

# **Vasopressin in septic shock: an individual patient data meta-analysis of randomised clinical trials**

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**Study protocol version:** 1.0

**Date of version:** 10 July 2017

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## **BACKGROUND**

### **Septic shock**

Septic shock is a life-threatening condition that results from a dysregulated immune response to infection.<sup>1</sup> A key pathophysiological feature is release of inflammatory mediators that lead to widespread vasodilatation, capillary leak and reduced systemic vascular resistance. Following initial fluid resuscitation, vasopressor therapy is often required to increase vascular resistance, raise mean arterial pressure and maintain perfusion of critical body tissues and organ systems.<sup>2</sup>

### **Rationale for vasopressin therapy**

The traditional approach to management of septic shock involves adrenergic (alpha, beta or combined) agonists, also known as catecholamines. Alpha-adrenergic agonists increase vascular tone and blood pressure while beta-agonists increase blood flow via inotropic and chronotropic effects. Both classes of drugs are associated with risks including reduction of cardiac output and regional blood flow for alpha-agonists and myocardial ischaemia and tachycardia with beta-agonists.<sup>2,3</sup> In addition to its action on adrenergic receptors, dopamine also acts on dopaminergic receptors which can result in unwanted side effects including immunosuppression, renal impairment and increased risk of arrhythmias.<sup>2</sup> These adverse effects have led to interest in adjunctive therapeutic strategies.

Vasopressin is an endogenous hormone that leads to an increased circulating volume in health by promoting water retention in the distal tubules and collecting ducts. However, in shock states vasopressin acts as a potent vasoconstrictor via V1a receptors on vascular smooth muscle.<sup>4</sup> A relative deficiency of vasopressin in septic shock has been described<sup>5</sup> and administration of exogenous vasopressin reduces catecholamine requirements and thereby it has been postulated to diminish the likelihood of catecholamine related side effects. Furthermore vasopressin may have additional benefits in terms of organ perfusion, due to the distribution of the family of vasopressin receptors in different vascular beds, and additional immunological effects compared to norepinephrine.

The Vasopressin and Septic Shock Trial (VASST) was the first large randomised comparison of vasopressin with norepinephrine.<sup>6</sup> Although there was no significant mortality benefit to addition

of low dose vasopressin in the overall population, there was a lower mortality in the subgroup of patients with less severe shock (<15 µg/min norepinephrine). Subsequent post-hoc analyses and other studies suggested a potential reduction in renal dysfunction with higher dose vasopressin,<sup>7-9</sup> as well as a potentially synergistic interaction with corticosteroid treatment.<sup>10,11</sup> This was specifically investigated in the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial which found that early vasopressin use compared to norepinephrine did not increase the number of renal failure-free days and there was no interaction with corticosteroids.<sup>12</sup> However, the investigators noted that the confidence interval included a potentially clinically relevant benefit for vasopressin, as well as a significantly reduced use of renal replacement therapy (RRT).

### **Importance of performing this review**

Although existing trials have not demonstrated clear superiority of vasopressin, there remain questions regarding which subgroups of patients may benefit the most (early versus late onset of shock and low versus high severity of shock) and the optimal dose of vasopressin. The Surviving Sepsis Campaign 2016 guidelines do not recommend vasopressin as a first-line agent and emphasise caution at doses higher than 0.03 U/min.<sup>13</sup>

Individual patient data (IPD) meta-analyses are considered the gold standard for synthesising information from RCTs.<sup>14</sup> The provision of the IPD reduces the need for imputation and estimation of non-published data, as well as providing increased statistical power for investigating differential treatment effects.<sup>15</sup> Therefore, the aim of this review is to use IPD meta-analyses to quantify the efficacy and safety of vasopressin therapy within RCTs for septic shock, both overall and in a priori defined subgroups.

## METHODS

### Criteria for considering studies for this review

#### *Types of studies*

- Non-crossover randomised controlled trials

#### *Types of participants*

- Human adults requiring vasopressor therapy for either hypotension due to sepsis or septic shock
- Hypotension, sepsis and septic shock are defined as per either:
  - The trial investigators
  - The 1992 International Sepsis Definitions Conference<sup>16</sup>
  - The 2001 International Sepsis Definitions Conference<sup>17</sup>
  - The 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) panel<sup>18</sup>

#### *Types of interventions*

- Vasopressin versus any other vasoactive comparator
  - Minimum duration for vasopressin therapy (3 hours and/or until ICU discharge)

#### *Outcome measures*

- Primary:
  - Efficacy – Mortality at day 28
  - Safety – Total number of serious adverse events (SAEs)
    - SAEs are defined as any event that is immediately life threatening, is permanently disabling, or severely incapacitating, or requires or prolongs inpatient hospitalisation.
    - As mortality is being assessed in a separate primary outcome, death will not be considered a SAE in the context of this analysis
- Secondary:
  - Rates of use of RRT (in patients without end stage renal failure)
  - Duration of RRT in all patients (and survivors / non-survivors separately)
  - Duration of shock in all patients (and survivors / non-survivors separately)
  - Duration of ventilation in all patients (and survivors / non-survivors separately)

- Renal failure free days to day 28
- Shock free days to day 28
- Ventilation free days to day 28
- ICU free days to day 28
- Long term mortality (maximum follow up day 60-180)
- ICU length of stay in all patients (and survivors / non-survivors separately)
- Hospital length of stay in all patients (and survivors / non-survivors separately)

## **Search strategy**

To identify randomised trials for inclusion we will use MeSH and free-text terms for various forms of the keywords 'vasopressin' and 'septic shock'. The 'Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE' filter will be used to identify only randomised controlled trials.<sup>19</sup>

The detailed search strategy for each database is given in appendix 1.

### *Electronic searches:*

- MEDLINE (inception to date of search)
- EMBASE (inception to date of search)
- Science Citation Index Expanded (inception to date of search)
- Cochrane Central Register of Controlled Trials (Latest issue)
- Clinicaltrials.gov (date of search)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (date of search)

### *Other searches:*

- Abstracts of major congresses (Society of Critical Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, and European Society of Intensive Care Medicine) for the previous 3 years from date of search
- Contacting authors of included trials and experts in the field
- Reference searching of included trials to identify further trials<sup>20</sup>

## **Study selection**

Duplicates will be removed from the search results. One author will screen titles and remove any reports that are clearly not eligible. Two authors will then independently screen abstracts for potentially eligible studies. Full text reports will be retrieved for studies identified by at least one of these authors. These will then be assessed for inclusion by two authors independently. There will be no restriction of studies by their sample size or language (non-English articles will be translated to English prior to data extraction, if this is feasible). All disagreements will be resolved by consensus and discussion with a third author.

A preliminary search of all databases revealed a total of approximately 2,000 references. After removal of duplicates, it is anticipated that around 1,500 titles will have to be screened and about 10-20 full texts will have to be obtained, leading to between 5 and 10 eligible trials.

## **Data procurement**

There will be two stages to the analysis. Initially, data will be extracted from the publications of eligible trials for an immediate analysis. The original investigators will also be contacted by email and invited to participate in the second stage, an IPD meta-analysis. We define 'original investigators' here as the corresponding author listed on the publication (or the lead of the writing committee if authorship is attributed to a collaborative group). If no reply is received, a reminder will be sent after 3 weeks. If the investigators decline the request to participate or no reply is received after reminder, only the aggregate study data will be extracted as far as possible from all publicly available reports of the study. If a trial investigator agrees to participate, they will be sent a written data use agreement confirming that their data:

- Will be used only for the purpose specified in this protocol
- Will remain their property at all times
- Will remain on secure servers at Imperial College London
- Will be accessed only by authorised members of the study team and will not be used for other purposes without the explicit approval of the trial investigator

Electronic transfer of anonymised and encrypted data will be requested after providing investigators with a list of required data. The datasets will then be cleaned with variables recoded as necessary, so as to allow for the construction of a combined dataset with common variables and definitions. Any errors or inconsistencies will be clarified at the data cleaning stage with the original investigators of the trial. A list of the data that will be requested appears in appendix 2.

## **Risk of bias assessment**

Risk of bias will be assessed by applying the Cochrane Risk of Bias tool.<sup>21</sup> It includes six domains that could affect the effect estimates due to systematic error. These are: sequence generation, allocation concealment, blinding of participants, healthcare providers and outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain will be rated as low, uncertain or high risk of bias. A trial will be rated to be at low risk of bias if all the domains are rated as low. Any unclear or missing information will be sought from the original investigators of the trial. Initially, these assessments will be done using the trial publications and supplementary information from the original researchers, but further assessments will be possible during the processing of the IPD.

## **Statistical analysis**

All analyses will be performed on an intention-to-treat (ITT) basis, where possible.<sup>22</sup> We will follow the initial approach taken by the NSCLC Meta-analyses Collaborative Group.<sup>23,24</sup> We will begin by estimating the overall intervention effects and generating forest plots using a conventional two-stage approach. This involves generating trial summary measures that are then combined by standard meta-analytical methods.<sup>19</sup>

For dichotomous outcomes such as mortality at day 28, we will use the numbers of events and patients to calculate the Mantel-Haenszel odds ratio. For continuous outcomes such as length of stay, we will use the mean and standard deviation to calculate the mean difference. Some continuous data may not be normally distributed. In the case of skewed data, we will perform a sensitivity analysis by applying a transformation to approximate a parametric distribution prior to meta-analysis. This will be compared to the non-transformed analysis with the latter being used if there is no significant difference between the two.



These estimates are then combined in a fixed-effect model that stratifies by trial. The results from this analysis will be compared to a random-effects model to assess for model robustness. The fixed-effect model assumes that the treatment effect is the same across studies and that all variation is due to sampling error, therefore greater weight is given to larger studies. In contrast, the random-effects model allows for different effects between the studies with the study means following a specified distribution, often assumed to be a normal distribution.

To explore the effect of patient characteristics on outcomes, we will perform regressions with the treatment by subgroup interaction term within trials and the interaction coefficients pooled across trials (for the two-stage analysis). We will then follow the guidance of Stewart and colleagues by fitting one-stage models with single-treatment covariate interactions and comparing these results to the two-stage models (assuming that the subgroup is not defined wholly by trial).<sup>25</sup> Aggregation bias will be assessed by separation of within and across trial information. If model results are similar between one-stage and two-stage models, we will present the results of the one-stage models.

Analyses will be performed in Stata SE version 12.1 (College Station, TX). We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Methodological Expectations of Cochrane Intervention Reviews (MECIR standards) for reporting systematic reviews.<sup>26,27</sup>

## **Dealing with missing data**

For trials where IPD are available but incomplete, we will impute missing data on a per trial basis using the chained equation methods described by Buuren and colleagues.<sup>28</sup> We anticipate a high degree of data completion and that missing data are likely to be missing at random. For trials where IPD are not available, we will seek as much relevant aggregate information as possible from trial investigators.

For continuous outcomes, the missing mean and the standard deviation will be imputed according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention*.<sup>19</sup> If it is not possible to calculate the standard deviation from the data available from the trial, the standard deviation will be imputed as the highest standard deviation in the other trials included under that outcome, fully recognising that this form of imputation will

decrease the weight of the study for calculation of mean differences and will bias the effect estimate to no effect in case of standardised mean difference. The impact of such imputation of either mean or standard deviation or both will be assessed by sensitivity analyses.

## **Heterogeneity and reporting bias**

We will explore heterogeneity by chi-squared test with significance set at P value 0.10, as well as by measuring the quantity of heterogeneity using  $I^2$ . Visual asymmetry in a funnel plot will be used to explore reporting bias if 10 or more trials are identified for a pairwise comparison.<sup>29,30</sup> The linear regression approach described by Egger and colleagues will also be performed to determine the funnel plot asymmetry.<sup>29</sup>

## **Subgroup and sensitivity analyses**

### *Subgroup analyses*

The following subgroup analyses will be performed:

- Onset of shock to vasopressin commencement (early versus late)
  - Early defined as  $\leq 12$  hours, late defined as  $> 12$  hours
- Severity of shock by vasopressor requirement at baseline (low versus high)
  - Low severity defined as  $< 15$   $\mu\text{g}$  of norepinephrine per minute or equivalent
  - High severity defined as  $\geq 15$   $\mu\text{g}$  of norepinephrine per minute or equivalent
- Severity of shock by lactate level at baseline (low versus high)
  - Low severity defined as lactate level  $\leq 2\text{mmol/l}$
  - High severity defined as lactate level  $> 2\text{mmol/l}$
- Severity of Acute Kidney Injury at baseline (low versus high)
  - Low defined as no AKI and stage 1 AKI (defined as per Mehta et al. 2007)<sup>31</sup> or Risk (RIFLE criteria)<sup>32</sup>
  - High defined as stage 2 & 3 AKI<sup>31</sup> or Injury & Failure (RIFLE criteria)<sup>32</sup>

- Low versus high risk of bias trials
  - Low risk defined as trial being at low risk of bias in all assessed domains
  - High risk defined as not being at low risk of bias

### *Sensitivity analyses*

We will perform sensitivity analyses to assess:

- The impact of not transforming skewed continuous data to approximate normality
- The impact of imputing the mean, standard deviation or both for aggregate data and of imputing data for individual patient's data (in the case of IPD).

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## APPENDIX 1 – SEARCH STRATEGY

### Medline (OvidSP) 1946 to date of search

1. exp Vasoconstrictor Agents/ or exp Catecholamines/
2. (vasopressin or vasopressins or argipressin or arginine or ADH or antidiuretic hormone).af.
3. ((vasoconstrictor\* or vasoactive) adj3 (agent or agents or drug or drugs or agonist or agonists)).af.
4. 1 or 2 or 3
5. exp sepsis/ or exp Systemic Inflammatory Response Syndrome/
6. (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood adj6 (poisoning or poisonings)) or (circulatory adj6 (failure or collapse))).af.
7. exp Hypotension/
8. (hypotension or hypotensive).af.
9. 7 or 8
10. exp Critical Care/
11. ((critical or intensive) adj6 (care or therapy)).af.
12. 10 or 11
13. 9 and 12
14. 5 or 6 or 13
15. 4 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. drug therapy.fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animals/ not humans.sh.

26. 24 not 25

27. 15 and 26

### **Embase (OvidSP) 1947 to date of search**

1. exp Vasoconstrictor Agent/ or exp Catecholamine/

2. (vasopressin or vasopressins or argipressin or arginine or ADH or antidiuretic hormone).af.

3. ((vasoconstrictor\* or vasoactive) adj3 (agent or agents or drug or drugs or agonist or agonists)).af.

4. 1 or 2 or 3

5. exp systemic inflammatory response syndrome/

6. (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood adj6 (poisoning or poisonings)) or (circulatory adj6 (failure or collapse))).af.

7. exp hypotension/

8. (hypotension or hypotensive).af.

9. 7 or 8

10. exp intensive care/

11. ((critical or intensive) adj6 (care or therapy)).af.

12. 10 or 11

13. 9 and 12

14. 5 or 6 or 13

15. 4 and 14

16. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/

17. ((((((random\* or factorial\* or crossover\* or cross over\* or cross-over\* or placebo\* or double\*) adj blind\*) or single\*) adj blind\*) or assign\* or allocat\* or volunteer\*).af.

18. 16 or 17

19. 15 and 18



## **Cochrane library (Wiley) (latest issue)**

#1 MeSH descriptor: [Vasoconstrictor Agents] explode all trees

#2 (vasopressin or vasopressins or argipressin or arginine or ADH or antidiuretic hormone)

#3 ((vasoconstrictor\* or vasoactive) near (agent or agents or drug or drugs or agonist or agonists))

#4 #1 or #2 or #3

#5 MeSH descriptor: [Sepsis] explode all trees

#6 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#7 (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood near (poisoning or poisonings)) or (circulatory near (failure or collapse)))

#8 MeSH descriptor: [Hypotension] explode all trees

#9 (hypotension or hypotensive)

#10 #8 or #9

#11 MeSH descriptor: [Critical Care] explode all trees

#12 ((critical or intensive) near (care or therapy))

#13 #11 or #12

#14 #10 and #13

#15 #5 or #6 or #7 or #14

#16 #4 and #15

**Science Citation index (ISI Web of Knowledge) (1900 to date of search) & Conference Proceedings (ISI Web of Knowledge) (1990 to date of search)**

#1 TS=(vasopressin or vasopressins or argipressin or arginine or ADH or antidiuretic hormone)

#2 TS=((vasoconstrictor\* or vasoactive) and (agent or agents or drug or drugs or agonist or agonists))

#3 #1 OR #2

#4 TS=(shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood AND (poisoning or poisonings)) or (circulatory AND (failure or collapse)))

#5 TS= ((hypotension or hypotensive) AND (critical or intensive) AND (care or therapy))

#6 #4 OR #5

#7 #3 AND #6

#8 TS=(random\* OR rct\* OR crossover OR masked OR blind\* OR placebo\* OR meta-analysis OR systematic review\* OR meta-analys\*)

#9 #7 AND #8

**ClinicalTrials.gov (date of search)**

random\* | Interventional Studies | sepsis or septic shock | Adult, Senior | Phase 2, 3, 4

**WHO ICTRP (available at <http://apps.who.int/trialsearch/>) (date of search)**

Sepsis or septic shock (condition in advanced search)

## APPENDIX 2 – Data required from original trial investigators

- Investigators are requested to supply anonymised data
- Investigators are permitted to supply data with alternative units but will need to specify this so that the necessary conversions can be performed centrally
- It is only required that investigators supply data from within their existing trial databases (extraction from other sources is not expected due to logistical constraints)
- Data validation checks will look for improbable and impossible values in each field; and investigators will be contacted to clarify where any issues arise
- The combined final dataset will include a variable to identify the trial for each patient as well as a unique patient ID

VARIABLE	DATA FORMAT	UNITS
<b><i>Baseline patient data (at the time of randomisation)</i></b>		
<b>Demographic</b>		
Anonymised patient ID	String	-
Age	Integer	years
Gender	Boolean	-
Race (as categorised by study)	String	-
<b>Composite scores</b>		
Acute Physiology and Chronic Health Evaluation (APACHE) II score	Integer	-
Sequential Organ Failure Assessment (SOFA) score	Integer	-
Simplified Acute Physiology Score (SAPS II)	Integer	-
<b>Physiological variables</b>		
Heart rate	Integer	beats/min
Mean arterial pressure	Integer	mmHg
Lactate	Integer	mmol/l
Serum creatinine	Integer	mg/dL
Ratio of partial pressure of oxygen (PaO <sub>2</sub> ) to fraction of inspired oxygen (FiO <sub>2</sub> )	Integer	kPa
Serum bilirubin	Integer	mg/dL
Platelets	Integer	×10 <sup>3</sup> /μL
Glasgow Coma Scale score (GCS)	Integer	-
<b>Misc</b>		
Receiving mechanical ventilation	Boolean	-
Receiving renal replacement therapy (RRT)	Boolean	-
Time from shock onset to study drug	Integer	hours
Norepinephrine dose at randomisation	Integer	μg/kg/min

<b><i>Trial intervention data</i></b>		
Random allocation	Boolean	-
Whether intervention received as per protocol	Boolean	-
<b><i>Patient outcome data</i></b>		
<b>Mortality</b>		
28 day all cause	Boolean	-
60 day all cause	Boolean	-
90 day all cause	Boolean	-
180 day all cause	Boolean	-
Within ICU	Boolean	-
Within hospital	Boolean	-
<b>Cardiovascular</b>		
Shock free days at day 28	Integer	days
Duration of shock	Integer	days
<b>Ventilation</b>		
Ventilator free days at day 28	Integer	days
Duration of ventilation	Integer	days
<b>Renal</b>		
Renal failure free days at day 28	Integer	days
Requirement for RRT	Boolean	-
Duration of RRT	Integer	days
<b>ICU free days</b>		
At day 28	Integer	days
<b>Length of stay</b>		
ICU	Integer	days
Hospital	Integer	days
<b>Serious adverse events</b>		
Serious adverse events	Integer	-
Type of serious adverse event (as categorised by study)	String	-