

Supplementary Appendix

Table S1. Drugs incorporated into vasoactive cost calculations and wholesale acquisition cost basis

Drug	Presentation Concentration	Presentation Type	WAC Price per Presentation*	WAC Price per Unit
Norepinephrine	4 mg/mL	1 mL vial	\$15.13	\$3.78/mg
Vasopressin	20 units/mL	1 mL vial	\$96.80	\$4.84/unit
Phenylephrine	10 mg/mL	10 mL vial	\$54.78	\$0.55/mg
Epinephrine	1 mg/mL	30 mL vial	\$100.00	\$3.33/mg
Dobutamine	1 g/250 mL	Premixed bag	\$14.17	\$14.17/g
Milrinone	20 mg/100 mL	Premixed bag	\$12.08	\$0.60/mg

\*As of December 1, 2015. WAC, wholesale acquisition cost

Table S2. Aggregate vasoactive agent dispensing

Drug and units	Total	Pre-Guideline	Post-Guideline	Difference
Norepinephrine, mg	99,348	47,024	52,324	+5,300
Vasopressin, units	70,220	42,000	28,220	-13,780
Phenylephrine, mg	142,180	68,330	73,850	+5,520
Epinephrine, mg	3,568	1,368	2,200	+832
Dobutamine, g	214	100	114	+14
Milrinone, mg	760	220	540	+320

Table S3. Patient outcomes in the sensitivity analysis (cohort design)

Outcome	Total (N=1148)	Pre-Guideline (n=573)	Post-Guideline (n=575)	Absolute risk or median difference (95% CI)	p <sup>†</sup>
ICU mortality	490 (42.7)	249 (43.5)	251 (41.9)	-1.5% (-7.3% to 4.2%)	0.40 <sup>‡</sup>
Hospital mortality	528 (46.0)	268 (46.8)	260 (45.3)	-1.6% (-7.3% to 4.2%)	0.60
New arrhythmia	153 (13.3)	74 (12.9)	79 (13.7)	0.8% (-3.1% to 4.8%)	0.68
Myocardial injury <sup>§</sup>	8 (3.2)	3 (2.4)	5 (4.1)	1.6% (-2.8% to 6.1%)	0.47
New Stage 2 or 3 AKI <sup>¶</sup>	247 (33.4)	126 (35.1)	121 (31.8)	-3.3% (-10.1% to 3.5%)	0.34
Initiation of CRRT <sup>††</sup>	165 (16.3)	80 (16.0)	85 (16.5)	0.5% (-4.0% to 5.0%)	0.83
SOFA at 72 hours after NE <sup>‡‡</sup>	7 (4, 11)	7 (4, 11)	7 (4, 11)	0 (-0.7 to 0.7)	0.55
SOFA change from baseline to 72 hours after NE <sup>‡‡</sup>	-3 (-5, 0)	-2 (-5, 0)	-3 (-5, -1)	-1 (-1.7 to -0.3)	0.03
Time to MAP >65 mm Hg, hours	0.25 (0.25- 0.28)	0.25 (0.25- 0.33)	0.25 (0.25-0.32)		0.47
Vasoactive duration, days	2.1 (0.9, 4.3)	2.2 (0.9, 4.3)	2.0 (0.9, 4.3)	-0.2 (-0.6 to 0.1)	0.92
Vasopressin duration, days	1.3 (0.6, 2.2)	1.4 (0.6, 2.4)	1.0 (0.5, 1.9)	-0.4 (-0.6 to -0.2)	0.01

Total vasoactive WAC, \$ <sup>§§</sup>	351 (121, 847)	401 (121, 915)	315 (121, 787)	-86 (-159 to -12)	0.11
Norepinephrine WAC, \$ <sup>§§</sup>	182 (121, 424)	182 (61, 363)	182 (121, 424)	0 (-29 to 29)	0.04
Vasopressin WAC, \$ <sup>§</sup>	0 (0, 387)	97 (0, 484)	0 (0, 290)	-97 (-144 to -50)	<0.01

Data presented as n (%), median (IQR), and median (95% CI).

<sup>†</sup>Per Pearson chi-square or Wilcoxon rank-sum, as appropriate. <sup>‡</sup>P-value from multivariable logistic regression analysis for the cohort effect with acute physiology and chronic health evaluation III and sequential organ failure assessment scores retained in the model. Post-guideline group OR 0.90 (95% CI 0.70-1.15). <sup>§</sup>Total N=247, Pre-Guideline n=124, Post-Guideline n=123; <sup>¶</sup>Total N=740, Pre-Guideline n=359, Post-Guideline n=381; <sup>††</sup>Total N=1015, Pre-Guideline n=500, Post-Guideline n=515; <sup>‡‡</sup>Total N=889, Pre-Guideline n=459, Post-Guideline n=430; <sup>§§</sup>Total N=1126, Pre-Guideline n=565, Post-Guideline n=561. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MAP, mean arterial blood pressure; NE, norepinephrine; SOFA, sequential organ failure assessment; WAC, wholesale acquisition cost.

Table S4. Per patient vasoactive agent dispensing in the sensitivity analysis (cohort design)

Amount of drug dispensed	Total (n=1126 <sup>†</sup> )	Pre-Guideline (n=565)	Post-Guideline (n=561)	Median Difference (95% CI)	p <sup>‡</sup>
Overall					
Norepinephrine, mg	48 (32, 112)	48 (16, 96)	48 (32, 112)	0 (-8 to 8)	0.04
Vasopressin, units	0 (0, 80)	20 (0, 100)	0 (0, 60)	-20 (-30 to -10)	<0.01
Restricted to patients dispensed particular medication <sup>§</sup>					
Vasopressin, units	80 (40, 160) (n=545)	100 (60, 160) (n=312)	60 (40, 140) (n=233)	-40 (-54 to -26)	<0.01
Phenylephrine, mg	160 (80, 400) (n=325)	170 (80, 400) (n=153)	160 (80, 400) (n=172)	-10 (-65 to 45)	0.28
Epinephrine, mg	8 (4, 16) (n=166)	4 (4, 20) (n=72)	8 (4, 16) (n=94)	4 (-0.4 to 8)	0.84
Dobutamine, g	1 (1, 2) (n=90)	1 (1, 2) (n=48)	2 (1, 3) (n=42)	1 (-0.3 to 1.7)	0.23
Milrinone, mg	40 (20, 80) (n=9)	30 (20, 40) (n=6)	140 (40, 360) (n=3)	110 (-164 to 384)	0.06

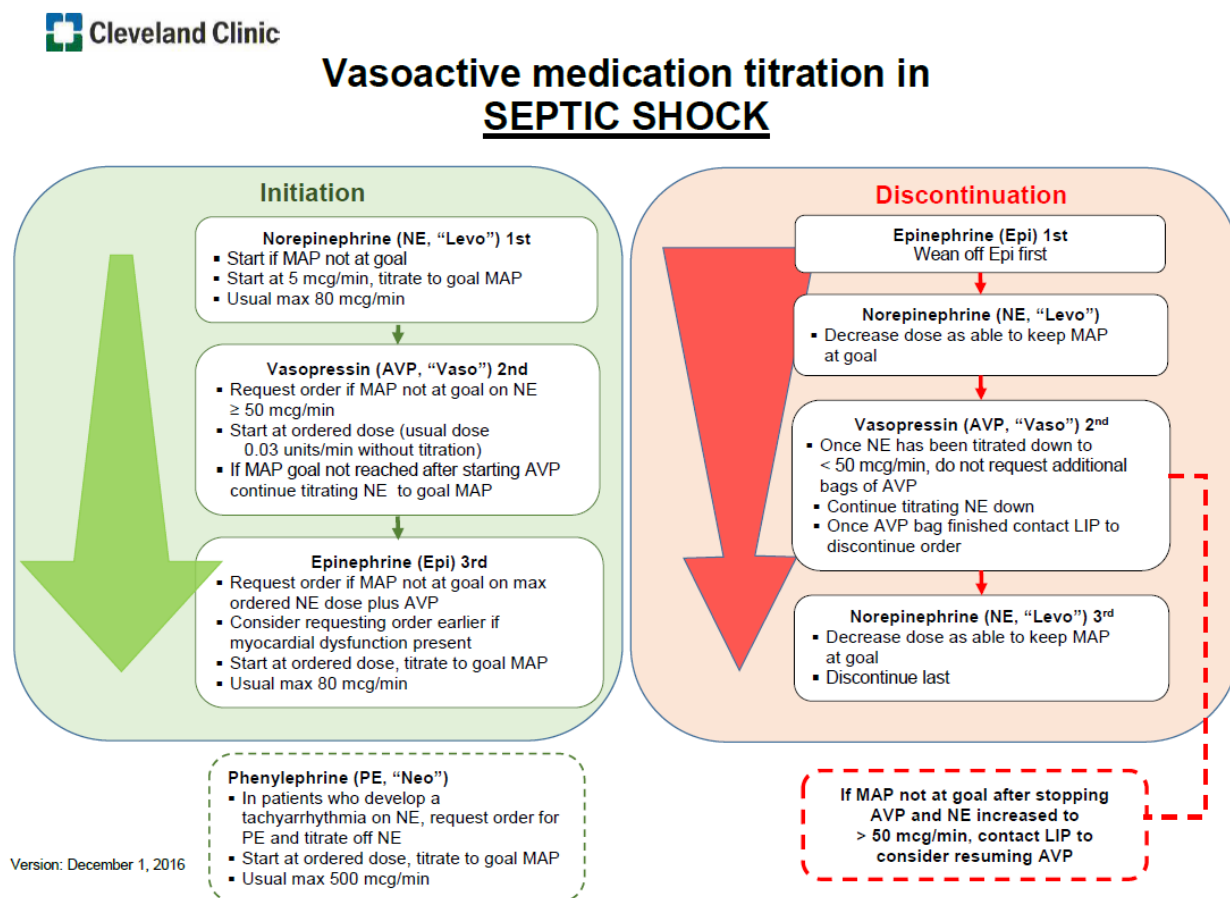
<sup>†</sup>22 patients did not have one or more vasoactive medications dispensed despite documentation of administration, therefore were excluded from the dispensing and cost analysis. <sup>‡</sup>Per Wilcoxon rank-sum test. <sup>§</sup>Reflects all vasoactive medication dispenses that were not returned to the pharmacy. Because patients rarely may have had the medication dispensed and not returned but not documented as administered (i.e., wasted) the number of patients in each group slightly exceeds the number of patients administered the medication. Each patient received norepinephrine, therefore overall dispensing reflects dispensing restricted to patients dispensed norepinephrine. Data presented as median (IQR).

Table S5. Processes of care and outcomes in the exploratory “per-protocol” analysis

	Pre-Guideline (n=309)	Post-Guideline (n=396)	Absolute risk difference or Median difference (95% CI)	p <sup>†</sup>
Processes of Care				
Started on AVP	133 (43.0)	89 (22.5)	-20.6% (-27.5% to -14.7%)	<0.01
NE dose at AVP start, mcg/min <sup>‡</sup>	15 (8, 20)	60 (50, 70)	45 (41 to 49)	<0.01
AVP replenishment bag requested <sup>‡</sup>	121 (91.0)	73 (82.0)	-9.0% (-18.3% to 0.0%)	0.05
NE dose when last AVP replenishment bag requested, mcg/min <sup>§</sup>	8 (1, 22)	50 (17, 50)	42 (28 to 56)	<0.01
Started on additional catecholamine vasopressor	216 (37.7)	209 (36.4)	-1.3% (-6.9% to 4.2%)	0.64
Started on corticosteroids	244 (42.6)	238 (41.4)	-1.2% (-6.9% to 4.5%)	0.68
Time to MAP >65 mm Hg, hours <sup>¶</sup>	0.25 (0.25, 0.33)	0.25 (0.25, 0.33)		0.59
Outcomes				
ICU mortality	104 (33.7)	124 (31.3)	-2.3% (-9.3% to 4.6%)	0.51
New arrhythmia	27 (8.7)	46 (11.6)	2.9% (-1.6% to 7.3%)	0.21
Myocardial injury <sup>††</sup>	2 (2.4)	2 (2.3)	0.2% (-4.7% to 4.4%)	0.93
New Stage 2 or 3 AKI <sup>††</sup>	54 (25.8)	74 (27.4)	1.6% (-6.4% to 9.5%)	0.70
Vasoactive duration, days	1.5 (0.6, 3.2)	1.8 (0.7, 3.6)	0.2 (-0.2 to 0.6)	0.16
Vasopressin duration, days	1.3 (0.4, 2.0)	0.8 (0.5, 1.5)	-0.4 (-0.1 to -0.7)	0.05
SOFA change from baseline to 72 hours after NE <sup>§§</sup>	-3 (-5 to -1)	-3 (-6 to -1)	0 (-0.5 to 0.5)	0.03

†Per Pearson chi-square or Wilcoxon rank-sum, as appropriate. ‡Pre-Guideline n=133, Post-Guideline n=89; §Pre-Guideline n=121, Post-Guideline n=73; ¶Presented as median (95% CI); ††Pre-Guideline n=82, Post-Guideline n=89; †††Pre-Guideline n=209, Post-Guideline n=270; §§ Pre-Guideline n=459, Post-Guideline n=430. Data presented as n (%) and median (IQR) unless otherwise specified. AVP = arginine vasopressin. NE = norepinephrine.

Figure S1. Vasopressin guideline for medical intensive care unit patients with septic shock



The vasopressin guideline was designed for utilization by bedside nurses with verbiage directed towards their actions. AVP, vasopressin; Epi, epinephrine; LIP, licensed independent practitioner; MAP, mean arterial blood pressure; NE, norepinephrine; PE, phenylephrine.