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Vascular leakage in dengue – clinical spectrum and influence of parenteral fluid therapy

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Abstract

Objective: Clinical management of dengue relies on careful monitoring of fluid balance combined with judicious intravenous (IV) fluid therapy. However, in patients with significant vascular leakage IV fluids may aggravate serosal fluid accumulation and result in respiratory distress.

Methods: Trained physicians followed suspected dengue cases prospectively at seven hospitals across Asia and Latin America, using a comprehensive case-report form that included daily clinical assessment and detailed documentation of parenteral fluid therapy. Applying Cox regression, we evaluated risk factors for the development of shock or respiratory distress with fluid accumulation.

Results: Most confirmed-dengue patients (1524/1734, 88%) never experienced dengue shock syndrome (DSS). Among those with DSS, 176/210 (84%) had fluid accumulation, and in the majority, (83%), this was detectable clinically. Among all cases with clinically detectable fluid accumulation, 179/447 (40%) were diagnosed with shock or respiratory distress. The risk for respiratory distress with fluid accumulation increased significantly as the infused volume over the preceding 24hrs increased (hazard ratio 1.18 per 10 ml/kg increase; p<0.001). Longer duration of IV therapy, use of a fluid bolus in the preceding 24 h, female gender and poor nutrition also constituted independent risk factors.

Conclusions: Shock and respiratory distress are relatively rare manifestations of dengue, but some evidence of fluid accumulation is seen in around 50% of cases. IV fluids play a crucial role in management, but they must be administered with caution. Clinically and/or radiologically detectable fluid accumulations have potential as intermediate severity endpoints for therapeutic intervention trials and/or pathogenesis studies.

Keywords: dengue, vascular leakage, clinical spectrum, IV fluid therapy, prospective

Introduction

With no specific therapy available, effective case management of patients with dengue relies on frequent monitoring and judicious use of intravenous (IV) fluids. Guidelines for fluid therapy in dengue patients differentiate between maintenance, rehydration, and shock resuscitation. Isotonic crystalloids are recommended for maintenance or rehydration, while colloid solutions are often recommended alongside crystalloids for shock resuscitation (1, 2). In patients with vascular leakage, however, IV fluid therapy can aggravate fluid accumulation and lead to respiratory distress (2, 3). Clinically detectable fluid accumulation is currently considered as a warning sign for severe dengue (1), but this association has not been formally validated.

The aetiology of vascular leakage in dengue is not well understood, yet the underlying increased capillary permeability constitutes the main pathological mechanism implicated in severe dengue. Factors believed to predispose to a more severe disease course include secondary infection with a heterologous serotype (4-6), host genetics (7), nutritional status (8, 9), gender (10, 11), and comorbidities such as lung disease (12), diabetes mellitus, or arterial hypertension (13, 14).

To date, use of IV fluids for dengue has not been evaluated using a standardized data collection instrument across multiple sites. Using the data from a large observational hospital-based study, we describe the presentation at first severe event for (a) shock, stratified by the presence of fluid accumulation; and (b) the subsequent occurrence of respiratory distress with fluid accumulation. We also assess the influence of IV fluid therapy on these parameters.

Methods

Details of the prospective observational study, performed in 11 hospitals in 7 endemic countries across 2 continents, have been published elsewhere (15). In short, patients were recruited upon hospital admission, and then followed daily for a median of 4.5 days (90% range 3-7 days) using a de-

tailed case report form (CRF) to document past medical history, clinical symptoms, examination findings and management, focusing in particular on fluid therapy; the purpose and type of IV fluid given (maintenance only, rehydration, shock resuscitation; crystalloid, colloid, blood), and the total volume in ml/kg/24h were recorded each day. Standard operating procedures described the definitions for all clinical signs and symptoms and provided guidelines for completing the CRF. Data were collected for 24 h-periods between daily clinical assessments scheduled at the same time each day. The study was conducted in accordance with GCP guidelines including WHO-trained clinical monitors. Dengue diagnostic testing was performed in each participating country in accordance with validated local protocols. According to the specific tests performed, criteria were defined for confirmed and highly suggestive infection, involving paired specimens for serologically confirmed dengue. Only 10% of the patients were classified as highly suggestive, the remaining 90% were confirmed by the diagnostic algorithm. Data were analysed using STATA version 12 (STATA corporation, College Station, Texas). Ethical clearance was obtained from the Institutional Review Board (IRB) of WHO and the respective IRB of each participating institution.

Definitions and endpoints

Shock was assessed clinically, and defined as a state of reduced end-organ perfusion presenting with weak pulse and/or narrowing of pulse pressure, and/or hypotension for age, plus cold, clammy skin or increased capillary refill time, or peripheral cyanosis, or skin mottling (15).

Fluid accumulation was based on clinical or radiological findings (CXR/USS). Clinical fluid accumulation was defined as a clinically detectable pleural effusion or ascites noted on any of the daily assessments. Radiological fluid accumulation was assessed within 24 hours of defervescence, and was defined as presence of a pleural effusion on CXR or a serosal fluid collection on ultrasound. CXR was available in the majority of the hospitals and was carried out in 88% of the patients. Respiratory distress was defined as nasal flaring, tachypnoea, or in-drawing and retractions of the chest wall.

We evaluated the association of IV fluid therapy with the events of interest, adjusting for known confounders as for example demographics and anthropometry. The parameters assessed were IV fluid administration before enrolment; number of days with IV fluid therapy before the day of the event; volume of IV fluid (per 10 ml/kg) and whether an IV fluid bolus was given during the preceding 24 h-period. As enrolment covariates we included day of illness (DOI), presence of comorbidities, referral status, and body mass index (BMI), using the WHO reference standards for underweight and overweight (Annex, Table S1) (16-18).

Analysis

The spectrum of the clinical manifestations of vascular leakage was stratified into three categories to allow for potential heterogeneity in the risk profiles. We describe the frequency of the presentation at first event for (a) fluid accumulation alone, (b) shock without fluid accumulation, and (c) shock with fluid accumulation (Figure 1), as well as the occurrence and evolution of respiratory distress.

We used Cox regression to explore associations between use of IV fluid therapy over time with subsequent development of shock without fluid accumulation, shock with fluid accumulation, and respiratory distress with fluid accumulation. Within each analysis, data were included while the person was at risk for the endpoint in question; thus for patients who experienced the event of interest, analysis was restricted to the days before it occurred. Cases who experienced the event on the study enrolment day were excluded from the Cox regression analysis since detailed information about prior IV fluid use was not available.

Patients who developed severe bleeding while at risk for any of the endpoints were excluded from the analysis. However, if a patient developed severe bleeding on the day of the event or subsequently (i.e. they had already ceased to be at risk for the endpoint), the explanatory variables were included from the preceding 24h time period. Apart from these exclusions for severe bleeding, patients who did not experience the relevant endpoint were considered at risk until being censored on illness day 10. To allow for time-dependent evolution of variables, the data were analysed at the level of person-day, i.e. one record for each ~24 h-period for each patient.

Univariable regressions were carried out with all covariates. A full multivariable model with the resulting covariates of the univariable analysis ($p < 0.2$) was run using a stepwise backward and forward selection algorithm with a significance level of 0.2 for removal/addition. Age group (<15/≥15 years) was included in all models as an a priori confounder. Any covariates not retained by the stepwise algorithm were again added and dropped manually one by one, and were kept in the model if the p-value was below 0.2.

Results

The 1501 dengue patients from Southeast Asia (SEA) and 233 from Latin America (LA) with confirmed dengue were included in this analysis (**Table 1**). The majority of the patients were children, due to the prevailing epidemiology in SEA and the participating hospitals; the hospital in Thailand, two of three hospitals in Vietnam, and the hospital in Nicaragua were paediatric facilities. Pre-

existing comorbidities (N=147) were reported in 11.8% of the adults (age≥15 years) and 6.3% of the children (age<15 years), mostly asthma (N=45), peptic ulcer (N=16), and arterial hypertension (N=14). 248 patients were referred from another inpatient facility or hospital, and 628 patients were referred from an outpatient facility. 8.4% of the patients (N=146) required ICU-level medical care at the time of enrolment.

Frequency of shock and severity at time of first event

A large majority (88%) of the 1734 hospitalized patients never experienced shock (N=1524; mean DOI at enrolment 4.48; 95%CI 4.43-4.54). Shock occurred in 210 patients, of whom 151 presented with shock at enrolment (mean DOI 4.92; 95%CI 4.78-5.06) and 59 developed shock after enrolment (mean DOI at enrolment 4.25; 95%CI 3.97-4.53, mean DOI at shock 5.75; 95%CI 5.45-6.05) (Figure 1).

In 821 patients (47%) none of the events (shock, fluid accumulation, or respiratory distress) occurred over the course of hospitalisation (mean DOI at enrolment 4.42; 95%CI 4.35-4.49), while 672 patients (39%) experienced fluid accumulation without shock (mean DOI at enrolment 4.56, 95%CI 4.49-4.64) and 17 patients experienced fluid accumulation and respiratory distress without shock.

At the first day of shock, 102 of 210 shock cases were diagnosed with shock only (mean DOI 4.83; 95%CI 4.66-5.01), 82 with shock plus fluid accumulation (mean DOI 4.79; 95%CI 4.58-5.01), and 22 with shock plus fluid accumulation and concurrent respiratory distress (mean DOI 4.23; 95%CI 3.82-4.64) (Figure 1).

Disease progression under prospective follow-up

Among the 672 patients with documented fluid accumulation who were never diagnosed with shock, 15 subsequently developed respiratory distress (2.2%). In total, respiratory distress with fluid accumulation was diagnosed in 32/1524 (2.2%) cases who never developed shock.

Among the DSS cases without fluid accumulation at the onset of shock (N=102), 70 developed fluid accumulation subsequently and 12 (12%) proceeded to respiratory distress with fluid accumulation, either concurrently or sequentially.

In addition, 8 of 82 DSS patients (10%) with fluid accumulation at initial presentation proceeded to develop respiratory distress. Altogether, respiratory distress was diagnosed in 49 cases with shock, including 22 cases of concurrent shock and respiratory distress with fluid accumulation, and 22 cases where respiratory distress developed after shock (Figure 1).

Detection of fluid accumulation

Fluid accumulation was documented in 868/1734 (50.1%) of all patients. Among the patients with fluid accumulation who never proceeded to shock or respiratory distress (N=657), 59% (389) were diagnosed by radiological methods only, while 41% had evidence of clinical fluid accumulation (clinical pleural effusion or ascites). In contrast, all 32 patients who were never diagnosed with shock, but developed respiratory distress with fluid accumulation, had clinically detectable fluid accumulation. Among the patients with shock, 177/210 (84%) had fluid accumulation and in 147 of these cases (83%) this was detectable clinically.

When we compared radiological versus clinical detection of fluid accumulation on 129 days with shock (110 patients) and 76 days with respiratory distress (60 patients) we saw high agreement rates (Table 2). In shock cases, clinical signs of fluid accumulation were recorded on 71/97 days with radiologically confirmed evidence of fluid accumulation (73.2%). In 16 cases, clinical signs of fluid accumulation were recorded which could not be verified by CXR or US. This mismatch was caused by absence of pleural effusion by CXR in 8 cases, absence of pleural effusion by ultrasound in 3 cases, and absence of ascites by ultrasound in 1 case. In another 3 cases, ascites was diagnosed clinically, but abdominal ultrasound was not performed and pleural effusion was absent on CXR.

For respiratory distress, clinical clinical signs of fluid accumulation were recorded on 64/68 days with radiological confirmed evidence of fluid accumulation (94%). A clinical pleural effusion was diagnosed which was not visible on CXR in three cases, and by ultrasound in one case.

Impact of IV fluid therapy

Overall, 943 patients (54.4%) received IV fluids during the prospective follow-up period. IV fluids were given on 3072 patient-days, representing 38.8% of the total patient-days under observation. 211 patients had already received IV fluid therapy before enrolment while being managed at another facility. The median number of days with IV fluids per patient was three (IQR 2-4). In 810 patients, IV fluids were administered on consecutive days (mean number of days 3.1; IQR 2-4 days). The median volume of IV fluid given for maintenance was 50.0 ml/kg per day (IQR: 29.8-71.6), for rehydration 50.0 ml/kg (IQR: 33.6-71.4), and for shock resuscitation 64.7 ml/kg (IQR: 39.1-89.3). As the total amount per 24 hours was recorded, these estimates are averages and may include times without any IV fluid. In the case of shock resuscitation, the total amount over 24h included a bolus of IV fluid.

To evaluate the impact of IV fluid therapy we selected the subset of patients in whom complications developed during the prospective follow-up period. Univariable regressions were first carried out separately for shock without fluid accumulation and shock with fluid accumulation, and subsequently combined as the profile of risk factors proved to be comparable (Annex, Table S2). In the univariable regressions, shock (combined) was significantly associated with age below 15 years (HR 2.09; p=0.020), underweight (HR 2.42; p=0.007), IV fluid administration before enrolment (HR 2.52; p=0.010), and increasing volume of IV fluid (per 10 ml/kg) in the preceding 24 h (HR 1.10; p=0.022) (Table 3). Respiratory distress with fluid accumulation was associated with age younger than 15 years (HR 4.38; p<0.001), referral from another inpatient facility (HR 2.88; p<0.001), and duration of IV fluid therapy (HR 1.99; p<0.001), amount of IV fluids in the preceding 24h (HR 1.33; p<0.001), as well as receipt of an IV fluid bolus in the preceding 24 h (HR 10.71; p<0.001) (Table 3).

Multivariable regressions were adjusted for age group and otherwise restricted to the most influential covariates with p<0.2 (Table 4). The risk for shock was significantly increased in females (adjusted hazard ratio [AHR] 2.05; p=0.031), in underweight patients (AHR 2.62; p=0.012) and in the cases that had received IV fluids before enrolment (AHR 2.60; p=0.033), adjusted for age group, and amount of IV fluid in the preceding 24 h (AHR 1.11; p=0.059). The risk for respiratory distress with fluid accumulation was increased in the age group <15 years (AHR 3.85; p=0.001), and with longer duration and greater volumes of IV fluid therapy. Longer duration of IV fluid therapy (AHR 1.66 per additional day; p=0.004), greater amounts of IV fluid therapy during the preceding 24 h (AHR 1.18 per 10 ml/kg; p<0.001), and IV fluid bolus administered in the preceding 24 h (AHR 2.90; p=0.005) each were independent risk factors for respiratory distress with fluid accumulation.

Discussion

A large proportion, 88%, of the 1734 hospitalized dengue patients in this prospective multicentre study never experienced shock, although in some cases pre-hospital treatment may have prevented complications. In contrast, fluid accumulation was documented in approximately half of the 1734 cases. The agreement between clinically and radiologically detected fluid accumulation was high, particularly when complications were present. However, minor fluid accumulation might not have been detected in some cases, especially in the absence of other clinical features suggesting vascular leakage. Not surprisingly, the proportion of cases with documented fluid accumulation was significantly larger among shock cases (84%; 95%CI 79-89%) than patients who never experienced shock (45%; 95%CI 43-48%). If present, fluid accumulation was detected by clinical assessment in 41% of the 657 cases who never progressed to shock or respiratory distress versus 83% of the 210 shock

cases. In all patients who never had shock, but were diagnosed with respiratory distress, fluid accumulation was detected in by clinical assessment.

Among all cases with clinical fluid accumulation identified at some point during the prospective evaluation, 179/447 (40%) also developed shock or respiratory distress. Thus, across the spectrum of vascular leakage manifestations, clinical fluid accumulation was associated with more severe disease.

Vascular leakage is the defining feature of severe dengue and is primarily responsible for intravascular volume depletion and shock, although the volume loss may be compounded by sweating, vomiting, diarrhoea, and reduced fluid intake. Respiratory distress is usually a late phenomenon, due to fluid accumulation in the pleural or peritoneal cavity, or occasionally to pulmonary edema in severe cases. However, clinical or radiological detection of fluid accumulation earlier in the illness course can be a useful indicator to assess the degree of underlying vascular leakage. Leakage severity is often quantified by measuring the degree of haemoconcentration, with a haematocrit change of greater than 20% typically used as an absolute cut-off to define presence of leakage in dengue (19), or with additional sub-stratification to assess severity (20). However, the utility of these methods is limited by the fact that an individual's baseline haematocrit is rarely known, and that parenteral fluid therapy may obscure significant changes. In several small focused studies fluid accumulation documented by ultrasound has been shown to correlate with disease severity (21-24) and to be more sensitive at detecting vascular leakage than haematocrit changes (25), although the lack of defined normal ranges for the parameters of interest and the lack of specificity of the findings have been highlighted as potential issues (26).

Our data confirm, in a much larger unselected population, that fluid accumulation is one of the key manifestations of dengue-induced vascular leakage, and support development of a systematic approach to detection, ideally to be used alongside systematic methods to identify haemoconcentration in suspected cases. The association we demonstrate between detection of fluid accumulation and development of severe disease also provides evidence for consideration of this phenomenon as a potential outcome measure for dengue research, whether identified by direct examination or quantified radiologically in more sophisticated settings. This is of particular interest as severe dengue remains a relatively rare event (27, 28).

These findings also highlight the conundrum surrounding the influence of IV fluid therapy on markers of vascular leakage. While fluid therapy is clearly crucial for management in many patients,

our results confirm the important role of parenteral fluid use in the evolution of respiratory distress in dengue cases with vascular leakage. We also observed an increased risk for shock in participants who had received IV fluids prior to enrolment, but whether the volume administered was adequate given the severity of leakage present before enrolment cannot be determined from these data. Of note however, most of the patients were previously healthy children, in whom even large volumes of parenteral fluid are usually rapidly excreted in normal circumstances; in such cases any degree of fluid accumulation indicates that abnormal permeability is present. Overload can undoubtedly be exacerbated by inappropriate fluid management, especially in the elderly or in individuals with underlying conditions that affect cardiovascular homeostasis. To capture the full impact of interactions between vascular leakage and fluid management, future studies will need to be very detailed, and to include repeated daily assessments, to correlate the amount of fluid given with the immediate impact on the medical condition of the patient.

In addition to the volume and duration of parenteral fluid therapy received, we identified several factors – age, undernutrition, and female sex – that were associated with poor outcome in the regression analyses. In line with many studies that have demonstrated a greater risk for vascular leakage and development of DSS among children than adults (10, 29, 30), in this study children (i.e. subjects <15 years) were 3.9 times as likely as adults to proceed to respiratory distress with fluid accumulation. Similarly, female patients are generally considered to have a higher risk of developing DSS and of dying from this complication than male patients; this could be related to health seeking behaviour since girls may be brought to hospital later and with more advanced disease (10). However, there has been more debate regarding the influence of nutritional status, with both under and overnutrition implicated in previous studies (31-34).

In conclusion, in this large prospective study of hospitalized confirmed-dengue patients in which a uniform data-collection instrument was applied at multiple sites across 7 countries in Southeast Asia and Latin America, we found that although the majority of patients did not experience severe dengue due to vascular leakage (either manifesting as shock or respiratory distress), evidence of fluid accumulation was documented in 50.1% of cases (868/1734), and 40% of patients (179/447) with clinically detected fluid accumulation were diagnosed with shock or respiratory distress. Fluid therapy was associated with a greater risk of developing respiratory distress. This relationship may partly reflect the severity of the underlying disease process. Evidence of fluid accumulation alone could potentially serve as an intermediate severity endpoint for dengue research studies, although further work is needed to develop clear definitions and detection thresholds for clinical and radiological fluid accumulation.

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Figure Legend

Figure 1. Manifestations of vascular leakage leading to fluid accumulation (FA) only, shock with/without FA, and respiratory distress (RD) with FA in 1734 dengue patients.

[1] In 3 patients the information for FA was not available.

[2] In 11 patients RD was the first event. FA was subsequently documented in 2 of those patients after RD was no longer present.

[3] In 1 patient RD only occurred before shock. In 1 patient FA only occurred before shock.

[4] In 2 patients RD occurred after shock.

[5] In 4 patients RD occurred on the same day as shock. Out of these 2 patients developed FA.

Table 1. Characteristics of 1734 study subjects at enrolment by continent

	Asia		**Latin America**	
	N	**%**	**N**	**%**
Age:				
- 0-14	897	60	165	71
- 15-44	587	39	58	25
- 45+	17	1	10	4
Sex:				
- Male	797	53	127	55
- Female	704	47	106	45
BMI*				
- Underweight	510	34	41	18
- Normal	682	45	114	49
- Overweight	289	19	69	30
DOI at time of enrolment				
- ≤3	202	13.5	74	31.8
- >3	1,299	86.5	159	68.2
History of comorbidity	102	6.8	45	19.3
Referral				
- from outpatient facility	564	37.6	64	27.5
- from inpatient facility	223	14.9	25	10.7
Medical protocol at enrolment				
- Standard	774	51.6	135	57.9
- Intermediate	597	39.8	82	35.2

- ICU-level	130	8.7	16	6.9
Total	1501		233	

* BMI categories: underweight in patients ≥19 years: BMI <18.5; overweight in patients ≥ 19 years: BMI >=25; underweight in patients <19 years: BMI < -1 SD according to WHO reference standard; overweight in patients <19 years: BMI >= 1 SD according to WHO reference standard.

Table 2. Comparison of radiological assessment of fluid accumulation (ultrasound or CXR) with clinical assessment on 129 days with shock (110 patients) and 76 days with respiratory distress (60 patients)

Shock		Clinical signs of FA		
		-	+	Total
Radiological evidence of FA	-	16	16	32
	+	26	71	97
	Total	42	87	129
Respiratory distress		Clinical signs of FA		
		-	+	Total
Radiological evidence of FA	-	8	4	12
	+	0	64	64
	Total	8	68	76

Table 3. Univariable Cox regression on risk factors for subsequent shock and respiratory distress with fluid accumulation (RD+FA). The subset of patients in the regression analysis includes those with event of interest developing during the prospective follow-up period and the patients where no event occurred (and follow-up information was available).

	No shock or RD N = 1478	**Shock N = 56**			**RD+FA N = 54**		
Demographics / anthropometry / referral history / past medical history							
	N (%)	**N (%)**	**HR (p-value)**	**95%CI**	**N (%)**	**HR (p-value)**	**95%CI**
Age group							
< 15 years	885 (59.9)	43 (76.8)	reference		47 (87.0)	reference	
>= 15 years	593 (40.1)	13 (23.2)	**2.09 (0.020)**	1.13-3.89	7 (13.0)	**4.38 (<0.001)**	1.97-9.70
Sex							
male	802 (54.3)	25 (44.6)	reference		25 (46.3)	reference	
female	676 (45.7)	31 (55.4)	1.50 (0.133)	0.88-2.54	29 (53.7)	1.36 (0.258)	0.80-2.33
BMI							
underweight	456 (30.9)	25 (44.6)	**2.42 (0.007)**	1.28-4.59	18 (33.3)	1.26 (0.474)	0.67-2.39
normal	692 (46.8)	15 (26.8)	reference		20 (37.0)	reference	
overweight	309 (20.9)	12 (21.4)	1.82 (0.121)	0.85-3.90	13 (24.1)	1.51 (0.244)	0.75-3.04
missing values	21 (1.4)	4 (7.1)			3 (5.6)		
Continent							
SE Asia	1279 (86.5)	46 (82.1)	reference		49 (90.7)	reference	
L America	199 (13.5)	10 (17.9)	1.22 (0.577)	0.61-2.45	5 (9.3)	0.65 (0.365)	0.26-1.65
DOI at time of enrolment							
<=3	251 (17.0)	13 (23.2)	reference		8 (14.8)	reference	
> 3	1227 (83.0)	43 (76.8)	1.94 (0.134)	0.82-4.64	46 (85.2)	2.38 (0.101)	0.84-6.68
Outpatient referral							
not referred	940 (63.6)	33 (58.9)	reference		38 (70.4)	reference	
referred	535 (36.2)	23 (41.1)	1.39 (0.231)	0.81-2.37	15 (27.8)	0.74 (0.315)	0.40-1.34
missing values	3 (0.2)	-			1 (1.9)		

Inpatient referral not referred referred missing values	 1291 (87.3) 186 (12.6) 1 (0.1)	 50 (89.3) 6 (10.7) -	 reference 0.85 (0.700)	 0.36-1.98	 37 (68.5) 17 (31.5) -	 reference **2.88 (<0.001)**	 1.62-5.12
Any past medical history not present present missing values	 1291 (87.3) 115 (7.8) 72 (4.9)	 44 (78.6) 6 (10.7) 6 (10.7)	 reference 1.46 (0.381)	 0.62-3.44	 44 (81.5) 6 (11.1) 4 (7.4)	 reference 1.44 (0.399)	 0.61-3.39

IV fluid management							
	N (%)	**N (%) or mean (95% CI)**	**HR (p-value)**	**95%CI**	**N (%) or mean (95% CI)**	**HR (p-value)**	**95%CI**
Fluid administration prior to enrolment/ referral no fluid fluid administered missing values	 879 (59.5) 136 (9.2) 463 (31.3)	 34 (60.7) 10 (17.9) 12 (21.4)	 reference **2.52 (0.010)**	 1.24-5.11	 31 (57.4) 11 (20.4) 12 (22.2)	 reference **2.16 (0.029)**	 1.08-4.31
Amount of IV fluids (per 10 ml per kg) in previous 24h		2.38 (1.51-3.25)	 **1.10 (0.022)**	 1.01-1.19	6.56 (5.43-7.70)	 **1.33 (<0.001)**	 1.25-1.40
Number of days with IV fluid therapy (until previous day)		0.7 (0.5-0.9)	 1.17 (0.279)	 0.88-1.56	1.6 (1.3-1.9)	 **1.99 (<0.001)**	 1.57-2.52
IV fluid bolus in previous 24h* no bolus bolus missing values		 54 (96.4) 1 (1.8) 1 (1.8)			 37 (68.5) 17 (31.5) -	 reference **10.71 (<0.001)**	 5.95-19.27

* only evaluated for respiratory distress with fluid accumulation as endpoint

Table 4. Multivariable cox regression on risk factors for subsequent shock (N=40) and respiratory distress with fluid accumulation (N=52) (Patients with severe bleeding while under risk for shock were excluded from the analysis as well as the patients with the outcome on first hospital visit.)

Predictor	**Shock**		**Respiratory distress with fluid accumulation**	
	AHR (p-value)	**95%CI**	**AHR (p-value)**	**95%CI**
Demographics / anthropometry / referral history				
Age group >= 15 years < 15 years	 reference 1.92 (0.106)	 0.87-4.25	 reference **3.85 (0.001)**	 1.69-8.77
Sex male female	 reference **2.05 (0.031)**	 1.07-3.95		
BMI underweight normal overweight	 **2.62 (0.012)** reference 1.94 (0.145)	 1.24-5.54 0.80-4.70		
Inpatient referral no yes			 reference 1.81 (0.064)	 0.97-3.39
IV fluid management				

Fluid administration prior to enrolment/ referral no fluid fluid administered	 reference **2.60 (0.033)**	 1.08-6.27		
Amount of IV fluids (10 ml per kg) in previous 24 hour period	1.11 (0.059)	1.00-1.23	**1.18 (<0.001)**	1.10-1.28
Number of days with IV fluid therapy (until previous day)			**1.66 (0.004)**	1.17-2.34
Fluid bolus administered in previous 24 hour period no yes			 reference **2.90 (0.005)**	 1.37-6.12