DENGUE INFECTION IN HEMATOLOGIC-ONCOLOGIC PEDIATRIC PATIENTS: AGGRAVATION OF ANEMIA AND BLEEDING RISK

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Abstract. We studied anemia and bleeding risk among hematologic-oncologic pediatric patients with dengue infection. A total of 907 patients suspected of having dengue infection were included in the study. They were categorized into 2 groups: 1) patients with confirmed dengue infection (*n*=843) and 2) patients with other febrile illnesses (*n*=64). Both groups included patients with underlying hematologic-oncologic diseases (55 *vs* 14) and without underlying disease (788 *vs* 50). Patients with underlying diseases were divided into 3 subgroups by risk: Subgroup A, anemia risk, including patients with thalassemia and hemoglobinopathies (*n*=39) and G6PD deficiency (*n*=6); Subgroup B, patients with bleeding risk, including hemophilia (*n*=7), von Willebrand disease (*n*=1) and thrombocytopenia (*n*=4); and Subgroup C, patients with anemia and bleeding risk, including oncologic diseases (*n*=12). Acute hemolysis in Subgroup A started during the febrile stage and required packed red cell transfusions. Bleeding risk in Subgroup B started during the early febrile stage with vasculopathy and continued to the late febrile stage with thrombocytopenia. These patients required factor concentrate and platelet concentrate transfusions. Anemia and bleeding risk in Subgroup C was greater among patients undergoing chemotherapy than those who had discontinued treatment. The greater the length of time since discontinuation of treatment, the lower risk. The case-fatality rate among dengue infected patients with underlying disease (2/55=3.64%) was significantly higher than those without underlying disease 0.63% (5/788).

Keywords: dengue infection, anemia, bleeding, hematologic-oncologic patients

INTRODUCTION

Dengue infection is one of the most common mosquito-borne viral diseases of public health significance (Rigau-Perez *et al*, 1998) caused by any of four serotypes (dengue 1- dengue 4). People in the endemic areas, especially children, are at higher risk of being infected. The clinical manifestations include asymptomatic, undifferentiated fever, dengue fever (DF), and severe disease character-

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ized by hemorrhage and shock, known as dengue hemorrhagic fever (DHF). The three stages of DHF (WHO, 1997) are: febrile, toxic and convalescent. The febrile stage lasts 2 to 7 days followed by an abrupt fall to normal or subnormal temperatures during the toxic stage lasting 24 to 48 hours and finally, a rapid clinical recovery during the convalescent stage. DHF is similar to DF, but has increased vascular permeability, inducing plasma leakage, and hemorrhage caused by vasculopathy, thrombocytopenia and coagulopathy. DHF is categorized into four grades (WHO, 1997). The milder grades (grades I and II) have minimal change in vital signs and are transient. The more severe grades (grades III and IV) are called dengue shock syndrome; they include circulatory failure manifested by a rapid, weak pulse, a narrow pulse pressure (<20 mmHg), hypotension with the presence of cold, clammy skin or profound shock, in which the pulse and blood pressure are undetectable.

This study presents the anemia and bleeding risk among hematologic-oncologic pediatric patients with dengue infection living in a tropical area.

MATERIALS AND METHODS

Subjects

A total of 907 patients (males 474, females 433) aged ≤18 years suspected of having dengue infection attending the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand from 2000 to 2010 were included in this study. The study was approved by the Faculty Ethics Committee and informed consent was obtained from parents. All patients were closely followed at the outpatient clinic beginning on the third day of fever until 24 hours after defervescence. Daily history taking, physical examination, tourniquet test and complete blood counts were routinely performed. Patients were hospitalized if they presented with any of the following warning signs or symptoms (WHO, 2009; Chuansumrit and Tangnararatchakit, 2010): severe abdominal pain, severe nausea and vomiting, thirst, irritability, restlessness, letheargy, behavioral change, cold clammy skin, clinical deterioration, poor appetite, oliguria, any bleeding except petechiae or ecchymosis, or abnormal laboratory findings of a hematocrit >42%, a hematocrit rise >10-15% from baseline or a platelet count <100,000/μl. Hospitalized patients were cared for following clinical practice guidelines for patients with dengue virus infection. Patients with severe DHF were admitted to the pediatric intensive care unit (Ramathibodi Clinical Practice Guideline, 2004).

Patients received supportive treatment, airway management, fluid and electrolyte therapy, and antibiotics when appropriate based on their clinical and laboratory findings. Patients with epistaxis received anterior nasal packing with gel foam. For patients with serious hemetamesis, a small nasogastric tube was gently inserted to assess for and drain blood from the stomach. Gastric lavage with cold water was not conducted. Patients also received ranitidine or omeprazole. Patients with hypermenorrhea received intravenous conjugated estrogen (Premarin) at a dose of 25 mg/kg every 6 hours for 24-48 hours.

Diagnostic criteria

The clinical manifestations of DF included mild or high grade abrupt onset fever, headache, retroorbital pain, muscles, bone or joint pain, nausea, vomiting and

rash. Bleeding was not common except for petechiae. Patients with DHF had similar signs and symptoms as DF patients but also had plasma leakage. Cases of DHF were characterized by four major clinical manifestations as defined by the World Health Organization (1997): 1) sustained high fever lasting 2 to 7 days; 2) a hemorrhagic tendency, such as a positive tourniquet test, petechiae or clinical bleeding; 3) thrombocytopenia (platelets ≤100,000/μl) and 4) evidence of plasma leakage caused by increased vascular permeability manifested as hemoconcentration (an increase in hematocrit of >20%) or pleural effusion. In this study, patients without evidence of hemoconcentration had a right lateral decubitus chest radiograph performed on the day after defervescence.

Dengue nonstructural protein 1 (NS1) antigen was tested for in the serum by enzyme immunoassay (Platelia Dengue NS1 AG kit, Biorad, Marnes-la-Coquett, France) beginning in 2007 or with a dengue NS1 antigen strip (Biorad, Marnes-la-Coquett, France) beginning in 2008.

Replacement therapy of blood components and factor concentrate

Replacement therapy with blood components when necessary was based on the clinical manifestations. These indications included: packed red cells (PRC) for volume replacement in patients with acute hemolysis and massive bleeding, fresh frozen plasma (FFP) for massive bleeding due to coagulopathy or other hereditary or acquired hemostatic defects, and volume replacement in cases with hemoconcentration, unstable blood pressure or rapid pulse unresponsive to crystalloid fluid replacement; cryoprecipitate was used to replace fibrinogen and platelet concentrate, either single or multiple donor, was used to maintain a platelet count ≥100,000/μl for patients with thrombocytopenia exhibiting bleeding manifestations except for petechiae and ecchymosis.

For patients with hemophilia or von Willebrand disease, factor VIII or IX concentrate was given to raise the level of the deficient factor VIII or IX clotting activity to 100% and the maintained at 40-60%. In cases of massive bleeding unresponsive to conventional blood component therapy of 10-20 ml/kg of FFP, 0.2-0.4 units of platelet concentrate (maximum 8-10 units) and 0.2 unit/kg of cryoprecipitate, recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) of 100 μg/kg was given in a single dose then repeated in 15-30 minutes for the second dose, and in 1-4 hours for subsequent doses. One to three doses were usually used.

Confirmation of dengue infection

Dengue virus infection was confirmed by virus isolation and/or presence of dengue specific IgM and IgG antibodies determined by capture enzyme-link immunosorbent assay (ELISA) in acute and convalescent sera. Primary dengue infection was defined by a ratio of IgM to IgG of ≥1.8, while the remainder were defined as having secondary dengue infection.

Statistical analysis

The chi-square and Fisher exact tests were used for discrete data, where appropriate. The Mann-Whitney *U* and Wilcoxon signed-rank tests was used for continuous data. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 907 pediatric patients suspected of having dengue infection from 2000 to 2010 were included in this study.

Their median age was 10.6 years with an interquartile range of 7.6 to 13.0 years. They were divided into two groups: group 1, 843 patients with confirmed dengue infection (DF 286, DHF 557); and group 2, 64 patients with other febrile illnesses (OFI) with negative results for dengue Ig M and Ig G antibodies. Patients in group 1 included 55 patients with underlying hematologic-oncologic disease (DF 22, DHF 33) and 788 patients without underlying hematologic-oncologic disease (DF 264, DHF 524). Patients in group 2 included 14 patients with underlying hematologic-oncologic diseases and 50 patients without underlying diseases. Patients with underlying hematologic-oncologic diseases were divided into 3 subgroups: Subgroup A with anemia risk, Subgroup B with bleeding risk and Subgroup C with anemia and bleeding risk (Table 1). Concerning patients with thalassemia and hemoglobinopathies, only two patients with beta-thalassemia major had undergone splenectomy. All patients with beta-thalassemia major and beta-thalassemia/Hb E disease received regular packed red cell transfusions every 4 weeks to keep the pre-transfusion hematocrit at 27-30%. Patients with iron overload received subcutaneous desferrioxamine at a dose of 20-40 mg/kg for 3-5 days per week. Patients with AE Bart's disease and hemoglobin H disease occasionally required packed red cell transfusions. Patients with hemophilia were comprised of 4 with severe hemophilia A, 2 with moderate hemophilia A and one with moderate hemophilia B. Patients with thrombocytopenia included one each for patients with chronic immune thrombocytopenic purpura (ITP), whose baseline platelet count was 99,000/µl, acute ITP whose platelet count was 91,000/µl, anticonvulsant induced thrombocytopenia, with a platelet count of 80,000/µl, and with acquired aplastic anemia with a partial-response whose platelet count was 40,000/µl. Oncologic patients at risk for having anemia and bleeding were patients with acute lymphoblastic leukemia (ALL) on maintenance chemotherapy (n=4); with ALL who had completed chemotherapy 4 years 4 months previously, and 2 months previously (n=2); with acute non-lymphoblastic leukemia (ANLL) 5 years 6 months and another 4 months post bone marrow transplantation (n=2); one each for patients with a pineal gland tumor, an eosinophilic granuloma, osteosarcoma and rhabdomyosarcoma who had completed chemotherapy 1 year 5 months, 2 years, 5 months and 2 months previously, respectively (n=4).

The median duration of fever in patients with dengue infection was 6 days (interquartile range 5-7 days) which did not differ from those with OFI.

The proportions of patients with underlying diseases who were diagnosed with DF 22 and DHF 33 were not significantly different from those without underlying disease (DF 264, DHF 524) with a p-value of 0.377. Among patients with DHF and underlying disease the proportions of those by grade (grade I, 11 cases; II, 13 cases; III, 6 cases; and IV, 3 cases) did not differ significantly from those without underlying disease (grade I, 174 cases; II, 235 cases; III, 84 cases; and IV, 31 cases) (p=0.847).

Nutritional status

The median Z scores for weight for age, height for age and weight for height among patients with underlying diseases were significantly lower than those without underlying disease (median -0.85, interquartile range -1.69 to 0.25 *vs* median 0.36, interquartile range -0.48 to 1.65; me-

Table 1
The diagnosis of patients with underlying hematologic-oncologic diseases in group 1 with dengue infection and group 2 with other febrile illnesses involving anemia (A), bleeding (B) and anemia and bleeding (C) risk.

	Number of patients	
	Group 1 (*n*=55)	Group 2 (*n*=14)
Subgroup A: Anemia		
Thalassemia and hemoglobinopathies		
β thalassemia major	5	0
β thalassemia / Hb E disease	12	2
AE Bart's disease	4	1[a]
Hb H disease with Hb Constant Spring or Pakse	3	3
Hb H disease	5	2
Homozygous Hb Constant Spring	2[b]	0
G6PD deficiency	5	1
Subgroup B: Bleeding		
Hemophilia A and B	6	1
von Willebrand disease type 2A	0	1
Thrombocytopenia		
ITP	2	0
Partially-response acquired aplastic anemia	0	1
Anticonvulsant induced thrombocytopenia	0	1
Subgroup C: Anemia and bleeding		
ALL on maintenance chemotherapy	3	1
ALL off chemotherapy	2	0
ANLL post bone marrow transplantation	2	0
Other[c]	4	0

[a]One patient had an additional Hb Constant Spring trait.
[b]One patient had an additional Hb E trait.
[c]One patient each had a pineal gland tumor, eosinophilic granuloma, osteosarcoma and rhabdomyosarcoma.

dian -0.37, interquartile range -1.28 to 0.88 *vs* median 0.48, interquartile range -0.34 to 1.26; median -0.67, interquartile range -1.23 to 0.22 *vs* median 0.05, interquartile range -0.77 to 1.42) with *p*-values of 0.0001, 0.0001 and 0.009, respectively.

Anemic manifestations

Anemia from acute hemolysis and hemoglobinuria was prominent among patients with thalassemia, hemoglobinopathies and G6PD deficiency (group 1A) beginning in the early febrile stage to the late febrile stage. Although some patients with DHF had increasing hematocrits due to plasma leakage, they still had low hematocrit levels. Patients with bleeding manifestation in groups 1B and 1C also exhibited acute blood loss, but the anemia was not as serious as in acute hemolysis in group 1A. Similar results were also found among patients with underlying disease (groups 2A, 2B and 2C) with OFI. Patients without underlying disease either

Table 2
Bleeding manifestations among patients with and without underlying hematologic-oncologic diseases.

Bleeding	Dengue fever n = 22/264	Dengue hemorrhagic fever n = 33/524	Other febrile illnesses n = 14/50
Petechiae	3/81	11/188	0/15
Ecchymosis	1/2	4/11	0/0
Gastrointestinal	0/3	7/71	1/1
Epistaxis	2/48	7/106	0/4
Hypermenorrhea	0/10	0/53	1/1
Hematuria	0/0	0/4	0/0
Gums	0/11	3/25	0/0
Retina	0/0	0/1	0/0

with dengue infection or OFI did not have anemia.

Bleeding manifestations

Bleeding manifestations were found more commonly among patients with underlying diseases and DHF, especially of the gastrointestinal tract (Table 2). Patients with underlying diseases had a lower risk of hypermenorrhea compared with those without underlying disease (p=0.05). The female to male ratio in patients with underlying diseases was 1:2 (23:46) while those without underlying disease was 1:1 (410:428). Bleeding manifestations were more common among patients with hemophilia, and thrombocytopenia (group 1B) starting during the early febrile stage with vasculopathy and in the late febrile stage, where additional thrombocytopenia existed. Bleeding was found among patients with oncologic disease (group 1C) based on the course of chemotherapy and the length of time since cessation of chemotherapy. In cases with ongoing chemotherapy , the occurrence of bleeding was higher than those finished with treatment. The longer the time period since discontinuation of treatment, the lower the risk for bleeding.

Hospitalizations

Patients with underlying diseases with dengue infection on average came to see the physician on the third day of fever (interquartile range 2-4 days), earlier than those without underlying disease (median 4 days, interquartile range 3-5 days) (p=0.042). Fifty-four of 55 patients with underlying disease (98.2%) required hospitalization; 755 of 788 without underlying disease (95.8%) required hospitalization. The median duration of hospitalization in patients with underlying diseases was 5 days (interquartile range 3-7 days), significantly longer than those without underlying disease (median 4 days, interquartile range 3-5 days) (p=0.0001).

Patients with or without underlying disease with OFI on average come to the physician on the third day of fever (interquartile range 3-5 days). The proportion of hospitalized patients with underlying diseases was 71.4% (10/14), which was not significantly different from those without underlying disease (42/50=84.0%). The median duration of hospitalization in patients with and without underlying diseases were similar at 4 days (interquartile range 3-6 days). The requirement for

Table 3
Laboratory findings in Group 1 with dengue infection and Group 2 with other febrile illnesses. Both groups consisted of patients without underlying disease and with underlying hematologic-oncologic diseases involving anemia (A), bleeding (B), and anemia and bleeding (C) risk.

	No underlying disease		Subgroup A: Anemia		Subgroup B: Bleeding		Subgroup C: Anemia and bleeding	
	Group 1 (n = 788)	Group 2 (n = 50)	Group 1A (n = 36)	Group 2A (n = 9)	Group 1B (n = 8)	Group 2B (n = 4)	Group 1C (n = 11)	Group 2C (n = 1)
Maximum Hct (%)								
Median	42.5	39.0	32.0	31.4	46.5	33.2	39.0	36.0[a]
Min-Max	15.0-60.0	29.0-48.0	23.7-48.0	18.7-38.6	34.0-55.0	21.5-37.9	33.3-48.0	-
Interquartile	39.6-45.6	35.7-42.0	27.5-35.8	24.1-35.3	41.5-49.8	24.3-36.8	35.0-45.0	-
Minimum Hct (%)								
Median	36.8	34.6	22.0	21.5	34.4	22.8[a]	30.9	32.0[a]
Min-Max	10.0-41.9	27.4-41.9	12.4-32.5	10.3-35.0	24.0-39.0	-	18.1-40.4	-
Interquartile	34.7-38-9	32.6-37.6	18.8-26.7	14.3-29.2	33.3-37.3	-	26.2-36.6	-
Minimum platelet count (/µl)								
Median	61,000	158,000	71,000	119,000	33,000	103,000	40,000	365,000[a]
Min-Max	7,000-297,000	6,000-449,000	19,000-401,000	29,000-354,000	10,000-180,000	71,000-418,000	8,000-146,000	-
Interquartile	36,000-90,000	83,750-206,000	49,250-103,500	62,500-170,000	14,500-76,000	77,500-340,750	18,000-44,000	-

[a] Only one sample was available.

Table 4

Required blood components and factor concentrate in Group 1 with dengue infection and Group 2 with other febrile illnesses. Both groups consisted of patients without underlying disease and with underlying hematologic-oncologic diseases involving anemia (A), bleeding (B), and anemia and bleeding (C) risk.

	No underlying disease		Subgroup A: Anemia		Subgroup B: Bleeding		Subgroup C: Anemia and bleeding	
	Group 1 (n = 788)	Group 2 (n = 50)	Group 1A (n = 36)	Group 2A (n = 9)	Group 1B (n = 8)	Group 2B (n = 4)	Group 1C (n = 11)	Group 2C (n = 1)
Packed red cells (cases)	19	0	24	5	2	1	2	0
Platelet concentrate (cases)	16	0	2	0	2	0	4	0
Fresh frozen plasma (cases)	12	0	1	0	3	0	1	0
Cryoprecipitate (cases)	7	0	0	0	3	1	1	0
Factor concentrate (cases)	19	0	1	0	5	0	1	0

hospitalization was significantly higher among patients with dengue infection compared to those with OFI (p=0.0001).

Laboratory investigations (Table 3)

For patients with dengue infection, the median maximal and minimal hematocrits in patients with underlying diseases were significantly lower than those without underlying disease (p=0.0001). The median maximal hematocrit (32.0%) and minimal hematocrit (22.0%) in group 1A were lower than those of group 1B (46.5% and 34.4%) and group 1C (39.0% and 30.9%) (p<0.0001) (Table 3). Patients with underlying diseases with OFIs (groups 2A, 2B and 2C) had significantly lower median maximal and minimal hematocrits than those without underlying disease (p=0.0001). For platelet counts, patients with dengue infection trended to have lower platelet counts than those with OFI but the difference was not significant.

Dengue virus isolation was carried out in 438 patients and revealed positive results in 100 patients (22.8%): serotype 1 (DF11, DHF34), serotype 2 (DF8, DHF22), serotype 3 (DF3, DHF13) and serotype 4 (DF1, DHF8). The remaining samples had negative results, including 19 patients with OFI. Patients with underlying diseases had a higher positive rate for dengue virus (14/37=37.8%) than those without underlying disease (86/401=21.4%) (p=0.023).

The dengue NS1 antigen test was performed in 277 patients and revealed positive results in 155 patients (56.0%). The remaining samples had negative results, including 25 patients with OFI. Patients with underlying diseases had a similar positive rate with the dengue NS1 antigen test (16/31=51.6%) compared to those without underlying disease (139/246=56.5%).

Required blood components and factor concentrate

Required blood component therapy was more common among patients with dengue infection than those with OFI and patients with underlying diseases required significantly greater amounts of blood components than those without underlying disease. The required packed red cell transfusions among patients in groups 1A (24/36=66.7%) and 2A (5/9=55.6%) were greater than other groups (p=0.0001) (Table 4). The required platelet concentrate transfusions in groups 1B (2/8=25.0%) and 1C (4/11=36.4%) were greater than the other groups (p=0.0001). Factor VIII concentrate, factor IX concentrate, prothrombin complex concentrate, fresh frozen plasma and cryoprecipitate were commonly utilized among patients with bleeding risk in groups 1B with hemophilia A and B. Recombinant activated factor VII was used as a rescue medication in cases of massive bleeding unresponsive to conventional blood component therapy in 22 patients with severe DHF (grade IV 13 cases, grade III 8 cases and grade II 1 case). Three patients had the underlying severe hemophilia A, ALL and beta-thalassemia/Hb E disease, while the remaining patients had no underlying disease. Fifteen patients survived and were discharged uneventfully while 7 patients, including two cases with underlying hemophilia and ALL, died.

Primary *vs* secondary response

Complete dengue specific antibody test results were available in 750 patients without underlying disease and 53 patients with underlying diseases while incomplete data was found in 40 patients. Concerning patients with underlying diseases, primary dengue infection was found in 13 patients (6 DF, 7 DHF). Patients with DF included one each with beta thalassemia major, AE Bart's disease, Hb H disease, ALL on maintenance chemotherapy, ANLL post stem cell transplantation for 4 months and rhabdomyosarcoma after completing chemotherapy for 2 months. Patients with DHF included 2 cases with beta thalassemia major with grade II DHF, 2 cases of beta thalassemia/Hb E disease with grade III DHF, one case of beta-thalassemia/Hb E disease with grade II DHF, one case each post ALL treatment (4 years 4 months) with grade I DHF, a pineal tumor post chemotherapy (1 year 5 months) with grade II DHF. The remaining patients had secondary dengue infection (8 DF, 32 DHF). The proportion of patients with underlying diseases having a secondary response (40/53=75.5%) was significantly lower than those without underlying disease (666/750=88.8%) (p=0.014). A significantly lower proportion of patients with secondary response was found in patients with thalassemia and hemoglobinopathies (73.3%), acute leukemia (50%) and other oncologic diseases (50%).

Case-fatality rate

The case-fatality rate in patients with dengue infection was 0.83% (7/843). No cases with OFI or DF died. All patients who died had grade IV DHF and came to see the physician or were referred to our hospital during the toxic stage of DHF. They all were in shock and had massive uncontrolled bleeding. Even though recombinant activated factor VII was administered, the bleeding only slowed temporarily then recurred. The case-fatality rate was higher among patients with underlying diseases (2/55=3.64%) than those without underlying disease (5/788=0.63%) (p=0.018). The case-fatality rate at our hospital was higher than that of the Thai Ministry of Public Health (<0.2%) since our hospital is a referral center.

DISCUSSION

The clinical signs and symptoms during fever cannot distinguish dengue infection from other febrile illnesses. Awareness, early recognition and close monitoring are essential for a favorable outcome with dengue infection, (Rigau-Perez *et al*, 1998). Although dengue virus isolation can be performed early in the illness, it is not available in most laboratories. The dengue NS1 ELISA (Chuansumrit *et al*, 2008) and strip tests (Chaiyaratana *et al*, 2009) are helpful for early diagnosis during the febrile stage. Dengue NS1 antigen can be positive during the first few days of fever. Therefore, it should be performed early in the febrile stage. A positive result can be found in both DF and DHF, but a negative result does not exclude dengue infection.

Anemia and bleeding were more prominent in patients with underlying hematologic-oncologic diseases. These manifestations occurred abruptly during the early febrile stage and were aggravated during the late febrile stage when thrombocytopenia presented. These clinical signs and symptoms differed from patients without underlying disease. Therefore, effective bleeding control by giving medication, platelet concentrate and factor concentrate is essential. In cases of uncontrolled massive bleeding unresponsive to conventional blood component therapy, recombinant activated factor VII is an effective rescue medication (Chuansumrit *et al*, 2005). Although the cost of recombinant activated factor VII is extremely high, appropriate use of one to three doses is cost-effective and lifesaving. Packed red cell transfusions to replace acute blood loss or acute hemolysis is also essential (Pongtanakul *et al*, 2005). Severe anemia can induce hemodynamic compromised and lead to hypoxemia, hypotension and shock. Prolonged shock can result in organ damage and disseminated intravascular coagulation. Efficient use of appropriate blood products is essential.

Grade IV DHF can be predicted by serum soluble thrombomodulin levels ≥10 ng/ml (Butthep *et al*, 2006) which can only be performed by ELISA technique in some laboratories. In clinical practice, the care of patients with acute febrile illness suspected of being dengue infection, close monitoring of signs, symptoms, hematocrit levels and platelet counts is necessary.

In cases with warning signs of severe dengue infection, immediate hospitalization for close monitoring and appropriate fluid replacement is important. Early and appropriate management may decrease avoidable complications.

Education of medical personnel is essential for early recognition of dengue infection, appropriate management and referral of patients with serious complications during the febrile stage. Educating parents and caregivers in the care of children with acute febrile illness is important, especially when to seek medical care. In this study, most of the patients with underlying diseases sought medical care earlier than those without underlying disease since they were aware of their own illnesses and the risk of spontaneous bleeding in patients with hemophilia, abrupt pallor from acute hemolysis in patients with thalassemia or hemoglobinopathies, or hemoglobinuria in patients with G6PD deficiency. The patients who died in this study presented to physicians or were referred for care during the toxic stage, which is the period with high risk for shock. Patients with dengue shock syndrome exhibiting uncontrolled massive bleeding are at high risk for death

(Srichaikul, 2003). Inappropriate treatment of shock leads to unfavorable outcomes (Srichaikul and Nimmannitya, 2000).

The severity of dengue infection depends on individual immune response (Kurane and Ennis, 1997), nutritional status (Thisayakorn and Nimmanitya, 1993), virulence of the microorganism and viral load (Vaughn *et al*, 2000). In this study, patients with underlying diseases had lower Z scores for weight for age, height for age and weight for height than patients without underlying diseases reflecting poorer nutritional status. Patients with underlying diseases were more likely to have a positive dengue virus in the serum than patients without underlying disease. Patients with underlying disease may have more viral replications resulting in manifestations of dengue infection. However, no viral load determinations were made in this study to confirm this hypothesis. The rate of secondary dengue infection was lower in patients with thalassemia, hemoglobinopathies and oncologic diseases reflecting a less competent immune response than patients without underlying disease.

Another challenge in caring for patients with underlying hematologic-oncologic diseases and DHF is the lack of an increasing hematocrit induced by plasma leakage, one of the diagnostic criteria for DHF. Apart from hemoconcentration, signs of plasma leakage can be alternatively demonstrated by the occurrence of a pleural effusion. Performing a chest x-ray in the right lateral decubitus position on the day after defervescence is useful in clinical practice. An accurate diagnosis is beneficial for patients individually and in research. Dengue infection has spread worldwide over the past five decades. There is an urgent need for effective management and eradication. Furthermore, comprehensive research is warranted.

In conclusion, pediatric patients with underlying hematologic-oncologic diseases living in tropical areas are prone to dengue virus infection with aggravated risk of anemia and bleeding. Awareness, early recognition and early diagnosis are important for a favorable outcome.

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