Clinical Course and Management of Dengue in Children Admitted to Hospital

A 5 Years Prospective Cohort Study in Jakarta, Indonesia

Mulya Rahma Karyanti, MD, MSc,† Cuno S.P.M. Uiterwaal, MD, PhD,† Sri Rezeki Hadinegoro, MD, PhD,* Maria A.C. Jansen, MD, PhD,† J.A.P. Hans Heesterbeek, PhD,‡ Arno W. Hoes, MD, PhD,† and Patricia Bruijning-Verhagen, MD, PhD,†*

Background: Dengue incidence is rising globally which was estimated 100 million per year, whereas in Indonesia was estimated 7.5 million per year. Dengue clinical course varies from mild dengue fever (DF) to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Patients, clinicians and care facilities would benefit if reliable predictors can determine at admission which cases with clinically suspected dengue will progress to DHF or DSS.

Methods: From 2009 through 2013, a cohort of 494 children admitted with clinically suspected dengue at a tertiary care hospital in Jakarta, Indonesia, was followed until discharge. We evaluated the clinical course and disease outcome of admitted patients and estimated the burden of dengue cases hospitalized over time.

Results: Of all 494 children, 185 (37%) were classified at admission as DF, 158 (32%) as DHF and 151 (31%) as DSS. Of DF patients, 52 (28%) progressed to DHF or DSS, 10 (5%) had other viral diseases. Of DHF patients, 9(6%) progressed to DSS. Of 33 routinely collected parameters at admission, duration of fever ≤4 days was the only significant predictor of disease progression ($P = 0.01$). Five cases (3%) admitted with DSS died. Between 2009 and 2013, annual dengue admissions declined, while distribution of disease severity remained stable.

Conclusions: Almost a third of children admitted to tertiary care with clinically suspected DF progress to DHF or DSS. Among routinely collected parameters at admission, only fever duration was significantly associated with clinical progression, emphasizing unpredictability of dengue disease course from parameters currently routinely collected.

Key Words: dengue infection, children, clinical progression

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Dengue continues to increase globally[1] and now reaches an estimated 100 million clinically apparent infections annually.[2] Dengue infection is a major international public health concern,[1] with infection transmission occurring in 128 countries and almost 4 billion people at risk, of which at least 70% live in Asia-Pacific region.[2,3] In Indonesia, annual incidence of dengue has increased from 0.05/100,00 in 1968 to 35–40/100,000 in 2013 with a peak at 85/100,000 in 2010.[4]

Dengue virus causes a spectrum of clinical disease ranging from self-limiting, mild symptoms classified as dengue fever (DF) to severe disease including dengue hemorrhagic fever (DHF) or life-threatening dengue shock syndrome (DSS).[5] Children are at the highest risk of developing severe clinical manifestations and represent about 90% of dengue related hospitalizations.[2] In some Southeast Asian countries, including Indonesia, a shift to older, adolescent age groups has been observed in recent years, which was accompanied by a changing pattern of clinical presentations of dengue.[4] This illustrates that dengue epidemiology is not stable over time and a high level of clinical suspicion is therefore warranted in all pediatric age groups. For this reason and due to seasonal incidence pattern, dengue poses a substantial burden on pediatric healthcare facilities during peak epidemic months.

A minority of symptomatic dengue cases are reported to progress to severe disease.[6] A detailed description of patients, covering full spectrum of pediatric dengue presenting to clinical care and including their outcomes, can support such awareness and help understand course of the disease. Importantly, it might unravel patient and clinical characteristics that, at early admission, predict dengue course severity, and thus support timely treatment and help reduce dengue care burden by optimizing the triage stage.

Most prognostic studies of dengue have been performed in adults and evaluated predictors for the outcome of severe dengue or mortality.[7–9] Studies on early predictors in pediatric patients admitted to hospital mostly focused on differentiating dengue infection from non-dengue or discriminating between non-severe dengue and severe dengue. Therefore, current prognostic evidence on children hospitalized with dengue is rather undetermined.

This study provides a comprehensive description of a large cohort of pediatric dengue patients admitted to a large tertiary hospital in Jakarta, to provide insights into disease course, treatment and outcome prediction. In addition, to characterize the burden of dengue on hospital facilities during epidemic peaks, we quantified contribution of dengue to all-cause and infectious diseases (IDs) pediatric admissions.

MATERIALS AND METHODS

Study Location

This study was conducted in Cipto Mangunkusumo hospital, a public tertiary hospital located centrally in Jakarta Province, that is a national referral center for a range of medical specialty services. It serves a population of 10 million in the urban region of Jakarta and is 1 of 14 national tertiary hospitals in Indonesia. The Child Health Department hosts 157 beds, including a 4-bedded pediatric intensive care unit (PICU) and a 20-bedded ID unit

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From the *Department of Child Health, Medical Faculty University of Indonesia, Jakarta, Indonesia; †Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; and ‡Theoretical epidemiology, Faculty of Veterinary Medicine, University of Utrecht, Utrecht, Netherlands.

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Address for correspondence: Mulya Rahma Karyanti, MD, MSc, Division of Infection and Tropical Pediatrics, Department of Child Health, Medical Faculty University of Indonesia, Dr. Cipto Mangunkusumo Hospital, Jl. Diponegoro No.71, Jakarta 10430. Email: karyanti@doctor.com.

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that accommodates children with clinically suspected dengue and other infections. Attending patients are a mix of self-referrals from nearby neighborhoods and referrals from regional primary or secondary healthcare centers. National protocols describe referral indications for dengue cases according to the level of healthcare required. The presence of at least one of the following characteristics is considered an indication for hospitalization at a tertiary care facility: age <1 year, obesity (Body Mass Index ≥95th percentile Center Disease Control and Prevention graph), co-morbidities like thalassemia or heart disease, organ involvement or a diagnosis of DSS.[1,5]

Study Population

According to local protocol, each patient is initially assessed in a triage unit. There, suspected dengue infection patients can be monitored for 24 hours, followed by either discharge or admission to ID unit depending on expected risk of progression to DHF. Patients with clinical DHF are immediately admitted to ID unit or, in case of DSS, to intensive care unit.

Admitted patients with (suspected) dengue are routinely monitored daily for physical signs and symptoms, as well as hematology (hemoglobin, hematocrit, leucocyte, platelet count) until normalization and defervescence. In case of encephalopathy or bleeding manifestations, additional diagnostics are performed to rule out other potential causes. For dengue serology, the presence of dengue IgM and IgG in acute-phase serum is assessed using a rapid immunochromatographic test (Panbio Dengue Duo Cassette). Dengue serology is routinely performed in blood samples on admission and, if indiscriminate, during convalescence. Patients with negative IgM on admission are retested after 24–48 hours. Disease course is scored daily throughout hospital stay based on 1997 WHO Dengue classification and severity grading (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D652).

Table, Supplemental Digital Content 1, http://links.lww.com/INF/D652. WHO Dengue classification 1997.

In brief, suspected DF is classified when there is acute febrile illness and 2 or more of the following: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations or leukopenia.[1] DHF is classified if (1) fever lasting 2–7 days; (2) hemorrhagic manifestations or positive Tourniquet test; (3) thrombocytopenia and (4) evidence of plasma leakage with laboratory findings of hemoconcentration or signs of pleural effusion, ascites or hypoproteinemia.[5] DHF has 4 severity grades according to presence or absence of spontaneous bleeding and severity of plasma leakage. DSS refers to DHF grades 3 and 4. Although more common in adults,[1] dengue in children may also present as atypical severe disease with organ failure, but without the typical transient increase in vascular permeability seen in DHF and DSS. Presence of severe organ involvement was therefore assessed, irrespective of DHF or DSS classification.[5]

Conclusive dengue infection diagnosis is based on serology testing for combinations of anti-dengue IgM antibody and anti-dengue IgG antibody. Positive IgM and negative IgG indicates primary dengue infection. Positive IgG and positive IgM indicates secondary infection. Positive IgG and negative IgM indicates indeterminate serology (prior infection).[5]

Standard dengue fluid management follows the WHO 1997 guidelines. This includes (1) for suspected DF: oral maintenance fluid or intravenous crystalloids if not able to receive fluids orally; (2) for clinically defined DHF: crystalloids with volume of maintenance plus 5%–7% to compensate intravascular fluid deficits, followed by titration to maintenance based on hemodynamic condition; (3) for patients with (imminent) shock or DSS: initial fluid resuscitation (20 mL of crystalloids/kg body weight), and additional fluid loads with colloids or crystalloids if indicated, followed by titration to maintenance within 48–72 hours based on hemodynamic condition. Blood products, including packed red cells and thrombocyte suspension, (with or without fresh frozen plasma or cryoprecipitate) are indicated for dengue related gastrointestinal bleeding, regardless of the thrombocyte level.

Data Collection

For our study, children between 1 month and 18 years of age with clinically suspected dengue infection, admitted from January 2009 to December 2013, were enrolled. History for duration of fever was obtained from parents' answer, but a few older children answered as well. Physical signs and symptoms, hemodynamic parameters, diagnostic testing results, medical interventions and dengue severity grading were recorded daily on a standardized case report form until discharge and entered into a database.

Statistical Analysis

We used descriptive statistics for patient demographics and disease grade upon admission. Next, given their disease grade at admission, patients were classified by disease progression status. Progression was defined as moving from DF to DHF/DSS, or as a change from a DHF non-shock (DHF grade 1 and 2) to DHF shock (DHF grade 3 and 4). Subsequently, among patients with DF (n = 185), possible prognostic markers (demography, medical history, clinical signs and symptoms at admission) for progression to DHF or DSS, were univariably evaluated using χ^2, Fisher exact, Student *t* test or Mann-Whitney *U* tests, where appropriate.

Treatment over disease course and hospital stay was assessed for each patient and summarized by final disease grade as assigned upon discharge. Serology results were compared between different final disease grades and tested using ANOVA.

Seasonal and time trends between 2009 and 2013 in dengue admissions in Cipto Mangukusumo hospital were analyzed by calculating number of cases of DF, DHF and DSS by month and year. To assess healthcare resource utilization and impact on facilities, we determined proportion of all-cause pediatric hospitalizations attributable to dengue and total number of bed-days per year, and separately for the peak dengue months in each year. We used dengue infected cases (DF, DHF and DSS) as numerators and number of all-cause pediatric hospitalizations (excluding neonatal admissions <1 month of age) per year and per month, as respective denominators. All data were analyzed using SPSS version 22.

Ethical approval for the study was obtained from the ethics committee of the Faculty of Medicine, University of Indonesia. Both parents signed Informed consent for collection of clinical data for study purposes.

RESULTS

Between January 2009 and December 2013, 494 patients met the clinical case definition for dengue. Mean age was 9.0 (4.4) years; most frequently admitted age-class was 10–14 years (35.8%). Median duration of fever was 4 days (IQR 1). Sixty three percent had signs of increased vascular permeability at admission (classified as DHF or DSS), 37% were classified as DF (Table 1).

Table 2 shows that 52 of 185 patients (28.1%) with initial DF developed DHF or DSS and that 9 of 158 patients with initial DHF (5.7%) progressed to DSS. Five cases diagnosed with DSS at admission died from refractory shock (3.3%). The mean age of these children was 5 years (IQR 4).

Table 3 shows signs and symptoms at admission by in-hospital progression status among 185 patients with DF at admission. Only duration of fever of <4 days was statistically significantly associated with progression from DF to DHF or DSS ($P = 0.01$).

TABLE 1. Characteristics of Patients Meeting the Clinical Dengue Case Definition at Admission

	Diagnosis at Admission			
	DF	DHF	DSS	Total
	185 (37%)	158 (32%)	151(31%)	494 (100%)
Age-group year (n, %)				
<1	7 (3.8)	10 (6.3)	4 (2.6)	21 (4.3)
1–4	28 (15.1)	13 (8.2)	29 (19.2)	70 (14.2)
5–9	58 (31.4)	47 (29.7)	58 (38.4)	163 (33.0)
10–14	67 (36.2)	59 (37.3)	51 (33.8)	177 (35.8)
≥15	25 (13.5)	29 (18.4)	9 (6.0)	63 (12.8)
Gender (n, %males)	91 (49.2)	85 (53.8)	79 (52.3)	255 (51.6)
Comorbidity present (n,%)*	9 (4.9)	2 (1.3)	3 (2.0)	14 (2.8)

* Comorbidities are thalassemia, anemia, tuberculosis, diabetes mellitus, leukemia, HIV and epilepsy.

TABLE 2. Dengue Diagnosis at Admission and Final Dengue Diagnosis (n)

Diagnosis at Admission Final Outcome	DF	DHF	DSS	Total
DF	123 (66.5%)	–	–`	123 (24.9%)
DHF	44 (23.8%)	149 (94.3%)	–	193 (39.1%)
DSS	8 (4.3%)	9 (5.7%)	146 (96.7%)	163 (33.0%)
Other viral disease	10 (5.4%)	0 (0.0%)	0 (0.0%)	10 (2.0%)
Dead (1 other virus and 4 DSS proven dengue serology)	–	–	5 (3.3%)	5 (1.0%)
Total	185 (100%)	158 (100%)	151 (100%)	494 (100%)

This was the critical phase when plasma leakage occurred which may lead to shock hypovolemic, after the febrile phase (3 days after the onset of fever). Hematemesis (n = 2), melena (n = 1) and encephalopathy (n = 1) at admission were only present in DF patients that subsequently progressed to DHF or DSS.

Table 4 describes treatment and hospitalization course by final disease grade, excluding the children who had another viral disease (n = 10). Of all admitted patients, 123 (25.4%) had a final diagnosis of clinical DF, 193 (39.9%) as DHF and 163 (33.7%) as DSS and 5 (1.0%) deaths (included 4 DSS proven dengue serology and 1 other virus). Overall median length of hospital stay was 4 days (IQR 2) and differed significantly by disease severity ($P < 0.001$). There was no severe organ involvement in children without DHF or DSS. Hematemesis, melena and encephalopathy were more diagnosed in children with DSS compared with children diagnosed with DF or DHF.

Four hundred eighty (97.2%) patients received intravenous fluid solution, whereas only 14 (2.8%) received oral fluid. There were some deviations from standard fluid management protocol: of DF patients, 13 (12%) received additional 5%–7% fluid replacement because of mild to moderate dehydration on admission, while 75 (43.4%) of DHF patients with grade 1–2 were only treated with maintenance without replacement. Among DSS patients, 138 (96.5%) received crystalloid for initial fluid resuscitation. Additional colloids were necessary in 61(40.4%) DSS patients because of insufficient hemodynamic response to crystalloid fluid resuscitation. Blood components were given to 13 children with final diagnosis in DSS for 12 times and in DHF 1 time, and additionally to 1 DSS case who died. The 4 clinical DSS cases who died were resuscitated with crystalloid and 3 cases were followed by colloid; however, 1 DSS case who died received maintenance fluid solution who was resuscitated before referred to our hospital. Only 1 DSS case who died with secondary dengue infection had recurrent shock and received PRC on day 1.

Table 5 shows serology results by final disease grade. Confirmation of primary dengue infection was obtained in 94 patients (19.8%), secondary infection was found in 224 patients (47.2%) and serology was indiscriminate in 121 patients (25.5%). In 36 patients (7.6%), dengue serology was negative for both IgG and IgM. Serology results differed by disease grade ($P < 0.03$). Negative serology was seen more frequently among DF patients (14% versus 5% and 6% among DHF and DSS, respectively), whereas secondary infection was associated with more severe dengue (36% among DF cases, 48% among DHF and 54% among DSS). Dengue serology of 5 dead cases confirmed 1 primary infection, 2 secondary infections and 1 indeterminate, and 1 negative.

Between 2009 and 2011, number of dengue patients declined and remained more or less stable thereafter. Distribution of disease severity did not change over time (Fig. 1). Proportion of all-cause hospital admissions (excluding neonatal) attributable to dengue declined from 4.3% in 2009 to 1.5% in 2012 and then increased in 2013 (2.0%). At ID unit, proportion of dengue admission declined from 36.4% in 2009 to 10.5% in 2012 (Table 6). Dengue admissions showed a clear seasonal pattern during the high epidemic year of 2009, while no clear pattern was observed in more recent years and the proportion of admissions for dengue at ID ward in any month varied between 0% and 36.4%, with lower percentages in last 3 years of the period considered (Fig. 1 and Table 6).

DISCUSSION

This study shows among 494 children with clinical dengue, 52 of 185 (28%) of patients admitted with DF progressed to DHF or DSS. Except for prior duration of fever, there were no

TABLE 3. Signs and Symptoms at Admission of 185 DF Cases With or Without Disease Progression

	DF, no progression; N = 123	DF to DHF/DSS; N = 52	*P*
Age-group (n, %)			0.78
<1 year	4 (3.3)	1 (1.9)	
1–4 years	20 (16.3)	6 (11.5)	
5–9years	39 (31.7)	16 (30.8)	
10–14 years	43 (35.0)	23 (44.2)	
>15 years	17 (13.8)	6 (11.5)	
Male (n, %)	62 (50.4)	24 (46.2)	0.61
Comorbidities (n)*	5 (4.1)	0 (100)	0.32
Days with fever prior to admission (n, %)			0.01
≤4	75 (61.0)	42 (80.8)	
>4	48 (39.0)	10 (19.2)	
Symptoms on admission†			
Anorexia	49 (45.4)	16 (37.2)	0.36
Nausea	64 (59.3)	25 (58.1)	0.90
Vomiting	52 (48.1)	21 (48.8)	0.94
Abdominal pain	46 (42.6)	22 (51.2)	0.34
Diarrhea	18 (16.7)	2 (4.7)	0.05
Headache	54 (50.0)	18 (41.9)	0.37
Myalgia	28 (25.9)	16 (37.2)	0.17
Arthralgia	16 (14.8)	5 (11.6)	0.61
Retro-orbital pain	11 (10.2)	3 (7.0)	0.76
Shiver	10 (9.3)	0 (0.0)	0.06
Malaise	27 (25.0)	9(20.9)	0.60
Sore throat	5 (4.6)	6 (14.0)	0.08
Cough	29 (26.9)	9 (20.9)	0.45
Signs on admission(n, %)**			
Positive tourniquet test	48 (39.0)	25 (48.1)	0.34
Distended abdomen	0 (0.0)	1 (2.3)	0.29
Hepatomegaly	15 (12.3)	10 (19.6)	0.21
Petechial	48 (39.0)	17 (32.7)	0.43
Epitaxis	21 (17.1)	6 (11.5)	0.35
Gum bleeding	1 (0.8)	0 (0.0)	1.00
Purpura	16 (14.8)	2 (4.7)	0.08
Hematemesis	0 (0.0)	2 (3.8)	0.09
Melena	0 (0.0)	1 (1.9)	0.30
Encephalopathy	0 (0.0)	1 (2.1)	0.08
Hematology findings			
Mean hematocrite day 3 (cutoff >40%)	6 (4.9)	1 (1.9)	0.81
Meanl eucocyte day 3 (cutoff <5000/μL)	23 (18.7)	12 (23.1)	0.22
Mean thrombocyte day 3 (cutoff <50,000/μL)	4 (3.3)	3 (5.8)	0.62

Final diagnosis as other viruses were not included in the analysis.

*Comorbidities are thalassemia, anemia, tuberculosis, diabetes mellitus, leukemia, HIV and epilepsy.

†Percentages are calculated based on available data.

other predictors at admission of disease progression among DF patients, although some rare disease manifestations (hematemesis, melena and encephalopathy) were only observed in patients that progressed. In addition, 9 of 158 (5%) of patients admitted with DHF progressed to DSS. This study has emphasized the unpredictability of dengue disease course from parameters currently routinely collected at admission.

Before further discussion of our findings, some limitations need to be addressed. In our study, the WHO 1997 clinical case definitions were used to classify dengue disease.[5] A newer classification was proposed by WHO in 2009, but this was not implemented in routine care for children in Indonesia during the course of this study. Additional training of health workers will be required before nation-wide implementation of the WHO 2009 dengue guidelines in Indonesia can be recommended. The main difference between the 1997 and 2009 WHO dengue guidelines is the classification of dengue severity. The WHO 1997 guideline classifies dengue infection into DF and 4 DHF categories (1–4), based on severity of plasma leakage and presence/absence of shock. The 2009 classification has 3 categories (1) DF without warning signs, (2) DF with warning signs and (3) severe dengue. The latter is defined as dengue with severe plasma leakage, severe bleeding or severe organ manifestation. Our study assessed bleeding and severe organ involvement separately, in addition to the 1997 disease grade. Importantly, none of our patients had bleeding or severe organ involvement without plasma leakage indicating that the 1997 classification captured all severe cases in our setting. Second, primary or secondary care health centers in Indonesia, usually have limited resources and laboratory facilities. They are managed by primary care physicians, and only few general pediatricians are locally available. The PICU facilities for DSS care are not available in all secondary healthcare centers. Our tertiary care hospital does have PICU facilities and the pediatric dengue population attending our hospital is a mix of referrals from primary and secondary care, and of self-referrals. Consequently, after triage the admitted dengue cases in our hospital are a reflection of that patient mix and generalizability of our findings to primary of secondary care setting may thus be limited. A strong feature of our study is that our cohort is relatively large and patient mix spans all severity levels of dengue, from mild to severe. Inclusion criteria and study monitoring were rigorously applied, and all patients were systematically and thoroughly assessed.

Given common peaks in dengue incidence and the strains on care facilities, it is important for physicians to have evidence-based tools that can discriminate between those at risk of progression to severe disease, and those that can be safely discharged early. However, from our study it is clear that at time of admission there currently are very few, if any, predictors of in-hospital outcome available. Duration of fever was the only statistically significant predictor, where progression was more likely to occur in those children with ≤4 days of fever prior to admission. However, positive predictive value of <4 days of prior fever was still too low for accurate and safe distinction in practice. Hematemesis, melena and encephalopathy, each very rare, were present only in children with DF that progressed to DHF or DSS, and obviously these are ominous signs in their own right. Therefore, we infer that at admission, using characteristics that currently are clinically available at that moment will not provide doctors in this setting with tools for accurate prediction of disease progression among children with DF.

Although there are comparable studies in adult patients,[7–9] there is limited insight for pediatric patients with dengue available from other studies, and they show substantial heterogeneity in settings [patient mix, referral and care systems, care practice (triage), dengue characteristics], and differ in research objectives. A study from Vietnam included 2301 hospitalized children with laboratory confirmed dengue.[10] Those with a history of vomiting, higher body temperature, a palpable liver and a lower platelet count had a higher risk of progressing to DSS after admission. It was concluded that a prediction model from such signs was of little clinical use because of very high false positive rates. Another study in 145 Brazilian children hospitalized with confirmed DF or DHF grade I or II, 23 patients progressed to use of advanced life support therapy or death.[11] At admission, lethargy, abdominal distension, pleural effusion and presence of hypoalbuminemia were found to predict such serious outcomes. A more recent Brazilian case-control study of hospitalized children with laboratory confirmed dengue, compared 69 patients with severe dengue (shock, severe bleeding, organ impairment and death) and 164 that did not develop severe dengue.[12] By design, this study could not estimate absolute risks but it did show that lethargy, dyspnea and abdominal

TABLE 4. Disease Course and Treatment by Final Diagnosis

	Final Diagnosis				
	DF (n = 123)	DHF (n = 193)	DSS (n = 163)	Death cases (n = 5)	*P*
Complications (n, %)					
Hematemesis	0 (0.0)	3 (1.6)	18 (11.1)	0 (0.0)	<0.001
Melena	0 (0.0)	3 (1.6)	15 (9.3)	1 (20.0)	<0.001
Encephalopathy	0 (0.0)	7 (3.6)	14 (8.6)	3 (60.0)	0.007
Length of stay (median days, range)	4 (1)	4 (2)	4 (2)	3 (1.5)	<0.001
Therapy					
Supportive fluid treatment (n, %)					<0.001
Oral only	6 (5.6)	3 (1.7)	2 (1.3)	1 (25.0)	
IV Maintenance only	87 (80.6)	75 (43.4)	57 (38.0)	0 (0.0)	
IV Maintenance + deficit 5%–7%	13 (12.0)	95 (54.9)	88 (58.7)	3 (75.0)	
Others	2 (1.9)	0 (0.0)	3 (2.0)	0 (0.0)	
Fluid resuscitation					
Crystalloid (yes) (n, %)	0 (0.0)	1 (0.5)	134 (96.4)	4 (100.0)	<0.001
Colloid (yes) (n, %)	0 (0.0)	1 (0.5)	59 (40.1)	2 (50.0)	<0.001
Blood products (%)					
Any PRC (n,%)	0 (0.0)	1 (0.5)	7 (4.3)	1 (20.0)	
Any TC (n,%)	0 (0.0)	1 (0.5)	2 (1.2)	0 (0.0)	
Any FFP (n,%)	0 (0.0)	0 (0.0)	10 (8.1)	0 (0.0)	
Any Cryo (n,%)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	

prc, pack red cells; ffp, fresh frozen plasma; tc, thrombocyte components; cryo, cryoprecipitate.

TABLE 5. Serology Results by Final Dengue Disease Stage

	Final Diagnosis at Discharge				
	DF (n = 118)	DHF (n = 190)	DSS (n = 162)	Death cases (n = 5)	*P*
Serology results (n, %)*					<0.03
IgM+/IgG–	26 (22.0)	37 (19.5)	30 (18.5)	1 (20.0)	
IgM+/IgG+	43 (36.4)	92 (48.4)	87 (53.7)	2 (40.0)	
IgM–/IgG+	32 (27.1)	52 (27.4)	36 (22.2)	1 (20.0)	
IgM–/IgG–	17 (14.4)	9 (4.7)	9 (5.6)	1 (20.0)	

* Percentages are calculated based on available data.

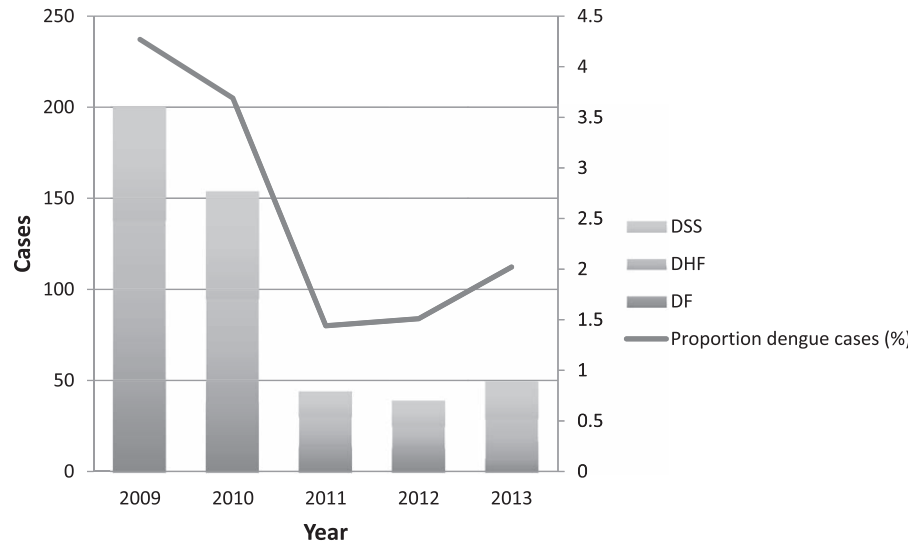

FIGURE 1. Number of dengue admission by disease grade and proportion of all-cause hospitalizations attributable to dengue (excluding neonatal admissions).

pain at admission were independent predictors of progression during hospital stay to severe dengue. Furthermore, several studies in Indonesia assessed patient and clinical characteristics of pediatric dengue cases by disease grade, but none assessed how patient and clinical characteristics upon admission correlated with disease progression thereafter.[13–15]

TABLE 6. Proportion of Dengue Cases During Peak Months Per Year

Year	Dengue peak months	Dengue* admissions/ all-cause pediatric hospital admissions (%)		Dengue* admissions/ all-cause admissions ID ward (%)	
2009	June	40/648	4.3	40/70	36.4
2010	March	20/570	3.7	20/48	29.4
2011	January	13/512	1.4	13/70	15.7
2012	April	8/462	1.5	8/68	10.5
2013	July	11/373	2.0	11/63	14.9

* Meeting clinical case definition for dengue on admission.

In summary, to our knowledge only 3 prior studies[10–12] evaluated characteristics at admission in predicting progression to more severe dengue during follow-up, the largest of which showed that the clinical downside of their prediction model was a high false positive rate. Based on the combined results from ours and other studies, we infer that for real gain in triage, treatment and hospital discharge efficiency, further detailed prognostic study of dynamic clinical predictors during hospitalization, rather than at admission, will be necessary.

Another important finding in our study is that all 61 dengue cases who progressed to higher severity during hospital-stay recovered with adequate fluid therapy, using mainly standard first-line treatment regimens with crystalloids. Fluid management for DHF and DSS cases who were referred to our hospital was adjusted according to clinical condition at admission. Additional colloids were required in less than half of DSS cases and blood products were administered only occasionally.

Because of the seasonality of dengue, infection rates typically show peaks that may well burden tertiary care treatment capacity. Over our study period, dengue admissions among all-cause pediatric hospital admissions varied between 1.5% and 4.3%, but severity of hospital admitted dengue was relatively stable. Of note, in some years, there appeared to be a complete absence of a seasonal pattern, with year-round low-grade transmission. In addition, we observed overall a decline over time in the number of admissions for dengue, which is in line with observations from regional[16] and national dengue surveillance.[4] What causes this change in seasonality is unknown, but it could be the result of a climatic trend towards shorter and less intense rainy seasons[17] as well as of improved vector control programs during rainy seasons, resulting in reduced vector populations,[18–20]or acquired immunity by the population to the circulating strains in those years.

CONCLUSION

Summarizing, almost a third of children admitted to tertiary care with clinically suspected DF progress to DHF. It proved not possible to accurately and usefully predict progression from DF to more severe dengue, based on routinely collected parameters at admission. Dynamic prognostic studies using time dependent clinical measurements are needed to better differentiate between dengue patients who can be sent home or referred to lower care, and dengue patients who are likely to progress to severe stages and need close in-hospital monitoring.

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