Vasopressin in Pediatric Critical Care

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Abstract

Vasopressin is a unique hormone with complex receptor physiology and numerous physiologic functions beyond its well-known vascular actions and osmoregulation. While vasopressin has in the past been primarily used in the management of diabetes insipidus and acute gastrointestinal bleeding, an increased understanding of the physiology of refractory shock, and the role of vasopressin in maintaining cardiovascular homeostasis prompted a renewed interest in the therapeutic roles for this hormone in the critical care setting. Identifying vasopressin-deficient individuals for the purposes of assessing responsiveness to exogenous hormone and prognosticating outcome has expanded research into the evaluation of vasopressin and its precursor, copeptin as useful biomarkers. This review summarizes the current evidence for vasopressin in critically ill children, with a specific focus on its use in the management of shock. We outline important considerations and current guidelines, when considering the use of vasopressin or its analogues in the pediatric critical care setting.

Keywords
- vasopressin
- pediatrics
- shock

Introduction

Since its isolation in the 1950s, vasopressin has been recognized as an essential posterior pituitary hormone with both antidiuretic and vasoconstrictor actions, and hence has primarily been used in the management of diabetes insipidus and acute gastrointestinal (GI) bleeding.[1] However, an increase in the understanding of its key functions in maintaining cardiovascular homeostasis prompted a renewed interest in the therapeutic roles for this hormone in the critical care setting in the late 1990s. The objective of this review is to summarize the current evidence for vasopressin in critically ill children, with a specific focus on its use in the management of shock.

The Physiology of Vasopressin

Vasopressin Receptor Physiology

Vasopressin is a unique hormone with complex receptor physiology and numerous physiologic functions beyond its well-known vascular actions and osmoregulation.[2] The effects of vasopressin on various vascular beds and tissues are complex, and are summarized in ►**Table 1**. The diversity of its actions is related to the location and density of tissue-specific G-protein–coupled vasopressin receptor subtypes, which are currently classified into V1 vascular (V1R), V2 renal (V2R), V3 pituitary (V3R), oxytocin-type receptors (OTR), and P2 purinergic receptors.[3] V1R are located on vascular smooth muscle and mediate vasoconstriction. However, in the pulmonary circulation, activation of V1R stimulates the release of nitric oxide (NO) and pulmonary vasodilation. V2R are located in the renal collecting duct where it is responsible for the hormone's antidiuretic action. It is also expressed in the vascular endothelium, where specific activation mediates vasodilation and the release of von Willebrand factor and factor VIIIc. OTR has equal affinity for vasopressin and oxytocin, and is hence known as the "nonselective" vasopressin receptor.[1] The many actions of vasopressin may be summarized as follows: (1) systemic vasoconstriction (via V1R); (2) vasodilation of the renal, cerebral, and potentially coronary circulations (via V2R- or OTR-mediated NO release); (3) decreased pulmonary vascular resistance via V1R-mediated pulmonary vasodilation and ANP release; (4) antidiuretic effect in the setting of increased serum osmolarity (V2R

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Table 1 Vasopressin receptor physiology, mechanism of action, and principle effects

Receptors	Signal pathway	Location	Principle effects
V1R	• Increases intracellular calcium via the phosphatidylinositol-biphosphonate pathway	• Vascular smooth muscle • Renal medulla • Platelets • Brain, testis, superior cervical ganglion, liver, cardiac myocytes	• Systemic vasoconstriction, pulmonary vasodilation • Selective renal *efferent* arteriolar constriction • Platelet aggregation
V2R	• Increased cAMP via the Gs and adenylate cyclase pathway • Mobilization of aquaporin channels	• Renal distal tubule and collecting ducts • Vascular endothelium	• Antidiuretic • VWF and FVIII:c release • NO-mediated vasodilation • Renal afferent arteriolar vasodilation
V3R	• Phosphokinase C pathway activation, increased cAMP	• Pituitary	• ACTH release
OTRs	• Increases intracellular calcium via the phospholipase C and phophoinositide pathway	• Myometrium, endometrium, ovary • Vascular endothelium • Heart	• Uterine contractions • NO-mediated vasodilation • ANP release
Purinergic (P2R)	• Increase in intracellular calcium via phospholipase C activation	• Myocardium • Cardiac endothelium	• Myocardial contractility • Selective coronary vasodilation

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrionatriuretic peptide; cAMP, cyclic adenosine monophosphate; FVIII:c, factor VIII: coagulant; NO, nitric oxide; OTR, oxytocin-type receptor; VWF, von Willebrand factor.

response); (5) increased glomerular filtration and maintenance of urine output through selective vasoconstriction of the efferent arterioles (V1R) and vasodilation of renal afferent arterioles (V2R) in the setting of shock; (6) endocrine effects through ACTH and increased plasma cortisol, as well as the stimulation of atrionatriuretic peptide (ANP), angiotensin-II, prolactin, and endothelin-I release; and finally (7) procoagulant effects, through the activation of platelet aggregation and the stimulation of von Willebrand factor and factor VIIIc.

Vasopressin Response during Shock

A biphasic vasopressin response has been described particularly in vasodilatory shock states where high levels are observed in the initial phase of hypotension, followed by inappropriately low levels as shock progresses.[4] Several mechanisms responsible for vasopressin deficiency during refractory shock have been proposed: depletion of neurohypophyseal stores, impaired baroreflex-mediated release of vasopressin, and downregulation of vasopressin production.[5] This latter mechanism is mediated by central NO production, and may also have important implications in the pathogenesis of critical illness-related adrenal insufficiency, as vasopressin also modulates adrenocorticotropic hormone (ACTH) production.[6] Inflammatory cytokines, such as interleukin-1β, tumor necrosis factor-α, and interferon-γ, may also contribute to vasopressin receptor downregulation and reduced efficacy of exogenous hormone.[7]

While absolute or relative vasopressin deficiency has been used to justify a role for exogenous vasopressin in catecholamine-refractory shock, supporting evidence for its existence in children is inconsistent. Several studies have demonstrated low endogenous hormone levels in children with vasodilatory shock prior to starting vasopressin[8,9]; however others report elevated levels and no difference between children with and without septic shock.[10] Depleted vasopressin stores have been identified in children following cardiopulmonary bypass; however, low levels were not accompanied by hemodynamic instability in all patients, nor did they reliably predict patients at higher risk of developing a low cardiac output state.[11] Possible reasons for inconsistencies in measured vasopressin levels between the adult and pediatric studies may be attributed to the difference in hemodynamic physiology seen in children.[12] While vasodilatory shock may be the predominant physiology in adult septic shock, pediatric sepsis more commonly presents with low cardiac index, high systemic vascular resistance, and a hemodynamic state that often changes over time, making it challenging to discriminate clinically.[13] Furthermore, there are several limitations to the measurement of plasma vasopressin.

Assessing Vasopressin Levels during Shock

While identifying vasopressin-deficient individuals and responsiveness to exogenous hormone is an attractive approach to management and prognosis in critically ill patients, the measurement of circulating plasma vasopressin levels is challenging because the mature hormone is unstable, has a short half-life, and circulates largely attached to platelets. Hence, the interpretation of static measurements of vasopressin may be misleading. Vasopressin is derived from a larger, more stable precursor peptide known as *copeptin*, which is secreted in an equimolar ratio to vasopressin. Copeptin reliably mirrors vasopressin release, and has therefore been proposed as a more sensitive and potential prognostic biomarker in sepsis. Copeptin is not specific to sepsis,

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however, and as one would expect given the stimuli for vasopressin response, elevated levels are observed in numerous other stressed and inflammatory states such as acute neurologic illnesses and myocardial ischemia.[14] High copeptin levels have also been observed in neonates with perinatal asphyxia,[15] and children with severe traumatic brain injury.[16] Copeptin reflects the severity of illness rather than changes in plasma osmolality, and has therefore been proposed as a promising prognostic biomarker in critical illness. However, at the present time, neither vasopressin nor copeptin has been shown to be robust markers for illness severity and clinical outcomes in critically ill children.

Vasopressin Pharmacology

The most commonly used and extensively researched forms of vasopressin in the setting of shock are arginine vasopressin (AVP) and terlipressin. The recommended doses for vasopressin for its indications in pediatric critical care are listed in ►**Table 2**.

Arginine Vasopressin

8-arginine vasopressin (AVP) is the native form of the hormone in most mammals. While original preparations were extracted from posterior pituitary cells, exogenous AVP is made as a synthetic peptide for intravenous, intramuscular, and subcutaneous administration. AVP has a plasma half-life of approximately 24 minutes, which lends itself to administration by continuous infusion during the management of vasodilatory shock.[17] Approximately 65% is cleared by renal elimination, whereas the remaining approximately 35% is metabolized by tissue peptidases. The reported effective dose ranges used in pediatric shock have been variable, ranging from 0.00005 to 0.002 U/kg/min.[8]

Terlipressin

Terlipressin (tri-glycyl lysine vasopressin) is a synthetic analogue of lysine vasopressin. Terlipressin is a prodrug and is slowly cleaved to lysine vasopressin in the circulation by renal and liver endothelial peptidases. Terlipressin has a similar pharmacodynamic profile but has a much longer effective half-life than AVP of approximately 6 hours, allowing it to be administered as an intravenous bolus in children (10–20 μg/kg). It has, however, also been used as a continuous infusion.[18]

Desmopressin

Desmopressin (*1-desamino-8-D-arginine vasopressin [DDAVP]*) is the synthetic analogue of AVP, and is available in a range of formulations: intranasal, injectable, and oral lyophilisate. It is a selective V2R agonist, and hence has 10 times the antidiuretic action of vasopressin, 1,500 times less vasoconstrictor action and hence minimal vasopressor activity, and a much longer half-life (158 minutes). It is also more potent that AVP in releasing factor VIII.[19] The primary indications for the use of DDAVP in critically ill children is in the management of central diabetes insipidus, and in the prevention of bleeding in patients with impaired platelet function, mild to moderate type 1 von Willebrand disease, or hemophilia A patients with factor VIII levels greater than 5%.[20]

Which Is the More Effective Vasopressin in Shock?

AVP exerts its principal cardiovascular effects via V1R and V2R stimulation. Terlipressin is believed to have higher selectivity for V1R than AVP (V1R/V2R ratio 2.2 vs. 1), and therefore more potent vasoconstriction. Its potential downside, however, is the risk of excessive systemic and pulmonary vascular resistance, and microregional vasoconstriction after bolus injection, which may be avoided with continuous low-dose terlipressin infusions.[21] Continuous low-dose terlipressin infusion (1.3 μg/kg/h) has been compared with AVP (0.03 U/min) and shown to reduce on open-label norepinephrine requirements in adults with septic shock.[22] Both AVP and terlipressin have been shown to restore arterial hypotension and reduce catecholamine requirements in experimental and clinical studies. However, there are no studies in either the

Table 2 Recommended vasopressin and terlipressin doses used in clinical practice and research studies

Indication	Dose	
	Vasopressin	Terlipressin
Cardiac arrest	0.4 U/kg IV per dose[43]	10–20 μg/kg per dose
Shock	0.0005–0.002 U/kg/min (0.5–2 mU/kg/minor 0.03–0.12 U/kg/h)	10–20 μg/kg Q4–12h; 10–20 μg/kg/h
Diabetes insipidus	2.5–10 units IM or subcutaneously 2–4 times per day or 0.0005–0.01 U/kg/h (0.5–10 mU/kg/h)[54]	
GI hemorrhage	0.002–0.01 U/kg/min (2–10 mU/kg/min or 0.12–0.6 U/kg/h)[24]	
Organ donor management	0.0005–0.001 U/kg/h (0.5 mU/kg/h)[55]	

Abbreviation: GI, gastrointestinal.

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adult or pediatric literature suggesting the superiority of one form of vasopressin to the other.

Safety Profile of Vasopressin in Critically Ill Children

Because of its potent vasoconstrictor action, potential adverse effects of vasopressin include increase in systemic vascular resistance and afterload, reductions in oxygen delivery, impaired tissues perfusion, and ischemic tissue injury. Thrombocytopenia and increases in aminotransferases activity and bilirubin concentrations have also been reported. These adverse effects appear to be dose-dependent, and more commonly noted with doses of greater than 0.04 U/min of vasopressin or 2 μg/kg/h of terlipressin.[23,24] However, some of the data are conflicting, and it is still unclear whether the hemodynamic alterations represent an adaptive response to stabilized blood pressure, or the impaired tissue perfusion is an epiphenomenon of the severity of underlying disease rather than a specific side effect of vasopressin or concurrent catecholamine pressor administration.[25] Systematic reviews in adults and pediatric trials to date have found no significant difference in adverse event rates between the vasopressin or terlipressin, and other catecholamine-based vasoactive agents.[8,26]

The Role of Vasopressin in the Management of Shock

Vasopressin and analogues have long been approved for use in diabetes insipidus, nocturnal enuresis, GI bleeding, hemophilia A, von Willebrand disease, and bleeding secondary to platelet dysfunction. Vasopressin is an attractive adjunctive agent in the management of shock states and cardiac arrest in adults and children for the following reasons: (1) It reverses the key mechanisms responsible for pathologic vasodilation and catecholamine resistance observed in vasodilatory and refractory shock; (2) despite its potent systemic vasoconstrictor properties, vasopressin has concurrent organ-specific vasodilator effects that may result in preserved vital organ perfusion; (3) vasopressin influences multiple other hormone responses that may modulate hypothalamic-pituitary-adrenal (HPA) axis dysfunction and cellular immune response during septic shock; and (4) vasopressin insufficiency, and an increased sensitivity to the pressor effects of exogenous vasopressin has been demonstrated in both adults and perhaps children with septic shock .

Evidence from Adult Trials

There are at least nine randomized controlled trials of AVP or terlipressin in the management of vasodilatory shock in adults.[27] The majority of these trials were in vasodilatory septic shock, and compared AVP or terlipressin to norepinephrine. The largest of these, the Vasopressin and Septic Shock Trial (VASST) evaluated the effect of low-dose AVP as an adjunctive agent compared with norepinephrine alone in 779 adult patients in septic shock and found no mortality benefit.[28] Although the authors had predicted that based on its vasoconstrictor potency, AVP would be more efficacious in the stratum of patients with more severe septic shock (baseline requirement of $\geq$ 15 μg/kg/min norepinephrine), they observed a significant reduction in mortality in the subgroup of patients with *less* severe septic shock (baseline of 5–14 μg/kg/min norepinephrine). While the authors concluded that these subgroup findings should be hypothesis generating only, it sparked further debate on whether higher doses of vasopressin should be used in patients with more severe shock, and the conclusion was that these doses should first be evaluated in future studies. However, recent systematic reviews of more than 30 clinical trials of almost 4,000 adult patients with septic shock have consistently failed to demonstrate any statistical significance in either mortality benefit or adverse event risk between vasopressin/terlipressin, and other adrenergic vasopressors such as norepinephrine, dopamine, epinephrine, or phenylephrine.[27,29]

Evidence in Pediatrics

A search of Medline and Embase from 1966 to August 2015 revealed a total of 40 published pediatric studies (35 in shock, 5 in cardiac arrest) evaluating the use of AVP or terlipressin, reporting on a collective total of only 642 children. The vast majority of studies were case reports or case series with only three randomized controlled trials to date. Baldasso et al evaluated the safety of prophylactic low-dose vasopressin infusion compared with placebo, in 24 hemodynamically stable, critically ill mechanically ventilated children at risk of developing sedation/analgesia-related hypotension.[30] They found that vasopressin increased the risk of hyponatremia and decreased urine output. The open-label trial by Yildizdas et al randomized 58 children with catecholamine refractory septic shock to terlipressin versus placebo, and found that while terlipressin significantly increased mean arterial blood pressure and oxygenation, there was no survival benefit (67.3 vs. 71.4%).[31] The Vasopressin in Pediatric Vasodilatory Shock trial evaluated low-dose vasopressin as an adjunctive vasoactive agent in vasodilatory shock and found no difference in the time to hemodynamic stability, organ-free failure days, and magnitude of vasoactive agent use between the vasopressin and placebo groups.[8] While there was no difference in the adverse event rates, there was a nonstatistically significant trend toward increased mortality in the vasopressin group (30.3 vs. 15.6%; $p = 0.24$).

Potential interaction between vasopressin and corticosteroids led to the hypothesis that the combination of these two hormones may be beneficial in the management of septic shock through the following mechanisms: vasopressin increases ACTH secretion by corticotropic cells through V1b receptors during stress[32]; corticosteroids and vasopressin both block ATP-sensitive potassium channels, the activation of which results in abnormal vasodilation; corticosteroids may also increase the sensitivity of V1R, which are suspected to be downregulated in sepsis.[33] A post hoc analysis of the VASST trial suggested that combined vasopressin and corticosteroid therapy was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids.[34] A subsequent open-label trial by Torgersen and colleagues demonstrated that higher doses of AVP (0.067 IU/min) resulted in improved hemodynamic control without

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increased adverse effects, compared with lower doses of 0.033 IU/min in patients with vasodilatory septic shock.[35] Pooled results from studies of vasopressin in addition to corticosteroids have failed to demonstrate a mortality benefit in adults with septic shock.[36] The combination of corticosteroids and vasopressin has not been systematically evaluated in children to date; however, randomized controlled trial of AVP in pediatric shock by Choong et al revealed no difference in outcomes in the subgroup of patients who received corticosteroids.[8] In summary, there is insufficient evidence at present supporting the routine use of vasopressin either alone or in combination with corticosteroids, in the setting of vasodilatory or septic shock.

Vasopressin in Cardiac Arrest

Experimental animal data suggest 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.[37] While, an *in-hospital* cardiac arrest, triple-blind, randomized controlled trial failed to demonstrated a survival advantage for vasopressin over epinephrine,[38] a comparison of vasopressin and epinephrine for *out-of-hospital* cardiac arrest in 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.[39] A systematic review and meta-analysis of five randomized controlled trials of vasopressin compared with epinephrine in adult patients with cardiac arrest revealed that there were no statistically significant differences between the two groups in return of spontaneous circulation (ROSC), death before hospital admission, within 24 hours, or before hospital discharge, or composite outcome of death or neurologically impaired survivors. Subgroup analyses also showed no statistical difference in these outcomes depending on the cardiac rhythm at presentation (ventricular fibrillation or tachycardia, pulseless electrical activity of asystole).[40]

There are only five published reports of AVP or terlipressin use in pediatric in-patients receiving cardiopulmonary resuscitation (CPR) who were unresponsive to conventional therapy (epinephrine and/or cardioversion). All these reports are retrospective or registry-based studies. The largest of these is from the American Heart Association National Registry of pediatric resuscitation, reporting on 1,293 consecutive pediatric patients with pulseless cardiac arrest in 176 North American hospitals between October 1999 and November 2004.[41] Only 5% of pediatric patients received vasopressin during cardiac arrest in this review. Vasopressin was most often given in a pediatric hospital (57%) and in an intensive care setting (76.6%). ROSC occurred in 32 of 71 (45%) patients, and survival to hospital discharge was 14%. Patients who were given vasopressin had longer arrest duration (median: 37 minutes) versus those who did not (24 minutes) ($p = 0.004$). In multivariate analysis, vasopressin was associated with worse ROSC but no difference in 24 hours or discharge survival.

A more recent randomized, double-blind trial comparing vasopressin-steroids-epinephrine (VSE) in combination in adults demonstrated that compared with epinephrine/saline placebo, VSE during CPR and stress-dose steroids in post-resuscitation shock resulted in a higher ROSC at 20 minutes, and an improved survival to hospital discharge with a favorable neurologic outcome (number needed to treat 11.9, 95% confidence interval [CI] 6.1–52.9).[42] Though results are interesting, they need to be validated with further study.

In summary, though vasopressin is recognized as a potential alternative vasopressor when standard therapies fail to restore spontaneous circulation, current evidence does not demonstrate any clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest in adult or pediatric patients.

Current Recommendations for Vasopressin in Pediatric Shock

The American Heart Association stated in their 2010 guidelines for cardiopulmonary resuscitation that there is currently insufficient evidence to recommend for or against the routine use of vasopressin during cardiac arrest.[43] The 2014 American College of Critical Care Medicine revision committee for the guidelines for hemodynamic support in children and neonates recommends against the use of vasopressin or terlipressin as routine adjunctive agents in vasodilatory shock, but they may be considered in catecholamine refractory shock with high cardiac index and low systemic vascular resistance (grade level 1D evidence; personal communication).[44] However, because these potent vasoconstrictors can reduce cardiac output, it is recommended that these drugs be used with cardiac output and $ScvO_2$ monitoring.

Other Uses of Vasopressin in Pediatric Critical Care

Postcardiopulmonary Bypass

The potential uses for vasopressin in this setting include relative endogenous vasopressin deficiency, systemic vasodilation postcardiopulmonary bypass, or systemic hypotension in the setting of pulmonary hypertension.[11] The first report of vasopressin use following cardiac surgery in pediatrics was by Rosenzweig et al in 1999.[9] While this and other case series report an increase in systolic blood pressure and a reduction in catecholamine requirements, these findings have not been substantiated by more recent, larger studies.[45,46] As the current evidence is primarily observational, the role of vasopressin in clinically important outcomes in this population remains uncertain.

Organ Donor Management

Hemodynamic instability is a common phenomenon in brain-dead patients being considered for organ donation. After an initial catecholamine storm, there is a loss of sympathetic tone and peripheral vasodilation, resulting in hypotension that, if untreated, compromises the perfusion of all organs and may contribute to rapid donor loss.[47] Catecholamines

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such as dopamine and norepinephrine were previously used as fist-line vasopressor agents; however, high-dose norepinephrine in donors is associated with increased cardiac graft dysfunction and higher mortality in recipients.[48] Vasopressin infusion therefore has a role in these patients not only in the treatment of diabetes insipidus but in preserving vascular tone while enabling a reduction or elimination of catecholamine use to achieve organ donor goals. Current Canadian guidelines recommend vasopressin as a first-choice vasopressor for adult and pediatric donor resuscitation.[49]

Pulmonary Hypertension

Because of its potential for pulmonary vasodilation, terlipressin has been used as rescue therapy in the management of severe pulmonary hypertension in neonates with congenital diaphragmatic hernia, perinatal asphyxia, and therapeutic hypothermia.[50,51] These studies are limited to case reports, and this indication has not been further evaluated in prospective trials to date.

Acute Esophageal Variceal Bleeding

The mainstay of maintaining hemostasis and preventing early rebleeding in acute variceal bleeding is the administration of vasoactive drugs and endoscopic sclerotherapy or band ligation.[52] The rationale for vasoactive drugs in this setting is to reduce portal pressure and subsequently variceal pressure. Clinical trials and meta-analyses are limited to the adult population, and demonstrate that endoscopic therapy in combination with vasoactive drug administration is superior in the management of variceal bleeding to any of these therapies in isolation. Suggested vasoactive agents include somatostatin or its analogue octreotide, vasopressin, or terlipressin. Published data do not demonstrate superiority of one vasoactive drug over another; however, octreotide is often preferred in children given the side-effect profile of vasopressin.[53]

Conclusion

Vasopressin has a unique physiology with catecholamine-sparing mechanisms for maintaining end-organ perfusion, which makes its use in critical care attractive. However, the evidence to date has not demonstrated clear efficacy for its routine use management of pediatric shock. Numerous questions remain that continue to fuel interest in research of this hormone in critical care, such as the role of copeptin as a biomarker in critically ill children, identifying the most appropriate dosing, timing of administration, and the most appropriate patients who may benefit from exogenous vasopressin replacement. While hormone therapy in the presence of absolute or relative deficiency has rationale, we have yet to fully understand the complex interplay of neuroendocrine response in sepsis and shock, and whether these responses are adaptive or maladaptive. Replacement therapy with exogenous hormones including vasopressin with the rationale of restoring normal or "physiologic" values, or to reverse target organ receptor resistance, may be too simplistic a therapeutic approach. The many controversies and ongoing debates ensure that this area of research will continue to evolve, which will hopefully enhance our ability to not only detect hormone dysfunction, but also predict outcome, and ultimately refine our diagnostic, therapeutic, and prognostic approaches in pediatric shock.

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