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Management of Pediatric emergencies: Septic shock

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ABSTRACT

Septic shock is a common cause of admission to the pediatric emergency and Pediatric Intensive Care Units requiring prompt recognition and management. The dynamic nature of the illness and the high mortality and morbidity rates associated with it make septic shock the most challenging disease to treat. Early recognition and aggressive time bound resuscitation is the key to successful outcome in children with septic shock. Therefore, guidelines for the management of septic shock laid down by the Surviving sepsis Campaign Committee are base on these principles. In this article, the physiologic principles behind shock states, the types of septic shock and the management of septic shock are discussed in detail with a special reference to resource restricted settings.

Key Words: sepsis, septic shock, physiologic principles, surviving sepsis campaign guidelines, Early goal directed Therapy, mixed venous oxygen saturation

INTRODUCTION

Shock is a clinical state characterized by inadequate tissue perfusion resulting from delivery of oxygen and metabolic substrates that is insufficient to meet metabolic demands. If unchecked, it leads to anaerobic metabolism and tissue acidosis thus causing irreversible cell damage. Treatment of shock should be aimed at maintaining the perfusion pressure above the critical point below which blood flow cannot be effectively maintained in individual organs. This is possible only with timely recognition and goal directed therapy. The outcome of unrecognized and untreated shock is universally lethal, be it in adults or children. [1,2,3]

Septic shock (SS) is a frequent cause of admission to the pediatric intensive care unit requiring prompt recognition and intervention. Septic shock and multi-organ dysfunction are the most common causes of death in patients with sepsis. The mortality rates associated with severe sepsis and septic shock reported from developed countries are 10% for children with severe sepsis and about 50% for children with septic shock.[4,5] The figures reported from Indian ICUs are also higher ranging from 40%-67%. [6, 7, 8] However, with increasing awareness of the importance of time sensitive goal-directed therapies we hope that this mortality rate will show a declining trend in future.

For the purpose of the article, the discussion of septic shock would be restricted to the physiologic principles, clinical features and management of septic shock on the basis of the surviving sepsis campaign guidelines. [9] The interested reader is referred to pediatric critical care books and literature available on sepsis and septic shock for a complete reading. [1, 2, 10,11]

PHYSIOLOGIC PRINCIPLES OF SHOCK

Determinants of tissue oxygen delivery

It has been seen that in children, unlike adults, oxygen delivery and not oxygen

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extraction is the major determinant of oxygen consumption and attainment of therapeutic oxygen consumption goal of *200 ml/min/m²* has been found to be associated with improved outcome.[12] As shock progresses or increases in severity, perfusion pressure is reduced below the ability of the organ to maintain blood flow. This decrease in oxygen delivery is associated with a decrease in cellular partial pressure of oxygen. When PO_2 falls below critical levels, oxidative phosphorylation comes to a halt and there is a shift from aerobic to anaerobic metabolism resulting in a rise in cellular and blood lactate concentration and a decrease in ATP synthesis. During this stage of shock, which occurs early in the course, *oxygen extraction* increases and this is reflected in the form of a low SVO2 (mixed venous oxygen saturation) thus implying more oxygen being extracted from the blood to combat the tissue hypoxia. It is at this stage that interventions to improve oxygen delivery by improving either the *oxygen content* or *cardiac* output might be helpful. Oxygen content can be improved by correcting anemia and/or providing 100% oxygen to the child with shock. [3, 10,11]

Factors affecting cardiac output

The cardiac output is a product of stroke volume and heart rate (CO = SV x HR). The relative ability of infants and children to augment cardiac output through increased heart rate is limited by their preexisting elevated heart rate, which limits proportionate increase in heart rate without compromising diastolic filling time. Also, the increased connective tissue content of the infant's heart and decreased actin and myosin content of the infant's heart limit the potential for acute ventricular dilatation. Thus, the other option is to increase the stroke volume (SV). SV is dependent on the preload, contractility and after load. [3, 10, 11]

The first step in the management of shock is to ensure adequate preload or end-diastolic volume. According to *Frank Starling* phenomenon, ventricular contraction and measures to improve the same will be effective only if the preload is adequate. In every stage of shock, therefore, optimal preload should be ensured even after starting measures to improve the contractility and afterload.

After ensuring optimal preload, we can target either the contractility (by using inotropic agents) or the afterload (by using vasodilators/vasopressors) depending on the type of shock. The perfusion pressure is dependent on both cardiac output and systemic vascular resistance (SVR) or the afterload. It should, however, be noted that an excessive increase in SVR might decrease the cardiac output (as in cold shock) and thereby the perfusion pressure. In such instances, one might have to use either a vasodilator and/or an inotrope to maintain the cardiac output. [1,3,10,11]

Contrary to the adult experience, low cardiac output and not low systemic vascular resistance was associated with increased mortality in pediatric septic shock. Attainment of the therapeutic goal of a cardiac index (CI) of 3.3-6.0 L/min/m² was associated with improved survival in these children.[13]

The above physiologic principles are common to all the types of shock whether it is septic, cardiogenic, obstructive or hypovolemic and form the basis for treatment.[10,11]

Concept of mixed venous oxygen saturation (SVO2)

Having understood the relation between oxygen content and delivery, we need to look at the relation between oxygen delivery and consumption too, as the concept of early goal directed therapy (EGDT) for management of septic shock stems from these physiological principles. [14] In this context, mixed venous oxygen saturation (measured at the level of pulmonary artery) emerges as a useful tool in assessing the relation between oxygen consumption and oxygen delivery (VO2 – DO2). According to Fick's principle, VO2 = CO x (CaO2 –CVO2), where CVO2 = mixed venous blood oxygen content. As with the oxygen content in the arterial blood, mixed venous blood oxygen content is dependent on the mixed venous saturation (SVO2), cardiac output, and amount of hemoglobin. SVO2 would decrease with one or more of the following pathologies: hypoxemia, increased

oxygen consumption or reduction in cardiac output. [10,11]

Normally, SVO2 is between 65-77% as the oxygen extraction is 20-30%. In shock, with decreased oxygen delivery to the tissues, the oxygen extraction at the tissue level increases. This will decrease the SVO2. In late stages of shock, oxygen delivery is compromised to such an extent that oxygen extraction ratio increases to 60%. At this point, cardiac output will have to increase to compensate for the decrease in arterial oxygen content; otherwise, SVO2 will decrease to 40%. At 40% SVO2, there is an imbalance between arterial oxygen supply and oxygen demand which inevitably leads to sever tissue hypoxia. Indeed, in patients with septic shock, even a decrease in SVO2 of 5% from its normal value (65-77%) represents a significant fall in tissue oxygen delivery and /or an increase in oxygen demand. [10] Since SVO2 gives an indirect measurement of tissue perfusion in the early stages of shock, it is being used as one of the resuscitation end points in the management protocol of septic shock.[1,10,14] However, owing to the need for pulmonary catheterization to measure SVO2, which is neither practical nor feasible in most centers, the concept of superior venacaval saturation (SCVO2) came into existence. The advantage of determining SCVO2 over SVO2 is that it requires the insertion of a standard central venous catheter. It can be measured continuously or intermittently.[15] However, whether measurement of SCVO2 is a good surrogate for measurement of SVO2 is still not clear. The absolute values of SCVO2 are almost always higher than that of SVO2 and the two parameters track one another closely over a range of hemodynamic status.[16] Also, one has to bear in mind that femoral central venous oxygen saturation which reflects oxygen consumption of the lower limbs and intra abdominal organs cannot be substituted for subclavian/internal jugular central venous oxygen saturation as the brain is the most important organ in our body and we are more interested in the oxygen consumption of the brain which is reflected in the saturation of the superior vena cava. [17]

Hemodynamics in pediatric septic shock

Septic shock in children is most commonly associated with severe hypovolemia. More often, this is only relative hypovolemia secondary to maldistribution of cardiac output. Thus it is imperative to have an adequate fluid resuscitation to ensure the effective preload to the heart. Children frequently respond well to aggressive volume resuscitation; however, the hemodynamic response of children who are fluid resuscitated seems diverse compared with adults. [3,13]

Ceneviva et al. described 50 children with fluid-refractory (>60 ml/kg in the first hour), dopamine-resistant shock. The majority (58%) showed a low cardiac output and high systemic vascular resistance state, and only 22% had low cardiac output and low vascular resistance. Hemodynamic states frequently progressed and changed during the first 48 hrs. Persistent shock occurred in 33% of the patients. There was a significant decrease in cardiac function over time, requiring addition of inotropes and vasodilators. Although decreasing cardiac function accounted for the majority of patients with persistent shock, some showed a complete change from a low output state to a high output and low systemic vascular resistance state.

Inotropes, vasopressors, and vasodilators were directed to maintain normal Cardiac Index (CI) and systemic vascular resistance in the patients. Attainment of the therapeutic goal of a CI of 3.3-6.0 L/min/m^2 was associated with improved survival. Thus it is clear from the above study that the hemodynamic presentation in children with septic shock may be heterogeneous and change over time and therefore constant monitoring of these children with changes in therapy as required is imperative for better outcome. [13]

Clinical features and laboratory markers of shock

The clinical features of shock in children can be grouped into two types, namely cold shock and warm shock (see Table 1). [1,3,9] It is important to differentiate between the two types, as not only the hemodynamics but also the choice of vasoactive agents differs in these

two types. One has to be careful in chosing the vasoactive agent in either of these types, as use of an inappropriate vasoactive agent may prove to be detrimental and cause more harm than good. Also, one has to bear in mind that the hemodynamics in children with septic shock keep changing with time and therefore only continuous monitoring of the clinical signs will help in keeping pace with these changes and provide scope for revisions in fluid and Vasoactive therapy.

Apart from abnormal values of superior vena caval oxygen saturation as mentioned above, serial base deficit and blood lactate values are important markers of systemic hypoperfusion and can be used as therapeutic end points in the monitoring and treatment of shock. [10,11]

Table 1. Clinical and Laboratory features of 'Cold shock' and 'Warm shock

Clinical / Lab parameters	Cold shock	Warm shock
1. Tachycardia	Present	Present
2. Pulses	Feeble	Bounding
3. Blood pressure	Normal or decreased (in late stages)	Normal or decreased (in late stages) with wide pulse pressure
4. Peripheries	Cool, mottled	Warm
5. CRT	>2 secs	Flush, <2 secs
6. Urine output	Decreased	Decreased
7. Sensorium	Altered	Altered
8. Urine Output	Decreased	Decreased
9. Scvo2	<70%	Usually > 70%
10. Lactate/ Base Deficit	Increased	Increased

MANAGEMENT OF SHOCK

The management of shock is aimed at restoration of microcirculation and improving organ tissue perfusion which can be achieved by early recognition, timely intervention with fluid therapy and considering vasoactive agents in fluid resistant shock. Inadequate early resuscitation results in multiple organ system failure and in death days to weeks after the initial presentation.[1] This has been confirmed by a recent meta-analysis which suggested that aggressive resuscitation efforts started early (before the onset of organ failure) may prove more beneficial than resuscitation carried out after the establishment of organ failure.[18] The management guidelines for septic shock in adults and children have been laid down by the Surviving Sepsis Campaign Committee which is a time bound guideline based on the concept of Early Goal Directed Therapy (EGDT). [14]

Early goal-directed therapy (EGDT) is a research innovation that uses a set of clinical and laboratory parameters including measurement of superior vena caval oxygen saturation lactate and base deficit to titrate therapeutic end points in patients with septic shock. Thus, EGDT is simply a protocol derived from components that have long been recommended as standard care for the septic patient in the setting of the Emergency and ICU. In a study of 263 adult patients, EGDT was associated with a 16% absolute risk reduction for in-hospital mortality, which to date is the largest mortality benefit demonstrated in septic shock.[14] The EGDT protocol has been modified and advocated for pediatric septic shock in the "surviving sepsis campaign guidelines" with similar resuscitation end points like ScvO2 >70 % ,decreased lactate, urine output > 1ml/kg/hr, CRT<2 sec, normal mental status and normal pulses with no difference between peripheral and central pulses. [9]

'SURVIVING SEPSIS CAMPAIGN' GUIDELINES

In 2004, an international group of experts in the diagnosis and management of sepsis representing 11 organizations published internationally accepted guidelines for management of patients with severe sepsis (*Surviving Sepsis Campaign Guidelines*).[9] The 2004 guidelines had been recently updated in January 2008 by incorporating the available evidence in the preceding 3 years. Also, a new evidence-based methodology system had been used for assessing the quality of evidence and strength of recommendations. These guidelines cover almost all aspects of management of children with severe sepsis and septic shock like early and aggressive resuscitation of septic shock with fluids and vasoactive agents, administration of adjuvant therapy, source control measures, and management of other organ dysfunction. The guidelines emphasize the importance of early recognition of shock and have therefore drawn out an action plan which is time bound from the time of recognition of shock. [9]

Before proceeding with the management guidelines, we need to understand the pharmacokinetic properties and role of various vasoactive agents mentioned in the guideline at different stages. This information would also be used as reference for the clinical questions to be discussed in the next issue (See Table 2). [1, 3]

Table 2: Vasoactive agents used in various types of shock

	Inotrope	Vasopressor	Vasodilator
Mechanism of action	Increases contractility and / or heart rate	Elevate SVR by increasing the tone of arterial circulation	Decrease arterial resistance, resulting in decreased afterload and increased cardiac output without affecting contractility
Indication	Cold shock with normal blood pressure, when blood pressure is low use in combination with a vasopressor	Warm shock with low blood pressure, cold shock with low blood pressure (used in combination with an inotrope),	Diminished peripheral perfusion with normal blood pressure, low cardiac output states
Examples	Dopamine, dobutamine, epinephrine, milrinone, *digoxin**,	Dopamine, epinephrine, *vasopressin#*, *norepinephrine#*,	Dobutamine, *Nitrogycerine$*, *nitroprusside$*, milrinone lactate$,

*Purely inotropic/chronotropic action; #Purely pressor effect;$ Purely vasodilator effect

Surviving sepsis campaign guidelines for the management of septic shock in children

According to the guideline, when a child presents with septic shock to the emergency/ ICU aggressive fluid resuscitation with crystalloids/colloids of up to 60 ml/kg as boluses of 20ml/kg is to be pushed by IV route over the first 15 minutes to achieve desired heart rates, and blood pressure. This strategy is a relatively inexpensive and feasible intervention, but underutilized. A possibility of fluid overload should be kept in mind specifically in malnourished children. This may however be overcome by intense clinical monitoring.

If a patient does not respond to aggressive fluid therapy (fluid refractory shock), central venous line should be placed and 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 septic shock be managed in intensive care setting. However, given the scarcity of ICU beds, the emergency physicians should be well equipped with the knowledge and skills required to resuscitate such children in the emergency department.

In case of shock refractory to dopamine or dobutamine, epinephrine or nor-epinephrine should be used depending on whether the child has cold shock or warm shock, respectively. If there is no response to the above catecholamines then the $ScvO_2$ (requires central venous catheter placement in the superior vena cava) should be monitored apart from clinical and hemodynamic variables and vasodilators/ Phosphodiesterase (PDE) inhibitors could 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 could be titrated depending on whether the child has cold shock or warm shock.

Use of adjuvant therapy

Steroids are to be used only in children with suspected or proven adrenal insufficiency. Pediatric data shows high prevalence of adrenal insufficiency in children with septic shock, especially catecholamine refractory shock. [19] As cortisol estimation results 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.

Based on a recent large trial in children which did not demonstrate any effect of recombinant activated protein C, it can be concluded that there is no role of recombinant activated protein C. [20] There are some data to suggest improved survival and reduced hospital stay with intravenous immunoglobulin (IVIG) in children with severe sepsis and septic shock. As the data are limited, IVIG may be considered in carefully selected group of children with severe sepsis. [21]

Administration of broad-spectrum antibiotics in parallel with fluid resuscitation to cover for the likely pathogens (including gram positive and gram negative) within 1 hr of diagnosis of septic shock / severe sepsis as well as reassessment of antibiotic therapy after microbiologic data is available, to narrow coverage, when appropriate is recommended . The choice may vary from unit to unit based on the sensitivity patterns. It is desirable to have surveillance data on microorganisms and their sensitivity.

Use of 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) are other measures to improve outcome in these patients. [22] 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. [9]

The evidence for beneficial effects of strict glycemic control is not very strong. However it is important to avoid hypoglycemia by proper monitoring.[23] Routine stress ulcer prophylaxis is not recommended.[24] Prophylaxis for deep vein thrombosis (DVT) may be useful specifically in post pubertal children with severe sepsis.[25] The recommendations of the committee are largely based on studies from developed countries where there are resources to do ECMO and pulmonary artery catheterization in PICU patients.

The guidelines discussed above cannot be universally applied to PICU/emergency departments from developing countries as these resources are not uniformly available across the country. Therefore, a modified algorithm for the management of septic shock in resource restricted settings is proposed (see

In conclusion, the dynamics of septic shock change with time and therefore early recognition, timely intervention and close monitoring are imperative for improving the mortality and morbidity associated with this condition. While managing these children, the

important physiologic principles of oxygen delivery, cardiac output and oxygen consumption should be kept in mind and therapy should be titrated to optimize these values. In the subsequent issue, we shall be looking at the evidence behind the recommended vasoactive agents used in septic shock.

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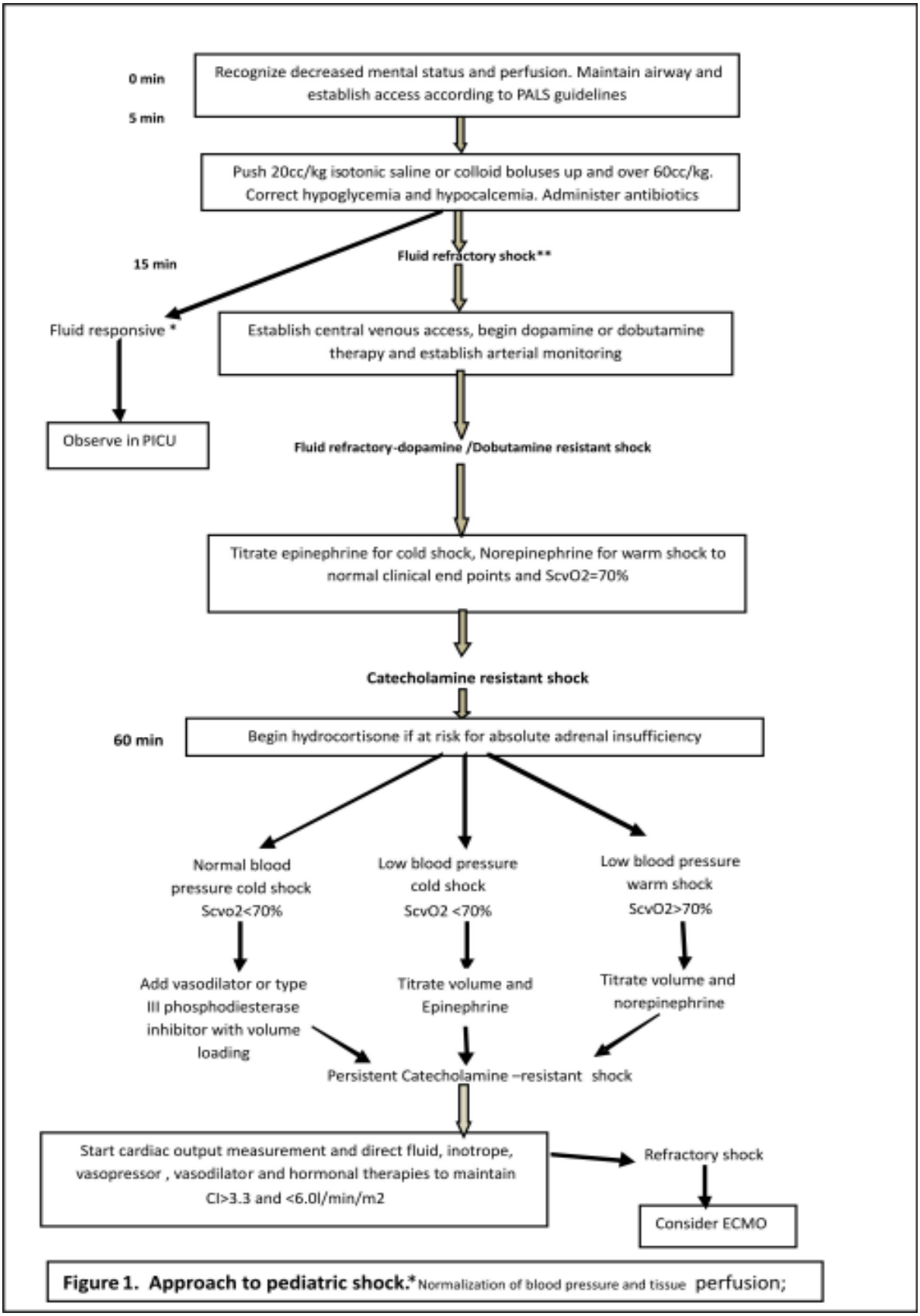
Editor's note

In the second part in the series on 'Management of Pediatric/Neonatal emergencies' we would be dealing with one of the most commonly encountered clinical conditions in pediatric emergency and intensive care units – septic shock . Since it is important to understand the physiologic principles involved in the management of septic shock before embarking upon evidence based management, we have restricted the discussion to physiologic principles of shock and standard guidelines for management of this dreaded condition in this issue. The clinical questions would be discussed in the forthcoming issues.

Figure 2. Approach to pediatric shock in resource restricted settings. *Normalization of blood pressure and tissue perfusion;hypotension, abnormal capillary refill or extremity coolness. Adapted from Surviving Sepsis Campaign**



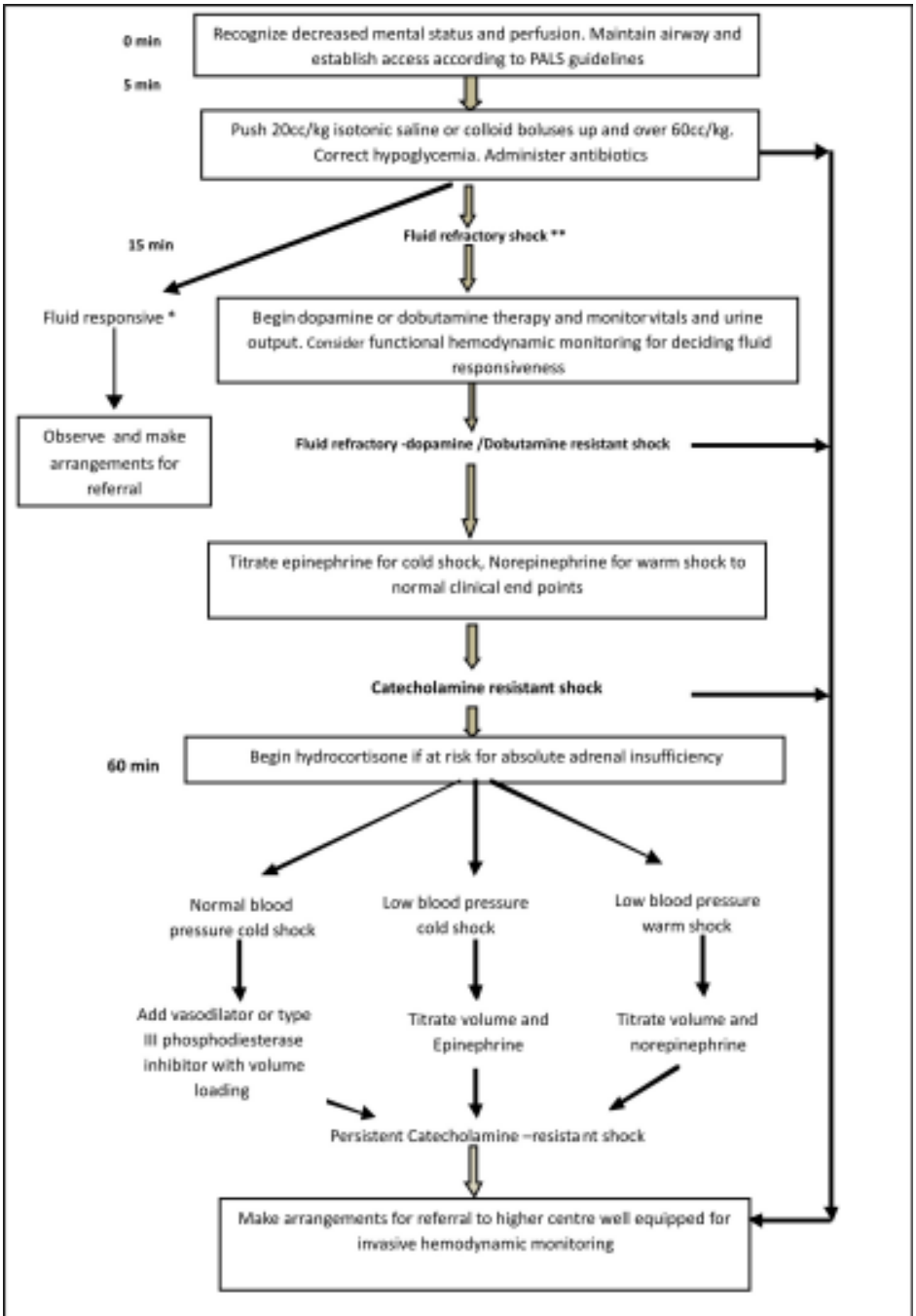


Figure 2. Approach to pediatric shock in resource restricted setting *Normalization of blood pressure and tissue perfusion;**hypotension, abnormal capillary refill or extremity coolness. Adapted from Surviving Sepsis Campaign guideline 2008