# VASOPRESSIN (ARGIPRESSIN) INFUSION IN REFRACTORY VASODILATORY SEPTIC SHOCK IN PICU - CHW

## PRACTICE GUIDELINE

## DOCUMENT SUMMARY/KEY POINTS

- Vasopressin infusion should be considered in cases of paediatric vasodilatory septic shock not responding to traditional vasopressors
- Concomitant use of stress dose corticosteroids should be initiated when initiating vasopressin infusion
- Dilution and dose of vasopressin infusion for septic shock is different from that for diabetes insipidus and other indications

## CHANGE SUMMARY

Changes from previous document:

- Updated literature review

## READ ACKNOWLEDGEMENT

- Relevant clinical staff in PICU are to read and acknowledge having read this guideline.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

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|---|---|---|
| **Approved by:** | SCHN Policy, Procedure and Guideline Committee | |
| **Date Effective:** | 1st January 2024 | **Review Period**: 3 years |
| **Team Leader:** | Staff Specialist | **Area/Dept**: PICU |

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# PROTOCOL

## Indication

Salvage therapy in cases of **refractory vasodilatory septic shock.**

Concomitant use of **stress dose corticosteroids** should be considered.

## Specific patient groups most likely to benefit

Vasopressin should be considered in a child or infant with vasodilatory septic shock resistant to high doses of other pressor agents such as noradrenaline >0.2 micrograms/kg/min.

**It may only be started after discussion with the intensivist.**

## Dose and duration of treatment

Current evidence would suggest a dose between 10 – 50 milliunits/kg/hour (0.01 units-0.05 units/kg/hr). Higher doses can and have been used but may lead to increasing adverse effects. Doses above 50 milliunits/kg/hour (0.05 units/kg/hour)can be used at the discretion of the attending Intensivist.

**Duration:** until blood pressure and cardiac output can be controlled with conventional pressor agents.

## Authorised prescribers

PICU registrars after discussion with consultant intensivist.

## Precautions

1. Acute ECG or biochemical evidence of myocardial ischaemia.
2. Previously documented chronic and/or severe liver dysfunction (INR >2, bilirubin >50) or clinical evidence of portal hypertension.
3. Documented or high suspicion of mesenteric ischaemia.

## Monitoring

The following should be monitored DAILY as indicators of specific organ function

| | |
|---|---|
| Cardiac | Creatine kinase<br>Troponin<br>ECG |
| Renal | Creatinine, urea<br>Urine output<br>Need for CRRT |
| Liver | Serum bilirubin<br>Liver enzymes<br>INR |
| Haematology | Platelet counts, WBC, CRP |
| Metabolic | Arterial pH, lactate, bicarbonate |
| Skin ischaemia | Skin monitoring of capillary refill<br>Pressure injuries |

**There is increased risk of mesenteric ischaemia. Serial clinical assessment should be performed to exclude this.**

In addition, serum and urine sodium, creatinine and osmolality should be recorded before using vasopressin and daily thereafter.

## DILUTION OF AQUEOUS VASOPRESSIN

Argipressin is the synthetic formulation of vasopressin that is used for exogenous administration. Avoid extravasation as it may cause tissue necrosis. It should be infused via a central line. Anaphylactic reactions have been reported with its use.

Note that the only available preparation of Argipressin (Pitressin®) available is extremely concentrated, for use in other clinical situations. **Thus, it is necessary to dilute this solution 100-fold prior to use** as follows.

**Argipressin (Pitressin®)** 20 units/mL × 1 mL ampoules

**Dilution:** (0.9% sodium chloride **OR** 5% glucose as diluent)

**Step 1:** Take 0.5 mL (10 units) of 20 unit/mL ampoule using a 1 mL syringe

**Step 2:** Add to 50 mL syringe of 0.9 % sodium chloride (or 5% glucose), using a long needle so that the concentrated solution does not stay in the region of the injection port

Final concentration = 10 units (U) per 50 mL
= 10 000 milliunits per 50 mL
= 200 milliunits (0.2 units) per mL

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N.B. This is only for Argipressin in Septic Shock

For Argipressin in Diabetes Insipidus, see separate policy – Acute Central Diabetes Insipidus.

The dilutions and doses of the drug are different for the two policies.

## INFUSION RATE GUIDE (concentration 200 milliunits/mL)

| Weight (kg) | Infusion rate 10 milliunts/kg/hr = 0.05 mL/kg/hr | | Infusion rate 25 milliunits/kg/hr = 0.125mL/kg/hr | | Infusion rate 50 milliunits/kg/hr = 0.25 mL/kg/hr | |
|---|---|---|---|---|---|---|
| | mU/hr (milliunits/hr) | mL/hr | mU/hr (milliunits/hr) | mL/hr | mU/hr (milliunits/hr) | mL/hr |
| 5 | 50 | 0.25 | 125 | 0.6† | 250 | 1.2† |
| 10 | 100 | 0.5 | 250 | 1.2† | 500 | 2.5 |
| 15 | 150 | 0.75 | 375 | 1.9† | 750 | 3.8† |
| 20 | 200 | 1 | 500 | 2.5 | 1000 | 5.0 |
| 25 | 250 | 1.2† | 625 | 3.1 † | 1250 | 6.3† |
| 30 | 300 | 1.5 | 750 | 3.8† | 1500 | 7.5 |
| 35 | 350 | 1.7† | 875 | 4.4† | 1750 | 8.8† |
| 40 | 400 | 2 | 1000 | 5.0 | 2000 | 10.0 |
| 45 | 450 | 2.2† | 1125 | 5.6† | 2250 | 11.3† |
| 50 | 500 | 2.5 | 1250 | 6.3† | 2500 | 12.5 |
| 55 | 550 | 2.7† | 1375 | 6.9† | 2750 | 13.8† |
| 60 | 600 | 3 | 1500 | 7.5 | 3000 | 15.0 |

† NB these figures have been rounded to a single decimal point

# APPENDIX 1 – Background and Literature Review

Vasopressin is a nonapeptide hormone secreted by the posterior pituitary. Its release is mediated either by high serum osmolality or by a hypotension/low right atrial pressure. It is rapidly metabolized and has a half-life of approximately 10 minutes.

Vasopressin acts via V1 receptors in blood vessels, causing vasoconstriction, and via V2 receptors in the renal tubules, causing anti-diuresis by mobilizing aquaporins to the cell membrane. Vasopressin provokes vasodilatation in some vascular beds via its action on oxytocin receptors.[1]

Normal plasma level of vasopressin in a well hydrated person is less than 4 pg/ml. Physiological water homeostasis at the renal collecting tubule occurs at 1-7 pg/ml and the vasoconstrictive action at 9-189 pg/ml.

Its main physiological function is maintenance of water balance, with little influence on haemodynamics. Exogenous vasopressin, however, can be a pressor agent in various shock states. It has hitherto been used in high dose (up to 1 unit/kg) to reduce GI haemorrhage.

Standard therapy for vasodilatory septic shock in adults and children consists of circulating volume resuscitation, antibiotics, catecholamines (usually Noradrenaline) and support of failing organ function. In many patients the pressor response to catecholamines is reduced, and high doses of catecholamines can produce serious side effects including mesenteric ischaemia, renal failure and liver impairment. A recent Cochrane review of trials of vasopressors in septic shock revealed no evidence that any adrenergic agent was superior to any other.[2]

Plasma vasopressin concentration shows a biphasic response in septic shock. Elevated concentrations are detected in the early period. Subsequently, vasopressin secretions become paradoxically insufficient in respect to the degree of hypovolaemia. One explanation is that secretory stores in the neurohypophysis may be depleted after prolonged stimulation of vasopressin release. Disturbed baroreflex function caused by autonomic failure in sepsis might also be an explanation.[1, 3-6]

A number of small-size studies and case reports,[7-12] in which vasopressin has been used in low dose (typically 10 – 100 mU/kg/hr compared with up to 1 unit/kg/dose in GI haemorrhage), in addition to other treatment, have suggested that it may maintain arterial pressure in patients who are refractory to other vasoconstrictor agents such as a combination of dopamine and noradrenaline. There are reports of vasopressin use in paediatric patients, ranging from age 3 days to 15 years, including a pre-term infant.[13, 14]

Beneficial effects of low dose vasopressin, which have been measured, include improved renal blood flow and GFR, with diuresis and amelioration of the degree of acute renal failure, decreased blood, renal and GI lactate. Doses beyond 40 mU/hour (equivalent to 48mU/kg/h for a 50kg patient) in adults were not associated with increased effectiveness and may have higher adverse effects.[15]

The use of vasopressin in advanced paediatric vasodilatory shock led to a decrease in inotropic requirement without compromising cardiac function.[16] Urine output and creatinine levels were adversely affected but were reversible. Increased bilirubin levels and decreased platelet counts were seen during vasopressin infusion.

Despite this, randomised trials have failed to show clinical benefits of vasopressin usage versus traditional vasopressors.[17-21] The largest randomized trial to date remains the VAAST trial,[21] which showed that infusion of vasopressin at 10-30mU/min (equivalent to 12

– 35mU/kg/h for a 50kg patient) in adult patients did not reduce mortality rates compared with noradrenaline. A post-hoc analysis of the VAAST trial data showed a significant decrease in mortality and organ dysfunction when steroids were given along with vasopressin compared with noradrenaline and steroids.[22] The addition of steroids during vasopressin infusion spared its requirements and reduced the duration and dose used in a small pilot RCT.[23]

The VANISH randomized clinical trial used a factorial (2x2), double-blinded study design to study the effect of vasopressin +/- hydrocortisone versus noradrenaline +/- hydrocortisone on kidney failure-free days in adult patients with septic shock. Vasopressin dose was titrated up to 60mU/min to maintain mean arterial blood pressure. Early use of vasopressin was not found to improve the number of kidney failure-free days, although the use of renal replacement therapy was lower in the vasopressin group. [24]

A randomized trial of vasopressin usage (30 – 120 mU/kg/hr) versus placebo in addition to open-label vasoactive agents in a heterogenous group of paediatric vasodilatory shock did not demonstrate any beneficial effects for vasopressin.[20] Conversely, there was a concerning trend of increased mortality in the vasopressin group. A trial focusing on terlipressin use in children similarly reported no benefit to mortality.[25]

The Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children recommends the addition of vasopressin in children with septic shock who require high-dose catecholamines.[26]

No adverse side effects have been reported related to low doses of vasopressin (up to 20mU/kg/hr), although in experimental animal models with higher doses, splanchnic vasoconstriction and mesenteric ischaemia have been noted. Dobutamine may prevent these. A recent study of blood flow to carotid, mesenteric, iliac and renal vascular beds concluded that blood flow is not impaired if the dose is less than 30 mU/kg/hr. [27] A systematic review suggested that vasopressin demonstrated similar rates of adverse events compared to traditional vasopressors.[17]

In summary, although its role in reducing mortality in septic shock is unproven, vasopressin can reduce noradrenaline requirements in advanced vasodilatory shock. There is suggestion of increased benefit if steroids are given at the same time. It may also reduce the need for renal replacement therapy.

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