Supplemental Digital Content 1

ARISE EGDT Resuscitation Algorithm (Modified from NEJM 2014; 371:1496-1506, Supplementary Appendix)

The resuscitation algorithm consisted of:

1. Supplemental oxygen titrated to achieve a peripheral oxygen saturation (SpO2) ≥ 93%.
2. A 500 ml or greater crystalloid or colloid fluid bolus administered every 30 minutes until the desired central venous pressure (CVP) was attained (≥ 8 mm Hg if self-ventilating and ≥ 12 mm Hg if receiving non-invasive or invasive mechanical ventilation).
3. Once the CVP target was achieved, a vasopressor infusion was commenced if the mean arterial pressure (MAP) was < 65 mm Hg. If the mean arterial pressure was > 90 mm Hg a vasodilator agent was commenced. The choice of vasopressor and vasodilator agents was at the discretion of the local study team.
4. If the preceding resuscitation goals were attained, the central venous oxygen saturation (ScvO2) was < 70% and the hematocrit was < 30%, red-cells were transfused to achieve a hematocrit ≥ 30%. Dobutamine, commencing at 2.5 μg/kg/minute and titrated every 30 minutes up to 20.0 μg/kg/minute, was specified if the ScvO2 was < 70% and the hematocrit was ≥ 30%.
5. Finally, if all preceding resuscitation goals were achieved and the ScvO2 remained below 70%, increasing respiratory support was recommended.

Once all the EGDT goals were achieved, monitoring continued for the remainder of the intervention period. If at any time during those 6 hours a resuscitation end-point fell below its goal, the algorithm was repeated from the beginning. A modified goal directed resuscitation algorithm incorporating the SpO2 and MAP goals was followed for patients randomized to EGDT in whom ScvO2 central venous catheter insertion was unsuccessful.

Supplemental Digital Content 2

Total IVT Prior to Vasopressor Algorithm

Total IVT prior to vasopressor (VP) was calculated assuming a constant rate of IV administration within recording intervals, given by the summation of:

- Total IVT prior to hospital (ED)
- If VP commenced prior to randomization (Rnd):
    - (IVT from ED to Rnd) × (Time ED to VP)/(Time ED to Rnd)
- If VP commenced within first 6 study hours (IVT_1 to IVT_6):
    - IVT from ED to Rnd
    - Sum IVT_1 to IVT_n where $n \leq$ Time VP (hour)
    - IVT_{n+1} × (Time VP (mins) / 60) where n = Time VP (hour)
- If VP commenced between study hours 6 to 24:
    - IVT from ED to Rnd
    - IVT from $T_0 - T_6$
    - $IVT_{6\text{-}24}$ × (Time VP (hours)-6) / 18
- If VP commenced between study hours 24 to 72:
    - IVT from ED to Rnd
    - IVT from $T_0 - T_6$
    - $IVT_{6\text{-}72}$ × (Time VP (hours)-6) / 66

Supplemental Digital Content Table 3. Proportion of vasopressor type at randomization, prior to CVC insertion and by order of inclusion in treatment.

	Randomization	**Pre-CVC**	**First VP**	**Second VP**	**Third VP**
All Randomized					
N	261	418	1,102	366	125
Norepinephrine	203 (78%)	316 (76%)	982 (89%)	182 (50%)	41 (33%)
Epinephrine	28 (11%)	40 (10%)	48 (4%)	74 (20%)	22 (18%)
Metaraminol	28 (11%)	61 (15%)	69 (6%)	24 (7%)	8 (6%)
Vasopressin	2 (1%)	1 (<1%)	3 (<1%)	86 (23%)	54 (43%)
Control Group					
N	131	222	523	185	63
Norepinephrine	104 (79%)	166 (75%)	457 (87%)	100 (54%)	19 (30%)
Epinephrine	15 (11%)	26 (12%)	29 (6%)	35 (19%)	9 (14%)
Metaraminol	12 (9%)	30 (14%)	36 (7%)	13 (7%)	5 (8%)
Vasopressin	-	-	1 (<1%)	37 (20%)	30 (48%)

VP – Vasopressor, CVC – central venous catheter.

Supplemental Digital Content Table 4. Summary statistics for catecholamine use within 72 hours of study enrolment, for those who received vasopressors.

Catecholamine	N	Median [IQR]	Min	Max
Norepinephrine				
Baseline (T0), mcg/min	191	6.7 [5, 12]	0	50
T1 – T6 Rates				
Maximum, mcg /min	883	10 [5, 20]	0.2	203
Average, mcg /min	883	8 [4, 15]	0.2	125
Hours of infusion	883	5 [4, 6]	1	6
T24				
Rate, mcg /min	582	6 [3, 14]	0	156
T72				
Rate, mcg /min	213	4 [1, 12]	0	485
Epinephrine				
Baseline (T0), mcg/min	42	6.3 [3.3, 15]	0.8	83
T1 – T6 Hourly Rates				
Maximum, mcg/min	86	13 [7, 20]	0.8	133
Average, mcg/min	86	10 [5, 17]	0.8	133
Hours of infusion	86	3 [2, 5]	1	6
T24				
Rate, mcg/min	37	6 [3, 16]	0	100
T72				
Rate, mcg/min	18	9 [1, 28]	0	120
Dual Norepinephrine & Epinephrine				
Maximum (T0) mcg/min	11	27 [13, 33]	6	70
Maximum (T1-T6) mcg/min	76	45 [31, 69]	6	233
Maximum (T24) mcg/min	34	41 [15, 65]	0	212
Maximum (T72) mcg/min	17	26 [13, 60]	0	530

Supplemental Digital Content Table 5. Associations of interventions and outcome variables with early administration of vasopressors (within 4 hours of ED arrival).

	Early VP	Late / No VP	P-value[1]
Number (%)	480 (30)	1,108 (70)	N=1,588
EGDT Group Assignment, N (%)	239 (50)	553 (50)	0.97
Gender = Male, N(%)	292 (61)	657 (59)	0.57
Age, years, median [IQR]	65 [51, 75]	66 [52, 76]	0.35
APACHE II Score, median [IQR]	18 [13, 23]	14 [10, 18]	<0.001
Study Inclusion Criteria			<0.001
Isolated Hypotension	255 (53)	598 (54)	
Isolated Hyperlactataemia	94 (20)	382 (35)	
Hypotension & Hyperlactataemia	131 (27)	128 (12)	
Charlson Comorbidity Index, median [IQR]	1 [0,2]	1 [0,2]	0.21
SOFA Scores, median [IQR]			
Baseline	6 [4, 8]	3 [2, 4]	<0.001
At 6 Hours	4 [4, 6]	2 [0, 4]	<0.001
At 24 Hours	7 [5, 9]	4 [1, 7]	<0.001
At 72 Hours	5 [2, 8]	2 [0, 5]	<0.001
CVC Placement (within 72 Hours)			
CVC – Number (%)	281 (59)	378 (34)	<0.001
CVC – Interval hours, median [IQR]	2.8 [1.9, 3.8]	5.4 [4.0, 7.0]	<0.001
SvO_2 – Number (%)	221 (46)	495 (45)	0.63
SvO_2 – Interval hours, median [IQR]	3.2 [2.6, 4.0]	4.5 [3.6, 5.8]	<0.001
Vasopressor without a CVC			
Number (%)	295 (61)	123 (20)	<0.001
Hours, median [IQR]	1.3 [0.7, 2.4]	0.9 [0.5, 1.9]	0.01
Intravenous Fluid, Total (L), median [IQR]			
Pre-vasopressor	3.0 [2.0, 3.7]	3.5 [2.5, 4.6]	<0.001
At 72 hours	6.1 [3.7, 8.8]	5.3 [3.4, 7.8]	<0.001
Invasive Ventilatory Support			
Number (%)	239 (50)	249 (22)	<0.001
Hours, median [IQR]	61 [22, 166]	67 [26, 167]	0.56
Continuous Renal Replacement Therapy			
Number (%)	109 (23)	105 (9.5)	<0.001

Hours, median [IQR]	72 [37, 166]	58 [19, 187]	0.32
Interval from ED to Antibiotic, minutes			
First Antibiotic, median [IQR]	48 [28, 77]	79 [46, 126]	<0.001
Correct Antibiotic, median [IQR]	66 [36, 140]	99 [55, 195]	<0.001
Length of Stay, hours			
Emergency Department, median [IQR]	3.4 [2.4, 4.8]	5.0 [3.6, 7.0]	<0.001
Intensive Care, median [IQR]	75 [43, 148]	54 [30, 116]	<0.001
Hospital, median [IQR]	241 [121, 467]	195 [121, 384]	0.04
Site of Sepsis, N(%)			0.10
Blood	65 (14)	96 (9)	
Lung	164 (34)	386 (35)	
Abdominal	41 (9)	83 (7)	
Urinary	81 (17)	226 (20)	
Central Nervous System	4 (1)	15 (1)	
Soft tissue	52 (11)	113 (10)	
Other	35 (7)	89 (8)	
Unknown	38 (8)	100 (9)	
Causative Organism, N(%)			0.04
Gram Positive	129 (27)	281 (25)	
Gran Negative	163 (34)	312 (28)	
Other (viral, fungal, etc)	37 (8)	93 (8)	
None Identified	151 (31)	422 (38)	
Mortality, N(%)			
ICU	90 (20)	74 (8)	<0.001
Hospital	118 (25)	125 (11)	<0.001
90 Days	131 (27)	166 (15)	<0.001

1. *P*-value by chi-squared test (N(%)), Wilcoxon rank-sum (median[IQR]), or t-test (mean(SD)).

ED – Emergency Department, APACHE – Acute Physiology and Chronic Health Evaluation, EGDT – Early Goal Directed Therapy, CVC – Central Venous Catheter, SvO_2 – Mixed Venous Saturation (CVC), SOFA – sepsis related organ failure assessment, IQR – Interquartile range, VP - vasopressor.

Supplemental Digital Content Table 6. Multivariable logistic regression for early (≤ 4-hours from ED arrival) initiation of vasopressor support, showing odds-ratios (OR), 95% confidence intervals (95%CI) and associated *P*-values for the listed covariates.

Covariate	OR	95% CI	P-value
Age (years)	0.98	0.98-0.99	0.001
Male Gender	1.13	0.87-1.47	0.37
APACHE II Score	1.11	1.08-1.13	<0.001
EGDT Group	0.93	0.72-1.20	0.56
IV fluid therapy prior to VP, L	0.63	0.58-0.69	<0.001
Study Inclusion Criteria			
Isolated Hypotension (base)	1.0	-	-
Isolated Hyperlactataemia	2.20	1.54-3.12	<0.001
Hypotension & Hyperlactataemia	0.41	0.29-0.57	<0.001
Site of Sepsis[1]			
Lung (base)	1.0	-	-
Blood	1.57	1.00-2.47	0.05
Abdomen	1.85	1.10-3.11	0.02
Urinary	1.23	0.84-1.79	0.28
Central Nervous System	0.63	0.18-2.27	0.48
Soft Tissue	1.09	0.70-1.70	0.70
Other	1.12	0.67-1.86	0.67
Unknown	1.10	0.67-1.81	0.71
Study Site ID[1]			<0.001
1	0.84	0.46-1.55	0.58
2	1.03	0.49-2.15	0.94
3	0.37	0.20-0.68	0.00
4	0.51	0.24-1.07	0.08
5	0.73	0.31-1.69	0.46
6	0.36	0.12-1.04	0.06
7	0.21	0.04-1.14	0.07
8	0.93	0.39-2.23	0.88
9	0.35	0.10-1.21	0.10
10	0.24	0.08-0.71	0.01
11	1.81	0.73-4.53	0.20

12	1.47	0.65-3.35	0.36
13	0.53	0.18-1.56	0.25
14	1.54	0.74-3.17	0.25
15	1.70	0.76-3.81	0.20
16	0.49	0.25-0.95	0.03
17	0.62	0.22-1.76	0.37
18	0.43	0.18-1.00	0.05
19	0.79	0.37-1.70	0.55
20	0.83	0.26-2.68	0.76
21	0.22	0.04-1.08	0.06
22	9.48	3.03-29.71	0.00
23	5.58	1.99-15.68	0.00
24	2.54	1.00-6.44	0.05
Other[2]	0.88	0.54-1.45	0.62

1. *P*-value by chi-squared test for overall significance for indicator variable.

2. Study sites with n<25 were collapsed into a single category.

APACHE – acute physiology and chronic health evaluation, EGDT – early goal directed therapy, IV-intravenous, VP – vasopressor.

Supplemental Digital Content Table 7. Associations of interventions and outcome variables with administration of vasopressor prior to CVC placement, in those receiving vasopressors.

	VP Pre-CVC	VP Only CVC	P-value[1]
Number (%)	418 (38)	684 (62)	N=1,102
EGDT Group Assignment, N (%)	196 (47)	383 (56)	0.003
APACHE II Score, median [IQR]	17 [13, 22]	16 [12, 21]	0.001
Study Inclusion Criteria			0.02
Isolated Hypotension	241 (58)	375 (55)	
Isolated Hyperlactataemia	83 (20)	185 (27)	
Hypotension & Hyperlactataemia	94 (22)	124 (18)	
Intravenous Fluid, Total (L), median [IQR]			
Pre-vasopressor	3.0 [2.1, 4.0]	3.3 [2.3, 4.5]	<0.001
At 72 hours	6.4 [3.9, 8.8]	5.9 [3.8, 8.5]	0.33
Invasive Ventilatory Support, Number (%)	199 (48)	263 (38)	0.003
CRRT, Number (%)	88 (21)	119 (17)	0.13
Length of Stay, hours			
Emergency Department, median [IQR]	3.9 [2.6, 5.6]	4.3 [3.1, 6.3]	<0.001
Intensive Care, median [IQR]	73 [39, 157]	72 [42, 145]	0.86
Hospital, median [IQR]	228 [120, 438]	240 [142, 470]	0.13
Mortality, N(%)			
ICU	73 (19)	85 (13)	0.01
Hospital	104 (25)	108 (16)	<0.001
90 Days	117 (28)	135 (20)	0.002

1. *P*-value by chi-squared test (N(%)), Wilcoxon rank-sum (median[IQR]), or t-test (mean(SD)).

APACHE – Acute Physiology and Chronic Health Evaluation, EGDT – Early Goal Directed Therapy, CVC – Central Venous Catheter, CRRT – Continuous Renal Replacement Therapy, SOFA – sepsis related organ failure assessment, IQR – Interquartile range.

Supplemental Digital Content Table 8. Multivariable logistic regression for 90-day mortality, showing odds-ratios (OR), 95% confidence intervals (95%CI) and associated *P*-values for the listed covariates.

Covariate	**OR**	**95% CI**	***P*-value**
Age (years)	1.02	1.01-1.03	<0.001
Male Gender	1.02	0.76-1.37	0.90
APACHE II Score	1.11	1.08-1.14	<0.001
EGDT Group	1.00	0.75-1.33	0.97
Early VP (≤ 4 hrs from ED)	1.56	1.11-2.20	0.01
IV fluid therapy prior to VP, L	0.96	0.89-1.04	0.29
Study Inclusion Criteria			<0.001
Isolated Hypotension (base)	1.0	-	-
Isolated Hyperlactataemia	2.32	1.57-3.44	<0.001
Hypotension & Hyperlactataemia	2.06	1.45-2.91	<0.001
Presumed site of infection[1]			<0.001
Lungs (base)	1.0	-	-
Blood	1.32	0.83-2.10	0.24
Abdominal	0.74	0.41-1.33	0.31
Urinary	0.38	0.24-0.60	<0.001
Central nervous system	1.08	0.29-4.03	0.91
Soft tissue	0.47	0.26-0.82	0.01
Other	0.68	0.38-1.22	0.19
Unknown	0.99	0.59-1.66	0.97
Study Site ID[1]			0.14
1	1.89	0.94-3.80	0.07
2	0.56	0.20-1.55	0.27
3	1.13	0.55-2.33	0.74
4	1.75	0.78-3.94	0.18
5	1.25	0.45-3.47	0.67
6	0.81	0.28-2.38	0.71
7	0.53	0.10-2.75	0.45
8	1.28	0.46-3.62	0.64
9	2.38	0.78-7.24	0.13
10	2.66	1.07-6.62	0.04
11	1.66	0.58-4.80	0.35

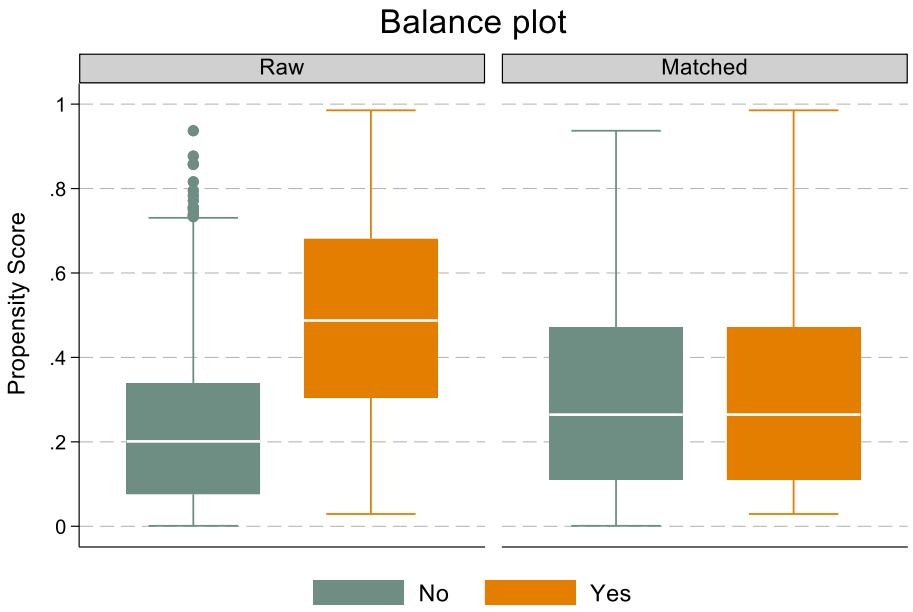
12	0.94	0.30-2.93	0.91
13	2.05	0.78-5.36	0.15
14	2.53	1.09-5.87	0.03
15	0.37	0.09-1.50	0.16
16	1.17	0.54-2.51	0.69
17	1.47	0.51-4.19	0.47
18	2.05	0.75-5.62	0.16
19	0.64	0.21-1.97	0.44
20	1.33	0.40-4.40	0.64
21	2.57	0.78-8.41	0.12
22	0.85	0.25-2.91	0.80
23	2.14	0.67-6.82	0.20
24	0.80	0.22-2.88	0.73
Other[2]	1.01	0.53-1.92	0.98

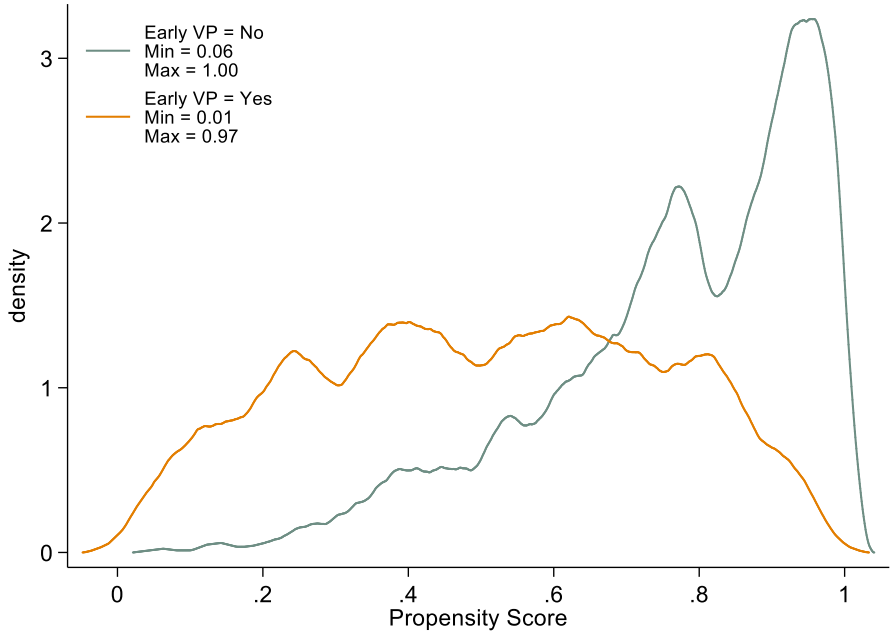
1. *P*-value by chi-squared test for overall significance for indicator variable.

2. Study sites with n<25 were collapsed into a single category.

APACHE – acute physiology and chronic health evaluation, EGDT – early goal directed therapy, IV-intravenous, VP – vasopressor.

Supplement Digital Content Figure 9. Propensity score balance and overlap plots for treatment effects model.





Variable	Obs	Mean	Std. Dev.	Min	Max
pscore	1,525	.6852459	.2387441	.0147179	.9990008

NB: Selected caliper: < 0.25 * SD(pscore) ~ 0.05

13 observations have no propensity-score matches within caliper .05