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Timing, predictors, and progress of third space fluid accumulation during preliminary phase fluid resuscitation in adult patients with dengue

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SUMMARY

Background: Fluid leakage remains the hallmark of dengue hemorrhagic fever (DHF). The applicability of currently recommended predictors of DHF for adults with dengue is questionable as these are based on studies conducted in children.

Methods: One hundred and two adults with dengue were prospectively followed up to investigate whether home-based or hospital-based early phase fluid resuscitation has an impact on clinical and hematological parameters used for the diagnosis of early or critical phase fluid leakage.

Results: In the majority of subjects, third space fluid accumulation (TSFA) was detected on the fifth and sixth days of infection. The quantity and quality of fluids administered played no role in TSFA. A reduction in systolic blood pressure appeared to be more helpful than a reduction in pulse pressure in predicting fluid leakage. TSFA occurred with lower percentage rises in packed cell volume (PCV) than stated in the current recommendations. A rapid reduction in platelets, progressive reduction in white blood cells, percentage rises in Haemoglobin (Hb), and PCV, and rises in aspartate aminotransferase and alanine aminotransferase were observed in patients with TSFA and therefore with the development of severe illness.

Conclusions: Clinicians should be aware of the limitations of currently recommended predictors of DHF in adult patients who are receiving fluid resuscitation.

1. Introduction

In the past two decades, there has been a dramatic increase in the global incidence of dengue and dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS).[1] More than 2.5 billion people are now at risk in more than 100 countries worldwide, and every year approximately 50 million infections occur, including 500 000 cases of DHF and DSS.[1] Although dengue was previously considered an illness mainly affecting children, it is now apparent that the illness increasingly involves adult populations living in endemic regions.[1–3] Furthermore, recent research highlights differences in clinical manifestations and disease progression in adults compared to children, suggesting that separate management protocols may be required for adults.[3–6] In Sri Lanka dengue has become the infectious disease of most concern, causing high morbidity and mortality in both pediatric and adult populations and, therefore, has direct and indirect economic costs.[7,8]

Plasma leakage is the most important phenomenon associated with severe dengue infection.[9,10] Profound thrombocytopenia and coagulopathy are also considered serious manifestations of the infection.[1,11] In addition, the occurrence of organ-specific complications, such as hepatitis and hepatic failure, myocarditis, and encephalitis or encephalopathy, either alone or in combination, have been increasingly described among adults with dengue.[1] The differences in severity of dengue with age[4] and the occurrence of DSS during the febrile phase of infection,[12] compared to its occurrence during the early afebrile phase in children, suggests possible differences in pathophysiology of severe dengue in adults.

The World Health Organization (WHO) management guidelines for severe dengue have been revised frequently since 2007, and the reviewers themselves highlight the need for refinements to disease classifications and clearer guidance for detecting severe illness based on further research.[1] As most of the known pathophysiological mechanisms of dengue still remain valid, the use of clinical and hematological parameters to detect plasma leakage remains the mainstay of detecting severe illness.[1] However, the current WHO guidelines for severity assessment and volume replacement are based on the studies of DHF and DSS in children.[1,3]

Patients with suspected dengue are often hospitalized for monitoring, although only severe cases of dengue and DHF need institutionalized care.[13] The reason for this is that there are no diagnostic or prognostic tools available to distinguish severe

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Table 1
WHO classification of dengue infections and grading of severity of DHF[a]

DF/DHF	Grade	Signs and symptoms	Laboratory
DF		Fever with two of the following: headache, retro-orbital pain, myalgia, arthralgia/bone pain, rash, hemorrhagic manifestations No evidence of plasma leakage	WBC $\leq 5 \times 10^9$/l Thrombocytopenia (platelet count $<100 \times 10^9$/l) Rising hematocrit (5–10%) No evidence of plasma loss
DHF	I	Fever and hemorrhagic manifestations (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia ($<100 \times 10^9$/l) Hematocrit rise >20%
	II	As in grade I, plus spontaneous bleeding	Thrombocytopenia ($<100 \times 10^9$/l) Hematocrit rise >20%
	III	As in grade I or II, plus circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness)	Thrombocytopenia ($<100 \times 10^9$/l) Hematocrit rise >20%
	IV	As in grade III, plus profound shock with undetectable blood pressure and pulse	Thrombocytopenia ($<100 \times 10^9$/l) Hematocrit rise >20%

WHO, World Health Organization; DF, dengue fever; DHF, dengue hemorrhagic fever; WBC, white blood cell count.
[a] This classification was first introduced in "*Dengue haemorrhagic fever: diagnosis, treatment, prevention and control*. 2nd ed. WHO: Geneva; 1997", available at http://www.denguevirusnet.com/guidelines/19-guidelines/42-who-dengue-guidelines-and-documents.html; it is available in the most recent guidelines: page 26 of "*Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever—revised and expanded edition*. Geneva: WHO; 2011" (Ref. 1). The WHO classification of dengue infections and grading of severity of DHF is available at http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/.

dengue from non-severe dengue, or dengue from other febrile illnesses at an early stage.[13] Most studies that have attempted to differentiate severe from mild dengue have been conducted in children.[3] In children, plasma leakage and, therefore, the development of the critical phase, is thought to occur around the time of defervescence and tends to last for about 48 h.[1] However, these studies showed that it was difficult to differentiate mild from severe dengue until the critical phase developed.[13] In contrast to children, we have experienced many adult patients developing third space fluid accumulation (TSFA) during early illness and developing critical illness during the febrile phase of dengue.[12]

The current recommended approach for the detection of dengue fever and the varying degrees of DHF are given in Table 1.[1] According to the classification, in addition to clinical features, the detection of dengue fever includes a white blood cell (WBC) count of $\leq 5 \times 10^9$/l, platelet count of $<150 \times 10^9$/l, and a rising hematocrit of 5–10% without TSFA. The different grades of DHF are based on critical phase plasma leakage (indicated by a rise in packed cell volume (PCV) ≥20%), and as the disease progresses there is a progressive weakness of pulse, narrow pulse pressure (≤20 mmHg), hypotension, and finally profound shock. However, the presence of TSFA is considered the most objective evidence for plasma leakage, while hypoalbuminemia is considered supporting evidence.[1] However, the value of hematological parameters is limited when baseline values are not available, and are doubtful in the presence of anemia, hemorrhage, and during the early phase of fluid resuscitation.[1] In order to prevent intravascular fluid depletion and maintain effective circulatory volume during the early phase, patients are often advised to consume adequate amounts of fluids, mainly solutes, at home. Unlike children, most adults are likely to comply with advice to increase fluid intake. It is also common practice to administer intravenous fluids to most hospitalized patients at maintenance rates or less in order to ensure an effective circulatory volume and venous access. This may mask the clinical and hematological parameters of early fluid leakage and at the same time lead to the development of TSFA. Furthermore, in many resource-poor tropical settings where dengue is endemic, facilities for imaging to detect TSFA are not readily available and an exclusively clinical approach can be subjective.

This study aimed to investigate whether home-based or hospital-based early phase fluid resuscitation contributes to TSFA and has an impact on clinical and hematological parameters used for the diagnosis of early or critical phase fluid leakage (degrees of DHF) and to investigate the timing and predictors of TSFA.

2. Methods

Over a 6-month period from July 2011, adult patients (age >12 years) who were clinically suspected of having dengue on admission to the Professorial Medical Unit, Colombo North Teaching Hospital, Ragama, Sri Lanka, were prospectively followed up using clinical, hematological, and biochemical parameters, and observed for the development of TSFA by serial ultrasonography of the chest and the abdomen. All patients who were later confirmed to have acute dengue by ELISA (PanBio Dengue Duo-antibody Test, Australia) and the hemagglutination inhibition test, were further studied. Data were collected prospectively on all patients suspected to have dengue using a detailed interviewer-administered form, and details of those in whom dengue was confirmed were entered into a Microsoft Access database and analyzed using the SPSS software package version 16.

As TSFA is the hallmark of varying degrees of DHF, clinical, hematological, and biochemical parameters, including those recommended in the WHO guidelines as being predictive of severity, were compared between those who developed TSFA and those who did not, in an attempt to detect critical illness during preliminary phase fluid resuscitation.

Oral temperature was measured using a mercury thermometer. A visual analogue scale numbered from 0 to 9 was used for assessment of symptom severity (generalized weakness and body pains). Blood pressure measurements were done using a mercury sphygmomanometer with the patient in the supine position. Oral fluid intake was measured by asking the patients to use a uniform measuring cup given on admission. Information on the quantity and type of intravenous fluids was obtained from the medical records. In patients who were not catheterized, urine output in females was measured after collecting urine into a bed pan, and in male patients urinating directly into a measuring jar.

All biochemical investigations and hematological investigations were carried out from the same laboratory to maintain the uniformity of results. Detection of TSFA was done using a semi-portable Toshiba Ultrasound Machine with a 3 MHz ultrasound probe.

All patients were managed according to the local guidelines for the management of adult dengue, published by the Ministry of Health, Sri Lanka, in collaboration with the Ceylon College of Physicians in 2010.[5]

Means were compared using the independent samples *t*-test, and equal variance was checked with Levene's test. Predictability of the development of TSFA by other parameters was calculated

using receiver operating characteristic curves. Pearson's bivariate correlation was used to assess correlations between parameters.

3. Results

Out of 168 patients who were selected for the study on admission to hospital, 102 (52 males; mean (standard deviation (SD)) age 28.3 (11.8) years) were confirmed as having an acute dengue infection. TSFA was detected in seven of these 102 patients (6.8%) at the time of admission (the mode (range) duration of illness in these seven patients at admission was 4 (3–5) days) and in 34 of 95 (37%) after admission. Of the 34/95 (36%) who developed TSFA after admission, 33 developed pleural effusion at a mean duration of 5.4 days (SD 1.4) and 21 developed ascites at mean duration of 5.8 days (SD 1.4) of illness (1/21 did not have pleural effusion). The majority of pleural effusions (72.7%) lasted 3 or more days and most cases of ascites (52.4%) lasted less than 3 days.

In the comparison of clinical, hematological, and biochemical parameters between those who had TSFA and those who did not at the time of admission to hospital, the parameters that were significantly different were lower platelet count and WBC count, and a higher aspartate aminotransferase (AST) (Table 2). None of the other parameters were significantly different. When comparing these parameters in patients who developed TSFA after admission and those who did not, significant differences were noted in the mean lowest WBC count, the mean lowest platelet count, the maximum percentage rises in Hb and PCV, the percentage reduction in mean systolic blood pressure, and the average maximum positive fluid balance (Table 2). None of the others were significantly different.

Parameters that significantly predicted TSFA are given in Table 3. The onset of TSFA could be predicted using: a 6.5% rise in PCV (sensitivity 61%, specificity 62%), a rise of 6.1% in Hb (sensitivity 55%, specificity 64%), lowest recorded platelet count of 48.5×10^9/l or less (sensitivity of 83%, specificity 51%), post-admission positive fluid balance of more than 777 ml/day (sensitivity 65%, specificity 64%), and a 6.5% reduction in systolic blood pressure (sensitivity of 50%, specificity of 66%). Non-significant parameters are given in Table 4. The duration of TSFA was negatively correlated with WBC count ($r = -0.361$, $p = 0.020$) and platelet count ($r = -0.585$, $p = 0.000$). There was no significant correlation with admission weight ($p = 0.125$), duration of fever ($p = 0.387$), lowest pulse pressure ($p = 0.299$), alanine aminotransferase (ALT) ($p = 0.241$), AST ($p = 0.328$), average fluid intake per day ($p = 0.118$), or fluid balance per day ($p = 0.129$). The duration of pleural effusion showed a significant positive correlation with severity of body aches (assessed on a visual analogue scale) ($r = 0.523$, $p = 0.001$), maximum percentage rise in PCV ($r = 0.526$, $p = 0.001$), and maximum percentage rise in Hb ($r = 0.525$,

Table 2
Comparison of parameters between those who developed and those who did not develop third space fluid accumulation[a]

Comparison of parameters at admission			
Parameter	TSFA	Non-TSFA	*p*-Value
Total number	7/102	34/95	
Illness duration at admission, days, mode/range	4 (3–5)	4 (2–6)	
Body weakness	7.5 (2.1)	6.9 (1.4)	0.326
Body aches	5.4 (2.7)	6.6 (2.3)	0.221
Hemoglobin, g/dl	14.7 (2)	13.6 (1.8)	0.1
Packed cell volume, l/l	43.8 (6.5)	41.2 (5)	0.19
WBC count, /l	7×10^9 (3.6)	3.8×10^9 (2.1)	0.055
Platelets, /l	24×10^9 (12)	94×10^9 (52)	0.000
AST, IU/l	291.8 (173.8)	137.3 (137.8)	0.022
ALT, IU/l	162.6 (89.7)	91.3 (85.1)	0.078
Systolic BP, mmHg	104.3 (11.3)	104.8 (13.1)	0.926
Diastolic BP, mmHg	71.4 (13.5)	70.9 (9.1)	0.887
Mean pulse pressure, mmHg	32.8 (7.6)	33.8 (8.4)	0.761
Comparison of parameters when TSFA developed after admission			
Parameter	TSFA	Non-TSFA	*p*-Value
Total number	34/95	61/95	
Illness duration at development, days	5.6 (1.4)		
Body weakness	7.32 (1.8)	7.16 (1.4)	0.63
Body aches	7.29 (1.9)	7.31 (1.7)	0.96
Average consumption of water, ml	620 (514)	491 (322)	0.14
Average consumption of solutes, ml	1461 (548)	1481 (374)	0.83
Average fluid balance, ml	1041 (472)	691 (425)	0.000
Highest hemoglobin, g/dl	14.66 (1.82)	14.28 (1.6)	0.3
Highest packed cell volume, l/l	44.16 (5.19)	43.4 (4.5)	0.46
Lowest WBC, /l	3.5×10^9 (1.5)	2.7×10^9 (1.3)	0.01
Lowest platelets, /l	30×10^9 (20)	49×10^9 (26)	0.000
Lowest systolic BP, mmHg	99.7 (14.51)	97.9 (8.91)	0.46
Lowest diastolic BP, mmHg	65.2 (9.6)	64.8 (7.7)	0.84
Lowest mean pulse pressure, mmHg	29.9 (9.1)	28.4 (4.9)	0.37
Maximum % rise in Hb, g/dl	8.7 (8.5)	4.6 (5.2)	0.02
Maximum % rise in packed cell volume	8.6 (8.7)	4.5 (5.5)	0.006
Maximum % reduction in WBC count	15.4 (20.5)	15.1 (19.3)	0.95
Maximum % reduction in platelets	50.6 (34.3)	47.7 (23.4)	0.63
Maximum % reduction in systolic BP	7.5 (8.6)	3.9 (5.8)	0.04
Maximum % reduction in diastolic BP	8 (9.5)	7.5 (8.7)	0.74
Maximum % drop in pulse pressure	11.4 (18.2)	9.8 (16.7)	0.69
Maximum AST, IU/l	424.1 (253.3)	244.3 (251.0)	0.03
Maximum ALT, IU/l	210.4 (149.9)	185.9 (210.8)	0.56

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; SD, standard deviation; TSFA, third space fluid accumulation; WBC, white blood cell.
[a] Results are mean (SD), unless stated otherwise.

Table 3
Parameters showing significant association with predicting third space fluid accumulation

Parameter	% rise or decline	*p*-Value	Sensitivity	Specificity
Hb	Rise of 6.1%	0.017	55%	64%
Packed cell volume	Rise of 6.5%	0.002	61%	62%
Platelet count	$<48.5 \times 10^9$/l	0.0000	83%	51%
Input output balance/day	>777 ml	0.002	65%	64%
Systolic blood pressure	6.5%	0.042	50%	66%

Table 4
Parameters not showing a significant association with predicting third space fluid accumulation

Parameter	*p*-Value
% rise of AST	0.881
% rise of ALT	0.810
Post-admission average water intake	0.342
Post-admission average solute intake	0.684
% reduction of pulse pressure	0.985

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

$p = 0.001$). The duration of ascites was positively correlated with the highest AST ($r = 0.598$, $p = 0.002$) and highest ALT ($r = 0.721$, $p = 0.000$). The mean lowest WBC count of 3×10^9/l seen in patients who developed bilateral pleural effusions ($n = 21$) was significantly less ($p = 0.042$) than the mean lowest WBC count of 4.1×10^9/l in patients with unilateral effusions ($n = 12$). There was no significant difference in other parameters between these two groups.

In this cohort, 41/102 patients developed TSFA and platelet counts $<100 \times 10^9$/l, suggesting DHF grade I according to current WHO criteria.[1] However, their maximum percentage increase in Hb and PCV were 8% and 8.6%, respectively. Only three of 102 patients had a ≥20% rise in PCV together with systolic blood pressure <90 mmHg, weak peripheral pulse and TSFA suggestive of DHF grade III according to current WHO criteria.

4. Discussion

In this study, the occurrence of TSFA during home-based management for dengue infection was seen in only a small proportion of patients, and in these patients it occurred during the febrile phase of the illness on or before the fourth day. Among patients who developed the complication after admission, TSFA occurred on the fifth and sixth day of the illness in the majority. However, ultrasonographic evidence of TSFA was detected as early as on the third day of illness in some patients, similar to previous reports in children.[14] Pleural effusions occurred earlier and persisted for longer than ascites, and were the common ultrasonographic sign of plasma leakage, similar to what has been observed in children.[14] As there was no significant difference in the quantity or quality of fluid intake between those who developed TSFA and those who did not, the complication seems to be primarily a result of increased capillary permeability during the disease process.

Lower platelet counts in the presence of relatively higher WBC counts and high AST levels were found in patients who developed TSFA (at admission or after admission) compared to patients who did not develop TSFA. Furthermore, lower WBC counts were observed in those who developed bilateral pleural effusions compared to unilateral effusions. Low platelet and WBC counts are helpful to differentiate dengue fever from other febrile illnesses,[13] and are associated with the development and progression of pleural effusions.[13,15] A rise in AST levels in severe dengue has also been documented previously.[16,17] Therefore, these observations predicting severe illness are in keeping with the previous findings documented for similar illness in children. The reduction in systolic blood pressure appeared to be more helpful in identifying adult patients who developed TSFA than the previously recommended reduction in pulse pressure.[3] Rising Hb and PCV remained useful as predictors of TSFA. A rise in PCV >6.5%, Hb >6.1%, the lowest platelet count below 48×10^9/l, and a positive fluid balance of 777 ml/day at any time of the illness compared to baseline while on fluid resuscitation, seemed to predict TSFA and, therefore, increased vascular permeability. This highlights the importance of recording baseline values in patients with fever in dengue endemic areas. Such data may also help solve some controversies when developing management guidelines. At present the availability of such data is very limited in developing countries where dengue is endemic.[18] The duration of TSFA correlated positively with body aches and the percentage rise in PCV and Hb, and correlated negatively with WBC count and platelet count. These parameters are known indicators of plasma leakage in dengue,[1] and remain valid as predictors of severe dengue in adults during fluid resuscitation.

In this cohort, although 41/102 patients had TSFA and platelet counts $<100 \times 10^9$/l without significant hemodynamic compromise mimicking DHF grade I according to current WHO criteria,[1] their maximum percentage increase in Hb and PCV were 8% and 8.6%, respectively, and were far below the recommended values for the detection of DHF grade I.[1] Only three of 102 patients had ≥20% rise in PCV, and all of them developed features suggestive of DHF grade III according to current WHO criteria.[1] Clinicians should be aware that patients who are on fluid resuscitation during the early phases of infection can develop DHF grade I without the expected rise in PCV, and rises ≥20% seem to indicate more severe stages of DHF.

This study highlights some limitations in the use of predictors of severity that are given in current dengue management guidelines for detecting and categorizing stages of severe dengue in adults in the phase of preliminary phase fluid resuscitation. This may be because these guidelines are based on pediatric studies. However, a rapid reduction in platelet counts, progressive reduction in WBC counts, percentage rises in Hb and PCV, reductions in systolic blood pressure, and rises in AST and ALT seem useful in detecting fluid leakage and therefore the development of severe illness.

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Ethics statement: Ethical permission for this study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka. Informed written consent was obtained from all the study participants.

Conflict of interest: No conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2012.12.021.

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