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Management of septic shock in children

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ABSTRACT

Septic shock is one of the common pediatric emergencies often encountered. Despite the advances in the preventive and therapeutic medicines, septic shock continues to be a major life threatening problem. This review article tries to highlight some of the management issues for the septic shock in children.

Key words: Sepsis, septic shock, diagnostic criteria, management

INTRODUCTION

Sepsis can occur as a result of localized infection or generalized infection. It can be caused by bacteria, virus, fungus and parasites. Children are more prone to the development of sepsis especially

* Infants
* Children with serious injuries
* On chronic antibacterial therapy
* Malnourished children
* With chronic medical problems
* Immuno suppressed children
* 3 months – 3 yr of age with occult bacteremia

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Organism varies with age of patient and immune status.

Neonates— E.coli, GBS, Listeria, Herpes virus

Older children—Strep pneumoniae, Neisseria meningitidis, Staph aureus,Toxic shock syndrome.

Immunocompromised Children— Nosocomial, Gram –ve, fungi, polymicrobial.

PATHOGENESIS

Shock is a state of circulatory disturbance which can affect multiple organ systems in the body. Septic shock in children is a prototype combination of hypovolemia, cardiogenic and distributive shock. The two forms of septic shock are **Warm shock** characterised by increased cardiac out put and decreased systemic vascular resistance and **Cold shock** characterised by decreased cardiac output and increased systemic vascular resistance.

Following the release of endotoxins and superantigens, inflammatory cascade gets activated. This leads to the release of arachidonic acid mediators, cytokines, interleukins, complement system, myocardial depressant factors which lead to the cascade of events that causes endothelial damage and microcirculatory dysfunction .Tumor necrosis factor causes increased vascular permeability, decreased vascular tone, fever. Arachidonic acid metabolites cause fever, ventilation perfusion disturbances, lactic acidosis. Myocardial depression is caused by TNF, increased beta endorphins, production of myocardial nitric oxide (1,2,3).

The predominant cause of mortality in adult septic shock is vasomotor paralysis. But in children low cardiac output and not low systemic vascular resistance, is associated with mortality. Also contrary to adults, oxygen delivery, not oxygen extraction, is the major determinant of oxygen consumption in children. Neonatal septic shock can be complicated by the physiologic transition from fetal to neonatal circulation. Acidosis and hypoxia associated with the sepsis can increase the pulmonary pressure resulting in persistent pulmonary hypertension (PPHN) and can lead to right heart failure (4,7).

CLINICAL FEATURES

Child presents initially with tachypnea, tachycardia, alteration of temperature. In the initial hyperdynamic phase, one can note the warm peripheries, bounding pulses. As the condition progresses myocardial failure and vascular leaks sets in, and can develop cool extremities, decreased urine output, altered mentation, delayed capillary filling time, low pulse volume. Due to anaerobic metabolism in tissue lactic acidosis sets in and can have acidotic breathing and myocardial failure. Skin may show features of erythema, jaundice, echymoses, petechiae . In advanced conditions it can progress to disseminated intravascular coagulation and multiorgan dysfunction syndrome. Hypotension is a late feature and therefore not useful to detect early shock (4-9).

Fig 1: Pathophysiology of septic shock(2)

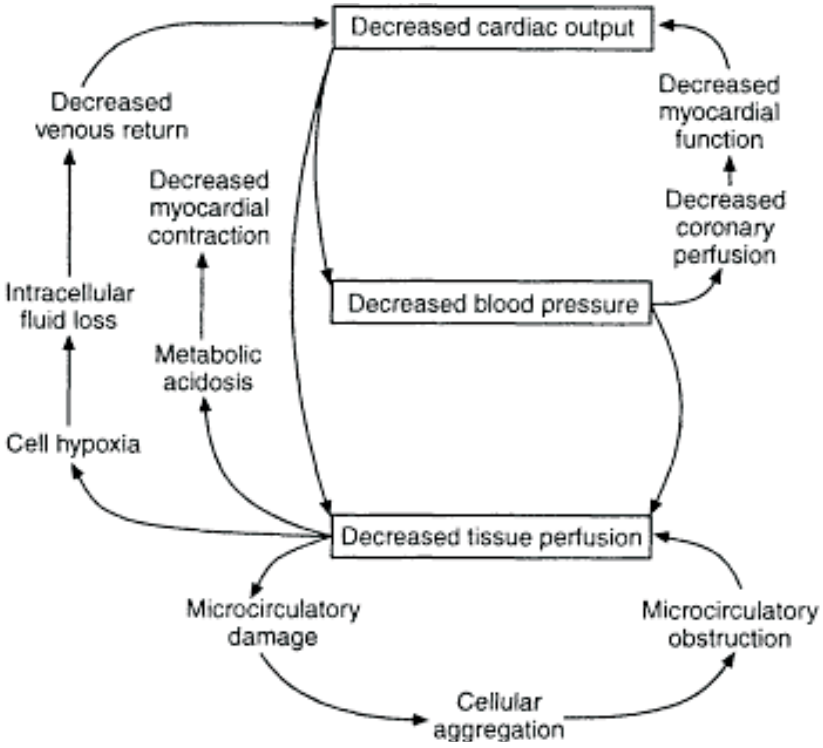


Table 1: Age related cut off values for vital parameters

age	Tachycardia (Per min)	Bradycardia (Per min)	Respiratory rate (per min)	BP systolic (mm Hg)
O-1 wk	>180	<100	>50	<65
1w-1m	>180	<100	>40	<75
1m-1y	>180	<90	>34	<100
2-5y	>140	NA	>22	<94
6-12y	>130	NA	>8	<105
13-18y	>110	NA	>14	<117

DIAGNOSIS

Based on the **INTERNATIONAL CONSENSUS DEFINITION FOR PEDIATRIC SEPSIS**(8,10).

Infection

Suspected or proven infection or a clinical syndrome associated with high probability of infection.

Systemic Inflammatory Response syndrome(SIRS)

Two out of four criteria out of which 1 must be abnormal temperature or abnormal leucocyte count

* Core temperature >38.5^{o} C or <36^{o} C
* Tachycardia heart rate > 2 S.D above mean in the absence of external stimuli, chronic drugs or painful stimuli or

Unexplained persistent elevation over (0.5-4 hr) or

In children <1 yr bradycardia (heart rate < 10th percentile) over 0.5 hr in absence of drugs , vagal stimuli

* Mean respiratory rate > 2 S.D above mean for age or

Acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia.

* Leukocyte count elevated/depressed for age/>10% immature neutrophils

SEPSIS

SIRS plus a suspected or proven infection

SEVERE SEPSIS

SEPSIS with one of the following

A…Cardiovascular dysfunction, defined as

Despite administration of > 40ml/kg/ isotonic iv bolus in 1 hour,

Hypotension < 5th centile for age /systolic BP<2 S.D below normal for age

OR

Need for inotropes to maintain BP

OR

Any 2 0f the following

Ø Unexplained metabolic acidosis (Base deficit >5mEq)

Ø 2. Lactate in arterial blood>2 times upper limit of normal

Ø 3. Urine output<0.5ml/kg/hr

Ø 4. Capillary filling time of >5 sec

Ø 5. Core to peripheral temp difference >3^{o}C

B… Acute respiratory distress syndrome is defined by the presence of PaO2/FiO2 < 200 mm Hg, bilateral infiltrates in chest radiograph and no evidence of left heart failure.

OR

Sepsis plus 2 or more organ dysfuction

SEPTIC SHOCK

Sepsis with cardiovascular organ dysfunction as described above

LABORATORY DIAGNOSIS

Hematology—thrombocytopenia, abnormal leucocyte counts,prolonged prothrombin time,prolonged activated partial thromboplastin time ,decreased fibrinogen,elevated fibrin split products . Peripheral smear can show elevated immature forms of neutrophils, toxic granules, Dohle bodies. Neutropenia is an ominous sign of sepsis (4,6,8,10).

Biochemically—Hyperglycemia (due to stress response) or Hypoglycemia (store exhaustion), Hypocalcemia ,acidosis, hypoalbuminemia.

In case of MODS—chest X-Ray features suggestive of ARDS ,abnormal renal function ,liver function can be seen.

In refractory cases we need to check serum cortisol levels to detect adrenal insufficiency

Culture of blood, urine to isolate the organism before starting antibiotics.

Imaging to detect the focus of infection (4,6,7,8,10).

MANAGEMENT

Management guidelines are published by American college of Critical Care medicine / Society for critical care medicine task force committee members and Surviving Sepsis Campaign (4-9).

Septic shock can be recognized before hypotension occurs, by a clinical triad that includes hypothermia or hyperthermia, altered mental status, and peripheral vasodilatation (warm shock) or cool extremities (cold shock). The purpose of treatment of shock is to maintain perfusion pressure above the critical point below which blood flow cannot be effectively maintained in individual organs. Because the kidney receives the second highest blood flow to any organ in the body, measurement of urine output and creatinine clearance can be used as an indicator of adequate perfusion pressure (4,7).

Rapid aggressive resuscitation with fluids and catecholamines reduces mortality. Early

goal directed resuscitation in early **6** hours of recognition of septic shock is needed for good outcome (4-9).

First 0 – 5 min

ABC OF RESUSCITATION

Recognise decreased mental status & perfusion. Establish & maintain airway and circulation according to Pediatric ADVANCED LIFE SUPPORT guidelines. IV /intra osseous access for maintaining circulation.

5 min – 15 min

The fluid resuscitation with crystalloids and colloids is of fundamental importance to survival of septic shock. Fluid boluses of 20ml/kg can be rapidly pushed in and some severe cases may require boluses of 60ml/kg or even upto 200ml/kg in first hour .Monitor for features of fluid overload in the form of basal rales (pulmonary edema), hepatomegaly (4-9).

Fluid choices include crystalloids (normal saline) and colloids (dextran, gelatin, or 5% albumin) based on task force recommendation. Meta-analysis of clinical studies comparing crystalloid and colloid resuscitation indicate no clinical outcome difference between colloids and crystalloids. As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. This fluid challenge can replace the intravascular fluid deficit. Most patients will need aggressive fluid therapy till capillary leaks settles. Along with correction of fluid deficit, we need to give the normal maintenance fluid (4,6,7,12-15).

Fresh-frozen plasma may be infused to correct abnormal prothrombin time and partial thromboplastin time but should not be pushed because it has hypotensive effects likely caused by vasoactive kinins (7). It is reasonable to maintain hemoglobin concentration within the normal range for age.

Correct hypocalcemia, hypoglycemia, acidosis(4-9). (Bicarbonate therapy is not recommended for pH>7.15 for the purpose of correcting hypotension)(4).

* Start early antibiotic based on the age group and general condition(4-11).

Neonate

Cefotaxime and aminoglycoside; add Vancomycin in nosocomial Infection (10).

Child

Cefotaxime,or Ceftriaxone ; add vancomycin for meningitis ,areas of pneumococcal resistance to cephalosporins (10).

Immunocompromised patient :Vancomycin and antipseudomonas agent (10).

Toxic shock: Penicillin and clindamycin (10).

Blood cultures has to be taken before antibiotic therapy ,administer broad-spectrum antibiotic therapy within 1 hr of diagnosis of septic shock and severe sepsis without septic shock ,reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage when appropriate and a usual 7-10 days of antibiotic therapy guided by clinical response (4,6,7,8,9,10,11).

15 min – 60 min

When an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion and resuscitation goals are not met, therapy with vasopressor agents should be started. Vasopressor therapy may also be needed in case of life-threatening hypotension, even when a fluid challenge is in progress and hypovolemia has not yet been corrected (4).

Intensive care admission with central vein access and arterial pressure monitoring should be considered and used in children with fluid-refractory shock (4-9).

Monitor

* Pulse oximeter

* Continuous electrocardiography
* Blood pressure-invasive ideally
* Temperature
* Urine output
* Glucose and ionized calcium

Dopamine and Norepinephrine are the first line inotropic agent in the management of septic shock. Compared to epinephrine these drugs cause less tachycardia and less effect on splanchnic circulation. As Norepinephrine increases mean arterial pressure with least effect on heart rate, it is found to be more potent than Dopamine in the septic shock in warm shock. Low-dose dopamine should not be used for renal protection as part of the treatment of severe sepsis (4).

In case of dopamine resistant shock we can use norepinephrine and epinephrine. Epinephrine can be used as a first-line choice for cold hypodynamic shock in children (7).

Dobutamine inotropic therapy is used only when cardiac output remains low despite fluid resuscitation and combined inotropic/ vasopressor therapy (4,7,9).

Cold shock- dopamine resistant or as first line, use epinephrine—titrate from 0.1-1 microgram/kg/min (7,9).

Warm shock- dopamine resistant titrate norepinephrine from 0.1-2 microgram/kg/ min (7,9).

60 Mins

If shock doesnot improve, recognise catecholamine resistant shock. The committee chose the most conservative diagnostic approach and defines adrenal insufficiency as a total cortisol level between 0 and 18 mg/dL. Based on the newer recommendation, steroid has to be used only after the demonstration of adrenal insufficiency. Begin hydrocortisone 50 mg/kg for shock, followed by the same dose as a 24-hr infusion (4,7,9).

Based on the recommendations if T4 or T3 level is low and sick euthyroid syndrome has been excluded, oral Levothyroxine or, if necessary, intravenous T3 preparation can be used to restore normal values for age (7,9).

Titrate the inotropes based on the blood pressure and systemic vascular resistance.

1. Shock with Low Cardiac index, Normal Blood Pressure, and High Systemic Vascular Resistance.

Vasodilators like Nitroprusside or Nitroglycerin are first line in patients with epinephrine-resistant shock. In patients who are resistant to such therapy or those who develop nitrovasodilator toxicity in the form of cyanide toxicity, methemoglobulinemia, one can use type III phosphodiesterase inhibitors such as Amrinone and Milrinone. Long half life of these drugs can cause reversible toxicities (hypotension,arrhythmias) ,which can be reversed by noreinephrine infusions (4-9). Other vasodilators used and reported in neonatal and pediatric septic shock include prostacyclin, phentolamine, pentoxifylline, and dopexamine (7).

2. Shock with High CI and Low Systemic Vascular Resistance .

Norepinephrine is the drug of choice for age-dependent dopamine resistance and titrate voume (7,9).

3. Shock with low CI and High Systemic Vascular Resistance Titrate volume and epinephrine (7,9).

Persistent catecholamine shock

Place pulmonary artery catheter

Direct therapy-fluid, vasopressor, vasodilator, inotropic support to maintain Mean Arterial pressure(MAP) ,Central venous pressure (CVP), Cardiac Index(CI) >3.3 and <6 l/min/$m^{2.}$

Consider Extra corporeal membrane oxygenation (ECMO) (4-9).

RESUSCITATION GOALS

* Capillary filling time of 2 secs
* Normal pulses with no differential between peripheral and central pulses
* Warm extremities
* Urine output 1 mL/kg/hr,
* Normal mental status,

* Normal blood pressure for age

* Superior venacaval oxygen saturation >70% after 6 hours or resuscitation is considered as a good outcome (4-9).

If the patient develops multiorgan dysfunction ,targeted organ support strategies are needed . In case of acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) low tidal volume and limitation of inspiratory plateau pressure strategy has to be used. Application of at least a minimal amount of positive end-expiratory pressure in acute lung injury has been recommended. Head of bed elevation in mechanically ventilated patients unless contraindicated and avoiding routine use of pulmonary artery catheters in ALI/ ARDS has been newly recommended(6,9).

In cases of bleeding manifestation due to DIC ,we need to replace coagulation factors, vitamin K and packed cells to maintain targeted hemoglobin.

Blood sugar has to be controlled and hypoglycemia has to be avoided by giving glucose at 4-6mg/kg/min (4,6,9).

Renal support has to be given in case of renal shut down. Based on newer recommendations , equivalence of continuous veno-venous hemofiltration and intermittent hemodialysis has been noted (6,9).

To prevent gastric stress ulcer, proton pump inhibitors or H2 blockers can be used especially in mechanically ventilated children (4,6,9).

MANAGEMENT CONSIDERATIONS IN NEWBORN

Septic shock should be suspected in any newborn with respiratory distress and reduced perfusion, particularly in the presence of a maternal history of chorioamnionitis or prolonged rupture of membranes. Septic shock has to be differentiated from shock due to congenital heart disease, which will require prostaglandin infusions for survival. Newborn septic shock is typically accompanied by increased pulmonary artery pressures which can cause right ventricle failure (7).

General management principles are same as the older children with some slight differences.

In newborns, rapid fluid boluses of 10 mL/ kg should be administered according to the committee recommendations . Up to 60ml/ kg may be needed in first hour(7,9). Packed red blood cell transfusion are given to maintain hemoglobin >12 g/dL. Crystalloids are the fluid recommended for use in newborns with hemoglobin >12 g/dl in shock (4,7,9).

In newborn the effect of dopamine on pulmonary vascular resistance should be taken into account. Usually, a combination of dopamine at low dosage 8-12microgram / kg/min) and dobutamine (up to 30 microgram/kg/min) is used; if the patient is not responding to the therapy, then epinephrine should be infused to restore normal blood pressure and perfusion (7,9).

In newborn, measures to treat PPHN are important (7).

* Correct hypoxia

* Correct acidosis with sodium bicarbonate –alkalinisation upto pH of 7.5 may be needed

* Maintain good systemic pressure to reduce the shunt

* Proper sedation to reduce the catecholamine release which can raise the pulmonary artery pressure

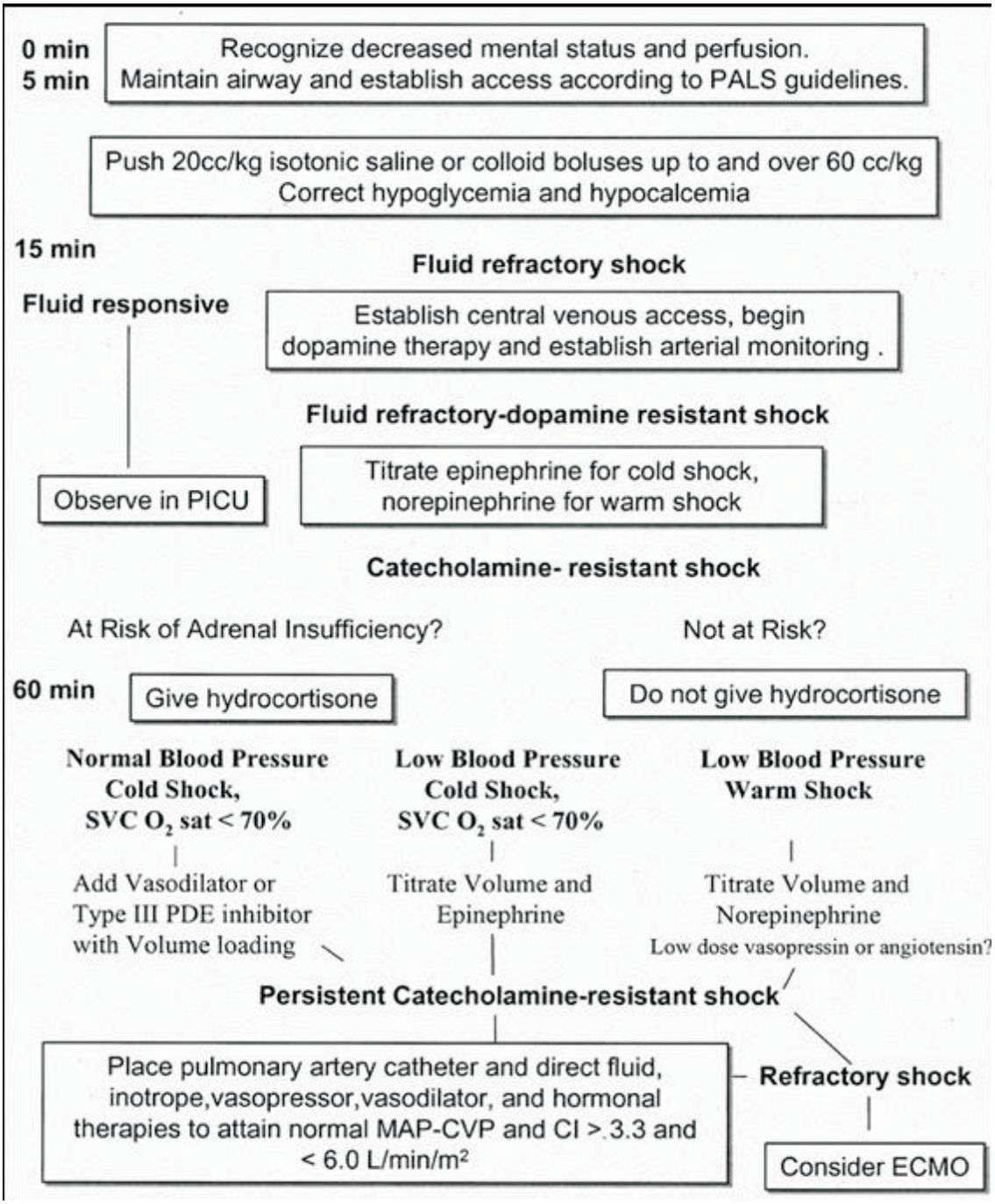
* Inhaled Nitric oxide to decrease the pulmonary pressure (7).

* Pulmonary vasodilators such as NO donors (Sildenafil) and Magnesium sulfate are under trial

Steroid has to be used only after the demonstration of adrenal insufficiency. Low dose Hydrocortisone has been used (3 mg/kg/ day) for 3-5 days. But the role of high dose steroids is controversial due to the long term effects in the brain development especially in very low birth weight infants (9).

Amrinone, Milrinone –can be used in the cases of cases with shock with increased peripheral vascular resistance (9,15-18).

Fig 2: Adapted from reference (7, 9)



NEWER THERAPEUTICS

Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high dose conventional vasopressors (4).

In refractory cases, exclude pericardial effusion, pneumothorax, ongoing blood loss, hypoadrenalism, hypothyroidism, inborn errors of metabolism, or cyanotic or obstructive heart disease. If all these are excluded ECMO can be used. The expected ECMO survival rate for newborn septic shock is currently 80%(4,6,7,9).

In severe cases of sepsis, exchange transfusion, Intravenous immunoglobulin can be tried (4, 15-18,20,21).

The newer recommendation is against the use of activated protein C in children (9).

There are trials reporting the efficacy regarding the use of methylene blue for the treatment of sepsis (22).

In case of severe sepsis with neutropenia (Absolute Neutrophil count <1500), granulocyte monocyte colony stimulating factors has shown to improve outcome in neonates.(15-18).

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