Recent Advances in Sepsis and Septic Shock

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ABSTRACT

Sepsis remains a common problem in all age groups. Recently surviving sepsis campaign has taken up a worldwide initiative by publishing international guidelines 2008 with a hope to disseminate information regarding management of sepsis for all age groups. This article presents a review of recent advances as they apply to pediatric age group supported by the available evidence with reference to standard definitions of pediatric sepsis and septic shock and management in the emergency room and pediatric intensive care unit. **[Indian J Pediatr 2008; 75 (8) : 821-830]** E-*mail: pkhilnani@vsnl.com*

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Pediatrics sepsis is a commonly seen problem. According to WHO 2006 data , pneumonia, diarrhea, neonatal sepsis are top on the list of killers of children.

Consensus definitions of sepsis were first published[1] and later updated in a consensus conference.[2] Better understanding of pathophysiology, new interventions and better use of existing therapies in the past decade included the publication of surviving sepsis campaign guidelines[3] recently revised.[4] In 2002 Carcillo et al published American college of critical care medicine clinical guidelines for hemodynamic support of neonates and children with septic shock.[5] These guidelines were widely disseminated through the Society of critical care medicine (SCCM) and the American heart association (AHA), as well as translated into Spanish and Portugese. These guidelines have been tested and the outcomes published by many centers.[6-9]

One Institution that put guidelines into practice reported improvement in outcomes1-3% in previously healthy and 7-10% in chronically ill children,[10] in line with best practice outcomes as targeted by the guidelines. Currently there are no published guidelines for resource limited countries. Intensive care chapter of the Indian Academy of Pediatrics is developing such quidelines applicable to resource limited environment.

At the World Federation of Pediatric Intensive Care and Critical Care Society (WFPICC) Sepsis forum discussion, Carcillo emphasized the importance of simple things such as early fluid therapy, early antibiotics, oxygen by nasal cannula, vasopressors by peripheral intravenous (IV) access to achieve a goal directed therapy can potentially avoid further deterioration and improve outcomes.

In the following discussion consensus definitions of sepsis and rapid cardiopulmonary assessment will be described followed by the recent advances in management of pediatric sepsis and septic shock.

DEFINITIONS

Following are the definitions published in 2005[2] related to sepsis and septic shock. Table 1 shows age-specific ranges for physiologic and laboratory variables.

A. SIRS(systemic inflammatory response syndrome)

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

1.Core temperature of >38.5°C or <36°C (Core temperature must be measured by rectal, bladder, oral, or central catheter probe).

2. Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period

OR

For children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital

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Table 1. Age Specific Vital Signs and Laboratory Values*

Age Group	Heart Rate		Respiratory Rate Breaths/min	Leukocyte Count x1000/cu m	SBP
	Tachycardia	Bradycardia			
0-1	>180	<100	>50	>34	<65
1wk-1mo	>180	<100	>40	>19,5 or<5	<75
1mo-1yr	>180	<90	>34	>17.5 or <5	<100
2-5yr	>140	NA	>22	>15.5 or <6	<94
6-12yrs	>130	NA	>18	>13.5 or<4.5	<105
13-< 18yr	>110	NA	>14	>11or <4,5	<117

*Lower values for heart rate, leukocyte count, SBP(systolic blood pressure) are for the 5th percentile and upper values for heart rate, respiratory rate or leukocyte count for the 95th percentile

heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.

3. Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.

4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

B. Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (*e.g.*, white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

C. Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

D. Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in table 2.

E. Septic shock

Sepsis and cardiovascular organ dysfunction as defined in table 2.

The detection of altered organ function in the acutely ill patient constitutes multiple organ dysfunction syndrome (two or more organs involvement). The terminology of dysfunction identifies this process as a phenomenon in which organ function is not capable of maintaining homeostasis. This process, which may be absolute or relative, can be more readily identified as a continuum of change over time.

Rapid cardiopulmonary assessment and clinical examination of a patient in shock because the shock can be fatal, the child must be assessed immediately and

Table 2. Organ Dysfunction Criteria

Cardiovascular dysfunction
Despite administration of isotonic intravenous fluid bolus >40 mL/Kg in 1 hr
Decrease in BP (hypotension) <5th percentile for age or systolic BP >2 SD below normal for age (*a*)OR
Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/Kg/min or dobutamine, epinephrine, or norepinephrine at any dose)OR
Two of the following
Unexplained metabolic acidosis: base deficit >5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: urine output <0.5 mL/kg/hr
Prolonged capillary refill: >5 secs
Core to peripheral temperature gap >3°C
Respiratory dysfunction (b)
PaO_2/FIO_2 <300 in absence of cyanotic heart disease or preexisting lung diseaseOR
$PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$ OR
Proven need (*c*) or >50% FIO_2 to maintain saturation >92% OR
Need for nonelective invasive or noninvasive mechanical ventilation (*d*)
Neurologic dysfunction
Glasgow coma score <11 OR
acute change in mental status with a decrease in Glasgow coma score >3 points from abnormal baseline
Hematologic dysfunction
Platelet count < 80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology /oncology patients) OR
International normalized ratio >2
Renal dysfunction
Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine
Hepatic dysfunction
Total bilirubin >4 mg/dL (not applicable for newborn)OR
ALT 2 times upper limit of normal for age

{BP*, blood pressure; ALT,* alanine transaminase. (*a*) See Table 1; (*b*) acute respiratory distress syndrome must include a PaO_2/FIO_2 ratio <200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure . Acute lung injury is defined identically except the PaO_2/FIO_2 ratio must be <300 mm Hg; (*c*) proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; (*d*) in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.}

comprehensively. In a healthy child the cardiovascular system has remarkable compensatory capability

There is generally a stability of BP and only an increase in heart rate and poor capillary refill time, until there is decompensation (with hypotension) which may lead to precipitous cardiac arrest.

In clinical examination one must note following points very carefully, 5th point regarding the urine out put is an important point in history.

• **Mental status :** Restlessness, agitation, anxiety, and progressive lethargy.

• **Skin:** Temperature (hyperthermia or hypothermia), color, capillary refill time (normal <2 seconds), turgor, peticheal rash may be present in meningococcemia or disseminated intravascular coagulation.

• **Cardiovascular :** By far, the most significant physical findings in septic shock results from autonomic responses to stress. In children tachycardia occurs early. The younger the child, cardiac output is more dependent on heart rate rather than on increase in stroke volume

Alteration in BP is a late manifestation of hypovolemia in children, occurring faster in children. Diastolic BP begins to fall early as vascular tone begins to decrease. Systolic BP is well maintained initially (normotensive shock) and only begins to fall once hemodynamic compromise is severe. Decreasing BP signifies decompensted stage of shock (Hypotensive Shock). Hepatic enlargemt and jugular venous distension with gallop rhythm may signify predominant cardiac involvement as a part of septic myocardial depression or myocarditis. In warm phase of septic shock capillary refill time may be normal, however signs of hyperdynamic circulation, widened pulse pressure, hyperdynamic apex beat are important signs. Capillary refill time of more than 5 seconds is abnormal. Cold shock is more common than warm shock signified by peripheral extremity (hands and feet) temperature in neonatal and pediatric age group. It should be noted that warm shock with delay in treatment or if untreated will eventually results in cold shock.

• **Respiratory :** Respiratory rate is increased to compensate for metabolic acidosis including lactic acidosis, secondly if acute respiratory distress syndrome (ARDS) is developing, progressive worsening of respiratory distress (tachypnea, nasal flaring, sternomastoid prominence, suprasternal and intersostal and subcostal retractions may occur with bilateral rales on auscultation or wheezes or unequal breath sounds depending upon presence of primary focus of infection in lungs.

• **Urine output :** Oliguria is most common leading to anuria.It is also important to remember that physical findings will vary according to the stage of shock (compensated or decompensated). In severe cases patients may present cardiopulmonary failure or cardiopulmonary arrest ; both situations need aggressive hemodynamic support (fluids, inotropes and or vasopressors) as well as endotracheal intubation and mechanical ventilatory support for survival.

EMERGENCY MANAGEMENT: (GOLDEN HOUR OF SEPSIS MANAGEMENT)

The treatment of septic shock in children is aimed at optimizing perfusion of critical vascular beds and preventing or correcting metabolic abnormalities arising due to cellular hypoperfusion. The ultimate goals are to prevent or reverse the defects in cellular substrate delivery and metabolism and to support entire patient until homoeostasis is restored. For all forms of shock, treating the underlying cause is mandatory. Speed is essential.

Delays in making the diagnosis and initiating treatment (fluid resuscitation as well as appropriate antibiotics), as well as suboptimal resuscitation, contribute to the developments of peripheral vascular failure and irreversible defects in oxygen use which can culminate in vital organ dysfunction. The most effective and sensitive physiological monitoring available is, repeated and careful physical examination by an experienced and competent observer.

Management of child with septic shock is best started by aggressive goal directed management in the emergency department.

Priorities of treatment

Two major priorities in treatment of septic shock in the golden hour are:

- Rapid assessment of patient's disease process
- Achievement of cardiopulmonary stability

TIME FRAME FOR MANAGEMENT OF SEPTIC SHOCK

• 0 min-5 min

Recognize decreased mental status and perfusion. Begin high flow oxygen. Establish IV/IO (Intravenous/ Intraosseous) access

• 5 min - 15 min

Initial resuscitation : Push fluid boluses of 20cc/Kg isotonic saline or colloid up to and over 60cc/Kg until perfusion improves or unless rales or hepatomegaly develop. Correct hypoglycemia and hypocalcemia. Begin antibiotics. Simultaneously with 2nd peripheral IV start inotrope

Shock not reversed?

(iii) 15 min-60 min

Fluid refractory shock : Begin Inotrope IV/IO.Dopamine up to 10 mic/Kg/min

(Use atropine/ketamine IV/IO/IM to obtain central access and airway if needed)

Reverse cold shock by titrating central dopamine,or if resistant (normal or low blood pressure) titrate central epinephrine (0.05-1 microgram/Kg/min)

Reverse warm shock with low blood pressure by titrating central norepinephrine (0.05-1microgram/Kg/min)

Shock not reversed?

- **60 min**

Recognize catecholamine resistant shock

Begin hydrocortisone (50mg/m^2/dose) if at risk for absolute adrenal insufficiency

Consider use of vasodilator or phosphodiestrase inhibitor such as milrinone if cold shock and normal blood pressure.

Consider vasopressin if warm shock with low blood pressure as last resort.

- **Beyond 60 min**

Transfer to PICU facility

Monitor CVP, Mean arterial pressure.Titrate fluids and inotropes to attain normal mixed venous oxygen saturation ScVO2>70

Depending on availability consider initiating further therapy* as indicated: Terlipressin, Levosimendan, Enoximone

*Relief of tamponade, such as pneumothorax, or pericardial tamponade,increased intra abdominal pressure due to fluid should be considered at any point

TIME FRAME GUIDELINES DISCUSSION

0-5 min

In the first five minutes initial assessment and management of child in shock includes recognition of decreased mental status, recognition of poor perfusion, administration of oxygen and establishment of intravenous access. High flow oxygen system (*e.g.*, Venturi masks) may be used.

All of the above are readily achieved in 1st five minutes.

However, If airway is unstable or the patient is lethargic or unresponsive and adequate oxygenation and ventilation is not achieved, endotracheal intubation and mechanical ventilation may be required. Implementation of this step may take additional time encroaching upon the interventions expected in 5-15 mnute or 15-60 minute time period as per the guidelines. Because mechanical ventilation abolishes or minimizes work of breathing, reduces oxygen consumption and improves oxygenation, early respiratory support benefits patients with severe shock in addition to those with ARDS/ pulmonary edema.

Unfortunately no objective clinical criteria specific to pediatric septic shock for timing of endotracheal intubation (other than the standard indications, which include shock) exists in literature. Therefore it is reasonable to consider endotracheal intubation when shock is persistent even after a volume resuscitation of >40-60 ml/Kg. Children with sepsis requiring aggressive fluid resuscitation frequently have worsening tachypnea and increasing oxygen requirement clinically depicting early ARDS.

The principles of lung-protective strategies(low tidal volumes and permissive hypercapnea) are applied to children as they are to adults. In premature infants, additional attention is paid to avoiding hyperoxemia to prevent retinopathy.

5-15 min:

INITIAL RESUSCITATION

Preload and volume replacement : Fluid therapy by peripheral or intraosseous access should be initiated after adequate control of airway and breathing has been accomplished. Preload optimization is most efficient way of increasing cardiac output. Rapid intravascular volume expansion guided by repeated clinical examination and urine output is frequently adequate to restore blood pressure and peripheral perfusion. Pulmonary edema with volume overload is rare in pediatric age group. Volume replacement of 20 ml/Kg with isotonic solutions such as normal saline or ringers lactate can be safely given and repeated if necessary (typically 40-80 ml /Kg may be required). Controversy continues about whether colloids or crystalloids are preferable.[11-13]

Choice of fluid for volume replacement

Crystalloids : Crystalloids are readily available ,cheap, convenient to use, free of side-effects. Crystalloids are rapidly distributed across intravascular and interstitial spaces. Volume 2-4 times of colloid is required for same 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 may be used , however may not be practical to use as a resuscitation fluid.

Albumin : Albumin should be used only in special circumstances *e.g.,* burns or documented hypoalbuminemia such as nephrotic syndrome. Recently one study in patients with malaria showed beneficial effect of albumin when compared to normal saline in fluid resuscitation.[12]

In resource limited countries cost of therapy is an issue while considering colloid solutions for expansion of plasma volume. In dengue shock syndrome three studies have looked at different fluid regimens with no significant differences[11, 13, 14] in outcomes.

METHOD OF FLUID ADMINISTRATION

A 60 ml syringe filled with fluid drawn *via* the fluid bag with a three way connection can be conveniently used to push fluid boluses in the absence of a volumetric pump.

Children normally have a lower BP than adults and can prevent reduction in BP by vasoconstriction and increasing heart rate. Therefore, BP by itself is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow.

Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of the adequacy of fluid resuscitation. Other practical ways to assess fluid overload are jugular venous distension, heart size and pulmonary congestion on chest radiographs. Bedside echocardiography (ECG) should be used if available to assess cardiac function and signs of fluid overload. Gold standard to measure intravascular volume status still remains the measurement of a central venous pressure.

HYPOCALCEMIA AND HYPOGLYCEMIA

Before cardiac output and perfusion pressure are restored with drugs, electrolyte abnormalities (such as ionized hypocalcemia) that might impair cardiac performances should be corrected.

Hypoglycemia should be corrected followed by maintenance glucase of 4-6 mg/Kg/min. Hyperglycemia should be avoided as it has been associated with poor outcomes from adult ICU studies. Pediatric evidence for empirical use of insulin to correct hyperglycemia is lacking except in diabetes mellitus. In pediatric sepsis therefore initially glucose free fluids may be preferred as long as blood sugar is low and being not frequently monitored. Insulin therapy may be used for persistent hyperglycemialow and being.

EARLY ANTIBIOTICS

After appropriate cultures are taken , early use of broad spectrum systemic antimicrobial therapy based on clinical suspicion is reasonable although no randomized studies exist in children. Commonly used antibiotics include a third generation cephalosporin such as ceftriaxone and an aminoglycoside such as amikacin. Adult data supports use of early appropriate antibiotics to impact favorably on morbidity from septic shock.[10]

Inotropic and vasoactive agents

Starting a second peripheral Intravenous line and dopamine should be considered since fluid administration is ongoing.

FLUID REFRACTORY SHOCH

15 min-60 min

Recognition of fluid refractory shock is important.

If signs of shock persist despite adequate volume replacement and perfusion of vital organs is jeopardized, Inotropic drugs may be used to improve cardiac outputs.[15] The effects of particular drug in an individual patient are unpredictable and must be closely monitored. Ketamine and atropine should be used to obtain airway control and central line access. Various agents commonly used in pediatric ICU to increase myocardial contractility or to achieve peripheral vasoconstriction include :

Dopamine: It has alpha, beta and dopaminergic (delta) actions that are dose dependant. At low doses (< 3 mcg/Kg/min) it primarily causes weak renal and splanchnic vasodilatation, and at 3mcg to 10 mcg/Kg/min it exerts a positive myocardial inotropic effect. At higher doses (> 10 mcg/Kg/min), it has strong vasoconstricting alpha effect, in addition to positive inotropic effect. So called 'Renal dose' of dopamine (2-5 mcg/Kg/min) for renal vasodilation has been over emphasized and is of less practical significance in clinical setting. The primary indication for dopamine is the need to increase myocardial contractility after preload restoration. Usual dose is 5-20 mcg/Kg/min titrated to desired effect. Dopamine (in doses >10 mcg/Kg/min) should preferably, be given via central line to prevent ischemic necrosis of the skin.

Dobutamine: It is selective beta 1 agonist. It causes an increase in cardiac contractility and reduces peripheral resistance. The reduction in afterload and improved myocardial performance lowers ventricular filling pressures. Usual dose is 5mcg to 20mcg/Kg/min. It should not be used alone in septic shock due to risk of

further drop in blood pressure. In combination with dobutamine, any of the following : dopamine, adrenaline, or noradrenaline can be used to prevent hypotension due to their vasoconstrictive action.

Adrenaline (Epinephrine): It is an alpha and beta adrenergic agonist. It is used in situations where dominant hemodynamic feature is peripheral vascular failure as in septic shock. At higher doses severe vasoconstriction can lead to lactic acidosis and renal and splanchnic ischemia. The usual dose is 0.1 mcg/Kg/min to 1 mcg/Kg/min. It should be titrated closely and minimum dose should be used for required effect.

Noradrenaline (Norepinephrine) : An alpha and beta agonist (alpha > beta effect). Cardiac contractility is increased but it also causes massive increase in myocardial oxygen consumption and afterload, so cardiac output may not actually increase. Usual dose is 0.05 -1 mcg/Kg/min. In warm septic shock with hypotension despite use of adrenaline secondary to intense vasodilatation, noradrenaline may be useful in increasing peripheral vascular resistance to improve BP.

60 minutes

RECOGNIZE CATECHOLAMINE RESISTANT SHOCK

Hydrocortisone therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency. Patients at risk include children with severe septic shock and purpura, children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. There is no clear consensus for the role of steroids or best dose in children with septic shock.[16-19] A dose of 50 mg/m^2/24hr has been recommended recently.[4]

At this point in time a decision to admit the patient to a PICU facility should have been made with further management guided by CVP monitoring, attaining normal mean arterial pressure and a mixed venous oxygen saturation >70%.

FURTHER MANAGEMENT IN PICU

Further titration of fluid and inotrope therapy will need invasive monitoring in the PICU. Attempt should be made to arrange transfer to a pediatric intensive care unit. In PICU the following therapies under the heading of "Beyond 60 min" may be feasible, therefore these will be discussed in detail for the clinician who may have access to the latest technology and medications.

Beyond 60 min

COLD SHOCK WITH NORMAL BLOOD PRESSURE

Primary goal is to titrate epinephrine to achieve mixed venous oxygen saturations (ScVO2) >70%.Secondary goal is to titrate fluid therapy(volume loading) before adding a vasodilator such as nitrosovasodilator, milrinone or inamrinone(same as amrinone). Caution should be used in using afterload reduction indiscriminately in septic shock without simultaneous inotropic support. Both nitroprusside and nitroglycerin lower systemic vascular resistence in children and are useful afterload reducing agents. These agents act via generation of nitric oxide. Nitroprusside has potent peripheral arterial vasodilating effects. Nitroglycerin is more potent venodilator and pulmonary vasodilator. Close monitoring and volume augmentation are frequently required when vasodilators are used to decrease pulmonary vascular resistance.

An alternative approach to improve cardiac contractility and lower systemic vascular resistance is based on the use of type III phosphodiesterase inhibitors (PDEI): Milrinone and Inamrinone.[20-25]

These are newer inotropic agents with properties of afterload reduction and myocardial diastolic relaxation (lusotropic effect). This class of agents, which includes milrinone and inamrinone [formerly amrinone, but the name was changed to avoid confusion with amiodarone], has a synergistic effect with beta-adrenergic agonists since the latter agents stimulate intracellular cAMP_production while the PDE inhibitors increase intracellular cAMP by blocking its hydrolysis. Since the PDE inhibitors do not depend on a receptor mechanism, they maintain their action even when the beta-adrenergic receptors are down-regulated or have reduced functional responsiveness. The main limitation of these agents is their need for normal renal function (for milrinone clearance) and liver function (for inamrinone clearance). Inamrinone and milrinone are rarely used in adults with septic shock because catecholamine refractory low cardiac output and high vascular resistance is uncommon; however, this hemodynamic state represents a major proportion of children with fluid-refractory, dopamine-resistant shock. Fluid boluses are likely to be required if inamrinone or milrinone are administered with full loading doses. Because milrinone and inamrinone have long half-lifes (1 -10 hours depending on organ function) it can take 3 to 30 hours to reach 90% of steady state Milrinone is commonly used for cardiogenic shock which is frequently associated with septic shock.

CLINICAL SIGNIFICANCE OF MIXED VENOUS OXYGEN SATURATION(SCVO2)

Because low CO is associated with increased O_2 extraction[26] $ScvO_2$ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue oxygen delivery is adequate, then assuming a normal arterial oxygen saturation of 100%, mixed venous saturation is > 70%. Assuming a

hemoglobin concentration of 10 gm/dL and 100% arterial O_2 saturation then a cardiac index (CI) > 3.3 L/min/m^2 with a normal oxygen consumption of 150 mL/min/m^2 (O_2 consumption = CI x (arterial O_2 content – venous O_2 content) results in a mixed venous saturation of > 70% because 150 mL/min/m^2 = 3.3 L/min/m^2 x [1.36 x 10 gm/dL + paO2 x 0.003] x 10 x [1 -0.7] . In an emergency department study in adults with septic shock, maintenance of superior vena cava O_2 saturation > 70% by use of blood transfusion to a hemoglobin of 10 gm/dL and inotropic support to increase cardiac output, resulted in a 40% reduction in mortality compared with a group in whom MAP and CVP were maintained at usual target values without attention to superior vena cava O_2 saturation.[27] Since 2002, Oliveira and colleagues reproduced this finding in children with septic shock reducing mortality from 39% to 12% when directing therapy to the goal of $ScvO_2$ saturation > 70% (personal communication).

Levosimendan[28-32]

Levosimendan is a promising new medication that increases Ca^{++}/actin/tropomyosin complex binding sensitivity and also has some Type III PDEI and ATP-sensitive K^+ channel activity. Because one of the pathogenic mechanisms of endotoxin induced heart dysfunction is desensitization of Ca^{++}/actin/ tropomyosin complex binding, this drug allows treatment at this fundamental level of signal transduction overcoming the loss of contractility that characterizes septic shock. It doesn't increase the myocardial oxygen requirement.

COLD SHOCK WITH LOW BLOOD PRESSURE

Epinephrine needs to be titrated to achieve ScvO2>70%. If ScvO2 is <70%norepinephrine should be added. Dobutamine may also need to be added. Milrinone may be considered as it is available in India. At the time of publication of this article levosimendan and enoximone are not freely available in India.

Enoximone[33, 34]

Enoximone is a Type III PDEI with 10 times_more $beta_1$ cAMP hydrolysis inhibition than $beta_2$ cAMP hydrolysis inhibition. Hence, it can be used to increase cardiac performance with less risk of undesired hypotension.

WARM SHOCK WITH LOW BLOOD PRESSURE

In patients with warm shock with low blood pressure primary goal is to titrate norepinephrine to achieve mixed venous oxygen saturation above 70 % indicating improved tissue oxygen delivery. Secondary goals include consideration of use of vasopressin if $ScVO_2$ continues to be less than 70%.

Vasopressin(VP)

In severe warm shock with hypotension resistant to noradrenaline,vasopressin may be tried as a last resort. Terlipressin is long acting vaspressin and is also available Vasopressin does not use catecholamine receptors, and its efficacy is therefore not affected by ongoing alpha-adrenergic receptor down-regulation. Actions of VP are mediated via its three receptor subtypes designated as V1 (V1R/V1a), V2 (V2R) and V3 (V1b).[35]

V1 vascular receptors are located on vascular smooth muscle and mediate vasoconstriction. Additionally, V1 receptors are found in the kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis. V1-receptor activation mediates vasoconstriction by receptor-coupled activation of phospholipase C and release of Ca++ from intracellular stores *via* the phosphoinositide cascade.[36, 37]

V2 renal receptors (V2R), which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V2 receptors interact with adenyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) and cause retention of water.[37] V3 pituitary receptors (formerly known as V1b) have central effects, such as increasing adrenocorticotropic hormone (ACTH) production, activating different G proteins, and increasing intracellular cAMP.[38]

VP also acts on oxytocin receptor which is important from the point of view of its vasodilator action on certain vital organs through nitric oxide (NO) mediated pathway. Blood flow within the coronaries, as well as the cerebral, pulmonary, and renal vascular beds, is preserved, promoting shunting to those areas. This regional vasodilation is likely the result of a complex interplay of vasopressin activity at V1 and endothelial V3 and oxytocin receptor sites producing an increase in nitric oxide release. In addition to these direct effects, vasopressin may also enhance or restore catecholamine sensitivity.

Synthetic vasopressin (8-arginine vasopressin) acts at the same receptor sites as endogenous vasopressin, producing an identical physiologic response.[38]

Terlipressin is a long acting analogue of vasopressin that has been shown to have higher affinity for vascular receptors than vasopressin and has demonstrated potent vasopressor effects in adult patients with norepinephrine resistant septic shock.[39]

Although angiotensin can also be used to increase blood pressure in patients who are refractory to norepinephrine, its clinical role is not as well defined.[40]

Phenylephrine is a another pure vasopressor with no

beta adrenergic activity.[41] Its clinical role is also limited. Vasopressors can be titrated to end points of perfusion pressure (MAP-CVP) or systemic vascular resistance that promote optimum urine output and creatinine clearance,[42,43,44] but excessive vasoconstriction compromising microcirculatorly flow should be avoided.

Low dose arginine vasopressin (AVP; in doses = 0.04 units/Kg/min) as an adjunctive agent has short term hemodynamic benefits in adults with vasodilatory shock. It is not currently recommended for treatment of cardiogenic shock, hence it should not be used without $ScvO_2$/cardiac output monitoring. Because vasopressin is destroyed by gastric trypsin, it must be administered parenterally.

Vasopressin is rapidly degraded by enzymes in the liver and kidneys, with elimination half-life of approximately 10 to 35 minutes.[35] Renal insufficiency and hepatic failure prolong its half-life. Vasopressin is available as a 20-unit/ml injection. For continuous intravenous infusion, it should be diluted with normal saline or 5% dextrose to a final concentration of 0.1 to 1 unit/ml. Administration through central venous access is recommended to minimize the risk of extravasation.

Studies of vasopressin in adults with vasodilatory shock have used infusion rates of 0.01 to 0.1 units/min. In pediatric patients, a vasopressin dose of 0.3 to 2 milliunits/Kg/min (equivalent to 0.0003 to 0.002 units/Kg/min or 0.01 to 0.12 units/Kg/hr) is recommended, based on the report by Rosenzweig.[45] The infusion should be titrated to optimize blood pressure and perfusion. It has been suggested that vasopressin infusions may be tapered over a 2 to 3 hour period, once blood pressure and the doses of concomitant catecholamine infusions are stabilized.

Vasopressin has been shown to increase mean arterial pressure, systemic vascular resistance, urine output in patients with vasodilatory septic shock and hyporesponsiveness to catecholamines.[45-50]

Terlipressin has been reported to reverse vasodilated shock in several pediatric studies.[51-54]

Despite all of the above studies, no study has shown the effect of low-dose AVP on clinically important outcomes such as mortality. Therefore its use can only be recommended as a last resort in warm hypotensive shock unresponsive to fluids and norepinephrine.

Beyond 60 min

Persistent Catecholamine Resistant Shock

One must rule out mechanical causes of catecholamine resistant shock such as tamponade due to pericardial effusion,pneumothorax or increased intra abdominal pressure (patients with severe ascitis in leaky phase of dengue shock syndrome). Beyond 60 minutes refractory shock has a high mortality, specially since measures described such as Extra corporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) are not readily available.

Therapeutic End Points

Therapeutic end points following above mentioned interventions are capillary refill of <2 seconds, normal pulses with no differential between peripheral and central pulses, warm limbs, urine output of >1 mL/Kg/hr, normal mental status, decreased lactate, and increased base deficit and mixed venous oxygen saturation of >70%.

When employing measurements to assist in identifying acceptable cardiac output in children with systemic arterial hypoxemia such as cyanotic congenital heart disease or severe pulmonary disease, arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation of oxygen.

Optimizing preload optimizes cardiac index. As noted above, BP by itself is not a reliable end point for resuscitation.

CONCLUSIONS

Sepsis is a common problem with high mortality in neonates and children. Infants and children are recognized to have more difficult intravenous access, therefore necessitating use of intraosseous access is required. Early fluid resuscitation (crystalloid or colloids) based on weight with 40-60 mL. kg or higher may be needed. Central line is sometimes difficult to insert, therefore use of peripheral dopamine has been included in guidelines. Decreased cardiac output and increased systemic vascular resistance tends to be most common hemodynamic profile. Dopamine is recommended as the initial agent for hemodynamic support. Early appropriate antibiotics, correction of hypoglycemia, hypocalcemia and avoiding hyperglycemia are recommended. Pediatric recommendations include use of rapid cardiopulmonary assessment and greater use of physical examination for achieving therapeutic endpoints. CVP monitoring should be attempted whenever possible. Early mechanical ventilation should be considered if hemodynamic instability continues beyond fluid therapy

Issue of high-dose steroids for therapy of septic shock remains unsettled, although recommendation include use of steroids for catecholamine unresponsive shock in presence of a suspected or proven adrenal insufficiency, further fluid therapy and inotropic support can be guided by CVP once a PICU facility is available, and mixed venous oxygen saturations can be monitored.

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