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Evaluating the Association Between Vasopressin Use and In-Hospital Mortality in Patients with Septic Shock

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Disclosure statement

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Presentation objective

Evaluate the mortality associated with adding vasopressin to both low-dose and high-dose vasopressors in patients with septic shock

Sepsis

- Uncontrolled, generalized, intravascular inflammatory response to infection
- Most common cause of death in intensive care units (ICUs)[1]
  - Increasing incidence over the last 10 years
  - In-hospital mortality rate of greater than 40%[2]
  - Most expensive condition to treat in 2013: $24 billion in annual costs[3]
- Treatment:
  - Fluid resuscitation (30 ml/kg)
  - Prompt administration of broad-spectrum antimicrobial agents
  - Vasoactive medications

Surviving Sepsis Guidelines

- Norepinephrine recommended as first-choice vasopressor (strong recommendation, moderate quality of evidence)
- Suggest adding either vasopressin (weak recommendation, low quality of evidence) or epinephrine (weak recommendation, low quality of evidence)
  - Raise MAP to target (recommended target of 65 mmHg)
  - Decrease norepinephrine requirements

Vasopressin mechanism

- Distinct mechanism compared to catecholamine agents
- Activates V1 receptors
  - Induces constriction of vascular smooth muscle cells through increased intra-cellular calcium and decreased nitric oxide induced vasodilation
- Endogenous levels initially increase in response to hypotension but quickly decline within 36 hours
- Maintains efficacy in acidotic state

VASST trial

- Multi-center, randomized, double-blind trial
- Patients receiving norepinephrine at a minimum rate of 5 mcg/minute were randomly divided into two groups:
  - Low-dose vasopressin (in addition to open-label vasopressors)
  - Norepinephrine (in addition to open-label vasopressors)
- Primary outcome: 28-day mortality after the initiation of study infusion
- Sub-group analysis that divided patients into additional two groups:
  - Less severe shock: Norepinephrine rate 5-14 mcg/minute at randomization
  - More severe shock : Norepinephrine rate ≥15 mcg/minute at randomization

VASST trial results

Outcome	Norepinephrine (n=382)	Vasopressin (n=396)	p-value
Time to study drug infusion - hours	**11.5 ± 9.4**	**11.9 ± 8.9**	**0.57**
28-day mortality – no (%)	150 (39.3)	140 (35.4)	0.26
90-day mortality – no (%)	188 (49.6)	172 (43.9)	0.11
More severe shock – NE ≥ 15 mcg/minute			
28-day mortality – no/total no (%)	85/200 (42.5)	88/200 (44.0)	0.76
90-day mortality – no/total no (%)	105/199 (52.8)	103/199 (51.8)	0.84
Less severe shock – NE 5-14 mcg/minute			
28-day mortality – no/total no (%)	65/182 (35.7)	52/196 (26.5)	0.05
90-day mortality – no/total no (%)	83/180 (46.1)	69/193 (35.8)	0.04

VANISH trial

- Factorial, double-blind, randomized trial
- Four groups:
  - Vasopressin and hydrocortisone
  - Vasopressin and placebo
  - Norepinephrine and hydrocortisone
  - Norepinephrine and placebo
- Primary outcome: Kidney failure-free days 28-days post randomization

VANISH trial results

Outcome	Vasopressin + hydrocortisone (n=100)	Vasopressin + placebo (n=104)	Norepinephrine + hydrocortisone (n=101)	Norepinephrine + placebo (n=103)
Time to study drug infusion - hours	**3.2 (1.8-5)**	**3.5 (2.5-5.4)**	**3.7 (1.7-5)**	**3.5 (1.4-5.4)**
28-day mortality – no/total no (%)	33/100 (33.0)	30/104 (28.8)	29/101 (28.7)	27/103 (26.2)
ICU mortality – no/total no (%)	32/100 (32.0)	26/104 (25.0)	24/101 (23.8)	27/103 (26.2)
Hospital mortality – no/total no (%)	35/100 (35.0)	33/104 (31.7)	31/101 (30.7)	29/103 (28.2)
Time to shock reversal - hours	50 (28-92)	59 (27-112)	46 (23-72)	44 (23-90)

Additional studies

Trial	Comparison	Outcomes
Reardon et al.[9] Single-center, retrospective, chart-review N=71	Vasopressin initiation within 6 hours of shock onset vs. vasopressin within 6-48 hours of shock onset	▪ Early vasopressin resulted in significantly less new-onset arrhythmias ▪ No difference in duration of catecholamine and vasopressin therapy ▪ No difference in mortality or ICU/hospital length of stay
Hammond et al.[10] Single-center, prospective, open-label study N=82	Early addition of vasopressin within 4 hours of septic shock onset vs. norepinephrine monotherapy	▪ Significantly shorter time to MAP target (7.6 vs. 5.7 hours; p=0.058) ▪ No difference in mortality, norepinephrine duration, vasopressin duration, or ICU/hospital length of stay
Hammond et al.[11] Single-center, retrospective, cohort study N=96	Early addition of vasopressin within 4 hours of septic shock onset vs. norepinephrine monotherapy	▪ Significantly shorter time to MAP target and hospital length of stay but no difference in ICU length of stay ▪ Significantly greater reduction in SOFA score at 72 hours post shock onset ▪ No difference in SOFA score at 6, 24, or 72 hours post shock onset ▪ No difference in in-hospital or 28-day mortality ▪ No difference in norepinephrine duration
Wu et al.[12] Single-center, retrospective, cohort study N=148	Vasopressin initiation for patients requiring ≥10 mcg/min of norepinephrine vs. patients requiring ≥50 mcg/min of norepinephrine	▪ No difference in time to MAP target, mortality, or ICU/hospital length of stay

Study rationale

Conflicting evidence and lack of recommendations regarding:

- Optimal candidates for vasopressin
- Optimal timing of vasopressin initiation
- Optimal timing of vasopressin discontinuation

High relative cost of vasopressin compared to other vasopressors prioritizes its optimization

Purpose

To evaluate outcomes for patients with septic shock based on the utilization of vasopressin

Research questions:

- Does the addition of vasopressin to low-dose vasopressors in patients with septic shock reduce in-hospital mortality?
- Does the addition of vasopressin to high-dose vasopressors in patients with septic shock reduce in-hospital mortality?

Design

Design: IRB-exempt, retrospective chart review of patients treated with vasopressors and diagnosed with septic shock

Time frame: January 1, 2018 to September 17, 2018

Setting: Intensive care unit (ICU) at Baptist Hospital of Miami

Sample size: 149 patients

Subject selection

Inclusion criteria

- ≥ 18 years old
- “Septic shock” documented in the medical record
- Vasopressor infusion

Exclusion criteria

- Pregnant
- “Cardiogenic shock” documented in the medical record
- Post-cardiothoracic surgery
- <12 hours on vasopressors

Comparator groups

Low-dose vasopressors:

≤ 0.2 mcg/kg/minute NE equivalents

- Patients treated with vasopressin
- Patients treated without vasopressin

High-dose vasopressors:

> 0.2 mcg/kg/minute NE equivalents

- Patients treated with vasopressin
- Patients treated without vasopressin

NE-norepinephrine

Study outcomes

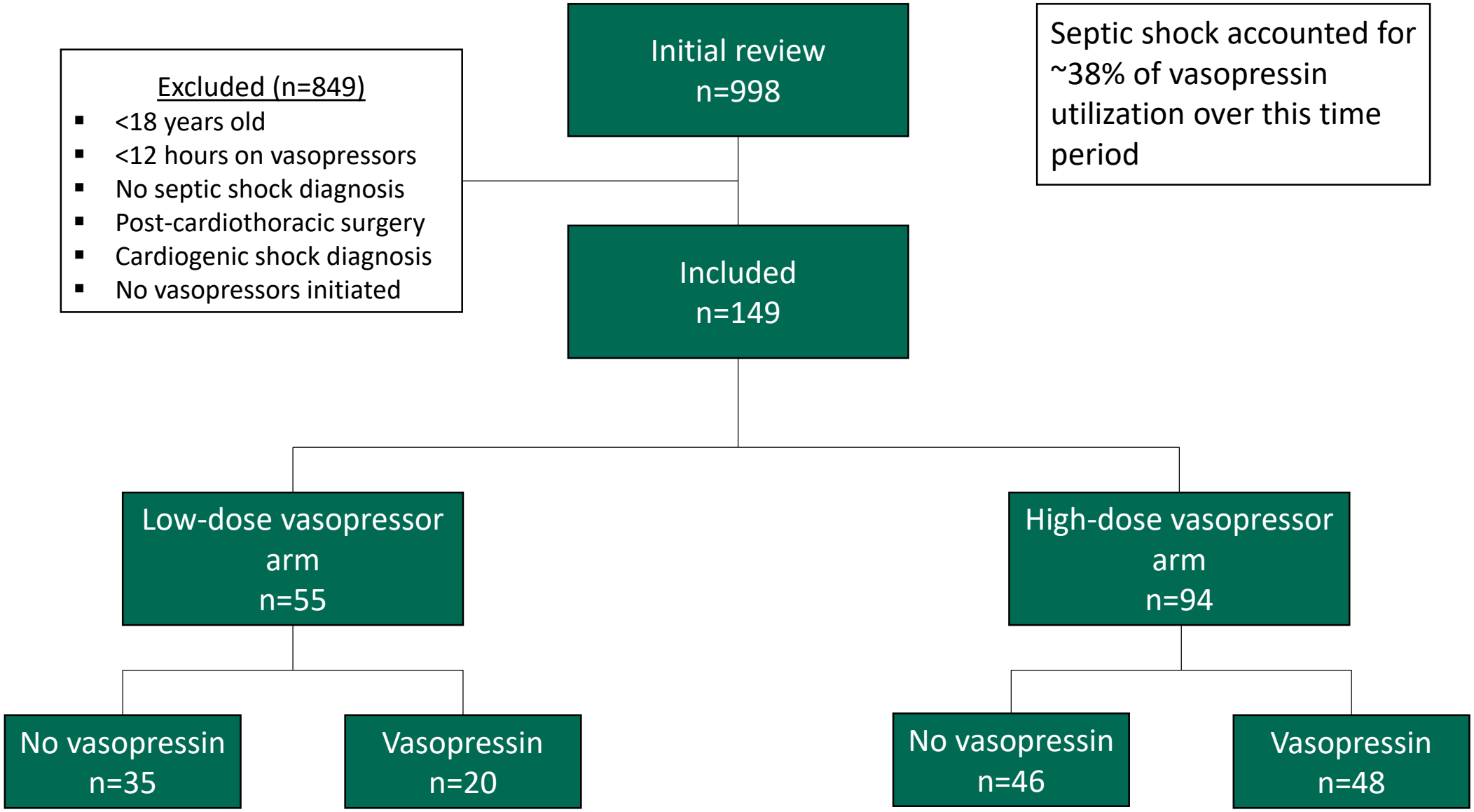
Primary outcome:

- In-hospital mortality from any cause or initiation of hospice care

Secondary outcomes:

- Total time on vasopressors (hours)
- Number of catecholamine agents required
- ICU length of stay (days)
- Hospital length of stay (days)

Subject selection



Septic shock accounted for ~38% of vasopressin utilization over this time period

Results: Low-dose arm

Baseline characteristics: Low-dose arm

Characteristics	No vasopressin (n=35)	Vasopressin (n=20)	p-value
Age - years	70.7 ± 13.7	63.7 ± 18.7	0.12
Male sex – no (%)	23 (65.7)	11 (55)	0.43
APACHE II score	18.1 ± 5.8	18.1 ± 7.0	1.00
SOFA score	5.1 ± 2.2	5.6 ± 2.6	0.45
Lactic acid – mg/dL	3.0 ± 1.9	3.2 ± 2.6	0.74
MAP – mmHg	65.3 ± 12.0	63.7 ± 8.8	0.60
NE-equivalent dose – mcg/kg/min	10.4 ± 5.4	10.6 ± 7.8	0.91

All baseline characteristics at time of vasopressor initiation
All values displayed as mean ± standard deviation unless otherwise noted
NE-equivalent dose equation from VASST trial
NE-equivalent = Norepinephrine + Epinephrine + (Dopamine/2) + (Phenylephrine/10)

Outcomes: Low-dose arm

	No vasopressin (n=35)	Vasopressin (n=20)	p-value
In-hospital mortality – no (%)	7 (20.0)	7 (35.0)	0.22

Secondary outcomes	No vasopressin (n=35)	Vasopressin (n=20)	p-value
Mean time on vasopressors - hours	52.6 ± 56.3	75.5 ± 40.2	0.12
Mean time on vasopressors for patients surviving to discharge - hours	45.3 ± 38.4	66.9 ± 41.2	0.06
Mean ICU length of stay - days	3.6 ± 2.8	10.1 ± 9.0	0.0002
Mean hospital length of stay - days	12.8 ± 12.5	30.6 ± 27.4	0.001
Number of catecholamines at time of inclusion	One agent: 35 (100)	No other agents: 4 (20) One agent: 14 (70) Two agents: 2 (10)	
Maximum number of catecholamines following inclusion	One agent: 34 (97) Two agents: 1 (3)	One agent: 10 (50) Two agents: 9 (45) Three agents: 1 (5)	

Additional data: Low-dose arm

	No vasopressin (n=35)	Vasopressin (n=20)
Steroids administered – no (%)	17 (49)	9 (45)
Midodrine administered – no (%) Average norepinephrine rate of 2.6 mcg/min at initiation	9 (26)	2 (10)
Mean time to vasopressin administration - hours (range)		10.8 (0-45.3)
Mean duration of vasopressin – hours (range)		40.7 (12.3-90.8)

Results: High-dose arm

Baseline characteristics: High-dose arm

Characteristics	No vasopressin (n=46)	Vasopressin (n=48)	p-value
Age - years	75.8 ± 10.8	73.2 ± 14.2	0.18
Male sex – no (%)	32 (69.6)	27 (56.3)	0.16
APACHE II score	21.2 ± 6.0	22.6 ± 6.5	0.28
SOFA score	6.0 ± 2.3	6.5 ± 3.1	0.38
Lactic acid – mg/dL	3.1 ± 1.9	4.7 ± 4.6	0.03
MAP – mmHg	67.1 ± 15.5	66.8 ± 15.3	0.93
NE-equivalent dose – mcg/kg/min	42.4 ± 49.2	58.2 ± 53.3	0.14

All baseline characteristics at time of vasopressor initiation
All values displayed as mean ± standard deviation unless otherwise noted
NE-equivalent dose equation from VASST trial
NE-equivalent = Norepinephrine + Epinephrine + (Dopamine/2) + (Phenylephrine/10)

Outcomes: High-dose arm

	No vasopressin (n=46)	Vasopressin (n=48)	p-value
In-hospital mortality – no (%)	20 (43.5)	34 (70.8)	0.007

Secondary outcomes	No vasopressin (n=46)	Vasopressin (n=48)	p-value
Mean time on vasopressors - hours	95.4 ± 86.8 Median: 74.2	171.7 ± 211.2 Median: 76.5	
Mean time on vasopressors for patients surviving to discharge - hours	81.9 ± 71.8 Median: 70.6	141.6 ± 142.1 Median: 70.5	
Mean ICU length of stay - days	7.3 ± 6.8 Median: 5.0	9.4 ± 15.2 Median: 5.0	0.39
Mean hospital length of stay - days	17.5 ± 12.0 Median: 14.0	16.1 ± 16.6 Median: 12.0	0.64
Number of catecholamines at time of inclusion	One agent: 35 (76) Two agents: 11 (24)	One agent: 35 (73) Two agents: 13 (27)	
Maximum number of catecholamines following inclusion	One agent: 37 (72) Two agents: 13 (28)	One agent: 22 (46) Two agents: 21 (44) Three agents: 4 (8) Four agents: 1 (2)	

Additional data: High-dose arm

	No vasopressin (n=46)	Vasopressin (n=48)
Steroids administered – no (%)	21 (45.7)	25 (52.1)
Midodrine administered – no (%)	20 (43.5)	19 (39.6)
Mean time to vasopressin administration - hours (range)		24.7 (0-177.3)
Mean duration of vasopressin – hours (range)		62.4 (1.8-403)

Limitations

- Higher vasopressin dose utilized than recommended by the Surviving Sepsis Guidelines
- Small sample size in low-dose vasopressor with vasopressin group (n=20)
- Potential for inaccurate charting of vasopressor initiation, rate change, and discontinuation
- Potential for inaccurate reporting of septic shock diagnosis in electronic medical record
- Unknown administration of fluid resuscitation prior to initiation of vasopressors
- Additional causes of mortality not accounted for
- Evaluated in-hospital mortality with unknown extended outcomes

Conclusions

- No in-hospital mortality benefit associated with vasopressin utilization in both the low- and high-dose arms
- No difference in duration of vasopressor therapy associated with vasopressin administration in both the low- and high-dose arms
- Opportunity for optimization of vasopressin utilization based on poor associated outcomes

Self-assessment question

- Which of the following is an outcome of the VASST trial?
  A. 28-day mortality benefit seen with initiation of vasopressin prior to norepinephrine
  B. Increased 28-day mortality for patients administered vasopressin
  C. Significantly more days free of organ dysfunction for patients administered vasopressin
  D. 90-day mortality benefit for patients with less-severe septic shock administered vasopressin

Self-assessment answer

- Which of the following is an outcome of the VASST trial?
  - A. 28-day mortality benefit seen with initiation of vasopressin prior to norepinephrine
  - B. Increased 28-day mortality for patients administered vasopressin
  - C. Significantly more days free of organ dysfunction for patients administered vasopressin
  - D. 90-day mortality benefit for patients with less-severe septic shock administered vasopressin

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