Russell JA, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. NEJM. 2008;358:877-87.

Clinical question posed by this trial: In patients with septic shock who have achieved guideline-based MAP goal with catecholamine-based vasopressors, does the addition of vasopressin versus norepinephrine reduce mortality?

Context:

- Vasopressors are a key component of life-saving resuscitation measures in patients with septic shock.[1]
- With multiple agents from which to choose, the optimal vasopressor regimen is still largely unknown.
- Patients in septic shock are thought to be relatively deficient in vasopressin, a peptide hormone that is released in response to decreases in blood volume, decreased intravascular volume, and increased plasma osmolarity.[2]
- Vasopressin acts directly on V1 receptors to constrict vascular smooth muscle and increase vascular response to catecholamines.
- Vasopressin is thus an attractive option as an adjunct to catecholamines in septic shock.

Methodology

Study design	Superiority RCT
Sequence generation	Appropriate (computer-generated) • Stratified by centre & "shock severity" (group 1: NE-equivalent 5-14 µg/min at baseline; group 2: NE – equivalent >15µg/min)
Allocation concealment	Adequate (Central randomization by phone)
Blinding	• Preparations of identical appearance • Patients, clinicians, adjudicators blinded • Hospital dispensary staff not blinded
Loss to follow-up	<1% (1 in vasopressin lost to follow-up)
Population analyzed	Modified intention-to-treat (included all who received study drug infusion, NOT all randomized patients)
Intervention	• Vasopressin started at 0.01 unit/min titrated to max of 0.03 units/min • NE 5 µg/min titrated to max of 15 µg/min + *Open-label catecholamine vasopressors at baseline and as needed if hypotensive despite max dose of study drug*
Outcomes	• **All-cause mortality at 28 days** • All-cause mortality at 90 days • Days alive & free of organ dysfunction during the 1st 28 days • Days alive & free of vasopressor use, mechanical ventilation, or renal replacement therapy • Days alive & <2 SIRS criteria • Days alive & free of corticosteroid use • LOS in ICU • LOS in hospital
Statistical power calculation	• N = 776 to find 10% ARR assuming 60% mortality rate in NE group; alpha = 0.05, power = 80%
Funding	Canadian Institute of Health Research

Participants

Setting	27 centres (Canada, Australia, USA)
Inclusion criteria	• > 16 y • Septic shock resistant to fluids (no response to 500 mL of NS or requirement for vasopressors) & low-dose NE
Relevant exclusion criteria	• Unstable coronary syndrome (MI during this episode) or underlying chronic heart disease (NYHA III-IV) & shock • Proven or suspected acute mesenteric ischemia • Raynaud's phenomenon, systemic sclerosis or vasospastic diathesis • Severe hyponatremia (serum Na < 130) • >24h since patient met entry criteria • Use of open-label vasopressin for BP support during current hospitalization • Estimated 6-month mortality ≥50% due to malignancy or other irreversible disease or death anticipated <12h • Physician & team not committed to aggressive care • Traumatic brain injury (GCS < 8 prior to sepsis onset)
Study size	• 6229 assessed for eligibility ○ 802 eligible & randomized ▪ 778 included in modified ITT analysis
"Average" patient	• Male 60% • Comorbidities ○ IHD ~15% ○ COPD 15% ○ Liver disease ~10% ○ CKD ~10% ○ Compromised immune system ~15% ○ Corticosteroid use ~20% ○ Cancer ~25% • White 85% • Age 61 y • MAP 73 • Serum lactate 3.5 mmol/L • Vasopressors (NE alone 57%, ≥2 agents 30%) ○ NE 21 µg/min ○ Epinephrine 9-15 µg/min ○ Dopamine 7.5 µg/min ○ Dobutamine 5-6.5 µg/kg/min ○ Milrinone 0.3-0.4 µg/kg/min ○ Phenylephrine ~150-160 µg/min • Corticosteroids 75% • Activated protein C 15% • Time from meeting inclusion criteria to study-drug infusion ~12h
Clinically-relevant baseline differences (NE vs vasopressin)	• Age (62 y vs 59 y) • Male (60% vs 62%) • Recent surgical hx (35% vs 38%) • Pre-existing conditions (e.g. cancer 27% vs 21%) • New organ failure (e.g. hematologic & coagulation 22 vs 30%) • No pathogen cultured (24% vs 18%) However, no differences in APACHE II (27) & serum lactate (3.5), 2 important prognosticators in sepsis

Results				
Binary outcomes	NE alone	Vasopressin + NE	Unadjusted RR	Absolute risk reduction
28-day mortality	39.3%	35.4%	0.90 (0.75-1.08)	3.9%
90-day mortality	49.6%	43.9%	0.88 (0.76-1.03)	5.7%
≥1 serious adverse event (excluding death)	10.5%	10.3%	0.99 (0.65-1.49)	0.2%
Continuous outcomes	NE alone	Vasopressin + NE	p-value	
ICU LOS	16	15	0.14	
Hospital LOS	26	27	0.23	

- No statistically significant difference in any single serious adverse event
- No statistically significant difference in days alive free of any or specific organ dysfunction
- No statistically significant difference in days free of corticosteroid use

Major Limitations:

Methods

- **Baseline differences?** Variable differences in multiple characteristics, however, APACHE II scores remain very similar.

Results

- **"Negative" trial, but… Statistically insignificant yet clinically meaningful difference in mortality**
  - Yep, it is legitimately *underpowered*
    - Calculated sample size (n=776) calculation assumed that approximately 427 deaths would occur
      - NE alone = 388 * 0.6 mortality rate = 233 deaths
      - Vasopressin + NE = 388 x 0.5 mortality rate = 194 deaths
    - Actual total deaths = 150 (NE alone) + 140 (vasopressin + NE) = 290 deaths
    - Deficit of 137 deaths to achieve adequate statistical power
- **Benefit in the subgroup with "less severe shock"?**
  - Patients were stratified based on baseline NE dose (5-14μg/min or >15μg/min), technically making VASST 2 RCTs
  - The strong trend in favor of vasopressin adjunctive therapy appears to be limited to patients with doses of vasopressors of 5-14 μg/min NE-equivalent (test for interaction p = 0.10 suggesting borderline/non-significance)
  - HOWEVER, trends in favor of an intervention – no matter how appealing – must be interpreted with extreme caution (i.e. essentially ignored) when clinically-important baseline differences exist in favor of the intervention
  - ALSO, the *a priori* hypothesis was that patients with HIGHER – not lower – baseline doses of catecholamine vasopressors (thought to be those with greater vasopressin deficiency) would gain a survival advantage from adjunctive vasopressin.

Generalizability

  - Saint Paul's Hospital was the main centre for this study; other sites include VGH, RCH & Richmond Hospital
  - **Overall, excellent generalizability to our patients!**
- **Excluded a HUGE proportion (>85%) of patients** assessed for eligibility, **including those most susceptible to the adverse event profile of vasopressin** (e.g. cardiac, mesenteric & limb ischemia)
- **This is a "catecholamine-sparing" study, not a "resistant to catecholamines" study**
  - Most patients had achieved target resuscitation MAP goals (mean MAP 72.5 mm Hg) prior to starting study drug
  - Therefore, this study does not answer the question of whether vasopressin is better at achieving resuscitation MAP goals; rather, it answers the question of whether adding vasopressin can MAINTAIN adequate MAP while reducing catecholamine doses (i.e. yes it can). The next questions to answer are 1) whether this can make a difference on clinical outcomes, and 2) whether we can use vasopressin as monotherapy in septic shock.

Conclusions:

- We cannot rule out the possibility of a reduction in mortality with the adjunctive use of vasopressin in septic shock with adequate perfusion pressures.
- This study does not provide support for use of vasopressin as monotherapy in septic shock, or for the use of vasopressin in catecholamine-resistant shock.

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[1] Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.

[2] Hollenberg SM, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004;32:1928-48.