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Pharmacologic support of infants and children in septic shock

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Abstract

Objectives: Septic shock (SS) is a frequent cause for admission to the pediatric intensive care unit, requiring prompt recognition and intervention to improve outcome. Our aim is to review the relevant literature related to the diagnosis and management of SS and present a sequential management for its treatment.

Sources: Non-systematic review of medical literature using the MEDLINE database. Articles were selected according to their relevance to the objective and according to the authors' opinions.

Summary of the findings: The outcome of sepsis and SS is dependent on the early recognition and implementation of time-sensitive goal-directed therapies. These include rapid aggressive fluid resuscitation followed by a well-designed pharmacotherapy. The goals of the resuscitation are the restoration of microcirculation and improved organ tissue perfusion. Clinical and laboratory markers are needed to assess the adequacy of the treatments. Altered pharmacokinetic and pharmacodynamic responses dictate that vasoactive agents should be adjusted to achieve the predetermined goals. In initial resuscitation with isotonic solutions (> 60 mL/kg), either crystalloid (normal saline) or colloid infusion could be used. Despite adequate fluid resuscitation, if: (a) wide pulse pressure, low blood pressure, or bounding pulses (high cardiac output, low systemic vascular resistance – SVR) are present, norepinephrine should be considered; (b) prolonged capillary refill, weak pulses, narrow pulse pressure, normotensive (low cardiac output, high SVR), dopamine, epinephrine or dobutamine should be considered. Adjunctive therapy with stress dose of corticosteroid is indicated in selected populations.

Conclusions: Septic shock hemodynamics is a changing process that requires frequent assessment and therapeutic adjustments.

J Pediatr (Rio J). 2007;83(2 Suppl):S36-45: Septic shock, sepsis, pediatric intensive care, fluid resuscitation, hemodynamic support, corticosteroids.

Introduction

A significant improvement in the outcome of sepsis and septic shock (SS) over the last few years has been in large part due to the utilization of aggressive fluid resuscitation and to the implementation of time-sensitive goal-directed therapies.[1-4] Early diagnosis of SS is paramount to initiate therapy. SS presents as a constellation of signs of infection, hemodynamic dysfunction and organ failure. The most common symptoms are hypothermia or hyperthermia, tachycardia, altered mental status, diminished (cold shock) or bounding peripheral pulses (warm shock), prolonged (> 3 seconds, cold shock) or brisk capillary refill (warm shock), mottled or cool extremities, and diminished urine output (< 1 mL/kg/h). A wide pulse pressure (diastolic blood

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pressure that is less than one-half the systolic pressure) is sometimes observed; hypotension, not always present, is a late sign of SS.

The lack of rapid restoration of adequate microcirculation triggers a cascade of inflammation and disseminated microthrombosis for which, in pediatrics, no effective treatment is available at present. It is not possible to evaluate the completeness of resuscitation by a single parameter; a comprehensive evaluation of clinical or biochemical measurements is needed.[5] Inadequate early resuscitation results in multiple organ system failure and in death days to weeks after the initial presentation. A report showed that every hour that went by without restoration of appropriate circulation was associated with a two-fold increase in mortality.[6]

During SS, the tissue oxygen supply is inadequate to meet metabolic demands, which are significantly increased in critical organs. Additionally, there is a maldistribution of cardiac output with increased blood flow to skeletal muscles at the expense of a relative hypoperfusion of the splanchnic circulation. Thus, the therapeutic goals are to restore effective intravascular blood volume, support the needs of an increased cardiac output and oxygen delivery while redirecting blood flow to essential organs and preventing microthrombosis.

Septic shock is further classified as fluid-sensitive septic shock, fluid-refractory septic shock (fail to improve with adequate volume resuscitation), catecholamine-resistant SS (fail to improve with fluids and catecholamines), and refractory septic shock (fail to improve with fluids, catecholamines and vasodilators). SS is a dynamic process; so vasoactive medications and their infusion dose may have to be changed and adjusted over time to maintain adequate organ perfusion and microcirculation. Vasoactive agents have varying effects on systemic vascular resistance (SVR) (i.e., vasodilators or vasopressors) and pulmonary vascular resistance, contractility (i.e., inotropy) and heart rate (chronotropes). Age of the patient and changes in the perfusion of liver and kidney affect the pharmacokinetics of vasoactive medications (available drug in serum). The pharmacodynamic response is affected by inflammation, nitric oxide production and down-regulation of receptors. Thus, the recommended infusion doses are approximations and should be adjusted to achieve predetermined goals of organ perfusion and microcirculation.

Initial assessment and management

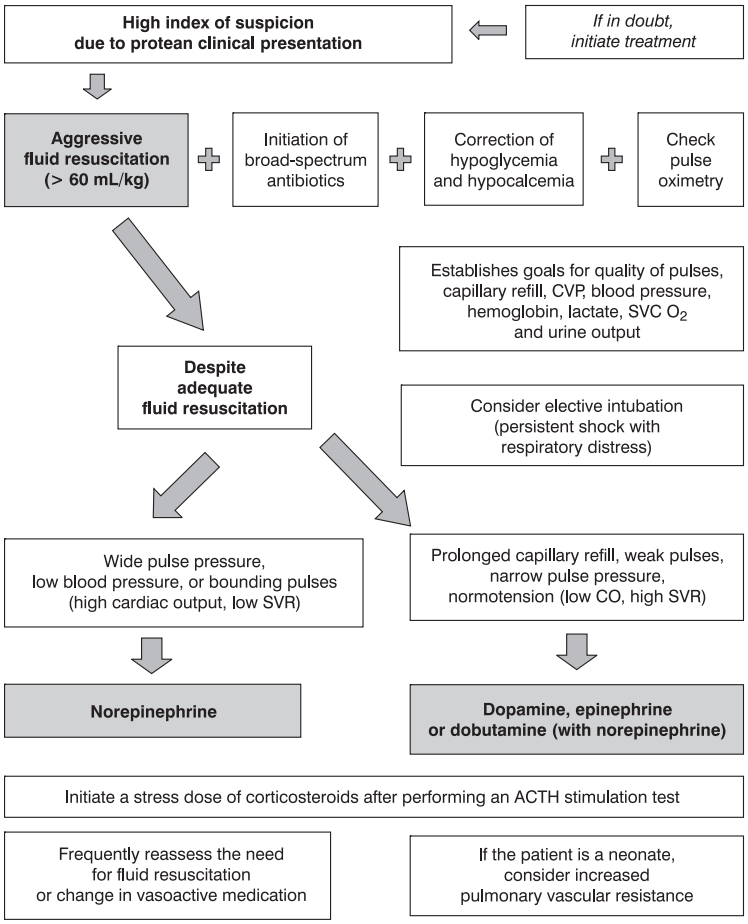
Initial resuscitation of infants and children centers on the administration of isotonic solutions in quantities of 20 mL/kg over 10 minutes repetitively while monitoring the patient's clinical response to treatment (Figure 1). There are no data that confirm the superiority of either crystalloid (normal saline) or colloid in children. All patients with SS suffer from some degree of relative hypovolemia secondary to systemic vasodilation, capillary leak, increased insensible loss, and diminished oral intake, and may require up to 200 mL/kg of intravenous fluids to adequately restore circulating volume. This fluid resuscitation does not lead to an increased incidence of acute respiratory distress syndrome (ARDS or non-hydrostatic pulmonary edema).[7] It is often necessary to begin treatment with vasoactive/inotropic medications concomitantly with the initiation of fluid resuscitation in patients who present with unstable hemodynamics (i.e.: low heart rate, low cardiac output). During and after initial fluid resuscitation, clinical and laboratory parameters regarding the patient's response to treatment should be evaluated. Clinical evidence of positive response includes increased strength of peripheral pulses, warmth of extremities, decreased pulse rate, narrowing and normalization of blood pressure, improvements in mental status and in urine output.

Unfortunately, clinical response to fluid resuscitation is a relatively insensitive indicator of the completeness of restoration of microvascular blood flow. The oxygen saturation of the superior vena cava (SVC O_2) (an indirect measurement of cardiac output and oxygen utilization) and serum lactate (the product of anaerobic metabolism) are markers to assess microcirculation.[5] Verification of increasing and acceptable measurements of SVC O_2 (> 70%) is recommended to demonstrate adequacy of systemic oxygen delivery relative to demand.[8] This finding is especially reassuring when serum lactate levels are declining. Elevated central venous oxygen saturations in the setting of increasing serum lactate may indicate the presence of cellular metabolic failure and inability to extract and consume oxygen.

Patients with inadequate resolution of shock in response to fluid resuscitation (fluid-refractory SS) require optimization of oxygen-carrying capacity and systemic oxygen delivery. Invasive monitoring of central venous pressure (CVP) is instituted to ensure that satisfactory right ventricular preload is present (CVP = 10-12), and oxygen-carrying capacity is optimized by transfusion of packed red blood cells to correct anemia (hemoglobin concentration > 10 g/dL). Recent reports put into question the ability of CVP to reflect adequacy of the preload favoring other measurements of cardiac output in response to a fluid challenge.[9] If despite these measures the patient continues to have incomplete response to resuscitation, it is necessary to institute pharmacologic therapy to support circulation.

Hemodynamics in pediatric SS

Adults and children have different adaptive responses that must be considered when selecting vasoactive agents. Among adult patients, the most common hemodynamic aberrations include diminished SVR and elevated cardiac



ACTH = adrenocorticotropic hormone; CVP = central venous pressure; SVC O_2 = oxygen saturation of the superior vena cava; SVR = systemic vascular resistance.

Figure 1 - Septic shock: simplified initial management

output. SVR is diminished due to decreased vascular responsiveness to catecholamines, alterations in α-adrenergic receptor signal transduction, and the elaboration of inducible nitric oxide synthase. After volume loading, cardiac output increases despite diminished ejection fraction, as a result of compensatory responses that include ventricular dilatation and increased heart rate.[10] Indeed, significant myocardial depression may be present among adult patients with SS. Pediatric patients demonstrate diverse hemodynamic profiles during fluid-refractory SS: 58% have low cardiac index responsive to inotropic medication ± vasodilators, 20% exhibit high cardiac index and low SVR responsive to vasopressor therapy, and 22% present both vascular and cardiac dysfunctions, necessitating the use of vasopressors and inotropic support.[7] The heterogeneity and changing pattern of the hemodynamic presentation, during the initial hours, dictate that an incorrect cardiotonic/vasoactive regimen should be suspected when there is unresponsiveness to fluid therapy and to vasoactive agents.

The relative ability of infants and children to augment cardiac output through increased heart rate is limited by their pre-existing elevated heart rate, which precludes proportionate increases in heart rate without compromising diastolic filling time (Table 1). Additionally, the increased connective tissue content of the infant's heart and diminished content of actin and myosin limits the potential for acute ventricular dilatation.[11]

Almost invariably there is relative hypovolemia often associated with a maldistribution of cardiac output. In the presence of respiratory distress, an elective tracheal intubation followed by mechanical ventilation will contribute to redistributing blood flow from respiratory muscles toward other vital organs. However, it is imperative to have an adequate fluid resuscitation before the intubation as the change from spontaneous breathing to positive pressure ventilation will decrease the effective preload to the heart. When sedatives and analgesics are used, a vasodilator effect could be observed, affecting tissue perfusion independent of

the presence of hypotension. In such situation, early vasoactive /inotropic support should be considered.

The maldistribution of blood flow with hypoperfusion of the splanchnic circulation, even when global cardiac output is normal or increased, represents a special challenge. One of the beneficial effects of potent vasopressors in sepsis is to redirect blood flow away from the skeletal muscles to the splanchnic circulation.

Pharmacologic agents for the support of pediatric SS

Pharmacologic support must be individualized as different hemodynamic abnormalities exist in pediatric patients, and the primary hemodynamic abnormalities present in a given patient may change with time and progression of the patient's disease.

The pharmacologic agents may be classified as inotropic medications, vasopressors, and vasodilators. Inotropic medications increase cardiac output by increasing myocardial contractility and/or heart rate. Vasopressors elevate SVR by increasing the tone of arterial circulation, and vasodilators decrease arterial resistance, resulting in decreased afterload and increased cardiac output without affecting contractility.

In many cases, a single drug may have combined effects that result in the alteration of contractility and SVR, or may have dose-dependent differential effects on contractility and SVR. Additionally, there is wide inter-individual variability with respect to the pharmacodynamics of these medications, resulting in different effects in different individuals at the same infusion rate. Lastly, the medications have direct effects on cardiovascular system, indirect effects mediated through the patient's autonomic nervous system, or mixed effects by both mechanisms. In this section, we review the pharmacodynamics of many of the medications commonly used to support patients in SS.

The medications traditionally used to support circulation in patients with sepsis and shock include vasopressors (dopamine, norepinephrine, and vasopressin) and inotropes (epinephrine, dobutamine, and milrinone). Newer medications, which include fenoldopam and levosimendan, may find application in the management of SS. Finally, in infants, special consideration and management are sometimes required in the management of pulmonary artery hypertension and calcium homeostasis.

Vasopressors

Vasopressor therapy is required in patients with diminished SVR. Patients in SS with diminished systemic resistance and elevated cardiac output will often have warm extremities, bounding peripheral pulses, widened pulse pressure, and normal or low blood pressure. In the presence of diminished cardiac output, peripheral perfusion is often compromised, and the blood pressure is often low. Vasopressor therapy is initiated to restore perfusion to vital organs; however, in the presence of diminished myocardial contractility, it may further compromise cardiac output. Therefore, appropriate monitoring is indicated. While the medications listed in this section have vasopressor activity, dopamine and norepinephrine also have some inotropic activity and may increase heart rate and contractility as well.

Table 1 -Threshold heart rates and perfusion pressure MAP-CVP or MAP-IAP for age (modified from The Harriet Lane Handbook[12])

	Heart rate (bpm)	MAP-CVP (cm H_2O)
Threshold rates		
Term newborn	120-180 bpm	55
Up to 1 year	120-180 bpm	60
Up to 2 years	120-160 bpm	65
Up to 7 years	100-140 bpm	65
Up to 15 year	90-140 bpm	65

MAP-CVP = mean arterial pressure – central venous pressure; MAP-IAP = mean arterial pressure – intraabdominal pressure.

Dopamine

Dopamine is a precursor of norepinephrine in the adrenal medulla and a neurotransmitter in the central nervous system. Dopamine produces systemic hemodynamic effects that are dose-dependent; however, some effects are indirectly mediated by the release of norepinephrine from sympathetic vesicles. In adults, with infusion rates of less than 3 μg/kg/min, it induces the activation of primarily dopaminergic (DA) receptors. At doses of 3-5 μg/kg/min, dopamine activates DA (80-100%) and β-adrenergic receptors (5-20%), and at doses of 5-10 μg/kg/min, it activates predominantly β-receptors with a small amount of α-adrenergic receptor activation. At doses above 10 μg/kg/min α-adrenergic receptor activation predominates. Dopamine has been traditionally used as a first line medication for the support of circulation, and has been used in many types of critical illnesses as a non-specific support for splanchnic and renal blood flow. Recent evidence puts these practices into question.

Dopamine dose-related effects are unpredictable across the pediatric population; many clinicians prefer to titrate medications that independently and specifically address the abnormalities of cardiac output and systemic resistance. Examples of this hemodynamic strategy would be the administration of dobutamine and a nitrovasodilator to the patient with low cardiac output and elevated systemic resistance, or the administration of dobutamine and norepinephrine to the patient with diminished cardiac output and low SVR. Such a strategy circumvents the inherent difficulty in using medications that are agonists to a broad range of cardiovascular receptors in patients with variable and changing hemodynamic abnormalities.

Dopamine has also been administered in the hope of augmenting splanchnic and renal blood flow, and preventing progression of acute renal failure. There is no evidence to support this practice, and several large trials and meta-analyses indicate that this practice is of no benefit.[13] In addition to this, emerging evidence indicates that dopamine has several deleterious side effects that may negatively impact morbidity and mortality, including decreased oxygen consumption and gastric mucosal pHi in the gut despite increased splanchnic blood flow,[14] impairment of gastric motility,[15] blunting of hypoxic respiratory drive in mechanically ventilated patients,[16] impairment in ventilation /perfusion matching with worsening of hypoxemia,[17] impairment of anterior pituitary hormone secretion and cell-mediated immunity, and aggravation of impaired thyroid function seen in critical illness.[18] Finally, the use of dopamine and other indirect acting inotropes/vasopressors in preterm infants and infants less than 6 months of age may be less effective because of the immaturity of norepinephrine-containing synaptic vesicles in the sympathetic nervous system.[19] This constellation of side effects, lack of efficacy, and imprecise targeting of hemodynamic variables have led some clinicians to prefer norepinephrine to dopamine as their initial vasopressor of choice. Other clinicians prefer dopamine as their first choice based on many years of successful clinical experience in the setting of hypotension and/or low cardiac output. It is recommended to initiate dopamine at 5 μg/kg/min and titrate not to exceed 10 μg/kg/min.

Norepinephrine

Norepinephrine is a direct agent and is naturally produced in the adrenal gland. It is a potent vasopressor that redirects blood flow away from the skeletal muscle to the splanchnic circulation even in the presence of decreased cardiac output.

The majority of adult patients with SS present diminished SVR to some degree, which results in maldistribution of cardiac output and organ hypoperfusion. Close to 20% of children with volume-refractory SS have low SVR.[7] In children with SS receiving sedatives or analgesics, the incidence of low SVR may be higher, and norepinephrine infusion could be the drug of choice.

Norepinephrine has been used extensively to elevate SVR in septic adults and children. Because of the fear of excessive vasoconstriction, norepinephrine has historically been avoided. The available evidence, however, does not support this bias.[20] In doses beginning as low as 0.02 μg/kg/min, norepinephrine has been titrated upward to increase SVR, elevate diastolic blood pressure, and decrease pulse pressure. Several reports have described the ability of norepinephrine to restore hemodynamic stability in adequately volume-resuscitated patients refractory to therapy with dopamine. When compared with dopamine, resuscitation with norepinephrine is associated with more rapid resolution of lactic acidosis,[21] and animal data suggest that norepinephrine use exerts a protective effect on renal blood flow in SS.[22] Human studies have also demonstrated an improvement in urine output,[21] and no deleterious effects on splanchnic perfusion in SS.[23] One study on adult patients has even recognized a survival advantage among adult SS patients treated with norepinephrine when compared with other vasopressors.[24]

The use of norepinephrine avoids concerns over age-specific insensitivity to dopamine. However, safe and effective use of norepinephrine is predicated upon several presumptions. First, patients have been effectively volume-resuscitated, as this is the first and most important treatment for SS. Through the provision of adequate volume resuscitation, excessive doses of norepinephrine can be avoided and then minimize complications secondary to excessive vasoconstriction. Second, through clinical, laboratory, and/or invasive monitoring techniques, we are careful to ensure that adequate cardiac output is maintained.

Excessive norepinephrine administration in a patient who is inadequately volume-resuscitated may mislead the clinician into believing that a patient is hemodynamically stable when, in fact, vital organ perfusion is compromised. In patients with impaired contractility, the additional afterload imposed by norepinephrine may substantially compromise cardiac output. In some patients with both impaired or marginal cardiac output and decreased systemic resistance, it may be necessary to support myocardial contractility through the addition of an agent such as dobutamine.

Vasopressin

Vasopressin (antidiuretic hormone) is synthesized in the hypothalamus. Under normal conditions, blood levels are kept constant at concentrations largely regulated by serum osmolarity. Vasopressin is rapidly metabolized by the liver and kidney with a half-life of 10-30 minutes.[25] Vasopressin is also released in response to decreases in blood pressure with serum levels increasing more than ten-fold to improve blood pressure via vasoconstriction.[26] At low concentrations, catecholamines exert stimulatory effects upon vasopressin release via central α-1 receptors, but at higher levels, they may inhibit vasopressin release by stimulating α-2 and β receptors.[27] Hypoxia, acidosis, endotoxin, and cytokines stimulate vasopressin release; nitric oxide inhibits its secretion.[27]

The actions of vasopressin are mediated by G-protein coupled receptors that are classified as V_1, V_2, V_3, and oxytocin receptors (OTR). V_1 receptors are located in vascular smooth muscle cells in the systemic, splanchnic, renal, and coronary circulations. Activation of V_1 receptors results in increased intracellular calcium concentrations, smooth muscle contraction, and vasoconstriction.[27] V_2 receptors mediate the antidiuretic actions of vasopressin in the nephron, and V_3 receptors play a role in secondary messaging in the anterior pituitary gland. OTR are located in the myometrium and mammary myoepithelial cells, where they mediate smooth muscle contraction, and are present on the surface of endothelial cells, where activation leads to increased endothelial cell calcium concentrations, activation of nitric oxide synthase, and elaboration of nitric oxide resulting in vasodilation.[27]

Patients with severe sepsis are very sensitive to exogenous administration of vasopressin.[28] In acute SS, an early ten-fold increase in vasopressin levels is noted. However, after more prolonged shock, vasopressin levels fall toward normal, resulting in relative vasopressin deficiency.[28,29] The cause of diminished vasopressin levels in sepsis may be related to impaired osmoregulation or impaired baroregulation, or to the inhibitory effects of increased nitric oxide on vasopressin release, both of which are conditions associated with severe sepsis.[27]

Exogenous administration of vasopressin produces blood pressure elevation in patients with SS, whereas it produces no pressor response in healthy patients. The mechanism for this exaggerated sensitivity to vasopressin is not clear.

In patients with catecholamine-refractory SS and elevated cardiac output with low systemic resistance, vasopressin is initiated in low doses and titrated to the desired clinical effect. In patients with persistent vasodilation unresponsive to catecholamines, vasopressin may be effective in restoring SVR and blood pressure.

In a personal note, we have used vasopressin in SS refractory to norepinephrine (> 1 µg/kg/min) despite adequate fluid resuscitation and corticosteroids. Vasopressin was titrated until a positive response was observed, and subsequently, norepinephrine infusion was amenable to be reduced. Hyponatremia is a common side effect that is generally observed after 24 h of drug infusion.

Vasopressin is a potent vasoconstrictor and may precipitate coronary, mesenteric, and cutaneous ischemia in high doses. There is evidence to suggest that vasopressin may produce neutral or beneficial effects on renal blood flow and urine output.[30] It is prudent to monitor cardiac output when initiating and titrating therapy with potent vasoconstrictors in patients with marginal cardiac output and diminished myocardial contractility. Addition of inotropic support in patients with decreased cardiac output may be required.

Inotropes

Inotropic medications are used to improve cardiac output in patients with diminished myocardial contractility. They are often administered concomitantly with vasopressors in patients with diminished SVR or with a vasodilator in patients with elevated systemic resistance. Milrinone and dobutamine possess some vasodilatory properties and decrease afterload while improving the contractile state of the myocardium. Epinephrine, depending upon the dose administered, may produce decrease in systemic resistance at low doses, or may elevate systemic resistance at higher doses, while increasing myocardial contractility. Dobutamine and epinephrine can increase myocardial oxygen consumption and may produce varying degrees of dysrhythmias and myocardial ischemia.

Epinephrine

Epinephrine is a direct agent that is naturally produced in the adrenal gland and the principal stress hormone with widespread metabolic and hemodynamic effects. Epinephrine is a naturally occurring catecholamine that possesses potent inotropic and chronotropic effects. Epinephrine infusions may be initiated at doses of 0.02 µg/kg/min and titrated upward (up to 1.0 µg/kg/min) to achieve the desired clinical response. Epinephrine is ideally administered through

a central venous catheter, but can be administered through an intraosseous needle or peripheral intravenous catheter until central access is achieved. Subcutaneous infiltration of epinephrine may result in soft tissue necrosis, which may be antagonized by subcutaneous infiltration with phentolamine.

Epinephrine is a reasonable selection for the treatment of patients with low cardiac output and poor peripheral perfusion as it increases heart rate and myocardial contractility.[31] Depending on the dose administered, epinephrine may exert variable effects on SVR. At low doses (generally considered to be < 0.3 µg/kg/min) epinephrine exerts greater β-2 adrenergic receptor activation, resulting in vasodilation in skeletal muscle and cutaneous vascular beds, shunting the blood flow away from the splanchnic circulation.[32] At higher doses, α-1 adrenergic receptor activation becomes more prominent and may increase SVR and heart rate. For patients with markedly elevated systemic resistance, epinephrine may be administered simultaneously with a vasodilator.

Adult patients have been noted to exhibit decreased intestinal mucosal pH in response to epinephrine infusion, but it is not known whether gut injury occurs in septic children receiving epinephrine infusions.[32] Epinephrine increases gluconeogenesis and glycogenolysis resulting in elevated serum glucose concentrations. As a side effect of gluconeogenesis stimulation, the skeletal muscle releases more lactic acid to be transported to the liver for glucose synthesis (the Cori cycle). As such, patients receiving epinephrine may demonstrate elevated lactic acid concentrations independent of any changes in organ perfusion. Thus, serum lactate concentrations must be followed closely while initiating epinephrine therapy as they may not strictly reflect oxygen supply-demand balance.[33]

Dobutamine

Dobutamine is a synthetic agonist with a complex stimulation of β-1, β-2, α-1 and α-2 adrenergic receptors directly or through a metabolite. Dobutamine increases myocardial contractility and heart rate. Dobutamine lowers systemic resistance in part by reflex withdrawal of sympathetic tone. This hypotensive effect is pronounced and seems to be more often observed in adult patients than in small children. Dobutamine is considered for patients with diminished cardiac output when accompanied with elevated SVR.[34] It is administered by continuous infusion of 3-20 µg/kg/min. In the setting of diminished contractility and output and diminished systemic resistance, dobutamine has been administered along with norepinephrine in order to normalize both indices of hemodynamic function.[35] Of significant interest, dobutamine at 5 µg/kg/min seems to increase splanchnic blood flow by a direct effect on the microvasculature, independent of increasing cardiac output.[36] A significant drop in blood pressure, unacceptable tachycardia, increased myocardial oxygen consumption, and atrial and ventricular dysrhythmias are undesirable potential side effects.

Milrinone

Milrinone is a phosphodiesterase type III (PDE III) inhibitor that produces its hemodynamic effects by inhibiting the degradation of cyclic AMP in smooth muscle cells and cardiac myocytes. PDE III inhibitors therefore work synergistically with catecholamines, which produce their hemodynamic effects by increasing the production of cyclic AMP. Milrinone is useful in the treatment of patients with diminished myocardial contractility and output and elevated SVR as it mediates increased contractility and output, and decreases systemic resistance.[37] Additionally, milrinone mediates its effects through mechanisms independent of adrenergic receptors and is not affected by the down-regulation and desensitization of these adrenergic receptors.

As a vasodilator, milrinone administration may result in decreased systemic blood pressure, and it may be necessary to administer volume infusion in order to correct or prevent hypotension. Milrinone has a long half-life of 2-6 hours, and as such, it may take several hours to reach steady state serum concentrations. In order to achieve rapid serum levels, some clinicians administer a loading bolus of 50 µg/kg over 10-30 minutes. This must be done with caution in patients with sepsis and shock as this may precipitate hypotension, requiring volume infusion and/or vasopressor infusion. Some clinicians divide the loading dose into a series of "mini-loads" which are given over a more prolonged period of time to minimize hypotension and test the patient's ability to tolerate the loading dose. The infusion dose of milrinone is 0.25-0.75 µg/kg/min. Because of its long half-life, it is advisable to stop milrinone infusion if serious side effects such as dysrhythmia, hypotension, or excessive vasodilation occur. Additionally, because milrinone is predominantly excreted in the urine, dosage may need to be adjusted in response to deteriorating renal function in order to avoid toxicity.

Vasodilators

Vasodilator medications are occasionally required in the treatment of septic pediatric patients with markedly elevated systemic resistance and normal or decreased cardiac output. Vasodilators decrease SVR and improve cardiac output by decreasing ventricular afterload. Some authors suggest the use of nitroprusside as first line vasodilator due to its short half life, because in case of hypotension, it could be rapidly reversed after the infusion is interrupted. Nitroprusside is infused at an initial rate of 0.5 µg/kg/min to a maximum dose of 10 µg/kg/min. It is necessary to observe for toxicity unique

to sodium nitroprusside, which includes sodium thiocyanate accumulation in the setting of renal failure, and cyanide toxicity with prolonged high-dose infusions. Other clinicians utilize milrinone as a vasodilator in situations of: a) refractory SS with profound myocardial dysfunction or high SVR; and b) pulmonary complications and suspectedly high pulmonary vascular resistance – acute respiratory distress syndrome (ARDS) or refractory hypoxemia.

Other drugs

Rescue from refractory shock has been described using two newer medications that share PDE activity. Levosimendan increases calcium sensitivity of the contractile apparatus, and exerts some type III PDE inhibitor activity. Enoximone is also a type III PDE inhibitor with more selectivity for the preservation of cyclic AMP produced by β-1 receptor activation in myocardial cells, and hence it improves cardiac performance with less risk of undesired hypotension.

Fenoldopam is a selective postsynaptic dopamine (D_1) agonist utilized to prevent renal failure in shock. Fenoldopam decreases peripheral SVR with increased renal and splanchnic blood flow. It is six times as potent as dopamine in producing renal vasodilation. Fenoldopam is infused at a dose between of 0.1-1 μg/kg^{-}/min.[38]

Thyroid dysfunction should be considered in the presence of individuals with abnormal chromosome 21, central nervous system diseases and pan-hypopituitary states. If T4 and T3 serum hormones are low, oral thyroxin (or intravenous liothyronine) should be administered. Some authors have described improvement in myocardial function after thyroid hormone supplementation in SS.

Corticosteroids

Stress dose of corticosteroids may have an indication in a selected patient population. Children are more likely to have absolute adrenal insufficiency defined by a basal cortisol < 7 μg/dL and/or an increment after adrenocorticotropic hormone (ACTH) stimulation < 18 μg/dL. Patients at risk of inadequate cortisol production include those with *purpura fulminans*, children who have previously received steroid therapies for chronic illness, and patients with pituitary or adrenal abnormalities.[39] Currently, ACTH stimulation test is recommended to be performed with 1 μg of intravenous corticotrophin instead of the high dose of 250 μg, which can mask adrenal insufficiency.[40]

The unresponsiveness to vasoactive agents observed during catecholamine-resistant SS is sometimes reversed by the administration of hydrocortisone.[41] The hydrocortisone dose should be titrated to the resolution of shock: 2-30 mg/kg/day divided every 6 h or 1-2 mg/kg/h as a continuous infusion. Corticosteroids should be weaned off after the resolution of SS, but maintained for a minimum of 5 to 7 days.

A syndrome of relative adrenal insufficiency (or dysfunction) has been described (baseline cortisol > 18 μg/dL with cortisol increment after ACTH stimulation < 9 μg/dL). The administration of prolonged hydrocortisone and fludrocortisone (6 mg/kg/d cortisol equivalent x 7 days) is recommended for adults with relative adrenal insufficiency. This practice is customary in some pediatric centers, but there are not enough data to recommend steroid therapy for adrenal dysfunction in the pediatric population.[42]

Glycemic control

Several studies have associated hyperglycemia with higher mortality among critically ill patients. Hyperglycemia is attributed to the peripheral resistance to insulin and increased gluconeogenesis. Peripheral resistance to insulin is proportional to the length and severity of the diseases and closely associated with the outcome.

A strict glycemic control, between 80-110 mg/dL, decreases mortality and morbidity in adult surgical patients.[43] Retrospective studies involving children seem to demonstrate similar results. However, it is challenging to maintain this strict control in pediatrics without hypoglycemic events; so a more liberal approach is often practiced. Glucose levels and the length of hyperglycemia are independently associated with mortality.[44] A higher mortality rate was associated with glucose above 178 mg/dL (odds ratio = 2.6) in one pediatric study.[45]

Pulmonary hypertension

Although inhaled nitric oxide therapy is the treatment of choice for uncomplicated persistent pulmonary hypertension of the newborn (PPHN), metabolic alkalinization remains an important initial resuscitative strategy during shock in neonates. PPHN in the setting of SS can be reversed when acidosis is corrected. For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in the reversal of PPHN. Extracorporeal membrane oxygenation (ECMO) remains the therapy of choice for patients with refractory PPHN and sepsis.[1]

ECMO is a viable therapy for refractory shock in neonates and children. It is important to remember that neonates could be exceedingly sensitive to hypocalcemia, hypoglycemia or the lack of thyroid hormone.[1]

Conclusions

The outcome of sepsis and SS is in part dependent on the implementation of time-sensitive goal-directed therapies. Early recognition of SS is paramount to the initiation of rapid

aggressive fluid resuscitation, followed by a well-designed pharmacotherapy. The goals of resuscitation are geared toward the restoration of microcirculation and improvement of organ tissue perfusion. Clinical and laboratory markers are needed to assess the adequacy of treatment. Altered pharmacokinetic and pharmacodynamic responses dictate that vasoactive agents should be adjusted to achieve the predetermined goals. SS hemodynamics is a changing process that requires frequent assessment and therapy adjustments. Adjunctive therapy with corticosteroids is indicated in selected cases. Treatment during the initial hours affects the outcome weeks later.

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