

# Low dose vasopressin in septic shock

The addition of low-dose vasopressin to the treatment of septic shock does not reduce mortality compared to the use of norepinephrine alone, but allows a rapid reduction in norepinephrine requirements.

Level of evidence: 1<sup>+</sup> (RCT with a very low risk of bias)

**Appraised by:** R Docking, K Rooney

**Citation:** Russell JA, Walley KR, Singer J *et al.* Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877-87.

**Lead author:** James A Russell

**Three-part clinical question:**

*Patients:* Septic shock.

*Intervention:* The addition of low dose vasopressin compared to the use of norepinephrine alone.

*Outcome:* Death at 28 days from any cause.

**Search terms:** Septic shock, intervention, RCT, vasopressin, norepinephrine.

**The study:** Multi-centre, double-blind, randomised controlled trial (RCT) with intention-to-treat analysis.

**Study patients:** Patients older than 16 with septic shock resistant to fluids and vasopressor use of >5 µg/min norepinephrine or equivalent within the last 24 hours, were recruited in their first 24 hours of treatment. Stratification of septic shock was based on pre-randomisation vasopressor levels. Exclusions included acute coronary syndrome or cardiogenic shock, greater than 24 hours elapsing since the patient met entry criteria, prior use of vasopressin, malignancy or proven/suspected acute mesenteric ischaemia.

**All patients:** received unlabelled 'study-drug' to reach a target mean arterial pressure (MAP) of 65-75 mm Hg. Open-label vasopressors were also used to reach/maintain target MAP during and after study drug titration (The open-label vasopressors were increased only if the target MAP was not reached on maximal study-drug infusion). Standard ICU care

of the septic patient was also given. The study-drug was continued for as long as required unless predetermined adverse events occurred (cardiac events, evidence of organ or tissue ischaemia, hyponatraemia).

**Control group** (n = 382; 382 analysed): Unlabelled norepinephrine infusions were started and titrated up to 15 µg/min.

**Experimental group** (n = 396; 396 analysed): Unlabelled vasopressin infusions were started and titrated up to 0.03 µ/min.

**EBM questions:**

1. *Do the methods allow adequate testing of the hypothesis? To an extent*, but the study may have been inadequately powered.
2. *Do the statistical tests used correctly test the results to allow differentiation of statistically significant findings? Yes*, the statistics used are appropriate, however the mortality rate was much lower than predicted by investigators (approximately 34% in both study groups vs 60% expected). This may have resulted in an inadequately powered study.
3. *Are conclusions valid in light of results? Yes*. There is no evidence from this RCT to support the use of vasopressin in preference to norepinephrine for septic shock.
4. *Did results get omitted and why? Yes*. One patient in the vasopressin arm was lost to follow-up.
5. *Did they suggest areas of further research? Yes*. They suggested future trials looking at vasopressin in 'less severe' septic shock.

**The evidence:**

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
28 day mortality	28 days	0.393	0.354	10%	0.039	NS
		95% confidence intervals:		-7% to 27%	-0.029 to 0.107	NS
90 day mortality	90 days	0.492	0.434	12%	0.058	NS
		95% confidence intervals:		-2% to 26%	-0.012 to 0.128	NS

  

Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value
Average length of ICU stay		16 (8-32)	15 (7-29)	0.14
Average length of hospital stay		26 (15-53)	27 (13-52)	0.23
Median rate of norepinephrine infusion (µg/min)		15	5	

6. *Did they make recommendations and are these appropriate?* **No.**
7. *Is this study relevant to my clinical practice?* Although this is a well-designed RCT, it does not address the issue of catecholamine-refractory septic shock – a setting where vasopressin is more commonly used. Important patient groups such as those with cardiac disease or with acute coronary syndrome were excluded from the trial, and as such we are unable to assess how common adverse events would have been in these groups.
8. *What level of evidence does this represent?* **1<sup>+</sup>**
9. *What grade of recommendation can I make on this alone?* **B**
10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **B**
11. *Should I change my practice in light of this study?* **Possibly not** – vasopressin is commonly used in catecholamine-refractory shock, which is not fully addressed by this RCT.
12. *Should I audit my practice because of this paper?* **No.**

**Appraised by:**

**Robert Docking**, ST2 Anaesthetics,  
Inverclyde Royal Hospital, Greenock  
robertiaindocking@doctors.net.uk

**Kevin Rooney**, Consultant in Anaesthetics and Intensive Care,  
Royal Alexandra Hospital, Paisley

Reviewed by Chris Cairns