dengue with shock and bleeding. The hyponatraemia could be related to the intake of plain water; the hyperkalaemia could be due to metabolic acidosis and the increased blood urea due to dehydration and shock.

Third section

Interpret the clinical picture and blood investigations on arrival in PICU.

What is the definitive management?

On arrival at the PICU, the patient's tachycardia had decreased slightly but she was still in shock and pale despite being given 300 ml (30–40 ml/kg) of 0.9% saline. The small reactive pupils could be the effect of benzodiazepine. Plasma leakage was clinically detected after the bolus fluids were administered. Upper gastrointestinal bleeding and other bleeding tendencies were consistent with severe dengue. These signs indicated ongoing plasma leakage and gastrointestinal bleeding.

Blood investigations: The blood glucose had decreased towards the normal level, consistent with an improving clinical state after fluid resuscitation. However, the haematocrit after resuscitation (haematocrit 26%) had dropped well below the patient's baseline haematocrit (day 2, haematocrit 26%) but the patient's hemodynamic status had not stabilized. This suggested that in addition to plasma leak, severe bleeding had occurred.

Continuation of case scenario:

In the PICU, two boluses of 10 ml/kg colloid solution were given over 2 hours. A urinary catheter was inserted for hourly measurement of urine output. Monitoring of vital signs and peripheral perfusion was continued every 15–30 minutes during this period. The definitive management was to group and cross-match fresh whole blood for transfusion as soon as possible.

17:30 to 19:30 After transfusion of 10 ml/kg of fresh whole blood over 2 hours, the patient's conscious level improved and she started to respond to her parents and surroundings. Her heart rate was 120 to 130/min with cold extremities and her CRT was 4 seconds. The repeat haematocrit was 27%.

20:00 to 22:00 Another 5 ml/kg of fresh whole blood was given over the next 2 hours The repeat blood glucose was 3.3 mmol/L. A dextrose 5% saline solution at 4 ml/kg/hour was added. The total intravenous fluid volume/hour was reduced to 7 ml/kg for 2 hours, then 5 ml/kg for 4 hours and 3 ml/kg for another 24 hours (see Table 16). A dextrose 10% saline infusion was used to manage hypoglycaemia (lowest blood glucose 1.5 mmol/L). Liver enzymes returned to normal values and ceftriaxone was stopped after 72 hours when blood cultures were negative. Dengue IgM was positive.

Table 16. Summary of fluid therapy and blood investigation results: fever began on 27 October

Date Time	HCT (lab) (%)	Bedside HCT (%)	IV fluid therapy	WBC (x 10^9/L)	PLT (x 10^9/L)
28 Oct	36		(Health centre)	4.0	340
31 Oct					
12:00	33 (ED)		NS 30–40 ml/kg	15.2	24
15:00 (PICU)	26	22	Colloid 20 ml/kg followed by fresh whole blood 10 ml/kg over 2 hours (17:30 to 19:30)	8.2	17
20:00	27	27	Fresh whole blood 5 ml/kg over 2 hours + Dextrose-saline 4 ml/hour		
22:00	35	35	Dextrose-saline 3 ml/hour + NS 4 ml/hour		
1 Nov					
02:00	32		Dextrose-saline 3 ml/hour + NS 2 ml/hour	7.6	29
06:00			Dextrose-saline 3 ml/hour		
12:00	34		Dextrose 10% saline 3 ml//kg/hour		
16:00	31		Dextrose 10% saline 3 ml/kg/hour plus breastfeeding	6.8	Clump
20:00	32		Dextrose 10% saline 3 ml/kg/hour plus breastfeeding		
2 Nov					
08:00	29		IV discontinued; breastfeeding	6.3	30
16:00	25		Breast + bottle feeding	5.5	21
3 Nov	21		General ward – normal feeding		57
4 Nov	25				82
5 Nov	29		Discharge		

HCT = haematocrit; IV = intravenous; NS = normal saline or 0.9% sodium chloride solution; PLT = platelets, WBC = white blood cell

4.4   *Case study four*

24 August

A previously well 24-year-old female was referred by a general practitioner for fever lasting three days, myalgia and weakness lasting for two days, tea-coloured urine and mild jaundice on the day of referral. A liver function test showed elevated liver enzymes and the test for hepatitis B surface antigen was negative. She was referred with a diagnosis of possible hepatitis A.

14:40 She was registered at the ED.

15:00 Observations at the triage counter showed that her temperature was 36.0°C; PR 110/min, RR 20/min and BP100/50 mmHg. Based on these findings she was given a triage rating of three (not urgent).

16:00 She was seen by an ED physician who took her history of fever lasting 3 days; anorexia and vomiting for 3 days and severe myalgia and dark-coloured urine. The physician noted the vital signs taken at 15:00. He further detected a tender epigastrium and a positive Murphy's sign. The diagnosis made by the ED physician was obstructive jaundice. Blood was sampled for the following investigations: CBC, liver function test, renal profile and urine microscopic examination. The patient was referred for a general surgery opinion.

16:15 She was reviewed by general surgery staff who re-took the history of epigastric pain for five days with worsening abdominal pain. She had generalized malaise together with loose stools and had vomited several times. She appeared distressed and dehydrated. In addition to the tender epigastrium and a positive Murphy's sign, the abdomen was soft and not distended with no guarding or rebound tenderness. Bowel sounds were present and per-rectal examination revealed no blood or mass. The vital signs at 15:00 and blood investigations taken at 16:00 were noted (Table 17). The surgical doctor made a diagnosis of urinary tract infection with a differential diagnosis of acute cholecystitis. Due to the unexplained thrombocytopenia and polycythaemia, he requested an ultrasound study of the abdomen (to exclude gall stones) and a referral to internal medicine.

Table 17. Results of blood sampled at 16:00, case study 4

Blood biochemistry		Liver function tests	
Sodium	138 mmol/L	Albumin	36 g/L
Potassium	3.9 mmol/L	Bilirubin	75 μmol/L
Urea	8.4 mmol/L	ALT	191 IU/L
Creatinine	158 μ3mol/L	AST	104 IU/L
CBC		Urine analysis	
WBC	6.9×10^9/L	Urine RBCs	100
Hb	172 g/L	Urine leukocytes	90
HCT	50%	Bacteria	3+
Platelet	4×10^9/L	Urobilinogen	68
		Bilirubin	50

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; RBCs = red blood cells; WBC = white blood cell

18:30 The patient was reviewed by a medical physician after the ultrasound study. The history was re-taken. Date of fever onset: 19 August (day 6 of fever on 24 August). Other complaints included vomiting, poor appetite, lethargy and a transient rash. On 24 August she experienced intense abdominal pain. The physician noted that the patient was flushed with a tinge of jaundice. Her temperature was 36.2°C, PR 120/min, BP 100/80 mmHg. She had cold extremities with weak and thready pulses. The lung fields were clear and tenderness in the epigastrium and petechiae in the lower limbs were detected. The physician made a diagnosis of compensated dengue shock in critical phase of illness and moved the patient to the resuscitation bay. Defervescence was estimated at 12:00 on 24 August.

Management:

The patient's actual body weight was 64 kg but based on her height, the ideal weight was estimated to be 50 kg. A blood sample was taken for group and cross-match. She was given a bolus of 10 ml/kg (500 ml) of 0.9% saline over 30 minutes followed by a 7 ml/kg/hour for 2 hours.

20:00 After 20 ml/kg (1000 ml) of 0.9 saline solution, the patient's abdominal pain resolved; she felt much better and her pulse volume was good. Her heart rate was 90/min and her BP was 110/73 mmHg. Her abdomen was soft and non-tender; Murphy's sign was negative. CBC was repeated together with other investigations (Table 18). She was admitted to the general medical ward.

The ultrasound study results were reviewed. They showed normal hepatic parenchyma, thickened gall bladder wall with wall oedema, no gall stones, no intrahepatic duct dilatation and no ascites. The radiological diagnosis was acalculous cholecystitis.

22:00 Intravenous fluid rate was reduced to 5 ml/kg/hour for 2 hours

24:00 Intravenous fluid rate was reduced to 3 ml/hour for 4 hours

25 August

04:00 Intravenous fluid rate reduced to 2 ml/kg/hour

08:00 Her general condition improved. She had passed urine three times during the night and it was lighter in colour. She was able to take oral fluids. The intravenous fluid was maintained at 1.5 ml/kg/hour.

26 August

08:00 Intravenous fluid therapy discontinued.

27 August

She was discharged, to be followed up a week later. Dengue IgM was positive.

Table 18. Serial laboratory results

Fever started on 19 August. Fluid resuscitation (20 ml/kg) was given between 18:30 and 20:00 on 24 August, followed by a step-wise reduction of fluid therapy from then through 25 August. Intravenous fluid therapy was discontinued on 26 August.

	24 Aug 16:00 4h PD	20:00 8h PD	24:00 12h PD	25 Aug 09:00 21h PD	16:00 28h PD	20:00 32h PD	26 Aug 06:00 42h PD	27 Aug
HCT(%)	50	43	43	44	42	41	41	40
WBC (10^9/L)	6.9	6.8	6.1	7.2	6.5	6.5	7.4	12.6
PLT (10^9/L)	4	6	5	5	2	5	5	31
Urea (mmol/L)	8.4	8.4		8.5	9.8		4.7	
Creatinine (mmol/L)	138	158		159	159		80	68
ALT (IU/L)	106	104		81				582
AST (IU/L)	198	191		142				1681

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCT = haematocrit; PD = post-defervescence; WBC = white blood cell

Lessons learnt: A diagnosis that was missed

It is not uncommon for dengue to be misdiagnosed at various phases of the disease course (see Section 1.3, Differential diagnoses of dengue). Viral hepatitis is one of the possible misdiagnoses, especially in the presence of jaundice and raised liver enzymes. However, jaundice is an uncommon observation in dengue: it is more often described in dengue patients in association with haemolysis or sepsis. Raised liver enzymes are common findings in both conditions (but AST is typically much higher than ALT in dengue). Therefore it is not surprising for the general practitioner (GP) to make a diagnosis of viral hepatitis. On the other hand, shock is an unusual feature of uncomplicated viral hepatitis. The shock was not recognized by the GP or the subsequent physicians who attended to her. When there is a strong suspicion of dengue, the doctor should look out for other clues such as petechiae and rash, which were indeed noted by the medical physician several hours later.

"Acute abdomen" is also another common presentation of dengue; in fact it is an important warning sign of severe dengue especially during the critical phase. It is not surprising for a clinician to misdiagnose this as acute cholecystitis or even acute appendicitis. It is important to note that the ultrasound findings of pericholecystic fluid collection and thickened (oedematous) gall bladder wall are often reported by radiologists as acalculous cholecystitis, but in actual fact these are well recognized features of dengue, especially in those with plasma leakage.

"Polycythemia" is another common misinterpretation of laboratory findings of dengue with haemoconcentration following plasma leakage. A high haematocrit accompanying thrombocytopenia and leukopenia in a patient with febrile illness should prompt a clinical suspicion of dengue with plasma leakage.

A shock that was missed

Dengue shock in its early stage can be easily missed, especially in adults − as shown in this case. This illustrates clearly that without careful assessment of peripheral perfusion (i.e. peripheral temperature, peripheral pulse volume and capillary refill time), a state of compensated shock can be overlooked as the patient's BP is still well maintained. It is important for clinicians to remember that touching the patient's extremities makes a big difference to the clinical assessment. The other important clue for shock here is the tachycardia in the absence of fever and/or other causes. Additional clues for early recognition of reduced perfusion include reduced urine output, concentrated urine and silent tachypnoea.

Once dengue shock is recognized, prompt fluid management as per the algorithm in Figure 5 stabilizes the patient's condition together with resolution of the severe abdominal pain. Table 18 shows the changes in CBC, renal profile and liver enzymes during admission. Note the rapid, followed by a more gradual decrease in haematocrit with fluid resuscitation and step-wise reduction in intravenous fluid therapy respectively. Despite the severe thrombocytopenia, she was not given any transfusion of blood products. Renal profile improved with fluid therapy but AST continued to increase even during the convalescent phase.

5. Annex

5.1 Textbox A: Good and bad clinical practice

	Good clinical practice	Bad clinical practice
1	Assessment and follow-up of patients with non-severe dengue and careful instruction about warning signs to watch out for	Sending patients with non-severe dengue home with no follow-up and inadequate instructions
2	Administration of paracetamol for high fever if the patient is uncomfortable	Administration of acetylsalicylic acid (aspirin) or ibuprofen
3	Obtaining a haematocrit level before and after fluid boluses	Not knowing when haematocrit levels are taken with respect to fluid therapy
4	Clinical assessment of the haemodynamic status before and after each fluid bolus	No clinical assessment of patient with respect to fluid therapy
5	Interpretation of haematocrit levels in the context of fluid administered and haemodynamic assessment	Interpretation of haematocrit levels independent of clinical status and fluid therapy
6	Administration of intravenous fluids for repeated vomiting or a high or rapidly rising haematocrit	Administration of intravenous fluids to all patient with non-severe dengue
7	Use of isotonic intravenous fluids for severe dengue	Use of hypotonic intravenous fluids for severe dengue
8	Giving just sufficient intravenous fluid volume to maintain effective circulation during the period of plasma leakage for severe dengue	Excessive or prolonged intravenous fluid administration for severe dengue
9	Avoiding intramuscular injections in dengue patients	Giving intramuscular injections to dengue patients
10	Intravenous fluid rate and frequency of monitoring and haematocrit measurement adjusted according to the patient's condition	Fixed intravenous fluid rate and unchanged frequency of monitoring and haematocrit measurement during entire hospitalization for severe dengue
11	Close monitoring of blood glucose, i.e. tight glycaemic control	Not monitoring blood glucose, unaware of the hyperglycaemic effect on osmotic diuresis and hypovolaemia
12	Discontinuation or reducing fluid therapy once haemodynamic status stabilizes	Continuation and no review of intravenous fluid therapy once haemodynamic status stabilizes.
13	Urine output is carefully recorded and included in assessment of haemodynamic status.	Urine output is not recorded or ignored in the assessment of fluid balance.

5.2   *Textbox B: Differential diagnosis of dengue fever*

Conditions that mimic the febrile phase of dengue infection	
Flu-like syndromes	Influenza, measles, chikungunya, infectious mononucleosis, HIV-seroconversion illness
Illnesses with a rash	Rubella, measles, scarlet fever, meningococcal infection, chikungunya, drug reactions
Diarrhoeal diseases	Rotavirus, other enteric infections
Illnesses with neurological manifestations	Meningoencephalitis Febrile seizures
Conditions that mimic the critical phase of dengue infection	
Infectious	Acute gastroenteritis, malaria, leptospirosis, typhoid, typhus, viral hepatitis, Acute HIV-seroconversion illness, bacterial sepsis, septic shock
Malignancies	Acute leukaemia and other malignancies
Other clinical pictures	Acute abdomen Acute appendicitis Acute cholecystitis Perforated viscus Diabetic ketoacidosis Kawasaki syndrome Lactic acidosis Leukopenia, thrombocytopenia and bleeding Platelet disorders Renal failure Respiratory distress (Kussmaul's breathing) Systemic lupus erythematosus

HIV = human immunodeficiency virus

5.3   *Textbox C: Warning signs*

Clinical	Abdominal pain or tenderness
	Persistent vomiting
	Lethargy, restlessness
	Mucosal bleed
	Liver enlargement > 2cm or tender enlarged liver
	Clinical fluid accumulation
Laboratory	Increase in haematocrit level concurrent with rapid decrease in platelet count

5.4   *Textbox D: Haemodynamic assessment: continuum of haemodynamic 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	Brisk (< 2 sec)	Prolonged (> 2 sec)	Very prolonged, mottled skin
Extremities	Warm and pink extremities	Cool peripheries	Cold, clammy extremities
Peripheral pulse volume	Good volume	Weak and thready	Feeble or absent
Heart rate	Normal for age	Tachycardia	Severe tachycardia with bradycardia in late shock
BP	Normal for age Normal pulse pressure for age	Normal systolic pressure but rising diastolic pressure Narrowing pulse pressure (≤ 20 mmHg in children) Postural hypotension	Hypotension (see definition below) Unrecordable BP
Respiratory rate (RR)	Normal for age	Quiet tachypnoea	Metabolic acidosis/hyperpnoea/ Kussmaul's breathing
Urine output	Normal	Reducing trend	Oliguria/anuria

Note: Definition of hypotension = systolic BP of < 90 mmHg or mean arterial pressure < 70 mmHg in adults or a systolic BP decrease of > 40 mmHg or < 2 standard deviation (SD) below normal for age.

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

5.5 Textbox E: Admission criteria

Warning signs	Any of the warning signs (see Textbox C)
Signs and symptoms related to hypotension (possible plasma leakage)	Dehydrated patient, unable to tolerate oral fluids Dizziness or postural hypotension Profuse perspiration, fainting, prostration during defervescence Hypotension or cold extremities Difficulty in breathing/shortness of breath (deep sighing breaths)
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
Findings through further investigations	Rising haematocrit Pleural effusion, ascites or asymptomatic gall-bladder thickening
Co-existing conditions	Pregnancy Co-morbid conditions, such as diabetes mellitus, hypertension, peptic ulcer, haemolytic anemias and others Overweight or obese (rapid venous access difficult in emergency) Infancy or old age
Social circumstances	Living alone Living far from health facility Without reliable means of transport

5.6 Textbox F: Discharge criteria

All of the following conditions must be present:

Clinical

No fever for 48 hours

Improvement in clinical status (general well-being, appetite, haemodynamic status, urine output, no respiratory distress)

Laboratory

Increasing trend of platelet count

Stable haematocrit without intravenous fluids

5.7 Textbox G: Home-care card for dengue (for patient or adult caregiver)

Home-care card for dengue

The patient should take this card with them to the health facility for each visit

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What should be done?
- Adequate bed rest
- Adequate fluid intake (> 5 glasses for an average-sized adult, or accordingly in children)
- e.g. milk, fruit juice (caution with diabetes patient), oral rehydration solution (ORS) or barley/rice water/coconut water
  Note: Plain water alone may cause electrolyte imbalance
- Take paracetamol (not more than 3 grams per day for adults; 10 mg/kg/dose, not more than 3 to 4 times in 24 hours in children)
- Tepid sponging
- Look for mosquito breeding places in and around the home and eliminate them

What should be avoided?
- Do not take acetylsalicylic acid (aspirin), mefenemic acid (ponstan), ibuprofen or other NSAIDs or steroids. If you are already taking these medications please consult your doctor
- Antibiotics are not necessary

If any of following is observed, the patient should be immediately taken to the nearest hospital; *these are warning signs for danger:*
- Bleeding:
  - red spots or patches on the skin
  - bleeding from nose or gums
  - vomiting blood
  - black-coloured stools
  - heavy menstruation/vaginal bleeding
- Frequent vomiting or not able to drink
- Severe abdominal pain
- Drowsiness, mental confusion or seizures
- Pale, cold or clammy hands and feet
- Difficulty in breathing
- Postural dizziness
- No urine output for 4–6 hours

Laboratory results monitoring

	1st visit					
Date						
Haematocrit						
White cell count						
Platelet count						

5.8 Textbox H: Calculations for normal maintenance of intravenous fluid infusion

Normal maintenance fluid per hour can be calculated on the basis of the following formula* (equivalent to Holliday-Segar formula):

   4 ml/kg/hr for first 10 kg body weight

   + 2 ml/kg/hr for next 10 kg body weight

   + 1 ml/kg/hr for subsequent kg body weight

*For overweight/obese patients calculate normal maintenance fluid based on ideal body weight (IBW), using the following formula:

   Female: 45.5 kg + 0.91(height–152.4) cm

   Male: 50.0 kg + 0.91(height–152.4) cm

(20, 21)

5.9 Textbox I: Hourly maintenance fluid regime based on ideal body weight

Estimated ideal body weight (IBW) (kg)	Normal maintenance fluid based on Holliday-Segar formula	
	ml/hour	ml/kg/hour
5	20	4
10	40	4
15	50	3.3
20	60	3
25	65	2.6
30	70	2.3
35	75	2.1
40	80	2
50	90	1.8
60	100	1.7
70	110	1.6
80	120	1.5

For adults with IBW > 50 kg, 1.5–2 ml/kg can be used for quick calculation of hourly maintenance fluid regime.
For adults with IBW <50 kg, 2–3 ml/kg can be used for quick calculation of hourly maintenance fluid regime.

5.10 *Textbox J: Estimated ideal body weight for overweight or obese adults*

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

5.11 **_Textbox K: Example of a monitoring chart for dengue: Vital signs and hourly fluid monitoring of dengue patients_**

Name: _____ Date of onset of fever: _____

Date and approx time of onset of warning signs: _____ Weight:_____

* Laboratory results should be tabulated under the time of blood sampling, not time of results being available

Date																						
Time*																						
HCT (%)																						
Platelet																						
WBC																						
Temperature (°C)																						
BP																						
Pulse rate (PR)																						
Respiratory rate																						
Crystalloids ml/kg/h Cum Vol																						

Colloids ml/kg/h Cum vol																											
Blood product Type ml/kg/h Cum vol																											
Oral quantity Cum oral																											
Cum input																											
Hourly urine																											
Cum urine																											
Others																											

WBC = white blood cell; Cum vol = cumulative volume i.e. total volume since start of treatment; Cum oral = cumulative oral intake since start of treatment; Cum input = cumulative intravenous and oral fluid input; Cum urine = cumulative urine i.e. total urine volume since start of treatment

5.12   *Textbox L: Choice of intravenous fluids for resuscitation*

Based on the three randomized controlled trials comparing the different types of fluid resuscitation regime in dengue shock in children, there is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. However colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock

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

Crystalloids

0.9% saline ("normal" saline)

0.9% saline is hypertonic at an osmolality of 308 mOsm/L and contains a high sodium and chloride 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, but repeated large volumes of 0.9% saline may lead to hyperchloraemic acidosis. Hyperchloraemic acidosis 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

Ringer's lactate has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolality of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatraemia. However, it is a suitable solution after 0.9% saline has been given and the patient's serum chloride level has exceeded the normal range. Ringer's lactate should probably be avoided in liver failure and in patients taking metformin where lactate metabolism may be impaired.

Colloids

The types of colloids are: dextran-based, hydroxyethyl starch and gelatin-based solutions.

One of the biggest concerns regarding their use is their impact on coagulation. Theoretically, dextrans bind to von Willebrand factor/Factor VIII complex and impair coagulation the most. However, this was not observed to have clinical significance in fluid resuscitation in dengue shock. Of all the colloids, gelatine has the least effect on coagulation but the highest risk of allergic reactions. Allergic reactions such as fever, chills and rigors have also been observed with Dextran 70. Dextran 40 and starch colloidal solutions can potentially cause an osmotic renal injury in hypovolaemic patients. There is an upper limit to the volume per kg body weight per day.

After two to three boluses of crystalloid without haemodynamic stability and particularly if the haematocrit is still elevated, it is essential to consider the switch to colloid resuscitation which is more effective in lowering the haematocrit. When the haematocrit is lowered and the patient's haemodynamic state improves, it indicates the restoration of the circulating volume. However, if there is no improvement in the haemodynamic state, it is essential to consider if severe bleeding has occurred.

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