Vasopressin in pediatric shock and cardiac arrest

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Objective: **To review the physiology and the published literature on the role of vasopressin in shock in children.**

Data Source: **We searched MEDLINE (1966–2007), EMBASE (1980–2007), and the Cochrane Library, using the terms *vasopressin*, *terlipressin*, and *shock* and synonyms or related terms for relevant studies in pediatrics. We searched the online ISRCTN-Current Controlled Trials registry for ongoing trials. We reviewed the reference lists of all identified studies and reviews as well as personal files to identify other published studies.**

Results: **Beneficial effects have been reported in vasodilatory shock and asystolic cardiac arrest in adults. Solid evidence for vasopressin use in children is scant. Observational studies have reported an improvement in blood pressure and rapid weaning off catecholamines during administration of low-dose vasopressin. Dosing in children is extrapolated from adult studies.**

Conclusions: **Vasopressin offers promise in shock and cardiac arrest in children. However, in view of the limited experience with vasopressin, it should be used with caution. Results of a double-blind, randomized controlled trial in children with vasodilatory shock will be available soon. (Pediatr Crit Care Med 2008; 9:372–379)**

KEY WORDS: child; cardiac arrest; inotrope; vasopressin; shock; septic shock

Shock and hemodynamic compromise are among the most dramatic, dynamic, and life-threatening problems faced in pediatric critical care, with an unacceptably high mortality rate of up to 53% (1). Aggressive volume resuscitation is the mainstay of the initial management of hemodynamic instability in children. Catecholamines are the most common vasoactive agents used to maintain blood pressure and vital organ perfusion. However, decreased vascular and myocardial sensitivity to catecholamines has been demonstrated in shock, and as a result, unacceptable adverse effects may precede the desired clinical effects (2). A few small comparative clinical trials and a systematic review reported no single catecholamine agent as superior in improving outcomes in shock (3).

The effects of catecholamine agents on the cardiovascular system in children and infants are not without controversy. They may increase the heart rate (via β-receptors), hence increasing myocardial oxygen consumption. In addition, if increased blood pressure occurs by increasing systemic vascular resistance, some end-organ perfusion may be compromised with high-dose catecholamine pressors (4). It has also been suggested that prolonged infusions of catecholamines in infants may impair myocardial performance, leading to a survival disadvantage (5). Hence, the evaluation of alternative and adjunctive therapies targeted at specific pathophysiologic pathways to reverse shock is important.

Vasopressin has been used since the 1950s primarily to treat patients with diabetes insipidus and to control gastrointestinal bleeding. However, only in the past decade has there been renewed interest in the use of *low-dose* vasopressin as a potent vasopressor as per its original description >100 yrs ago (6). Encouraged by reports in adult patients with cardiac arrest and vasodilatory shock, some authors have proposed that arginine vasopressin and its analogs are potentially beneficial agents for the treatment of shock and cardiopulmonary arrest in children (7).

The objective of this article is to review the physiology of vasopressin and the rationale for its use in shock and in critically ill children in the context of published clinical studies. We searched MEDLINE (1966–2007), EMBASE (1980–2007), and the Cochrane Library, using the terms *vasopressin*, *terlipressin*, and *shock* and synonyms or related terms for relevant studies in pediatrics. We searched the online ISRCTN–Current Controlled Trials registry (http://www.controlled-trials.com) for ongoing trials. We reviewed the reference lists of all identified studies and reviews as well as personal files to identify other potential studies.

Physiology of Vasopressin

Vasopressin is synthesized in the hypothalamus as the prohormone prepro-vasopressin. Prepro-vasopressin is degraded to pro-vasopressin, which migrates along neuronal axons to the posterior pituitary, where it is subsequently released in three fragments: vasopressin, neurophysin II, and copeptin. Most newly synthesized vasopressin is stored intracellularly, and only 10% to 20% of the total hormonal pool within the posterior pituitary can be readily released under appropriate stimuli (8). Once secreted into the circulation, vasopressin is accompanied by its carrier protein, neurophysin II, which does not appear to have any independent biological activity. The function of copeptin is unclear. Vasopressin is cleaved by vasopressinase and has a half-life of approximately 5–15 mins, which is why vasopressin is administered by continuous infusion during the management of vasodilatory shock (9).

Vasopressin is responsible for multiple physiologic functions, the most well-

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known being vasoconstriction of vascular smooth muscle and osmoregulation. The vasopressor effect of this pituitary extract was first observed by Drs. Oliver and Schäfer (6) in 1895; however, it was 20 yrs before its strong antidiuretic effects were recognized, at which point this hormone was renamed *antidiuretic hormone* (10). After its isolation and synthetic preparation were accomplished by Du Vigneaud et al. (11) in 1954 (Du Vigneaud subsequently was awarded the Nobel Prize), it was recognized that the same hormone in the posterior pituitary possessed both antidiuretic and vasopressor effects. However, it is now recognized that vasopressin has many other physiologic functions, including effects on memory, sleep cycles, temperature regulation, hemostasis, insulin, and corticotropin release (12). The effects of vasopressin on various vascular beds and tissues are complex and at times appear to be paradoxic. The diversity of its actions are related to the location and density of tissue-specific G-protein-coupled vasopressin receptor subtypes, which are currently classified into V1 vascular, V2 renal, V3 pituitary, oxytocin, and P2 purinergic receptors (Table 1) (13). V1 vascular receptors are located on vascular smooth muscle and mediate vasoconstriction. However, in the pulmonary circulation, vasopressin activation of V1 receptors mediates the release of nitric oxide (NO) and causes pulmonary vasodilation, in contrast to its vasoconstrictive action in the systemic circulation. Oxytocin receptors are a subset of vasopressin receptors found in the uterus, in the mammary gland, and, more recently, in endothelial cells of human umbilical vein, aorta, and pulmonary artery. Vasopressin's binding to oxytocin receptors increases intracellular calcium, stimulating the release of NO and thus mediating vasodilation. Purinergic P2 receptors are located in cardiac endothelium and may play a role in cardiac contractility and selective coronary vasodilation. Vasopressin therefore not only is important in the control of water balance and cardiovascular regulation but also is actively involved in coordinating the autonomic and endocrine responses to homeostatic disturbances.

Regulation of Vasopressin Secretion. The normal plasma vasopressin concentration in hemodynamically stable patients ranges between 1 and 7 pg/mL, depending on the level of hydration and osmolality. The most important stimuli for vasopressin release are increased plasma osmolality, hypotension, and hypovolemia. Under normal conditions, vasopressin plays a minimal role in the vascular regulation of blood pressure, and its main role is in the regulation of water balance (14). During this time, secretion is regulated primarily by changes in plasma osmolality via input from osmoreceptors, and vasopressin levels may rise as high as 20 pg/mL during maximal urine osmolality (15). Vasopressin secretion is also under the control of the sympathetic nervous system. Under resting conditions or when stretched, baroreceptors inhibit vasopressin secretion. Decreased activity due to low blood pressure decreases baroreceptor neuronal output and results in the release of vasopressin from the hypothalamus. Nonosmotic stimuli, such as hypovolemia and hypotension, shift the osmotic threshold for vasopressin release to the left, without altering the slope or sensitivity of the relationship of vasopressin and plasma osmolality (16). Therefore, regardless of plasma osmolality, during the initial phase of shock extremely high levels of vasopressin, in the range of 300–1800 pg/mL, can be observed (17). At these plasma concentrations, vasopressin is a critical mechanism for maintaining systemic vascular resistance and arterial blood pressure, and baroregulation overrides osmoregulation. There is an exponential inverse relationship between plasma vasopressin levels and the degree of hypotension. Small reductions in blood pressure to the order of 5% to 10% from baseline usually have little or no effect on plasma vasopressin, whereas a 20% to 30% decrease results in a 20- to 30-fold increase in serum vasopressin levels (18).

Other important secretagogues of vasopressin include endotoxin and proinflammatory cytokines (i.e., interleukin-1β, interleukin-6, tumor necrosis factor-α) (19, 20). Other nonosmotic stimuli, such as pain, nausea, hypoxia, anesthetic agents, and various endogenous and exogenous chemicals, such as norepinephrine and acetylcholine, may also trigger vasopressin release (21, 22).

Vasopressin Levels in Shock. A biphasic vasopressin response has been described, particularly in vasodilatory shock states where high levels are observed in the initial phase of profound hypotension, followed by inappropriately low levels to the order of 3–10 pg/mL as shock progresses (23–25). It seems unlikely that increased vasopressin clearance from the plasma accounts for vasopressin depletion, given observations that vasopressinase levels remain undetectable in this scenario (26). Several mechanisms responsible for vasopressin deficiency have been proposed, including the depletion of neurohypophyseal stores, impaired baroreflex-mediated release of vasopressin attributable to autonomic dysfunction, and down-regulation of vasopressin production by increased central NO production (15). The NO-mediated inhibition of vasopressin release may also have important implications in the pathogenesis of adrenal insufficiency, which is commonly observed in critically ill patients, as vasopressin modulates adrenocorticotropic hormone production (12, 27). Recent studies suggest that cytokines, such as interleukin-1β, tumor necrosis factor-α, and interferon-γ, may also contribute to vasopressin receptor down-regulation and reduced efficacy of

Table 1. Vasopressin receptor physiology

Receptors	Location	Principle Effects
V1R	• Vascular smooth muscle	• Vasoconstriction
	• Kidney, platelets, bladder, spleen, testis	• Selective renal efferent arteriolar constriction
	• Myocardium	• ? inotropy
V2R	• Renal collecting duct	• Antidiuretic
	• Endothelium	• Coagulation factor release
V3R	• Pituitary	• ACTH release
Oxytocin (OTR)	• Reproductive and nonreproductive tissue	• Uterine contractions
	• Vascular endothelium	• NO mediated vasodilation
	• Heart	• ANP release
Purinergic (P2R)	• Myocardium	• ↑ Cardiac contractility
	• Cardiac endothelium	• Selective coronary vasodilation

ANP, atrionatriuretic peptide; ACTH, adrenocorticotropic hormone; NO, nitric oxide.

exogenous hormone (28). These observations of endogenous absolute or relative vasopressin deficiency in critically ill adults have been used to justify a role for exogenous vasopressin infusions in patients in refractory shock.

Supporting data for absolute or relative vasopressin deficiency from pediatric studies, however, are limited and inconsistent. While Choi et al. (29) identified inappropriately low vasopressin levels in children with septic shock and Rosenzweig et al. (30) in postcardiotomy shock (median 4.8 pg/mL ± 4.2 SD), Leclerc et al. (31) observed a median admission vasopressin level in children with meningococcal septic shock of 41.6 pg/mL, while Lodha et al. (32) reported that serial vasopressin levels were elevated for up to 96 hrs in children with septic shock (41.4–259 pg/mL). There are several possible explanations for the discrepancy between findings in the pediatric and adult populations. There are hemodynamic differences at presentation between children with septic shock and their adult counterparts (33). Low cardiac index, high systemic vascular resistance shock is more common than vasodilatory shock in children, and this hemodynamic status often changes over time (34). The observations in adults clearly identify endogenous vasopressin deficiency, especially in vasodilatory shock, while the pediatric studies are inconsistent in that both cold and warm shock patients were not distinguished. These clinical differences between children and adults with shock reflect the age-related complexity of pathophysiologic mechanisms, which extends beyond vasopressin dysregulation. Therefore, the reliability of endogenous vasopressin level as a marker for use and indeed response to exogenous vasopressin infusions has not been adequately explored in children.

Measurement of Vasopressin Levels. A limitation of measuring circulating vasopressin levels is that the mature hormone is unstable, has a short half-life, and is largely attached to platelets, which are not measured in plasma. Accordingly, vasopressin concentration in platelet-rich plasma is approximately five- to six-fold higher than that in platelet-depleted plasma (35). Hence, interpretation of static measurements of vasopressin may be misleading. Copeptin, a stable peptide of the vasopressin precursor, is secreted in an equimolar ratio and thus mirrors the production of vasopressin. Plasma copeptin measurements recently were shown to be much more stable and easy to determine, and therefore copeptin has been proposed as a more sensitive and a potential prognostic marker in patients with sepsis (35, 36).

A Role for Vasopressin in Shock

It is now well recognized that vasopressin has multiple physiologic functions beyond the control of water balance and cardiovascular regulation. Hence the name *antidiuretic hormone* is outdated, although the term *vasopressin* is still not indicative of its function beyond the vascular and renal systems. Vasopressin also plays an important role in homeostasis during shock states, like septicemia, and cardiopulmonary arrest. There is evidence that the human body discharges vasopressin as an adjunct stress hormone to catecholamines in life-threatening situations, such as shock and cardiac arrest (12). Vasopressin has been recognized as an important stress hormone after thermal injury in children and during congestive heart failure in neonates (37). Vasopressin levels have been noted to be higher in patients with cardiac arrest who were successfully resuscitated compared with those in whom spontaneous circulation was not restored (12). The most promising therapeutic role for vasopressin is in the management of vasodilatory shock states and cardiopulmonary resuscitation.

Vasopressin in Vasodilatory Shock. The efficacy of vasopressin has been demonstrated in various groups of patients with vasodilatory shock, including sepsis, postperfusion syndrome following cardiopulmonary bypass, and prolonged hemorrhage, and in hemodynamically unstable organ donors (38–42). Vasodilatory shock may result from many causes, and they share common pathogenic mechanisms that are responsible for vascular smooth muscle dysfunction and vascular hyporesponsiveness to catecholamines (2). Vasopressin is an attractive agent in this setting as it reverses the mechanisms responsible for vasoplegia and catecholamine resistance.

Vasoconstrictor Effects of Vasopressin. Vasopressin directly inactivates adenosine triphosphate sensitive potassium channels in vascular smooth muscle, a critical mechanism responsible for the pathologic vasodilation and resistance to catecholamine pressors that characterize vasodilatory shock (43). In addition, vasopressin blunts the increase in cyclic guanosine monophosphate induced by NO and atrionatriuretic peptide and inhibits the production of interleukin-1β, mechanisms strongly implicated in the pathogenesis of vasodilation (43). While inappropriately low plasma vasopressin levels have been described in adults and pediatric patients with vasodilatory shock, such patients appear to demonstrate a hypersensitivity to the pressor effects of exogenous vasopressin (15, 23, 38). The overall effect of vasopressin on systemic blood pressure is minimal at normal plasma concentrations and in healthy individuals (8, 44). Although vasopressin infusions of 0.2–2 units/min rarely affect blood pressure in euvolemic or normotensive subjects, low-dose infusions of 0.04 units/min substantially increase systemic pressure in patients with catecholamine-refractory hypotension. It is likely that because plasma vasopressin is low in this condition, its vascular receptors are available for occupancy by exogenous hormone. In contrast, exogenous norepinephrine may not increase receptor occupancy to the same extent, as endogenous concentrations of norepinephrine are high, which in turn may cause desensitization of receptors (45). Furthermore, there is evidence for adrenergic receptor downregulation in addition to hyperpolarization from the activation of potassium-adenosine triphosphate channels, which results in decreased vascular sensitivity to catecholamines despite high endogenous concentrations and exogenous infusions. The administration of low-dose vasopressin, however, has been shown to not only initiate vasoconstriction but also potentiate the vasoconstrictor effects of catecholamine pressors (46).

Vasodilator Effects of Vasopressin. Although vasopressin is a potent systemic vasoconstrictor, the same low-dose infusion of vasopressin concurrently causes vasodilation in pulmonary, cerebral, and coronary circulations via oxytocin receptor stimulation and endothelial NO release (13). Low-dose vasopressin may thus be more beneficial in preserving vital organ perfusion when compared with catecholamine pressors. Investigators have demonstrated in patients with septic shock that low-dose vasopressin not only improved mean arterial blood pressure and cerebral perfusion pressure but also spared the microcirculation to the mesenteric and renal beds when compared with norepinephrine or phenylephrine (41, 47–49).

Renovascular Effects. Paradoxically, vasopressin (or antidiuretic hormone) increases urine output and creatinine clearance in patients with septic shock when compared with norepinephrine (41). This effect has been attributed to V1-receptor-mediated, selective renal efferent arteriolar constriction. In contrast, increasing doses of catecholamine vasopressor agents increase the resistance in both afferent and efferent glomerular arterioles, which can contribute to decreased glomerular filtration rate and creatinine clearance and thus decreased urine output (50).

Endocrine Effects. Vasopressin is a potent stimulator of adrenocorticotropic hormone and, consequently, cortisol release (51), which are important considerations given the prevalence of adrenocortical dysfunction in the critically ill population (52). The interaction of corticotropin and vasopressin release in shock is complex and incompletely understood, and the influence of exogenous administrations of vasopressin and steroids on the respective axes is being explored (28, 53). Since corticosteroids have been shown to reverse tachyphylaxis against exogenous catecholamines, it has been suggested through an ovine model of endotoxemia that methylprednisolone may reverse vasopressin hyporesponsiveness (28). Vasopressin has also been reported to mediate atrial natriuretic factor and angiotensin II secretion as well as stimulate prolactin and endothelin I release (54). This latter effect on prolactin secretion plays a significant role in the cellular immune response, which in turn has important implications in the critically ill population with septic shock.

In summary, vasopressin is an attractive adjunctive or alternative to catecholamine vasoactive agents in vasodilatory shock for the following reasons: Vasopressin reverses the principle pathologic mechanisms responsible for vasoplegia, patients with vasodilatory shock exhibit an increased sensitivity to the pressor effects of vasopressin, low-dose vasopressin restores responsiveness to catecholamine resistance, and vasopressin has concurrent organ-specific vasodilator effects that may hence preserve vital organ flow. In this era of "endocrine support" in the critically ill, the final rationale for the use of vasopressin is to restore a physiologic hormone deficiency state.

Clinical Application of Vasopressin in Pediatric Shock—The Evidence. The evidence for the use of low-dose vasopressin in catecholamine-resistant vasodilatory shock states in adults is increasing, and the current literature demonstrates its efficacy on short-term clinical end points, such as mean arterial blood pressure, systemic vascular resistance, and decreased catecholamine requirements (25, 39–41). However, the beneficial effects on important patient outcomes, such as mortality, are yet to be determined. The Vasopressin in Septic Shock Trial (VASST) was recently completed (55). VASST analyzed 779 adult patients in septic shock requiring vasopressors for ≥6 hrs and having at least one additional dysfunctional organ system present for <24 hrs. These patients were randomized to receive low-dose infusion of vasopressin or norepinephrine (NE). Overall, there was no difference in 28-day survival between groups (35.4% vs. 39.3%, $p = .27$). However, when groups were stratified according to severity of hypotension (requiring >15 μg/min or <15 μg/min NE at enrollment), the patients receiving lower dose NE had improved survival with vasopressin (26.5% vs. 35.7%, $p = .05$). This result persisted at 90 days, when mortality was 35.8% vs. 46.1% ($p = .04$). However, it is acknowledged that the observed benefit in the low-dose NE subgroup may be due to chance. There were no differences in mean arterial blood pressure, although the addition of vasopressin to NE predictably resulted in a reduction in NE dose. Digital ischemia was somewhat more common in the vasopressin group ($p = .06$), while cardiac arrest was slightly more common in the NE group ($p = .11$).

Inspired by studies from the adult literature, some investigators have reported the successful use of vasopressin or terlipressin (the long-acting synthetic analog triglycyl-lysine-vasopressin) (Table 2). Solid evidence in children remains scant, as these studies are primarily observational in nature. However, each of these studies observed an improvement in blood pressure during the administration of low-dose vasopressin, enabling a rapid wean off catecholamine agents, and none reported adverse effects related to vasopressin. Improvement in systemic blood pressure was not necessarily associated with improved survival. Admittedly, in many of the earlier studies vasopressin was used as rescue therapy where shock was deemed refractory. Furthermore, pediatric studies have included a variety of patients with catecholamine refractory shock as opposed to restricting its use specifically to patients with vasodilatory shock for which there is good scientific rationale.

The multicenter, double-blind, randomized controlled Vasopressin in Pediatric Shock (VIP) trial, conducted on behalf of the Canadian Critical Care Trials Group, was recently completed. This is the first prospective trial of its kind in pediatric patients with vasodilatory shock, and it was designed to examine the effect of low-dose vasopressin on more clinically relevant outcomes (56). As mortality is acknowledged to be an impractical end point in pediatric critical care trials (57), the VIP trial examined the efficacy of low-dose vasopressin as an adjunctive agent on outcomes, such as time to hemodynamic stability and organ dysfunction, as well as the safety of its use in this setting.

Vasopressin During Cardiopulmonary Resuscitation. Experimental protocols for cardiopulmonary resuscitation (CPR) in adults and animals have suggested that vasopressin is superior to epinephrine in increasing vital organ blood flow, in particular coronary arterial and cerebral blood flow, when administered intravenously as well as endobronchially or via intraosseous route (58, 59). In a prospective study of 40 patients with out-of-hospital ventricular fibrillation resistant to electrical defibrillation, a significantly larger number of patients who received 40 units of vasopressin intravenously compared with 1 mg of epinephrine were successfully resuscitated and survived for 24 hrs (60). However, an in-hospital cardiac arrest, triple-blind, randomized controlled trial failed to demonstrated a survival advantage for vasopressin over epinephrine (61). Subsequently, a comparison of vasopressin and epinephrine for out-of-hospital cardiac arrest, which included 1,186 adult patients, demonstrated a significantly better outcome among patients with asystole who received vasopressin, although no significant difference in outcome was demonstrated in patients with ventricular tachycardia or pulseless electrical activity (79). The European Resuscitation Council recommends 40 units of vasopressin as an initial vasopressor in adults with shock-refractory ventricular fibrillation as an alternative to 1 mg of epinephrine (class IIb recommendation) (80), while the 2005 American Heart Association guidelines recommend that 40 units of intravenous or intraosseous vasopressin may replace the first or second dose of

Table 2. Pediatric studies of vasopressin in pediatric shock

Reference	Study Type	Condition	Vasopressin Dose[a]	n	Findings
Lechner, 2007[62]	Retrospective review	Neonates with catecholamine resistant post-CPBP vasodilatory shock	0.0001–0.001 U/kg/min	17	Increased MAP, decreased vasopressor requirements
Meyer, 2006[63]	Case series	Catecholamine-refractory shock and acute renal injury in ELBW infants	0.0002–0.006 U/kg/min	6	Increase in MAP and urine output. Two survivors
Meyer, 2006[64]	Case series	Catecholamine-resistant septic and cardiogenic shock in ELBW infants	0.0002–0.002 U/kg/min	3	Increased MAP and weaning of pressors in patient with septic shock. Death in two patients with cardiogenic shock
Masutani, 2005[65]	Retrospective review	Catecholamine-resistant hypotension	0.0002–0.004 U/kg/min	15	Increase in MAP and urine output. Low vasopressin levels in all six measured. Five deaths
Vasudevan, 2005[66]	Case series	Septic shock	0.0003–0.002 U/kg/min	3	Increase in MAP and urine output, catecholamine pressors weaned off. One death
Lechner, 2004[67]	Case report	Post-CPBP shock	0.00005–0.0003 U/kg/min	1	Increase in MAP, weaned off all vasoactive drugs and extubated within 24 hours
Efrati, 2004[68]	Case series	Shock: septic, hemorrhagic, trauma and cardiogenic	0.0003–0.002 U/kg/min	8	Increase in MAP, decreased in ventilatory support. One survivor
Leibovitch, 2003[69]	Case report	Septic shock	0.002–0.004 U/kg/min	1	Increase in MAP and urine output. Catecholamine pressors discontinued
Tobias, 2002[70]	Case series	Vasodilatory shock	0.0025–0.006 U/kg/min	2	Increase in MAP, decrease in catecholamine pressors. One (brain) death
Liedel, 2002[71]	Case series	Vasodilatory shock	0.0006–0.008 U/kg/min	5	Increase in MAP, decrease in catecholamine pressors. Three deaths
Katz, 2000[72]	Retrospective, case-controlled	Organ donors	0.0007 (SD 0.0011) U/kg/min	34	Increase in MAP, decrease in α-agonists in cases
Rosenzweig, 1999[32]	Case Series	Post-CPBP shock	0.0003–0.002 U/kg/min	11	Increase in MAP. Weaned off vasoactive infusions. Vasopressin deficiency in four patients. Two deaths

Reference	Study Type	Condition	Terlipressin Dose	n	Findings
Papoff, 2007[73]	Case series	Catecholamine-resistant septic shock	10 μg/kg/bolus, followed by infusion of 10–20 μg/kg/hr	2	Increase in MAP, increased urine output. Death in both patients
Zeballos, 2006[74]	Case report	Septic shock	10–20 μg/kg/hr	1	Increase in MAP, significant cutaneous vasoconstriction
Rodriguez-Nunez, 2006[75]	Prospective cohort study	Catecholamine refractory shock	20 μg/kg Q 4 hrs	16	Increase in MAP, reduction in catecholamine infusions. Death in nine patients
Matok, 2005[76]	Retrospective review	Septic shock	7 μg/kg Q 12 hrs – 20 μg Q 6 hrs	14	Increase in MAP, reduction in catecholamine infusions. Death in eight patients
Rodriguez-Nunez, 2004[88]	Case series	Septic shock	20 μg/kg/Q 4 hrs	4	Increase in MAP, decrease/withdrawal of Norepinephrine
Peters, 2004[77]	Case report	Septic shock	500 μg over 20 mins, Q 6 hrs (13 μg/kg)	1	Increase in MAP, discontinuation of NE
Matok, 2004[78]	Case report	Septic shock	7 μg/kg Q 12 hrs	1	Increase in MAP and perfusion

CPBP, cardiopulmonary bypass; ELBW, extremely low birth weight infants; MAP, mean arterial blood pressure; NE, norepinephrine.
[a]All doses converted to U/kg/minute and corrected to 4 decimal places from original references.

epinephrine in cardiac arrest in adults (class indeterminate) (81).

In pediatric asphyxial animal models, vasopressin alone during CPR was less effective than epinephrine alone, whereas vasopressin plus epinephrine was as effective as epinephrine alone (82). However, when cardiac arrest was evoked by ventricular fibrillation, the combination of vasopressin and epinephrine was superior to either drug alone for resuscitation (83). A retrospective case series of children with cardiac arrest suggested that vasopressin (0.4 units/kg per dose) is beneficial during prolonged pediatric cardiac arrest, following failure of conventional CPR (84). A second retrospective case series of pediatric cardiac arrests unresponsive to epinephrine found that return of spontaneous circulation was achieved in six of eight episodes that were treated with 15–20 μg/kg of terlipressin, and four of those patients survived without neurologic sequelae (85). In the largest series

of vasopressin use in pediatric in-hospital cardiac arrest, Duncan et al. (86) found that return of spontaneous circulation occurred in 32 of 71 (45%) patients, and survival to hospital discharge was 14%. Because of the current evidence, vasopressin is recognized as a potential alternative vasopressor when standard therapies fail to restore spontaneous circulation. However, no firm recommendations exist concerning the use of vasopressin for CPR in infants and children.

Vasopressin Dosage and Safety. Although vasopressin infusions have been used in critical care for >50 yrs, low-dose infusions for hemodynamic instability are relatively recent in adults and novel in pediatrics. The most common use of intravenous infusions of vasopressin in children is to control gastrointestinal hemorrhage and the treatment of diabetes insipidus; however, the data regarding the safety of this drug in the management of shock in children are limited. The pediatric dosing for vasopressin infusion in vasodilatory shock is extrapolated from adult data. Table 2 lists the published pediatric experience with low-dose vasopressin in shock states. The dose ranges used in these patients were variable, with maximum doses of up to 0.008 units/kg/min. The upper dose limit considered safe in adults with vasodilatory shock is 0.04 units/min. Doses beyond this range were not associated with increased effectiveness but may have resulted in increased adverse events (87).

Reported adverse effects related to exogenous vasopressin include coronary ischemia, increased myocardial afterload, ischemic skin lesions and wound complications, new-onset tachyarrhythmias, and splanchnic hypoperfusion (88). The adverse effects of vasopressin are dose related, and experience suggests that these observed side effects may be limited at doses up to 0.04 units/min. Complications appear to be more commonly reported when there is coadministration of vasopressin and prolonged use of moderate- to high-dose norepinephrine (87, 89, 90). The actions of vasopressin on the heart are complex, and the studies are seemingly contradictory. Depending on the species studied, the dose used, and the experimental model, vasopressin can cause coronary vasoconstriction or vasodilation and exert positive or negative inotropic effects. V1-receptor-mediated coronary vasoconstriction is a dose-dependent phenomenon that may be attenuated by the endothelial vasodilating actions mediated via the oxytocin receptor or P2 receptor. When cardiac contractility is studied independently of coronary perfusion, vasopressin may have a positive inotropic effect at low doses. In addition to its vascular effects on coronary blood flow, vasopressin has mitogenic and metabolic effects on the heart (43).

Data on the effects of vasopressin administration on the splanchnic microvasculature are also conflicting. Some studies in sepsis reported increased ileal or gastric Pco_2 gap with low-dose vasopressin compared with norepinephrine, indicating splanchnic hypoperfusion (49, 91), although these are in contrast to the findings of Dubois et al. (47) and others (40, 41), who suggested no worsening in microcirculatory alterations.

Because of the potent vasoconstrictor action of vasopressin, the possibility of impaired capillary blood flow and tissue oxygenation with vasopressin administration remains a concern. It is difficult to draw general conclusions from current reports because these side effects are also reported with norepinephrine and may be complicated by underlying disease processes (4, 9, 39). Furthermore, previous isolated clinical observations and studies on the effects of vasopressin used indirect measurements of tissue perfusion with inherent methodological constraints. More recent studies (47, 92, 93) have used more reliable methods of measuring microcirculatory perfusion, such as laser Doppler flowmetry and orthogonal polarization spectral imaging, and these studies as well as future such studies will provide invaluable information with respect to microcirculatory responses during vasopressor therapy in advanced vasodilatory shock.

CONCLUSION

Vasopressin is a promising agent in shock and during cardiopulmonary resuscitation; however, the recommendations for its use in the pediatric literature are based on limited clinical data. It is clear that vasopressin may have an emerging role in pediatrics, but it should be embraced with caution. Despite numerous reports and small observational studies describing the successful and potentially life-saving effects of vasopressin in children, its benefits have only been reported in patients with vasodilatory shock and adults with asystolic cardiac arrest. Results of adult experience cannot be generalized to the pediatric population, as adults and children differ in physiology, predisposing diseases, and even shock management strategies (34). Adults and children have different adaptive responses that must be considered when assessing their hemodynamic status and selecting vasoactive agents.

A further challenge to our ability to select the most appropriate patients who may benefit from vasopressin therapy is the inaccuracy with which we can predict their hemodynamic status by physical exam (94). Awareness of evolving hemodynamic status during shock in children dictates that the fluid and vasoactive regimens be constantly reevaluated when there is a poor response. Generalized conclusions about the action of vasopressin on microcirculatory perfusion should be made with caution. The dosage, the vasopressin-analog used, the child's hemodynamic physiology, and severity of illness are all important factors to consider in assessing the efficacy of vasopressin in pediatrics. While we acknowledge that vasopressin is a valuable adjunct in catecholamine-resistant shock states, the results of major clinical outcome studies must be awaited before vasopressin is introduced into standard treatment protocols. Its administration is not without risks, particularly when combined with prolonged use of moderate- or high-dose pressor agents. The use of vasopressin, like any empirical therapy, requires assessment of therapeutic end points and surveillance for potential adverse effects, using clinical and biochemical markers of end-organ perfusion, measurements of cardiac index, oxygen utilization indexes, and monitoring of the microcirculatory homeostasis, which are all important tools during the titration of vasoactive therapy in critically ill patients (94).

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