REVIEW ARTICLE

Therapeutic Applications of Vasopressin in Pediatric Patients

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Context: Reports of successful use of vasopressin in various shock states and cardiac arrest has lead to the emergence of vasopressin therapy as a potentially major advancement in the management of critically ill children.

Objective: To provide an overview of physiology of vasopressin, rationale of its use and dose schedule in different disease states with special focus on recent advances in the therapeutic applications of vasopressin.

Data Source: MEDLINE search (1966-September 2011) using terms "vasopressin", "terlipressin", "arginine-vasopressin", "shock", "septic shock", "vasodilatory shock", "cardiac arrest", and "resuscitation" for reports on vasopressin/terlipressin use in children and manual review of article bibliographies. Search was restricted to human studies. Randomized controlled trials, cohort studies, evaluation studies, case series, and case reports on vasopressin/terlipressin use in children (preterm neonates to 21 years of age) were included. Outcome measures were analysed using following clinical questions: indication, dose and duration of vasopressin/terlipressin use, main effects especially on systemic blood pressure, catecholamine requirement, urine output, serum lactate, adverse effects, and mortality.

Results: 51 reports on vasopressin (30 reports) and terlipressin (21 reports) use in pediatric population were identified. A total of 602 patients received vasopressin/terlipressin as vasopressors in various catecholamine-resistant states (septic - 176, post-cardiotomy - 136, other vasodilatory/mixed shock - 199, and cardiac arrest - 101). Commonly reported responses include rapid improvement in systemic blood pressure, decline in concurrent catecholamine requirement, and increase in urine output; despite these effects, the mortality rates remained high.

Conclusion: In view of the limited clinical experience, and paucity of randomized controlled trials evaluating these drugs in pediatric population, currently no definitive recommendations on vasopressin/terlipressin use can be laid down. Nevertheless, available clinical data supports the use of vasopressin in critically ill children as a rescue therapy in refractory shock and cardiac arrest.

Key words: *Cardiac arrest, Children, Shock, Terlipressin, Vasopressin.*

Vasopressin (AVP) was one of the first synthesized peptide hormones, used to treat diabetes insipidus (DI) and gastrointestinal (GI) hemorrhage for the last five decades [1]. It was discovered by Oliver and Schafer in 1895 by demonstrating the vasopressor effects of posterior pituitary extracts, while Farini and Velden described its antidiuretic effects by successfully treating DI with neurohypophyseal extracts, providing the name antidiuretic hormone [2]. Later, Vigneaud and Turner isolated vasopressin and proved that the same neurohypophyseal hormone possessed both antidiuretic and vasopressor activity [1,3].

Currently, vasopressin and terlipressin (AVP/TP) have emerged as promising agents for the management of refractory shock in critically ill children. However, their effects on various vascular beds and tissues are complex and sometimes apparently paradoxical.

PHYSIOLOGY AND PHARMACOLOGY

Synthesis and metabolism of vasopressin

Vasopressin, a nonapeptide with a disulphide bridge between two cysteines, is synthesized in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei as a prohormone "preprovasopressin". It is degraded to provasopressin before reaching posterior pituitary along the neuronal axons, and is finally converted to the active vasopressin releasing neurophysin-II and co-peptin [4].

Only 10-20% of the intracellular stores are available for immediate release in response to appropriate stimuli; however, secretion diminishes on sustained stimulus. Vasopressin synthesis, transport and storage takes about 1-2 hours [4]. It is metabolised by renal and hepatic vasopressinase enzymes with 5-15% urinary excretion. Vasopressin has a short half life (5-15 minutes) and pressor effect lasts for 30-60 minutes.

Mean serum levels usually remain below 4 pg/ml under normal conditions, which can go upto 10-20 pg/mL as an antidiuretic response [4-5]. In vasodilatory shock, a biphasic response is observed and initial high levels (upto 30-300 pg/mL) gradually fall as the shock progresses so

as to reach as low as 4-30 pg/mL after 36 hours of established shock [4-5].

Regulation of vasopressin secretion

In healthy subjects, AVP secretion is primarily regulated by changes in the plasma osmolarity sensed by peripheral osmoreceptors near hepatic portal veins and central osmoreceptors in the subfornical organ nuclei of the brain. Low plasma volume and arterial blood pressure (BP) increase AVP levels without disrupting normal osmoregulation. Atrial and ventricular baroreceptors sense change in plasma volume while aortic arch and carotid sinus receptors signal BP changes. More than 10% reduction in BP is needed to induce a response, as against 1% change in plasma osmolarity [4-6].

Other important stimuli include pain, hypoxia, nausea, pharyngeal stimuli, and hormones (*e.g.* norepinephrine, acetylcholine, histamine, dopamine and angiotensin-II), endotoxins and pro-inflammatory cytokines. Vasopressin release is inhibited by opioids, γ-aminobutyric acid (GABA), atrial natriuretic peptide (ANP) and nitric oxide (NO) [4-5].

Vasopressin Receptors

Vasopressin acts via G-protein coupled receptors, which are classified according to the location and second messenger pathways into V_1 (Vascular), V_2 (Renal), and V_3 (Pituitary). Additionally, AVP also exerts some action via OTR (Oxytocin) and P_2 (Purinergic) receptors [4,7]. (***Table* I**)

SYSTEMIC EFFECTS

The major functions of vasopressin include osmoregulation and vasoconstriction. Under normal conditions, its main role is in regulation of water balance with minimal effect on BP. Vasopressin also plays a role in other physiological functions e.g. hemostasis, temperature regulation, memory, sleep cycle, and insulin and corticotrophin release [8-9].

Vasoconstrictor effects

Vasopressin binds to vasopressin specific membrane bound V_1 receptors ($AVPR_1A$) in vascular smooth muscles and leads to vasoconstriction by increasing intracellular calcium levels via phosphoinositide

TABLE I VASOPRESSIN RECEPTORS PHYSIOLOGY

Receptors	Organs/Tissues	Effects	Intracellular Signaling/ transmitters
V_1 R (V_1 receptors, previously	Vascular smooth muscle	Vasoconstriction?	Increased intracellular Ca^{++} via Phosphoinositide pathway
V_{1a} receptors)	Myocardium	Inotropy	Increased intracellular Ca^{++}
	Platelets	Platelet Aggregation	Selective renal efferent arteriolar constriction via local NO release
	Kidney	Diuresis	
	Myometrium	Uterine contraction	
	Liver	Glycogenolysis	
	Bladder, spleen, adipocytes, testis	Vasodilation	
	Brain	Role in social memory, circadian rhythm, emotional learning, stress adaptation	
V_2 R (V_2 receptors)	Renal collecting duct	Increased permeability to water	Increased cAMP via adenylate cyclase
	Vascular smooth muscles	Vasodilation	NO mediated
	Vascular endothelium	Release of von-willebrand factor/VIII	
V_3 R (Previously V_{1b} receptors)	Pituitary	Neurotransmitter ACTH release	Phosphokinase C pathway, Increased cAMP via G protein
Oxytocin (OTR) receptors	Uterus, mammary gland	Smooth muscle contraction	Phospholipase C mediated increased intracellular Ca^{++}
	Vascular endothelium	Vasodilation	Increase in intracellular Ca^{++} mediated NO release
	Heart	ANP release	
Purinergic (P_2 R) receptors	Myocardium	Increased cardiac contractility	Increase in intracellular Ca^{++}
	Cardiac endothelium	Selective coronary vasodilation	NO mediated

ACTH – Adrenocorticotrophic Hormone, ANP – atrial natriuretic peptide, NO – nitric oxide, cAMP – cyclic adenosine mono phosphate, cGMP – cyclic guanosine monophosphate

pathway. In septic shock, AVP also restores vascular tone, by blocking K^+-sensitive ATP channels in dose dependent manner, and via amelioration in increased c-GMP levels by decreasing inducible NO-synthase enzymes [4-5,7].

Vasodilator effects

Unlike catecholamines, vasopressin induces vasodilatation in pulmonary, renal and cerebral circulation through V_2R or OTR mediated NO release [10-11]. Vasodilator effect is exhibited particularly at low doses unlike its dose dependent vasoconstrictor effect.

Pulmonary vascular effects

Vasopressin induces pulmonary vasodilatation via V_1R mediated release of endothelium derived NO [11]. This is particularly relevant in septic shock, where increased pulmonary vascular tone and resistance is usually seen. Vasopressin also decreases pulmonary arterial pressure in normal or hypoxic conditions mediated via ANP [12].

Renal effects

The complex renal effects are determined by interplay between osmoregulatory and renovascular effects. Antidiuretic effect is mediated via V_2R, located on the basolateral membrane of tubular epithelium of the collecting ducts, increasing intracellular c-AMP levels through adenylate cyclase pathway. It leads to fusion of aquaporin vesicles with luminal membrane increasing intracellular water content, which further equilibrates osmotically with interstitial fluid resulting in concentrated urine [4,7]. Paradoxically, low dose vasopressin in septic shock exhibit diuretic effect, possibly through V_1R mediated selective renal efferent arteriolar constriction, NO mediated afferent arteriolar vasodilatation, and down regulation of V_2R [7,13].

Endocrine effects

In pharmacologic doses, AVP increases plasma cortisol level through V_3R mediated ACTH release, effect most likely mediated via NO and c-GMP [9]. This is particularly important in critically ill children, given the prevalence of adrenocortical dysfunction. Vasopressin is reported to mediate ANP and angiotensin-II secretion as well as stimulate prolactin and endothelin-I release [9].

Effects on coagulation system

Vasopressin causes aggregation of human platelets. Selective V_2-agonist desmopressin stimulates factor VIIIc, von Willebrand factor, and plasminogen activator release from vascular endothelial cells, promoting effective platelet adhesion. Based on this effect vasopressin has been used to treat bleeding due to functional platelet disorders [14].

VASOPRESSIN ANALOGUES

Terlipressin

Terlipressin (triglycyl lysine-vasopressin) is a longer-acting analogue containing 12 amino acids, and is slowly cleaved to lysine-vasopressin by endo-and exopeptidases in liver and kidney over 4-6 hrs, making intermittent bolus use feasible rather than continuous infusion.

Relative to AVP, its affinity for V_1R is higher than V_2R (2.2:1 compared to 1:1). Additionally, terlipressin does not appear to increase fibrinolytic activity, unlike vasopressin [15]. Terlipressin has been extensively studied and used in adults with acute variceal bleeding and hepatorenal syndrome, before emerging as potential therapeutic option in a variety of shock states [16].

Desmopressin

Desmopressin or DDAVP (1-deamino-8-D-arginine vasopressin) is selective V_2-agonist with an antidiuretic-to-vasopressor ratio 4000 times than that of AVP [17,18].

THERAPEUTIC APPLICATIONS

Approved uses for vasopressin and analogs include DI, nocturnal enuresis, gastrointestinal bleeding, hemophilia-A, von-Willebrand disease, and bleeding due to platelet dysfunction. Currently, vasopressin is emerging as a potent vasopressor to treat vasodilatory shock states and cardiac arrest; however, it is still not recognized as a standard of care and is being evaluated in trials. Indications and doses of vasopressin/analogs are given in ***Table* II** and various studies evaluating its therapeutic uses in children are summarized in ***Web Table* I**.

Nocturnal enuresis

DDAVP is used to treat nocturnal enuresis, caused by maturational delay in normal nocturnal increase in AVP secretion [18].

Diabetes insipidus

In DI, renal tubular collecting ducts are unable to concentrate urine which can be Central or Nephrogenic. Central DI is due to congenital or acquired deficiency of AVP secretion. Nephrogenic DI arises from defective or absent vasopressin receptor sites or aquaporins with resultant inappropriate response to vasopressin.

In Central DI, vasopressin increases cellular permeability of collecting ducts, resulting in renal reabsorption of water and forms the mainstay of treatment [19]. Vasopressin may also be used safely to diagnose type of DI due to shorter half life with lesser risk of volume overload. Doses are variable and titrated according to serum/urinary sodium and osmolality, and urine output [20].

TABLE II INDICATIONS AND DOSES OF VASOPRESSIN AND ANALOGS [63-64]

Indication	Drug	Dose
Nocturnal enuresis	DDAVP	Intranasally: 5-20 µg (in children > 6 years)Orally: 0.2-0.4 mg/d at bedtime
Central diabetes insipidus	DDAVP	Intranasally: 5-30 µg/d Q 8-12 hr Orally: 0.05-0.2 mg/d Q 8-12 hr IV/SC: 2-4 µg/d Q 8-12 hr
	AVP	IM/SC: 2.5-10U/dose 2-4 times/day IV infusion: 0.0005 U/kg/hr initially, double every 30 min upto 0.01 U/kg/hr
Hemophilia-A, von Willebrand disease, platelet dysfunctions	DDAVP	Intranasally: <50 kg - 150 µg; >50 kg - 300 µg IV: 0.3 µg/kg (>3 months), repeat if needed, give 30 min before procedure
Bleeding esophageal varices	AVP	Initial IV bolus 0.3 U/kg (maximum: 20 U) followed by infusion: 0.002-0.01 U/kg/min
	TP	IV: 10 – 20 µg/kg every 4 – 6 hrs or 1 – 2 mg Q 4 – 6 hr (in adolescents & adults)
Refractory vasodilatory shock	AVP	IV infusion: 0.0005-0.002 U/kg/min (variable, from as low as 0.00005 U/kg/min upto 0.008 U/kg/min)
	TP	IV bolus: 10 – 20 µg/kg every 4 – 6 hrs IV infusion: 10 µg/kg/hr
Cardiac arrest	AVP TP	IV bolus: 0.4 U/kg IV bolus: 10 – 20 µg/kg

DDAVP – Desmopressin, AVP – Arginine Vasopressin, TP – Terlipressin, IV – intravenous, IM – intramuscular, SC – subcutaneous

Bleeding esophageal varices

Upper GI bleeding is reported in 6-25% of PICU admissions [21-22]; however, incidence of serious lower GI bleeding has not been well established [23]. Use of vasopressin is intended to decrease portal venous pressure and optimize clotting and hemostasis. Although it may provide effective control of bleeding, vasopressin is still a secondary treatment option, as evidence supporting improved survival is scarce [24].

Presently, endoscopic sclerotherapy or band ligation is considered to be the first-line therapy for bleeding esophageal varices followed by vasoactive drugs i.e. octreotide (somatostatin analogue), vasopressin and terlipressin [25].

Vasodilatory shock states

Vasodilatory shock can be the final common pathway in a variety of shock states including sepsis, post-perfusion syndrome following CPB, prolonged hemorrhage, hypovolemia, anaphylaxis, cardiogenic shock and carbon monoxide poisoning. They share common pathogenic mechanisms responsible for vascular smooth muscle dysfunction and hyporesponsiveness to catecholamines e.g. activation of ATP sensitive K^+-channels, NO-synthase stimulation and vasopressin deficiency [26-27]. This relative deficiency is attributable to (*i*) depleted neurohypophyseal AVP stores, (*ii*) autonomic dysfunction leading to impaired baro-reflex mediated release, (*iii*) increased neurohypophyseal NO production, and (*iv*) central inhibitory effects of increased norepinephrine on AVP production [5,7,27].

Vasopressin has emerged as a useful therapeutic option in vasodilatory shock to reverse the mechanisms responsible for vasoplegia and catecholamine resistance.

Dose in pediatric shock is not very well documented and is extrapolated from adult data. In various studies, vasopressin was used in a dose of 0.00005 to as high as 0.008 U/kg/min [28,29]; however, in a RCT evaluating vasopressin in pediatric shock, vasopressin was used in dose range of 0.0005-0.002 U/kg/min [30]. TP dose used in the RCT was 20 µg/kg/6h for maximum 96 hours [31].

Septic shock

In septic shock, catecholamines often have a diminished vasopressor action and more than half of the patients succumbing to sepsis die from advanced cardiovascular failure, which is refractory to conventional therapy. In these patients, vasopressin hypersensitivity is observed with significant increase in BP, mediated via: (*i*) direct V_1R mediated vasoconstriction;(*ii*) unlike catecholamine receptors, absolute or relative AVP deficiency allow V_1R to remain available and block mechanisms inducing their downregulation; (*iii*) absent bradycardia reflex in critically ill patients with autonomic failure; (*iv*) potentiating vasopressor efficacy of catecholamines through blockage of ATP sensitive K^+-channels and

resulting membrane hyperpolarization and vasodilation; and (*v*) finally, increased ACTH and cortisol release [4-5,7,9,27]. Vasopressin induced selective pulmonary, coronary, cerebral vasodilatation, and improved urine output and creatinine clearance, make it more beneficial in preserving vital organ functions in sepsis as compared to catecholamines [10-13].

However, judicious use of AVP/TP is warranted, as characteristic vasodilation seen in adult septic shock is a late feature of pediatric septic shock, where myocardial dysfunction is more common and the majority of septic shock cases have low cardiac index with only about 20% presenting in the typical warm shock [32]. Additionally, children in septic shock often change hemodynamic profile and as the disease progresses, transformation from vasodilatory shock to a hypodynamic shock with high systemic vascular resistance (SVR) is not uncommon. Therefore, AVP/TP should be used with cardiac output (CO) and central venous oxygen saturation ($ScvO_2$) monitoring, as they can reduce CO due to potent vasoconstriction [33].

Post-cardiopulmonary bypass vasodilatory shock

Post CPB vasodilatory hypotension, not associated with primary cardiogenic or septic shock, has been reported in nearly 10% of cardiac surgeries [34]. This is attributed mainly to systemic inflammatory response activated by CPB via endothelial injury, release of cytokines and other inflammatory mediators, as well as to nonspecific activators e.g. surgical trauma, blood loss or transfusion, and hypothermia. Other contributory factors include prolonged CPB, long term ACE inhibitor or beta blocker therapy, or post-bypass amiodarone and phosphodiestrase-III inhibitors.

Apart from these mechanisms, inappropriately low AVP secretion may be another important factor in producing low SVR hypotension. Low dose vasopressin therapy in this condition has been shown to improve BP as well as restore catecholamines sensitivity by a mechanism similar to that seen in septic shock [34].

Anaphylactic shock

Acute cardiovascular collapse in anaphylaxis results from immune mediated release of inflammatory mediators producing systemic vasodilation and increased capillary permeability, resulting in mixed distributive-hypovolemic shock [35]. Optimal vasoactive action of vasopressin *i.e.* vasoconstriction in skin, skeletal muscle, intestine and fat, with relatively less coronary and renal vasoconstriction, and cerebral vasodilatation, has supported the use of AVP in adrenaline refractory anaphylactic shock.

Currently, no controlled trials or guidelines on AVP use in anaphylactic shock are available, and its use is recommended on the basis of case reports and laboratory experiences, In different cases reports, 2-15 U (0.03-0.15U/kg) vasopressin have been used [36-38].

Hemorrhagic shock

Patients with advanced hemorrhagic shock usually respond poorly to both volume and catecholamine therapy due to resistant vasodilation secondary to accumulated vasodilatory metabolites produced by ischemic-reperfusion injury and coexisting severe acidosis inactivating catecholamine receptors. These patients with complete cardiovascular collapse have an extremely poor prognosis and AVP has been used as a rescue therapy in such cases considering its inherent vasopressor effect. Vasopressin also decreases bleeding by shifting the blood away from the subdiaphragmatic site of injury to the vital organs. This specific effect may be life-saving in patients with uncontrolled hemorrhage resulting from subdiaphragmatic injury [39].

As RCTs evaluating the role of vasopressin in hemorrhagic shock are currently unavailable, even limited clinical and laboratory data available may support its use in selected patients, who would otherwise rapidly collapse [40-42].

Pediatric cardiopulmonary resuscitation

Cardiac arrest in children is often the terminal result of progressive respiratory failure or shock rather than sudden primary cardiac event as commonly seen in adults. Prolonged CPR often has dismal prognosis, along with severe neurological impairment among survivors. For more than four decades, epinephrine has been the drug of choice in cardiac arrest for restoring spontaneous circulation based on its ability to maintain diastolic BP and subsequent blood flow to heart. However, adult and pediatric studies have shown no clear survival benefit of epinephrine and rather elucidated adverse effects [43-44].

Vasopressin causes profound vasoconstriction with shunting of blood to heart and brain, and unlike epinephrine, this vasoconstriction continues even in presence of severe acidosis that accompanies cardiopulmonary arrest. Additionally, vasopressin has shown to improve cerebral perfusion during CPR with better neurologic outcome in animal studies. It also enhances myocardial oxygen delivery without marked increase in consumption observed with catecholamine mediated β_1-adrenergic receptor activation.

In RCTs of in-hospital and out-of-hospital arrests in adults, vasopressin had comparable efficacy to

epinephrine [45,46]. Although improved return of spontaneous circulation (ROSC) with vasopressin therapy was demonstrated in a few pediatric reports [47-49], two other reports failed to demonstrate any survival benefit [50,51]. Therefore, further research is necessary to evaluate the long term outcome and safety of vasopressin in pediatric CPR. During CPR, vasopressin can also be given endotracheally in the same IV dose, if IV/IO route can not be accessed rapidly [52].

Vasopressin during organ recovery

Low dose AVP infusion has been evaluated as a vasopressor in critically ill children treated for DI during brain death and organ recovery in a retrospective matched-controlled study. AVP has shown good pressure effects and they were more likely to wean from alpha agonists than controls, without adverse affect on transplant organ function [53].

Pulmonary hypertension

Vasopressin has been successfully used in infants with pulmonary hypertension secondary to congenital diaphragmatic hernia [54-56] and after correction of total anomalous pulmonary venous return [57] refractory to other conventional therapies, to improve BP and to decrease pulmonary artery pressure.

Sedation related hypotension

One RCT evaluated the role of low-dose vasopressin infusion to prevent sedation/analgesia related hypotension in non-septic, hemodynamically stable but critically ill children, considering the fact that vasopressin leads to redistribution of mesenteric blood. However, AVP therapy was associated with decreased urine output, hyponatremia, and rebound hypotension, thus limiting the prophylactic vasopressin use for sedation-related hypotension [58].

Current recommendations on vasopressin use

American College of Critical Care Medicine Clinical Guidelines 2007 for hemodynamic support of pediatric and neonatal septic shock recommended that AVP/TP can be used in catecholamine-resistant shock with high cardiac index and low SVR. However, as these agents can reduce CO, they should be used with CO/$ScvO_2$ monitoring [33]. Pediatric Sepsis Guidelines for resource-limited countries developed by Intensive Care Chapter of Indian Academy of Pediatrics recommended AVP therapy as a last resort in patients with catecholamine-resistant warm shock [59].

Although, latest American Heart Association guidelines have recommended the use of one dose of vasopressin to replace either the first or second dose of epinephrine in treatment of adult cardiac arrest, no recommendations were made on its routine use in pediatric patients [60,61]. European Resuscitation Council guidelines 2010 also did not support or refute the use of AVP/TP as an alternative to or in combination with adrenaline in any cardiac arrest rhythm; however, these drugs could be used in cardiac arrest refractory to several adrenaline doses [62].

Cost-effectiveness

Cost of the vasopressin may be an inhibiting factor at current market values, as it costs around 25-30 times than that of adrenaline. Still, AVP therapy is not as expensive as extended ICU stay of even one day with costlier antibiotics, and it would help in lowering the overall long-term cost in patient care [63-64]. As no RCT is currently available to determine the cost-effectiveness of vasopressin, significant clinical benefits would need to be demonstrated to cost-justify the routine substitution of adrenaline with vasopressin in cardiac arrest.

Adverse Effects

Due to potent vasoconstrictor action, there is always a concern that vasopressin therapy may impair capillary blood flow and tissue oxygenation. Safety data of vasopressin in pediatric patients are limited and a number of adverse effects were reported depending upon dose and duration, underlying disease process, co-morbidities, and concurrent use of other vasopressors. Complications are more common when vasopressin is co-administered with moderate to high dose of norepinephrine [5].

Cardiac complications include coronary ischemia, myocardial infarction, ventricular arrhythmias (ventricular tachycardia and asystole), and severe hypertension [64]. Other reported adverse effects include severe GI ischemia leading to bowel necrosis, hyponatremia, anaphylaxis, bronchospasm, urticaria, angioedema, rashes, venous thrombosis, local irritation at injection site, and peripheral vasoconstriction leading to cutaneous gangrene [65].

CONCLUSION

While vasopressin continues to be a useful agent to treat DI and GI hemorrhage, it is emerging as a potentially life saving therapy in critically ill children with a variety of vasodilatory shock. Both adult and pediatric studies have demonstrated the efficacy of rescue AVP therapy in reversing shock due to sepsis or following cardiotomy/CPB, when other vasopressors are escalated to high infusion rates with potential adverse effects. Limited laboratory and adult data along with a few pediatric

reports support the use of vasopressin as an adjunctive therapy for prolonged cardiac arrest and irreversible hypovolemic and anaphylactic shock. However, large controlled trials are necessary to define the efficacy, dosage, ideal initiation time, and safety profile in children, as evidence is limited due to the retrospective nature of existing studies and small numbers of patients.

Thus, vasopressin is not a standard of care as of now and it should be considered as a rescue therapy in situations like catecholamine-refractory shock and cardiac arrest in children, with close monitoring for adverse effects.

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