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Clinical Scenario: You have a patient that looks very ill, is febrile and hypotensive. You astutely recognize he is in septic shock. You send off all the appropriate studies and begin early goal directed therapy. However despite aggressive fluid administration and the use of several catecholamines his MAP remains below 65. If only there was some super drug out there that could help correct all this…

P: In patients presenting in vasodilatory septic shock
I: Does the use of vasopressin
C: In addition to the current standard of care
O: Help improve patient morbidity and or mortality

Quick Review:
Donald Landry (1990's) noted profound hypotension in a patient with bleeding varices with discontinuation of vasopressin. Patient was in septic shock. Further studies showed patients in septic shock had increased pressor sensitivity to vasopressin and had a deficiency of vasopressin. Vasopressin acts on V1a receptors to potently constrict vascular smooth muscle.

Emanuel Rivers (2001) – Early goal directed therapy to optimize cardiac preload, afterload, and contractility. First 6 hours aggressive fluid administration, vasopressors, pRBC transfusions and dobutamine to establish CVP 8-12, MAP 65-90, ScvO2 >70%, HCT >30%

Surviving Sepsis Campaign (2008) – "We recommend either norepinephrine or dopamine as the first choice vasopressor agent…" "We suggest that epinephrine, phenylephrine, and vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin 0.03 units/min may be added to norepinephrine…" "There is no high-quality primary evidence to recommend one catecholamine over another."

Article	Study Type	Patient Population	Results	Conclusions	Limitations
Russell, James, A., et. al. NEJM 358;9 (Feb 28 2008) 877-887. Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock.	Multi-center, randomized, stratified, double blind trial. Primary outcome - Death from any cause assessed at 28 days after start of infusion Secondary outcome - 90 day mortality; days alive - free of organ dysfunction, vasopressor use, mechanical ventilation,	778 patients from 27 centers Inclusion -Patients >16 yo in septic shock resistant to fluids and requiring low dose NE at least 5 micrograms per minute Drug Infusion Vasopressin at 0.03 U/m NE at 15 microg/m	Death at 28 days 35.4% vs. 39.3% Death at 90 days 43.9% vs. 49.6%, no difference in organ dysfunction SAE 10.3% vs. 10.5% Less severe shock mortality 26.5% vs. 35.7% at 28 days and 35.8% vs. 46.1% at 90 days	No significant difference in 28 day mortality rate No significant difference in 90 day mortality rate No significant difference in SAE Vasopressin allowed rapid lowering on NE infusion while maintaining MAP	Vasopressin levels were not measured to guide dosing or duration of infusion Studied the effects of low-dose vasopressin as a "catecholamine-sparing drug" Mean time from study entry to drug infusion was 12 hours Only low dose

	RRT, SIRS, steroid use; length of stay in ICU and hospital; adverse events		More cardiac arrests occurred in the NE group (8/11) and more digital ischemia in the vasopressin group (8/10)	Observed overall mortality considerably lower than the expected 60% Vasopressin may be more beneficial in less severe septic shock	vasopressin was used Excluded patients with ACS and severe heart failure
Russell, James A., et al. Critical Care Medicine 37;3 (2009) 811-818. Interaction of vasopressin infusion, corticosteroid treatment, and mortality in septic shock	*Post hoc* sub study of previous VASST trial Primary outcome -28 day mortality Secondary outcome -90 day mortality; days alive and free from organ dysfunction over the first 28 days	VASST trial 589 patients were treated with corticosteroids Inclusion - Same as above Different steroids were used but no statistically significant difference among dosing or type	Death at 28 days 35.9% vs. 44.7% Death at 90 days 45.2% vs. 55.5% With no steroids death at 28 days 33.7% vs. 21.3% Vasopressin + steroids has less organ dysfunction suggested by increased days alive and free from shock, mechanical ventilation, renal failure, and any organ failure Steroids significantly increased vasopressin levels by 33% (6 hours) and 67% (24 hours) Significant higher rate of cardiac death in NE + steroids	Statistically significant decrease in 28 day mortality with vasopressin + steroids In patients not treated with steroids, vasopressin associated with increased mortality Vasopressin decreased total NE dose similarly in steroid vs. non-steroid treated pts Patients treated with steroids had increased severity of illness at baseline	Retrospective study Use of corticosteroids was not randomized, blinded, or controlled Same as previous trial

Luckner, Gunter, et al. Crit Care Med 35;10 (2007) 2280-2285. Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock	Retrospective, controlled study Primary outcome -Treatment efficacy; hemodynamic response Secondary outcome -Prevalence of adverse events and changes in laboratory variables	78 patients Inclusion -Institutional AVP database – comparable patients in vasodilatory shock who received vasopressin at 0.033 and 0.067 U/min from Jan 1, 1999 to December 31, 2006	No difference in prevalence of increase in MAP first 30 minutes 87.2% vs. 87.2% During first 24 hours NE doses significantly more reduced in patients receiving high dose AVP Significantly increased serum transaminase in low dose AVP 71.8% vs. 28.2% No significant change in cardiac index 69.2% vs. 53.8% Platelet count significantly decreased in both groups 94.8% vs. 84.6 Significant increase in total bilirubin 48.7% vs. 71.8% Significant decrease in lactate and increase in pH in high dose AVP group Patients receiving high dose AVP were greater % female had statistically significant higher MODS score	High dose AVP more effective in reducing NE dosages High dose AVP resulted in higher MAP, lower CVP, lower mean pulm artery pressure, and lower NE requirements High dose AVP resulted in significantly increased perfusion pressures and sustained "Higher AVP dosages seem to have been more effective to reverse vasodilatory shock in our study population" Hypothesized low dose AVP was too low to exert sufficient V1a receptor mediated vasoconstriction Since NE baseline was the same, only AVP dosage determined decrease in catecholamine support Low dose AVP may reverse CV failure but inadequate to stabilize HD function with high NE requirements High dose AVP	Retrospective study Small study size Comparison of patient groups at two different time periods Statistically significant differences in baseline characteristics of sex and MODS score Unable to evaluate skin ischemia in study

				improved acid-base variables and decreased lactate indicating better organ perfusion	
Choong, Karen, et al. Am J Respir Crit Care Med (Jul 16 2009) Epub. Vasopressin in Pediatric Vasodilatory Shock – A Multi-center Randomized Controlled Trial	Multi-centered, double blind, randomized, placebo controlled trial Primary outcome -Time to vasoactive-free hemodynamic stability Secondary outcomes -30 day mortality; change in organ dysfunction; organ failure-free days, vasoactive-free days, ventilator-free days in 30 days; length of PCCU stay; urine output; MAP; rates of SAE	65 patients Inclusion -Patients 1 month to 17 yo with indwelling arterial and central venous catheters within 24 hours of dx of vasodilatory shock Drug Infusion Vasopressin infused at 0.0005 U/kg/min to max of 0.002 U/kg/min vs. NS placebo	Median time to hemodynamic stability was 49.7h vs. 47.1h No significant difference in vaso-active-free, organ-failure-free, organ dysfunction scores, and length of PCCU stay No significant difference in markers of end organ perfusion Rates of death 30% vs. 15.6% Use of steroids 60.6% vs. 65.6% No significant difference in mortality with use of steroids No significant difference in AE, SAE	No evidence of favorable HD parameters with low dose vasopressin Mortality twice as high in vasopressin group but not statistically significant, majority from non-septic causes No potential side effects reported in previous studies seen Vasopressin dosage may have been insufficient, timing not optimal, or children may have progressed from warm to cold shock No deaths attributed to study drug	Feasibility due to nature of patient population Small numbers of any single type of patient Limited funding Had to evaluate vasopressin as adjunctive, catecholamine sparring agent Choice of time to hemodynamic stability as primary outcome Trial size

Bottom Line: I would continue to consider vasopressin as a second line agent in patients presenting in vasodilatory septic shock.

At this time clinical trials have not proven that vasopressin improves mortality and morbidity in adults or children. However, proponents argue that the dose of vasopressin used was ineffective and it was not given quick enough in accordance with EGDT. There is still conflicting evidence whether increasing vasopressin doses result in worsening side effects such as coronary ischemia, ischemic skin lesions, reduced cardiac output, tachyarrhythmia, and splanchnic hypoperfusion. To date pressor catecholamines have never been tested in a well-designed trial but are the current standard of care. Anecdotally, my short experience in the ICU the patients started on norepinephrine + vasopressin seemed to respond better than patients on norepinephrine + phenylephrine.