RESEARCH ARTICLE

REVISED Quantum of fluids in hospitalised patients with dengue fever and the presence of warning signs: a pilot cross-sectional study [version 2; peer review: 1 approved with reservations, 2 not approved]

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Abstract

Background: The World Health Organization in 2009 revised categories of dengue fever severity into classes A, B, and C based on the presence or absence of warning signs. The quantum of oral and intravenous fluids (IVF) in hospitalised patients with Group B (warning signs) has, to our knowledge, not been studied. Oral fluids in hospitalised patients and monitoring administration with the help of patients' relatives have not been assessed.

Methods: Consecutive patients with dengue fever and warning signs were studied for 48 hours after hospitalisation. Patients were asked to consume 4-5 l of fluids. Maintenance and bolus IVF were administered depending upon the presence of compensated or hypotensive shock. Intake and urinary output were monitored by the patient's attendant. Total fluids (oral and intravenous) were divided by a number of anthropometric measurements. The significance of warning signs, compensated and hypotensive shock, thrombocytopenia, bleeding episodes and the need for transfusions, and organ impairment were considered in relation to the total amount of fluids received daily.

Results: In total, 43 patients were studied. Patients with obesity and hypotensive shock received significantly more fluids on Day 1; taller patients and those with tachycardia, higher haematocrit and elevated creatine kinase correspondingly received more on Day 2. Hypotensive shock was significantly correlated with fluids/BSA, fluids/weight and fluids/BMI, while laboratory parameters correlated most strongly with fluids/BMI.

Conclusions: Most adults with dengue and warning signs seem to require >100 ml/kg/day of fluids during their stay. Advising a similar amount of fluids at home during epidemics may further reduce the need for admissions. Participation of patients and their relatives in the

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Any reports and responses or comments on the article can be found at the end of the article.

bedside management of fluid administration may go a long way in preventing morbidity and mortality. Adults probably need a better anthropometric measurement to decide on the quantum of fluids to be given.

Keywords

dengue, fluid requirements, warning signs, guidelines, Pondicherry outbreak

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REVISED Amendments from Version 1

The warning signs have been used in the 2009 WHO definition. The other factors apart from warning signs that necessitate admission in dengue Group B such as, pregnancy and diabetes have been removed. Hypotension has been defined as BP<90mmHg, and hence there are fewer patients with hypotensive shock. Tachycardia alone without other features of shock has been removed.

New compensated shock, developing on Day 2 has been included. Fluid intake with respect to the presence of one, two and three warning signs have been included in the tables. Lab data such as hepatitis and myositis have been removed, while the actual SGOT, SGPT and CK total levels have been retained. ECG heart rate and clinical fluid accumulation also have a correlation with fluid supplementation.

Patients, individually who mattered in compensated shock and hypotensive shock have been described.

See referee reports

Introduction

Dengue fever is an acute arboviral febrile illness transmitted by *Aedes* mosquitoes and has four serotypes: DENV1, DENV2, DENV3, and DENV4¹. It has been reported in over 70 countries and is endemic in the tropics, where ≥ 2.5 billion people are at risk²⁻⁴. India is a category A endemic country²; in such countries dengue strains the already over-stretched health care system, and increases the economic burden due to hospitalization, absence from school, loss of productivity, loss of tourism revenue, and out-of-pocket expenses^{2,4}. Even this burden is a gross underestimate due to underreporting of cases and deaths, poor networking of healthcare facilities, and interstate/inter-regional differences in the availability of optimal healthcare⁵. The number of reported dengue cases in Pondicherry, South India had fallen from >3500 in 2012 to <500 in the year 2016, with a reported total mortality of just six cases during those five years⁶.

Guidelines by the World Health Organization (WHO) have been used to manage patients with dengue for ~45 years⁷. Until 2009, dengue cases were classified as dengue fever, dengue haemorrhagic fever and dengue shock syndrome, and appropriate management protocols were prescribed by WHO and national guidelines⁸. The revised classification by severity categorised patients into dengue fever without warning signs (Class A), with warning signs (Class B), and those with severe dengue (Class C)⁸. The warning signs include abdominal pain or tenderness, hepatomegaly, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy and restlessness, and increase in haematocrit associated with fall in platelet counts. Patients in Group B must be admitted for the administration of fluids and observation during the critical phase, while patients in Group C should receive emergency care and/or urgent referral. Volume replacement guidelines by the WHO have been based on studies in children⁹. The quantum of fluids to be administered to patients in Group B has not been studied so far. Previously, only two studies had described the trends in fluid requirements

over the patients' entire hospital stay but using the earlier dengue severity classification^{10,11}. Two other studies, one each from Malaysia and Nicaragua, had described the effectiveness of drinking one litre of fluid before hospital admission^{12,13}.

Even though only patients in class B and C require admission, most patients with dengue fever are often admitted due to inability to differentiate it from other acute febrile illnesses or from non-severe dengue itself⁹. Guideline-based administration of intravenous fluids (IVF) are based on patients' weight and are generally a step-down regimen as the patient's clinical and laboratory parameters improve. This is often not practical in primary care due to the shortage of doctors and nurses to monitor as prescribed in the guidelines, spacing constraints, and availability of 24-hour laboratory services. Surveillance for severe dengue is generally poor in countries with epidemics. This often leads to overcrowding at hospitals and clinics with dengue fever/mild illness. In association with overworked medical personnel and confusion among the lay public, this overcrowding often predisposes to less-than-optimal care for patients with severe dengue and increased mortality⁴.

In view of such a scenario, we decided to study patients hospitalized with dengue warning signs, wherein, they could be monitored and administered fluids, even with a low doctor/nurse-to-patient ratio, by informing patients in advance what their daily fluid intake was expected to be and using the assistance of their relatives in measuring fluid intake and output. This study aimed to find out the quantity of fluids adult patients with dengue fever and warning signs received to maintain hemodynamic stability and to discern which anthropometric measurement-based fluid requirements correlated best with manifestations of severe dengue.

Methods

Study setting

The study was conducted in Pondicherry during the 2017 dengue epidemic. All consecutive adolescent and adult patients admitted to Unit 3 of the Department of General Medicine, Indira Gandhi Medical College & Research Institute, with a confirmed diagnosis of dengue fever between 11 October 2017 and 08 November 2017 were recruited for the study. Ethics approval was obtained from the Institute Ethics Committee to obtain and record data from all febrile patients (IEC/PP/2016/44). Written informed consent was obtained from all participants to use their clinical and laboratory data.

Patients with probable/confirmed dengue fever were admitted in the male medical ward (MMW), female medical ward (FMW), and a newly created dengue ward (DW). A total of 15 beds each had been added to the existing strength of FMW (60 beds) and MMW (70 beds) for ease of providing care. When these wards became full, newer patients were admitted into the DW (30 beds), which had a nurse available on all shifts, but without additional residents or house surgeons. The MMW and FMW were staffed by three nurses in the morning shift and two each in the afternoon and night shifts. The DW had two nurses in the morning and one each in the other two shifts. Each Unit was

allotted 26 beds (26/130). Two faculty members, three residents, and three house surgeons of Unit 3 oversaw treatment of these patients. All doctors worked from 8:30 AM to 4:30 PM on weekdays, and from 8:30 AM to 1:00 PM on weekends. House surgeons managed night ward duties on a daily rotation, while residents stayed nights once a week. The nurse-to-patient ratio was 1:26. The doctor-to-patient ratio during office hours and beyond 04:30 PM were 1:5 and 1:35 respectively. Patients could have one attendant/relative stay with them in the ward as part of hospital policy.

Patients

All patients 13 years or older examined in the outpatient or emergency department or with an acute febrile illness and a probable diagnosis of dengue fever were considered for the study. Such patients underwent a focussed clinical examination at the time of admission that included vitals, gums, skin, pallor, jugular venous pulse, oedema, hepatosplenomegaly, respiratory auscultation for crackles and diminished breath sounds. A complete blood count, liver function tests, renal function tests, creatine kinase, dengue IgM and NS1, urinalysis, chest radiograph, and electrocardiogram (ECG) were performed as part of routine care for febrile patients with suspected dengue. Patients were shifted to the wards after being stabilized in the emergency department. Those confirmed to have dengue fever by either dengue IgM or NS1 antigen positivity and had had warning signs at admission were considered eligible, and informed consent sought was obtained for inclusion in the study. Patients unwilling to participate, patients having dengue without warning signs, and those with an alternative diagnosis for the cause of acute febrile illness were excluded. Day 1 began at 8:00 AM on the following day after admission, and all patients were monitored for 48 hours until 8:00 AM of Day3.

All patients had been admitted into the hospital because of one or more of the following warning signs: persistent vomiting, abdominal pain, poor oral intake, dizziness, hypotension or shock, tachycardia during the afebrile phase of illness, severe thrombocytopenia, and mucosal bleed. Associated diabetes, pregnancy, alcoholism, obesity, and referral for admission from a peripheral health centre with poor transport facilities were considered as indicators for admission by the Emergency Department physician⁸.

Definitions

Patients were classified into those with Class B dengue and those with Class C, based on WHO guidelines⁸. Class C included those with serositis, compensated and hypotensive shock, severe impairment in one or more organs, and severe bleeding requiring blood products. Postural symptoms were defined by the presence of either dizziness, light-headedness, feeling faint, palpitations, or sweating while sitting or standing from the supine position. Postural hypotension (PH) was considered when the systolic BP fell ≥ 20 mm and/or the diastolic blood pressure (DBP) fell ≥ 10 mm when the patient stood upright for two minutes after getting up from the supine position. In those patients with postural symptoms, blood pressure was recorded in the sitting position with legs dangling down. Postural BP measurements were done at

least twice daily and the higher fall in BP was noted. The postural BP in the morning was taken under the supervision of the consultant taking rounds, while the evening and night shift recordings were taken by either the duty resident or house surgeon. Tachycardia was when the pulse rate was ≥ 100 beats/minute. The presence of either tachycardia with weak pulse and cool peripheries or postural hypotension defined compensated shock. One of the following was considered as hypotensive shock: pulse pressure was ≤ 20 mmHg, systolic blood pressure (SBP) was < 90 mmHg, feeble pulse with severe tachycardia or the patient was restless. Serositis was defined by the new onset development of ascites and/ or pleural effusion. Organ impairment was defined by either/or the presence of acute kidney injury (Acute Kidney Injury Network criteria)¹⁴, transaminases elevation ≥ 1000 IU, and new onset cardiac arrhythmias^{1,15}. Patients were overweight when the body mass index (BMI) was ≥ 25 kg/m². Bleeding was defined by the presence of new bleeding from any site- gums, nose (epistaxis), gastrointestinal (hematemesis, melena or haematochezia), respiratory (hemoptysis), uterine (menorrhagia/metrorrhagia) or skin (purpura or petechiae). Severe bleeding was considered when patients required RBC transfusions. Warning signs were defined by the presence of one or more of the following: abdominal pain, vomiting, hepatomegaly, mucosal bleeding, lethargy and restlessness or rapid fall in platelet count with increasing haematocrit. Severe thrombocytopenia was defined by a platelet count of $< 50 \times 10^9/L$.

Observations and treatment

Anthropometry (height, weight, BMI and body surface area) were measured on Day 1. BMI and body surface area (BSA) was calculated using the [QxMD Calculate](#) mobile app (version 7.0.6.0), using the De Bois formula. Pulse rate, SBP, DBP, pulse pressure, systolic postural fall (SBP fall) and diastolic postural fall (DBP fall) were measured at least twice daily during both days. More frequent measurements were done in those with postural symptoms and when receiving bolus IVF. Similarly, examination for abdominal tenderness, hepatomegaly, ascites, pleural effusion, altered consciousness was performed twice daily. Urea/creatinine, LFT and CK-total were done once at admission and again 48 hours later to monitor trends. CBC was performed twice daily during the 48 hours for all patients, and every 6th hourly in those with bleeding or 20% increase in haematocrit.

All patients were asked to drink 4–5 l of oral fluids cumulatively (a combination of water with or without oral rehydration salt, water with 5 tsp glucose, fresh juice, tender coconut water, buttermilk, milk, and dilute millet or rice porridge). The patients and their relatives were instructed to keep five 1-l bottles at the bedside to be filled up with water or oral rehydration salts each morning for easy monitoring. Other beverages were accounted as follows using two disposable paper cups of 200 ml and 100 ml each: a glass of juice, water with 5 tsp glucose, tender coconut water or porridge as 200 ml; 1 glass of buttermilk or milk as 100 ml. The total quantity of oral fluids was rounded-off to the nearest 100 ml. IVF was initiated for those in with postural symptoms, hypotension, shock, abdominal pain, persistent vomiting, or those with poor oral intake. Either normal saline or ringer lactate was administered as maintenance fluids, at the

rate of 100 ml/hour, calculated using the following formula: $\{1500 \text{ ml} + [\text{weight (kg)} \times 20 \text{ ml/kg/day}]\} = 2500 \text{ ml}$, for a 50-kg person). Boluses of normal saline (500 ml) were given for those patients in shock and in those with significant postural fall in blood pressure. Dextrose saline (5% DNS) was administered for patients with poor calorie intake and in those with hepatic dysfunction. The empty fluid bottles were retained at the patient's bedside cupboard to keep count of IVF to the nearest 500 ml. The attendants of patients who could document both oral and IVF intake on paper were exempted from keeping bottle counts. Fluid intake was measured at the end of Day 1 and Day 2. Urine output was measured every 6th hourly. The total fluid counts (oral +intravenous) for each day was divided by each patient's weight, height, BMI and BSA. A measuring jar cut out from an IVF bottle, was used for measuring urine output (Figure 1). Attendants were instructed to inform and/or note down the colour and quantity of urine and urgently bring to notice if there was no urine output for six continuous hours. Outcome measures were the total oral fluids and total intravenous fluid administered, low urine output (<500 ml/day), bleeding episodes and need for transfusion, compensated and hypotensive shock, and organ dysfunction such as hepatitis and myositis.

Statistical analysis

Data were entered in an Excel spread sheet and thence imported into IBM SPSS for Windows v22 for statistical analysis. Frequencies of clinical symptoms, examination findings, and severe organ involvement were calculated. Chi-square analysis (Fischer's exact test for frequencies <5) was used to compare the presence of symptoms, signs, and investigations among those who had received more than 5 l fluid/day with those who had not. Means $\pm$ standard deviations were calculated for continuous variables (clinical, lab, and treatment) and compared between the two groups receiving and not receiving 5 l fluids on both days using t-test. Bivariate correlations were performed between fluid administration (based on weight, height, BMI, and BSA on both days) and clinical/lab values. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient condition and fluid consumption

Of the 43 patients, 30 were female. Most patients were admitted on the fourth (n=9), fifth (n=8), and seventh (n=7) days of fever. The diabetic had dizziness at admission, while the pregnant lady had had rising haematocrit with fall in platelet counts from the referring health center. Males had a significantly higher postural fall compared to females and had higher haematocrit and CK values. At admission, all patients had had warning signs, while 39 continued to have warning signs on Day 1, and on further evaluation and investigations, 16 of them also had signs of severe dengue (Class C-AKI, arrhythmia, and either hypotensive or compensated shock) (Table 1). In total, 27 were afebrile on Day 1, and 36 on Day 2. BMI was comparable between males and females (24.79 ± 6.45 versus 23.98 ± 4.92). A platelet count of $<100 \times 10^9/\text{L}$ was seen in 21 and 23 patients on Day 1 and Day 2, respectively, with bleed-manifestation in seven (three with gum bleeds and one each

with epistaxis, metrorrhagia, haemoptysis and hematochezia). Only four patients had an increase in haematocrit $\geq 20\%$ on Day 2 compared with the previous day. Obese individuals and patients with hypotensive shock received significantly more fluids on Day 1 than adolescents (Table 2). There was no significant difference in fluids received in those with and without warning signs.

Nine (9/12) patients with compensated shock became hemodynamically stable on Day2, while two (2/12) continued to remain in compensated shock. The first was a 13-year-old girl with vomiting, anterior epistaxis and elevated CK (>1000), with persistent DBP fall on both days and had received 4450 ml and 7800ml on successive days. The second was a 21-year-old man, with bleeding gums, CK 674 and persistent postural fall in BP, who had received 9000 and 7000ml on each day respectively. Ten patients developed new compensated shock on Day2, one of them being a hypotensive shock on Day1 that had improved. Among the three patients with hypotensive shock on Day1, two improved, and the third was a 37-year-old female admitted on third day of fever who continued to be hypotensive on Day2 and required 8900ml and 6200 mL on each day respectively. The second new hypotensive patient on Day2 was a 30-year-old female with metrorrhagia, dyspnea and compensated shock and had received 10200mL on Day1 and 1750mL on Day2 with two RBC transfusions.

Bleeding was not significantly related to platelet counts, haematocrit, liver dysfunction, or CK elevation. Severe thrombocytopenia, bleeding, and compensated shock did not correlate with any anthropometry-related fluid calculation. Hypotensive shock had significant correlations with fluids/BSA, fluids/weight and fluids/BMI, while laboratory parameters correlated with best with fluids/BMI (Table 3). None of them developed

Figure 1. A crude container for measuring urinary volume.

Table 1. Clinical and lab values in patients who received ≥ 5 l/d fluids on Day 1 and Day 2. Values are given as mean $\pm$ standard deviation where indicated.

Variables	< 5L fluids on D1 (18)	≥ 5 L fluids on D1 (25)	Significance	< 5L fluids on D2 (15)	≥ 5 L fluids on D2(28)	Significance
Age (Years $\pm$ SD)	28.2 $\pm$ 14.6	29.8 $\pm$ 10.8	0.67	33.8 $\pm$ 13.1	26.6 $\pm$ 11.5	0.06
Adolescents (n)	7	4	0.09	2	9	0.17
Fever duration (days $\pm$ SD)	6.33 $\pm$ 1.49	6.12 $\pm$ 2.42	0.74	7.07 $\pm$ 2.57	5.75 $\pm$ 1.60	.045
Abdominal pain (n=7)	4	3	0.37	5	2	0.02
Vomiting (n=26)	12	14	0.48	9	17	0.96
Fluid accumulation clinical(n=2)	1	1	0.81	2	0	0.04
Mucosal bleed (n=5)	3	2	0.38	3	2	0.21
Dizziness (n=12)	4	8	0.48	5	7	0.56
Hepatomegaly (n=13)	5	8	0.76	5	8	0.76
Warning signs (n=39)	15	24	0.15	15	24	0.12
One warning sign (n=14)	3	11	0.06	5	9	0.93
Two warning signs (n=17)	6	11	0.48	6	11	0.96
Three warning signs(n=6)	4	2	0.18	3	3	0.40
ECG HR at admission (beats/min $\pm$ SD)	90.4 $\pm$ 15.3	89.9 $\pm$ 28.9	0.94	76.7 $\pm$ 28.1	97.6 $\pm$ 17.3	0.04
Pulse Day1 (Beat/min $\pm$ SD)	87.1 $\pm$ 11.8	89.1 $\pm$ 14.6	0.63	80.7 $\pm$ 11.2	87.6 $\pm$ 11.0	0.04
Pulse Day2 (Beats/min $\pm$ SD)	83.5 $\pm$ 11.2	86.0 $\pm$ 11.9	0.48	80.7 $\pm$ 11.2	87.6 $\pm$ 11.0	0.03
Compensated shock Day1 (n)	3	9	0.16	2	10	0.11
Compensated shock Day2 (n)	6	6	0.50	5	7	0.56
New compensated shock Day2(n)	5	5	0.55	5	5	0.25
Hypotensive shock Day1 (n)	0	3	0.21	0	3	0.18
Hypotensive shock Day2 (n)	0	2	0.21	1	1	0.64
Weight (kg $\pm$ SD)	54.4 $\pm$ 13.4	59.4 $\pm$ 9.8	0.17	55.1 $\pm$ 11.6	58.5 $\pm$ 11.6	0.37
Height (m $\pm$ SD)	1.59 $\pm$ 0.84	1.57 $\pm$ 0.65	0.53	1.54 $\pm$ 0.52	1.60 $\pm$ 0.74	0.008
BMI (kg/m ² $\pm$ SD)	22.4 $\pm$ 6.2	25.4 $\pm$ 4.3	0.06	24.4 $\pm$ 5.2	24.1 $\pm$ 5.4	0.84
Obesity (n)	4	14	0.02	4	14	0.13
BSA (m ² $\pm$ SD)	1.5 $\pm$ 0.1	1.6 $\pm$ 0.1	0.21	1.5 $\pm$ 0.1	1.5 $\pm$ 0.1	0.17
HCT Day1 ($\pm$ SD)	37.2 $\pm$ 6.8	37.7 $\pm$ 6.1	0.80	34.1 $\pm$ 6.9	39.3 $\pm$ 5.3	0.008
HCT Day2 ($\pm$ SD)	36.0 $\pm$ 5.3	38.3 $\pm$ 7.5	0.80	34.0 $\pm$ 5.2	39.1 $\pm$ 6.8	0.01
SGOT Day1 (U/L $\pm$ SD)	121.5 $\pm$ 79.5	103.5 $\pm$ 86.9	0.57	83.91 $\pm$ 55.4	129.0 $\pm$ 93.7	0.12
SGPT day1(U/L $\pm$ SD)	50.2 $\pm$ 47.3	36.6 $\pm$ 46.3	0.35	50.1 $\pm$ 52.1	38.1 $\pm$ 44.1	0.43
CK total (U/L $\pm$ SD)	452.4 $\pm$ 393.9	262.7 $\pm$ 243.2	0.16	112.1 $\pm$ 85.1	469.5 $\pm$ 337.2	0.001

ECG, electrocardiogram; HR, heart rate; BMI, body mass index; BSA, body surface area; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CK, creatine kinase.

fluid overload, pulmonary oedema, ARDS or admission into intensive care unit (ICU). There was no mortality. Raw data are available on Harvard Dataverse¹⁶.

Patient attitude towards drinking fluids

Patients' inability/hesitancy to drink fluids as instructed by the staff were due to poor taste, nausea, vomiting, abdominal pain,

dizziness on sitting up or walking to the restroom, inability to use the restroom following increased fluid intake, and poor cleanliness of the common restrooms. Patients referred from peripheral health centres for admission also felt that care was incomplete without IVF, preferring IVF over oral fluids, and often demanded IVF. In those who received IVF, problems encountered include wrong beliefs that they should not eat or

Table 2. Fluid requirements on Day 1 and Day 2. Values are given as mean $\pm$ standard deviation.

	Fluids on Day1 (mL) (mean $\pm$ SD)			Fluids on Day 2 (mL) (mean $\pm$ SD)		
Oral fluids (mean $\pm$ SD)	3834.88 $\pm$ 1872.15			4673.33 $\pm$ 2101.31		
Intravenous fluids (mean $\pm$ SD)	2318.60 $\pm$ 1170.11			1702.33 $\pm$ 1263.11		
Total fluids (mean $\pm$ SD)	6141.86 $\pm$ 2448.20			6433.72 $\pm$ 2793.37		
Variables (Yes/No)	Yes	No	Significance	Yes	No	Significance
Male gender (n=13)	7134.6 $\pm$ 2848.9	5711.6 $\pm$ 2165.3	0.08	8700 $\pm$ 2585.9	5451.6 $\pm$ 2333.1	<0.001
Adolescents (n=11)	5086.3 $\pm$ 1824.0	6504.6 $\pm$ 2552.6	0.09	7909.0 $\pm$ 2539.4	5926.5 $\pm$ 2730.1	0.04
Obese (n=18)	7044.4 $\pm$ 2822.4	5492.0 $\pm$ 1948.1	0.03	7136.1 $\pm$ 3173.0	5929.0 $\pm$ 2426.3	0.16
Warning signs (n=39)	6248.7 $\pm$ 2501.5	5100.5 $\pm$ 1747.3	0.37	6298.7 $\pm$ 2881.2	7750.0 $\pm$ 1239.6	0.32
Compensated Shock 1 (n=12)	6712.5 $\pm$ 1934.3	5920.9 $\pm$ 2615.0	0.34	6354.5 $\pm$ 2819.8	6460.9 $\pm$ 2819.8	0.74
Hypotensive shock1 (n=3)	10283.3 $\pm$ 2976.7	5831.2 $\pm$ 2140.5	0.00	10266.6 $\pm$ 6146.2	6212.5 $\pm$ 2630.9	0.01
Compensated shock2 (n=12)	6058.3 $\pm$ 2953.7	6174.1 $\pm$ 2177.7	0.87	6407.6 $\pm$ 3858.4	6445.0 $\pm$ 2267.1	0.96
Hypotensive Shock 2 (n=2)	9650.0 $\pm$ 1060.6	5970.7 $\pm$ 2370.6	0.03	3975.0 $\pm$ 2370.6	6553.6 $\pm$ 2761.9	0.20
New Compensated shock 2 (n=10)	5925.0 $\pm$ 3065.1	6207.5 $\pm$ 2281.4	0.75	6370.0 $\pm$ 3972.6	6453.0 $\pm$ 2408.5	0.93
Bleeding, severe (n=2)	9000.0 $\pm$ 1400.0	5927.5 $\pm$ 2383.0	0.03	4950.0 $\pm$ 2807.5	6545.0 $\pm$ 2795	0.34

Table 3. Significant correlations of severe dengue manifestations with anthropometry-related fluid calculations.

Variables	Fluids/BSA Day1	Fluids/Weight Day 1	Fluids/BMI Day2	Fluids/BSA Day2	Fluids/Weight Day2
Hypotensive Shock Day1	0.476	0.468	0.347	0.381	
Hypotensive Shock Day2	0.331	0.378			
Fluid accumulation				0.367	
Hematocrit Day1			0.372	0.330	0.404
Hematocrit Day2			0.463	0.477	0.455
Hematocrit 20% increase			-0.311	-0.311	
SGOT			0.410		
CK total			0.562	0.507	0.613
ECG heart rate		-0.329			

BSA, body surface area; SGOT, serum glutamic oxaloacetic transaminase; CK, creatine kinase.

drink while receiving IVF, unavailability of IVF stands on occasions (due to requirement by most patients in the ward), thrombophlebitis, delay in nurse or a doctor reaching them to disconnect the IV line so that they could use the toilet and then reconnect it again, difficulty in sleeping in a comfortable position because of the cannula, and washing after using the toilet (IV cannula in the left wrist/hand).

Discussion

There are 50–100 million new cases of dengue annually, with the vast majority of them in individuals >15 years of age^{4,17}.

Dengue began being reported in Pondicherry from 2007 onwards¹. A study from a hospital in Pondicherry during 2017 described the peak incidence of dengue between September and October; the dengue seroprevalence among antenatal mothers and children with fever was found to be 25.8%¹⁸. Severe dengue is more common in children¹⁹. The mean age of patients with severe dengue in our study was 30 $\pm$ 12 years, compared to 26 $\pm$ 11 years in those without severe dengue. Reports from India show that confirmed cases are being described mostly in the 21–30 years age group¹. Even though dengue shock requires admittance to an ICU, we managed all patients in the wards due to a shortage of

beds in the ICU³. None of our patients developed other indications of ICU care such as ARDS, cardiogenic shock, encephalitis, or secondary pneumonia.

Fluid calculation during the critical phase is calculated as follows: 100 ml/kg for the first 10 kg (1000 ml), 50 mL/kg for the second 10 kg (500 ml) and 20 ml/kg for >20 kg up to 50 kg (600 ml), and 5% deficit, calculated as 50 ml/kg up to 50 kg (2500 ml) which yields a total of 4600 ml for a 50 kg person for about 48 hours²⁰. Since 33/37 patients had severe dengue, the fluids administered were much higher than this amount during each day of the two-day study. Some studies have shown that the new WHO guidelines increased the sensitivity of identifying patients with severe illness, with a risk of over-admission and increased workload, which would not be desirable in endemic regions that were resource-limited⁷. In a study from a tertiary hospital at Singapore, some cases of dengue with warning signs were safely managed in outpatient settings, but this practice cannot be extrapolated to other settings of primary/secondary care⁷. Most patients with severe illness progressed within a day of developing warning signs⁷. Thus, our study attempted to find out whether a range of fluid requirement would satisfy most patients (at least in a hospital) with dengue and warning signs without the minute assistance of a doctor or a nurse.

Only four studies have quantified the fluid requirements of patients with dengue, among which two have been performed in hospitalised patients^{10–13}. Three had used the earlier WHO classification for severity of dengue: dengue fever, dengue haemorrhagic fever and dengue shock syndrome. The actual requirements of fluids in these three subtypes have not been quantified and vary with individuals; it depends on the availability of resources, staff, and place of treatment. Two studies had reported fluid requirements from admission to discharge^{10,11}. A large prospective study of 1501 patients in Asia and Latin America with children constituting 65% described fluid accumulation, shock, and respiratory distress in relation to IV fluids, especially boluses. Median IVF volumes for maintenance, rehydration, and resuscitation were 50, 50 and 64.7 l/kg, respectively. The quantity of oral fluids consumed was not reported¹¹. Another Sri Lankan study had shown that the quantity of fluid consumed had no impact on the development of third space fluid accumulation⁹. We are the first to assess fluid (oral and IVF) requirements based on the severity classification of A, B, and C. We had practical difficulties with both oral and IVF (as listed under Results), but persisted in explaining the need for fluids, especially by mouth.

Fluids losses into the third spaces may occur even prior to the fourth day of fever and it is imperative that fluid replacement begins early, especially prior to admission, beginning at home¹⁰. Our study showed that the maximum total fluids (13,700 and 14,100 ml on Day 1 and Day 2, respectively) had been administered on the fourth day of fever (Figure 2). During the first two days of fever, it is difficult to predict whether the disease may progress to shock (compensated or hypotensive) and hence fluid supplementation is important. In the Sri Lankan study auditing the trends in fluid requirements, 6267 ml was the mean

requirement on the fourth day of fever similar to that of our study (6141 ml on Day 1 and 6433 ml on Day 2)¹⁰.

The Malaysian study showed that reading out advice from a dengue home care card to patients attending primary care clinics improved fluid intake by at least one litre and reduced hospitalization rates¹². They also found that a fluid chart maintained by the patient improved awareness of fluid intake and enhanced compliance. In Nicaragua, where the amount of fluid was also quantified, drinking five glasses of fluids prior to being seen by a doctor was protective against hospitalization¹³. The various liquids ingested in that study included juices, lemonade, milk, coffee, tea, and oral rehydration salts. We did not advise tea or coffee because of their weak diuretic action. We also suggested tender coconut water, dilute millet or rice porridge. Promoting high fluid intake was suggested to make an economic impact in countries with dengue fever¹³. We suggested an empirical 4–5 litre count based on the 100 ml/kg for an average 50 kg person, to account for both maintenance and replacement fluids arising from losses due to vomiting, diarrhoea, high fever, anorexia and poor intake in hot and humid weather conditions.

Volume replacement guidelines are based on studies in children and hence caution was advised in order to avoid fluid overload¹⁷. Intravenous fluids were given at a mean volume of 110 ml/kg over a mean of 25.3 hours in infants in a Vietnamese study which studied both patients with dengue hemorrhagic fever and dengue shock syndrome¹⁷. This contrasted with a mean IVF volume of 40.44 ml/kg (2318.6 ml/57.33 kg) on Day 1 and 29.69 ml/kg (1702.33 ml/57.33 kg) on Day 2 in our study. Hence the requirement of administered fluids is much lower when considered for their weights. A different anthropometric measurement may perhaps be useful in adults to gauge actual requirements, since the BSA and BMI correlated better with laboratory parameters of severe dengue in our study. Fluids/BSA correlated best with hypotensive shock on both days, while fluids/BMI correlated significantly with all the lab predictors of severe dengue.

Limitations

This study had very small numbers due to the fact it was an audit of treatment practices in a single treating unit in Medicine (total of five units) during an epidemic that lasted 2 months. The dengue species was not known. The blood pressure was measured using a mercury sphygmomanometer, where errors in a few millimetres could probably misclassify patients with compensated and hypotensive shock. Also, some patients with severe postural symptoms had their BP checked in the sitting position, which could have led to a higher pulse pressure being recorded. The ECG heart rate was documented only at admission and patients could have been misclassified as having or not having a warning sign during Day 1 of the study. For logistic reasons, the study began only at 0800 AM of the following day after admission and hence the fluid administration for patients with shock or warning signs during the previous hours was not quantified. This amount may have been higher since all patients had been admitted initially with warning signs.

Figure 2. Box-plot showing fluids received on the two days of the study.

Conclusions

Most adults hospitalised with dengue fever and warning signs seem to require >100 mL/kg/day of fluids during their hospital stay without developing symptoms of fluid overload. Even this amount was not sufficient to help two patients (2/12) recover with compensated shock and prevent one patient from worsening to hypotensive shock. The quantum of fluids given in this study is over and above what has been described in the national guidelines, which are weight-based calculations. Abdominal pain, overweight individuals, tachycardia on ECG, hypotensive shock, increasing haematocrit and elevated CK levels were significantly associated with having received >5 l/day. Patients with warning signs may in addition have compensated shock (dizziness and postural hypotension) and severe organ impairment (arrhythmia) which may be missed at admission during epidemic-like situations. Since some patients developed warning signs on the third day of fever, it would be prudent to sometimes lower the threshold for admission in patients who come to the emergency department. Advising a larger amount of fluids (as in our study) at home during dengue epidemics could probably further reduce the need for admissions and/or development of severe dengue- a fraction of the fluid quantity that we administered our

patients had already shown to reduce hospitalization rates in two other studies. In resource-poor settings, letting patients and their attendants participate in the acute bedside management of dengue with warning signs may go a long way in preventing morbidity in dengue fever.

Data availability

Harvard Dataverse: Quantum of fluids in hospitalised patients with dengue and warning signs- a pilot cross-sectional study. <https://doi.org/10.7910/DVN/SKEJAM>¹⁶.

This project contains information on the fluids consumed and patient blood values.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Reviewer Report 03 July 2019

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Suranjith L. Seneviratne

Royal Free London NHS Foundation Trust, London, UK

In this study, the authors have attempted to use a very small cohort of patients with dengue infections (43 patients) to describe some aspects regarding their fluid requirements and management.

Some of the groups analysed in Table 2 had only 2 patients. This would introduce a high level of bias and it would not be possible to make reliable conclusions using such small numbers. The authors should combine their data with that of a clinical group managing a bigger number of dengue patients and this may then allow them to arrive at more reliable conclusions.

It would not be appropriate for day 1 to be considered from 8.00am on the following day after admission. Important information on fluid requirements from the point of admission to this arbitrarily defined time would thus be missed.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dengue.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 31 May 2019

<https://doi.org/10.5256/f1000research.20749.r49299>

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Siripen Kalayanaroj

Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand

The objective of this study is to find out the quantity of fluids adult patients with dengue fever and warning signs received to maintain hemodynamic stability and to discern which anthropometric measurement based fluid requirements correlated best with manifestation of severe dengue.

The authors underscored warning signs (WS) but the definition they used was different from the reference #8 that they had cited. Because of the different WS definitions, the enrolment criteria and exclusion criteria were not clear which then resulted in a non-homogeneous study population. They include both shock and non-shock patients, i.e. dengue with WS and severe dengue on the time of admission. So the results might not be relevant. In addition in Table 1 the results revealed that on day 1; number of cases with compensated shock increased from 4 (day 1) to 7 (day 2) in < 5L group and in > 5L group reduced from 7 (day 1) to 6 (day 2). The number of cases with hypotensive shock reduced from 7 (day 1) to 5 (day 2). Were these shock patients on day 1 and 2 the same patients or different ones?

The same results on day 2: number of cases with compensated shock increased from 3 (day 1) to 6 (day 2) and number of cases with hypotensive shock increased from 1 to 2 and in < 5L group. In > 5L group compensated shock reduced from 8 (day 1) to 7 (day 2) and from 6 (day 1) to 3 (day 2) for hypotensive shock. Were these shock patients on day 1 and 2 the same patients or different ones?

For the above results even in > 5L group, this amount of fluid > 5L seemed not very effective in maintaining hemodynamic stability, still there were > 50% of cases with shock or developed shock (if not the same patients).

Please clarify number of study cases, 41 (in the abstract) or 43 in the results and Table 1. Because of different definition, number of severe dengue cases increased! But by looking mean platelet

count, mean HCT, mean AST/ALT, it seemed that the majority of enrolled case were not severe. But in more severe cases, this fluid amount could not prevent shock in at least 14 cases (33%) in this study.

The following definitions in this study were different from standard?

- Warning signs (WS) that were not in the references: poor oral intake, dizziness, hypotension or shock, tachycardia during the afebrile phase, severe thrombocytopenia, associated diabetes, pregnancy or alcoholism, referral for admission from a peripheral health center, obese patients.
- Hypotension was considered when systolic blood pressure was < 100 mmHg
- Tachycardia defined compensated shock.
- Hypotensive shock = Pulse pressure $\leq$ 20 mmHg or Systolic BP < 90 mmHg or feeble pulse or the patients was restless.
- Organ impairment was defined as:
 - Transaminase elevation > 3 times.
 - CK elevation > 3 times.
- Thrombocytopenia = Platelet count, 150,000/cumm.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 02 April 2019

<https://doi.org/10.5256/f1000research.19911.r45298>

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Anon Srikiatkhachorn

Institute for Immunology and Informatics, Department of Cell and Molecular Biology, University of Rhode Island, Providence, RI, USA

The manuscript by Ramathan and colleague describes the fluid administration in patients hospitalized for dengue with warning signs (DWS) and evaluate the characteristics related to the amount of fluid received. The important aspect of this work in the “real world” setting where close monitoring of all dengue cases by medical staff may be less than optimum and the patients and relatives play important roles in the primary intervention, namely fluid administration.

Although the manuscript addresses an important issue, there are a number of problems in the methodologies and interpretations. The number of cases included in this report is rather small and the enrolment criteria included those that are not true warning signs. These include co-morbidity such as pregnancy, alcoholism, and social reasons. It is not clear how many of cases were enrolled based on these criteria. Further, definitions of severe dengue in this manuscript are different to those according to the WHO 2009 classification and have been expanded to include: a 20% increase in hematocrit reading, at least 3 fold increase in transaminase or CPK levels. The expanded definitions for warning signs and severe dengue in this manuscript may cause confusions to readers and limit the generalizability of the findings in this report.

Although detailed information regarding staffing of the medical wards was provided this does not clearly convey the measurable indicators of work load and man power utilized for patient care. Measurable indicators such as the ratio of cases to medical and nursing staffs should provide a clearer picture.

Tachycardia was used as an indicator of compensated shock. Tachycardia itself can occur from other reasons including fever, anxiety and discomfort that are not related to volume status. It is not clear whether all cases with tachycardia had been tested for postural hypotension before assigning them as severe.

It is notable that the average amounts of fluid received by dengue cases in this study were substantially more than previously reported. A manuscript from Kalaratne et al¹ was referenced to indicate fluid requirement comparable to this study. Upon reviewing this reference, the amount of fluid administered in DF and DHF cases was approximately 3000 ml per day, which is significantly less than the amount given in this current work. Although there were no report of respiratory complications such as pulmonary edema in this series, careful administration of fluid must be exercised to avoid fluid overload and respiratory complications. This also calls into question the accuracy of the estimated amount of fluid in this study.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dengue clinical manifestations, disease mechanisms, and clinical management.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Apr 2019

Stalin Viswanathan, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India

Dear Sir,

The following modifications have been made with regard to your comments for perusal.

1. As you rightly said, this is a small study and it has been mentioned in the title - a pilot study, partly because of the short duration of the epidemic and a single centre study.
2. All patients were enrolled because of the admitting diagnosis - "Dengue with warning signs". It is only after complete statistical analysis, that some of them have been found to have other features of severe dengue such as postural hypotension or an arrhythmia discovered on ECG
3. The enrolment criteria did not include pregnancy, obesity or alcoholism or diabetes as stated. These factors were considered by the admitting emergency department

physician. But the diabetic male and pregnant lady in our study had warning signs. The statement in the manuscript as "warning signs" have been suitably modified.

4. The expanded definitions to include severe dengue had been removed and the original retained. Thus the results section and the tables have been corrected accordingly. Thus hepatitis, myositis and hematocrit increase have been deleted.
5. The nurse-patient and doctor-patient ratio have been added in the section accordingly.
6. As per your comments, tachycardia alone without other symptoms have been NOT considered as compensated shock. Thus the tables with compensated shock and hypotensive shock have been changed. All patients (not only with tachycardia) were checked for postural hypotension on both days.
7. Our patients received more fluids than the one cited in the text, partly because some of them had compensated shock or hypotensive shock along with one or more warning signs noted at the time of admission. Thus they received more boluses and instructions to attendants to serve more fluid drinks. Patients with warning signs are often not checked for postural fall in the emergency department, and similarly, the pulse pressure is often not keenly looked at, and narrowing pulse pressure is often missed. Only in one 30-year-old lady with metrorrhagia, dyspnea, and compensated shock was there a suspicion of fluid overload since she received 10200mL on Day 1 and hence only 1750mL on Day 2. But CXR and USG showed no evidence of either effusion or edema and, therefore she received only RBC transfusions for uterine bleeding.

Regards and thank you.
Stalin V

Competing Interests: None

Reviewer Report 25 March 2019

<https://doi.org/10.5256/f1000research.19911.r45296>

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Siripen Kalayanaroj

Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand

The authors underscored warning signs (WS) but the definition they used was different from the references¹ that they cited. Because of the different WS definitions, the enrolment criteria and exclusion criteria were not clear, which resulted in a non-homogeneous study population. They include both shock and non-shock patients, i.e. dengue with WS and severe dengue on the time of admission. So, the results might not be relevant.

In addition, in Table 1 the results revealed that on day 1, the number of cases with compensated shock increased from 4 (day 1) to 7 (day 2) in the <5L group and reduced from 7 (day 1) to 6 (day 2)

in the $\geq 5L$ group. The number of cases with hypotensive shock reduced from 7 (day 1) to 5 (day 2). Were the shock patients on day 1 and 2 the same patients or different ones?

The same results on day 2: the number of cases with compensated shock increased from 3 (day 1) to 6 (day 2) and number of cases with hypotensive shock increased from 1 to 2 and in the $< 5L$ group. In the $\geq 5L$ group, compensated shock reduced from 8 (day 1) to 7 (day 2) and from 6 (day 1) to 3 (day 2) for hypotensive shock. Were the shock patients on day 1 and 2 the same patients or different ones?

For the above results, even in the $\geq 5L$ group, the amount of fluid didn't seem very effective in maintaining hemodynamic stability. Still, there were more than 50% of cases with shock, or that developed shock (if not the same patients).

Please clarify number of study cases, 41 (in the abstract) or 43 (in the results and Table 1). Because of different definitions, the number of patients with severe dengue increased, but by looking at the mean platelet count, mean HCT and mean AST/ALT, it seems that the majority of enrolled case were not severe. But in the more severe cases, this fluid amount could not prevent shock in at least 14 cases (33%) in this study.

The following definitions in this study were different from standard:

- Warning signs (WS) that were not in the references: poor oral intake, dizziness, hypotension or shock, tachycardia during the afebrile phase, severe thrombocytopenia, associated diabetes, pregnancy or alcoholism, referral for admission from a peripheral health center and obese patients.
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- Tachycardia defined compensated shock.
- Hypotensive shock = pulse pressure 20 mmHg or systolic BP < 90 mmHg or feeble pulse or the patients was restless.
- Organ impairment was defined as:
 - Transaminase elevation > 3 times.
 - CK elevation > 3 times.
- Thrombocytopenia = platelet count, 150,000/cumm.

References

1. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. 2009.
[PubMed Abstract](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: dengue

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 12 Apr 2019

Stalin Viswanathan, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India

Dear Sir,

The following modifications have been made by us with regard to your comments for your perusal.

1. The abstract has been corrected to include 43 patients as in the rest of the manuscript.
2. The definitions of warning signs have been included as in WHO 2009 guidelines. The other criteria such as pregnancy and diabetes which are only indicators for admissions and categorizing under Group B have been mentioned separately. nevertheless, both the male diabetic and pregnant lady had warning signs at admission.
3. Tachycardia as a single criterion for compensated shock has been removed.
4. Hypotension has been rewritten as BP <90mmHg and the results have been modified accordingly.
5. Organ impairment with regard to hepatitis has been removed. Since myositis is only part of the expanded dengue syndromes without a clear cut-off level, 3x levels were originally considered significant. But they have been excluded now. Only transaminases and CK levels are mentioned.
6. Thrombocytopenia has been removed and only severe thrombocytopenia <50,000 has been retained.
7. As you have rightly remarked, the majority was not severe. Even the severe cases, were because of having a pulse pressure <20mmHg, postural drop in BP or hypotension. Patients were taken into the study when the admitting diagnosis was warning signs - they could have had postural hypotension, or they may have worsened further when the study began at 08 AM. We did not foresee this, and the true picture of having some severe dengue among the cohort was available only after the statistical analysis.

8. In view of alteration in definitions, the numbers of hypotensive and compensated shock have changed. These have been incorporated, along with the clarification in the results regarding new patients who developed compensated or hypotensive shock. A new row (new compensated shock on Day 2) has been added in the table.

Regards,
Stalin V

Competing Interests: None

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