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SYMPOSIUM ON PICU PROTOCOLS OF AIIMS

Management of Septic Shock

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Abstract Septic shock is an important cause of mortality in children with sepsis. The incidence of septic shock is 2–4% of admissions in western pediatric intensive care units and 40%–67% for Indian PICUs. Early goal-directed resuscitation that includes aggressive fluid resuscitation of up to 60 mL/kg as boluses of 20 mL/kg by IV push, to achieve desired heart rates and blood pressure, has emerged as mainstay of treatment in the initial stage. Crystalloids are the preferred fluids, while colloids may be used in some situations. Fluid refractory shock warrants use of vasoactive drugs. Dopamine is the first choice. Dobutamine and low dose epinephrine are the preferred inotropic drugs while nor-epinephrine is a vasopressor. Children with cold shock and normal blood pressure may benefit from nitrosodilators like nitroprusside and nitroglycerine. Inodilators such as milrinone are also useful in this situation. Targeting clinical therapeutic end-points assists the management. Good supportive care is also essential for improving the outcomes.

Keywords Fluids · Goal directed treatment · Septic shock · Vasoactive drugs

Introduction

Severe sepsis and septic shock are the two major causes of death in children with sepsis. Severe sepsis is defined as sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions [1]. Septic shock in a child with sepsis is defined by the presence of: 1) Hypotension (systolic BP <70 mm Hg in infant; <70 +2 × age after one year of age) OR 2) Need for vasoactive drug to maintain BP above 5th centile range (dopamine >5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) OR 3) Signs of hypoperfusion- any three of the following: decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time >3 s, tachycardia, core (rectal/oral) to peripheral (skin-toe) temperature gap >3°C, and urine output <1 mL/kg/h (<20 mL/h in >20 kg child) OR 4) Sepsis and cardiovascular organ dysfunction.

The reported incidence of severe sepsis and septic shock is relatively low in children admitted in the western pediatric intensive care units (usually 2 to 4%) [2, 3], the figures are much higher (40%–67%) for Indian PICUs [4, 5]. The reported mortality rates are about 10% for children with severe sepsis and about 50% for children with septic shock [2, 5, 6]. Such high mortality rates highlight the need to diagnose severe sepsis and septic shock early and institute a comprehensive management strategy to improve the outcomes.

Unlike adults, low cardiac output and not low systemic vascular resistance (vasomotor paralysis), is associated with mortality in pediatric septic shock [7, 8]. In a study by Ceneviva et al., most children (almost 60%) had low cardiac output and high systemic vascular resistance (*Cold shock)* at presentation [9]. These differences in the pathophysiology necessitate specific guidelines for management of septic shock in pediatric patients which are distinct from the adult guidelines.

Recently, consensus guidelines for the management of severe sepsis and septic shock were published [10]. These guidelines have been adapted to low-resource settings [11]. The protocol presented here is based on these guidelines [10, 11].

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Early Recognition of Septic Shock

The first hours following the diagnosis of severe sepsis and septic shock are known as the "**golden hours**" as it is during this period that aggressive hemodynamic resuscitation has been shown to be associated with higher survival rates and reduced organ dysfunctions [12, 13]. After the "golden hours", aggressive hemodynamic resuscitation is no longer effective in restoring the organ function or in decreasing the mortality [14]. In an Indian pediatric hospital, there was a 9-fold increase in the odds for survival if shock was corrected in the emergency department [15].

The major cause of loss of 'golden hours' in our country may be due to the three major delays: delay in recognition, delay is transport and delay in initiating treatment. The clinical diagnosis of early septic shock is possible with presence of the following in a setting of suspected infection: hypothermia or hyperthermia along with clinical signs of decreased perfusion, including decreased mental status, prolonged capillary refill time of >2 s or flash capillary refill, diminished or bounding peripheral pulses, mottled cool extremities, or decreased urine output of <1 ml/kg/h. Blood pressure, a hemodynamic variable, drops only in late shock and should not be relied on to make the diagnosis; however, its presence in a child with clinical suspicion of infection is confirmatory. The shock may further be classified as: *Cold shock*: characterized by decreased perfusion including decreased mental status, decreased urine output, *capillary refill >2 s, diminished peripheral pulses and mottled cool extremities. Warm shock*: is characterized by decreased perfusion including decreased mental status, decreased urine output, and *flash capillary refill and bounding peripheral pulses.*

Principles of Management

Initial Treatment of Child with Suspected Septic Shock

The concept of *'Early goal-directed resuscitation'* has emerged as a life saving strategy. This includes aggressive fluid resuscitation of up to 60 mL/kg as boluses of 20 mL/kg (Table 1) by IV push to achieve desired heart rate and blood pressure. This strategy is a relatively inexpensive and feasible intervention, but is underutilized. A possibility of fluid overload, specifically in malnourished children, may be overcome by intensive clinical monitoring.

If a patient does not respond to aggressive fluid therapy, vasoactive drugs should be started. Dopamine is recommended as the first line agent in children who are in shock despite fluid resuscitation (60 mL/kg). Dobutamine is to be used as the first choice in children with normal BP and low cardiac output (cold shock), as indicated by poor peripheral perfusion.

It is desirable that all children with suspected septic shock be managed in Intensive care setting.

Choice of Fluid for Volume Replacement

The use of isotonic crystalloid such as Ringers Lactate or Normal saline is recommended for the initial fluid resuscitation in septic shock as they are readily available, convenient to use, free of side-effects, and are rapidly distributed across intravascular and interstitial spaces. Higher volume of crystalloids in comparison to colloids may be required for similar degree of volume expansion, and the effect may be transient due to leak in the interstitial space. Colloids (starch, gelatins) produce greater and more sustained increase in plasma volume, but they may not be readily available. Fresh frozen plasma, that is frequently used in patients with disseminated intravascular coagulation to supplement clotting factors should not be used as a resuscitation fluid.

Large RCTs and systematic reviews do not suggest any major survival benefits with the use of the colloids [16, 17]. Pediatric studies suggest equal effectiveness of normal saline degraded gelatin solution in septic shock; though higher volumes of saline were required [18].

Method of Fluid Administration

For the initial volume expansion, it is suggested that boluses of 20 mL/kg be administered over 10–15 min.This may be achieved by gravity method or by push-pull method using a 3-way stop-cock. In one study from Chennai, administration of large volume of fluids by pull push

Table 1 Therapeutic endpoints of resuscitation of septic shock

- Normalization of the heart rate
- Capillary refill of ≤2 s
- Well felt dorsalis pedis pulses with no differential between peripheral and central pulses
- Warm extremities
- Normal range of systolic pressure and pulse pressure
- Urine output >1 mL/kg/h, and
- Return to baseline mental status tone and posture.
- Normal range respiratory rate.

Other end points that have been widely used in adults and may logically apply to children include central venous pressure of 8–12 mmHg and mean arterial pressure (MAP)

method using a 3 way stop-cock increased the incidence of hepatomegaly and showed a trend towards a greater need for intubation [19]; this suggests need for caution with rapid administration of fluids in a setting without universal access to ventilator support. This study also did not observe faster resolution of shock in the fast infusion group [15].

Practical ways to assess fluid overload are jugular venous distension, increasing liver span, signs of pulmonary edema and pulmonary congestion on chest radiograph. Measurement of central venous pressure (CVP) and bedside echocardiography should be used at tertiary care centers, if available to assess adequacy of intravascular volume, cardiac function and signs of fluid overload.

Achievement of all therapeutic goals is needed to define shock resolution in fluid and inotrope responsive shock [15]. Discontinuing fluid therapy, based on achievement of some and not all the goals results in inadequate resuscitation.

Management in Intensive Care Setting

In case of fluid refractory shock, central venous line should be inserted and vasoactive drugs like dopamine or dobutamine be started based on the hemodynamic profile at that time.

In case of shock refractory to dopamine or dobutamine, epinephrine or nor-epinephrine can be used depending on whether the child has cold shock or warm shock, respectively. If there is no response to the above catecholamines, then $ScvO_2$ [20] (requires central venous catheter placement in the superior vena cava) can be monitored apart from clinical and hemodynamic variables and vasodilators/Phosphodiesterase (PDE) inhibitors can be added in children with normal blood pressure and cold shock with $ScvO_2$ <70%. In children with low blood pressure, either epinephrine or nor-epinephrine can be titrated depending on whether the child has cold shock or warm shock.

Early Initiation of Appropriate Antimicrobial Therapy

Administration of broad-spectrum antibiotics to cover the likely pathogens (including gram positive and gram negative) within 1 h of diagnosis of septic shock/severe sepsis as well as reassessment of antibiotic therapy after microbiologic data is available, to narrow the coverage, is recommended.

At least two blood cultures should be obtained before starting antibiotics, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 h) inserted [2, 10].

The choice of antibiotics may vary from unit to unit based on the sensitivity patterns. In children with no localization, start a third generation cephalosporin and aminoglycoside. Cloxacillin/vancomycin is added if staphylococcal infection is suspected.

Source Control

All patients presenting with severe sepsis should be evaluated for the presence of focus of infection amenable to source control measures, specifically drainage of an abscess or local focus of infection, debridement of infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination [10].

Use of Adjuvant Therapy Like Steroids

Steroids are to be used only in children with suspected or proven adrenal insufficiency. Pediatric data show high prevalence of adrenal insufficiency in children with septic shock, especially catecholamine refractory shock [21]. As cortisol estimation may take time; it may be appropriate to take a sample for the assay, start hydrocortisone and decide about its continuation after assessing response and considering the results of the assay.

In a study from Chandigarh, there was a trend towards earlier reversal of shock (median 49.5 h vs 70 h) and lower inotropes requirement (median [10th–90th centile] inotropes score: 20 [15–60] vs. 50 [20–80], P=0.15) in the hydrocortisone treated patients as compared to controls; however, the difference was not statistically significant [22].

Mechanical Ventilation

Due to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation. In children with septic shock, work of breathing (WOB) may represent 15% to 30% of oxygen consumption and therefore contributes to the development of lactic acidosis. The early use of mechanical ventilation, aided by sedation and paralysis provides several advantages. It reduces the work of breathing and allows for redistribution of limited cardiac output to vital organs. Mechanical ventilation with positive end-expiratory pressure (PEEP) also improves oxygenation and decreases peripheral vascular resistance and left ventricular afterload.

It is reasonable to consider endotracheal intubation when the shock is persistent even after a volume resuscitation of more than 40–60 mL/kg.

Acute lung injury frequently accompanies patients with septic shock. These patients require early intubation and mechanical ventilation.

One should implement lung protective ventilation strategy like low tidal volume, use of positive end-expiratory pressure

(PEEP) and limitation of inspiratory plateau pressure to prevent lung injury and/or limit injury in acute respiratory distress syndrome (ARDS) [23].

An important aspect is use of agents for sedation/analgesia after careful selection; one should avoid etomidate and propofol for fear of adrenal suppression and metabolic acidosis, respectively. The authors usually use midazolam infusion along with fentanyl for sedation and analgesia in mechanically ventilated children. One may have to use neuromuscular blocking agents if patient-ventilator asynchrony cannot be taken care of by sedation.

Blood Products

The optimal hemoglobin for a critically ill child with severe sepsis is not known. A multicenter trial reported similar outcomes in stable critically ill children managed with a transfusion threshold of 9.5 g/dL [24]. It is reasonable to maintain hemoglobin concentration at a minimum of 10 g/dL [25].

Platelet transfusion should be done when counts are $<5{,}000/mm^3$ regardless of apparent bleeding. Platelet transfusion may be considered when counts are 5,000–$30{,}000/mm^3$ and there is significant risk of bleeding. Higher platelet counts ($\geq 50{,}000/mm^3$) are typically required for surgery or invasive procedures [10].

Coagulation disturbances (increased PT, INR, APTT) are commonly seen in patients with severe sepsis and septic shock. However, correction of these abnormalities do not necessarily improve the outcomes in all the patients and unnecessarily exposes the child to the risks of blood product transfusions [26]. There are no studies to suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding. Hence, fresh frozen plasma (FFP) is indicated only in selected patients with coagulation abnormality who have any of the following:

- Active bleeding
- Before surgery
- Before invasive procedure
- To reverse warfarin effect

When required the FFP infusion should be given relatively rapidly to achieve effective factor levels.

Other Supportive Care

The evidence for beneficial effects of strict glycemic control is not very strong. However, it is important to avoid hypoglycemia by proper monitoring [27]. The authors avoid blood glucose values of more than 180 mg/dL and may use low dose insulin infusion for bringing down the blood glucose below 180 mg/dL.

Routine stress ulcer prophylaxis is not recommended [28]. Children with upper gastrointestinal bleeds are managed as per protocol [29].

Prophylaxis for deep vein thrombosis (DVT) may be useful specifically in post pubertal children with severe sepsis [30].

Low serum ionized calcium concentration is associated with myocardial dysfunction and hypotension [31, 32]. Ionized hypocalcemia is common in children with sepsis admitted to PICU [33, 34]. Currently available data indicates that calcium administration has no effect or is detrimental in septic animals and postoperative cardiac infants [35] Ionized hypocalcemia should be corrected in patients with seizures, tetany, laryngospasm or those receiving digoxin.

Renal Replacement Therapy

Renal replacement for ARF may include peritoneal dialysis, intermittent hemodialysis, or continuous renal replacement therapies (CRRTs) [19, 36].

Activated Protein C

Surviving sepsis guidelines and a recent RCT recommend against using rhAPC (recombinant human activated protein C) in children [11, 37].

Intravenous Immunoglobulin

A recent randomized controlled study of polyclonal immunoglobulin in pediatric sepsis syndrome patients showed a significant reduction in mortality and length of PICU stay, and less progress to complications, especially disseminated intravascular coagulation [38]. Therefore, immunoglobulin can be considered in children with severe sepsis [10]. However, the high cost of therapy has to be considered while deciding its use.

The Algorithm/Management Plan: Fig. 1

The First 5 min

In the first five minutes, the initial assessment and management of child in shock includes recognition of decreased mental status, recognition of poor perfusion, and administration of oxygen and establishment of intravenous access. High flow oxygen system (e.g. Venturi masks) may be used. Two large bore intravenous cannulae should be inserted; if this is not successful, intraosseous access should be obtained and crystalloids should be infused as fast as possible. Mechanical ventilation is indicated if child has respiratory failure.

Management from 5–40 min

- Initial fluid resuscitation: Rapid infusion of boluses of 20 mL/kg isotonic saline each, up to 60 mL/kg, titrated toward achievement of therapeutic goals of shock resolution or unless rales or hepatomegaly develop.
- Correct hypoglycemia and hypocalcemia.
- Begin antibiotics (third generation cephalosporin and an aminoglycoside).
- Establish a second peripheral IV line or central line (particularly, if the child needs vaso-active drug infusion).
- Fluid therapy by peripheral or intraosseous access should be initiated while adequate control of airway and breathing is being accomplished. Volume replacement with 20 mL/kg of isotonic solutions such as normal saline or Ringers lactate can be safely given and repeated if necessary. Typically 40–60 mL/Kg is required to correct hypovolemia [15, 18]. In some children, fluid infusion of up to 200 mL/kg may be required; this, however, would be based on the assessment of individual patients. If patient is severely malnourished, a careful monitoring should be done to detect fluid overload early.

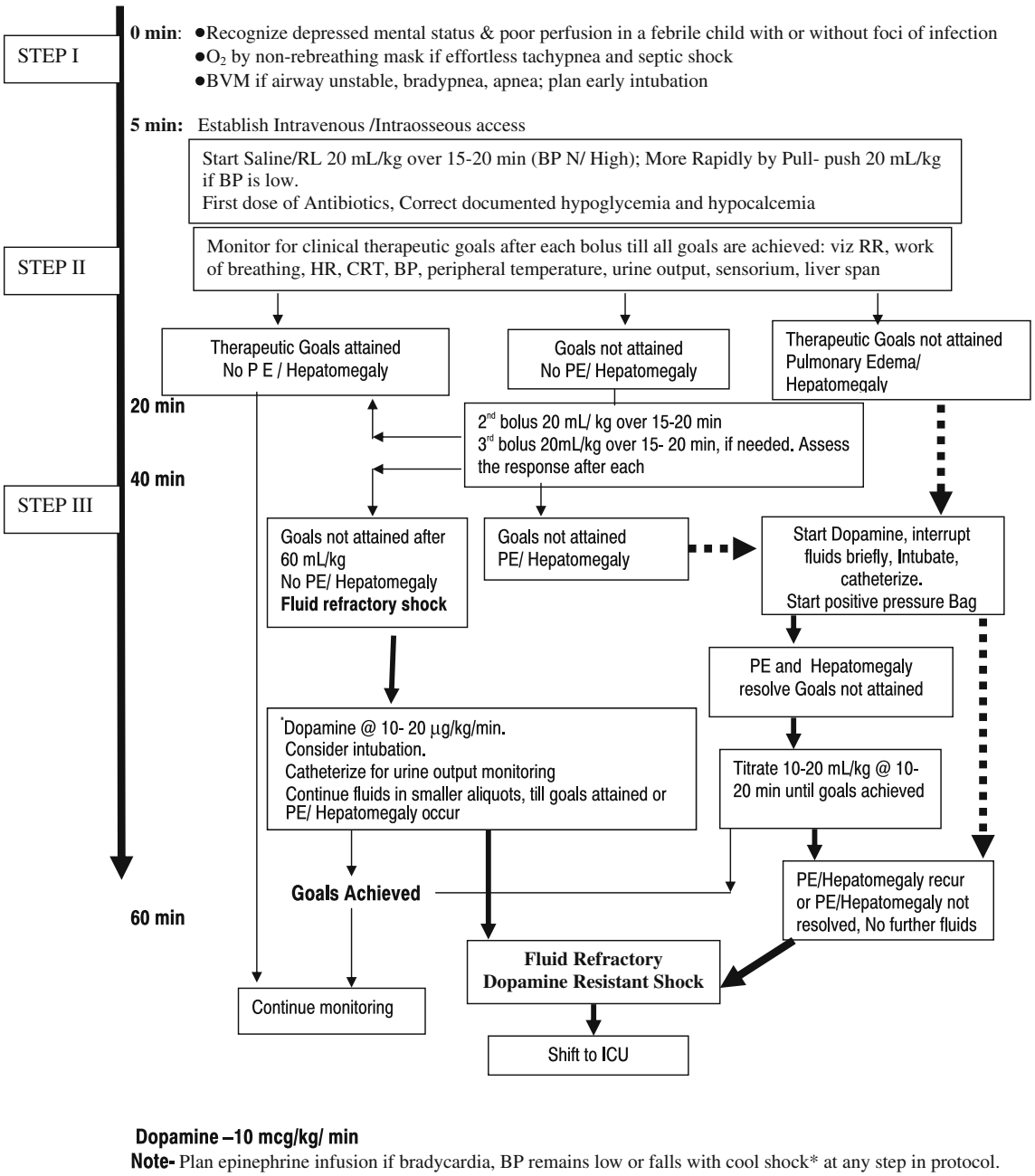

Fig. 1 Algorithm-pediatric septic shock (adapted from reference 11)

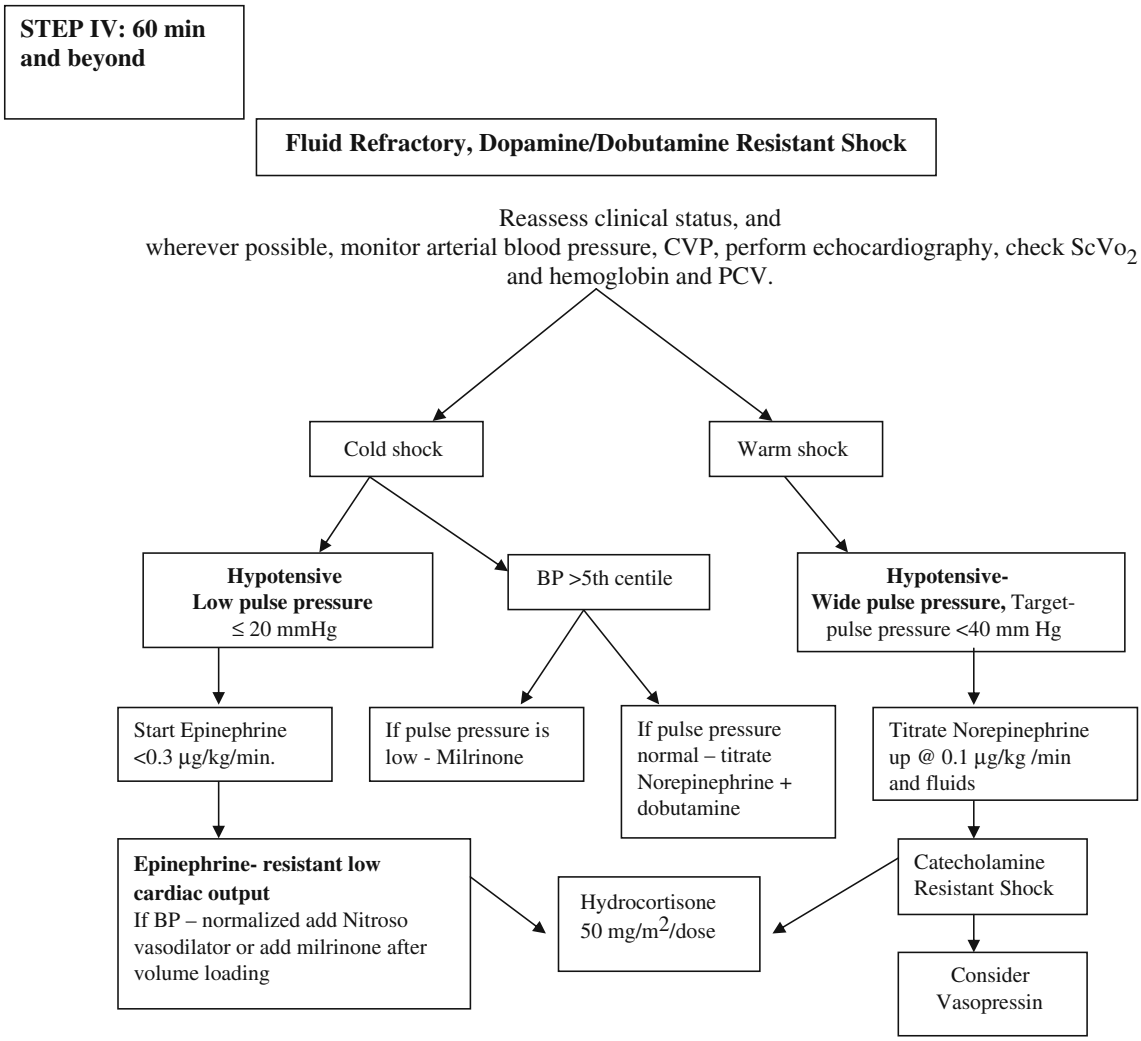

Fig. 1 (continued)

- Consider endotracheal intubation when shock is persistent even after a volume resuscitation of 40–60 mL/kg.
- Monitor the patient by performing the rapid cardio pulmonary assessment to see whether therapeutic goals (Table 1) have been achieved or not, or there is deterioration,which is determined at the end of each fluid bolus. After each assessment, decide about the need for further fluids infusion or need for inotrope support and intubation [15, 39].

Management: 40 min Onwards

Following adequate intravascular volume repletion, continued presence of hypotension and/or poor perfusion warrants the initiation of vasoactive drug therapy. Children with fluid refractory shock should have a central venous line placed; in the emergency setting, femoral vein is usually chosen.

The vasoactive drug of choice with fluid refractory septic shock is Dopamine, started at a infusion rate of 10 µg/kg/min. The infusion is accurately delivered using an infusion pump (body weight X 15 will give the amount of dopamine in mg to make 50 mL of infusion; such a solution infused at 1 mL/h will deliver 0.5 µg/kg/min); in settings where infusion pump is not available, the medication could be infused using pediatric micro-drip sets. Fluid boluses should not be administered through single lumen catheters used for vasoactive drug infusion, to avoid infusion of high doses of the vasoactive drugs. Mixing of more than one vasoactive drug in the same infusion set or infusion syringes is not recommended even when limited numbers of intravenous access ports are available.

For cold shock, reversal is attempted by titrating dopamine, or if resistant (normal or low blood pressure) by using epinephrine (0.05–0.3 μg/kg/min) delivered through a central catheter.

Children with warm shock (wide pulse pressure and low blood pressure) should receive nor-epinephrine infusion; the dose is 0.1–1 μg/kg/min; the infusion should be prepared in 5% dextrose or 5% dextrose with normal saline; dilution with normal saline is not recommended.

Persistent narrow pulse pressure and/or prolonged capillary refill even after the use of dopamine is labeled as fluid refractory dopamine resistant septic shock. The low cardiac output state may be improved with addition of dobutamine (up to 20 μg/kg/min) or low dose epinephrine (<0.3 μg/kg/Min); dobutamine is the preferred drug.

Management After 60 min

A child with catecholamine refractory shock (a child who has not responded to the management outlined above) should be transferred to PICU; monitoring of CVP and arterial pressure would help in the management. The management includes titration of fluids and vasoactive drugs to resolve shock. Echocardiography may be beneficial in decisions regarding further fluid administration and use of vasoactive drugs.

It is recommended that corticosteroids (hydrocortisone 50 mg/m^2/24 h, followed by 50 mg/m^2/day in 4 divided doses intravenously for 5 to 7 days) be given to those children with catecholamine resistant shock who have proven adrenal insufficiency or are at risk for adrenal insufficiency. Corticosteroids should not be used routinely in children with septic shock.

Children in cold shock may be further categorized in two sub-groups. First are children with low blood pressure. In these children, the dose of epinephrine should be titrated to achieve normal mean arterial pressure for age. Once this is achieved but the other goals of therapy are not yet achieved, one should consider adding a vasodilator [9] such as nitroprusside (0.3–4 μg/kg/min) and nitroglycerine (0.5–5 μg/kg/min), which are pure vasodilators with very short half life, or milrinone (0.5–1 μg/kg/min; a loading dose of 50 μg/kg is avoided in children with hypotension) which has both vasodilator as well as inotropic effects. Nitrosovasodilators are used in children with epinephrine- resistant low cardiac output and elevated systemic vascular resistance. Use of phosphodiestrase inhibitor- milrinone- should be strongly considered if low cardiac and high vascular resistance state persists inspite of epinephrine and nitrosovasodilators. Starting milrinone may require additional volume loading, and titrating up the dose of epinephrine to check the vasodilatation and maintain BP.

In children with cold shock and normal blood pressure with low pulse pressure, phosphodiestrase inhibitor such as milrinone would be the drug of choice. However, if the pulse pressure is normal or high, norepinephrine and dobutamine should be titrated up.

Vasopressin therapy may be considered if patient has warm shock with low blood pressure unresponsive to norepinephrine [40]. There is a limited experience in children, with vasopressin as a rescue therapy in catecholamine resistant shock [41, 42]. Deleterious effects of vasopressin on renal functions and platelet counts should be considered [43].

A meticulous search for the causes of persistent catecholamine resistant shock should be made. One must rule out mechanical causes of catecholamine resistant shock such as tamponade due to pericardial effusion, pneumothorax or increased intrabdominal pressure.

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