Epidemiology of Vasopressin Use for Adults with Septic Shock

Emily A. Vail¹, Hayley B. Gershengorn^{2,3,4}, May Hua¹, Allan J. Walkey⁵, and Hannah Wunsch^{6,7}

¹Department of Anesthesiology, Columbia University, New York, New York; ²Department of Medicine, and ³Department of Neurology, Albert Einstein College of Medicine, New York, New York; ⁴Montefiore Medical Center, New York, New York; ⁵Boston University Department of Medicine, Boston, Massachusetts; ⁶University of Toronto Department of Anesthesiology, Toronto, Ontario, Canada; and ⁷Sunnybrook Health Sciences Center, Toronto, Ontario, Canada

ORCID ID: 0000-0002-1849-5780 (E.A.V.).

Abstract

Rationale: Vasopressin may be used to treat vasodilatory hypotension in septic shock, but it is not recommended by guidelines as a first- or second-line agent. Little is known about how often the drug is used currently in septic shock.

Objectives: We conducted this study to describe patterns of vasopressin use in a large cohort of U.S. adults with septic shock and to identify patient and hospital characteristics associated with vasopressin use.

Methods: This was a retrospective cohort study of adults admitted to U.S. hospitals with septic shock in the Premier healthcare database (July 2008 to June 2013). We performed multilevel mixed-effects logistic regression with hospitals as a random effect to identify factors associated with use of vasopressin alone or in combination with other vasopressors on at least 1 day of hospital admission. We calculated quotients of Akaike Information Criteria (AIC) to determine relative contributions of patient and hospital characteristics to observed variation.

Measurements and Main Results: Among 584,421 patients with septic shock in 532 hospitals, 100,923 (17.2%) received

vasopressin. A total of 6.1% of patients receiving vasopressin received vasopressin alone, and 93.9% received vasopressin in combination with other vasopressors (up to five vasopressors in 15 different combinations). The mean monthly rate of vasopressin use increased from 14.5 to 19.6% over the study period, representing an average annual relative increase of 8% ($P < 0.001$). The median hospital rate of vasopressin use for septic shock was 11.7% (range, 0–69.7%). Patient demographic and clinical characteristics, including patient age (adjusted odds ratio, 0.71 for age > 85 yr compared with the reference group of age < 50 yr; 95% confidence interval, 0.69–0.74) and acute respiratory dysfunction (adjusted odds ratio, 3.25; 95% confidence interval, 3.20–3.31), were responsible for the majority of observed variation in vasopressin use (quotient of AICs, 0.56). However, hospital of admission also contributed substantially to observed variation (quotient of AICs, 0.37).

Conclusions: Approximately one-fifth of patients with septic shock received vasopressin, but rarely as a single vasopressor. The use of vasopressin has increased over time. The likelihood of receiving vasopressin was strongly associated with the specific hospital to which each patient was admitted.

Keywords: vasoconstrictor agents; septic shock; practice variation

(Received in original form April 12, 2016; accepted in final form July 12, 2016)

Supported by National Institutes of Health National Institute on Aging grant K08AG051184 (M.H.) and National Institutes of Health NHLBI grant K01HL116768 (A.J.W.).

Author Contributions: E.A.V. coordinated the study and drafted the manuscript. H.B.G. designed the study, performed data analysis, and revised the manuscript. M.H. helped to design the study and revised the manuscript. A.J.W. helped to design the study and revised the manuscript. H.W. conceived of and designed the study, purchased access to study data, and helped to draft the manuscript. All authors were involved with interpretation of the data and read and approved the final manuscript.

Correspondence and requests for reprints should be addressed to Emily Vail, M.D., 630 West 168th Street, P&S Box 46, New York, NY 10032. E-mail: eav2113@cumc.columbia.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 13, No 10, pp 1760–1767, Oct 2016

Copyright © 2016 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201604-259OC

Internet address: www.atsjournals.org

Vasopressin is a potent noncatecholamine vasopressor agent that may be used in the treatment of shock (1). Since the first description of exogenous administration to humans with vasodilatory shock and the discovery of relative vasopressin deficiency in patients with septic shock, the physiologic effects and clinical efficacy of vasopressin have been extensively studied (2–5). In particular, several studies examining physiological outcomes in patients with septic shock demonstrated that vasopressin has a catecholamine-sparing effect and may improve kidney function and reduce tachyarrhythmia at low to moderate infusion rates (6–10).

Current guidelines state that vasopressin may be used as an adjunctive agent in combination with norepinephrine for the treatment of adults with septic shock, but little is known about its use by clinicians (11). Observational studies of vasopressin use in adults have reported rates of use between 1 and 41%; however, practice patterns and factors associated with use of vasopressin during septic shock are unclear (12–15). We conducted this study to describe patterns of vasopressin use in a large cohort of adults in the United States with septic shock and to identify patient and hospital characteristics associated with vasopressin use. We hypothesized that rates of vasopressin use for the treatment of adults with septic shock would vary widely between hospitals, after accounting for patient case mix.

Portions of this work, in abstract form, were previously presented (16, 17).

Methods

Human Subjects

The study protocol was reviewed by the Institutional Review Boards of Columbia University Medical Center and Albert Einstein College of Medicine, which granted waivers of informed consent (IRB-AAAC3172[Y5M00] and IRB-2013-2602, respectively).

Study Design

We conducted a retrospective cohort study of acute care hospital admissions captured in the Premier healthcare database, which contains administrative (Ninth International Classification of Disease Clinical Modification [ICD-9-CM] and Current Procedural Terminology codes)

and pharmacy claims data collected at time of discharge from approximately 20% of U.S. acute care hospitalizations (18).

Premier data have been used extensively for studies of medication use among hospitalized patients (19, 20).

Study Cohort

We identified adult patients with septic shock admitted to a participating hospital between July 1, 2008 and June 30, 2013. Severe sepsis was identified from ICD-9-CM codes using the method described by Angus and colleagues (21). We defined septic shock as the presence of severe sepsis and a pharmacy claim of at least one of five vasopressors (vasopressin, norepinephrine, phenylephrine, dopamine, or epinephrine) on at least 1 day during the hospital admission, consistent with the clinical definition of septic shock used throughout the study period (22).

Patients were excluded from the study if they were younger than 18 years of age on the day of admission or if they were admitted to a primarily pediatric hospital (with a mean patient age < 18 yr during the study period). We also excluded patients admitted to Premier hospitals that treated fewer than 13 patients with septic shock (representing the lowest 5th percentile of septic shock admission rates among the cohort) during the study period to avoid inclusion of hospitals with practice patterns informed by the least amount of clinical experience with septic shock management.

Outcomes

Our primary outcome was use of vasopressin, alone or in combination with other vasopressors, on 1 or more days of admission. We examined patient and hospital characteristics expected to affect rates of vasopressin use. Patient demographics included age, race (white, African American, or other), type of health insurance (private, Medicare, or Medicaid) and the number of chronic comorbid diseases as defined by Elixhauser and colleagues (23).

Acute organ dysfunction during hospitalization was identified using the individual components of the Angus method for severe sepsis (21). Vasopressor and inotrope (dobutamine, milrinone, or amrinone) use was identified from pharmacy claims data using a previously validated method (24). Mechanical ventilation and renal replacement therapy

during hospitalization were defined by billing codes. Surgical admissions were defined as hospitalizations during which patients underwent one or more major diagnostic or therapeutic surgical procedures, identified by ICD-9-CM procedure codes and classified according to the schema developed by the Healthcare Cost and Utilization Project (25).

Specialty of the admitting physician (including critical care and pulmonary medicine, surgery, internal medicine, cardiology, or other specialty) was determined using the method developed by Fawzy and colleagues (15). Cardiopulmonary resuscitation (CPR) was identified using ICD-9-CM codes previously used in administrative datasets (26, 27).

We determined rates of in-hospital mortality and durations of intensive care unit (ICU) and hospital length of stay from ICU and hospital bed charges (reported in whole days) and patient discharge status as coded by Premier (death, home, skilled nursing facility or long-term acute care hospital, or hospice).

We report mortality and discharge status as percentages and ICU and hospital length of stay as medians and interquartile ranges. Hospital-level variables included number of acute care beds, teaching status, urban location, and U.S. geographic region (Northeast, South, Midwest, and West) as defined by Premier (18).

Statistical Analysis

We calculated rates of vasopressin use, alone and in combination with other vasopressor agents in the cohort, and examined changes in the rate of overall vasopressin use over time. We performed univariate analyses using chi-square tests, *t* tests, and Wilcoxon rank-sum tests, where appropriate.

To identify factors associated with use of vasopressin, we performed multilevel mixed-effects logistic regression with hospitals as a random effect. We included patient age, sex, race, number of comorbid diseases and each individual acute organ dysfunction, ICU admission, major surgery during admission, year of hospital admission, and hospital characteristics as model covariates.

To summarize variation in vasopressin use across cohort hospitals, we calculated rates of vasopressin use at each study hospital and then calculated the adjusted median odds ratio (AMOR) (28). Quotients of Akaike information criteria (AIC) were used to compare relative contributions of

patient- and hospital-level characteristics and hospital of admission to the observed variability (29, 30).

We performed three sensitivity analyses: (1) restricting the analysis to the subgroup of patients who received two or more vasopressor agents during hospitalization; (2) restricted to those patients who received 2 or more days of vasopressors; and (3) restricted to patients who did not undergo CPR, to exclude use of vasopressin that might occur during an attempted resuscitation.

Statistical significance was defined as a P value < 0.05 for all analyses. However, given the size of the dataset, we also assessed clinical significance. All analyses were performed using Stata 13.1 (StataCorp LP, College Station, TX).

Results

After exclusions (Figure 1), 584,421 patients in 532 U.S. hospitals were included in the cohort. For characteristics of the hospitals, *see* Table E1 in the online supplement. Of the cohort, 52% were men; median age was 69 years (interquartile range [IQR], 57–79). Patients had a median of five (IQR, 3–6)

Elixhauser comorbidities (*see* Table E2 for a complete description). Patients also had a high burden of acute organ system dysfunction throughout hospitalization, including cardiovascular (61.4%), pulmonary (52.4%), and renal (56.3%).

Of the cohort, 84.5% of patients were admitted to an ICU, 59.6% were mechanically ventilated, and 15.0% received renal replacement therapy; 18.7% of patients underwent a major surgical procedure during admission. Overall in-hospital mortality was 29.4%. Median hospital length of stay was 11 days (IQR, 6–19 d). Patients admitted to an ICU were admitted for a median duration of 4 days (IQR, 2–9 d) on their first admission and 5 days (IQR, 2–10 d) overall. Of the surviving cohort ($n = 412,839$), 40.9% were discharged to home directly from the hospital.

Vasopressor Use

Overall, norepinephrine was the most commonly administered vasopressor (57.3% of cohort, $n = 335,135$) and 17.2% of the cohort received vasopressin ($n = 100,923$; Table 1). Of patients who received vasopressin, 6.1% ($n = 6,146$) received vasopressin alone (1.1% of all patients). Vasopressin was used in patients who also

received all possible combinations of other vasopressors (*see* Table E3 for a complete list of vasopressor combinations used among the cohort), and patients who received vasopressin, either alone or in combination with other vasopressors, were more likely to receive inotropes than those who did not receive vasopressin (20.7 vs. 7.7%, $P < 0.001$). Among the cohort, mean monthly rates of vasopressin use increased consistently over the study period (from 14.5 to 19.6%), representing an average annual relative increase of 8% ($P < 0.001$).

Patients received vasopressors for a median of 2 hospital days (IQR, 1–3; full range, 1–197 d). Duration of vasopressin use was slightly shorter than duration of overall vasopressor use (median, 1 d; IQR, 1–2 d; versus median 2 days, IQR, 1–3 d). Median time from admission to initiation of vasopressin was longer among patients who underwent major surgery during admission (4 d; IQR, 2–11 d vs. 2 d; IQR, 1–6 d; $P < 0.001$) (Table 2).

Patient- and Physician-Level Factors Associated with Vasopressin Use

In unadjusted analyses, patients who received 1 or more days of vasopressin were younger than patients who did not receive

Figure 1. Cohort creation flowchart.

Table 1. Combinations of vasopressors received by adults with septic shock

Vasopressor	Any Use	Single Agent	First Agent*	2 Vasopressors in Combination: 142,110 (24.3)				
				VASO	NE	PHENYL	DOPA	EPI
VASO	100,923 (17.2)	6,146 (1.1)	8,959 (1.5)	—	23,145 (4.0)	4,320 (0.7)	2,308 (0.4)	1,682 (0.3)
NE	335,135 (57.3)	137,133 (23.5)	178,717 (30.6)	—	—	33,598 (5.8)	36,414 (6.2)	12,230 (2.1)
PHENYL	236,593 (40.5)	102,627 (17.6)	124,458 (21.3)	—	—	—	13,544 (2.3)	8,939 (1.5)
DOPA	187,364 (32.1)	67,765 (11.6)	99,892 (17.1)	—	—	—	—	5,930 (1.0)
EPI	111,683 (19.1)	26,497 (4.5)	33,848 (5.8)	—	—	—	—	—
Total	584,421 (100)	340,168 (58.2)	445,874 (76.3)	—	—	—	—	—

Definition of abbreviations: DOPA = dopamine; EPI = epinephrine; NE = norepinephrine; PHENYL = phenylephrine; VASO = vasopressin.

Data presented as n (% of cohort).

*First agent: patients who received only one vasopressor agent during hospital admission or received only one vasopressor agent on the first day of vasopressor treatment.

vasopressin (median age, 66 [IQR, 56–77] yr vs. 69 [IQR, 58–79] yr; $P < 0.001$; Table 3). Patients who received vasopressin also had several indicators of increased severity of illness, including higher rates of ICU admission (92.2 vs. 82.9%, $P < 0.001$), higher rates of all types of acute organ dysfunction during hospitalization (Table 3), higher rates of mechanical ventilation (83.7 vs. 54.6%, $P < 0.001$), and higher rates of renal replacement therapy (24.3 vs. 13.1%, $P < 0.001$).

Patients who received vasopressin had higher unadjusted in-hospital mortality rates (55.7 vs. 23.9%, $P < 0.001$) and longer unadjusted lengths of first ICU (median 5 [IQR, 2–11] d vs. 4 [IQR, 2–9] d, $P < 0.001$) and hospital stays (median 11 [IQR, 4–21] d vs. 11 [IQR, 6–18] d, $P < 0.002$). Patients who received vasopressin were more likely to be admitted by a pulmonologist, intensivist, or surgeon than patients who did not receive vasopressin (Table 3).

Multivariable Logistic Regression Analysis

After multivariable modeling, there was not a strong relationship between patient

age, sex, and race and vasopressin use (Table 4). Patients receiving vasopressin were significantly more likely to have specific organ dysfunctions ($P < 0.001$), were more likely to undergo major surgery during admission (adjusted odds ratio [aOR], 1.34; 95% confidence interval [CI], 1.31–1.37; $P < 0.001$), and were more likely to be admitted to an ICU (aOR, 1.44; 95% CI, 1.39–1.48; $P < 0.001$) than patients who did not receive vasopressin.

Hospital-level factors significantly associated with vasopressin use included larger size (>500 beds as the reference group), location in the U.S. West (aOR, 2.03; 95% CI, 1.51–2.72; $P < 0.001$ compared with the Midwest), and teaching status (aOR, 1.28; 95% CI, 1.02–1.61; $P = 0.03$). Year was also significantly associated with use of vasopressin (aOR in year 2013, 1.60; 95% CI, 1.54–1.66; $P < 0.001$ compared with year 2008).

Variation in Vasopressin Use

The median hospital rate of vasopressin use for septic shock admissions was 11.7%,

with substantial variability between institutions (range, 0–69.7%). Patient-level factors determined the majority of observed variation in vasopressin use (quotient of AICs, 0.56), but unexplained interhospital variation was also a substantial contributor to variability (AIC quotient, 0.37), whereas measured hospital characteristics (e.g., teaching hospital, number of beds) were not (AIC quotient, 0.001) (Table 5).

The AMOR for hospitals was 2.65 (95% CI, 2.48–2.84), meaning that patients admitted to hospitals with high rates of vasopressin use were 2.65 times more likely to receive vasopressin than identical patients admitted to hospitals with low rates of vasopressin use. The magnitude of this association was greater than that for any single patient- or hospital-level factor except for the presence of acute respiratory organ dysfunction (aOR, 3.25; 95% CI, 3.20–3.31) (Table 4).

Sensitivity analyses including only patients who received 2 or more days of vasopressor treatment, at least two different vasopressors, and exclusion of patients who received in-hospital CPR resulted in similar AMORs (2.71 [95% CI, 2.53–2.92], 2.64 [95% CI, 2.47–2.82], and 2.65 [95% CI, 1.51–2.71], respectively). Full models are presented for each sensitivity analysis in Table E4.

Discussion

In this study, vasopressin was used for almost 20% of 500,000 U.S. adults with septic shock. Vasopressin was used most often in combination with one or more other vasopressor agents, with steadily

Table 2. Time to first vasopressor initiation

	Days from Admission to Vasopressor Initiation			P Value
	All Patients	Major Surgical Admission	Medical Admission	
Any vasopressor	2 (1–4)	2 (1–6)	2 (1–4)	<0.001
Vasopressin	3 (1–7)	4 (2–11)	2 (1–6)	<0.001
Norepinephrine	2 (1–5)	3 (1–8)	2 (1–4)	<0.001
Phenylephrine	3 (1–7)	3 (1–7)	3 (1–7)	<0.001
Dopamine	2 (1–4)	3 (1–8)	2 (1–4)	<0.001
Epinephrine	3 (1–8)	4 (1–10)	3 (1–8)	<0.001

Data presented as median (interquartile range).

Table 3. Characteristics of patients receiving vasopressin alone or in combination with other vasopressor agents

	Any Vasopressin (n = 100,923) (17.3%)	No Vasopressin (n = 483,498) (82.7%)	P Value
Patient characteristics			
Age, yr	66 (56–77)	69 (58–79)	<0.001
Male	54.9	51.4	<0.001
Race			<0.001
White	64.0	68.0	
African American	13.9	13.1	
Other	22.0	18.9	
Primary insurance provider			<0.001
Private	19.0	15.4	
Medicare	62.1	68.2	
Medicaid	11.2	9.8	
Other/unknown	7.7	6.6	
No. of comorbidities*	5 (3–6)	5 (3–6)	<0.001
Major surgical admission†	18.6	18.7	<0.001
Hospital care			
Specialty of admitting physician			<0.001
Pulmonary/critical care medicine	15.2	8.1	
Surgery	20.1	15.4	
Cardiology	3.8	4.3	
Internal medicine	60.8	72.2	
Other	0.1	0.1	
ICU admission	92.2	82.9	<0.001
Acute organ dysfunction			
Cardiovascular	77.7	58.0	<0.001
Pulmonary	75.6	47.5	<0.001
Neurologic	23.4	19.4	<0.001
Hematologic	33.9	22.2	<0.001
Renal	67.2	54.0	<0.001
Hepatic	13.2	4.3	<0.001
Mechanical ventilation	83.7	54.6	<0.001
Renal replacement therapy	24.3	13.1	<0.001
Other vasopressors			
Norepinephrine	80.2	52.6	<0.001
Phenylephrine	46.2	39.3	<0.001
Dopamine	33.4	31.8	<0.001
Epinephrine	31.3	16.6	<0.001
Outcomes			
In-hospital mortality	55.7	23.9	<0.001
First ICU length of stay, d	5 (2–11)	4 (2–9)	<0.001
Survivors	17 (10–28)	11 (7–19)	<0.001
Nonsurvivors	4 (2–9)	3 (1–8)	<0.001
Hospital length of stay, d	11 (4–21)	11 (6–18)	0.002
Survivors	11 (10–28)	11 (7–19)	<0.001
Nonsurvivors	6 (2–14)	7 (3–15)	<0.001
Discharge location of hospital survivors (n = 412,839)			<0.001
Home (with or without services)	34.4	41.7	
LTACH or SNF	49.1	44.4	
Same or other acute care hospital	7.0	5.8	
Hospice care	8.8	7.3	

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; LTACH = long-term acute care hospital; SNF = skilled nursing facility.

Data presented as percentage or median (IQR).

*As defined by Elixhauser and colleagues (23).

†As defined by Healthcare Cost and Utilization Project (25).

increasing use over the time studied. Vasopressin use was clearly more common among patients with a higher burden of acute organ dysfunction and among those

receiving more intensive healthcare, including ICU admission, mechanical ventilation, renal replacement therapy, and inotrope treatment. Increased use of

inotropes among patients receiving vasopressin is consistent with prior work by Gordon and colleagues (31) and may reflect higher rates of myocardial dysfunction with increased severity of illness or a decrease in cardiac output caused by unopposed afterload from vasopressin.

A substantial amount of variation in vasopressin use was attributable to the admitting hospital, with patients in higher-use hospitals more than 2.5 times as likely to receive vasopressin as those in low-use hospitals. These findings add to a growing body of literature describing significant interprovider and interhospital variations in practice throughout critical care medicine, including but not limited to the use of intravascular monitors (30), vasoactive medications (32), and blood transfusions (33).

Recent systematic reviews and metaanalyses of studies of vasopressin use in septic shock were substantially influenced by the outcome of the Vasopressin and Septic Shock trial, the largest randomized clinical trial of vasopressin to date (4, 5, 34). Although trials have established the safety and efficacy of vasopressin in the treatment of vasodilatory septic shock and inform current clinical guidelines, they do not address the actual use of vasopressin by clinicians. Our findings are similar to other observational studies of vasopressor use in shock that demonstrate wide variation in rates of vasopressin use between different countries, hospitals, and eras (12–15). However, previous work did not focus exclusively on septic shock, examine patient and hospital-level factors associated with vasopressin use, or describe changing patterns of vasopressin use over time.

We observed a consistent and statistically significant increase in the rate of vasopressin use over the study period. This increase may reflect increasing clinician interest in the use of vasopressin in septic shock after the February 2008 publication of the Vasopressin and Septic Shock Trial (VASST) trial results (34), just months before the onset of our study period. However, considering the negative trial result, a consistent and enduring increase in clinician adoption of vasopressin is unexpected. Furthermore, despite evidence of potential benefit in the subgroup of patients with less severe sepsis in the VASST trial, we found that vasopressin use was associated with several markers of increased severity of illness.

Table 4. Patient- and hospital-level factors associated with receipt of vasopressin in septic shock

	OR	95% CI	P Value
Patient characteristics			
Age, yr			
<50	Ref	—	—
50–64	0.96	(0.94–0.99)	0.01
65–74	0.90	(0.88–0.93)	<0.001
≥85	0.71	(0.69–0.74)	<0.001
Female vs. male	0.95	(0.93–0.96)	<0.001
Race			
White	Ref	—	—
African American	1.05	(1.02–1.07)	<0.001
Other	1.00	(0.98–1.03)	0.95
Primary insurance provider			
Private	Ref	—	—
Medicare	0.95	(0.96–0.97)	<0.001
Medicaid	0.89	(0.87–0.92)	<0.001
Other/unknown	0.95	(0.92–0.99)	0.01
Year of admission			
2008	Ref	—	—
2009	1.07	(1.03–1.10)	<0.001
2010	1.15	(1.11–1.19)	<0.001
2011	1.47	(1.42–1.52)	<0.001
2012	1.54	(1.49–1.60)	<0.001
2013	1.60	(1.54–1.66)	<0.001
Comorbid disease			
Each additional comorbidity*	0.97	(0.96–0.97)	<0.001
Organ dysfunction			
Cardiovascular	2.56	(2.51–2.60)	<0.001
Respiratory	3.25	(3.20–3.31)	<0.001
Neurologic	0.99	(0.97–1.01)	0.37
Hematologic	1.62	(1.60–1.65)	<0.001
Renal	1.75	(1.72–1.78)	<0.001
Hepatic	1.98	(1.93–2.03)	<0.001
Major surgical admission† versus medical admission	1.34	(1.31–1.37)	<0.001
ICU admission	1.44	(1.39–1.48)	<0.001
Hospital-level characteristics			
No. of beds			
500+	Ref	—	—
400–499	0.77	(0.53–1.11)	0.16
300–399	0.78	(0.56–1.11)	0.17
200–299	0.57	(0.41–0.79)	0.001
100–199	0.57	(0.41–0.80)	0.001
<100	0.28	(0.19–0.41)	<0.001
U.S. Region			
Midwest	Ref	—	—
South	1.10	(0.86–1.41)	0.45
Northeast	1.39	(1.02–1.38)	0.04
West	2.03	(1.51–2.72)	<0.001
Urban location	1.23	(0.97–1.56)	0.08
Teaching hospital	1.28	(1.02–1.61)	0.03
AMOR	2.65	(2.48–2.84)	

Definition of abbreviations: AMOR = adjusted median odds ratio; CI = confidence interval; ICU = intensive care unit; OR = odds ratio.

*As defined by Elixhauser and colleagues (19).

†As defined by Healthcare Cost and Utilization Project (20).

Alternatively, the observed increase in vasopressin use over time may reflect an increasing preference for vasopressin over dopamine as a second vasopressor agent, driven first by observational (13, 35) and trial evidence (36) published before and during our study demonstrating

higher rates of arrhythmia and death among patients treated with dopamine and later by the 2012 Surviving Sepsis Campaign (SSC) guidelines, which incorporated this evidence into a recommendation against the use of dopamine in most patients (11).

Table 5. Amount of variability in vasopressin use explained by patient and hospital characteristics

	Quotient of AICs
Patient characteristics	0.56
Hospital characteristics	0.001
Individual hospital	0.37

Definition of abbreviation: AIC = Akaike information criteria.

Quotient of AICs = $(AIC_{full} - AIC_{reduced}) / (AIC_{full} - AIC_{null})$, where AIC_{full} = AIC for the multivariable multilevel logistic model including all patient-level, hospital-level, and clustering variable information; $AIC_{reduced}$ = AIC for the multivariable multilevel logistic model excluding one of the variable sets; AIC_{null} = AIC for the multivariable multilevel logistic model, including no independent variables or clustering (29, 30).

Consistent with SSC guidelines, most patients who received vasopressin did so in combination with at least one other vasopressin agent (11, 37). However, dopamine, not vasopressin, was the most commonly chosen vasopressor used in combination with norepinephrine among cohort patients. Observed variation in vasopressin use may also reflect ambiguity in the SSC guidelines, which state only that vasopressin “can be added to norepinephrine to either raise mean arterial pressure to target or to decrease norepinephrine dose, but should not be used as the initial vasopressor” (11). It is notable that none of the SSC guidelines specifically endorse its use. Moreover, evidence of comparative efficacy of specific vasopressor combinations and long-term benefit is still lacking.

Limitations

This study is limited by the use of administrative data (38, 39). Specifically, we cannot be sure that there was not residual confounding due to differences in case mix and severity of illness. We were unable to examine many factors expected to contribute to a clinician’s choice of a vasopressor (or vasopressors) for a given patient, including an individual’s hemodynamics, the need for inotropic support, and availability of an ICU bed. Although the majority of hospitals in the dataset contributed data during each study month, some hospitals did not continuously contribute data to Premier during the study period; changes in participating hospitals,

case mix, and variability in providers over time may contribute to observed trends in vasopressor use.

The study dataset does not contain data on specific vasopressor doses or distinguish between bolus and infusion administration. Furthermore, granularity of pharmacy data in the Premier dataset is limited to calendar days, so we were unable to distinguish between simultaneous and sequential use of vasopressors administered on the same calendar day. Similarly, because ICD-9-CM codes included in the dataset are not time stamped, we were unable to ensure that vasopressor use and severe sepsis occurred concomitantly during all hospitalizations.

Among patients meeting septic shock criteria in the dataset, 5% were excluded

because they were classified by Premier as outpatients: these patients most likely died in Emergency Departments before hospital admission. Vasopressin use among moribund patients may have been higher than in the study cohort, leading us to underestimate overall rates of vasopressin use among patients with septic shock. Similarly, because vasopressin was rarely used as the initial vasopressor among the cohort, use of vasopressin was limited to the subgroup of patients who did not die during initial treatment with other, first-line vasopressor agents. Although we attempted to address some of these limitations with specific sensitivity analyses, the possibility of misclassification bias remains.

Conclusions

In a large cohort of U.S. adults with septic shock, we found that approximately one-fifth of patients received vasopressin, but rarely as a single vasopressor. Vasopressin use increased substantially over time and varied primarily in association with patient-level factors, including a variety of markers of higher severity of illness. The likelihood of receiving vasopressin was also very strongly associated with the specific hospital to which each patient was admitted. Further work is necessary to determine whether variation in nontrial use of vasopressin administration impacts patient outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Russell JA. Bench-to-bedside review: vasopressin in the management of septic shock. *Crit Care* 2011;15:226.
- Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997;25:1279–1282.
- Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997;95:1122–1125.
- Serpa Neto A, Nassar AP, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Damasceno MC, Russell JA. Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials. *Crit Care* 2012;16:R154.
- Polito A, Parisini E, Ricci Z, Picardo S, Annane D. Vasopressin for treatment of vasodilatory shock: an ESICM systematic review and meta-analysis. *Intensive Care Med* 2012;38:9–19.
- Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999;47:699–703. [Discussion, pp. 703–705].
- Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002;96:576–582.
- Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Bachetoni A, D'Alessandro M, Van Aken H, Pietropaoli P, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care* 2009;13:R130.
- Lauzier F, Lévy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med* 2006;32:1782–1789.
- Luckner G, Dünser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, et al. Arginine vasopressin in 316 patients with advanced vasodilatory shock. *Crit Care Med* 2005;33:2659–2666.
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al.; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
- Narat S, Thongprayoon C, Kittanamongkolchai W, Cheungpasitporn W, Erdogan A, Carrera P, Kashanie K. [Abstract] Changing trends in the use of vasopressors in intensive care unit: a 7-year study [abstract]. *Crit Care Med* 2014;42:A1450.
- Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, Ranieri VM, De Backer D, Payen D. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) study. *Crit Care Med* 2006;34:589–597.
- Beck V, Chateau D, Bryson GL, Pisipati A, Zanotti S, Parrillo JE, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Timing of vasopressor initiation and mortality in septic shock: a cohort study. *Crit Care* 2014;18:R97.
- Fawzy A, Evans SR, Walkey AJ. Practice patterns and outcomes associated with choice of initial vasopressor therapy for septic shock. *Crit Care Med* 2015;43:2141–2146.
- Vail E, Gershengorn HB, Li G, Wunsch H. Epidemiology of vasopressor use among adults with septic shock in the United States [abstract]. Presented at the American Society of Anesthesiologists' Annual Meeting. October 27, 2015, San Diego, CA. Abstract A4014.
- Vail E, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of vasopressin use among adults with septic shock in the United States [abstract]. *Am J Respir Crit Care Med* 2016;193:A6148.
- About Premier healthcare database. 2015 [accessed 2016 Jan 24]. Available from: <http://www.premierinc.com/transforming-healthcare/healthcare-performance-improvement/premier-research-services/>
- Herzig SJ, Rothberg MB, Guess JR, Gurwitz JH, Marcantonio ER. Antipsychotic medication utilization in nonpsychiatric hospitalizations. *J Hosp Med* 2016;11:543–549.
- Hauptman PJ, Blume SW, Lewis EF, Ward S. Digoxin toxicity and use of digoxin immune fab: insights from a national hospital database. *JACC Heart Fail* 2016;4:357–364.
- 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;29:1303–1310.
- Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–1256.
- Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
- Fawzy A, Bradford M, Lindenauer PK, Walkey AJ. Identifying vasopressor and inotrope use for health services research. *Ann Am Thorac Soc* 2016;13:414–418.
- Healthcare Cost and Utilization Project. HCUP Procedure Classes. 2014 [accessed 2015 Aug 31]. Available from: <http://www.hcup-us.ahrq.gov/toolsoftware/procedure/procedure.jsp>
- Ehlenbach WJ, Barnato AE, Curtis JR, Kreuter W, Koepsell TD, Deyo RA, Stapleton RD. Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. *N Engl J Med* 2009;361:22–31.

- 27 Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Iwai S, Jain D, Sule S, Ahmed A, *et al.* Regional variation in the incidence and outcomes of in-hospital cardiac arrest in the United States. *Circulation* 2015;131:1415–1425.
- 28 Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, Råstam L, Larsen K. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;60:290–297.
- 29 Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer-Verlag; 2001.
- 30 Gershengorn HB, Garland A, Kramer A, Scales DC, Rubinfeld G, Wunsch H. Variation of arterial and central venous catheter use in United States intensive care units. *Anesthesiology* 2014;120:650–664.
- 31 Gordon AC, Wang N, Walley KR, Ashby D, Russell JA. The cardiopulmonary effects of vasopressin compared with norepinephrine in septic shock. *Chest* 2012;142:593–605.
- 32 Hernandez AF, Li S, Dokholyan RS, O'Brien SM, Ferguson TB, Peterson ED. Variation in perioperative vasoactive therapy in cardiovascular surgical care: data from the Society of Thoracic Surgeons. *Am Heart J* 2009;158:47–52.
- 33 Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr, Peterson ED, Gammie JS, Song HK. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010;304:1568–1575.
- 34 Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, *et al.*; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877–887.
- 35 De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med* 2012;40:725–730.
- 36 De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779–789.
- 37 Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, *et al.*; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
- 38 Iwashyna TJ, Odden A, Rohde J, Bonham C, Kuhn L, Malani P, Chen L, Flanders S. Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. *Med Care* 2014;52:e39–e43.
- 39 Cooke CR, Iwashyna TJ. Using existing data to address important clinical questions in critical care. *Crit Care Med* 2013;41:886–896.