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José Irazuzt, Kevin J. Sullivan

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REVIEW ARTICLE

Current Opinions in Pediatric Septic Shock

José Irazuzta[1], Kevin J. Sullivan[2]

Abstract:
Objectives: Our aim is to describe the current clinical practice related to the management of septic shock (SS).
Methods: Review of medical literature using the MEDLINE database. Articles were selected according to their relevancy to the objective and according to the author's opinion.
Summary of the findings: The outcome from SS is dependent on an early recognition and a sequential implementation of time-sensitive goal-directed therapies. The goals of the resuscitation are rapid restoration of micro circulation and improved organ tissue perfusion. Clinical and laboratory markers are needed to assess the adequacy of the treatments. Initial resuscitation involves the use of isotonic solutions (>60ml/kg) either crystalloid (normal saline) or colloid infusion often followed by vasoactive medications. Altered pharmacokinetics and pharmacodynamics responses dictate that vasoactive agents should be adjusted to achieve predetermined goals. An assessment of central venous pressure complements clinical and serological findings to tailor therapies. Elective airway instrumentation and mechanical ventilation as well as adjunctive therapy with stress dose of corticosteroid are indicated in selected populations. In neonates, a special attention to the presence of electrolyte imbalance and increase pulmonary vascular resistance needs to be considered early.
Conclusions: Septic shock hemodynamic is a changing process that requires frequent assessment and therapeutic adjustments.

Key words: *septic shock, pediatric intensive care, fluid resuscitation, hemodynamic support, corticosteroids*
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Introduction

Aggressive fluid resuscitation and implementation of time-sensitive goal-directed therapies.[1-4] has produced a significant improvement in the outcome of septic shock (SS). Early diagnosis is paramount to initiate therapy. Septic shock 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 / hr). A wide pulse pressure (diastolic blood 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 are needed [5]. Inadequate early resuscitation results in multiple organ system failure and 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 tissue oxygen supply is inadequate to meet metabolic demands and there is a maldistribution of cardiac output with increased blood flow to skeletal

José Irazuzta[1], MD. and Kevin J. Sullivan, MD[1,2]
[1] Division of Pediatric Critical Care Medicine, University of Florida Health Science Center, Jacksonville, Florida, (USA)
[2] Department of Pediatric Anesthesia and Critical Care Medicine, Nemours Children's Clinic, Jacksonville, Florida (USA)

Corresponding Author: Jose Irazuzta, MD
Division of Pediatric Critical Care Medicine
Wolfson Children's Hospital, Third Floor
800 Prudential Drive
Jacksonville, FL 32207
Phone: (904) 202 – 8758
E-mail: jose.irazuzta@jax.ufl.edu

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muscles at 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.

Classification

Septic shock is classified as fluid sensitive SS, fluid refractory SS (fail to improve with adequate volume resuscitation), catecholamine resistant SS (fail to improve with fluids and catecholamines), and refractory SS (fail to improve with fluid, catecholamines and vasodilators). Septic shock is a dynamic process, vasoactive medications and their infusion dose may have to be changed and adjusted over time to maintain adequate organ perfusion. 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 (chronotopes). Age of the patient and changes in the perfusion of liver and kidney affects the pharmacokinetics of vasoactive medications (available drug in serum). The pharmacodynamics 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

Fluid Management

Initial resuscitation of infants and children centers on the repeated administration of isotonic solutions in quantities of 20 ml/kg over five minutes while monitoring the patient's clinical response to treatment. There is no data that confirms the superiority of either crystalloid (normal saline) or colloid (albumin or heterostarch) in children. Patients suffer from effective 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 increase incidence of acute respiratory distress syndrome (ARDS or non-hydrostatic pulmonary edema) [7]. During and after each fluid challenge a clinical evaluation of the patient's response to treatment is noted. Clinical evidence of positive response includes increase strength of peripheral pulses, warmth of extremities, decrease pulse rate, narrowing and normalization of blood pressure, improvements in mental status, and later on of urine output. Often 60 ml/kg of fluid is administered on the initial 20 minutes.

Assessment of Fluid Management

Almost invariably there is a pervasive hypovolemia. Invasive monitoring of central venous pressure (CVP) is instituted as soon as possible to achieve the goals of an appropriate fluid resuscitation and to ensure that an adequate right ventricular preload is present (CVP = 10 – 12 cm H2O). Repeated fluid boluses are needed trough the initial 24 hrs to maintain the CVP goals.

In the presence of respiratory distress, an elective tracheal intubation followed by mechanical ventilation, will contribute to redistribute 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. Ketamine is often utilized for invasive procedure as it maintains systemic vascular resistance. [1]

Tissue Oxygen Delivery

If despite these measures the patient continues to have incomplete response to resuscitation it is necessary to institute pharmacologic therapy to support the circulation. It is often necessary, in patients who present with unstable hemodynamics (i.e.: low heart rate, low cardiac output) to begin treatment with vasoactive/inotropic medications concomitantly with the initiation of fluid resuscitation. This one should be initiated on a peripheral venous access if no central venous access is available. 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.

Unfortunately, clinical response to fluid resuscitation or hemodynamic support is a relatively insensitive indicator of the completeness of restoration of microvascular blood flow. The oxygen saturation of the superior vena cava (SVC 02) (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 02 (> 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. In pediatrics it is sometimes difficult to obtain rapid access on the superior vena cava.

Patients may require optimization of oxygen carrying capacity by transfusion of packed red blood cells to correct anemia. A commonly accepted target is to reach a hemoglobin concentration > 10 grams / deciliter. Hypoglycemia or hypocalcemia needs to be rapidly corrected to have a stable hemodynamic function.

Hemodynamics in Pediatric Septic Shock

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 Systemic vascular resistance (SVR) and elevated cardiac 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. After volume-loading, the 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 dysfunction necessitating the use of vasopressors and inotropic support [7]. The heterogeneity and changing pattern of the hemodynamic presentation, during the initial hours, dictates that an incorrect cardiotonic/vasoactive regimen should be suspected when there is unresponsiveness to fluid therapy and 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. Additionally, the increased connective tissue content of the infant heart and diminished content of actin and myosin limits the potential for acute ventricular dilatation [11].

Pharmacologic Agents for the Support of Pediatric Septic Shock

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 the 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 either 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 the circulation in patients with sepsis and shock includes 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 is 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

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.

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 indirect mediated by the release of norepinephrine from sympathetic vesicles. In adults, with infusion rates of less than 3 ug/kg/min induce activation of primarily dopaminergic (DA) receptors. At doses of 3-5 ug/kg/min dopamine activates DA (80-100%) and β – adrenergic receptors (5-20%), and at doses of 5-10 ug/kg/min activates predominantly β-receptors with a small amount of α-adrenergic receptor activation. At doses above 10 ug/kg/min α-adrenergic receptor activation predominates. Dopamine has been traditionally used as a first line medication for the support of the circulation, and has been used in many types of critical illness as a non-specific support for splanchnic and renal blood flow. Recent evidence calls 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 without benefit [12]. 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 [13], impairment of gastric motility [14], blunting of hypoxic respiratory drive in mechanically ventilated patients [15], impairment in ventilation / perfusion matching with worsening hypoxemia [16], impairment of anterior pituitary hormone secretion and cell-mediated immunity, and aggravation of impaired thyroid function seen in critical illness [17]. Finally, the use of dopamine and other indirect acting inotropes/vasopressors in preterm infants and infants less than six months of age may be less effective because of immaturity of norepinephrine containing synaptic vesicles in the sympathetic nervous system [18]. This constellation of negative side effects, lack of efficacy, and imprecise targeting of hemodynamic variables has 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 mcg/kg/min and titrate not to exceed 10 mcg/kg/min.

Norepinephrine

Norepinephrine is a direct agent that does not require intermediaries and is naturally produced in the adrenal gland. It is a potent vasoppresor 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 infusion the incidence of low SVR may be higher.

Norepinephrine has been used extensively to elevate SVR in septic adults and children. Because of fear of excessive vasoconstriction norepinephrine has historically been avoided. The available evidence, however, does not support this bias [19]. In doses beginning as low as 0.02 mcg/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 [20], and animal data suggests that norepinephrine use exerts a protective effect on renal blood flow in SS [21]. Human studies have also demonstrated an improvement in urine output [20], and no deleterious effects on splanchnic perfusion in SS [22]. One study on adult patients has even recognized a survival advantage among adult SS patients treated with

norepinephrine when compared with other vasopressors [23].

Thus, despite traditional role of dopamine, we recognize the value of norepinephrine in patients refractory to dopamine, and often use norepinephrine as our first line vasopressor instead of dopamine. 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 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 give the clinician the appearance of a patient with stable hemodynamics 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 liver and kidney with a half-life of 10 – 30 minutes [24]. 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 [25]. At low concentrations catecholamines exert stimulatory effects upon vasopressin release via central α1 receptors, but at higher levels may inhibit vasopressin release by stimulating α2 and β receptors [26]. Hypoxia, acidosis, endotoxin, and cytokines stimulate vasopressin release; nitric oxide inhibits its secretion [26].

The actions of vasopressin are mediated by G-protein coupled receptors that are classified as V1, V2, V3, and oxytocin receptors (OTR).V1 receptors are located on vascular smooth muscle cells in the systemic, splanchnic, renal, and coronary circulations. Activation of V1 receptors results in increased intracellular calcium concentrations, smooth muscle contraction, and vasoconstriction [26]. V2 receptors mediate the antidiuretic actions of vasopressin in the nephron, and V3 receptors play a role in secondary messaging in the anterior pituitary gland. Oxytocin receptors 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 NO resulting in vasodilation [26].

Patients with severe sepsis could be very sensitive to exogenous administration of vasopressin [27] at a dose range between 0.0003-0.002 Units/k/min.

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 a relative vasopressin deficiency [27, 28]. The cause of diminished vasopressin levels in sepsis may be related to impaired osmoregulation or impaired baroregulation, the inhibitory effects of increased NO on vasopressin release, both of which are conditions associated with severe sepsis [26].

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 catecholamines refractory SS and elevated cardiac output with low systemic resistance, vasopressin is initiated in low doses and titrated to desired clinical effect. In patients with persistent vasodilation unresponsive to catecholamines, vasopressin may be effective in restoring SVR and blood pressure. 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 [29]. As with norepinephrine use, it is prudent in patients with marginal cardiac output and diminished myocardial contractility to monitor cardiac output when initiating and titrating therapy with potent vasoconstrictors. Addition of inotropic support in patients with decreased cardiac output may be required. The dose range is between 0.0003-0.002 Units/kg/min.

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 a vasodilator in patients with elevated systemic resistance. Milrinone and dobutamine possess some vasodilatory properties and decrease afterload while improving 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 to varying degrees may produce dysrrhythmias 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 ug/kg/min and titrated upward (up to 1.0 mcg/kg/min) to achieve the desired clinical response. Epinephrine is ideally administered through a central venous catheter, but can be administered through an intra-osseous needle or peripheral intravenous catheter until central access is achieved. Subcutaneous infiltration of epinephrine may result in soft tissue necrosis that 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 [30]. Depending on the dose administered, epinephrine may exert variable effects on SVR. At low doses (generally considered to be < 0.3 ug/kg/min) epinephrine exerts greater β-2 adrenergic receptor activation resulting in vasodilation in skeletal muscle and cutaneous vascular beds resulting in shunting of blood flow away from the splanchnic circulation [31]. 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 [31]. Epinephrine increases gluconeogenesis and glycogenolysis resulting in elevated serum glucose concentrations. As a side effect of gluconeogenesis stimulation, skeletal muscle liberated 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 [32].

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 [33]. It is administered by continuous infusion of 3-20 ug/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 [34]. Of significant interest dobutamine at 5 ug/kg/min seems to increase splanchnic blood flow by a direct effect in the microvasculature independent of increasing cardiac output. [35] A significant drop in blood pressure, unacceptable tachycardia, increased myocardial oxygen consumption, atrial and ventricular dysrrhythmias 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 [36]. Additionally, milrinone mediates its effects through mechanisms independent of adrenergic receptors and are not affected by 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 with initiation of the infusion in order to correct or prevent hypotension. Milrinone has a long half-life of 2-6 hours, and as such 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 ug/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 a 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 ug/kg/min. Because of its long half-life, it is advisable to stop milrinone infusion if serious side effects such as dysrrhythmia, 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 starting nitroprusside as first line vasodilator due to its short half life, where in case of hypotension this one could be rapidly reversed after the infusion is interrupted. Nitroprusside is infused at an initial rate of 0.5 mcg/kg/min to a maximal dose of 10 mcg/kg/min. It is necessary to observe for toxicity unique to sodium nitroprusside which include sodium thiocyanate accumulation in the setting of renal failure, and cyanide toxicity with prolonged high-dose infusions. Other clinicians utilize milrinone as vasodilator in situations of: a) refractory SS with profound myocardial dysfunction or high SVR; and b) patients pulmonary complications and suspected higher 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 improves cardiac performance with less risk of undesired hypotension.

Fenoldopam is a selective post-synaptic dopamine (D1) 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 ug/kg-/min [37].

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 IV triiodothyronine) 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 selected patient population. Children are more likely to have absolute adrenal insufficiency defined by a basal cortisol < 7 mcg/dL and/or an increment after ACTH stimulation < 18 mcg/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 [38]. Currently, adrenocorticotropic hormone stimulation test (ACTH) is recommended to be performed with 1 mcg of IV corticotrophin instead of the high dose of 250 mcg which can mask adrenal insufficiency [39].

The unresponsiveness to vasoagents observed during catecholamine resistant SS is sometimes reversed by the administration of hydrocortisone (40). The hydrocortisone dose should be titrated to resolution of shock. 2 to 30 mg/kg/day divided every 6 hrs or 1 to 2 mg/kg/hr 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) have been described (basal cortisol > 18 mcg/dL with cortisol increment after ACTH stimulation < 9 mcg/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 is no enough data to recommend steroid therapy for adrenal dysfunction in the pediatric population [41].

Pulmonary Hypertension

Although inhaled nitric oxide therapy is the treatment of choice for uncomplicated PPHN, metabolic alkalinization remains an important initial resuscitative strategy during shock in neonates. PPHN in the setting of SS can reverse when acidosis is corrected. For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in reversal of PPHN. ECMO remains the therapy of choice for patients with

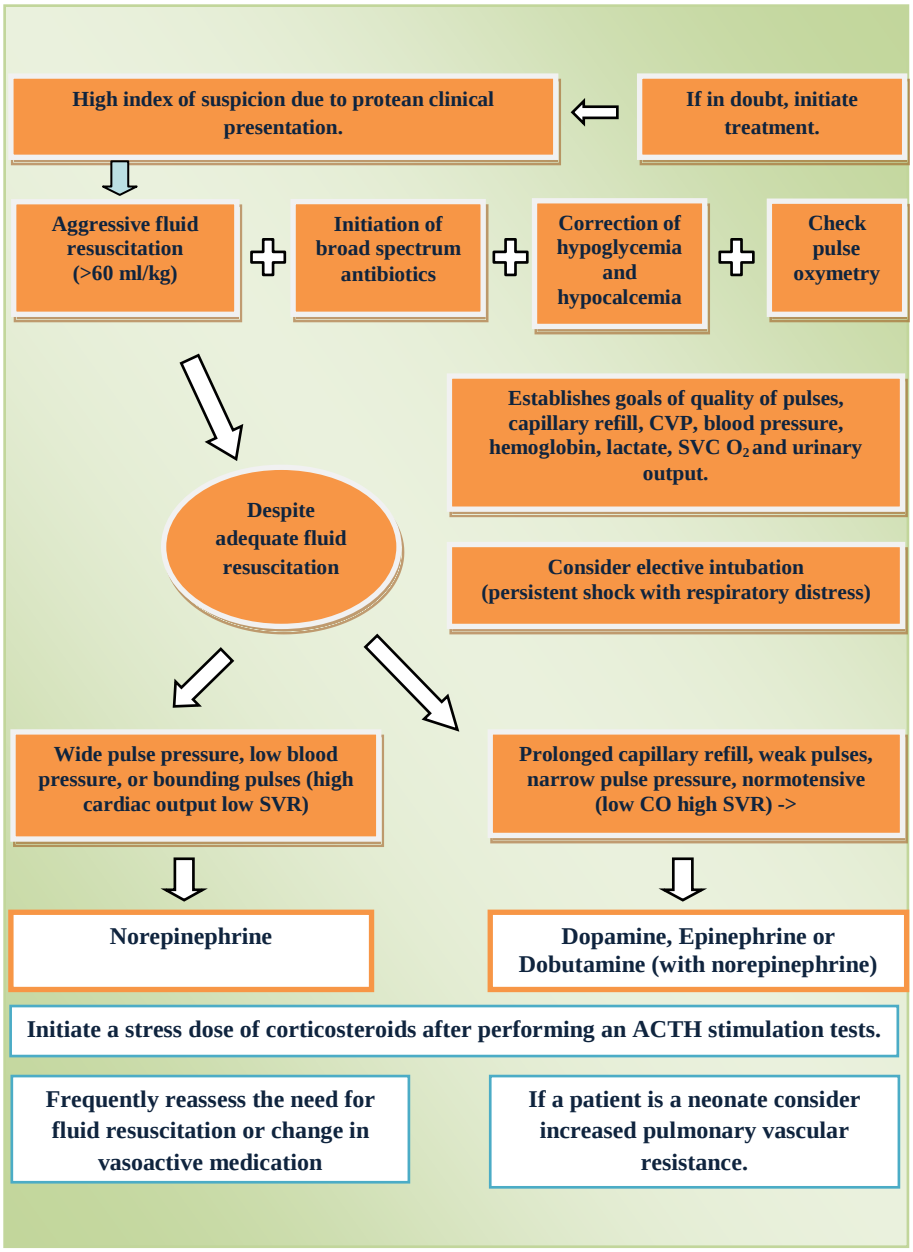

Figure 1. Septic shock: Simplified initial management

refractory PPHN and sepsis [1].

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

Conclusions

The outcome from sepsis and septic is in part dependent on the implementation of time-sensitive goal-directed therapies. Early recognition of SS is paramount to be able to initiate a rapid aggressive fluid resuscitation followed by an organized pharmacotherapy. The goals of the resuscitation are geared toward restoration of micro circulation and improved organ tissue perfusion, clinical and laboratory markers are needed to assess adequacy of treatment. Altered pharmacokinetics and pharmacodynamics responses dictate that vasoactive agents should be adjusted to achieve predetermined goals. Septic shock hemodynamic is a changing

process that requires frequent assessment and therapy adjustments. Adjunctive therapy with corticosteroids is indicated in selected cases. The treatment of the initial hours affects the outcome weeks later.

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