Outcome of Dengue in Hospitalized Jamaican Children

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ABSTRACT

Background: *Dengue fever is hyper-endemic in Jamaica with exponential rates of infection in successive outbreaks. The absence of local data and the potential for massive outbreaks in a country where a third of the population are children formed the basis for this study.*

Methods: *We evaluated the outcome of dengue in children hospitalized at the University Hospital of the West Indies (UHWI), Mona, Jamaica, during the island-wide dengue fever epidemic of 2012. This retrospective study reports all physician-diagnosed cases of dengue in hospitalized children aged less than 15 years.*

Results: *A total of 134 hospitalized children with physician-diagnosed dengue were included. One hundred and eighteen (88%) had a confirmatory dengue laboratory test. One hundred and twenty (90%) were uncomplicated and 14 (10%) had severe dengue. Severe disease was significantly associated with a longer duration between disease onset and hospital admission (*p = *0.0076). Main co-morbidities were sickle cell disease (14%) and asthma (13%) however, neither was associated with increased mortality. Duration of hospitalization was longer for patients with sickle cell disease. Children with short stature were significantly more likely to have severe dengue [Z-score height-for-age < 2.0; OR 6.46 (1.61, 25.88),* p = *0.016]. There were five deaths with a case fatality rate of 3.73%. Prior use of non-steroidal anti-inflammatory drugs was documented in four deaths.*

Conclusion: *Delayed presentation and short stature were significantly associated with severe dengue. Children with sickle cell disease had longer hospital stay. The case fatality rate was 3.73%. Use of safe and efficacious dengue vaccines should mitigate the effects of dengue-attributable childhood morbidity and mortality.*

Keywords: *Aedes aegypti* epidemic, Chikungunya, children, Dengue, Jamaica, non-steroidal anti-inflammatory agents (NSAIDS), Zika virus

Resultados Clínicos del Dengue en los Niños Jamaicanos Hospitalizados

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RESUMEN

Antecedentes: *La fiebre del dengue es hiperendémica en Jamaica, con índices exponenciales de infección en sus brotes sucesivos. La ausencia de datos locales y la posibilidad de brotes masivos en un país donde un tercio de la población son niños formaron la base para este estudio.*

Métodos: *Se evaluaron los resultados clínicos del dengue en niños hospitalizados en el Hospital Universitario de West Indies (HUWI), Mona, Jamaica, durante la epidemia de fiebre de dengue en todo el país en 2012. Este estudio retrospectivo reporta todos los casos de dengue diagnosticados por los médicos en niños hospitalizados menores de 15 años.*

Resultados: *Se incluyó un total de 134 niños hospitalizados con dengue diagnosticado por el médico. A ciento dieciocho (88%) se les realizó un examen de laboratorio para confirmar el dengue. Ciento veinte (90%) no presentaban complicaciones, y 14 (10%) tenían un dengue severo. La enfermedad severa se hallaba significativamente asociada con una duración más larga del tiempo entre el comienzo de la enfermedad y el ingreso al hospital (*p = *0.0076). Las principales comorbilidades fueron la enfermedad de células falciformes (14%) y el asma (13%). Sin embargo, ninguna estuvo asociada con un aumento de la*

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mortalidad. La duración de la hospitalización fue más prolongada para los pacientes con enfermedad de células falciformes. Los niños de baja estatura fueron significativamente más propensos a tener dengue severo [puntuación z de estatura para la edad < 2.0; OR 6.46 (1.61, 25.88), p = *0.016]. Hubo cinco muertes para una tasa de letalidad de 3.73%. El uso previo de fármacos antiinflamatorios no esteroideos fue documentado en cuatro muertes.*

Conclusión: *La demora en acudir al médico y la baja estatura se asociaron significativamente con el dengue severo. Los niños con enfermedad de células falciformes tuvieron una estadía hospitalaria más larga. La tasa de letalidad fue del3.73%. Uso de vacunas seguras y eficaces contra el dengue debe mitigar los efectos de la morbilidad y la mortalidad infantil atribuible al dengue.*

Palabras claves: *Aedes aegypti*, epidemia, Chikungunya, niños, agentes antiinflamatorios no esteroideos (AINES), dengue, Jamaica, virus del Zika

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INTRODUCTION

The World Health Organization (WHO) estimates that over 2.5 billion people, (40%) of the world's population live in areas of the world where 50 to 100 million dengue infections occur annually (1). Of the 22 000 annual deaths, children account for the significant majority (1).

The dengue virus is a small single-stranded RNA Flavivirus with four serological types. It is transmitted to humans through the bite of infected *Aedes aegypti* mosquitoes. The disease spectrum of clinical presentations varies from mild to severe, with an unpredictable clinical course and outcome (2). The revised WHO 2009 criteria classified the disease into dengue and severe dengue, the latter applies to those with severe plasma leakage, severe haemorrhage, or severe organ impairment (3). The revised classification further divided non-severe dengue into dengue with, or without warning signs [abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement > 2 cm, or increase in haematocrit concurrent with rapid decrease in platelet count] (3).

The dengue virus continues to spread exponentially in the Caribbean and the Americas. The Pan American Health Organization (PAHO) in May 2014 reported a five-fold increase in dengue cases between 2003 and 2013, "one of the worst years for dengue in the hemisphere's history, with 2.3 million reports, including 37 705 severe cases and 1289 deaths" (4). The dengue virus is endemic to Jamaica; dengue-like illness was first reported in 1824 (5−9). Periodical epidemics have occurred since the virus was first isolated in 1968, with an exponential rise in the reported number of cases (4−9). The Ministry of Health (MOH), Jamaica, reported 1521 notified cases in the 2007 outbreak (6). In 2012, there were 5903 suspected cases representing almost a four-fold increase (9). In Jamaica, massive dengue outbreaks have been linked to impoverished communities in vector vulnerable areas with poor vector control measures (10). In 2014, there was an epidemic of Chikungunya fever in the Caribbean and the Americas, in an area of the world which was previously naïve to this disease with over 1.7 million confirmed cases reported (11, 12). In 2016, there is a Zika virus epidemic in Latin America, also spread by the *Aedes aegypti* mosquito, following the WHO declaration of "an epidemic of international concern" (13, 14). This potential for exponential spread of the *Aedes aegypti* dengue vector in Jamaica is manifested in the recent Chikungunya fever outbreak of 2014, the current Zika virus and dengue fever outbreak of 2016 on the background of the dengue fever outbreak of 2012, now being reported (15, 16).

Purpose: There is a paucity of studies on dengue in the paediatric population and the outcome of children hospitalized with dengue from the English-speaking Caribbean, including Jamaica. This study aims to provide data to improve and guide management decisions to reduce the dengue-attributable morbidity and mortality among paediatric patients. We hypothesized that the morbidity and mortality of dengue infection is significantly higher in paediatric patients with co-morbid conditions than those without. We evaluated the outcome of dengue infection in paediatric patients hospitalized at the University Hospital of the West Indies (UHWI), Mona, Jamaica, during the island-wide dengue fever outbreak of 2012. Our objectives included identification of epidemiological factors (age, gender, body mass index (BMI), co-morbidities, previous dengue infection) associated with severe dengue disease among children with dengue hospitalized at the UHWI during 2012. We documented the outcome (alive *vs* death, case fatality rate) of hospitalized patients with dengue infection. We also determined and compared the clinical outcomes (uncomplicated *vs* severe) of dengue infection in children with and without co-morbid conditions.

SUBJECTS AND METHODS

This was a retrospective descriptive study of all physician-diagnosed cases of dengue in children aged less than 15 years who were admitted to the paediatric wards of the UHWI in 2012. Data regarding demographic, clinical characteristics, laboratory investigations and outcomes were extracted from the patient records, University hospital of the West Indies Haematology and Chemistry Laboratories and the Public Health case notifications to the Jamaican, Ministry of Health (MOH).

Amidst the outbreak, the MOH issued a Dengue Fever Clinical Management protocol that included updated case definitions, recommendation on laboratory testing and other investigations, admission criteria and a stepwise management approach. Prior to this release and in some instances thereafter; the diagnostic paradigm of DF/DHF/DSS was utilized at UHWI. Additionally the MOH issued a public advisory prohibiting the use on NSAIDs in suspected cases of dengue infection.

Laboratory confirmation testing was performed at the UHWI and two private laboratories, using commercially available enzyme-linked immunosorbent assay (ELISA) test kits. At UHWI, immunoglobulin M (IgM) and immunoglobin G (IgG) antibodies were detected using SD BIOLINE Dengue IgM/IgG Capture ELISA (Standard Diagnostics, Inc, St Ingbert, Germany). At both private laboratories, SD BIOLINE Dengue Duo (NS1 Ag + Ab Combo) Capture ELISA were used (Standard Diagnostics, Inc, St Ingbert, Germany). Results for all other laboratory investigations were obtained from the UHWI laboratory. Values were adjusted, where appropriate, for age. Haemoconcentration was assessed as a haematocrit greater than 20% rise above baseline value for age. Thrombocytopenia, was only collected in those with platelets counts lower than 100 x 10^9/L.

Each data extraction sheet was assigned a unique study code. Personal identifiers were not transcribed to the data extraction sheet. A separate document linking the study code to the patient's hospital registration number and name was kept in confidential records files and made accessible only to the primary investigator. Patients' medical records and data extraction sheets were safely secured.

A nthropometric measurements of the children were computed using Z-scores [WHO Anthro software] (17). Data were entered into a database and analysed using a statistical programme [Epi Info software version 7.1.5] (18). Chi-squared analysis, or Fisher's exact test where appropriate when used for categorical variables. Continuous variables were analysed by student *t*-test. Predictors of disease severity were determined by computation of odds ratio with a 95% confidence interval. Statistical significance was taken at the level $p < 0.05$. Medical records of all eligible participants were chosen on the basis of the specific problem under investigation. Ethical approval was obtained from the Ethics Committee of the Faculty of Medical Sciences of The University of the West Indies and UHWI prior to commencement of the study.

RESULTS

One hundred and thirty-four children were hospitalized with a physician-diagnosed dengue during June to December 2012, 118 (88.06%) had a confirmatory laboratory test by ELISA. Of these, 120 (89.55%) were uncomplicated dengue cases (both dengue with and without warning signs) and 14 (10.45%) were complicated, severe dengue.

Selected characteristics by disease severity among uncomplicated *vs* severe dengue is shown (Table 1). Age-range was two months to 15.3 years (mean age 5.60 years). Sixty-three (47.01%) were 0–4 years (Table 1). Disease severity was not statistically associated with mean age ($p = 0.34$) or age groups ($p = 0.661$). Of the five patients that died, four were less than five years old and age was not predictive for mortality [OR 4.75 (CI, 0.52, 43.63)]. Males comprised the majority. (Table 1). Gender was not associated with disease severity [OR 1.42 (CI 95th 0.45, 4.50), $p = 0.402$] nor death [OR 3.17 (CI, 0.34, 29.12), $p = 0.290$] (Table 1).

Clinical features of children admitted are shown (Table 2). Co-morbidities included sickle cell disease 19 (14%), asthma 18 (13%), renal impairment two (15%) and congenital heart disease, one (0.75%). None had multiple conditions. Only sickle cell disease and asthma were statistically relevant, however, neither predicted disease severity or death (Table 3).

Disease severity was associated with longer duration between onset of symptoms and hospital admission (Table 1). There was no association between this duration and asthma and sickle cell disease ($p = 0.187$ and $p = 0.360$, respectively). Thus underlying co-morbidity was not a confounder in delayed presentation. There was no association between delay in medical treatment and death ($p = 0.09$). Duration of hospitalization was longer in severe dengue compared to uncomplicated cases ($p = 0.03$). Mean duration of hospital stay was 4.28 ± 3.47 days (Table 1). Children with sickle cell disease had a significantly longer stay, (mean duration of 7.31 ± 6.74, $p = 0.0001$). Body mass index (BMI) was analysed for 101 (75%) patients, aged ≥ 2 years; whereas weight for length (WL) was used for those less than two years, 33 [24.62%] (Fig). There was no statistical difference in the anthropometric parameters between genders (Table 1). Short stature as defined by a height for age (HA) Z-score less than -2.0 was significantly associated with severe dengue (Table 3). There were no other co-morbidities in this subgroup, so this was not a confounder. There was no statistical difference in the elapsed time between onset of symptoms and admission in this group compared to the rest of the study population ($p = 0.156$). There was no association between over nutrition and tall stature with disease severity as shown (Table 3).

Most patients had primary dengue infection (Ig M only) 101 (75%) compared to 17 (13%) with secondary infection (Ig M and Ig G). Of major significance, none of the patients with severe dengue had secondary infection. Other laboratory results are shown (Table 4). Seventy-nine (59%) had thrombocytopaenia, of these six (8%) had a platelet value below 20 000 u/L. Leuopenia had similar frequency of 79 (59%). Six (4%) had a haematocrit value greater than 40% for age. Sixty-two (46%) patients had deranged prothrombin time or partial thromboplastin time (PT/PTT) for age, of which 54 (87%) had only the PTT component abnormal. Liver function test (LFT) was documented in 92 (69%). When adjusted by age only 10

Table 1: Characteristics of paediatric patients hospitalized with dengue fever in 2012 at UHWI

	Overall (n = 134)	Uncomplicated dengue (n = 120)	SD (n = 14)	*p*-value
Mean age				
male (n = 77)	5.56 ± 4.41	0.92		
female (n = 57)	5.65 ± 4.25			
Age group				
0−4 years	63 (47.01%)	58 (48.33%)	5 (35.71%)	
5−9 years	38 (28.36%)	33 (27.5%)	5 (35.71%)	0.661
10−15 years	33 (24.63%)	29 (24.17%)	4 (28.57%)	
Gender				
male	76 (56.72%)	67 (55.83%)	9 (64.29%)	
female	58 (43.28%)	53 (44.17%)	5 (35.71%)	
Duration between onset and admission				
mean	4.22 ± 2.13	4.05 ± 2.02	5.64 ± 2.56	0.0076
Duration of hospitalization				
mean	4.28 ± 3.47	4.03 ± 2.77	6.36 ± 8.20	0.0271
Z score weight for age (n = 134)				
Overall	0.13 ± 1.62	0.17 ± 1.64	-0.19 ± 1.47	0.440
Male	0.02 ± 1.62			0.223
Female	0.33 ± 1.63			
Z score height for age **(n = 134)**				
Overall	0.14 ± 1.92	0.22 ± 1.90	-0.54 ± 2.01	0.163
Male	0.10 ± 1.84			0.774
Female	0.20 ± 2.03			
Z score BMI **(n = 101)**				
Overall	-0.26 ± 1.87	-0.32 ± 1.94	0.20 ± 1.13	0.372
Male	-0.23 ± 2.05			0.868
Female	-0.29 ± 1.60			
Z score weight for length **(n = 33)**				
Overall	0.32 ± 1.71	0.33 ± 1.77	0.2 ± 0.38	0.922
Male	-0.09 ± 1.44			0.096
Female	0.96 ± 1.95			

Table 2: Clinical features in children hospitalized with dengue fever in 2012 at UHWI

Clinical features	**Frequency**	**Per cent**
Vomiting	62	46.27%
Rash	53	39.55%
Headache	52	38.81%
Abdominal pain	39	29.10%
Petechiae/ecchymoses	35	26.12%
Eye pain	23	17.16%
Arthralgia	20	14.93%
Diarrhea	15	11.19%
Hematemesis	12	8.96%
Epistaxis	11	8.21%
Myalgia	10	7.46%
Hepatomegaly	10	7.46%
Hematuria	7	5.22%
Hepatosplenomegaly	5	3.73%
Jaundice	3	2.24%
Splenomegaly	1	0.75%
Melena	1	0.75%
Tourniquet test	(n = 134)	
Positive	49	36.57%
Negative	35	26.12%
not documented	50	37.31%

Table 3: Statistical evaluation for co-morbidities and severe dengue or death in children hospitalized with dengue fever in 2012 at UHWI

	Severe Dengue OR (CI 95%)	**Death OR (CI 95%)**
Gender (male *vs* female)	1.42 (0.45 − 4.50)	3.17 (0.34 − 29.12)
Co-morbidity		
sickle cell	1.69 (0.42 − 6.72)	4.20 (0.65 − 26.98)
Asthma	1.91 (0.47 − 7.64)	n = 0
z score < -2.0	**Severe Dengue OR (CI 95%)**	**Fisher-Exact *p*-value**
height (n = 11)	6.46 (1.61 − 25.88)	0.016
weight (n = 5)	6.5 (0.99 − 42.82)	0.085
BMI (n = 20)	0.41 (0.02 − 2.57)	0.345
weight for length (n = 0)	Not calculated	
z score > 2.0		
height (n = 14)	0.54 (0.07 − 4.42)	0.482
weight (n = o)	Not calculated	
BMI (n = o)	Not calculated	
weight for length (n = 0)	Not calculated	

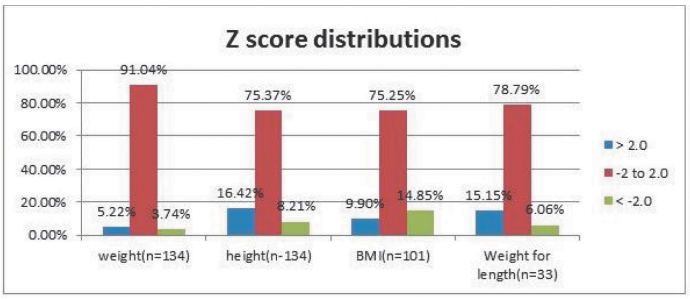

Figure: Distribution of z-scores for anthropometric parameters in paediatric patients hospitalized with Dengue during 2012 at UHWI.

Table 4: Laboratory findings in children hospitalized with Dengue in 2012 at UHWI

Laboratory findings	Frequency	Percentage
Deranged PT/PTT (n = 62)		
PT	2	3.23%
PTT	54	87.10%
Both	6	9.67%
Thrombocytopenia (< 100 x 10^9/L) (n = 79)	79	58.96%
50−100	43	54.43%
< 50	30	37.97%
< 20	6	7.60%
Leukopaenia (< 4 x10^9/L)	79	58.96%
Hyponatremia (Na<130 mEq/L)	18	13.43%
Hypoalbuminemia	10	7.46%
Haemoconcentration	6	4.48%
Elevated AST ≥ 1 000 per liter (U/L)	4	2.99%
Elevated BUN	2	1.49%
Hypernatraemia (Na>150 mEq/L)	1	0.75%

AST: aspartate aminotrans-ferase; BUN: blood urea nitrogen; PT/PTT: prothrombin time or partial thromboplastin time

(13%) and four (3%) of patients in the entire study population had hypoalbuminaemia and elevated aspartate aminotransferase (AST) greater than 1000 U/L, respectively.

Of the 134 patients in this study, 120 (90%) were uncomplicated dengue and 14 (10%) were severe dengue. The distribution of severity of illness by various age groups is shown (Table 1). Disease severity was not statistically associated with mean age ($p = 0.34$) or age groups ($p = 0.661$). Of the five patients that died, four of them were less than five years old. However age was not associated with death [OR 4.75 (CI, 0.52, 43.63)]. Males compromised the majority of patients overall, likewise for both strata of severity as shown (Table 1). Gender was not associated with disease severity [OR 1.42 (CI 95th 0.45, 4.50), $p = 0.402$]. Similarly, there was no association between gender and death the [OR 3.17 (C.I, 0.34, 29.12), $p = 0.290$].

Short stature as defined by a HA Z-score less than -2.0 was found to be significantly associated with severe dengue as shown (Table 4). In this group of patients there were no comorbidities thus this was not a confounding factor. Furthermore, there was no statistical difference in the elapsed time between onset of symptoms and admission in this group compared to the rest of the study population ($p = 0.156$). There was no association between over-nutrition and tall stature with disease severity as shown.

Only sickle disease 19, (14.18%) and asthma 18, (13.43%) had frequencies to facilitate statistical analysis as shown (Table 4). However, there was no statistical relevance between them and either disease severity or death (Table 4).

Five of 134 patients died giving a case fatality rate of 4%. All had laboratory confirmed dengue. Two were referred from peripheral hospitals.

The first death occurred in a four-year old male, without chronic conditions. He was transferred from a peripheral hospital, for intensive care. He had 12 days of fever, vomiting, diarrhoea and a generalized tonic-clonic convulsion. He was given a non-steroidal anti-inflammatory drug (NSAID). He was alert, confused and was receiving a dopamine infusion. Examination included; heart rate (HR) 146/min, respiratory rate (RR) 68/min, temperature 38.0 °C, blood pressure (BP) was unrecordable, liver span of 12 cm and coffee ground nasogastric (NG) return. Investigations revealed haemoglobin (Hb) 10.5 g/dL, platelets 17 x 10^9/L, white cell count (WBC) 17.7 x 10^9/L, nil haemoconcentration for age, blood urea nitrogen (BUN) 10.5 mmol/L, creatinine 137 umol/L, bicarbonate (HCO3) of 2 mmol/L, alanine aminotransferase (ALT) 1109 U/L and aspartate aminotransferase (AST) 3676 U/L. Intravenous fluid (IV) bolus at 10 mL/Kg and ephedrine infusion were commenced, thereafter BP was 70/42 mmHg and HR 88/min. Patient was transfused with fresh frozen plasma (FFP), while awaiting platelet transfusion. Two hours after arrival, patient had fresh blood-stained sputum and unrecordable BP. He expired despite resuscitative measures. No post mortem was requested.

The second case was a 15-year old male with HbSC disease, who had five days of fever, headache, abdominal pain and coffee ground vomitus. He was previously assessed to have an acute viral illness at a different institution and prescribed an NSAID. At presentation he was alert, with HR 109/min, RR 32/min, temperature 36.0 °C, BP 78/50 mmHg, liver span of 12 cm, and tender spleen of 6 cm span. Investigations revealed Hb 12.8 g/dL, platelets 17 x 10^9/L, WBC 17.7 x 10^9/L, deranged partial thromboplastin time (PTT) for age, nil haemoconcentration for age, BUN 10.2 mmol/L, creatinine 98 umol/L, HCO3 12 mmol/L, albumin 23 g/L and AST 6145 U/L.

Electrocardiogram (ECG) showed sinus rhythm. He was transfused with fresh frozen plasma (FFP), thereafter BP was 100/64 mmHg and HR 128/min. Fluid resuscitation was continued to correct his dehydration. Eight hours after admission he became drowsy, tachyponaeic and tachycardic. Arterial blood gas (ABG) revealed pH 7.109, pCO2 17.5, HCO3 5.3. Intravenous sodium bicarbonate infusion was administered, intensive care unit admission was requested, however, no space was available. Repeat Hb was 9.1 gm/dL with further derangement of his PTT. The patient arrested, there was difficult intubation requiring emergency tracheostomy during

resuscitation. Despite aggressive management he expired at 20 hours after admission. Autopsy revealed serous effusions; bilateral pleural effusion with pulmonary collapse and ascites.

The third case was an eight-month-old-male transferred from a peripheral hospital with a six day history of fever, lethargy and two days of petechial rash, vomiting and bloody diarrhoea. He was given a NSAID during course of illness. At presentation, he was ill looking, lethargic with moderate respiratory distress, HR 180/min, BP 36/16 mmHg, RR 32/min, temperature 37.5 °C, displaced cardiac apical impulse, liver span of 7 cm, with purpura to lower limb and coffee grounding NG return. Investigations revealed Hb 10.8 g/dL, platelets 12 x 10^9/L, WBC 10.7 x 10^9/L, deranged PTT adjusted for age, nil haemoconcentration for age, BUN 6.3 mmol/L, creatinine 98 umol/L, HCO3 16 mmol/L, albumin 23 g/L, ALT 122 U/L and AST 385 U/L. Intravenous fluid (IV) bolus was instituted and he referred for ICU admission. The patient's clinical situation deteriorated with worsening hypotension despite fluid resuscitation. The patient died, before ICU arrival, within 24 hours of admission despite aggressive resuscitative attempts. The fourth was a four-year old female with HbSS disease with a steady state Hb of 7.9 g/dL and splenectomy, with seven days of fever and anorexia, two days of abdominal pain, rash and pain in the legs. She was given an NSAID during course of illness. When evaluated, she was ill-looking with respiratory distress, afebrile, HR 150/min, BP 130/90 mmHg, RR 65/min, tender liver of 7.5 cm span and coffee grounding return. Investigations revealed Hb 6.7 g/dL, platelets 111 x 10^9/L,WBC 13.3 x 10^9/L, deranged PTT adjusted for age, nil hemoconcentration for age, BUN 2.7 mmol/L, creatinine 50 umol/L, HCO3 20 mmol/L, albumin 23 g/L and AST 6145 U/L. Aterial blood gas on oxygen revealed pH 7.51, pCO2 34.6, pO2 132.1, HCO3 29. Chest radiograph showed bilateral opacities. Patient's respiratory distress worsened with decline in Hb to 4.8, g/dL prompting ICU admission and mechanical ventilation. Fresh frozen plasma (FFP) and exchange blood transfusion were administered. Post-exchange transfusion, her clinical status deteriorated with increased haemorrhagic tendency; haematuria, haematemesis and BP 0f 34/24 despite intensive treatment. The patient expired at 22 hours after admission. Autopsy revealed congestive cardiac failure, bilateral pleural effusion, pulmonary oedema and focal haemorrhagic cystitis.

The fifth was a three-year old male with Down syndrome, congenital heart disease and chronic kidney disease, with a 10-day history of fever, vomiting and diarrhoea. The patient had no history of NSAID use during the course of illness. He was ill-looking at presentation. Examination findings included HR 126/min, RR 58/min, temperature 37.0 °C, BP was normal. Pertinent blood investigations revealed haemoglobin (Hb) 9.5 g/dL, platelets 70 x 10^9/L, white cell count (WBC) 6.7 x 10^9/L, nil haemoconcentration for age, blood urea nitrogen (BUN) 7.5 mmol/L, creatinine 104 umol/L, bicarbonate (HCO3) of 18 mmol/L, alanine transaminase (ALT) and aminotransferase (AST) were not seen. Supportive management was employed. On the second day of admission, the child developed haematemesis with deranged PTT and decline in Hb 7 g/dL. Fresh frozen plasma (FFP) was administered, while blood was being prepared for transfusion the patient developed shock unresponsive to resuscitative measures.

DISCUSSION

Jamaica's dengue outbreak in 2012 yielded 5903 suspected cases; 2426 (41%) occurred in children aged less than 14 years and 816 (14%) were laboratory-confirmed (9). DENV-1 was the serological dengue type responsible for the outbreak (9). There were 11 confirmed deaths, aged seven months to 57 years, with nine males. Our institution recorded 134 hospitalized cases in the paediatric department between June and December 2012. Eighty-eight per cent were laboratory-confirmed. Severe dengue was associated with delayed presentation and short stature. Co-morbidities were not linked to severe disease or mortality, although prior use of NSAIDs occurred in four of the five deaths. Case fatality approached 4%.

During the height of the dengue outbreak, resource constraints affected laboratory testing. Alternatively, testing was done at two private laboratories for those that could have afforded it. This resulted in12% of children who were hospitalized not having serological confirmation but were clinically physician-diagnosed as a consequence of fulfilling the case definition criteria. Nevertheless in the context of an epidemiological outbreak in a resource constrained setting, to have 88% of hospitalized patients with laboratory confirmation was commendable. Retrospective analysis of those without laboratory confirmation agreed with the fulfillment of the case definition criteria. The sensitivity of physician diagnosis of dengue, in light of the outbreak, is high and validated our decision to include all cases here, regardless of laboratory confirmation.

We found no association between dengue severity and age. Young age was also not statistically predictive of mortality. This was similar to a report of 240 children, aged four months to 13 years by Kabra *et al* (19). In contrast, Anders *et al* reported highest death rates in the youngest children (20). While Hammond *et al* who studied dengue severity in all age groups, found that severe dengue was found predominantly in infants four to nine months of age and in children five to nine years old (21).

Our study did not observe an association between gender and disease severity or death. In contrast, a meta-analysis of 198 studies on factors associated with dengue shock syndrome in suggested a significant association between female gender and DSS (22). Like gender, there have been conflicting reports on the association between nutritional status and severity of disease. Different studies analysed different anthropometric parameters. Our study included multiple parameters in order to delineate any possible associations. We found no relationship in weight for age, BMI for age, or weight for length and dengue severity, when applied to under and over

nutrition. This was similar to Marón's study on the nutritional status of children with dengue fever in El Salvador (23). They reported no difference in the weight for age, BMI for age, or height for age between those with dengue fever and dengue haemorrhagic fever. Likewise a study in Vietnamese infants found no association between nutritional status and dengue severity (24). In contrast, Pichainarong *et al* examined nutritional status in 105 children in Thailand and reported that obesity was significantly associated with the severity of DHF (25). However, they used growth chart parameters and not z-scores in assigning nutritional status. Other reports from that same country found that undernourished patients had a higher risk of developing severe dengue than normal or obese patients (26).

Significant in our study was the association between short stature and disease severity. However, short stature did not affect disease outcome. Short stature may be referenced to earlier malnutrition leading to growth stunting, long-term. Although, the height distribution amongst the general paediatric population compared to those dengue patients not hospitalized is unknown. This finding may therefore be linked to previous reports of dengue in impoverished Jamaican communities and poor vector control (8). However, this observation contrasts with others (23, 27). Differences in study design, type of growth charts used, ethnicity, possibility of different dengue strains and diagnostic paradigms can be the possible reasons for the contrasting findings amongst these studies including ours.

The only statistically relevant co-morbidities found in this study were sickle cell disease and asthma, however, neither was statistically predictive of severe disease or mortality. In contrast, dengue outcome is negatively affected by co-morbidities in adult population, where the non-communicable diseases, notably diabetes mellitus, hypertension, allergies, renal disease and myocarditis/pericarditis accentuated the effects of dengue and *vice versa* (28). There is a paucity of studies and none in Jamaica, identifying trends in dengue infection amongst paediatric sickle cell patients. The few reports obtained were ill-defined and focussed on adult patients (29−31). At the University Hospital of the West Indies, a significantly higher case fatality ratio for dengue, 12.5% among primarily adults with either haemoglobin SC disease, or homozygous SS disease was identified when compared to that of the general population 0.41% [$p < 0.0001$] (32). This trend of severe dengue disease in SCD patients is significant given the fact that in Jamaica, the sickle cell gene (HbS) is present in 10% and HbC in 3.5% of the population (33).

Five of 134 patients expired giving a case fatality rate (CFR) of 3.73%. If adjusted to include only laboratory confirmed cases then it would be 4.24%. This CFR is relatively high compared to other reports. The lowest CFR of 0.25% was for three different institutions, however, the study population of 132 480 was significantly greater than ours (18). Regionally, Kumar *et al* reported a CFR of 1.7% in Barbados and Mena *et al* in Dominican Republic had an overall CFR of 5.1% (34, 35). This relative high CFR could be attributed to higher dengue-attributable morbidity of the patients. Four of our five deaths occurred within 24 hours of admission, each critically ill at the point of admission to this institution. Two were transferred from outlying hospitals specifically for intensive care. This higher CFR at referral institutions where patients are critically ill at time of presentation has also been reported (36).

CONCLUSION

In this study of 134 children, aged less than 15 years, with physician-diagnosed dengue hospitalized at the University Hospital of the West Indies, during the Island-wide dengue fever outbreak of 2012, delayed presentation and short stature were significantly associated with severe dengue. Co-morbidities were not associated with severe disease or mortality, but sickle cell disease patients had significantly longer duration of hospital stay. Our case fatality rate of 4% was relatively high in comparison to other institutions.

The WHO recommended Phase III dengue vaccine trials implementation in endemic areas. Although recent randomized, placebo-controlled clinical trials in Latin America and Asia, revealed safety and efficacy of the tetravalent dengue vaccines in over thirty thousand children, there are currently no licensed dengue vaccines (37). Vaccines for these three mosquito-borne diseases must be seriously considered to mitigate the morbidity, mortality, loss of workforce hours and healthcare costs these epidemics inflict. Finally, eradication of the *Aedes aegypti* mosquito must be accomplished to halt the health effects of dengue, CHIKV and ZIKA V.

AUTHORS' NOTE

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