

Supplementary Online Content

Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA*. doi:10.1001/jama.2017.2841

eFigure 1. Study Timeline

eFigure 2. Examples of Actual Temporal Patterns of Norepinephrine Use for Patients With Septic Shock in Two Individual Hospitals

eFigure 3. Changes in Whole Cohort Rates of Vasopressor Use Over Time

eFigure 4. Assessment of the Relationship Between Relative Changes in Norepinephrine vs Alternate Vasopressor Use Among Shortage Hospitals During Quarters of 2011

eFigure 5. Summary Information on Unclassified Hospitals

eTable 1. Characteristics of Patients Stratified by Admission to Shortage, Consistent Use, or Unclassified Hospitals

eTable 2. Primary Model

eTable 3. Difference-in-Differences Model

eTable 4. Primary Model for “Negative Control” Patients

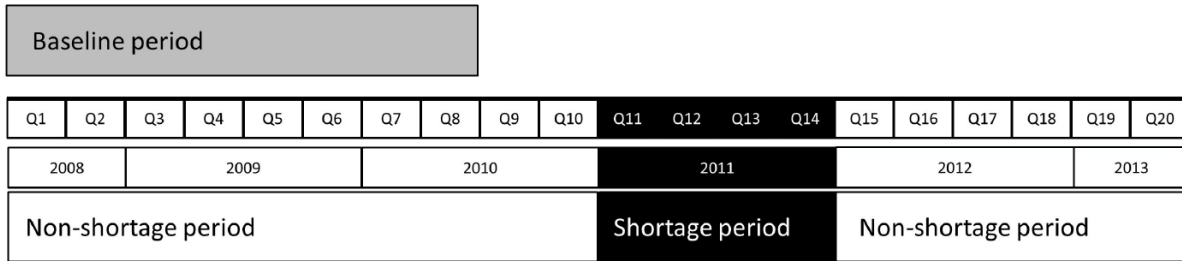
eTable 5. Additional Sensitivity Analyses of Primary and Difference-in-Difference Models

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

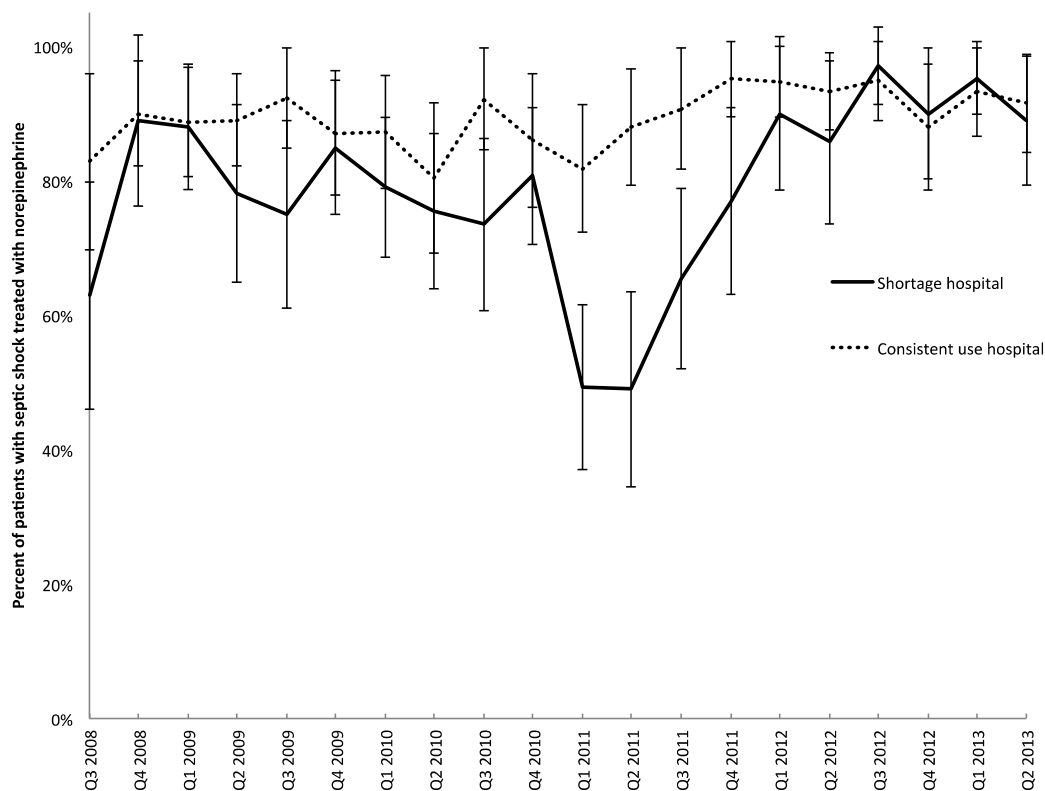
eFigure 1. Study Timeline

Baseline period represents data used to calculate the mean norepinephrine use for patients with septic shock in each hospital. Shortage period represents the period during which there was a reported nationwide shortage of norepinephrine. Of note, not all hospitals experienced a shortage during the same quarters of 2011 (defined as a >20% relative reduction in norepinephrine use for a given quarter in 2011). Thus, shortage hospitals could have quarters of shortage and quarters of non-shortage during the overall shortage period of 2011. Data from all quarters shown were included in all models.



eFigure 2. Examples of Actual Temporal Patterns of Norepinephrine Use for Patients With Septic Shock in Two Individual Hospitals

One shortage hospital, n = 931 and one consistent use hospital, n = 1,164. Bars represent 95% confidence intervals.

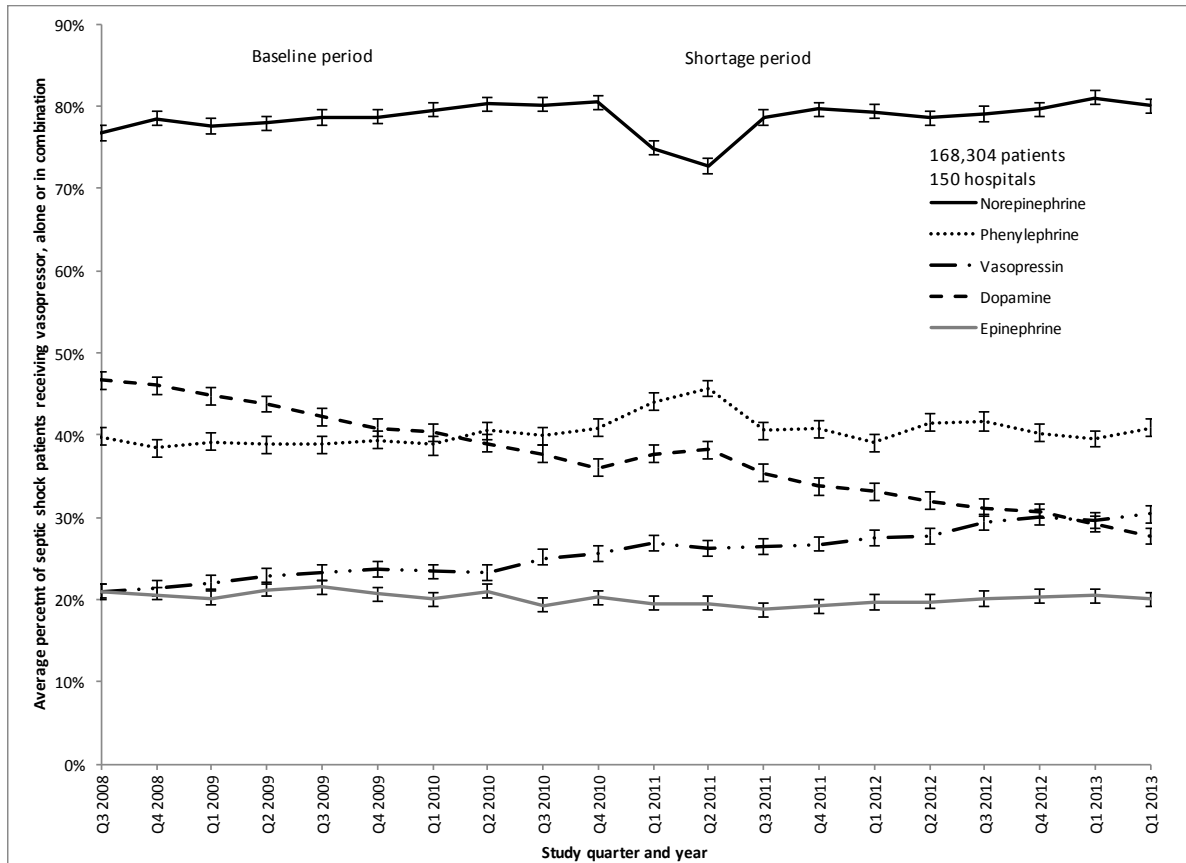


	2008		2009		2010		2011		2012		2013	
	Shortage Hospital, n	Consistent Use Hospital, n	Shortage Hospital, n	Consistent Use Hospital, n	Shortage Hospital, n	Consistent Use Hospital, n	Shortage Hospital, n	Consistent Use Hospital, n	Shortage Hospital, n	Consistent Use Hospital, n	Shortage Hospital, n	Consistent Use Hospital, n
Q1	NA	NA	50	62	62	63	67	66	30	75	63	59
Q2	NA	NA	41	82	57	51	49	58	35	75	45	59
Q3	35	35	40	52	49	51	52	43	35	58	NA	NA
Q4	27	60	53	54	62	50	39	61	40	50	NA	NA

Q = quarter of the year; NA = not applicable

eFigure 3. Changes in Whole Cohort Rates of Vasopressor Use Over Time

This includes all shortage hospitals (n=26), consistent use hospitals (n=102), and “other” unclassified hospitals (n=22). Total n = 168,304. Tests for trend in vasopressor use over time were assessed using linear regression. P <0.001 for change in all vasopressors overtime, except for epinephrine (P=0.001).



Year	Total patients, n					
	2008	2009	2010	2011	2012	2013
Q1	NA	8,805	8,787	9,295	8,773	9,230
Q2	NA	8,434	8,362	8,298	8,119	8,075
Q3	7,751	7,984	8,071	8,063	7,716	NA
Q4	8,198	8,884	8,614	8,538	8,307	NA

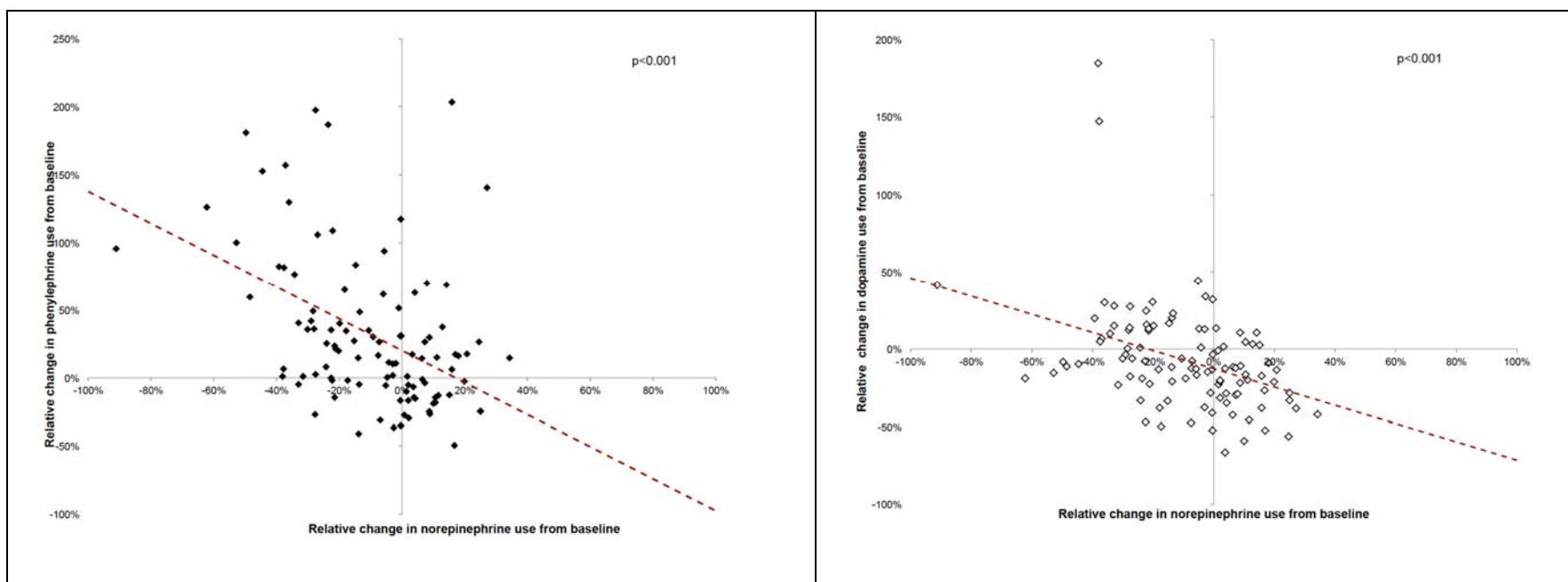
Q = quarter of the year; NA = not applicable

eFigure 4. Assessment of the Relationship Between Relative Changes in Norepinephrine vs Alternate Vasopressor Use Among Shortage Hospitals During Quarters of 2011

Each dot represents data from patients with septic shock in an individual hospital in a given quarter of 2011. We correlated the relative change from baseline in quarterly use of norepinephrine (in 2011) and each other vasopressor in shortage hospitals using unadjusted multilevel linear regression with hospital as a random effect to account for non-independence of observations. The lines on the graphs correspond to the estimated regression line with corresponding p-values.

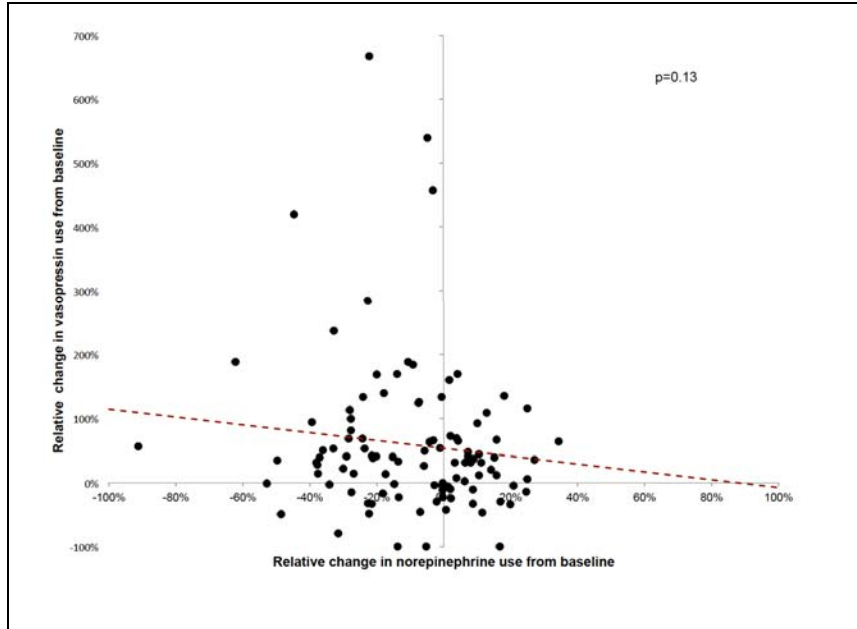
A. norepinephrine vs. phenylephrine

B. norepinephrine vs. dopamine

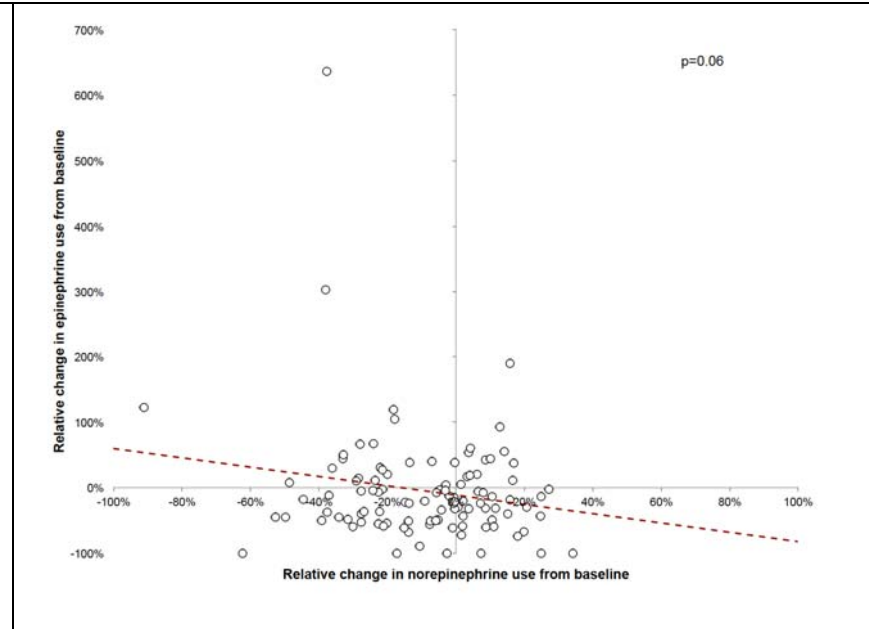


eFigure 4 (continued). Assessment of the Relationship Between Relative Changes in Norepinephrine vs Alternate Vasopressor Use Among Shortage Hospitals During Quarters of 2011

C. norepinephrine vs. vasopressin

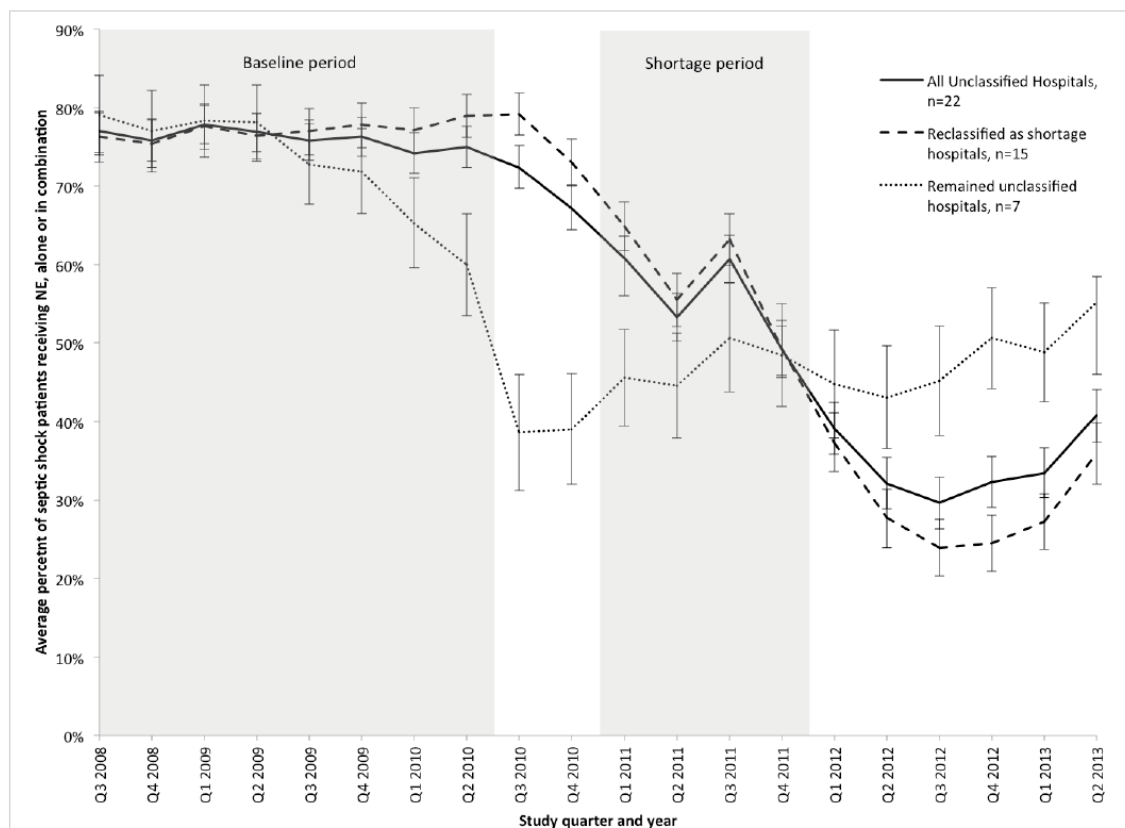


D. norepinephrine vs. epinephrine



eFigure 5. Summary Information on Unclassified Hospitals

Summary information on unclassified hospitals (n = 22) showing the distribution of hospitals with regard to patterns of norepinephrine use and which hospitals were reclassified as shortage hospitals when using a definition of shortage that excluded postshortage data (n = 15)



Total patients, n						
	2008	2009	2010	2011	2012	2013
Q1	NA	1,118	1,093	1,172	851	861
Q2	NA	1,106	1,057	1,042	776	824
Q3	973	1,097	1,022	1,015	737	NA
Q4	1,029	1,093	1,085	956	803	NA

IQR = interquartile range; NA = not applicable; Q = quarter of the year

eTable 1. Characteristics of Patients Stratified by Admission to Shortage, Consistent Use, or Unclassified Hospitals

	Total Cohort	Shortage Hospitals ^a	Consistent Use Hospitals ^b	Unclassified hospitals ^c	P Value
Number of admissions	168,304	27,835 (16.5)	120,759 (71.8)	19,710 (11.7)	
Women, n (%)	79,012 (47.0)	12,950 (46.5)	56,721 (47.0)	9,341 (47.4)	0.17
Age in years, median (IQR)	68 (57-79)	69 (57-79)	68 (57-79)	68 (57-79)	<0.001
Race, n (%)					<0.001
Caucasian	111,163 (66.1)	18,848 (67.7)	80,759 (66.9)	11,556 (58.6)	
African-American	22,495 (13.4)	3,151 (11.3)	16,255 (13.5)	3,089 (15.7)	
Other	34,646 (20.6)	5,836 (21.0)	23,745 (19.7)	5,065 (25.7)	
Insurance, n (%)					<0.001
Private	27,835 (16.5)	4,497 (16.1)	19,902 (16.5)	3,426 (17.4)	
Medicare	110,968 (65.9)	18,082 (65.0)	79,999 (66.3)	12,887 (65.4)	
Medicaid	17,807 (10.6)	3,226 (11.6)	12,594 (10.4)	1,987 (10.1)	
Other/unknown	11,694 (7.0)	2,030 (7.3)	8,264 (6.8)	1,400 (7.0)	
Number of comorbid diseases^d, median (IQR)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-7)	<0.001
Discharge year					<0.001
2008	15,949 (9.5)	2,564 (9.2)	11,383 (9.4)	2,002 (10.2)	
2009	34,107 (20.3)	5,602 (20.1)	24,091 (20.0)	4,414 (22.4)	
2010	33,834 (20.1)	5,588 (20.1)	23,989 (19.9)	4,257 (21.6)	
2011	34,194 (20.3)	5,477 (19.7)	24,532 (20.3)	4,285 (21.2)	
2012	32,915 (19.6)	5,547 (19.9)	24,201 (20.0)	3,167 (16.1)	
2013	17,305 (10.3)	3,057 (11.0)	12,563 (10.4)	1,685 (8.6)	
Acute organ dysfunction^e, n (%)					
Cardiovascular	120,461 (71.6)	20,165 (72.4)	86,015 (71.2)	14,281 (72.5)	<0.001
Respiratory	108,745 (64.6)	17,333 (62.3)	78,833 (65.3)	12,579 (63.8)	<0.001
Renal	102,129 (60.7)	17,194 (61.8)	72,931 (60.4)	12,004 (60.9)	<0.001
Hematologic	47,923 (28.5)	8,209 (29.5)	33,710 (27.9)	6,064 (30.8)	<0.001
Neurological	38,151 (22.7)	6,357 (22.8)	27,271 (22.6)	4,523 (23.0)	0.40
Hepatic	14,029 (8.3)	2,268 (8.2)	9,981 (8.3)	1,780 (9.0)	0.001
Vasopressor use, n (%)^f					
Norepinephrine	132,250 (78.6)	21,678 (77.9)	98,549 (81.6)	12,023 (61.0)	<0.001
Phenylephrine	68,008 (40.4)	10,549 (37.9)	47,946 (39.7)	9,513 (48.3)	<0.001
Dopamine	62,731 (37.3)	11,443 (41.1)	43,445 (36.0)	7,843 (39.8)	<0.001
Vasopressin	43,095 (25.6)	7,242 (26.0)	30,367 (25.2)	5,486 (27.8)	<0.001
Epinephrine	33,870 (20.1)	4,884 (17.6)	25,118 (20.8)	3,868 (19.6)	<0.001
ICU admission, n (% of patient cohort)	158,469 (94.2)	26,271 (94.4)	113,406 (93.9)	18,792 (95.3)	<0.001
Type of admission, n (%)					<0.001
Medical	99,554 (59.1)	16,709 (60.0)	71,370 (59.1)	11,475 (58.2)	
Surgical^g	68,750 (40.9)	11,126 (40.0)	49,389 (40.9)	8,235 (41.8)	

eTable 1 (continued). Characteristics of Patients Stratified by Admission to Shortage, Consistent Use or Unclassified Hospitals

	Total Cohort	Shortage Hospitals ^a	Consistent Use Hospitals ^b	Unclassified hospitals ^c	P Value
Outcomes					
Hospital mortality, n (%)	62,239 (37.0)	10,060 (36.1)	44,898 (37.2)	7,281 (36.9)	0.005
Resource use					
First ICU LOS, median (IQR)	6 (3-11)	6 (3-11)	6 (3-12)	6 (3-11)	<0.001
Hospital LOS, median (IQR)	13 (7-22)	13 (7-22)	13 (7-23)	13 (7-23)	0.64
Discharge location for survivors, n (%)					<0.001
Home	37,118 (35.0)	6,923 (39.0)	25,237 (33.3)	4,958 (39.9)	
LTACH/SNF	52,845 (49.8)	8,417 (47.4)	38,957 (51.4)	5,471 (44.0)	
Hospice	8,775 (8.3)	1,103 (6.2)	6,573 (8.7)	1,099 (8.8)	
Other	7,327 (6.9)	1,332 (7.5)	5,094 (6.7)	901 (7.3)	

^a Defined as hospitals meeting three criteria: 1) > 20% relative decrease in norepinephrine use from baseline in at least one quarter of 2011; 2) return to norepinephrine use rates within 10% relative to the baseline rate by the second quarter of 2012; and 3) no more than one quarter of norepinephrine use > 20% below baseline before or after 2011.

^b Defined as hospitals in which norepinephrine use that did not decrease by > 20% in any quarter of 2011

^c Defined by not meeting criteria required for inclusion as a shortage or consistent use hospital

^d As defined by Elixhauser et al.¹

^e As defined by Angus et al.²

^f Alone or in combination with one or more additional vasopressors.

^g As defined by Healthcare Cost and Utilization Project.³

ICU: intensive care unit, IQR: interquartile range, LOS: length of stay, LTACH: long-term acute care hospital, SD: standard deviation, SNF: skilled nursing facility, US: United States

eTable 2. Primary Model

Patient-level mixed effects logistic regression analysis: Association between change in hospital norepinephrine use and hospital mortality rates

n = 27,835	Mortality for exposed patients with septic shock, n (%)	Mortality for unexposed patients with septic shock, n (%)	aOR (95% CI)	P Value
Admission during shortage quarter	777 (39.6)	9,283 (35.9)	1.15 (1.01-1.30)	0.03
Patient age- years				
<50	64 (28.1)	884 (28.1)	Reference	
50-64	220 (37.4)	2,359 (32.4)	1.48 (1.34-1.63)	<0.001
65-84	377 (41.7)	4,597 (37.4)	1.95 (1.76-2.17)	<0.001
≥ 85	116 (48.1)	1,443 (45.8)	2.79 (2.46-3.16)	<0.001
Sex				
Male	400 (38.2)	4,878 (35.3)	Reference	
Female	377 (41.3)	4,405 (36.6)	1.08 (1.02-1.13)	0.007
Race				
Caucasian	479 (37.1)	5,902 (33.6)	Reference	
Black	130 (45.0)	1,213 (42.4)	1.19 (1.08-1.31)	<0.001
Other	168 (44.3)	2,168 (39.7)	1.10 (1.01-1.19)	0.03
Insurance				
Private	98 (34.3)	1,309 (31.1)	Reference	
Medicare	527 (41.1)	6,317 (37.6)	1.16 (1.07-1.27)	0.001
Medicaid	100 (41.2)	958 (32.1)	1.13 (1.02-1.26)	0.02
Other/unknown	52 (34.9)	699 (37.2)	1.36 (1.20-1.53)	<0.001
Number of Elixhauser comorbidities^a	NA	NA	0.95 (0.94-0.96)	<0.001
Acute organ dysfunction^b				
Cardiovascular	616 (42.4)	7,156 (38.2)	1.48 (1.39-1.57)	<0.001
Respiratory	614 (48.5)	7,261 (45.2)	3.50 (3.29-3.73)	<0.001
Neurologic	240 (49.2)	2,423 (41.3)	1.17 (1.10-1.25)	<0.001
Hematologic	238 (44.0)	3,127 (40.8)	1.30 (1.22-1.38)	<0.001
Hepatic	90 (55.6)	1,170 (55.6)	1.98 (1.80-2.18)	<0.001
Renal	535 (44.1)	6,362 (39.8)	1.46 (1.38-1.55)	<0.001
Type of admission				
Medical	563 (46.1)	6,492 (41.9)	Reference	
Surgical ^c	214 (29.0)	2,791 (26.9)	0.48 (0.44-0.52)	<0.001
Year of hospital discharge				
2008	NA	950 (37.1)	Reference	
2009	NA	2,152 (38.4)	1.02 (0.91-1.13)	0.76
2010	NA	2,034 (36.4)	0.92 (0.83-1.02)	0.11
2011	777 (39.6)	1,216 (34.6)	0.66 (0.58-0.74)	<0.001
2012	NA	1,909 (34.4)	0.62 (0.56-0.70)	<0.001
2013	NA	1,022 (33.4)	0.58 (0.52-0.66)	<0.001
ICU admission				
No	28 (30.4)	404 (27.5)	Reference	
Yes	749 (40.1)	8,879 (36.4)	0.88 (0.77-1.00)	0.047
Hospital characteristics				
Bed size				

eTable 2 (continued). Primary Model

n = 27,835	Mortality for exposed patients with septic shock, n (%)	Mortality for unexposed patients with septic shock, n (%)	aOR (95% CI)	P Value
>500	301 (40.4)	2,731 (34.5)	Reference	
400 – 499	161 (40.8)	2,026 (37.1)	1.10 (0.78-1.54)	0.59
300 - 399	254 (43.6)	3,160 (38.1)	0.84 (0.60-1.17)	0.31
200 - 299	22 (17.9)	760 (31.0)	0.69 (0.46-1.04)	0.08
100 - 199	26 (31.3)	462 (35.3)	0.99 (0.65-1.51)	0.98
< 100	13 (41.9)	144 (33.0)	0.60 (0.35-1.04)	0.07
Teaching status^d				
Non-teaching hospital	305 (36.5)	4,922 (35.2)	Reference	
Teaching hospital	472 (41.9)	4,361 (36.7)	0.96 (0.74-1.24)	0.76
Location^d				
Rural	31 (36.1)	562 (34.4)	Reference	
Urban	746 (39.8)	8,721 (36.0)	1.03 (0.74-1.45)	0.84
US region				
Midwest	85 (29.8)	1,623 (31.9)	Reference	
Northeast	118 (54.4)	1,301 (48.5)	2.05 (1.44-2.92)	<0.001
South	434 (39.9)	4,129 (35.9)	1.56 (1.22-2.00)	<0.001
West	140 (37.8)	2,230 (33.8)	1.25 (0.97-1.63)	0.09

^aAs defined by Elixhauser et al.¹

^bAs defined by Angus et al.²

^cAs defined by Healthcare Cost and Utilization Project.³

^dAHA defines a teaching hospital as a hospital with an AMA-approved residency program, a member of the Council of Teaching Hospitals (COTH) or a ratio of full-time equivalent interns and residents to beds of .25 or higher. Hospitals are considered to be Urban based upon location within a metropolitan Core Based Statistical Areas (CBSA).

aOR: adjusted odds ratio, CI: confidence interval, ICU: intensive care unit, US: United States; NA: not applicable

eTable 3. Difference-in-Differences Model

Difference-in-differences model, including both shortage and consistent use hospitals to assess the association between change in hospital norepinephrine use during shortage quarters in 2011 and hospital mortality rates

n=148,591	aOR (95% CI)	P Value
Difference-in-differences estimator	1.17 (1.06-1.31)	0.003
Admitted to a) a shortage hospital^a during a quarter of 2011 with decreased norepinephrine use or b) a consistent use hospital^b during 2011	0.98 (0.90-1.07)	0.67
Admitted to a shortage hospital^a	0.98 (0.87-1.10)	0.76
Patient age, years		
<50	Reference	
50-64	1.35 (1.30-1.41)	<0.001
65-84	1.76 (1.69-1.84)	<0.001
≥ 85	2.56 (2.43-2.71)	<0.001
Sex		
Male	Reference	
Female	1.05 (1.02-1.07)	<0.001
Race		
Caucasian	Reference	
Black	1.14 (1.09-1.18)	<0.001
Other	1.10 (1.07-1.14)	<0.001
Insurance		
Private	Reference	
Medicare	1.15 (1.11-1.19)	<0.001
Medicaid	1.10 (1.05-1.15)	<0.001
Other/unknown	1.21 (1.15-1.28)	<0.001
Number of Elixhauser comorbidities^c	0.95 (0.95-0.96)	<0.001
Acute organ dysfunction^d		
Cardiovascular	1.47 (1.43-1.51)	<0.001
Respiratory	3.43 (3.34-3.52)	<0.001
Neurologic	1.17 (1.14-1.20)	<0.001
Hematologic	1.30 (1.27-1.34)	<0.001
Hepatic	2.09 (2.01-2.18)	<0.001
Renal	1.51 (1.47-1.54)	<0.001
Type of admission		
Medical	Reference	
Surgical ^e	0.50 (0.49-0.52)	<0.001
Year of hospital discharge		
2008		
2009	0.98 (0.93-1.02)	0.29
2010	0.90 (0.87-0.95)	<0.001
2011	0.67 (0.62-0.73)	<0.001
2012	0.65 (0.62-0.68)	<0.001
2013	0.63 (0.60-0.67)	<0.001
ICU admission		
No	Reference	
Yes	0.92 (0.87-0.98)	0.005
Hospital characteristics		
Bed size		
>500	Reference	

eTable 3 (continued). Difference-in-Differences Model

	aOR (95% CI)	P Value
400 – 499	1.04 (0.90-1.20)	0.62
300 - 399	1.06 (0.91-1.23)	0.45
200 - 299	1.06 (0.91-1.23)	0.45
100 - 199	0.97 (0.82-1.15)	0.73
< 100	0.74 (0.43-1.27)	0.28
Teaching status^f		
Non-teaching hospital	Reference	
Teaching hospital	0.97 (0.87-1.08)	0.59
Location^f		
Rural	Reference	
Urban	1.10 (0.90-1.33)	0.35
US region		
Midwest	Reference	
Northeast	1.39 (1.20-1.61)	<0.001
South	1.22 (1.08-1.38)	0.001
West	1.13 (0.98-1.30)	0.09

^aDefined as hospitals meeting three criteria: 1) more than 20% relative decrease in norepinephrine use from baseline in at least one quarter of 2011; 2) return to norepinephrine use rates within 10% relative to the baseline rate by the second quarter of 2012; and 3) no more than one quarter of norepinephrine use more than 20% below baseline before or after 2011.

^bDefined as hospitals in which norepinephrine use did not decrease by more than 20% in any quarter of 2011.

^cAs defined by Elixhauser et al.¹

^dAs defined by Angus et al.²

^eAs defined by Healthcare Cost and Utilization Project.³

^f AHA defines a teaching hospital as a hospital with an AMA-approved residency program, a member of the Council of Teaching Hospitals (COTH) or a ratio of full-time equivalent interns and residents to beds of .25 or higher. Hospitals are considered to be Urban based upon location within a metropolitan Core Based Statistical Areas (CBSA).

aOR: adjusted odds ratio, CI: confidence interval, ICU: intensive care unit, US: United States

eTable 4. Primary Model for “Negative Control” Patients

Patient-level mixed effects logistic regression analysis showing the association between change in hospital norepinephrine use and hospital mortality rates for patients with severe sepsis (who did not receive any vasopressors during the hospitalization)

	Mortality for exposed patients with severe sepsis, n (%) (total n=12,276)	Mortality for unexposed patients with severe sepsis, n (%) (total n=146,518)	aOR (95% CI)	P Value
Admission during shortage quarter	605 (4.9)	7,524 (5.1)	0.96 (0.87-1.07)	0.51
Patient age, years				
<50	35 (2.1)	445 (2.3)	Reference	
50-64	88 (3.1)	1,153 (3.4)	1.65 (1.48-1.85)	<0.001
65-84	272 (5.0)	3,506 (5.3)	3.49 (3.11-3.91)	<0.001
≥ 85	210 (9.2)	2,424 (8.7)	6.58 (5.84-7.41)	<0.001
Sex^a				
Male	296 (5.2)	3,570 (5.2)	Reference	
Female	309 (4.7)	3,958 (5.1)	0.93 (0.89-0.98)	0.003
Race				
Caucasian	363 (4.6)	4,860 (4.9)	Reference	
Black	95 (3.8)	788 (3.9)	0.86 (0.79-0.94)	0.001
Other	147 (7.9)	1,880 (6.9)	0.98 (0.91-1.07)	0.71
Insurance				
Private	65 (3.6)	936 (4.3)	Reference	
Medicare	459 (5.5)	5,652 (5.6)	0.70 (0.64-0.76)	<0.001
Medicaid	50 (4.3)	472 (3.5)	0.84 (0.75-0.94)	0.003
Other/unknown	31 (3.4)	468 (4.7)	1.18 (1.05-1.33)	0.005
Number of Elixhauser comorbidities^b	NA	NA	1.01 (1.00-1.02)	0.05
Acute organ dysfunction^c				
Cardiovascular	152 (5.2)	2,237 (6.8)	1.91 (1.81-2.02)	<0.001
Respiratory	170 (13.2)	1,953 (14.1)	3.80 (3.54-4.08)	<0.001
Neurologic	168 (8.3)	1,706 (7.1)	1.72 (1.62-1.83)	<0.001
Hematologic	120 (4.3)	1,654 (4.7)	1.40 (1.32-1.49)	<0.001
Hepatic	23 (17.2)	240 (15.5)	3.18 (2.74-3.69)	<0.001
Renal	390 (5.6)	4,609 (5.6)	1.70 (1.61-1.79)	<0.001
Type of admission				
Medical	556 (5.3)	6,857 (5.4)	Reference	
Surgical ^d	49 (2.7)	671 (3.3)	0.48 (0.45-0.53)	<0.001
Year of hospital discharge				
2008	NA	743 (6.0)	Reference	
2009	NA	1,611 (5.8)	0.97 (0.88-1.06)	0.48
2010	NA	1,629 (5.3)	0.86 (0.78-0.94)	0.001
2011	605 (4.9)	1,091 (5.0)	0.80 (0.72-0.89)	<0.001

eTable 4 (continued). Primary Model for “Negative Control” Patients

	Mortality for exposed patients with severe sepsis, n (%) (total n=12,276)	Mortality for unexposed patients with severe sepsis, n (%) (total n=146,518)	aOR (95% CI)	P Value
2012	NA	1,566 (4.5)	0.70 (0.64-0.77)	<0.001
2013	NA	888 (4.7)	0.71 (0.64-0.79)	<0.001
ICU admission				
No	343 (3.7)	4,343 (3.9)	Reference	
Yes	262 (8.8)	3,185 (8.9)	1.70 (1.60-1.81)	<0.001
Hospital characteristics				
Bed size				
>500	140 (4.1)	1,486 (4.5)	Reference	
400 – 499	135 (3.9)	1,851 (5.2)	1.11 (0.68-1.80)	0.68
300 - 399	277 (7.1)	3,188 (6.1)	0.82 (0.51-1.32)	0.41
200 - 299	15 (2.4)	421 (3.7)	0.60 (0.33-1.08)	0.09
100 - 199	29 (4.8)	479 (4.9)	0.74 (0.41-1.33)	0.32
< 100	9 (3.7)	103 (2.6)	0.47 (0.22-1.01)	0.05
Teaching status^e				
Non-teaching hospital	333 (5.7)	4,817 (5.4)	Reference	
Teaching hospital	272 (4.2)	2,711 (4.8)	0.75 (0.52-1.09)	0.13
Location				
Rural	38 (3.8)	830 (5.0)	Reference	
Urban	567 (5.0)	6,698 (5.2)	0.90 (0.56-1.44)	0.65
US region				
Midwest	59 (3.3)	1,153 (3.8)	Reference	
Northeast	119 (9.9)	1,518 (8.9)	2.59 (1.57-4.29)	<0.001
South	271 (3.9)	2,966 (4.3)	1.51 (1.06-2.15)	0.02
West	156 (6.9)	1,891 (6.3)	2.03 (1.4-2.93)	<0.001

^a missing data n=1

^bAs defined by Elixhauser et al.¹

^cAs defined by Angus et al.²

^dAs defined by Healthcare Cost and Utilization Project.³

^eAHA defines a teaching hospital as a hospital with an AMA-approved residency program, a member of the Council of Teaching Hospitals (COTH) or a ratio of full-time equivalent interns and residents to beds of .25 or higher. Hospitals are considered to be Urban based upon location within a metropolitan Core Based Statistical Areas (CBSA).

aOR: adjusted odds ratio, CI: confidence interval, ICU: intensive care unit, US: United States

eTable 5. Additional Sensitivity Analyses of Primary and Difference-in-Difference Models

Models	Septic Shock cohort					
	Cohort(s)		No. of deaths/total No. of patients (%)	Absolute mortality difference, % (95% CI)	Adjusted Odds Ratio (95% CI)	P Value
Primary model excluding data after the shortage year (2011)	Shortage hospitals	Admission during a non-shortage quarter	6,352/17,270 (36.8)	NA	Reference	
		Admission during a quarter of 2011 in which norepinephrine use fell more than 20% below baseline	777/1,961 (39.6)	2.8 (0.6-5.1)	1.14 (1.01-1.29)	0.04
Difference-in-differences model excluding data after the shortage year ^b	Shortage and consistent use hospitals	Difference-in-differences estimator	NA	NA	1.13 (1.01-1.26)	0.04
Primary model reclassifying shortage hospitals and excluding data after the shortage year ¹	Shortage hospitals	Admission during a non-shortage quarter	9,971/26,875 (37.1)	NA	Reference	
		Admission during a quarter of 2011 in which norepinephrine use fell more than 20% below baseline	1,437/3,807 (37.8)	0.7 (-0.01 to 2.3)	1.11 (1.01-1.23)	0.03
Difference-in-differences model reclassifying shortage hospitals and excluding data after the shortage year ^b	Shortage and consistent use hospitals	Difference-in-differences estimator	NA	NA	1.09 (1.00-1.18)	0.06
Primary model excluding patients transferred in from another acute hospital	Shortage hospitals	Admission during a non-shortage quarter	8,281/22,892 (36.2)	NA	Reference	
		Admission during a quarter of 2011 in which norepinephrine use fell more than 20% below baseline	686/1,728 (39.7)	3.5 (1.2-5.9)	1.11 (0.97-1.27)	0.11

eTable 5 (continued). Additional Sensitivity Analyses of Primary and Difference-in-Difference Models

Models	Cohort(s)		No. of deaths/total No. of patients (%)	Absolute mortality difference, % (95% CI)	Adjusted Odds Ratio (95% CI)	P Value
Difference-in-differences model excluding patients transferred in from another acute hospital ^b	Shortage and consistent use hospitals	Difference-in-differences estimator	NA	NA	1.15 (1.03-1.29)	0.02
Primary model including all non-surgical patients who received one or more days of vasopressors ^a	Shortage hospitals	Admission during a non-shortage quarter	11,093/34,590 (32.1)	NA	Reference	
		Admission during a quarter of 2011 in which norepinephrine use fell more than 20% below baseline	1,317/4,220 (31.2)	-0.9 (-2.3 to 0.6)	1.05 (0.95-1.16)	0.33
Difference-in-differences model including all non-surgical patients who received one or more days of vasopressors ^a	Shortage and consistent use hospitals	Difference-in-differences estimator	NA	NA	1.07 (0.98-1.15)	0.12
Admission during a quarter of 2011 in which norepinephrine use fell more than 20% below baseline, stratified by reduction amount	Shortage hospitals	No reduction	9,283/25,874 (35.9)	NA	Reference	
		20 - 25% reduction	238/621 (38.3)	2.4 (-1.3 to 6.4)	1.10 (0.91-1.33)	0.32
		26 - 35% reduction	271/656 (41.3)	5.4 (1.7-9.3)	1.29 (1.07-1.56)	0.007
		> 35% reduction	268/684 (39.2)	3.3 (0.3-7.1)	1.07 (0.89-1.28)	0.49

Patient-level variables in the models include: patient age, sex, race, insurance type, number of Elixhauser comorbidities, acute organ dysfunctions, type of admission (medical or surgical), year of hospital discharge, ICU admission. Hospital-level variables include bed size, teaching status, location (urban versus rural) and US region. Model of non-surgical patients excludes type of admission.

CI: confidence interval; NA: not applicable

^a Categorization of shortage hospitals and quarters was based on the original cohort of patients who received 2 or more days of vasopressors.

eReferences

1. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8-27.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
3. HCUP Procedure Classes. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, 2014. (Accessed August 31, 2015 at: www.hcup-us.ahrq.gov/toolssoftware/procedure/procedure.jsp.)