

Pathophysiology and management of dengue hemorrhagic fever

AMPAIWAN CHUANSUMRIT, MD & KANCHANA TANGNARARATCHAKIT, MD

Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence to:

Professor A. Chuansumrit, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand
E-mail: raajs@mahidol.ac.th

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SUMMARY

Dengue infection is caused by any of four dengue virus serotypes. The clinical manifestations range from asymptomatic infection to undifferentiated fever, dengue fever and dengue hemorrhagic fever (DHF). DHF is characterized by sustained high fever for 2–7 days; bleeding diathesis such as positive tourniquet test, petechiae, epistaxis and hematemesis; thrombocytopenia with platelet counts $\leq 100 \times 10^9/L$ and plasma leakage due to increased vascular permeability evidenced by hemoconcentration, pleural effusion and ascites. Bleeding diathesis is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy. The three stages of clinical presentations are classified as febrile, toxic and convalescent. The toxic stage, which lasts 24–48 hours, is the most critical period, with rapid plasma leakage leading to circulatory disturbance. The severity of DHF varies from mild (World Health Organization grades I and II), with minimal and transient change in vital signs, to severe (World Health Organization grades III and IV), with threatened shock (e.g. blood pressure 100/90 mmHg) or profound shock. There is no specific treatment for DHF. Intensive supportive care is the most important aspect of management. Early recognition of the disease and careful monitoring for circulatory disturbance are essential. Optimal fluid therapy to maintain the functions of the vital organs during the critical period and effective control of bleeding episodes will lead to favorable outcomes. Administration of recombinant activated factor VII is suggested whenever massive bleeding does not respond to blood component therapy.

INTRODUCTION

Dengue infection is one of the most common mosquito-borne viral diseases of public health significance. It has been identified as a clinical entity since 1780.¹ Clinical descriptions of the Australian outbreak in 1897 reported that 30 children died.² The clinical manifestations of dengue infection range from asymptomatic infection to undifferentiated fever, an influenza-like symptom known as dengue fever, and a severe, sometimes fatal disease characterized by hemorrhage and shock known

as dengue hemorrhagic fever (DHF). The first and second epidemics of DHF occurred in Manila in 1954 and 1956, followed by the third in Bangkok in 1958. Since then, DHF has spread throughout tropical Asian countries and has expanded globally.³

Dengue virus is a positive-stranded encapsulated RNA virus that belongs to the *flavivirus* genus of the *Flaviviridae* family. The genomic RNA is approximately 11 kb in length and is composed of three structural protein genes that encode the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an

enveloped (E) protein and seven non-structural (NS) proteins, NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5. The NS proteins are assumed to be involved in the replication of viral RNA. The proteins are synthesized as a large and single-polypeptide precursor of approximately 3400 amino acids. They are transmitted among humans by *Aedes* mosquitoes such as *Aedes aegypti* and *Aedes albopictus*. There are four distinct serotypes, namely dengue 1 to 4. Infection with any of the four serotypes causes similar clinical symptoms that may vary in severity, depending on a number of risk factors including virus virulence, viral load and host response. The genotypic differences of dengue virus appear to be associated with the difference in virulence. For instance, dengue serotype 2 of Southeast Asian genotype is associated with DHF while the original American genotype is associated with dengue fever.⁴⁻⁶ Moreover, E protein gene and the 5'- and 3'-untranslated regions of genomic RNA have determinants that may influence the efficiency of dengue virus replication in dendritic cells.^{5,6}

CLINICAL PRESENTATION

The three stages of clinical presentation are named febrile, toxic and convalescent.⁷ The patients initially develop an abrupt onset of high fever (39–40°C) with malaise, headache, nausea, vomiting, myalgia and, sometimes, abdominal pain. During the acute febrile stage, which lasts 2–7 days, hemorrhagic manifestation is invariably present but usually mild (Table 1). Petechial hemorrhage on the skin is commonly found. Also, a positive tourniquet test is frequently observed. Bleeding at the nose, gastrointestinal tract and gums is relatively less common compared with petechiae, but may be severe. Recently, menorrhagia has been more prevalent because of the increasing number of affected adolescents. However, hematuria is extremely rare. Hepatomegaly is commonly found, and the liver is usually soft and tender. Thrombocytopenia and rising hematocrit due to plasma leakage are usually detectable before the onset of the subsequent toxic stage. An abrupt fall to normal or subnormal levels of temperature, varying degrees of circulatory disturbance will develop, known as the toxic stage, lasts 24–48 hours. Ultimately, the majority of patients have rapid uneventful recovery without sequelae in the convalescent stage.

Table 1. Bleeding manifestations among 257 children with dengue hemorrhagic fever

Bleeding manifestations	Number of patients	%
Petechiae	100	42.7
Epistaxis	53	22.6
Gastrointestinal bleeding	36	15.4
Menorrhagia	25	10.7
Gum bleeding	14	6.0
Ecchymosis	4	1.7
Hematuria	2	0.9

DIAGNOSTIC CRITERIA

The clinical diagnosis of DHF⁷ is based on four major characteristic manifestations: (i) sustained high fever lasting 2–7 days; (ii) hemorrhagic tendency such as a positive tourniquet test, petechiae or epistaxis; (iii) thrombocytopenia (platelet count $\leq 100 \times 10^9/L$); and (iv) evidence of plasma leakage manifested by hemoconcentration (an increase in hematocrit $\geq 20\%$ above average for age, sex and population), pleural effusion and ascites. Close observation, serial hematocrit and daily platelet count monitoring are suggested in order to accomplish the clinical diagnostic criteria. Pleural effusion can be demonstrated by a chest X-ray in right lateral decubitus view at 12–24 hours after defervescence. These applications may be problematic in a busy pediatric practice in a dengue-endemic area. A study in Vietnam suggested to use fever and hemoconcentration together with either bleeding or thrombocytopenia as clinical criteria of DHF.⁸ However, some patients with bleeding or anemia will not have a rising hematocrit. Therefore, the minimal criteria should include fever and evidence of plasma leakage together with either bleeding or thrombocytopenia. Further evaluation in a large prospective series from other dengue-endemic regions is warranted.

The severity of DHF is categorized into four grades:⁷ grade I, without overt bleeding but positive for tourniquet test; grade II, with clinical bleeding diathesis such as petechiae, epistaxis and hematemesis; grade III, circulatory failure manifested by a rapid and weak pulse with narrowing pulse pressure (≤ 20 mmHg) or hypotension, with the presence of cold clammy skin and restlessness; and grade IV, profound shock in which pulse and blood pressure are not detectable. It is note-

worthy that patients who are in threatened shock or shock stage, also known as dengue shock syndrome, usually remain conscious.

The diagnosis of dengue infection is confirmed by testing positive for either virus isolation using culture or polymerase chain reaction from the clinical specimens such as serum in the early febrile stage, or serological studies. The positive serological studies define as a fourfold or more increase in the hemagglutination inhibition test between acute and convalescent sera or positive test for dengue-specific IgM/IgG performed by enzyme-linked immunosorbent assay (ELISA). The secondary dengue infection is defined when the hemagglutination inhibition titer was 1:2560 or more, or the ratio of IgG and IgM was > 1.8.

PATHOGENESIS

The pathogenesis of DHF is poorly understood. DHF caused by primary or secondary dengue infection is due to the occurrence of abnormal immune response involving production of cytokines or chemokines, activation of T-lymphocytes and disturbance of the hemostatic system. The elevated mediators include C3a, C5a, tumor necrosis factor- α , interleukin (IL)-2, IL-6, IL-10, interferon- α and histamine.⁹⁻¹⁴ Halstead described the antibody-dependent enhancement whereby, upon the second infection with a heterotypic dengue virus,¹⁵ the subneutralizing concentration of the cross-reacting antibody from the previous infection may opsonize the virus and enhance its uptake and replication in the macrophage or mononuclear cells. Secondary infection with a heterotypic dengue virus is associated with increased risk of developing DHF in individuals who have recovered from a primary dengue virus with a first serotype. The level of T-cell activation in a secondary dengue infection is also enhanced, occurring as a phenomenon known as original antigenic sin,^{16,17} and is undergoing programmed cell death. Many dengue-specific T-cells are of low affinity for the infected virus and show higher affinity for other, probably previously encountered serotypes. Profound T-cell activation and death during acute dengue infection may suppress or delay viral elimination, leading to the higher viral loads and increased immunopathology found in patients with DHF.¹⁶

Interstitial dendritic cells located in the epithelia are believed to constitute the first line of the innate host

against invading of dengue virus after the initial bite by an infected mosquito. Infected dendritic cells migrate to regional lymph node along with their maturation process. Early activation of NK cell and type I interferon-dependent immunity may be important in limiting viral replication at the early time of dengue infection.¹⁸ Dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) is a C-type lectin that is expressed on certain dendritic cells to facilitate their dissemination *in vivo*. The genetic variation in DC-SIGN may have impact on the outcome after dengue virus exposure. Recently, an A-to-G transition located at nucleotide -336 in the promoter region of DC-SIGN was found to be associated with an outcome of dengue infection.^{19,20} The A-to-G transition alters a sequence for an Sp1 binding site and diminishes promoter activity. In a case-control study in Thailand, it was found that -336 A/G polymorphism in DC-SIGN was associated with a reduced risk of severe dengue fever.¹⁹

PATHOPHYSIOLOGY

Evidence of plasma leakage

The plasma leakage is due to the increased vascular permeability²¹ induced by several mediators such as C3a, C5a during the acute febrile stage and prominent during the toxic stage. The evidence of plasma leakage includes hemoconcentration, hypoproteinemia/hypoalbuminemia, pleural effusion, ascites, threatened shock and profound shock. The rising hematocrit may not be evidenced because of either severe bleeding or early intravenous fluid replacement.

Bleeding tendency

The bleeding diathesis is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy.

Vasculopathy

A positive tourniquet test indicating the increased capillary fragility is found in the early febrile stage. It may be a direct effect of dengue virus as it appears in the first few days of illness during the viremic phase.¹⁵

Thrombocytopenia and platelet dysfunction

Patients with DHF usually have platelet counts less than $100 \times 10^9/L$ as shown in Figure 1. Thrombocytopenia is

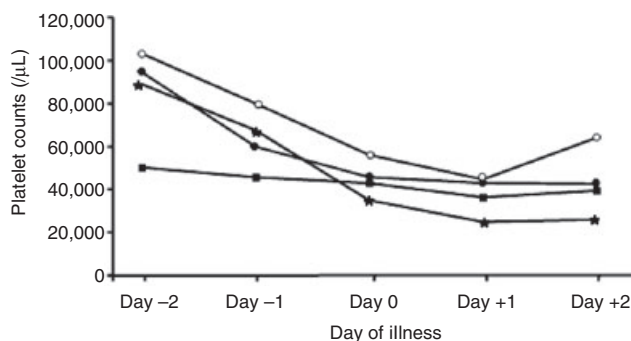


Figure 1. The platelet counts of children with dengue hemorrhagic fever grades I ($n = 78$) (○), II ($n = 112$) (●), III ($n = 40$) (☆) and IV ($n = 16$) (■). Day 0 is the day of defervescence, Day -1 and Day -2 are 1 day and 2 days before defervescence, and Day +1 and Day +2 are 1 day and 2 days after defervescence.

most prominent during the toxic stage. The mechanisms of thrombocytopenia include decreased platelet production and increased peripheral destruction. Na Nakorn *et al.* studied the bone marrow of patients with DHF during the acute febrile stage and found marked hypocellularity with a decrease in megakaryocytes, erythroblasts and myeloid precursors.²² The finding was later explained by the direct dengue virus infection of hematopoietic progenitor cells and stromal cells.²³ Additionally, the increased peripheral destruction is markedly prominent during 2 days before defervescence. The bone marrow then revealed hypercellularity with an increase in the megakaryocyte, erythroblast and myeloid precursors. Hemophagocytosis of young and mature erythroid and myeloid cells, lymphocytes and platelets was observed.²² Survival of patients' and transfused platelets was markedly decreased^{24,25} because of immune-mediated injury of platelets.²⁶ In 1987 Funahara *et al.*²⁷ demonstrated interaction *in vitro* between platelets and dengue virus-infected endothelial cells inducing platelet aggregation and subsequent lysis that resulted in thrombocytopenia. Subsequently, the number of platelets is rapidly increased in the convalescent stage and reaches the normal level within 7–10 days after the defervescence.

Platelet dysfunction as evidenced by the absence of adenosine diphosphate (ADP) release was initially demonstrated in patients with DHF during the convalescent stage by Mitrakul *et al.* in 1977.²⁴ The subsequent

study during the febrile and early convalescent stages by Srichaikul *et al.* in 1989²⁸ also demonstrated the impaired platelet aggregation response to ADP that returned to a normal response 2–3 weeks later. An increase in plasma β -thromboglobulin and platelet factor 4, indicating increased platelet secretory activity, was observed.²⁸ The platelet dysfunction might be the result of exhaustion from platelet activation triggered by immune complexes containing dengue antigen.²⁶

Coagulopathy

During the acute febrile stage, mild prolongation of the prothrombin time and partial thromboplastin time, as well as reduced fibrinogen levels, have been demonstrated in several studies.^{24,29} Variable reductions in the activities of several coagulation factors, including prothrombin, factors V, VII, VIII, IX and X, antithrombin and α_2 -antiplasmin, have been demonstrated. Fibrin degradation product or D-dimer is slightly elevated.¹¹ In 2002 Wills *et al.* reported the coagulation abnormalities in 167 Vietnamese children with dengue shock syndrome.³⁰ Low levels of anticoagulant proteins C and S and antithrombin III were found to be associated with increasing severity of shock, presumably due to plasma leakage. Elevated levels of tissue factor, thrombomodulin and plasminogen activator inhibitor-1 reflect endothelial, platelet and/or monocyte activation and may be a secondary response to direct activation of fibrinolysis by the dengue virus. The coagulation abnormality is well compensated for in the majority of patients without circulatory collapse.

Most of the patients have serum aspartate transaminase (AST) and alanine transaminase (ALT) levels three- and twofold higher than normal, respectively. There is focal necrosis of hepatic cells, swelling appearance of Councilman bodies and hyaline necrosis of Kupffer cells. Proliferation of mononuclear leucocytes and less frequently polymorphonuclear leucocytes occurs in the sinusoids and occasionally in the portal areas.

HIGH-RISK PATIENTS

Because of progress in comprehensive care techniques, the mortality rate among patients with DHF in Thailand has progressively declined from 13.7% in 1958 to 0.17% in 2001. However, the mortality rate has remained unchanged up to the year 2004. Nevertheless, high-risk patients are prone to serious complications resulting in

a higher mortality rate: up to 15% in patients receiving improper management³¹ and 100% in dengue shock syndrome with massive uncontrolled bleeding.³² The high-risk patients include the following:

- Prolonged shock: Patients with prolonged shock often have complications with metabolic acidosis and hypoxemia that may precipitate disseminated intravascular coagulation and further aggravate bleeding complications.
- Massive bleeding: Patients with massive bleeding or unrecognized concealed bleeding, especially in the gastrointestinal tract, may develop lethal shock, irreversible hepatic and renal failure leading to multi-organ failure and death.
- Obesity: Patients with obesity are at risk of under-treatment or over-treatment in terms of intravenous fluid replacement. Also, the venous access is difficult especially during the critical period of the toxic stage. Compared with malnourished patients or patients with normal weight for age, overweight patients are more susceptible to have a severe degree of DHF.³³
- Infants less than 1 year of age: Newborns may contract dengue infection through vertical transmission. The clinical presentations vary from mild to severe degrees.^{34,35} Additionally, Kalayanaroj and Nimmannitya reported 245 (5.3%) infants out of 4595 hospitalized patients with confirmed dengue infection between 1995 and 1999.³⁶ The age of peak incidence was 8 months with a range of 5–11 months. These infants acquired the maternal dengue antibody since birth and, by 5–11 months of age, these passively acquired antibodies decreased to a certain level and hence enhanced primary dengue infection leading to the clinical manifestation of DHF.³⁷ The infants sometimes presented with unusual manifestations such as convulsion, encephalopathy and associated infections. Proper management is often delayed because of the difficulty in early diagnosis of dengue infection. Moreover, complications such as hepatic dysfunction and fluid overload were more commonly found in infants compared with children and adults. As a result, the case–fatality rate was higher at 1.2%.³⁶

Unusual manifestation of neurological complications or hemolysis

The unusual manifestation of hepatic encephalopathy^{38,39} was possibly due to hypotension, cerebral

edema, microvascular or frank hemorrhage, hyponatremia and fulminant hepatic failure. Most patients had extremely elevated serum levels of AST and ALT, and exhibited alteration of consciousness, seizure or neurological deficit during the febrile stage. In addition, very rare cases of encephalitis, encephalomyelitis and transverse myelitis with positive dengue virus and/or IgM in the cerebrospinal fluid were reported.^{40–42} The overall case–fatality rate was 5%.⁴⁰

Patients with underlying diseases such as thalassemia disease, glucose 6-phosphate dehydrogenase (G6PD) deficiency and hemophilia may have unusual manifestations resulting in difficulty in early diagnosis. For instance, a patient with hemolytic anemia of thalassemia disease or G6PD deficiency may not exhibit hemoconcentration. On the contrary, they may be even more anemic because of acute hemolysis followed by hemoglobinuria that can lead to renal insufficiency. In addition, patients with a congenital bleeding disorder may aggravate more bleeding complications during the clinical presentation of DHF with bleeding diathesis.⁴³

MANAGEMENT

There is no specific treatment for DHF. Therapy for DHF is wholly symptomatic and aims at controlling the clinical manifestations of shock and hemorrhage. Patients who do not receive a proper treatment usually die within 12–24 hours after shock ensues. The most important aspect in managing patients with DHF is close observation by the attending physicians and nurses with frequent clinical and laboratory monitoring.

Adequate fluid replacement to overcome the plasma leakage

During the febrile stage, nurturing parental care for the patient is essential. For preventing starvation and dehydration, ingestion of adequate soft diet and drink is encouraged. For reducing fever, frequent tepid sponge bath and paracetamol are provided. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are contraindicated. The patient with suspected dengue infection should have daily follow-up at the outpatient clinic starting from the third day of fever to defervescence for 24 hours approaching the convalescent stage. The mortality and morbidity rates of patients

with DHF can be reduced by early hospitalization and optimal supportive care (Figure 2).

Fresh frozen plasma (FFP) is helpful in maintaining effective intravascular volume and restoring the coagulation factors. However, transfusion-transmitted disease is a constraint to be considered. Virus-inactivated FFP is not routinely available especially in economically less developed countries. Nevertheless, prompt and adequate fluid replacement to overcome massive plasma leakage is a medical emergency.

After proper management in the toxic stage for 24–48 hours, the fluid in the extravascular space spontaneously returns to the intravascular space. Patients uneventfully recover. Good prognostic signs are adequate urine output and regaining of appetite. A confluent petechial rash with characteristic scattered round areas of pale skin (without petechiae) is commonly found at the lower extremities during the convalescent stage.

Effectiveness of bleeding control

Evidence of bleeding includes any visualized bleeding such as epistaxis, hematemesis, menorrhagia, melena and hematochezia. Also, internal bleeding especially at the gastrointestinal tract may be concealed and difficult to recognize in the presence of hemoconcentration. After the clinical evaluation of adequate volume replacement, internal bleeding should be suspected in the following conditions: (i) patients with refractory shock, who have a hematocrit of less than 40%, or a rapid drop in hematocrit, e.g. from 50% to 40%; (ii) patients whose systolic and diastolic blood pressure are elevated or normalized, but the pulse is still rapid, i.e. > 130/minute in the child and > 150/minute in the infant; and (iii) patients with a drop in hematocrit of more than 10% with 10 hours of fluid replacement.

The risk factors for bleeding include the duration of shock, ingestion of aspirin or NSAID, administration of large amounts of plasma expander such as dextran 40 and Haemaccel, and the improper management in the febrile and toxic stages. The administration of excessive intravenous fluid to induce a rapid rise in blood pressure may aggravate bleeding by the sudden increased circulatory blood flow to the area of vascular damage such as gastric mucosa.

Adjuvant therapy should be described, for instance, tranexamic acid to prevent fibrinolysis especially in the mucous membrane of the oral cavity, intravenous

conjugated estrogen of 25 mg at 6-hour interval in 24 hours for menorrhagia and H₂ blocker for gastritis.

Platelet concentrate from either single or random donors is indicated for controlling massive bleeding. The dose of platelet concentrate is 0.2–0.4 unit/kg with a maximum of 8–10 units. Packed red blood cells are indicated for patients who exhibit massive bleeding. Fresh frozen plasma is indicated for patients who have massive bleeding due to coagulopathy, or circulatory failure, which does not respond to intravenous crystalloid replacement. However, no evidence supports the benefit of preventive transfusion of platelet concentrate and FFP in patients with DHF⁴⁴ as the risk of bleeding is not solely based on the number of platelet counts^{33,45} or coagulopathy.⁴⁶

Role of recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) has shown its effectiveness in the management of severe uncontrolled bleeding in both patients with and without pre-existing coagulopathy. rFVIIa enhances thrombin generation and also enhances the activity and function of both patients' and transfused platelets. The mechanism appears to be a direct activation of factor X on the surface of activated platelets. The increased thrombin generation results in a firm fibrin clot⁴⁷ stabilized by factor XIII and activates thrombin-activable fibrinolysis inhibitor, leading to a down-regulation of fibrinolysis.⁴⁸

Effective control of massive bleeding unresponsive to conventional blood component therapy was first reported in two Thai girls with grade IV DHF in 2000.⁴⁹ An initial dose of 60–90 µg/kg of rFVIIa was given, followed by continuous infusion of 16.5 µg/kg/hour. Subsequently, rFVIIa was used in controlling life-threatening bleeding in 15 Thai children with grades III and IV DHF between 2000 and 2002.⁵⁰ One to three doses of 100 µg/kg rFVIIa were given at intervals of 4 hours according to the bleeding symptoms. The treatment of rFVIIa was assessed as having an effective response in eight patients (53.3%) that signified the complete cessation of bleeding without recurrence within 48 hours. An ineffective response was found in seven patients (46.7%) including recurrent bleeding ($n = 2$), temporarily slowed down ($n = 3$), continued bleeding ($n = 1$) and occurrence at a new site ($n = 1$). The result revealed that the earlier initiation of rFVIIa (6 hours) in the mainly grade III DHF yielded a more

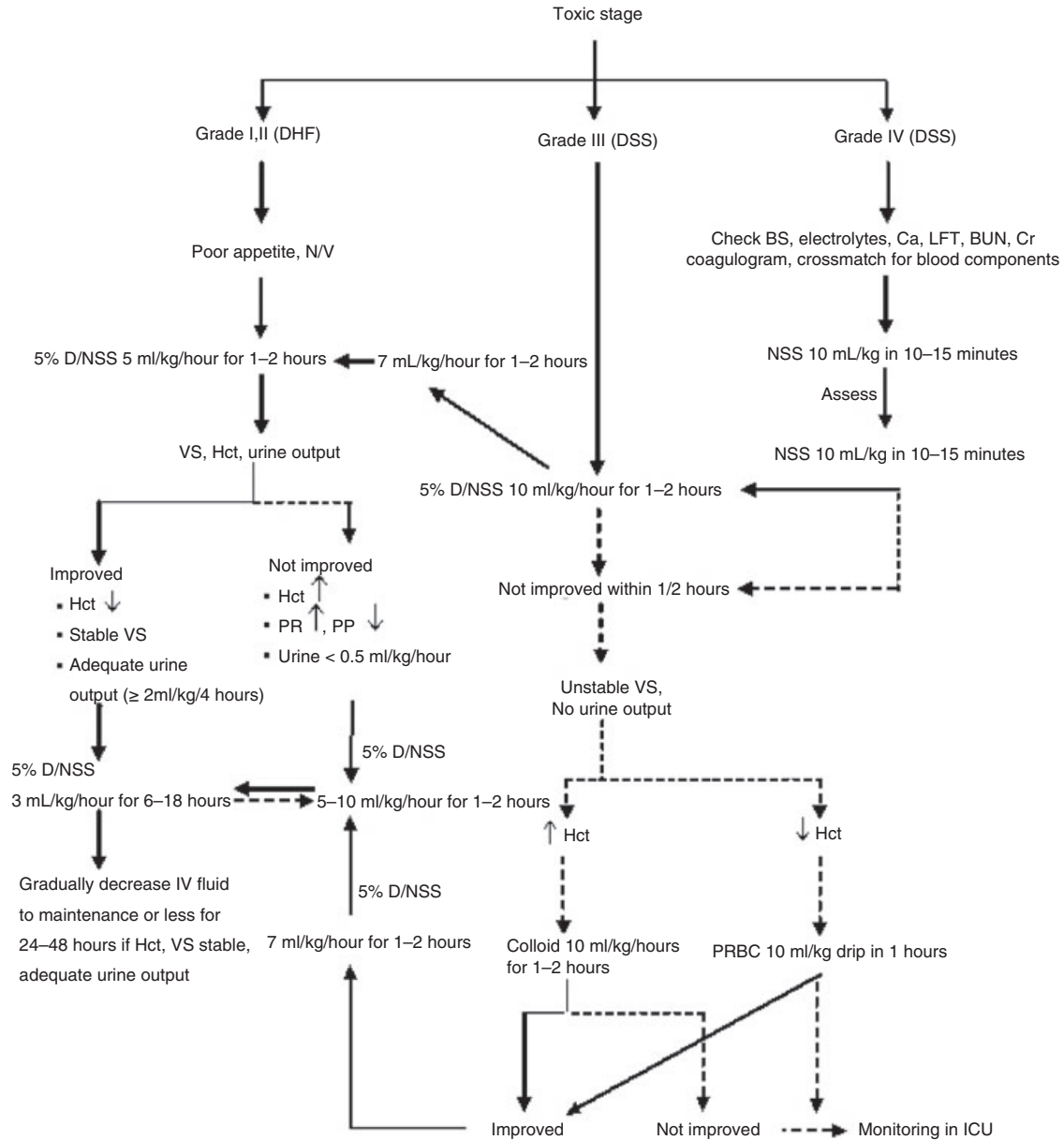


Figure 2. Algorithm for treating patients with dengue hemorrhagic fever during the toxic stage. Adapted from Ramathibodi Clinical Practice Guideline.^{54,55} — improved; -----, not improved; colloid, includes Dextran 40, Haemacel®, 5% albumin or fresh frozen plasma; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; VS, vital signs; BS, blood sugar; N/V, nausea and vomiting; LFT, liver function test; Cr, creatinine; BUN, blood urea nitrogen; PR, pulse rate; PRBC, packed red blood cells; CVP, central venous pressure; PP, pulse pressure; IV, intravenous; Hct, hematocrit.

effective response (66.7%) than the delayed initiation (29.8 hours) in the mainly grade IV DHF (33.3%). Moreover, patients previously administered ibuprofen or the volume expanders dextran 40 and Haemacel tended to

have a less effective response (28.6%) than patients without associated medications (75.0%). The case-fatality rate was 20% (3/15). No clinical evidence of thromboembolic complication was observed.

This rFVIIa therapy is suggested whenever the unresponsiveness of massive bleeding to blood component therapy is recognized. Massive blood loss signifies that blood loss is greater than 1.5 mL/kg/minute within 20 minutes⁵¹ or 150 mL/minute.⁵² Also, massive blood loss is signified by the replacement of 50% blood volume in less than 3 hours.⁵³ Unresponsiveness to conventional blood component therapy signifies that the bleeding does not slow down even though the patient has already received 10 mL/kg of FFP, 0.2 unit/kg of platelet concentrate (maximum 8–10 units) and 0.2 unit/kg of cryoprecipitate. The suggested dose of rFVIIa is 100 µg/kg at 15- to 30-minute intervals until the bleeding is significantly reduced, followed by 100 µg/kg at 2- to 4-hour intervals. One to two doses are usually used at 15- to 30-minute intervals and two to four doses are usually used at 2- to 4-hour intervals. After the bleeding is completely stopped, the final dose may be given to achieve hemostasis. From 2000 to 2004, a total of 43

patients with massive uncontrolled bleeding, mainly in dengue shock syndrome in Thailand, were treated with rFVIIa. The effective response was 62.8% (27/43) and the case–fatality rate was 25.6% (11/43).

CONCLUSIONS

The prominent features of DHF are shock and hemorrhage. Shock is caused by rapid plasma leakage resulting from increased vascular permeability. Bleeding is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy. There is no specific treatment for DHF; intensive supportive care is the most important aspect of management. Early recognition of the disease and circulatory disturbance is essential and appropriate intravenous fluid replacement can modify the severity of the disease. rFVIIa is very effective in controlling severe hemorrhage in this disease.

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