CHEST

Use and Outcomes of Peripheral Vasopressors in Early Sepsis-Induced Hypotension Across Michigan Hospitals

A Retrospective Cohort Study

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BACKGROUND: Vasopressors traditionally are administered via central access, but newer data suggest that peripheral administration may be safe and may avoid delays and complications associated with central line placement.

RESEARCH QUESTION: How commonly are vasopressors initiated through peripheral IV lines in routine practice? Is vasopressor initiation route associated with in-hospital mortality?

STUDY DESIGN AND METHODS: This retrospective cohort study included adults hospitalized with sepsis (November 2020-September 2022) at 29 hospitals in the Michigan Hospital Medicine Safety Consortium, a Collaborative Quality Initiative sponsored by Blue Cross Blue Shield of Michigan. We assessed route of early vasopressor initiation, factors and outcomes associated with peripheral initiation, and timing of central line placement.

RESULTS: Five hundred ninety-four patients received vasopressors within 6 h of hospital arrival and were included in this study. Peripheral vasopressor initiation was common (400/594 [67.3%]). Patients with peripheral vs central initiation were similar; BMI was the only patient factor associated independently with initiation route (adjusted OR [aOR] of peripheral initiation [per 1-kg/m^2 increase], 0.98; 95% CI, 0.97-1.00; $P = .015$). The specific hospital showed a large impact on initiation route (median OR, 2.19; 95% CI, 1.31-3.07). Compared with central initiation, peripheral initiation was faster (median, 2.5 h vs 2.7 h from hospital arrival; $P = .002$), but was associated with less initial norepinephrine use (84.3% vs 96.8%; $P = .001$). We found no independent association between initiation route and in-hospital mortality (32.3% vs 42.2%; aOR, 0.66; 95% CI, 0.39-1.12). No tissue injury from peripheral vasopressors was documented. Of patients with peripheral initiation, 135 of 400 patients (33.8%) never received a central line.

INTERPRETATION: Peripheral vasopressor initiation was common across Michigan hospitals and had practical benefits, including expedited vasopressor administration and avoidance of central line placement in one-third of patients. However, the findings of wide practice variation that was not explained by patient case mix and lower use of first-line norepinephrine with peripheral administration suggest that additional standardization may be needed.

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KEY WORDS: central access; central line; central venous catheter; hypotension; peripheral vasopressor; sepsis; septic shock; vasoactive medication; vasopressor

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ABBREVIATIONS: aOR = adjusted OR; CVC = central venous catheter; HMS = Michigan Hospital Medicine Safety Consortium; IQR = interquartile range; PIV = peripheral IV; SSC = Surviving Sepsis Campaign

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Take-home Points

Study Question: How are vasopressors initiated in routine practice and what impact does initiation route have on patient outcomes?

Results: In this multihospital cohort study of patients with sepsis requiring vasopressor therapy, 400 of 594 patients (67.3%) underwent vasopressor initiation peripherally. Wide variation was found in peripheral vasopressor use across hospitals, which was not explained by differences in patient case mix. Compared with central vasopressor initiation, peripheral initiation was associated with faster administration (median, 2.5 h vs 2.7 h from hospital arrival; $P = .002$) and less first-line norepinephrine use (84.3% vs 96.8%; $P = .001$), but no difference in in-hospital mortality (32.3% vs 42.2%; adjusted OR, 0.66; 95% CI, 0.39-1.12).

Interpretation: Peripheral vasopressor initiation was common across Michigan hospitals and showed practical benefits without apparent patient harm, although the wide practice variation suggests that additional standardization may be needed.

Vasopressors are recommended broadly to treat hypotension in patients with sepsis and septic shock.[1] Vasoactive medications traditionally are administered via central venous access, based on case reports of catastrophic tissue injury caused by extravasation of vasopressors from peripheral IV (PIV) lines.[2-4] However, administering vasopressors through PIV lines—or peripheral vasopressor administration—has several potential advantages, including expediting vasopressor initiation[5] and avoiding central line placement and associated complications in some patients.[6,7] Cohort studies suggest that peripheral vasopressors may be safe for short durations in the perioperative period[8] and for longer durations with monitoring in the ICU.[6,9-11] Thus, the 2021 Surviving Sepsis Campaign (SSC) guidelines suggest initiating vasopressors peripherally to avoid delays, but still advise placing central access as soon as feasible.[1]

Despite the accruing safety data and recent guidelines supporting peripheral vasopressor initiation, little is known about how vasopressors are initiated in practice. The SSC grades peripheral vasopressor data as very low quality[1] because most studies have been small and have been undertaken at a single center.[9-11] These studies also lack consistency in their approach to peripheral vasopressor administration, using protocols with different PIV line monitoring requirements and allowing different vasopressor agents and durations.[6,12-15] As a result, hospital vasopressor policies vary widely regarding both whether peripheral vasopressors are permitted and, if so, how they can be administered.[16] This variation in safety protocols and policies has made it challenging to develop best practices for peripheral vasopressor use. It is not clear how peripheral vasopressors are used in practice and whether route of administration impacts patient outcomes.

In this study, we examined peripheral vasopressor use across Michigan hospitals. We aimed to understand practice patterns for vasopressor initiation via PIV lines, factors associated with peripheral initiation, and the effects of initiation route on mortality. We also evaluated timing of central line placement to understand how central access is approached after peripheral vasopressor initiation.

Study Design and Methods

We performed a retrospective cohort study of patients hospitalized with sepsis and hypotension at 29 hospitals participating in the Michigan Hospital Medicine Safety Consortium's (HMS) sepsis initiative from November 2020 through September 2022. HMS is a Collaborative Quality Initiative sponsored by Blue Cross Blue Shield of Michigan (e-Appendix 1, 2). At each hospital, a random sample of hospitalized patients with community-acquired sepsis is selected for inclusion in the HMS sepsis cohort (e-Appendix 2). Data are abstracted into a centralized registry by trained abstractors at each hospital. A standard set of exclusions apply, including pregnancy, age younger than 18 years, and admission via interhospital transfer (see e-Appendix 2 for a complete list of HMS sepsis cohort exclusions). In this study, we further limited the cohort to patients with hypotension

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and vasopressor initiation within 6 h of hospital arrival. Hypotension was defined as systolic BP of < 90 mm Hg, systolic BP of < 100 mm Hg with a history of hypertension, or mean arterial pressure of < 65 mm Hg. Patients receiving vasopressors without documented hypotension also were presumed to be hypotensive and were included. Qualifying vasopressors included norepinephrine, epinephrine, phenylephrine, dopamine, vasopressin, and angiotensin II. These vasopressors could be administered as either continuous or push doses. Vasopressors administered during CPR or only during a procedure were excluded. Patients were excluded if they had a treatment limitation of no central access documented at hospital presentation.

Route of vasopressor initiation was collected in the HMS sepsis cohort data set. Peripheral initiation was defined as administration of the initial vasopressor through a PIV line. Central initiation was defined as administration of the initial vasopressor through a central line: temporary (nontunneled) central venous catheter (CVC), tunneled CVC, peripherally inserted central catheter, port, or temporary hemodialysis catheter. Central lines could be preexisting (present before hospital arrival) or new (placed after hospital arrival). Data abstractors were advised to record route of vasopressor initiation, when available. If route of vasopressor initiation was not documented explicitly in the chart and central access was present, abstractors were advised to assume the central access was used, using the following preferred order: temporary CVC over peripherally inserted central catheter or port. Patients who received an initial vasopressor through a midline catheter, intraosseous line, or unknown route were excluded. Midline catheters are placed in peripheral veins, but are used less commonly than PIV lines and may have lower extravasation rates.[17] Similarly, intraosseous lines provide central access, but are temporary and potentially less secure than other central lines.[18,19] Data on vasopressor dose and concentration, PIV line size and location, individual central line complications (eg, pneumothorax, venous injury, arrhythmias), peripheral vasopressor extravasation events, and PIV line removal for complication were not available.

In our primary analyses, we evaluated practice patterns of peripheral vasopressor initiation and tested for differences in patient characteristics and outcomes by route of vasopressor initiation. First, we compared baseline patient characteristics, illness severity, admission times, and management practices (eg, vasopressor timing and fluids received) by route of vasopressor initiation. We also evaluated the association between route of vasopressor initiation and hospital vasopressor policy, as reported in a fall 2021 survey of HMS hospitals, which was published previously.[16] We used χ^2 tests for categorical variables and *t* tests for continuous variables. We used kernel density plots and histograms to compare time to peripheral vs central vasopressor initiation.

Next, we measured the association between (1) patient characteristics and peripheral initiation and (2) route of initiation and patient outcomes using multilevel logistic regression models. For the primary analysis, we pooled hospitals with fewer than 15 eligible hospitalizations in the multilevel models. These hospitals were excluded in sensitivity analyses. In all models, patient characteristics were treated as fixed effects and hospital was treated as a random effect. First, we used a multilevel logistic regression model of peripheral initiation. The effect of hospital on peripheral initiation was assessed using a median OR, which measures variation between hospitals not explained by individual characteristics in the model. A median OR of 1.0 implies that the odds of peripheral vasopressor initiation is equivalent across hospitals; the larger the median OR, the stronger the hospital-level effects are in driving between hospital differences in vasopressor initiation routes. We also calculated an intraclass correlation, which measures variation at the hospital level compared with total variation. Second, we used multilevel logistic regression models for primary and secondary outcomes. All models were adjusted for prespecified baseline patient characteristics and markers of presenting illness severity: age, admission from a postacute care facility, hospitalization in the prior 90 days, kidney disease, liver disease, congestive heart failure, peripheral vascular disease, malignancy, BMI, lactate, creatinine, mechanical ventilation within 6 h of hospital arrival, altered mental status, and predicted mortality score, which was calculated using a logistic regression model developed and validated in the HMS sepsis cohort.[20]

The primary patient outcome was in-hospital mortality. Secondary patient outcomes were 30-day mortality, 90-day mortality, hospital length of stay of > 7 days, and mechanical ventilation or new dialysis during the admission. We also collected information on two types of complications, which were abstracted based on documentation in the electronic health record: (1) documented skin necrosis or ischemia from peripheral vasopressor use and (2) documented central line

removal for complication: suspected or known central line-associated blood stream infection; catheter thrombus; DVT; pulmonary embolus; and catheter migration, malposition, or malfunction. The reason for central line removal was not collected. These complication rates were not compared using multivariable models given the low event rate.

In secondary analysis, we evaluated time to new central line placement among patients with peripheral vasopressor initiation. Data on central line placement and vasopressor duration were collected through hospital day 4. After initiation, route of ongoing vasopressor administration was not available. Therefore, after a central line was placed, if a vasopressor was still being administered, it was assumed that the central line was used for subsequent vasopressor administration. We performed univariable comparisons of unadjusted baseline characteristics, illness severity, management practices, and in-hospital mortality between patients who had a new central line placed on day 1 vs those who had no central line through day 4, using χ^2 and t tests. Preexisting central lines were excluded. Analysis was carried out in SAS version 9.4 software (SAS Institute) and StataMP version 16.1 software (StataCorp). The study was reviewed by the University of Michigan Institutional Review Board (Identifier: HUM00188852) and deemed exempt.

Results

The HMS sepsis cohort included 7,039 patients during the study period. Five hundred ninety-four patients (8.4%) received vasopressors within 6 h and were included in this study (Fig 1). Patients were hospitalized across 29 HMS hospitals, which had diverse characteristics including bed size (median, 304 [interquartile range (IQR), 189-365]) and case mix (median, 1.71 [IQR, 1.55-1.87]) (e-Table 1). Included hospitals also had differing vasopressor policies, with 12 of 29 hospitals (41.3%) requiring or recommending central vasopressor administration and 13 of 29 hospitals (44.8%) allowing peripheral vasopressor use (e-Table 1).[16] Mean number of patients per hospital was 20 (range, 1-65) (e-Fig 1). In the primary analysis, 15 of 29 hospitals (51.7%) had fewer than 15 eligible hospitalizations each.

Of the 594 patients who met study inclusion criteria, vasopressors were initiated via PIV line in 400 patients (67.3%) (Fig 1). However, the proportion of peripheral initiation varied by hospital: among hospitals with ≥ 15 observations per hospital, the proportion of peripheral initiation ranged from 27.8% to 93.8% (e-Fig 1). In contrast, 154 of 594 patients (25.9%) underwent vasopressor initiation through central lines, primarily temporary CVCs (n = 131 [85.1%]) (Fig 1, e-Table 2). The remaining 40 of 594 patients (6.7%) underwent vasopressor initiation through midline catheters, intraosseous lines, or unknown access and were excluded from the primary analysis.

Baseline characteristics and illness severity were similar between patients with peripheral vs central vasopressor initiation (Table 1).[16,20] Most patients were admitted through the ED (552/554 [99.6%]). Vasopressor initiation routes were similar across admission times (day vs night, weekday vs weekend). Initiation route was not associated with type of hospital vasopressor policy (Table 1, e-Fig 2). Compared with central initiation, peripheral initiation was faster (time from hospital arrival to vasopressor initiation: median, 2.5 h [IQR, 1.1-3.6 h] vs 2.7 h [IQR, 1.6-4.5 h]; mean ± SD, 2.46 ± 1.60 h vs 2.95 ± 1.63 h; $P = .002$) (e-Fig 3) and was associated with less use of norepinephrine as the first vasopressor (84.3% vs 96.8%; $P = .001$). Peripheral initiation was associated with similar cumulative fluid volumes to hour 6 (median, 2,350 mL [IQR, 1,500-3,270 mL] vs 2,380 mL [IQR, 1,614-3,000 mL]; $P = .795$) and rates of initial admission to the ICU from the ED (91.5% vs 89.0%; $P = .564$). In adjusted analysis, BMI was the only prespecified patient factor associated with peripheral vasopressor initiation; the association was weak (adjusted OR [aOR] per 1-kg/m^2 increase, 0.98; 95% CI, 0.97-1.00, $P = .015$) (Table 2). In contrast, the treating hospital had a significant association with peripheral initiation (median OR, 2.19; 95% CI, 1.31-3.07; intraclass correlation, 0.17), suggesting 17% of the variance in use of peripheral vasopressor initiation is attributable to the treating hospital. Results were similar in sensitivity analyses excluding hospitals with fewer than 15 observations (e-Table 3).

We found no association between route of vasopressor initiation and patient outcomes (Table 3). Peripheral vs central initiation was associated with similar in-hospital mortality (32.3% vs 42.2%; aOR, 0.66; 95% CI, 0.39-1.12), 90-day mortality (46.8% vs 54.5%; aOR, 0.77; 95% CI, 0.46-1.28), mechanical ventilation during admission (44.5% vs 49.4%; aOR, 0.96; 95% CI, 0.47-1.98), new dialysis during admission (7.3% vs 9.1%; aOR, 0.78; 95% CI, 0.34-1.77), and hospital length of stay of > 7 days (40.8% vs 44.2%; aOR, 0.88; 95% CI,

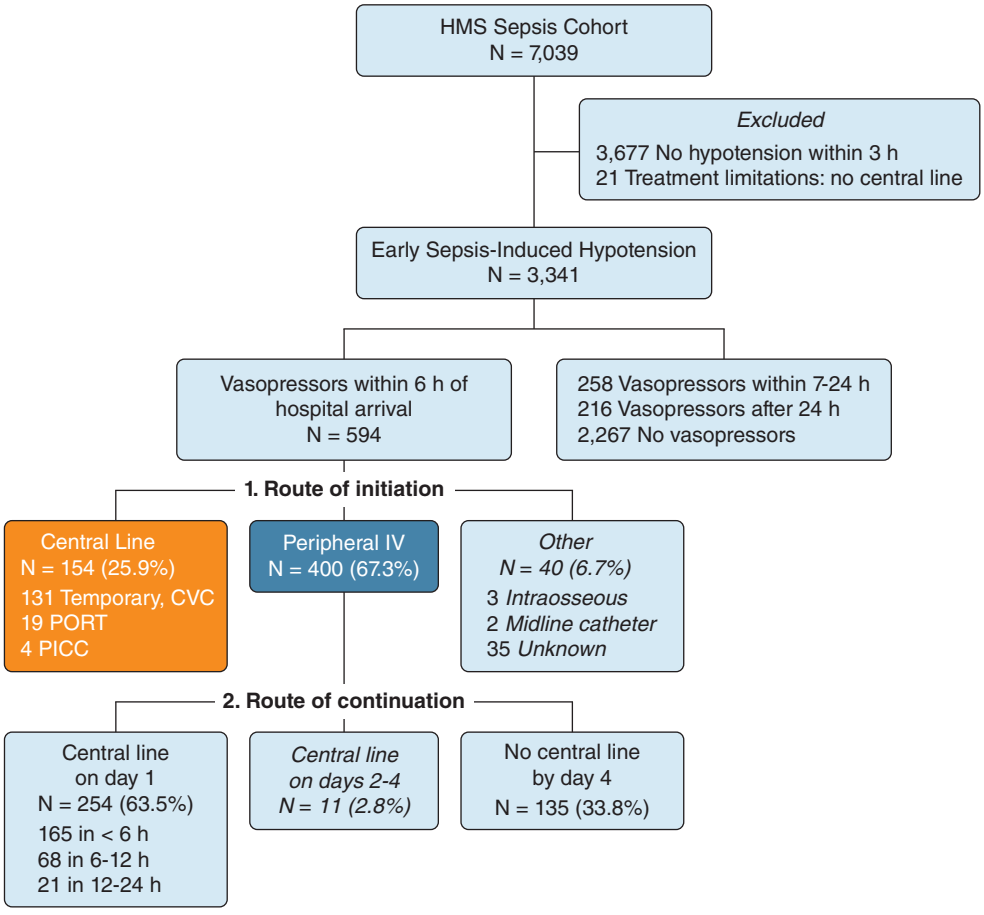

Figure 1 – *Study flow diagram showing route of vasopressor initiation and continuation. (1) Route of initiation: In the primary analysis, we compared patients with vasopressors initiated through a central line (orange box; n = 154) vs peripheral IV (dark blue box; n = 400). Patients with other route of vasopressor initiation (n = 40; italics) were excluded from the primary analysis because of the frequency of unknown route. (2) Route of continuation: In the secondary analysis, we compared patients initiated on vasopressors peripherally who received a central line on day 1 (n = 254) vs those who did not receive a central line by day 4 (n = 135). Patients who underwent central line placement on days 2 through 4 were excluded from this secondary analysis because of small sample size (n = 11; italics). Time is calculated from hospital arrival to time of central line placement. Central line includes any of the following forms of central access: temporary (nontunneled) CVC, tunneled CVC, temporary hemodialysis catheter, port, or PICC. Hospital days are defined from the start of a patient's hospital encounter, with day 1 being the day of hospital arrival. Early sepsis-induced hypotension is defined as any of the following within 3 h of hospital arrival: systolic BP < 90 mm Hg, systolic BP < 100 mm Hg with a history of hypertension, or mean arterial pressure of < 65 mm Hg. Patients receiving vasopressors without documented hypotension also were presumed to be hypotensive and were included. CVC = central venous catheter; HMS = Michigan Hospital Medicine Safety Consortium; PICC = peripherally inserted central catheter.*

0.56-1.38). Results were similar in sensitivity analyses excluding hospitals with fewer than 15 observations (e-Table 4). Major complications were rare. Only 4 of 554 patients (0.7%) had a central line removed because of a complication. No patients experienced necrosis or tissue ischemia resulting from a peripheral vasopressor.

Among patients who underwent vasopressor initiation peripherally, most (254/400 [63.5%]) had a central line placed on hospital day 1, including 165 patients (41.3%) who had a central line placed within 6 h of hospital arrival (Fig 1). Most central lines placed on days 1 through 4 were temporary CVCs (248/291 [85.2%]) (e-Table 5). However, 135 of 400 patients (33.8%) had no central line placed through hospital day 4 (Fig 1). Only 12 patients (2.0%) were still receiving peripheral vasopressors on day 4; the rest were alive and off of vasopressors, alive and receiving vasopressors through central access, or had died (Fig 2).

Compared with patients with a central line placed on day 1, patients who avoided central line placement were less sick. Specifically, they showed less baseline chronic kidney disease (46.7% vs 64.6%; $P = .001$) and congestive heart failure (21.5% vs 35.4%; $P = .004$) and lower severity of illness on presentation (eg, median initial lactate, 2.8 vs 4.0 mM; $P < .01$) (e-Table 6). Patients who avoided central lines also were less likely to receive multiple vasopressors on hospital day 1 (15.6% vs 58.7%; $P < .01$), had shorter vasopressor duration (median, 2 days vs 3 days; $P <$

TABLE 1] Baseline Characteristics and Initial Sepsis Management Practices by Route of Vasopressor Initiation

Variable	Peripheral Initiation (n = 400)	Central Initiation (n = 154)	*P* Value[a]
Baseline characteristics			
Age, y	70 (60-78)	70 (62-78)	.977
Male sex	208 (52.0)	71 (46.1)	.214
Admitted from LTAC, SNF, SAR, or AR	70 (17.5)	41 (26.6)	.086
Hospitalized in prior 90 d	140 (35.0)	59 (38.3)	.467
Baseline functional impairments[b]	0 (0-5)	0 (0-5)	.568
Charlson comorbidity index	4 (2-5.5)	3 (2-5)	.659
Comorbidities			
Hypertension	240 (60.0)	85 (55.2)	.304
Diabetes	72 (18.0)	30 (19.5)	.687
Kidney disease (moderate or severe)	231 (57.8)	87 (56.5)	.789
Liver disease	44 (11.0)	16 (10.4)	.836
Chronic lung disease	139 (34.8)	44 (28.6)	.166
Congestive heart failure	123 (30.8)	46 (29.9)	.840
Coronary artery disease	235 (58.8)	81 (52.6)	.190
Cerebrovascular disease	53 (13.3)	16 (10.4)	.361
Peripheral vascular disease	48 (12.0)	15 (9.7)	.453
Malignancy[c]	93 (23.3)	35 (22.7)	.896
BMI, kg/m^2	27.7 (22.5-33.2)	28.9 (24.1-34.5)	.063
Admitted from ED	399 (99.8)	153 (99.4)	.479
Day shift admission (7 AM-7 PM)	255 (63.8)	94 (61.0)	.554
Weekday admission (Monday-Friday)	287 (71.8)	106 (68.8)	.498
Hospital policy requires or recommends central vasopressors only[d]	138 (34.5)	58 (37.7)	.486
Illness severity on presentation			
Lactate, mM[e]	3.5 (1.9-6.5)	3.7 (2.0-6.2)	.820
Creatinine, mg/dL[f]	1.8 (1.2-3.0)	1.8 (1.2-2.9)	.351
P_{AO_2} to F_{IO_2} ratio[g]	300 (119-476)	300 (99-476)	.452
Mechanical ventilation within 6 h[h]	125 (31.3)	58 (37.7)	.151
Altered mental status[i]	270 (67.5)	113 (73.4)	.180
CPR on day 1	47(11.8)	14 (9.1)	.370
Predicted mortality score[j]	0.44 (0.26-0.63)	0.44 (0.30-0.67)	.273
Management practices			
Initial vasopressor			
Norepinephrine	337 (84.3)	149 (96.8)	.001
Phenylephrine	22 (5.5)	1 (0.6)	...
Epinephrine	28 (7.0)	3 (1.9)	...
Dopamine	13 (3.3)	1 (0.6)	...
Other (vasopressin, angiotensin II)	0 (0)	0 (0)	...
Received > 1 vasopressor on day 1	171 (42.8)	61 (39.6)	.502
Time from arrival to vasopressor initiation, h	2.5 (1.1-3.6)	2.7 (1.6-4.5)	.002

(Continued)

TABLE 1] *(Continued)*

Variable	Peripheral Initiation (n = 400)	Central Initiation (n = 154)	*P* Value[a]
Duration of vasopressor use, d[k]	2 (2-4)	2 (2-4)	.425
Cumulative fluids by hour 6, mL	2,350 (1,500-3,270)	2,380 (1,614-3,000)	.795
First level of care after ED: ICU	366 (91.5)	137 (89.0)	.564

Data are presented as No. (%) or median (interquartile range). AR = acute, or inpatient, rehabilitation; LTAC = long-term acute care; SAR = subacute rehabilitation; SNF = skilled nursing facility.
[a]Determined using χ^2 test for categorical variables and *t* test for continuous variables.
[b]No. of functional limitations based on six core activities of daily living: eating, bathing, dressing, toileting, transferring, and taking medications.
[c]Includes solid tumors with and without metastasis, leukemia, and lymphoma.
[d]Classification based on fall 2021 survey of Michigan hospitals.[16]
[e]Maximum within 6 h of hospital arrival.
[f]Maximum on day 1. If a patient arrived after 6 PM on day 1 and had no day 1 laboratory test results, day 2 laboratory test results were used.
[g]Minimum within 3 h of hospital arrival.
[h]Within 6 h of hospital arrival.
[i]Documented deviation from baseline cognitive status on hospital day 1 or 2.
[j]Predicted mortality score was calculated using a model developed and validated within HMS to predict 90-d mortality among the Michigan Hospital Medicine Safety Consortium sepsis cohort.[20] A value of 0.44 corresponds to a predicted mortality of 44%. This model includes the following patient characteristics and markers of illness severity: dementia, metastatic or other cancer, liver disease, peripheral vascular disorders, baseline function status, age, altered mental status, positive COVID-19 test results, diabetes, total comorbidity index, maximum lactate in the first 6 h of encounter, mechanical ventilation within 6 h, prior hospitalizations, minimum P_{AO_2} to F_{IO_2} ratio within 3 h and vasopressors delivered within 6 h.
[k]Information about vasopressor use was available through hospital day 4.

.01), and were less likely to be admitted initially to the ICU from the ED (85.2% vs 95.3%; $P = .001$) (e-Table 6). Unadjusted in-hospital mortality was lower among patients who avoided central line placement vs patients who had a central line placed on day 1 (21.5% vs 37.4%; $P = .001$).

TABLE 2] Patient Characteristics Associated With Peripheral Vasopressor Initiation

Variable	Adjusted OR[a] for Peripheral Initiation (95% CI)	*P* Value
Age, per y	1.01 (0.99-1.03)	.626
Admission from a postacute care facility (LTAC, SNF, SAR, or AR)	0.69 (0.37-1.31)	.231
Hospitalized in the prior 90 d	0.93 (0.55-1.57)	.773
Kidney disease (moderate or severe)	0.89 (0.54-1.47)	.620
Liver disease (moderate or severe)	0.98 (0.45-2.14)	.964
Congestive heart failure	1.05 (0.63-1.73)	.852
Peripheral vascular disease	1.22 (0.58-2.54)	.575
Malignancy[b]	0.75 (0.42,-1.34)	.305
BMI, per kg/m^2[c]	0.98 (0.97-1.00)	.015
Initial lactate, per mM[d]	1.02 (0.95-1.08)	.664
Initial creatinine, per mg/dL[e]	1.03 (0.94-1.13)	.497
Mechanical ventilation within 6 h[f]	0.77 (0.43-1.37)	.343
Altered mental status[g]	0.74 (0.42-1.31)	.274
Predicted mortality score[h]	1.59 (0.26-9.58)	.612
Hospital effect, median OR (95% CI)	2.19 (1.31-3.07)	Not applicable

N = 554 patients with vasopressors initiated through a peripheral IV or central line. Patients with other routes of initiation were excluded. AR = acute, or inpatient, rehabilitation; HMS = Michigan Hospital Medicine Safety Consortium; LTAC = long-term acute care; SAR = subacute rehabilitation; SNF = skilled nursing facility.
[a]Multilevel logistic regression model for peripheral vasopressor initiation, adjusted for factors listed in the first column.
[b]Malignancy included solid tumors with and without metastasis, leukemia, and lymphoma.
[c]Missing for 33 patients and was imputed using age and sex.
[d]Maximum lactate within 6 h of hospital arrival.
[e]Maximum creatinine on day 1. If a patient arrived after 6 PM on day 1 and had no day 1 laboratory test results, day 2 laboratory test results were used.
[f]Mechanical ventilation within 6 h of hospital arrival.
[g]Documented deviation from baseline cognitive status on day 1 or 2.
[h]Predicted mortality score was calculated using a model developed and validated within Michigan Hospital Medicine Safety Consortium to predict 90-d mortality among the HMS sepsis cohort. The model includes patient characteristics and markers of illness severity as detailed in the legend for Table 1.

TABLE 3] Outcomes by Vasopressor Initiation Route

Variable	Peripheral Initiation (n = 400)	Central Initiation (n = 154)	Adjusted OR[a] (95% CI)
In-hospital mortality[b]	129 (32.3)	65 (42.2)	0.66 (0.39-1.12)
30-d mortality	162 (40.5)	75 (48.7)	0.76 (0.45-1.27)
90-d mortality	187 (46.8)	84 (54.5)	0.77 (0.46-1.28)
Mechanical ventilation during admission	178 (44.5)	76 (49.4)	0.96 (0.47-1.98)
New dialysis during admission	29 (7.3)	14 (9.1)	0.78 (0.34-1.77)
Hospital length of stay > 7 d	163 (40.8)	68 (44.2)	0.88 (0.56-1.38)
Central line removed because of complication	2 (0.5)	2 (1.3)	Not applicable[c]

Data are presented as No. (%), unless otherwise indicated. N = 554 patients with vasopressors initiated through peripheral IV or central line. Patients with other routes of initiation were excluded. BMI was missing for 33 patients and was imputed using age and sex.
[a]Multilevel logistic regression models, adjusted for age, place of resident before admission, hospitalization in prior 90 d, chronic kidney disease, chronic liver disease, congestive heart failure, peripheral vascular disease, malignancy, BMI, maximum initial lactate, maximum creatinine day 1, mechanical ventilation within 6 h of arrival, altered mental status, and predicted mortality score.
[b]Primary outcome.
[c]Regression model not performed because of low event rate.

Discussion

In this study of community-onset sepsis admissions across 29 diverse Michigan hospitals, peripheral vasopressor initiation was common. More than two-thirds of patients underwent vasopressor initiation via a PIV line. However, ongoing use of peripheral vasopressors was rare, with more than one-half of patients initiated on peripheral vasopressors undergoing central line placement within 1 day of hospital arrival.

We found no association between route of vasopressor initiation and patient outcomes. Specifically, we found no association between route of initiation and mortality across multiple time points, mechanical ventilation, new dialysis, or length of hospitalization. Although CIs were wide because of the small sample size, point estimates all favored peripheral initiation. Furthermore, no cases of tissue ischemia or necrosis resulting from peripheral vasopressor use were documented. These findings add to the growing evidence that peripheral vasopressor initiation seems to be safe.[9-11,21]

Our findings also provide insight into how vasopressor initiation routes are selected in practice. Patients with peripheral vs central initiation showed similar baseline characteristics and severity of illness, and the decision to initiate vasopressors peripherally did not seem to be driven by patient factors. Additionally, we found that peripheral initiation was used broadly, not just overnight or on weekends when resources or staffing may be strained. Rather, we observed a wide range in peripheral vasopressor initiation across hospitals. Indeed, the specific hospital was the main driver of vasopressor initiation route, suggesting variation in practice patterns not explained by differences in patient case mix across hospitals. Interestingly, hospital-reported vasopressor policy, which might be expected to drive differences across hospitals, did not correlate with vasopressor initiation route. This suggests the existence of unmeasured hospital-level factors, such as local norms or provider comfort, driving differences in peripheral vasopressor initiation across hospitals.

Although route of vasopressor initiation was not associated with mortality, we found it was associated with two key aspects of early sepsis management. First, peripheral vasopressor initiation occurred earlier after hospital arrival than central initiation. Although the median difference was small (12 min), peripheral initiations were concentrated earlier and the average time to peripheral initiation was 30 min faster. This finding confirms a proposed advantage of peripheral vasopressors: that they help to expedite vasopressor initiation by avoiding delays caused by central line placement.[5] Second, peripheral initiation was associated with less use of norepinephrine as a first-line vasopressor, consistent with a study of first-line vasopressor use in Canada.[22] Whether this difference represents an increased use of phenylephrine and epinephrine or an avoidance of peripheral norepinephrine is not clear. Unlike norepinephrine, phenylephrine and epinephrine can be used in push doses that can be administered peripherally during emergencies. However, this is unlikely to explain fully the differential norepinephrine use, given that we excluded vasopressor use during CPR from our data set. The lower use of peripheral norepinephrine also could

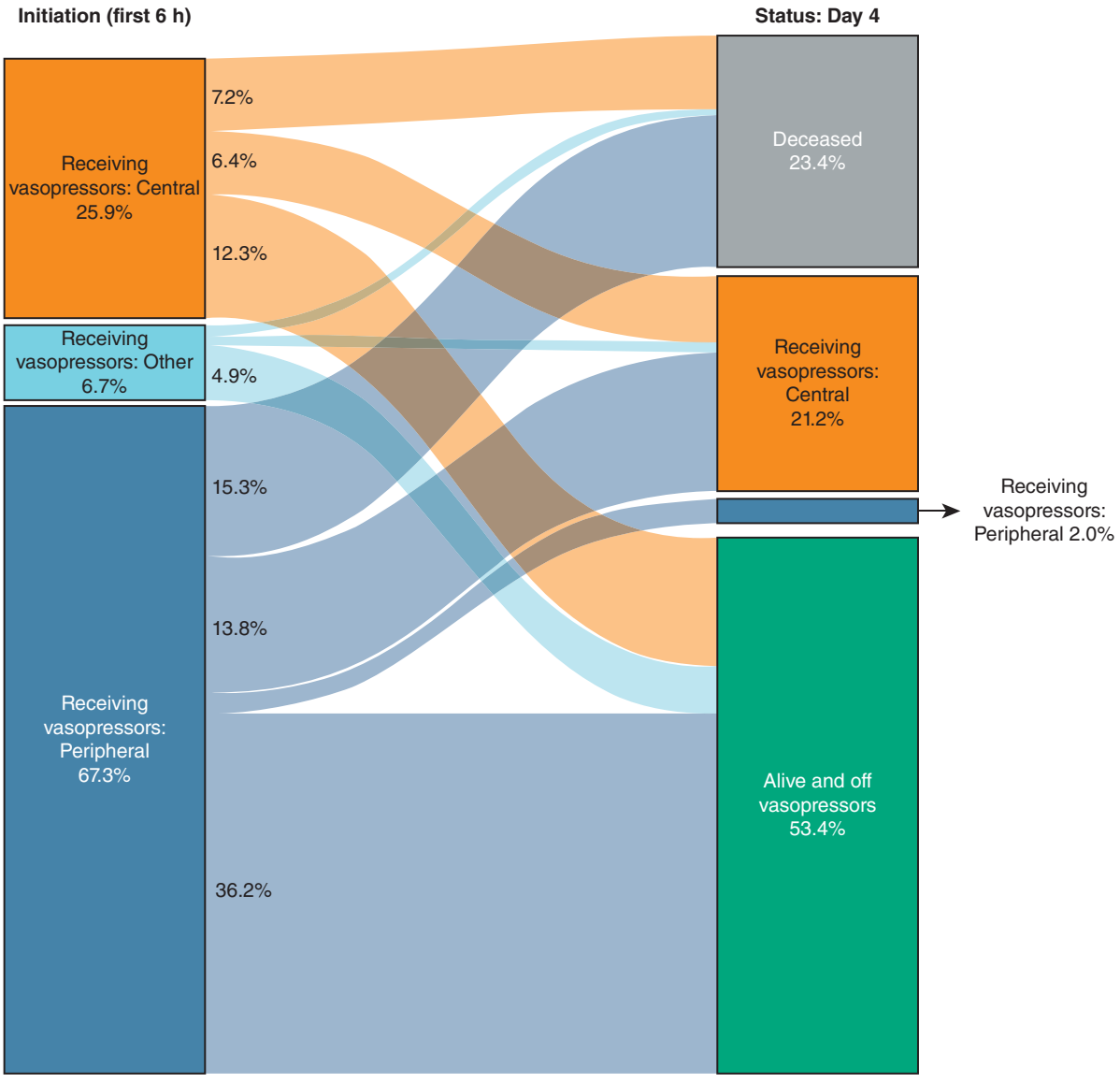

Figure 2 – *Sankey diagram showing route of vasopressor administration at initiation and on hospital day 4. N = 594 patients started on vasopressors within 6 hours of hospital arrival. "On vasopressors: Central" indicates patients receiving vasopressors through a nontunneled (temporary) or tunneled central venous catheter, temporary hemodialysis catheter, port, or peripherally inserted central catheter. "On vasopressors: Other" indicates patients receiving vasopressors through an intraosseous line, midline catheter, or unknown route. "On vasopressors: Peripheral" indicates patients receiving vasopressors through a peripheral IV.*

reflect residual safety concerns about peripheral vasopressors, particularly norepinephrine.[23] Although early case reports of tissue injury caused by peripheral norepinephrine extravasation have been published,[2-4,24] more recent studies have included hundreds of patients receiving peripheral norepinephrine without significant complications, particularly compared with other vasopressor agents.[9,11,21] Regardless, our finding that norepinephrine is used less frequently with peripheral initiation is worrisome given that the SSC guidelines strongly recommend norepinephrine as the first-line vasopressor in sepsis.[1]

Another proposed benefit of peripheral vasopressor use is the potential avoidance of central line placement. In our study, most patients who received vasopressors that were started peripherally had a central line placed within 12 h, consistent with the suggestion from the 2021 SSC guidelines to transition vasopressors to central administration when feasible.[1] However, one-third of patients who received vasopressors that were started peripherally avoided central line placement altogether. This is consistent with prior studies showing overall decreased rates of central line placement after the implementation of institutional protocols for peripheral

vasopressor administration.[6,25-27] Notably, in our study, patients who avoided central lines showed lower initial illness severity and primarily received a single vasopressor agent for short durations (most for ≤ 2 days). This suggests that providers are willing to continue vasopressors peripherally beyond initiation in less sick patients. However, further evaluation is needed to understand and describe accurately the clinical practice of peripheral vasopressor use, including drug concentration, dosing, duration of peripheral administration, monitoring parameters, and patient or practice factors that contribute to providers' decision-making regarding the timing of central line placement.

Our study had several limitations. First, the cohort was limited to patients treated in hospitals in Michigan and may not reflect practice outside Michigan. However, this multihospital cohort includes a diverse set of hospitals with a range of size, rural and urban locations, and vasopressor policies. Second, this study used data collected by trained abstractors for the purposes of performance measurement and quality improvement. Therefore, although the data are high quality, not all data available in the electronic health record are abstracted into the HMS sepsis registry (eg, PIV line size and location, complication details). Third, although we found no association between route of vasopressor initiation and patient outcomes, it is possible that we were underpowered to detect associations because of the cohort size. However, we tested multiple outcomes, and the point estimates all suggested benefit of peripheral administration. Also, although we adjusted for patient factors, it is not possible to remove fully the risk of confounding, given the retrospective nature of this study.

Interpretation

In conclusion, peripheral initiation of vasopressors is common across Michigan hospitals. Approximately two-thirds of patients are initiated on vasopressors peripherally, of whom one-third avoid central line placement. By contrast, ongoing use of peripheral vasopressors is rare. Our study adds to the growing evidence supporting peripheral vasopressor initiation as a safe practice with practical advantages, including expedited vasopressor initiation and central line avoidance for less sick patients. However, the wide practice variation across hospitals and decreased use of first-line norepinephrine peripherally suggest that better standardization may be needed for this common practice.

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Additional information: The e-Appendixes, e-Figures, and e-Tables are available online under "Supplemental Data."

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