

Comparing Early versus Late Administration of Vasopressors in Septic Shock

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Disclosures

No conflicts of interest to disclose

Background

- Greater than 50% of hospital deaths are due to sepsis
 - Mortality increases with disease severity

Sepsis

10 – 20%
mortality

Severe Sepsis

20 – 40%
mortality

Septic Shock

40 – 80%
mortality

- Over \$24 billion spent in the US on sepsis related hospital expenses in 2013
 - Cost of hospital sepsis management ranks highest among admissions for all disease states

SEP-1 Core Measures

- Introduced by the Centers for Medicare and Medicaid Services with an aim to reduce preventable sepsis-related mortality
- Vasopressor initiation required within 6 hours of septic shock presentation if hypotension persists after fluid administration

Bai, *et al.*

- Enrolled 213 patients with septic shock
- Significantly increased 28-day mortality when norepinephrine administered ≥ 2 hours after septic shock onset (late-NE) compared to < 2 hours after septic shock onset (early-NE)
 - 29.1% vs. 43.3% 28-day mortality in early-NE vs. late-NE

CENSER Trial

- Enrolled 310 patients with sepsis with hypotension
- Median time from emergency room arrival to norepinephrine administration in early norepinephrine group vs. standard treatment group
 - 93 vs. 192 min; $p < 0.001$
- Shock control rate by 6 hours was significantly higher in early norepinephrine group
 - 118/155 [76.1%] vs. 75/155 [48.4%]; $p < 0.001$
- 28-day mortality was not different between early norepinephrine group vs. standard treatment group
 - 15.5% vs. 21.9%; $p = 0.15$

Study Objective

To determine if early initiation of vasopressors in patients with septic shock decreases sepsis-related mortality

Methodology

Single-center

Retrospective

Cohort

Patient Selection

Inclusion Criteria

- ≥ 18 years of age
- Patient in ED or ICU
- Septic shock diagnosis
- Recipient of vasoactive agent

Exclusion Criteria

- Patient on general medicine floor
- Shock due to another cause
- Unable to determine time of septic shock onset

Patient Selection

- Severe sepsis (all three criteria must be met):
 - Suspected/documentated infection
 - ≥ 2 SIRS Criteria:
 - Temperature: $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Heart Rate: > 90 bpm
 - Respirations: >20 breaths per minute
 - White Blood Cell Count: $>12,000$ cu mm, $<4,000$ cu mm or $>10\%$ bands
 - Evidence of organ dysfunction (one of the following):
 - SBP <90 mmHg or MAP <65 mmHg
 - SBP decrease >40 mmHg
 - Acute respiratory failure with new need for invasive or non-invasive mechanical ventilation
 - Creatinine >2.0 mg/dL
 - Urine output <0.5 mL/kg/hr for 2 consecutive hours
 - Total bilirubin > 2 mg/dL
 - Platelet count $<100,000$
 - INR >1.5 or aPTT >60 seconds
 - Lactate >2 mmol/L

Patient Selection

Septic Shock:

Severe sepsis present

AND

Persistent hypotension (evidence by one of the following on two consecutive readings):

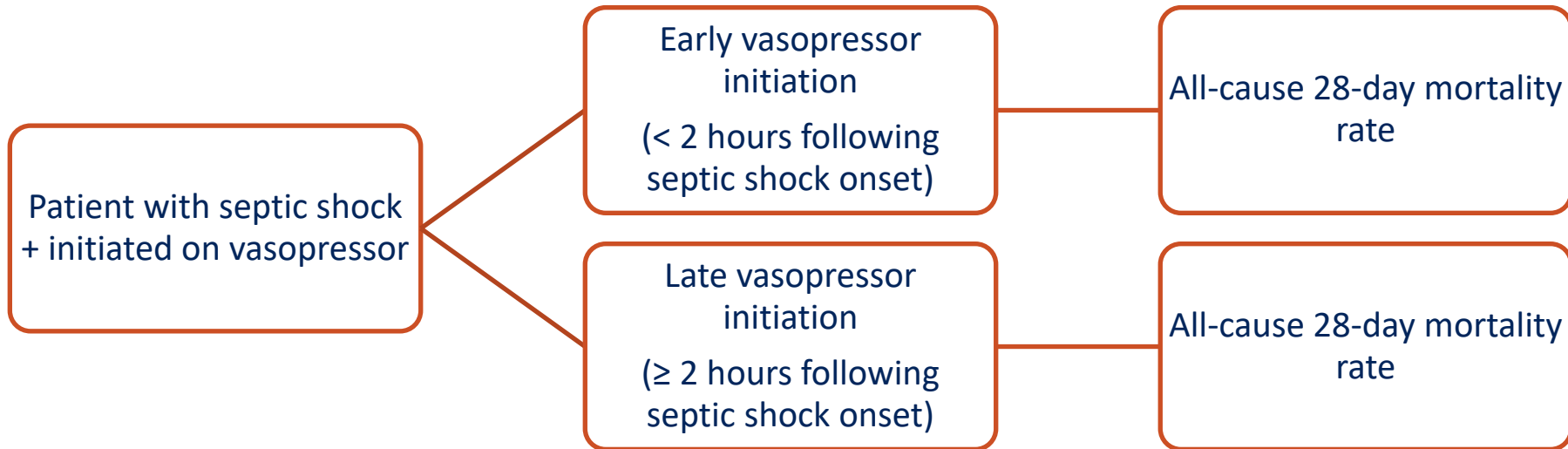
- SBP <90 mmHg
- MAP <65 mmHg
- Decrease in SBP >40 mmHg

OR

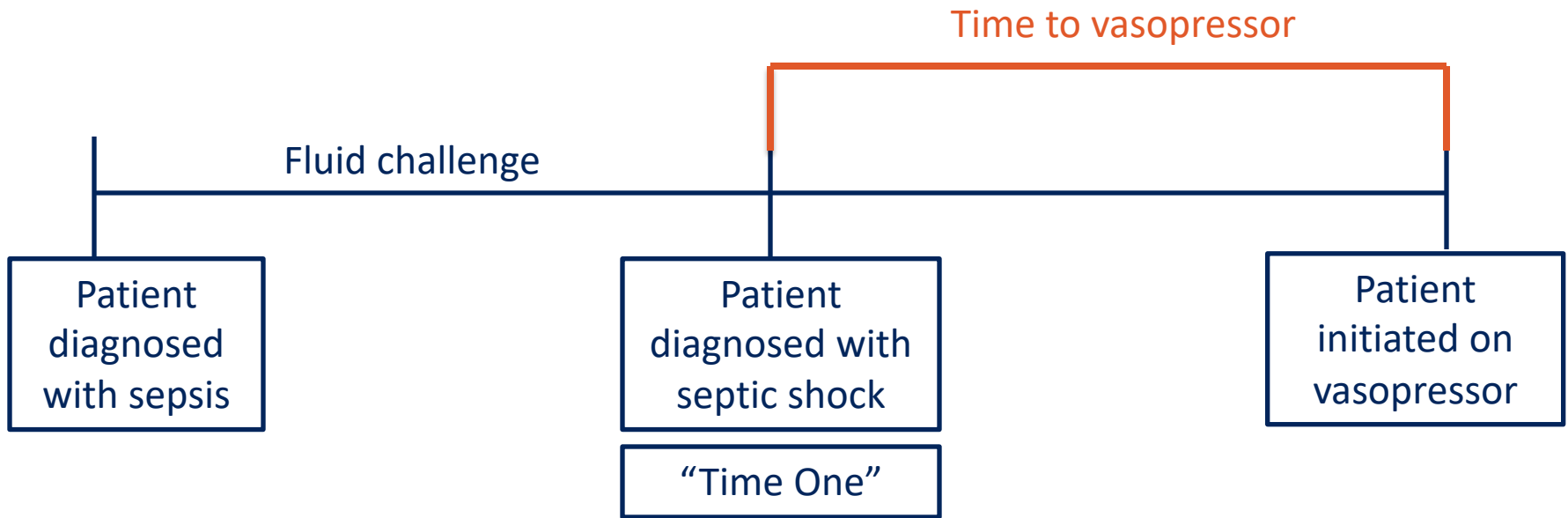
Tissue hypoperfusion evidenced by:

- Initial lactate level result ≥ 4 mmol/L

Methodology



Methodology



Outcomes

Primary Outcome

- 28-day mortality

Secondary Outcomes

- Time to normalization of lactate
- Time to normalization of MAP
- Time to second vasopressor
- Hospital mortality
- Duration of vasopressor therapy
- Length of ICU stay
- Length of hospital stay
- Time to central line
- Extravasation

Statistical Analysis

Demographic
and clinical
characteristics

- Descriptive statistics

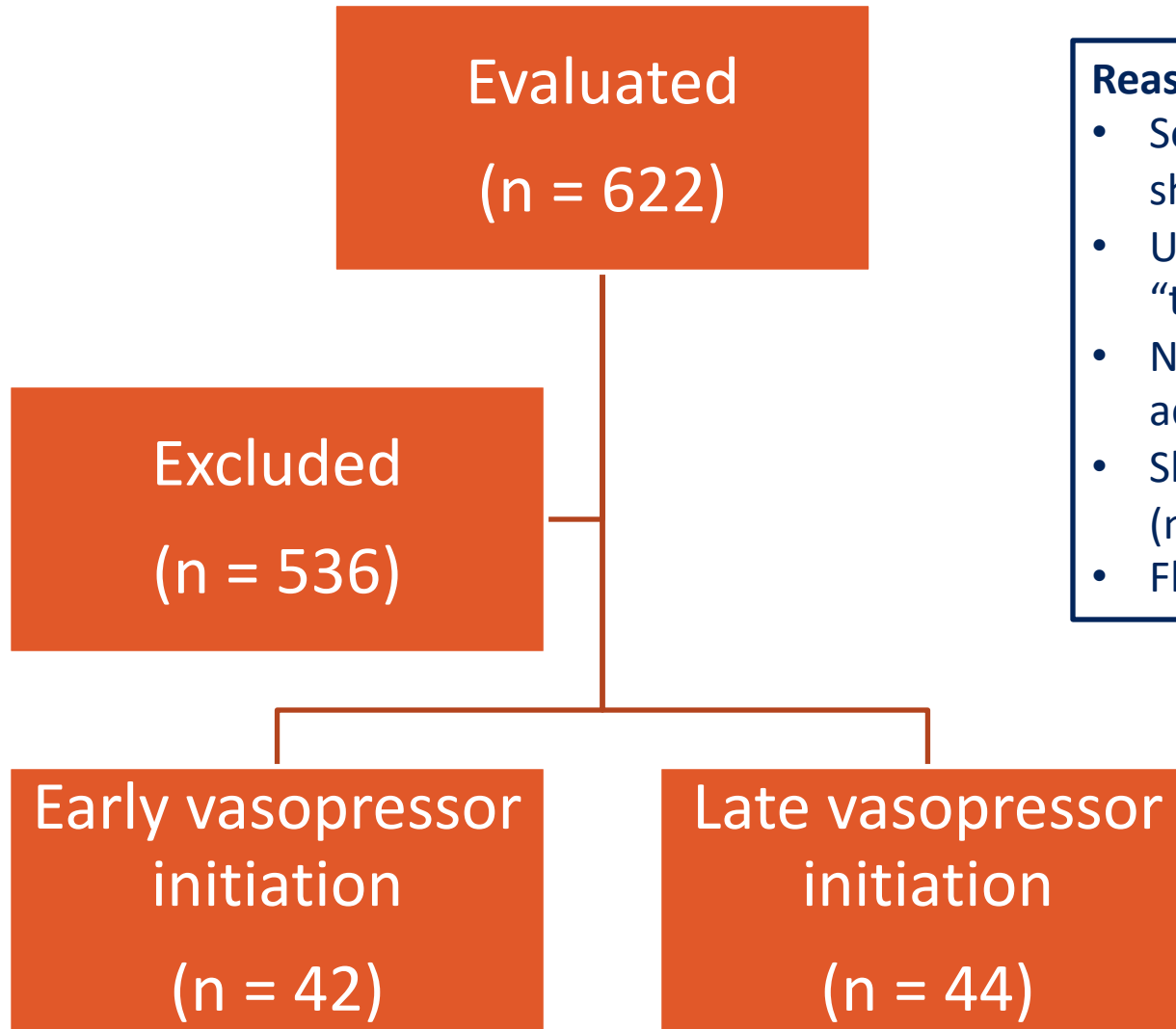
Categorical data

- Chi-square (χ^2)
- Fisher's Exact test

Continuous data

- Student's t-test
- Mann-Whitney U test

Patient Allocation



Reason for Exclusion:

- Sepsis without septic shock (n = 431)
- Unable to determine “time one” (n = 65)
- No vasopressor administered (n=23)
- Shock not due to sepsis (n =15)
- Floor patient (n = 2)

Baseline Characteristics

Characteristic	Early Vasopressor Initiation (n = 42)	Late vasopressor Initiation (n = 44)	P-value
Age, yr	60.1 ± 13.1	59.6 ± 15.2	0.858
Male sex, n (%)	22 (52.4)	26 (59.1)	0.531
Race, n (%)			0.986
Caucasian	26 (61.9)	28 (63.6)	
African American	15 (35.7)	15 (34.1)	
Other	1 (2.4)	1 (2.3)	
Weight, kg	90.7 ± 38.2	85.8 ± 24.8	0.481
SOFA Score	10.6 ± 3.2	9.9 ± 3.4	0.337
Initial Serum Lactate, mg/dL	4.7 ± 3.7	3.8 ± 2.7	0.215
Day of sepsis development	1.12 ± 0.33	1.34 ± 1.0	0.179

Baseline Characteristic

Characteristic	Early vasopressor initiation (n = 42)	Late vasopressor initiation (n = 44)	P-value
ICU Service, n (%)			0.572
Medical ICU	37 (88.1)	39 (88.6)	
Cardiac ICU	0 (0)	0 (0)	
Surgery ICU	0 (0)	0 (0)	
Anesthesia ICU	5 (11.9)	4 (9.1)	
Trauma ICU	0 (0)	1 (2.3)	

Baseline Characteristics

Characteristic	Early vasopressor initiation (n = 42)	Late vasopressor initiation (n = 44)	P-value
Vasoactive agent, n (%)			
Norepinephrine	42 (100)	43 (97.7)	0.326
Epinephrine	11 (26.2)	6 (13.6)	0.144
Dopamine	1 (2.4)	2 (4.5)	0.584
Vasopressin	24 (57.1)	20 (45.5)	0.278
Angiotensin II	1 (2.4)	1 (2.4)	0.529
Phenylephrine	1 (2.4)	1 (2.3)	0.973
Time to vasopressor initiation, hrs	0.61 ± 0.57	10.1 ± 13.3	<0.001

Baseline Characteristics

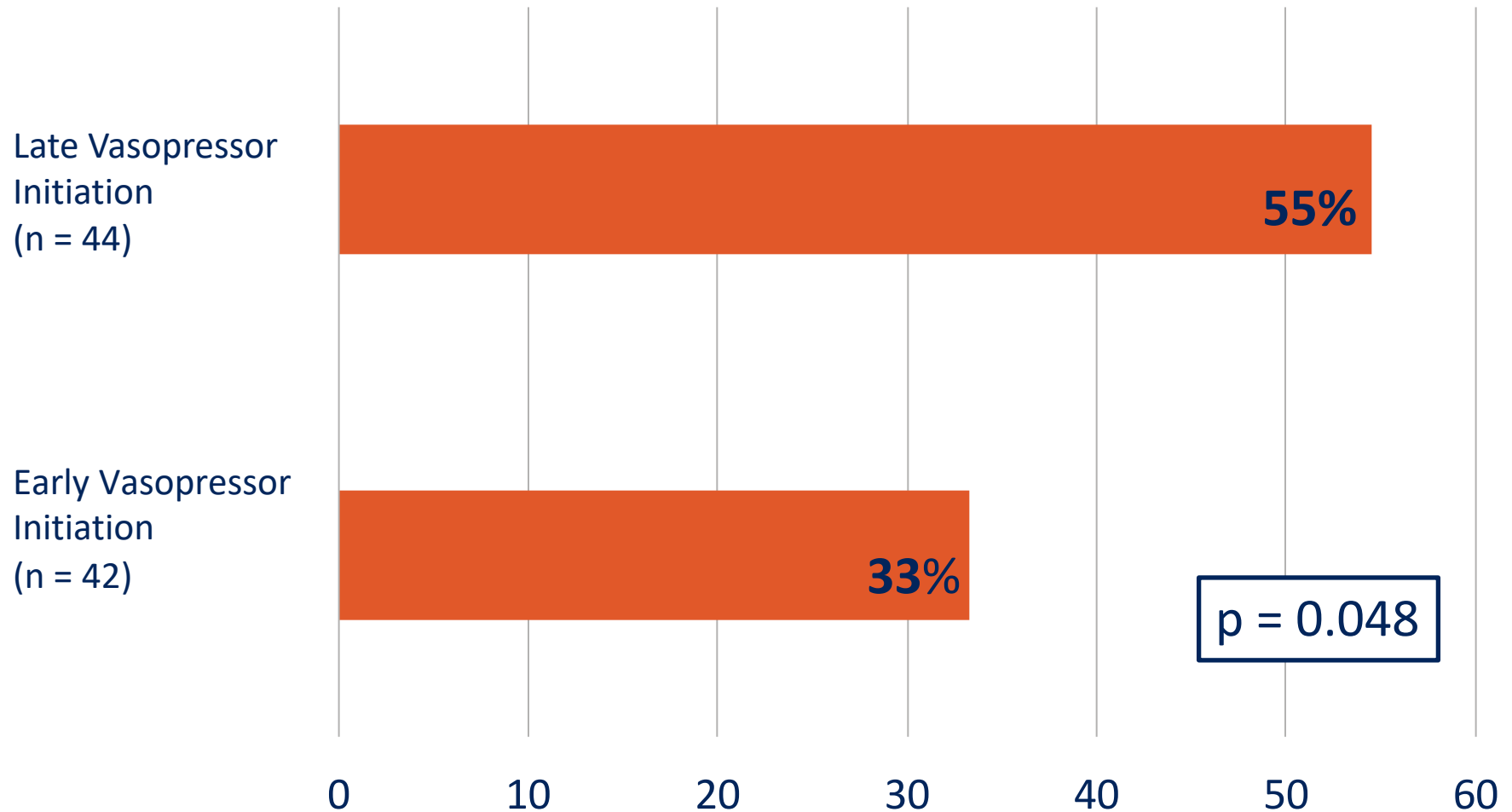
Characteristic	Early vasopressor initiation (n = 42)	Late vasopressor initiation (n = 44)	P-value
Infection, n (%)			0.596
Documented	29 (69.0)	28 (63.6)	
Suspected	13 (31.0)	16 (36.4)	
Primary Site of Infection, n (%)			
Blood	20 (47.6)	21 (47.7)	0.992
Respiratory	13 (30.9)	14 (31.8)	0.931
Genitourinary	12 (27.3)	10 (22.7)	0.535
Intraabdominal	9 (21.4)	9 (20.5)	0.912
Skin and Soft Tissue	4 (9.5)	4 (9.1)	0.945
Wound	1 (2.4)	1 (2.3)	0.973

Baseline Characteristics

Characteristic	Early vasopressor initiation (n = 42)	Late vasopressor initiation (n = 44)	P-value
Time to antimicrobials, min	43.7 ± 98.6	93.6 ± 289.9	0.294
Antimicrobials within 60 minutes, n (%)	33 (78.6)	36 (81.8)	0.705
Appropriate antimicrobials, n (%)	39 (92.9)	40 (90.9)	0.526
Initial fluid administration, n (%)	38 (90.4)	38 (86.4)	0.552
Duration of fluid administration, min	141.3 ± 293.9	87.8 ± 126.8	0.273
Amount of fluid received, L	2.2 ± 1.5	2.2 ± 1.6	0.990
Corticosteroids received, n (%)	27 (64.3)	17 (38.6)	0.017
Hydrocortisone/vitamin C/thiamine received, n (%)	13 (30.9)	6 (13.6)	0.053

Primary Outcome

28-day Mortality



Secondary Outcomes

Outcome	Early vasopressor initiation (n = 42)	Late vasopressor initiation (n = 44)	P-value
Time to normalization of lactate, hrs	19.3 ± 31.8	24.1 ± 43.0	0.594
Time to normalization of MAP, hrs	8.3 ± 13.2	19.7 ± 25.9	0.013
Time to second vasopressor, hrs	9.9 ± 12.1	23.1 ± 28.0	0.041
Hospital mortality, n (%)	14 (33.3)	24 (54.5)	0.048
Duration of vasopressor therapy, hrs	64.7 ± 49.1	59.9 ± 57.8	0.684
Length of ICU stay, days	7.8 ± 6.4	8.3 ± 6.7	0.707
Length of hospital stay, days	13.9 ± 11.8	12.2 ± 8.5	0.457
Time to central line, hrs	1.4 ± 1.5	7.8 ± 10.3	<0.001
Documented extravasation, n (%)	0 (0)	1 (2.3)	0.326

Discussion

- In patients with early vasopressor initiation, shorter time to:
 - Resolution of hypotension
 - Second vasopressor
 - Normalization of lactate
- Appropriate sepsis related treatment
 - Time to antimicrobials
 - Appropriate antimicrobials
 - Norepinephrine
 - Fluid resuscitation
- Patients with early vasopressor initiation more likely to receive corticosteroids or hydrocortisone/Vitamin C/thiamine

Limitations

Retrospective, single center

Limited 28-day mortality data

Determination of septic shock onset

Severity of illness on presentation

Conclusions

- In patients with septic shock, those with an early vasopressor initiation have a decreased 28-day mortality rate compared to patients who have a late vasopressor initiation
- Patients with an early vasopressor initiation had a shorter duration of hypotension compared to those with a late vasopressor initiation

Moving Forward

- Avoid prolonged durations of hypotension
 - Consideration for early vasopressor initiation
 - Consideration for addition of second agent if hypotension present with first vasopressor
- Prompt resuscitation with vasopressors should be considered as part of initial resuscitation for septic shock

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