Supplemental Digital Content 1

Table S1: Additional Baseline Demographics and Outcomes

Characteristic	Result
Height (cm), mean (SD)[a]	166.8 (11)
Secondary Contributor to Shock, n (%)	
Hypovolemia	132 (21.4)
Cardiac dysfunction	108 (17.5)
Metabolic derangement	61 (9.9)
Neurologic dysfunction	33 (5.4)
Intoxication	18 (2.9)
Trauma	7 (1.1)
Past Medical History, n (%)	
Hypertension	345 (56)
Diabetes	188 (30.5)
Immune Suppression	100 (16.2)
Heart Failure	95 (15.4)
Liver Disease	95 (15.4)
Hematologic malignancy	82 (13.3)
Metastatic cancer	76 (12.3)
CKD with no hemodialysis	76 (12.3)
CKD with hemodialysis	55 (8.9)
AIDS	14 (2.3)
Adverse Events, n (%)[b]	
Atrial Fibrillation	99 (16.1)
Ventricular Tachycardia	25 (4.1)
Myocardial Infarction	25 (4.1)
Peripheral Ischemia	7 (1.1)
Ventricular Fibrillation	5 (0.8)

[a]n = 11 missing values

[b]Time frame is within the first 24 hours of shock onset

Abbreviations: AIDS = acquired immunodeficiency syndrome; CKD = chronic kidney disease; SD = standard deviation

Table S2: Specific Vasopressor and Fluid Administration Data

Characteristic	Result (n=616)
Vasopressor Data[a, b]	
Norepinephrine Use	
0-3 hours, n (%)	349 (56.7)
Lowest infusion dose (mcg/min)	5 (2.8-10)
Highest infusion (mcg/min)	10 (5.3-20)
3-6 hours, n (%)	402 (65.3)
Lowest infusion dose (mcg/min)	7.4 (4-14.4)
Highest infusion (mcg/min)	10 (5.1-20)
6-12 hours, n (%)	466 (75.6)
Lowest infusion dose (mcg/min)	5.3 (2-12)
Highest infusion (mcg/min)	11.9 (6-23.1)
12-24 hours, n (%)	472 (76.6)
Lowest infusion dose (mcg/min)	4.6 (2-11.2)
Highest infusion (mcg/min)	11.9 (5.5-24)
Phenylephrine Use	
0-3 hours, n (%)	45 (7.3)
Lowest infusion dose (mcg/min)	50 (22.5-100)
Highest infusion (mcg/min)	80 (45-144.8)
3-6 hours, n (%)	49 (8)
Lowest infusion dose (mcg/min)	50 (20-100)
Highest infusion (mcg/min)	100 (50-162.5)
6-12 hours, n (%)	67 (10.9)
Lowest infusion dose (mcg/min)	50 (25-125)
Highest infusion (mcg/min)	100 (58.8-200)
12-24 hours, n (%)	75 (12.2)
Lowest infusion dose (mcg/min)	75 (25.9-150)
Highest infusion (mcg/min)	150 (80-270)
Epinephrine Use	
0-3 hours, n (%)	26 (4.2)
Lowest infusion dose (mcg/min)	8 (5-10)
Highest infusion (mcg/min)	10 (5.8-19.3)
3-6 hours, n (%)	18 (2.9)
Lowest infusion dose (mcg/min)	5.7 (3.6-13.9)
Highest infusion (mcg/min)	8.6 (5-15.3)
6-12 hours, n (%)	34 (5.5)
Lowest infusion dose (mcg/min)	4.8 (1.7-10)
Highest infusion (mcg/min)	9.4 (3.9-13)
12-24 hours, n (%)	42 (6.8)
Lowest infusion dose (mcg/min)	3 (1-10)
Highest infusion (mcg/min)	7.3 (3.2-16)

Dopamine Use		
0-3 hours, n (%)		22 (3.6)
Lowest infusion dose (mcg/min)		5 (2.8-10)
Highest infusion (mcg/min)		7 (4.8-15)
3-6 hours, n (%)		22 (3.6)
Lowest infusion dose (mcg/min)		4 (1.5-7.1)
Highest infusion (mcg/min)		6 (3-11)
6-12 hours, n (%)		17 (2.8)
Lowest infusion dose (mcg/min)		5 (1.5-10)
Highest infusion (mcg/min)		8 (3.8-20)
12-24 hours, n (%)		14 (2.3)
Lowest infusion dose (mcg/min)		5 (1.8-11.5)
Highest infusion (mcg/min)		13.5 (3-20)
Vasopressin Use, n (%)		
0-3 hours		57 (9.3)
3-6 hours		88 (14.3)
6-12 hours		154 (25)
12-24 hours		190 (30.8)
Fluid Data[a, b]		
Crystalloid Products (mL)		
0-3 hours	n=460	1068.5 (484.3-2000)
3-6 hours	n=405	500 (173-1000)
6-12 hours	n=459	726 (353-1196)
12-24 hours	n=463	1085 (579-1881)
Total over 24 hours	n=558	3080.5 (1640-4939.5)
Colloid Products (mL)		
0-3 hours	n=39	250 (150-500)
3-6 hours	n=38	348.5 (239.5-514)
6-12 hours	n=63	500 (100-581)
12-24 hours	n=76	315 (200-616.5)
Total over 24 hours	n=140	500 (250-750)
Blood Products[c] **(mL)**		
0-3 hours	n=35	330 (300-660)
3-6 hours	n=45	350 (300-680)
6-12 hours	n=83	350 (300-600)
12-24 hours	n=88	352 (300-600)
Total over 24 hours	n=167	550 (323-840)

[a]Timeframe is within the first 24 hours of shock onset unless otherwise stated

[b]Data presented as median (interquartile range) unless otherwise stated

[c]Blood product fluid volume consists of packed red blood cells, platelets and fresh frozen plasma

Abbreviations: NEE = norepinephrine equivalents

Table S3: Low Versus High Vasopressor Infusion Dose Use

Characteristic[a,b]	Low Vasopressor Infusion Dose Use (<15 mcg/min NEE) (n=426)	High Vasopressor Infusion Dose Use (≥15 mcg/min NEE) (n=190)	P Value
Demographic Data			
Age (years), mean (SD)	63.6 ± 15.2	64 ± 15.4	0.79
Weight (kg), mean (SD)[c]	79.9 ± 28	86.3 ± 29.9	0.01
Height (cm), mean (SD)[d]	166.2 ± 11.1	168.2 ± 10.7	0.04
Male, n (%)	224 (52.6)	113 (59.5)	0.11
Race, n (%)			
Caucasian	266 (62.4)	103 (54.2)	0.05
African American	61 (14.3)	48 (25.3)	0.001
Other	26 (6.2)	6 (3.1)	0.13
Not reported	73 (17.1)	33 (17.4)	1
APACHE III mean (SD)	89.7 ± 25.6	111.6 ± 28	<0.0001
SOFA	9 (7-11)	11 (8-13)	<0.001
Location at Start of Shock, n (%)			
ED	188 (44.1)	85 (44.7)	0.89
ICU	158 (37.1)	55 (28.9)	0.05
Floor	70 (16.4)	42 (22.1)	0.09
PACU	3 (0.7)	1 (0.5)	1
Other	7 (1.6)	7 (3.7)	0.14
ICU Type, n (%)			
Medical	237 (55.6)	105 (55.3)	0.92
Medical/Surgical	91 (21.4)	48 (25.3)	0.29
Surgical	42 (9.9)	13 (6.8)	0.23
Cardiothoracic	19 (4.5)	14 (7.4)	0.14
Other	37 (8.6)	10 (5.2)	0.14
Secondary Contributor to Shock, n (%)			
Hypovolemia	87 (20.4)	45 (23.7)	0.36
Cardiac dysfunction	72 (16.9)	36 (18.9)	0.54
Metabolic derangement	38 (8.9)	23 (12.1)	0.22
Neurologic dysfunction	23 (5.4)	10 (5.3)	1
Intoxication	11 (2.6)	7 (3.7)	0.45
Trauma	4 (0.9)	3 (1.6)	0.68
Length of Stay Prior to Shock Onset, n (%)			
0-2 days	302 (70.9)	123 (64.7)	0.12
3-7 days	61 (14.3)	29 (15.3)	0.76
8-14 days	29 (6.8)	17 (8.9)	0.35
>14 days	34 (8)	21 (11.1)	0.22

Past Medical History, n (%)					
Hypertension		246 (57.7)		99 (52.1)	0.19
Diabetes		128 (30)		60 (31.6)	0.7
Immune Suppression		71 (16.7)		29 (15.3)	0.66
Heart Failure		67 (15.7)		28 (14.7)	0.75
Hematologic malignancy		54 (12.6)		28 (14.8)	0.39
Metastatic cancer		47 (11)		29 (15.3)	0.17
CKD with no hemodialysis		52 (12.2)		24 (12.6)	0.89
CKD with hemodialysis		37 (8.7)		18 (9.5)	0.75
Liver disease		48 (11.3)		47 (24.7)	<0.0001
AIDS		9 (2.1)		5 (2.6)	0.77
Lactate (mg/dL)					
Highest in the peri-shock period[e,f]		3.1 (1.5-4.4)		3.2 (1.8-5.6)	0.52
Highest in the 0-24 hours after shock onset[g]		2.4 (1.4-4.1)		4.6 (2.3-8.6)	<0.0001
Vasopressor Data					
Vasopressor use, n (%)					
Norepinephrine		384 (90.1)		189 (99.5)	<0.0001
Vasopressin		85 (20)		152 (80)	<0.0001
Phenylephrine		59 (13.8)		55 (28.9)	<0.0001
Epinephrine		14 (3.3)		49 (25.8)	<0.0001
Dopamine		22 (5.2)		16 (8.4)	0.1
Total vasopressor amount (mg NEE)		7.4 (3.8-12.8)		36.5 (28.1-56.7)	<0.0001
Vasopressor infusion dose (mcg/min NEE)		5.1 (2.5-8.9)		25.3 (19.5-39.4)	<0.0001
Fluid Data					
Pre-shock fluid[h] (mL)	n=271	1088 (264-2150)	n=110	1000 (300-1622)	0.33
Total fluid[i, j] (mL)	n=397	3467 (2000-5341)	n=185	3391 (1620-5348)	0.53
Other Medications					
Hydrocortisone use (≥200 mg/day), n (%)		107 (25.1)		73 (38.4)	0.0008
Propofol or Dexmedetomidine Use, n (%)					
Ever received within first 24 hours		196 (46)		107 (56.3)	0.02
Outcomes Data					
Mechanical ventilation within first 24 hours, n (%)		234 (54.9)		148 (77.9)	<0.001
ICU LOS (days)	n=423	5 (3-11)	n=190	6 (3-12)	0.18
Hospital LOS (days)	n=424	13 (7-23)	n=189	12 (6-21.5)	0.41
Mortality, n (%)		95 (22.3)		96 (50.5)	<0.0001
Adverse Events, n (%)					
Atrial Fibrillation		69 (16.2)		30 (15.8)	

Ventricular Tachycardia	11 (2.6)	14 (7.4)
Myocardial Infarction	13 (3.1)	12 (6.3)
Peripheral Ischemia	5 (1.2)	2 (1.1)
Ventricular Fibrillation	1 (0.2)	4 (2.1)

[a]Data presented as median (interquartile range) unless otherwise stated

[b]Timeframe is within the first 24 hours of shock onset unless otherwise stated

[c]n = 2 missing values (low vasopressor infusion dose); n = 1 missing value (high vasopressor infusion dose)

[d]n = 6 missing values (low vasopressor infusion dose); n = 5 missing values (high vasopressor infusion dose)

[e]n = 37 missing values (low vasopressor infusion dose); n = 13 missing values (high vasopressor infusion dose)

[f]Highest lactate in the peri-shock period is defined as the highest lactate in the 12 hours before and 12 hours following shock onset

[g]n = 47 missing values (low vasopressor infusion dose); n = 5 missing values (high vasopressor infusion dose)

[h]Pre-shock fluid assessment is the period within the 12 hours prior to shock onset

[i]Crystalloid plus colloid fluid plus blood product fluid volume

[j]Blood product fluid volume consists of packed red blood cells, platelets and fresh frozen plasma

Abbreviations: AIDS = acquired immunodeficiency syndrome; APACHE = acute physiology and chronic health evaluation; CKD = chronic kidney disease; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; NEE = norepinephrine equivalents; PACU = post-anesthesia care unit; SD = standard deviation; SOFA = sequential organ failure assessment

Table S4. Primary analysis results

Analysis[a]	Odds Ratio (95% CI)
Vasopressor dose intensity exposure at 0-6 hours[b]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.39 (1.08, 1.81)
With 1000 mL fluid administration	1.26 (1.04, 1.53)
With 2000 mL fluid administration	1.14 (0.98, 1.34)
With 3000 mL fluid administration	1.04 (0.88, 1.21)
Vasopressor dose intensity exposure at 0-24 hours[c]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.33 (1.16, 1.53)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[d]	
Never high	ref.
Early high/late low	0.95 (0.39, 2.31)
Early low/late high	2.53 (1.41, 4.57)
Always high	2.84 (1.59, 5.07)

[a]Each model is adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease

[b]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.019) for the analysis at the 0-6-hour time point.

[c]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.137) for the analysis at the 0-24-hour time point.

[d]Vasopressor dosing intensity (VDI) was categorized for the time periods of 0-6 and 0-24 hours as low-dose vasopressor infusion (VDI < 15 mcg/min NEE) or high-dose vasopressor infusion (VDI ≥ 15 mcg/min NEE). We then classified the VDI across the two time periods into four categories: 1) never high (VDI was < 15 mcg/min NEE for both time periods); 2) early high and late low, (VDI was ≥ 15 mcg/min NEE during the first 6 hours, but titrated < 15 mcg/min NEE by the end of the 24 hour period); 3) early low and late high (VDI was < 15 mcg/min NEE for the first 6 hours, but titrated ≥ 15 mcg/min NEE by the end of the 24 hour period); and 4) always high (VDI was ≥ 15 mcg/min NEE during the first 6 six hours and remained elevated for the entire 24 hour period).

Abbreviations: APACHE = Acute physiology and chronic health evaluation; CI = confidence interval; ICU = intensive care unit; NEE = norepinephrine equivalents; ref. = reference category

Table S5. Absolute changes in mortality across categories of fluid and vasopressor exposure intensity at 0-6 hours after shock onset

Characteristic[a, b, c]	Mortality (%)	Difference (95% CI)
No fluid		
5 mcg/min NEE	31.6	ref.
15 mcg/min NEE	37.4	5.8 (1.2, 10.5)
25 mcg/min NEE	43.6	12.1 (2.3, 21.9)
35 mcg/min NEE	50.1	18.5 (3.4, 33.6)
1000 mL fluid		
5 mcg/min NEE	30.7	ref.
15 mcg/min NEE	34.7	3.9 (0.6, 7.4)
25 mcg/min NEE	38.9	8.2 (1.1, 15.4)
35 mcg/min NEE	43.0	12.6 (1.5, 23.7)
2000 mL fluid		
5 mcg/min NEE	29.8	ref.
15 mcg/min NEE	32.0	2.2 (-0.4, 4.8)
25 mcg/min NEE	34.3	4.6 (-0.8, 9.9)
35 mcg/min NEE	36.7	6.9 (-1.3, 15.3)
3000 mL fluid		
5 mcg/min NEE	28.9	ref.
15 mcg/min NEE	29.4	0.5 (-1.9, 3.1)
25 mcg/min NEE	30.0	1.1 (-3.9, 6.3)
35 mcg/min NEE	30.6	1.7 (-6.1, 9.5)

[a]Estimates are derived from a logistic regression model of cumulative fluid administration and average vasopressor dose (in norepinephrine equivalents) during the initial 0-6-hour period after shock.

[b]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.019).

[c]The model is adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease.

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; ICU = intensive care unit; NEE = norepinephrine equivalents; ref. = reference rate

Table S6. Results of sensitivity analysis

Analysis[a]	Odds Ratio (95% CI)
Random effects analysis[b]	
Vasopressor dose intensity exposure at 0-6 hours[c]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.40 (1.08, 1.83)
With 1000 mL fluid administration	1.27 (1.05, 1.55)
With 2000 mL fluid administration	1.15 (0.98, 1.34)
With 3000 mL fluid administration	1.04 (0.88, 1.22)
Vasopressor dose intensity exposure at 0-24 hours[d]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.37 (1.19, 1.57)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[e]	
Never high	ref.
Early high/late low	0.95 (0.39, 2.33)
Early low/late high	2.55 (1.41, 4.63)
Always high	2.91 (1.62, 5.25)
Analysis adjusted for baseline fluid administration[f]	
Vasopressor dose intensity exposure at 0-6 hours[g]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.59 (1.14, 2.2)
With 1000 mL fluid administration	1.36 (1.07, 1.73)
With 2000 mL fluid administration	1.17 (0.96, 1.42)
With 3000 mL fluid administration	1.00 (0.81, 1.24)
Vasopressor dose intensity exposure at 0-24 hours[h]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.48 (1.21, 1.81)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[e]	
Never high	ref.
Early high/late low	0.91 (0.32,2.63)
Early low/late high	3.24 (1.51,6.98)
Always high	3.67 (1.67,8.06)
Analysis adjusted for baseline mean arterial pressure	
Vasopressor dose intensity exposure at 0-6 hours[i]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.43 (1.06, 1.91)
With 1000 mL fluid administration	1.29 (1.04, 1.60)
With 2000 mL fluid administration	1.16 (0.98, 1.39)
With 3000 mL fluid administration	1.05 (0.87, 1.27)
Vasopressor dose intensity exposure at 0-24 hours[j]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.57 (1.29, 1.89)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[e]	
Never high	ref.
Early high/late low	1.23 (0.47, 3.23)
Early low/late high	2.87 (1.47, 5.60)
Always high	3.24 (1.64, 6.39)

Analysis adjusted for baseline mean arterial pressure and fluid administration	
Vasopressor dose intensity exposure at 0-6 hours[k]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.58 (1.14, 2.19)
With 1000 mL fluid administration	1.36 (1.07, 1.73)
With 2000 mL fluid administration	1.17 (0.96, 1.42)
With 3000 mL fluid administration	1.01 (0.81, 1.25)
Vasopressor dose intensity exposure at 0-24 hours[l]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.48 (1.21, 1.81)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[e]	
Never high	ref.
Early high/late low	1.01 (0.35, 2.94)
Early low/late high	3.24 (1.51, 6.97)
Always high	3.63 (1.65, 7.95)
Analysis restricted to patients surviving past the first 24 hours[m]	
Vasopressor dose intensity exposure at 0-6 hours[n]	
Increase in vasopressor rate (per 10 mcg/min NEE)	
With no fluid administration	1.36 (1.05, 1.77)
With 1000 mL fluid administration	1.23 (1.02, 1.50)
With 2000 mL fluid administration	1.12 (0.96, 1.31)
With 3000 mL fluid administration	1.02 (0.87, 1.19)
Vasopressor dose intensity exposure at 0-24 hours[o]	
Increase in vasopressor rate (per 10 mcg/min NEE)	1.32 (1.14, 1.52)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[e]	
Never high	ref.
Early high/late low	0.74 (0.29,1.91)
Early low/late high	2.45 (1.34,4.46)
Always high	2.69 (1.49,4.84)

[a]Each model is adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease

[b]Random effects logistic regression with random intercept term for center.

[c]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.019) for the analysis at the 0-6-hour time point. ICC for center effect was 0.013 (95%CI 0.00-0.35).

[d]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.181) for the analysis at the 0-24-hour time point. ICC for center effect was 0.015 (95%CI 0.00-0.32).

[e]Vasopressor dosing intensity (VDI) was categorized for the time periods of 0-6 and 0-24 hours as low-dose vasopressor infusion (VDI < 15 mcg/min NEE) or high-dose vasopressor infusion (VDI ≥ 15 mcg/min NEE). We then classified the VDI across the two time periods into four categories: 1) never high (VDI was < 15 mcg/min NEE for both time periods); 2) early high and late low, (VDI was ≥ 15 mcg/min NEE during the first 6 hours, but titrated < 15 mcg/min NEE by the end of the 24 hour period); 3) early low and late high (VDI was < 15 mcg/min NEE for the first 6 hours, but titrated ≥ 15 mcg/min NEE by the end of the 24 hour period); and 4) always high (VDI was ≥ 15 mcg/min NEE during the first 6 six hours and remained elevated for the entire 24 hour period).

[f]Logistic regression model adjusted for baseline fluid administration (n=386).

[g]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.007) for the analysis at the 0-6-hour time point.

[h]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.215) for the analysis at the 0-24-hour time point.

[i]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.046) for the analysis at the 0-6-hour time point.

[j]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.487) for the analysis at the 0-24-hour time point.

[k]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.009) for the analysis at the 0-6-hour time point.

[l]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.241) for the analysis at the 0-24-hour time point.

[m]Logistic regression model restricted to survivors of the first 24 hours (n=607). Only 9/616 (1.5%) of patients died within the first 24 hours.

[n]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.025) for the analysis at the 0-6-hour time point.

[o]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.167) for the analysis at the 0-24-hour time point.

Abbreviations: APACHE = Acute physiology and chronic health evaluation; CI = confidence interval; ICU = intensive care unit; NEE = norepinephrine equivalents; ref. = reference category

Table S7. Analysis of vasopressor dosing intensity expressed as mcg/kg/min

Analysis[a]	Odds Ratio (95% CI)
Vasopressor dose intensity exposure at 0-6 hours[b]	
Increase in vasopressor rate (per 0.15 mcg/kg/min NEE)	
With no fluid administration	1.39 (1.06, 1.81)
With 15 mL/kg fluid administration	1.24 (1.02, 1.49)
With 30 mL/kg fluid administration	1.11 (0.95, 1.29)
With 45 mL/kg fluid administration	0.99 (0.83, 1.18)
Vasopressor dose intensity exposure at 0-24 hours[c]	
Increase in vasopressor rate (per 0.15 mcg/kg/min NEE)	1.35 (1.17, 1.56)
Vasopressor dose intensity titration categories at 0-6 and 0-24 hours[d]	
Never high	ref.
Early high/late low	0.46 (0.18, 1.14)
Early low/late high	2.73 (1.56, 4.78)
Always high	2.45 (1.59, 5.07)

[a]Each model is adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease

[b]There was a significant interaction between vasopressor exposure and fluid administration (Likelihood ratio test p=0.025) for the analysis at the 0-6-hour time point.

[c]There was no significant interaction observed between vasopressor exposure and fluid administration (Likelihood ratio test p=0.758) for the analysis at the 0-24-hour time point.

[d]Vasopressor dosing intensity (VDI) was categorized for the time periods of 0-6 and 0-24 hours as low-dose vasopressor infusion (VDI < 0.2 mcg/kg/min NEE) or high-dose vasopressor infusion (VDI ≥ 0.2 mcg/kg/min NEE). We then classified the VDI across the two time periods into four categories: 1) never high (VDI was < 0.2 mcg/kg/min NEE for both time periods); 2) early high and late low, (VDI was ≥ 0.2 mcg//kg/min NEE during the first 6 hours, but titrated < 0.2 mcg/kg/min NEE by the end of the 24 hour period); 3) early low and late high (VDI was < 0.2 mcg/kg/min NEE for the first 6 hours, but titrated ≥ 0.2 mcg/kg/min NEE by the end of the 24 hour period); and 4) always high (VDI was ≥ 0.2 mcg/kg/min NEE during the first 6 six hours and remained elevated for the entire 24 hour period).

Abbreviations: APACHE = Acute physiology and chronic health evaluation; CI = confidence interval; ICU = intensive care unit; NEE = norepinephrine equivalents; ref. = reference category

Figure S1: Flow diagram of patient enrollment

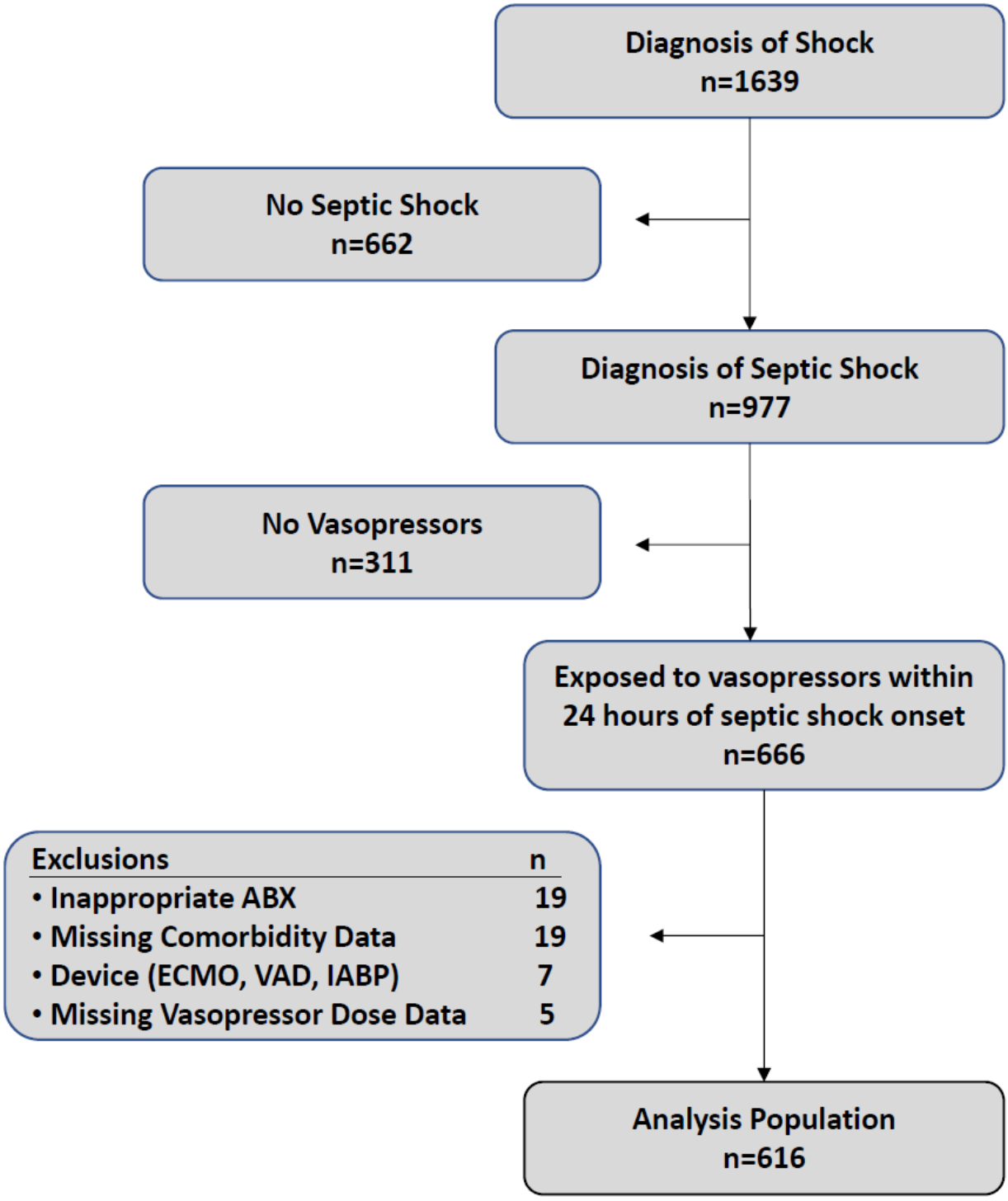


Figure S2. Predicted mortality as a function of the average vasopressor dose over the initial 24 hours after shock onset

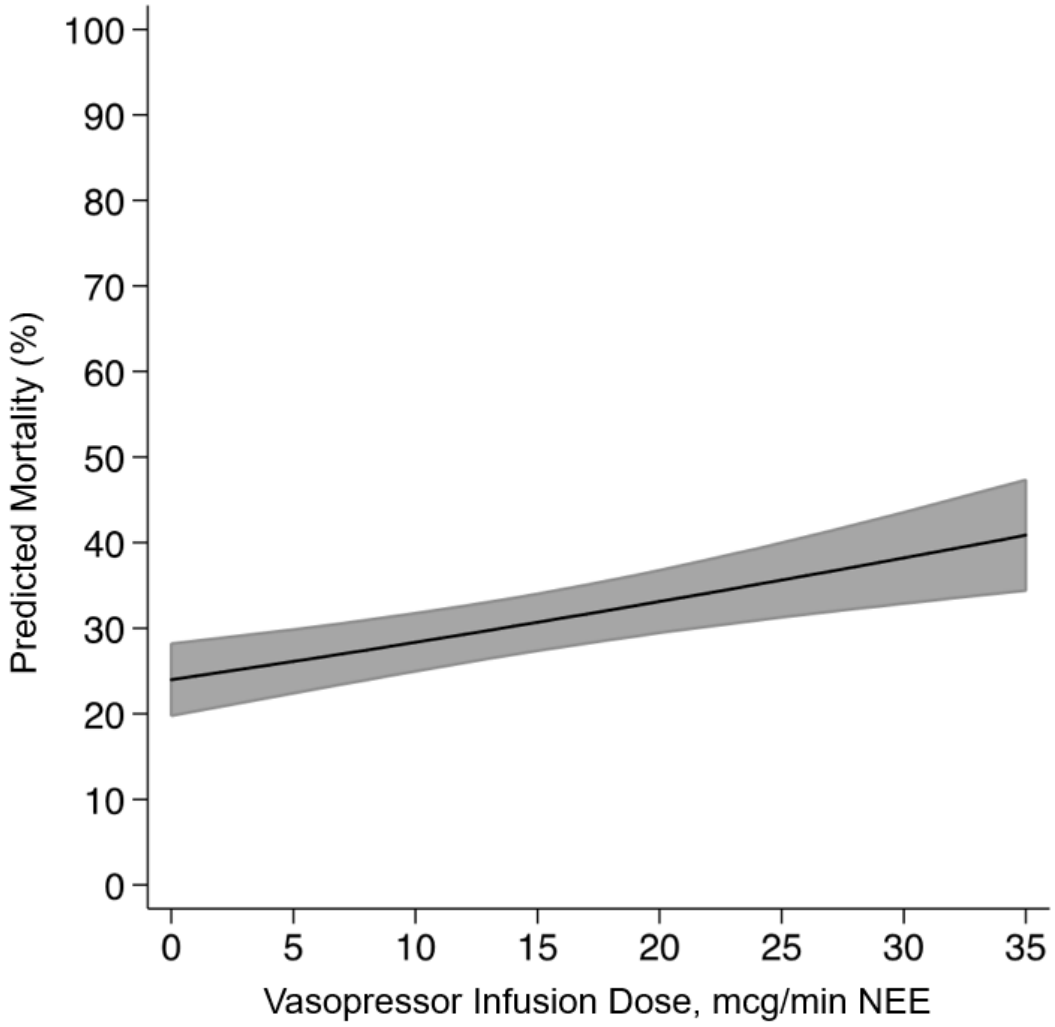
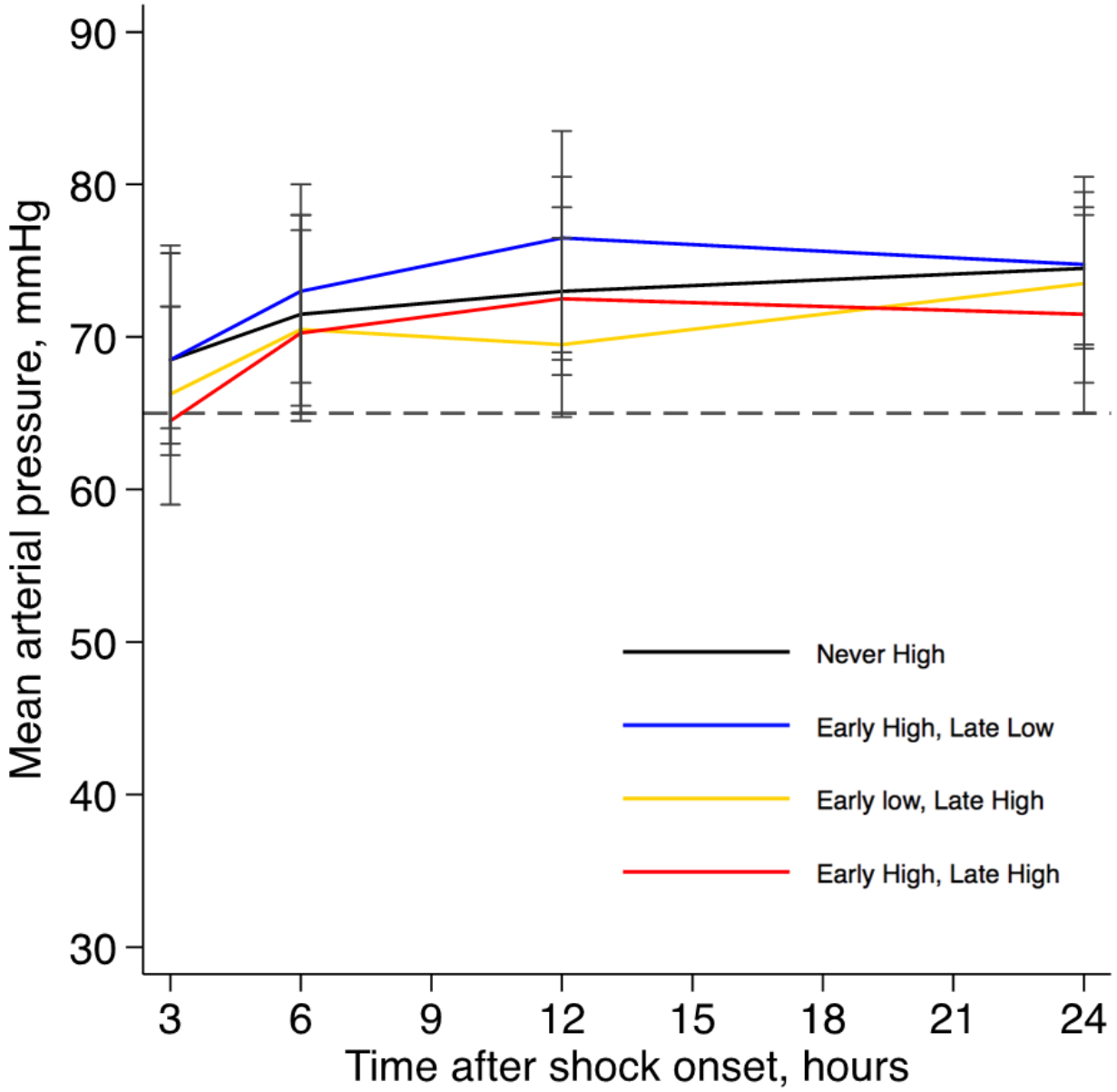


Figure depicts adjusted mortality risk as a function of the median vasopressor infusion dose over the initial 24 hours after shock onset (odds ratio: 1.33 (1.16, 1.53) per 10 mcg/min NEE increase.

Model adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease.

Abbreviations: APACHE = Acute physiology and chronic health evaluation; ICU = intensive care unit; NEE = norepinephrine equivalents

Figure S3. Mean arterial pressure during the initial 24 hours after shock onset



The figure shows the median mean arterial pressure over each time interval, stratified by vasopressor titration category defined as follows: vasopressor dosing intensity (VDI) was categorized for the time periods of 0-6 and 0-24 hours as low-dose vasopressor infusion (VDI < 0.2 mcg/kg/min NEE) or high-dose vasopressor infusion (VDI ≥ 0.2 mcg/kg/min NEE). We then classified the VDI across the two time periods into four categories: 1) never high (VDI was < 0.2 mcg/kg/min NEE for both time periods); 2) early high and late low, (VDI was ≥ 0.2 mcg/kg/min NEE during the first 6 hours, but titrated < 0.2 mcg/kg/min NEE by the end of the 24 hour period); 3) early low and late high (VDI was < 0.2 mcg/kg/min NEE for the first 6 hours, but titrated ≥ 0.2 mcg/kg/min NEE by the end of the 24 hour period); and 4) always high (VDI was ≥ 0.2 mcg/kg/min NEE during the first 6 six hours and remained elevated for the entire 24 hour period).

Figure S2. Predicted mortality as a function of the average vasopressor dose over the initial 24 hours after shock onset

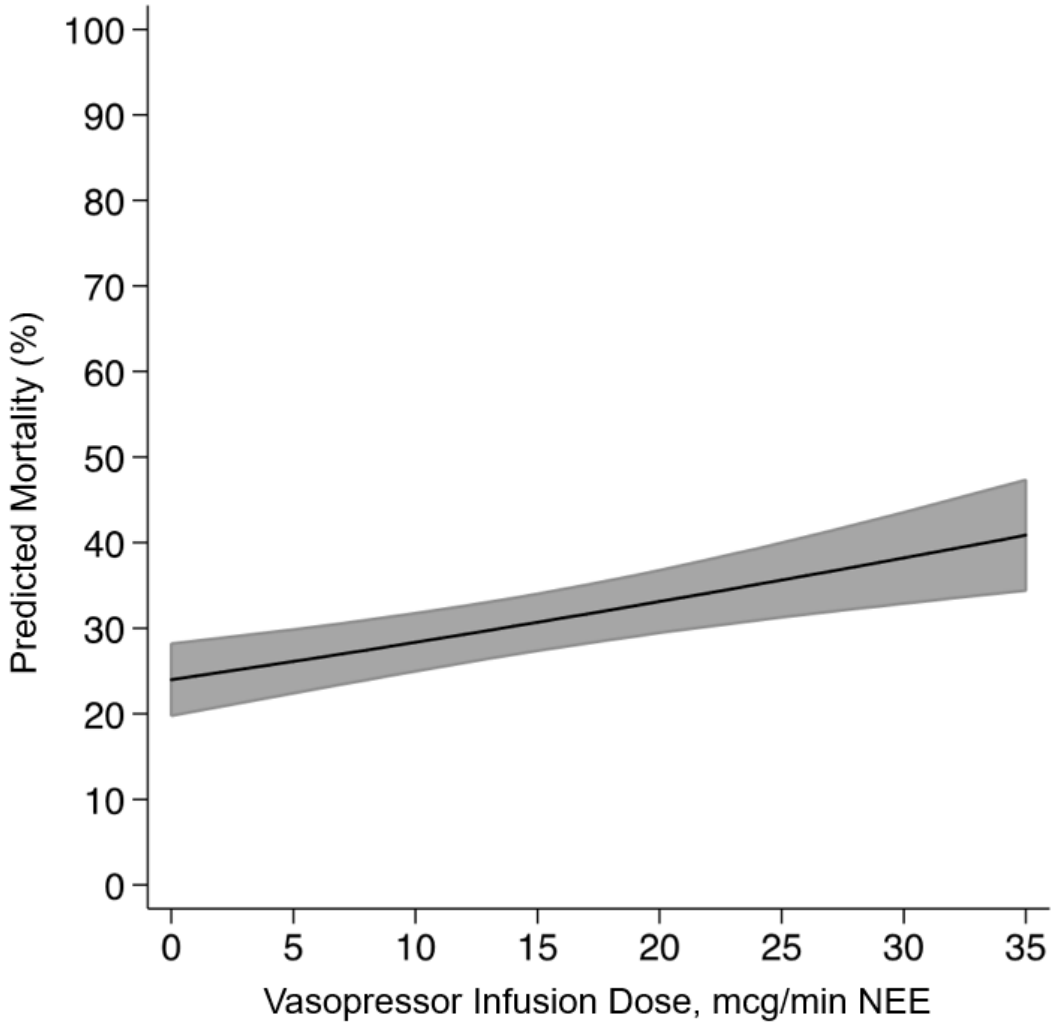


Figure depicts adjusted mortality risk as a function of the median vasopressor infusion dose over the initial 24 hours after shock onset (odds ratio: 1.33 (1.16, 1.53) per 10 mcg/min NEE increase.

Model adjusted for age, sex, height, weight, APACHE III score, mechanical ventilation, corticosteroid administration, location of shock onset, hospital length of stay prior to shock onset, treating ICU type, heart failure, metastatic cancer, diabetes mellitus, hematologic cancer, renal disease, and liver disease.

Abbreviations: APACHE = Acute physiology and chronic health evaluation; ICU = intensive care unit; NEE = norepinephrine equivalents

Protocol S1

Study:	**Observation of VariatiOn in fLUids adMinistEred and CHaracterizAtion of vaSoprEssor Requirements in Shock**
Acronym:	**VOLUME/CHASERS**
Version:	**2.2.1**
Date:	**September 27, 2017**
Principal Investigator:	**JT Tina Chen, MD**

Site Investigator Signature

Date

Table of Contents

1. ABBREVIATIONS & DEFINITION

1.1 Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CHASERS	Characterization of vasopressor requirements in shock
BP	Blood pressure
CO	Cardiac output
CVP	Central venous pressure
DNR	Do not resuscitate
ED	Emergency department
ICU	Intensive care unit
IVC	Inferior vena cava
MAP	Mean arterial pressure
OR	Operating room
PaOP	Pulmonary artery occlusion pressure
PLR	Passive leg raise
SCCM	Society of Critical Care Medicine
SOFA	Sequential organ failure assessment
SSC	Surviving Sepsis Campaign
SV	Stroke volume
SVV	Stoke volume variability
UOP	Urine output
VOLUME	Observation of variation in fluids administered in shock

1.2 Definitions

Dynamic physiologic measurement: A change in hemodynamic measurements in response to intravascular volume expansion or changes in intrathoracic pressure.

Home: Level of residence or health care facility where the patient was residing prior to hospital admission.

Length of stay: discharge hospital day minus hospital admission day.

Maintenance fluids: Any IV fluid (without medication) infusing at a rate greater than your institution's standard for KVO.

Passive leg raise test: A postural maneuver in which a patient is moved from a 45-degree semi-recumbent position to supine with legs raised 45-degrees to mimic the effect of volume expansion.

Renal replacement therapy (RRT): Intermittent hemodialysis, continuous renal replacement therapy, continuous veno-venous hemofiltration.

Shock: Systolic pressure less than 90 mmHg, or requiring vasopressor to maintain a mean arterial blood pressure greater than 65 mmHg

Start of Shock: the time point when shock is identified.

Static physiologic measurement: A hemodynamic measurement taken at a single point in time.

Hospital day: The day of admission is the hospital day 1.

Study hospital: Defined as the hospital where the patient was enrolled.

2. PROTOCOL SUMMARY

Title: Observation of VariatiOn in fLUids adMinistEred in Shock (VOLUME) and CHaracterizAtion of vaSoprEssor Requirements in Shock (CHASERS)

Objectives: to conduct a multicenter observational cohort study to determine the variability in fluid resuscitation in shock in a broad range of areas in hospitals and treatment areas.

1. To characterize the methods used to guide volume resuscitation and vasopressor use in patients with shock and determine the frequency by which clinicians use static physiologic data, dynamic physiologic data or empiric clinical exam methods in their evaluation of shock to determine fluid responsiveness and vasopressor use (Table 1).

2. To determine whether the use of dynamic physiology methods, static physiology methods, or other empiric clinical exam methods to assess volume resuscitation in patients with shock are associated with variable fluid requirements and change in SOFA score. We hypothesize that the volume of fluid and dose of vasopressors administered during the first 24 hours of shock and subsequent organ failure will vary depending on whether dynamic, static or other empiric clinical exam methods were used to determine fluid responsiveness and vasopressor use.

3. To explore using propensity score analysis whether the use of dynamic or static methods to determine volume resuscitation vs. other empiric clinical exam methods lead to improved hospital survival in shock.

Table 1: Methods commonly used in assessing volume status and prediction of fluid responsiveness.

Methods	Static Physiology Measurement	Dynamic Physiology Measurement	Empiric/Clinical Exam
Definition	A hemodynamic measurement taken at a single point in time.	A change in hemodynamic measurement in response to intravascular volume expansion or changes in intrathoracic pressure	Use of any other non-physiologic measurements to determine fluid responsiveness. This may include following weight-based guidelines for fluids, focused physical exam, laboratory data, etc.
Examples	CVP PaOP Global end diastolic volume	Passive leg raise test or fluid challenge with change in CO or SV assessed by ultrasound, pulse contour analysis, impedance, etc. Pulse pressure variation IVC variation with respiration	Vital signs Cardiopulmonary exam Capillary refill Peripheral pulse evaluation Skin exam

			Serum lactate level Weight-based fluid delivery

Goal: The overall goal is to conduct a multicenter observational cohort across a broad range of hospitals, including patients in the emergency department, ICU and non-ICU areas to determine the variability to in shock resuscitation and the modalities used to determine the amount of fluids and vasopressor to administer. We will explore for outcome differences associated with this variability.

Study Design: A four-week large prospective observational study across multiple hospitals to determine the amount of fluids and vasopressors administered within 24 hours of meeting study criteria for shock and whether dynamic or static measures of fluid responsiveness were obtained. We will allow participation of sites who are able to collect data for shorter periods of time.

Inclusion Criteria: (Patient must meet all inclusion criteria):

1. Age ≥ 18 years admitted to the participating hospital.
2. Patients in the emergency department, intensive care unit, PACU, or any hospital floor. For patients not in the ICU, there must be plans to transfer to an intensive care unit when an ICU bed is available for patient.
3. Patients with shock as defined by:
   - Need for vasopressor therapy (at any dose) to keep MAP >65 mmHg
     Or
   - Systolic BP < 90 mmHg

Exclusion Criteria: (A Patient who meets any one of the following criteria will be excluded from the study):

1. Patients previously enrolled into this study.
2. Patients who were in the operating room at time of shock and fluid bolus.
3. Patients admitted to an ICU after cardiac surgery. Patients with primarily cardiogenic shock as etiology for their shock
4. Patients transferred from another hospital or emergency room to the study hospital.

3. PROTOCOL DESCRIPTION

3.1 Background

Fluid resuscitation is a mainstay of treatment for most patients with shock. In conjunction with antibiotics, fluids and hemodynamic support have been shown to be an essential component of sepsis treatment, and early fluids were administrated as part of both the standard and interventional arms of the large trials of early goal directed therapy in sepsis.[1,2] While clinical guidelines support the use of 30 cc/kg as initial resuscitation, there appears to be substantial variation in practice between clinicians for determining exactly how much fluids to administer in shock.[3-5] In two French prospective trials, there were high center to center variations on methods of assessing fluid responsiveness. Common triggers for the early fluid

bolus were from clinical exam changes such as low blood pressure, UOP, tachycardia or high lactate. Less than a quarter of fluid bolus were given as a result of any physiologic assessment, whether it be static or dynamic measurements.[5] While adequate volume resuscitation is an important part of treatment paradigms to allow for adequate preload and cardiac output, excessive volume resuscitation appears to be associated with organ failure and worsened clinical outcomes.[6,7] An important part of this variation appears to be the decision of how to determine the patient's hemodynamic response to additional fluid administration. While many studies show that dynamic measures such as the passive leg raise test or volume expansion with non-invasive measures of stroke volume variability are good predictors of response to cardiac output to fluid challenges, there are few studies to predict whether the volume of fluid administered or important clinical outcomes are related to the use of these dynamic measures.[8-10] For example, in a small randomized controlled trial, dynamic physiologic measurement using pulse pressure variation and passive leg raise with stroke volume variation lowered the total fluid administered in patients with septic shock as compared with using static measurement (CVP); however, it did not hasten shock resolution nor conferred mortality.[11]

In recognizing the practice variability and the lack of robust data to indicate the clinical benefits for one method over another, current guidelines in shock resuscitation agree on the need for determination of fluid responsiveness but give flexibility in terms of methods used to determine the need for additional fluid administration. For example, the sepsis CMS core measures (SEP-1) requires that within 6 hours of initial fluid resuscitation with 30 cc/kg, there is a repeat assessment of volume status and perfusion which can be a focused physical exam, or 2 physiologic measures that include both static physiological measures like central venous pressure or dynamic physiologic measures like bedside ultrasound or passive leg raise test.[12] The most recent Surviving Sepsis Campaign recommends reassessment of additional fluid administration after the initial 30 cc/kg bolus with a clinical exam and *available* physiologic variables which include vital signs. It is also recommended that dynamic physiologic parameters be used over static physiologic measures when available but gives this a weak recommendation with low quality of evidence.

As such, there is great variability in the methods used to determine fluid administration beyond the initial bolus. Whether empiric non-physiologic exam-based strategies or static/dynamic physiology-based strategies are used to guide the decision on how much fluids to give in shock can depend on the patient's condition and co-morbidities, preferences of clinicians, and the expertise and availability of specific equipment to determine physiologic targets. This natural variability can be exploited with statistical approaches such as propensity score to create a quasi-experimental state to examine variable outcomes from the use of static or dynamic measures of fluid responsiveness in septic shock.

Additionally, there is very limited literature to guide clinicians in how to dose and titrate vasopressor medicines to achieve optimal hemodynamic endpoints while minimizing associated harms. This has immediate impact within critical care given the high mortality attributable to septic shock while also acknowledging the associated mortality with commonly encountered adverse events associated with the vasopressor administration, specifically acute atrial fibrillation. Indeed, it could be that there is little difference between agents with regards to the ability to restore perfusion, but the discriminating factors for drug selection may lie in the comparative safety between agents, especially within subpopulations of septic shock patients. In addition, many patients, particularly the elderly, have comorbidities requiring the need for oral antihypertensive therapies and the effect of these medications prior to admission likely complicates clinical assessment and the administration of appropriate resuscitation therapies. In the setting of vasopressor use, there is little published evidence guiding clinicians as to how vasopressors should be titrated to achieve resuscitation endpoints for patients still experiencing effects from their home

antihypertensive therapy. Research that pragmatically addresses vasopressor administration to improve clinical outcomes, while also minimizing harms, is needed by critical care clinicians in everyday practice.

Leveraging the expertise of the Discovery Network with the reach of SCCM to recruit a varied number of sites to contribute the large number of patients needed for such analysis can present a unique opportunity to examine a common clinical question with potentially high impact and implications for the clinical care of critically ill patients.

4. STUDY POPULATION

4.1 Inclusion Criteria

Patients meeting all inclusion criteria during the 14-day study period are eligible for the cohort:

1. Age ≥ 18 years admitted to the participating hospital.

2. Patients in the emergency department, intensive care unit, PACU, or any hospital floor. For patients not in the ICU, there must be plans to transfer to an intensive care unit when an ICU bed is available for patient.

3. Patients with shock as defined by:
   - Need for vasopressor therapy (at any dose) to keep MAP >65 mmHg
     Or
   - Systolic BP < 90 mmHg

   Start of shock was defined as the first documented time of either event, which is earliest. See VOLUME-CHASERS Case Report Form instructions for assessing and determining type of shock

4.2 Exclusion Criteria:

Patients who meet any one of the following criteria will be excluded from the study:

1. Patients previously enrolled into this study.
2. Patients who were in the operating room at time of shock and fluid bolus.
3. Patients admitted to an ICU after cardiac surgery. Patients with primarily cardiogenic shock as etiology for their shock
4. Patients transferred from another hospital or emergency room to the study hospital.

Table 2: Rationale for Exclusion

Exclusion criteria	**Rationale**
Previously enrolled into this study	Violates statistical assumption of sample independence
In the OR at the time of shock	Difficulty determining etiology of shock and methods used to determine fluid responsiveness in the operating room

Admitted to an ICU after cardiac surgery or cardiac care unit	More likely due to cardiogenic shock or post-operative shock with very different fluid management than distributive or hypovolemic
Transferred from another hospital or emergency room to the study hospital	Incomplete data availability and collection for exposure and outcomes

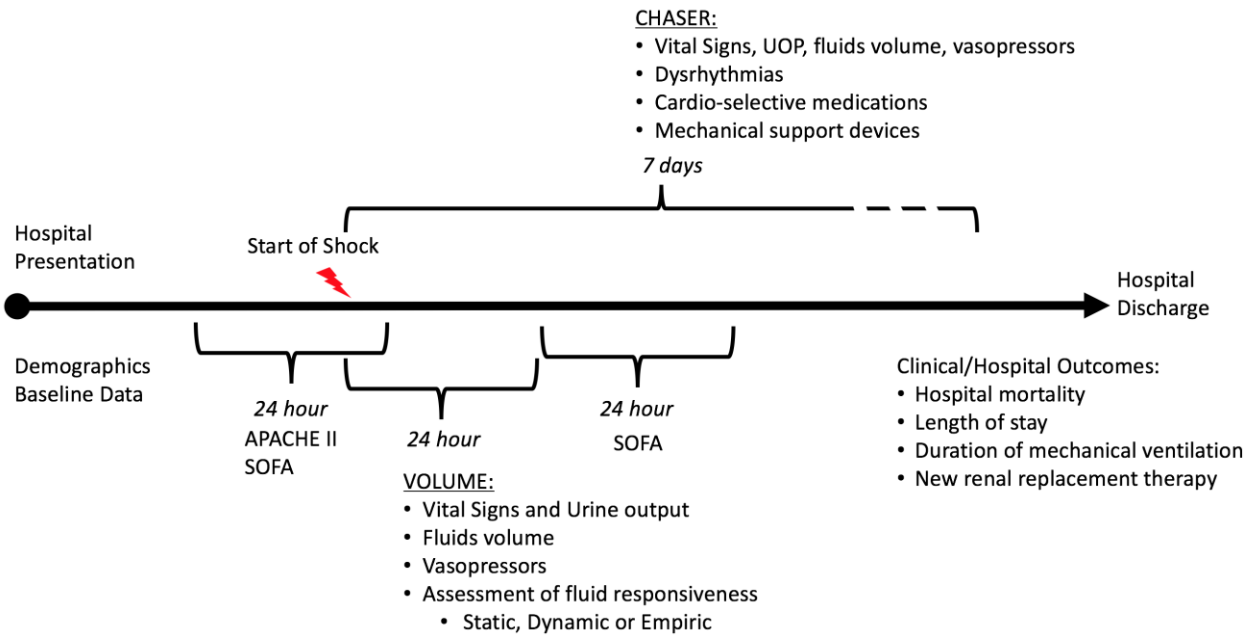
5. STUDY DESIGN

We plan to do a two-week, prospective observational study across multiple hospitals to determine the amount of fluids administered within 24 hours of meeting study criteria for shock and whether dynamic or static measures of fluid responsiveness was obtained. We will allow participation of sites who are able to collect data for shorter periods of time.

6. DATA COLLECTION

Patients will be screened for inclusion and exclusion criteria over a 14-day consecutive period. This 14-day period must begin at any time within a 3-month window starting on September 1st, 2017. Patients who meet all inclusion and no exclusion criteria should be enrolled for data collection.

Data will be collected on consecutive patients who meet all inclusion criteria and no exclusion criteria. Index time is defined as the hospital day and time at which the patient meets the shock criteria on chart documentation (initiation of vasopressors or systolic blood pressure < 90 mmHg, whichever is first documented). All data will be entered into a secure web-based electronic case report form. Data collection is summarized below. See Case Report Form and Case Report Form instructions for more details.



Each participating institution will submit the protocol to their local IRB for approval. As only de-identified data with no dates will be collected, this will qualify for expedited review with waiver of informed consent and HIPAA authorization. To facilitate IRB approval, templates for IRB applications will be made available for investigators to use in their local IRB process.

Investigators will be selected from a range of institutions participating in the Discovery Network. We will provide a Manual of Operations and online Case Report Forms. Training webinars will be conducted for all participating sites, and the webinars will be stored on the SCCM website to be available for investigators and their teams.

6.1 Background Assessments

1. Demographics and admission data (including age, sex, race, ethnicity)
2. Weight recorded from medical record, if available
3. Height recorded from medical record, if available

6.2 Baseline Data

Hospital Admission

1. ICU admission before or after study entry
2. Indicate primary etiology of shock
   - Septic shock
   - Hypovolemic shock from bleeding, volume depletion, etc.
   - Cardiogenic shock
   - Anaphylactic shock
   - Other distributive shock not described above
   - Other non-distributive shock not described above
3. Indicate the potential primary contributor of shock
   - Sepsis
   - Hypovolemia (bleeding, dehydration, diarrhea, volume loss outside of the body)
   - Cardiac dysfunction
   - Neurologic (seizure, stroke, intracranial hemorrhage, subdural hematoma, coma)
   - Trauma (any trauma including head trauma)
   - Intoxication (overdose, alcohol intoxication, alcohol withdrawal)
   - Metabolic (diabetic ketoacidosis, metabolic acidosis, hyperkalemia)
   - Other distributive shock not described above
   - Other non-distributive shock not described above
4. Location of patient at the time of shock recognition
   - ED
   - Non-ICU, non-ED ward of the hospital
   - ICU (If checked, indicate the type of ICU)
     i. Medical ICU
     ii. Surgical ICU
     iii. Medical Surgical ICU
     iv. Cardiothoracic surgical ICU
     v. Trauma ICU
   - Other (e.g. Burn, Neurologic unit)
5. Indicated the existence of concomitant diagnosis, in addition to shock within the first 24hour before or after start of shock
   - Acute exacerbation of asthma or COPD or other obstructive lung process
   - Pregnancy

- Abdominal injury: i.e., intra-abdominal air, intra-abdominal hypertension, abdominal surgery.
- Left sided chest wall surgery or disorder: i.e., chest trauma, thoracotomy, pneumothorax.

6. History of congestive heart failure
   - indicate if the patient had an echocardiogram to confirm the history of congestive heart failure
   - document known ejection fraction.

6.3 APACHE III and SOFA Score peri-Shock

1. Baseline APACHE III (Record values within the 24-hour peri-shock, defined as the 12 hours before and 12 hours after start of shock.): if only one value available, enter the same value for both highest and lowest. Including: temperature, heart rate, respiratory rate, sodium, potassium, total bilirubin, creatinine, hematocrit, white blood cell, platelets, lactate, vasopressors infusion > 1 hour. If patient was in the hospital for < 12 hours prior to shock, use whatever time where documentation is available.
2. If no arterial blood gas during that 24-hour period, indicate whether the patient receive non-invasive ventilation and/or non-invasive ventilation at any time in the 24-hour period
   - If on non-invasive or invasive ventilation at any time, indicate lowest SpO2/FiO2 while on positive pressure ventilation.
3. Mental status assessment
   - Indicate Glasgow Coma Score if available
   - If no Glasgow coma score available, indicate the worse mental status off continuous intravenous sedation within the 24-hour peri-shock period.
4. Chronic health conditions (include all that is listed on patient's medical condition)
   - AIDS, not including HIV positivity without AIDS
   - Leukemia
   - Lymphoma
   - A solid tumor with metastasis
   - Immune suppression
   - Hepatic failure with coma or encephalopathy
   - Congestive heart failure
   - Chronic renal failure without dialysis
   - Chronic hemodialysis or peritoneal dialysis
   - Lower extremity amputation

6.4 First 24 Hours After Start of Shock

1. Enter fluids and vital signs for the 1st hour after start of shock, hours 0-3, 3-6, 6-12, and hours 12-24 after start of shock (enter only on basis on what is documented and date and time stamp of documentation).
   - Amount of fluid given, in mL
   - Indicate type of fluid: crystalloid, colloids, or blood products (packed red blood cell, platelet, fresh frozen plasma, and cryoprecipitate)
   - Vital signs, including heart rate, SBP, MAP, CVP, and urine output
   - indicate if mechanical ventilation was used
   - Vasopressors use: total dose of dopamine, norepinephrine, epinephrine, vasopressin ≥ 0.03 units/min given during that time period

1. Indicate if any of the following physiologic measurements were documented as measured or performed during the first 24 hours from the start of shock.
   - Central venous pressure documented
   - Pulmonary arterial occlusion pressure documented

- Pulse pressure variation documented
- Critical care ultrasound performed
- Stroke volume variation documented
- Passive Leg Raise Test performed and physiologic measurements such as SV, CO, BP/MAP, or ultrasound were documented before and after PLR
- Fluid challenge performed and physiologic measurement such as SV, CO, BP/MAP, or ultrasound were documented before and after PLR

6.5 48 hours after the Start of Shock (Post-resuscitation)

1. SOFA score: post resuscitation organ failure (enter highest and lowest value within the 24-hour period starting 48 hours after the start of shock). If only one value available, enter the same value for highest and lowest. Values include: MAP, total bilirubin, creatinine, urine output, lactate, and vasopressors infusion lasting > 1 hour. If none available within this period of time, carry forward the last known value closest to this time frame within 12 hours before or after this period.
2. Oxygenation: indicated if mechanical ventilation was required at any time in the 24-hour period starting 48 hours after the start of shock and the lowest available peripheral saturation, PaO2 and corresponding FiO2. If mechanical ventilation was not required, will record the highest oxygen delivery device during the same period.
3. Mental status assessment
   - Indicate Glasgow Coma Score if available
   - If no Glasgow coma score available, indicate the worse mental status off continuous intravenous sedation within the 24-hour peri-shock period.

6.6 Daily Data

Daily data on hemodynamics, vasopressor use, fluids, arrhythmia, and medications will be collected for each day of shock requiring vasopressors up to 7 days for each patient from time of enrollment.

6.7 Hospital Outcome

1. Hospital length of stay defined by hospital discharge day based on hospital day count minus hospital admission day based on hospital day count.
2. ICU length of stay (ICU discharge day minus ICU admission day based on hospital day count)
3. Patient status on hospital discharge
4. Renal replacement therapy at any time prior to discharge
5. Invasive mechanical ventilation use during this hospitalization
   - If yes, indicate if the patient on mechanical ventilation through an ET tube or tracheostomy at hospital discharge
   - If not on mechanical ventilation at the time of hospital discharge, indicate the duration of mechanical ventilation

7. STATISTICAL ANALYSIS

All data will be sent to Emory University for statistical analysis. To avoid unnecessary delays from site-specific negotiations for a data use agreement, a uniform multicenter collaborative agreement for data sharing will be developed. All sites must sign off on the agreement prior to participation.

Statistical analysis will consist of summary statistics of total fluid volume and type of fluid and amount of vasopressor given within the first 24 hours of meeting study criteria. Our primary exposure variable will the method used to assess need for additional volume, including the use of a dynamic physiologic method (such as passive leg raise or fluid challenge leading to a change in SVO2, non-invasive or invasive measures of cardiac output or stroke volume) versus the use of a static physiologic measures (CVP, PWCP) versus other empiric clinical exam measures (based on recommended guidelines of 30 cc/kg or clinical exam indicative of improved perfusion by blood pressure, lactate, skin exam ,etc., as advocated by CMS guidelines as initial indicators of hypoperfusion), to assess need for additional volume. Our primary outcome measure will be amount of fluids infused in the first 24 hours. The percentage of patients in whom static and dynamic physiologic measures of fluid responsiveness was used will be calculated for the entire study and at each site. Secondary analysis will examine the doses of vasopressors required in which static or dynamic physiologic measures are used. Univariate analysis comparing fluid volume and vasopressor use in the first 24 hours after study entry will be performed, followed by multivariate linear regression stratified by site to account for possible site-specific effects to determine predictors of more fluid.

Lastly, propensity scores for use of dynamic measures of fluid responsiveness will be calculated for each patient. Patients will be matched by propensity score for use of dynamic or static physiologic measures and multivariate analysis will be used to determine relationship between the actual use of dynamic or static measures of fluid responsiveness on the amount of fluid administered and hospital mortality in patients with similar propensity for dynamic or static hemodynamic measures.

8. RISK ASSESSMENT

As this is an observational study with no intervention, the only risk to the patient is that of breach of privacy.

8.1 Minimization of Risks

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. There are no study procedures, and there are no consent forms that pose a potential risk to privacy. All data will be sent to the clinical coordinating center in a secured fashion via an electronic data collection form. All data will be collected and stored securely, and the only information transmitted to the coordinating center will be devoid of personal health information. Performing this study under waiver of informed consent will minimize risk to privacy, as there will be fewer paper records that have potential to cause a security breach.

8.2 Risks in Relation to Anticipated Benefits

We do not anticipate any direct benefit to subjects for participation in this study, but this is balanced against the minimal risk from limited data collection.

9. HUMAN SUBJECTS

9.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The EDs, ICUs, and other acute care areas of participating sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests nor procedures will be performed as part of the screening process. Study exclusion criteria neither unjustly exclude classes of individuals from

participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

9.2 Minorities and Women

There will be no exclusion on the basis of race or gender. With regard to pregnant women, they will not be specifically excluded.

9.3 Justification of Including Vulnerable Subjects

Almost all patients with shock could be considered vulnerable due to acute illness and possible impairment of decision making capacity. Several U.S. task forces have deemed it permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment."[13] Research Ethics Commission has held the view that it is permissible to include incapable subjects in research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits **similar** to that available in the clinical setting or "if the net additional risks of participation are not substantially greater than the risks of standard treatment."[13] As this is a non-interventional study that aims to collect clinically available data, the only risk to study participation is a potential risk to privacy for the patient, which is similar to that encountered in standard clinical settings.

9.4 Waiver of Informed Consent

We are applying for a waiver of informed consent to collect clinically obtained data for the proposed one week observational cohort. As per federal regulation 45 CFR 46.116d, VOLUME would meet the required four criteria for a waiver of informed consent:

1. The research involves no more than minimal risk to the subjects: this is an observational study and no personal health information will be transmitted outside the study hospital. Obtaining written consent would actually pose greater risk to the subject due to the requirements to maintain these paper records.

2. The waiver will not adversely affect the rights and welfare of the subjects: this study has no intervention, and all data collected are typical data obtained from inpatients.

3. The research could not be practically carried out without a waiver: VOLUME studies patients when they first develop shock. It is neither practical nor possible to consent patients or to find family for consent for data collection and may risk consent bias as only patients who are well enough or who have family readily available could be consented for this study.

4. When appropriate, the subject will be provided with additional pertinent information after participation: there is no intervention planned and no data generated that would not already be part of the medical record of the patients. Thus, no additional pertinent information will be shared with the subject after participation.

References:

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