

Review Article

Guidelines for treatment of septic shock in resource limited environments

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Abstract. WHO 2005 data points to sepsis in form of pneumonia, diarrhea, and neonatal sepsis as major killers of children in the resource limited countries of Asia and Africa. However, currently there are no specific published guidelines for treatment of severe sepsis in resource limited circumstances. An expert panel drawn from all over India, met to discuss and draw guidelines for management of pediatric septic shock that are applicable to resource limited countries. The group evaluated strength of published data and expert opinion for clinical practice and feasibility of delivery of care at various levels of resource constraints, keeping in view unique patient population and limited availability of equipment and resources. Issues for discussion included simplified definitions and reliable clinical indicators of septic shock, fluid resuscitation, graded inotropic and vasopressor support, corticosteroid therapy, timing and indication for endotracheal intubation and use of positive end expiratory pressure/mechanical ventilation, initial empirical antibiotic therapy, correction of hypoglycemia and glycemic control, role of immunoglobulin, and blood and blood products. Evidence has been graded and levels of evidence indicated wherever applicable. The expert group recognized and listed potential barrier to implementation of existing American College of Critical Care Medicine guidelines for treatment of septic shock in resource limited countries, adopted simplified definitions of septic shock, tachycardia, tachypnea and hypotension, and developed step-wise algorithmic approach for treating septic shock. Evidence based treatment recommendations include early oxygen therapy, fluid resuscitation based on blood pressure, use of dopamine in fluid refractory shock, early use of antibiotics, early intubation and assisted ventilation, correction of hypoglycemia and emphasis on use of physical examination for achieving therapeutic endpoints. These interventions have brought the mortality down and can be easily applied even at primary and/or secondary level health facilities. Interventions recommended after above steps were based on

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consensus rather than evidence. These include stress dose steroid therapy, use of vasopressors and inodilators, and central venous pressure and echocardiography to guide fluid and vasoactive drug infusion, which require transfer to a pediatric intensive care unit. Strict glycemic control is not recommended. Evidence on benefit of several other interventions viz. use of vasopressin as vasopressor, use of intravenous immunoglobulins, renal replacement therapy, use of plasmapheresis etc. is emerging. The expert group observed that further research evaluating individual components of guidelines and relative benefit of each of these interventions in resource limited setting is needed, as also the benefit of adherence with standardized protocol. Pediatric sepsis guidelines suitable for resource limited settings are presented for resource limited settings. Several unresolved issues were identified for further research.

Keywords: Children, emergency care, septic shock, fluid resuscitation, vasoactive drugs

1. Introduction

Consensus definitions of sepsis were first published and later updated in a consensus conference [1,2]. Better understanding of pathophysiology, and existing therapies and development of new interventions in the past decade led to publication of 'Surviving sepsis campaign guidelines and American College of Critical Care Medicine (ACCM) clinical guidelines for hemodynamic support of neonates and children with septic shock [3, 4]. These guidelines were widely disseminated, were translated into Spanish and Portuguese, and have been tested and the outcomes published by many centers in Europe and America [5–7]. However, there are several potential barriers to the adherence and implementation of the guidelines in resource-limited settings.

Global data from WHO 2006 points to sepsis in form of pneumonia, diarrhea and neonatal sepsis as a major killer of children, more so in resource limited countries of Asia and Africa [8]. Sepsis (bacterial or viral) was a major cause of admission to an Indian pediatric intensive care unit (PICU) with multiple organ failure and resulted in high mortality [9]. Currently there are no published guidelines suited to resource-limited environment.

2. Aims and objectives

The aim was to develop guidelines for treating severe sepsis and septic shock appropriate for resource-limited settings after a review of published guidelines, available studies on severe sepsis and septic shock especially from resource limited countries. The objectives for the expert group were as follows:

- 1) Recognize and list potential barriers to implementation of ACCM guidelines in resource-limited settings,
- 2) Simplify the definitions of sepsis and septic shock

- 3) Describe rapid cardiopulmonary assessment as applicable to a child with suspected septic shock
- 4) Present the guidelines/recommendations for management of pediatric sepsis and septic shock in the first few hours with available resources.

3. Methodology

Initial discussions were held at the Annual Conference of Indian Academy of Pediatrics at Mumbai in January 2007 and later at the National Congress on Pediatric Critical Care, Delhi in December 2007. An expert representative panel drawn from all over India, under aegis of Intensive Care Chapter of Indian Academy of Pediatric met to discuss and draw guidelines for clinical practice and feasibility of delivery of care in pediatric patient with sepsis, keeping in view unique patient population and varying limited availability of equipment and other resources at various health facilities. Discussion included issues such as simplified definitions and reliable clinical indicators of septic shock, early fluid therapy, graded inotropic and vasopressor support, corticosteroid therapy, timing of endotracheal intubation and use of positive end expiratory pressure (PEEP)/assisted ventilation, initial empirical antibiotic therapy, correction of hypoglycemia and glycemic control, role of intravenous immunoglobulin (IVIG), and blood and blood products. A draft was prepared and circulated among the members of expert group for comments and critique. The suggestions received from the group were incorporated to prepare the final document.

4. Potential barriers to implementation of published sepsis guidelines

4.1. Limited availability of technology: *Monitoring/equipment/therapy*

There are limited numbers of intensive care unit beds available in developing countries [10]. According

to one estimate, in India there were only 0.04 PICU beds per 100,000 population in 2002, in contrast to 9.4 beds/100,000 in Australia [11,12]. Hence, most of the seriously ill children are treated at a health facility other than a PICU. There is a huge variation in the capacity of various health care delivery centers to take care of sick children [10,11].

The equipments [multisign monitors, pulse oximeters, central venous pressure (CVP) and invasive arterial pressure monitors, infusion pumps and mechanical ventilators] required to follow the ACCM guidelines may be non-available or available in very limited numbers depending on the level of health care delivery centre (Fig. 1).

Similarly, the laboratory support (complete blood counts, serum chemistry, arterial blood gases, lactate measurement, ionized calcium, radioimaging, echocardiography, microbiology laboratory and blood bank) that is required to follow the ACCM guidelines may be non-available or be available for a very limited time of the day.

4.2. *Inadequate number and/or inadequately trained staff*

Inadequate number and/or inadequately trained doctors and nurses at primary and secondary level facilities who are not conversant with the sepsis treatment guidelines and/or are not proficient in obtaining vascular access/airway control/mechanical ventilation.

4.3. *Limited availability of medications*

Fluids, commonly used antimicrobials, and some vasoactive drugs are available at most facilities but expensive antibiotics and vasoactive drugs such as amrinone, milrinone, norepinephrine, etc. are available scarcely.

4.4. *Inadequate transport facilities*

Availability of transport with mobile intensive care services has significantly improved survival rate from meningococcal disease in the United Kingdom [13]. Non-availability of appropriate transport facility may interfere with timely referral for optimal and specialized care and affect the outcome [14]. Of 733 children transported to tertiary pediatric emergency service (PGIMER Chandigarh) in mid 2004, two third had traveled more than 100 km by road. Only 15% of them had emergency drugs and intravenous fluid administration facility during transport. One third of these patients required fluid resuscitation on arrival (Singhi S, unpublished data).

4.5. *Delay in care-seeking*

This is an important issue in most settings and often leads to greater severity of illness and poor outcomes. Nine percent neonates, 5% infants and 1.5% of children 1–5 years arriving at pediatric emergency department (ED) of at PGIMER in 2003 were in shock and required fluid resuscitation on arrival [15].

4.6. *Other diseases: Malaria/dengue*

The ACCM guidelines do not discuss the issues related to malaria and dengue, which are important differentials in a child with fever and shock in many regions of Asia and Africa. Malaria, and dengue were important cause of sepsis and multiple organ failure in children admitted to an Indian PICU with fever and shock [16]. Most patients with dengue shock syndrome would respond simply to oxygen and fluid resuscitation, which may not be as aggressive as in septic shock [17]. In malaria, fluid management may be different; one study from Africa suggests benefit from use of albumin [18].

4.7. *Malnutrition- different management?*

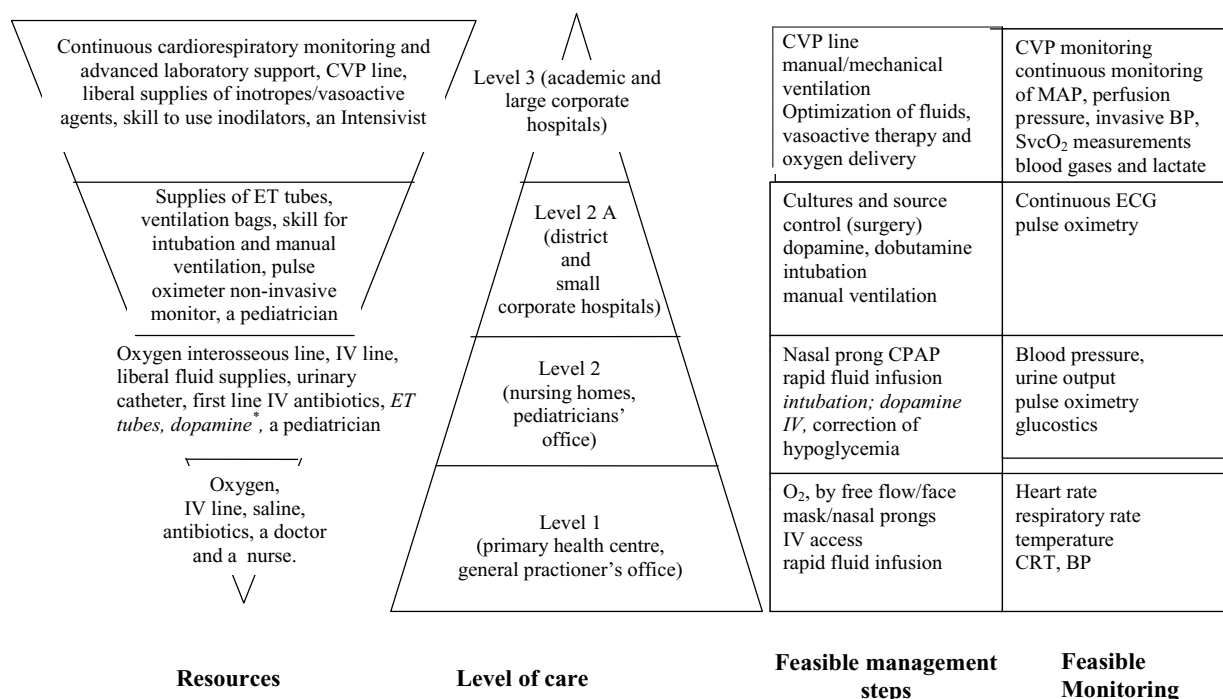
Severe malnutrition is not uncommon in Asia and Africa. These children are more susceptible to sepsis due to associated poor immunologic response [19,20]. Moderate to severe malnutrition was diagnosed in 53% of children admitted to a PICU in Brazil [21]. There are concerns about the adverse effects of aggressive fluid therapy in malnourished children; especially in those with edematous malnutrition. The current WHO guidelines on the management of severe malnutrition recommend small fluid boluses and thereafter use of blood transfusion [22].

4.8. *Is the issue of drug resistant organisms more important in developing world?*

This needs consideration while developing the guidelines on empiric antimicrobial therapy for severe sepsis/ septic shock. Data on the subject that resistance is high is scarce, perhaps due to rampant misuse of broad-spectrum antimicrobials, which is likely to promote development of drug resistant organisms [23].

4.9. *High costs of therapy, and PICU care*

High cost of intensive care is an important deterrent in the management of sick children and implementation of treatment guidelines in the recommended timeframe.



*Not available universally at all level 2 facilities
 CVP = Central venous pressure; ET = Endotracheal; IV = Intravenous; CPAP = Continuous positive airway pressure; MAP = Mean arterial pressure; BP = Blood pressure; ScvO₂ = Central venous oxygen saturation.
 ECG = Electrocardiography; CRT = Capillary refill time.

Fig. 1. Feasibility of various steps in treatment and monitoring of septic shock at primary, secondary and tertiary levels health care facilities with respect to available resources.

4.10. Spectrum of diseases

Pneumonia, diarrhea and central nervous system infections are much more common in contrast to USA where severe sepsis in low-birth weight and very low-birth weight make up 25% of cases [8,16,24,25].

5. Definitions

The group reviewed the definitions of sepsis and septic shock published in 2005 and found most of the definitions acceptable for resource-limited settings [2]. One proposed modification was in the definition of systemic inflammatory response syndrome (SIRS); in the original definition, two of the four criteria have to be present to identify SIRS. The experts suggest that one of these two criteria must be abnormal temperature or leukocyte count. Age related values for defining tachycardia, tachypnea and hypotension were simplified (Table 1) [26,27].

Septic shock was defined as presence of the following in a child with sepsis:

- 1) Hypotension [systolic blood pressure (BP) <5th percentile] OR
- 2) Need to use a vasoactive drug to maintain BP above 5th percentile range OR
- 3) Signs of hypoperfusion-any three of the following: decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time >3 sec, tachycardia (heart rate as defined in Table 1), core (rectal/oral) to peripheral (skin-toe) temperature gap >3°C, and urine output <1 mL/kg/hr (< 20 mL/hr in > 20 kg child). OR
- 4) Sepsis and cardiovascular organ dysfunction as defined in Table 2 [1-4].

6. Rapid cardiopulmonary assessment and clinical examination

Two major priorities in treatment of septic shock are rapid assessment of patient's disease process and

Table 1

Age specific upper and/or lower limits of heart rate to define tachycardia and bradycardia, respiratory rate to define tachypnea, and systolic blood pressure to define hypotension*, wide and narrow pulse pressure**

Age group	Heart rate (/min) mean (range)	Respiratory rate breath/min	Systolic blood pressure, mmHg (range)
Up to 1 month	140 (100–190)	> 60	< 60
2 months to 1 year	130 (80–180)	> 50	< 70
1 to 5 years	80 (60–140)	> 40	< 70 + (2 × age in years)
6–10 years	80 (60–130)	> 30	< 70 + (2 × age in years)
> 10 years	75 (60–100)	> 30	< 90

*For heart rate lower values are approximate 5th percentile and upper values 95th percentile, for blood pressure the values are 5th percentile and for respiratory rate 95th.

**Wide pulse pressure diastolic blood pressure less than or equal to half of systolic blood pressure, or difference > 40 mmHg; narrow pulse pressure: < 20 mmHg.

achievement of cardiopulmonary stability. Because the shock can be rapidly fatal, the child must be assessed immediately and comprehensively. During clinical assessment, one must note following points very carefully [26,27].

6.1. Appearance

Restlessness, agitation, anxiety, progressive lethargy, and decreased responsiveness are signs of impaired mental status.

6.2. Airway patency and stability

6.3. Breathing

Respiratory rate is increased in response to tissue hypoxia and to compensate for metabolic acidosis. Progressive worsening of respiratory distress (tachypnea, nasal flaring, suprasternal and intercostal and subcostal retractions) with bilateral rales or wheezes or unequal breath sounds on auscultation are signs of primary focus of infection in lungs, or early acute respiratory distress syndrome [3,4].

6.4. Circulation (cardiovascular)

Heart rate, adequacy of central and peripheral pulse, systolic and diastolic BP, skin color, capillary refill time (CRT) and temperature of extremities should be noted. Tachycardia occurs early in response to falling cardiac output and is the most significant physical findings in septic shock [3,4,26,27].

6.4.1. BP

A fall in BP is a late manifestation of low cardiac output in children. Children can prevent reduction in BP by vasoconstriction and an increase in heart rate and may have features of poor peripheral perfusion in presence of normal BP. Diastolic BP falls early causing wide pulse pressure as vascular tone begins to decrease. Systolic BP begins to fall causing narrow pulse pressure once hemodynamic compromise is severe. Hepatomegaly and jugular venous distension with gallop rhythm may signify predominant cardiac involvement as part of septic myocardial depression or myocarditis. Petechial rash may be present in meningococemia or disseminated intravascular coagulation.

6.4.2. CRT

Capillary refill time of more than 3 sec is abnormal. In warm phase of septic shock, capillary refill time may be normal, however signs of hyperdynamic circulation (bounding pulse, widened pulse pressure, hyperdynamic apex beat) are present. Warm shock if untreated will progress to cold shock. Cold shock is more common than warm shock. It is characterized by cold extremities in pediatric patients.

6.5. Urine output

Oliguria is common and may progress to anuria. Assessment of urine output in the last 6 hr is helpful. In severe cases patient may present with cardiopulmonary failure or cardiopulmonary arrest; both situations need aggressive hemodynamic support as well as endotracheal intubation and ventilatory support for survival [26,27].

Table 2
Organ dysfunction criteria

Cardiovascular dysfunction (a)
Hypotension (systolic blood pressure < 70 mmHg in infant; < 70 + 2 × age after one year of age) OR
Need for a vasoactive drug to maintain blood pressure above 5th percentile range OR
Signs of hypoperfusion- any three: Decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time >3 sec, tachycardia (heart rate as defined in Table 1), core (rectal/oral) to peripheral (Skin-toe) temperature gap > 3°C, and urine output < 1 mL/kg/hr (< 20 mL/hr in > 20 kg child),
Respiratory dysfunction (b)
Proven need for supplemental oxygen(c) or > 50% FiO ₂ to maintain saturation >92% OR
Need for nonelective mechanical ventilation (d) OR
PaO ₂ /FiO ₂ < 300 in absence of cyanotic heart disease or preexisting lung disease OR
PaCO ₂ > 65 Torr or 20 mmHg over baseline PaCO ₂
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/mm ³ 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 > 1 mg/dL
Hepatic dysfunction
Total bilirubin > 4 mg/dL (not applicable for newborn) OR, alanine transaminase 2 times upper limit of normal for age

(a)See Table 1; (b) acute respiratory distress syndrome must include a PaO₂/FIO₂ ratio < 200 mmHg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO₂/FIO₂ ratio must be < 300 mmHg; (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. FiO₂ = Fraction of oxygen in inspired air; PaO₂ = Partial pressure of oxygen in arterial blood; PaCO₂ = Partial pressure of carbon dioxide in arterial blood.

7. Cardio-pulmonary stabilization

The treatment of septic shock in children is aimed at optimizing perfusion of critical vascular beds and tissue oxygenation and prevention or correction of 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 homeostasis is restored [3, 4,26,27].

A time sensitive protocolized approach to resolve shock in severe sepsis should be implemented; be it a health centre, or a physician's office or an ED or hospital ward. This includes the following [26,27]:

- 1) Resuscitation of the ABCs on arrival, as per the Pediatric Advance Life Support guidelines;
- 2) Early administration of large volumes of isotonic fluids;
- 3) Greater use of physical examination therapeutic end-points of shock resolution;
- 4) Early initiation of inotrope infusion and early intubation where indicated; and
- 5) Correction of hypoglycemia (Level 1a) [4,28].

Every effort be made to resolve shock in the initial hr of resuscitation in the ED as it is associated with a

steep decline in mortality rate in sepsis [7,25,26]. A time sensitive, goal directed approach to the management of septic shock in ED by trained front line staff using physical examination therapeutic end-points has had a favorable impact on the overall survival in a single center study from India, resuscitation directed towards achievement of clinical therapeutic goals of shock resolution resulted in decline in overall mortality rate to 17.6% (95% confidence interval-11.9–24.8%) as compared to historical hospital mortality of 50% [29].

8. Management guidelines for septic shock

Following discussion will involve the specific timing, grading of evidence practical feasibility of each intervention mentioned in the pediatric sepsis guidelines flow chart (Fig. 2a). For simplicity sake, components of this flow chart are divided into 4 steps (I–IV) to address recommended interventions according to clinical condition, time and available resources. Grading of the literature (mentioned in list of references at the end of the article) and levels of recommendations is based on published ACCM criteria (Table 3) [3,4].

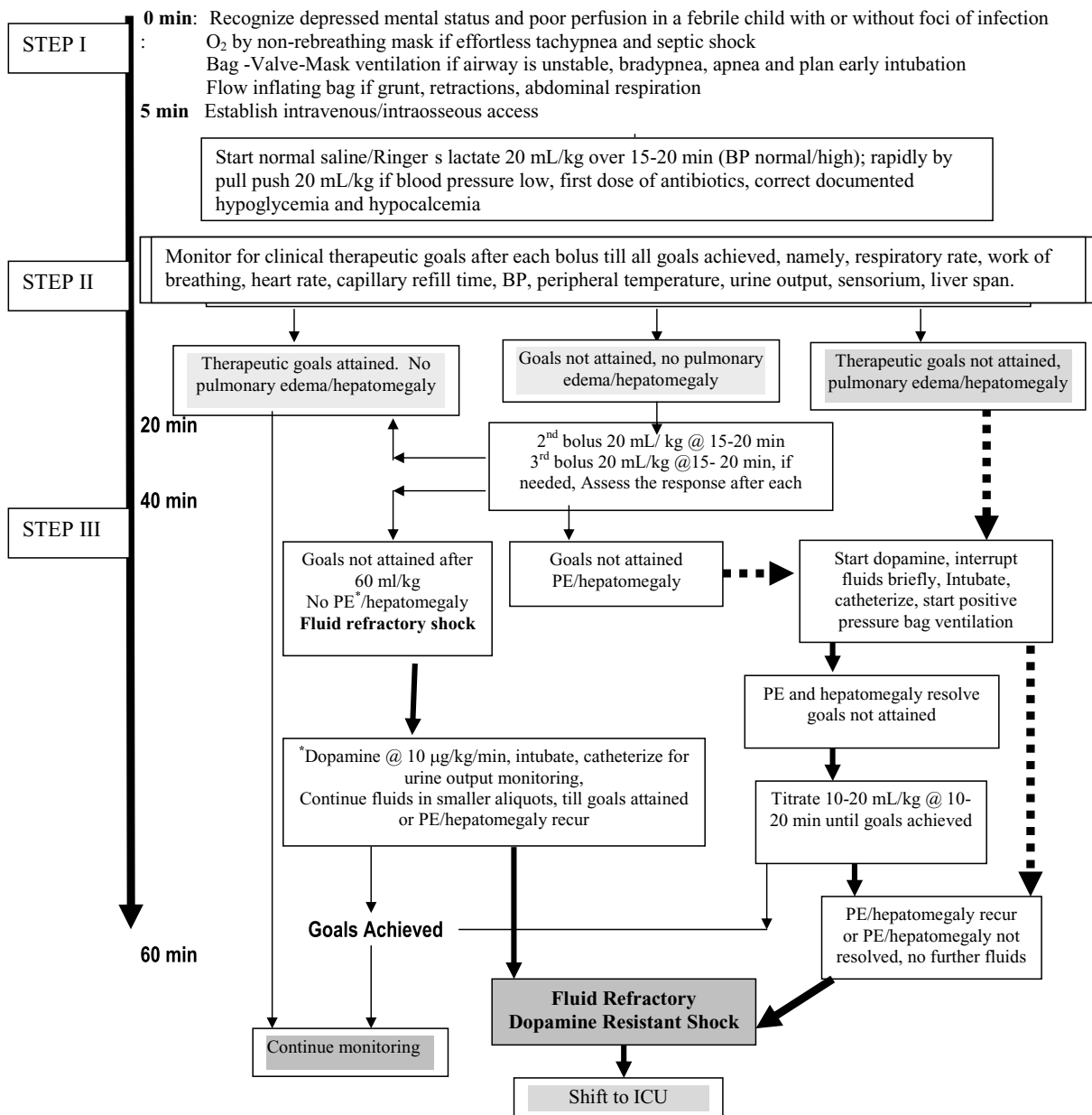


Fig. 2a. Management algorithm for treatment of pediatric septic shock for resource limited countries recommended by Indian Academy of Pediatrics intensive care chapter. Algorithm for initial assessment and treatment within first hr, and dopamine/dobutamine resistant shock. PE = pulmonary edema.

8.1. STEP I: 0–5 min

- 1) Recognize depressed mental status and decreased perfusion.
- 2) Begin high flow oxygen (Level 3).
- 3) Establish intravenous/intraosseous (IO) access (Level 2) [26,27]

In the first 5 min 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. If intravenous access cannot be obtained, IO access should be obtained; this is recommended for all age groups. High flow oxygen system (e.g. Venturi masks) or non-rebreathing mask may be

used (Level 3). All of the above are readily achievable in first 5 min [26,27].

However, if airway is unstable or the patient is lethargic or unresponsive and adequate oxygenation and ventilation is not achieved, start bag-valve mask ventilation and plan early endotracheal intubation and mechanical ventilation (Level 3). Other indications for intubation are hypotension on arrival or during therapy, convulsive seizures refractory to two doses of benzodiazepine, persistently low Glasgow Coma Scale of less than 8 and signs of raised intracranial pressure. Implementation of this step may take additional time encroaching upon the interventions expected in the next 60 min as per the guidelines [26,27,29].

8.2. STEP II: 5–40 min

- 1) Initial fluid resuscitation: Rapid infusion 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 (Level 1).
- 2) Correct hypoglycemia and hypocalcemia (Level 1).
- 3) Begin antibiotics (third generation cephalosporin and an aminoglycoside) (Level 2)
- 4) Establish a second peripheral intravenous line or central line if feasible (for possible inotrope: dopamine) (Level 2)

Fluid therapy by peripheral or IO access should be initiated while adequate control of airway and breathing is being accomplished. Rapid intravascular volume expansion guided by repeated clinical examination (and urine output) is frequently adequate to restore peripheral perfusion and BP [26,27,29–32].

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 may be required to correct hypovolemia; in some the need may be as high as 120 mL/kg in the first hr [28,29]. It has been suggested that malnourished child may get fluid overloaded with aggressive volume replacement; caution and a slower rate of infusion is advised (Level 3). This issue needs to be systematically studied.

Clinical scenarios where larger volumes are needed to achieve therapeutic end points are warm septic shock and shock due to gastro-intestinal sepsis. Presence of pulmonary edema and shock is an indication that more fluids may be needed to resolve shock [26].

Whether therapeutic goals have been achieved, remained status quo or have deteriorated is determined at the end of each bolus by performing the rapid cardiopulmonary assessment (Table 4, therapeutic goals). This assessment takes less than a minute and helps to decide whether further fluids may be given, or stopped and inotrope initiated and intubated. It also helps to decide whether further fluids may be titrated after intubation and inotrope infusion [26,27,29].

8.2.1. Choice of fluid for volume replacement

We recommend that isotonic crystalloid such as Ringers, lactate or normal saline be used for the initial fluid resuscitation in septic shock (Level 1).

In resource-limited countries where cost of therapy is distinct consideration, crystalloids should be preferred over colloids. Studies that evaluated different types of fluids in dengue shock syndrome found no significant difference in outcomes [17,32,33]. The only randomized controlled trial comparing normal saline and a colloid (polymer from degraded gelatin in saline) in pediatric septic shock conducted in India using clinical end-point and CVP (10–12 cmH₂O) showed that both normal saline and gelatin polymer solution were equally effective as resuscitation fluid with respect to restoration of plasma volume at the end of 1 hr [28]. Normal saline, up to 110 mL/kg and gelatin polymer solution up to 70 mL/kg was required in the first hr [30].

8.2.2. Method of fluid administration

We suggest that fluids be given in boluses of 20 mL/kg (Level 1); in hypotensive patients as rapidly as possible by pull push method using a three way stop-cock (Level 1), and in others by gravity method over 15–20 min (Level 2) [29,34].

The ACCM guidelines recommend administration of the boluses as fast as possible, which can only be administered by pull push method using a three way stop-cock [34]. However, a recent prospective study from India shows that administration of fluids by pull push method using a three-way stop-cock increased the incidence of hepatomegaly/pulmonary edema and a greater need for intubation [29]. This randomized control trial compared the impact of 40 mL/kg of fluid over 15 min followed by dopamine with further titration of therapy to achieve therapeutic goals (fast infusion group) versus 20 mL/kg over 20 min up to a maximum of 60 mL/kg over one hr followed by dopamine (slow infusion group) in septic shock. By 60 min, a similar proportion (83%) of patients in the study and the control groups had resolution of shock. However, at 20 min, the

Table 3

American College of Critical Care Medicine guidelines for Evidence-based Medicine rating system for strength of recommendation and quality of evidence supporting the references

Rating System for References
A: Randomized, prospective controlled trial
B: Nonrandomized, concurrent or historical cohort investigations
C: Peer-reviewed, state of the art articles, review articles, editorials, or substantial case series
D: Non-peer reviewed published opinions, such as textbook statements or official organizational publications
Rating System for Recommendations
Level 1: Convincingly justifiable on scientific evidence alone
Level 2: Reasonably justifiable by scientific evidence and strongly supported by expert critical care opinion
Level 3: Adequate scientific evidence is lacking but widely supported by available data and expert opinion

Table 4

Therapeutic endpoints of resuscitation of septic shock

1. Normalization of the heart rate
2. Capillary refill of ≤ 2 sec
3. Well felt dorsalis pedis pulses with no differential between peripheral and central pulses
4. Warm extremities
5. Normal range of systolic pressure and pulse pressure
6. Urine output > 1 mL/kg/hr, and
7. Return to baseline mental status tone and posture
8. 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

Table 5

Sign of pulmonary edema and myocardial dysfunction

Airway: Airway instability, froth, new onset cough
Breathing: Decreased or increased respiratory rates requiring respiratory support in the absence of neuromuscular diseases, onset of grunt, retractions, abdominal respirations, new rales or wheeze, drop in saturations
Circulation: Bradycardia, gallop, hypotension, hepatomegaly
Disability: Agitation, fighting the mask, combativeness and thirst for water
If, any one or a cluster of signs of deterioration are noted during fluid therapy, further fluid administration is discontinued, an appropriate inotrope infusion initiated and intubation is performed [27,35].

fast infusion group that had received double the volume than that of the slow infusion group, had significantly higher incidence of pulmonary edema and need for intubation [29].

Development of pulmonary edema and hepatomegaly should be anticipated during fluid administration. These are signs of fluid overloaded and can be a helpful indicators of the adequacy of fluid resuscitation. In some patients, evidence of pulmonary edema and hepatomegaly may be present on arrival, as acute respiratory distress syndrome and myocardial dysfunction may co-exist in severe sepsis. Clinical signs suggestive of myocardial dysfunction or pulmonary edema on arrival or its development during fluid therapy are shown in Table 5 [26,27,29].

Other practical ways to assess fluid overload are jugular venous distension, heart size and pulmonary congestion on chest radiograph (Level 3). Measurement of CVP and bedside echocardiography should be used at tertiary care centers, if available to assess ad-

equacy of intravascular volume, cardiac function and signs of fluid overload (Level 2) [26,33].

Patients who develop pulmonary edema and hepatomegaly after fluid boluses should be intubated and given positive pressure ventilation. Care must be taken to provide ventilation with PEEP [26,35]. This can be achieved in resource limited settings using a bag-valve or Mapleson C-circuit with Jackson Rees modification with a collapsible bag and a PEEP valve/bain's circuit if a mechanical ventilator is not available. If the cardiopulmonary assessment shows resolution of features of pulmonary edema and hepatomegaly and persistence of shock after the procedure, further boluses of 10–20 mL/kg over 10–20 min should be titrated until shock resolves or pulmonary edema/hepatomegaly recur [29]. It is important to appreciate that the incidence of cardiogenic or non-cardiogenic pulmonary edema is more frequent with inadequate fluid resuscitation, and features of pulmonary edema/ hepatomegaly usually resolve dramatically following intubation enabling fur-

Table 6
Choice of empirical antibiotic in patients with septic shock with respect to clinical settings

Clinical Setting	Usual pathogens	Preferred therapy	Alternate therapy
Unknown source, community acquired	<i>Salmonella typhi/ paratyphi</i> <i>Streptococcus pneumoniae</i> <i>Hemophilus influenzae</i> Enterobacteriaceae <i>Bacteroides fragilis</i> <i>Enterococcus faecalis</i> Think of malaria and dengue	Ceftriaxone plus Metronidazole OR Meropenem OR Imipenem	Quinolone (ciprofloxacin/levofloxacin) plus either Metronidazole OR Clindamycin
Lung source	<i>Streptococcus pneumoniae</i> <i>Hemophilus influenzae</i> <i>Staphylococcus aureus</i> <i>Mycoplasma pneumoniae</i>	Ceftriaxone/ cefotaxime/ Amoxicillin + clavulanic acid and azithromycin/ clarithromycin	Substitute new fluoroquinolone (levofloxacin/gatifloxacin) for macrolide
Intravenous line sepsis	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i> (MSSA) Klebsiella Enterobacter Serratia	Vancomycin plus Meropenem OR Imipenem OR Cefepime OR Piperacillin-tazobactam	May substitute linezolid for vancomycin Add antifungals if fungus suspected
Urosepsis	Enterobacteriaceae	Ceftriaxone OR Cefotaxime OR Quinolone Ceftriaxone	Aztreonam OR Ampicillin + amikacin
Meningitis	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> Meningococcus		Add vancomycin if drug resistant pneumococci suspected
Intraabdominal source	Enterobacteriaceae <i>Bacteroides fragilis</i> Enterococci	Ceftriaxone plus Metronidazole OR Piperacillin-tazobactam OR Meropenam OR Imipenem	Quinolone (ciprofloxacin/levofloxacin) plus either Metronidazole OR Clindamycin

ther titration of fluid until shock resolves. If however, shock does not resolve following intubation and bag-valve ventilation, and pulmonary edema/hepatomegaly persists further volume should be withheld. If the saturations are maintained within the normal range, isolated signs of pulmonary edema such as froth and rales may be ignored until acceptable ranges of heart rate, perfusion and BP with normal pulse pressure (approximately 40 mmHg) are attained [29,36].

If shock does not resolve following 60 mL/kg and no signs of pulmonary edema/hepatomegaly are noted, elective intubation should be performed. Since shock can worsen during or following intubation, initiation of an appropriate inotrope infusion often improves the safety profile of this procedure, particularly in warm shock [26,27].

Achievement of all therapeutic goals (Table 4) is needed to define shock resolution in fluid and inotrope

responsive shock. Discontinuing fluid therapy based on achievement of some and not all the goals may result in inadequate resuscitation [29].

8.2.3. Early antibiotic therapy and infection control

Antibiotics should be administered within 1 hr of the identification of severe sepsis, if possible, after appropriate cultures have been obtained (Grade 1D) [37, 38].

8.2.3.1. Initiation of antibiotic therapy

Intravenous antibiotic therapy should be started within the first hr of recognition of severe sepsis. Early use of broad-spectrum antimicrobial therapy based on clinical suspicion is reasonable although no randomized studies exist in children [8]. Data from adults clearly supports use of early appropriate antibiotics to impact favorably on morbidity from septic shock (Level 2) [37, 38].

Table 7
Doses of various antibiotics in pediatric septic shock

Drug	Dose	Frequency	Route
Ampicillin	50 mg/kg/dose	6 hourly	IV, IM
Ampicillin + sulbactam	50 mg/kg/dose of ampicillin	6 hourly	IV or IM
Amikacin	> 10 yr: 20 mg/kg on day 1, then 15 mg/kg, 1 wk-10 yr: 25 mg/kg on day 1, then 18 mg/kg, Neonates: < 30 wks: 15 mg/kg on day 1, then 7.5 mg/kg, > 30 wks-term: 10 mg/kg, Term 15 mg/kg	Once daily	IV or IM
Amoxicillin	50 mg/kg/dose	8 hourly, 12 hourly (for babies <1 wk), 6 hourly (2-4 wks)	IV, IM
Amoxicillin + clavulanic acid	Dose same as amoxicillin 4:1	8 hourly	IV, IM
Amphotericin B	0.5-1.5 mg/kg/day Total dose 30-35 mg/kg	Infusion with D5W, over 4-8 weeks	IV
Amphotericin B lipid/liposomal	2-3 mg/kg/day over 1 hr Total dose 20-60 mg/kg	Infusion with D5W, over 2-4 weeks	IV
Fluconazole	12 mg/kg stat 6-12 mg/kg/dose	Once daily	IV
Itraconazole	5 mg/kg/dose	12-24 hourly	IV, oral
Voriconazole	6 mg/kg/dose stat over 2 hr, repeat after 12 hr, then 4 mg/kg/dose	12 hourly	IV, oral
Ceftriaxone	50 mg/kg/dose	12 hourly	IV or IM
Cefepime	50 mg/kg/dose	8 hourly	IM or IV
Cefotaxime	50 mg/kg/dose	4-6 hourly, 12 hourly for neonates,	IV
Ceftazidime	50 mg/kg/dose	6-8 hourly	IV, IM
Gentamicin	> 10 yrs: 7 mg/kg on day 1, then 5 mg/kg/dose, 1 wk-10 yr: 8 mg/kg on day 1, then 6 mg/kg, Neonates: 5 mg/kg	Once daily	IV, IM
Cloxacillin	50-100 mg/kg/dose	4-6 hourly	IV
Vancomycin	10 mg/kg/dose Neonates: 10 mg/kg/dose	6 hourly 8 hourly	IV over 1 hr
Piperacillin + tazobactam	Piperacillin: 75-100 mg/kg/dose	6 hourly	IV
Ticarcillin + clavulanic acid	50-75 mg/kg/dose	6 hourly	IV
Cefoperazone sulbactam	50 mg/kg/dose of cefoperazone	8 hourly	IV
Meropenem	40 mg/kg/dose	8 hourly	IV
Imipenem + cilastin	25 mg/kg/dose of imipenem	6 hourly	IV

IV = Intravenous; IM = Intramuscular; D5W = Five percent dextrose in water.

8.2.3.2. Choice of initial antibiotic therapy

The initial empiric antibiotic therapy should include one or more drugs that have activity against the likely pathogens and that penetrate the presumed source of sepsis. Therapy should be broad enough since there is little margin for error in critically ill patients. Based on the clinical scenario, the probable infecting organism should be covered (Table 6). Commonly used antibiotics include a third generation cephalosporin such as ceftriaxone and an aminoglycoside such as amikacin (Level 3).

A Gram stain of potentially infected material often

permits a rapid presumptive diagnosis. Cultures are required for precise diagnosis. Most of the primary and secondary level centers may not have the facility for blood cultures. Moreover, many patients would have received antibiotics prior to reporting to a health facility.

8.2.3.3. Dose of antibiotics

All patients should receive a full loading dose of each antibiotic (Table 7). Appropriate dosage modifications have to be made for abnormal renal or hepatic function.

8.2.3.4. Duration

The antibiotic regimen should always be reassessed after 48 hr on the basis of clinical and if available, microbiological data, with the aim to use a narrow spectrum antibiotic to prevent the development of resistance, to reduce toxicity and the costs. Typically, the duration should be 7–14 days.

8.2.3.5. Source control

Every patient presenting with severe sepsis should be evaluated for the presence of a focus of infection that is amenable to source control measures e.g. drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device etc. [3,4].

8.2.4. Hypoglycemia

Hypoglycemia should be checked for and corrected (Level 2). Hyperglycemia should be avoided (Level 2).

Hypoglycemia can have devastating neurological consequences and should be diagnosed early and treated immediately (Level 1) [39]. Hypoglycemia has been shown to be associated with morbidity and mortality in critically ill children with very severe pneumonia, malaria and severely ill malnourished children [40,41]. Hyperglycemia also has been shown to be associated with morbidity and mortality in critically ill [42,43]. However, the effects of intensive glucose control on mortality in critically ill children are unknown. The beneficial effect of strict glycaemic control in adults (blood glucose < 150 mg/dL) using insulin therapy is being challenged. Use of intensive insulin therapy may place the critically ill patients with sepsis at increased risk of hypoglycemia (Level 2) [44]. Insulin therapy is not recommended at this time to achieve strict glycaemic control in sepsis (Level 2); however one may consider use of insulin if the child had significant glycosuria and polyuria leading to difficulty in fluid management [44, 45].

8.2.5. Calcium and hypocalcemia

Before cardiac output and perfusion pressure are restored with drugs, ionized hypocalcemia that might impair cardiac performances should be corrected (Level 2).

Ionized hypocalcemia is common in neonates and children with sepsis admitted to PICU [46,47]. Administration of calcium in septic patients with ionized hypocalcemia may transiently improve BP [48]. However, there is no evidence to suggest a survival benefit [49].

8.2.6. Monitoring and therapeutic endpoints

Monitoring for therapeutic end points is an integral part of the management particularly in the first few hours. We recommend use of clinical therapeutic end points to monitor the response to therapy (Table 4). These endpoints can easily be followed in resource limited settings. Meticulous clinical monitoring for therapeutic endpoints without high technology facilities has shown a dramatic reduction in mortality in Vietnamese children presenting with moderate dengue shock syndrome and in Indian children treated for septic shock in an ED [17,29].

End-points such as O₂ saturation and CVP can be monitored at secondary level facilities. Use of electrocardiography monitor can give reliable continuous heart rate record. In absence of a monitor, heart rate could be determined by auscultation periodically; this may be done before, during and after a fluid bolus has been administered.

CVP of 8–12 mmHg have been widely used in adults and may logically apply to children as also other methods to analyze cardiac filling (such as echocardiography) and central venous oxygen saturation (SvcO₂). Arterial-venous oxygen content difference may be a better marker than SvcO₂ to identify acceptable cardiac output in children with systemic arterial hypoxemia, such as cyanotic congenital heart disease or severe pulmonary disease [3].

8.2.6.1. BP

BP monitoring assists in decision-making regarding the rate of fluid infusion, the need for vasoactive agents and further titration of dose of appropriate agent. In vasodilatory or warm shock, with wide pulse pressure narrowing of pulse is an additional therapeutic goal. Although it is said that in children with shock, the non-invasive BP measurements may be unreliable and it is desirable to monitor invasive intra-arterial BP, it is not be feasible in majority of resource limited facilities.

8.2.7. Limitations of clinical therapeutic endpoints

All the clinical end points may not be applicable in some patients. While normalization of heart rate is one of the most reliable signs of shock resolution, other causes of tachycardia may be fever, anxiety, pain and SIRS. It may also be the only sign of ongoing seizure activity in a sedated, muscle-relaxed child. Antipyretic and analgesics, antiseizure medications, source control and mother's close proximity can often help in achievement of normal range of heart rate in appropriate clinical scenarios. On the other hand, heart rate, which

falls within the normal range for age, in the presence of severe respiratory distress or impending respiratory failure and shock, is an ominous sign [3,4].

Poor peripheral perfusion may be the result of cool environmental temperatures in very young infants. Recognition and resolution of shock in these young patients will depend on normalization of mental status, respiratory rates and heart rates [26,27].

There are concerns about the use of capillary refill and pulse volume, as there may be significant inter-observer variability [50]. This issue could partially be addressed by having one health care worker to monitor a child at different time points.

Accurate urine output monitoring by catheterization in fluid unresponsive shock is useful especially in settings without access to CVP monitoring. It is important to record initial volume after catheterization and then record the output. However, it may fail to provide information when polyuria or anuria occurs as complications of renal diseases with septic shock.

8.2.8. Unresolved issues and place of other therapeutic end-points in resource limited settings

- 1) The expected time frame for achieving the end-points needs more evidence. Moreover, the time to achieve various therapeutic endpoints may be variable. After each therapeutic change, there may be improvement in some of the monitoring parameters, even if they are not normal. There are no guidelines for defining response for each of the monitoring parameters.
- 2) Arterial blood gas/and lactate estimations are available in a few centers; use of SvcO₂ is still beyond reach of most centers.
- 3) Ability to place central lines particularly subclavian or internal jugular for CVP monitoring is still limited. Measurements obtained using femoral lines may not be reliable. This capacity needs to be built. Now disposable CVP manometers are available, which a pediatrician can use easily.
- 4) Use of echocardiography for determining the cardiac filling is also not practical in many centers. Wherever these facilities are available, the same can readily be practiced.
- 5) An important issue that needs to be addressed is the definition of therapeutic end-points for severely malnourished children.

8.2.9. Frequency of monitoring

The minimum monitoring schedule should include recording of the above mentioned parameters at 0, 5, 20, 30, 40 and 60 min (as per the algorithm for the management of septic shock). Of all the parameters, urine output and mental status may need some time to document improvement.

8.3. STEP 3: 40–60 min

8.3.1. Recognize fluid refractory shock

Begin inotrope by intravenous or IO route. Dopamine 10 µg/kg/min (Level 2) (obtain central venous access and airway if needed and feasible) (Level 1). Reverse cold shock by titrating dopamine, or if resistant (normal or low BP) titrate central epinephrine (0.05–0.3 µg/kg/min) (Level 2). Reverse warm shock with wide pulse pressure and/or low BP by titrating central norepinephrine (Level 2). Following adequate intravascular volume repletion, continued presence of hypotension and/or poor perfusion (fluid refractory shock) warrants the consideration of vasoactive therapy, which should be goal directed [4,36].

If signs of shock persist despite adequate volume replacement and perfusion of vital organs is jeopardized, vasoactive drugs may improve cardiac output and perfusion [51]. Optimal preload is essential before vasoactive therapy is contemplated [52]. Regardless of the vasoactive drug therapy used, increasing cardiac output and oxygen delivery to supranormal levels is not recommended; these have failed to demonstrate benefit in critically ill patients with sepsis [53,54].

The choice of vasoactive drug used would depend on the patient's condition after adequate volume resuscitation. Some of pediatric patients may have adult type manifestation of high cardiac output, vasodilatation and hypotension. Clinically, it will manifest as tachycardia, flush capillary refill, low-to-low normal BP and wide pulse pressure (warm shock). Such patients may do well with vasopressors alone [3,4,51].

Children with septic shock more often have myocardial dysfunction with compensatory vasoconstriction. This leads to a state of low cardiac output, with high cardiac filling pressure and high systemic vascular resistance, which clinically manifests as tachycardia, signs of hypoperfusion, prolonged capillary refill, cold extremities and low-to-low normal BP and narrow pulse pressure (cold shock). In these children, inotropic support becomes the first choice of cardiovascular support [4,51].

As a generalization inotropic support should be started in case of fluid refractory cold shock [36]. A vasopressor should be started to restore adequate BP and organ perfusion, while a combination of inotrope together with a vasopressor is warranted in warm shock [4, 51].

8.3.2. Vasopressors: Which one?

The expert group agrees with the use of dopamine as the first line vasopressor for fluid refractory hypotensive shock in the setting of low systemic vascular resistance. Children with septic shock more often have myocardial dysfunction and low cardiac output hence it is preferable to combine inotropy with a vasopressor effect. Dopamine in mid or higher doses with or without dobutamine can be used as first line drugs for giving this kind of support (Recommendation: Level 2, Grade and Class of recommendation: Grade B.). Dopamine increases mean arterial pressure through an increase in cardiac output and peripheral resistance (primarily by increasing cardiac index). However, in children the age specific insensitivity to dopamine has to be kept in mind before starting dopamine particularly in infants < 6 months [4,55].

8.3.3. Inotropic therapy: Which one?

Patients with low cardiac output (myocardial failure) despite adequate fluid resuscitation will require inotropy. Dobutamine (5 to 20 $\mu\text{g}/\text{kg}/\text{min}$) is the agent of choice for inotropic effect. However, dobutamine alone may be inadequate in a hypotensive patient. In absence of cardiac output measurement, hypotensive patients with sepsis may have low, normal or increased cardiac output. Therefore, dobutamine is usually combined with a vasopressor such as dopamine or norepinephrine to increase the peripheral vascular resistance. The combination of norepinephrine and dobutamine was associated with a lower serum lactate trend [56].

The low cardiac output state, characterized by persistent narrow pulse pressure and/or prolong capillary refill, even after use of dopamine, may be improved with addition of dobutamine (up to 20 $\mu\text{g}/\text{kg}/\text{min}$) or low dose epinephrine (< 0.3 $\mu\text{g}/\text{kg}/\text{min}$) (Recommendation: Grade B, Grade and Class of recommendation: Level 2) [4,36,51].

When a child in septic shock does not improve and the goals of treatment are not achieved even after dopamine and/or dobutamine infusion the shock is labeled as fluid refractory, dopamine/dobutamine resistant shock. Dopamine resistant shock may reverse with epinephrine or norepinephrine infusion (Fig. 2b) [3,4].

Epinephrine is usually not considered as first line therapy for septic shock due to its negative effects on gastric blood flow and lactate. Its use should be limited and should be reserved for cases of extreme hemodynamic collapse like a post arrest state [26,27]. The dose should be titrated to minimum required for the desired effect; higher doses cause severe vasoconstriction, splanchnic ischemia and lactic acidosis [36].

At various stages of sepsis or the treatment, thereof a child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the clinical state [3].

8.4. STEP IV: Beyond 60 min

Recognize dopamine-dobutamine resistant shock

8.4.1. Transfer to PICU

- 1) If possible, monitor CVP, Echocardiography, mean arterial pressure (Level 2)
- 2) Begin hydrocortisone (50 $\text{mg}/\text{m}^2/\text{day}$) if child is at risk for absolute adrenal insufficiency (Level 2)
- 3) Titrate fluids and vasoactive drugs to resolve shock based on CVP, echocardiography to achieve therapeutic goals.

8.4.2. Corticosteroids in septic shock

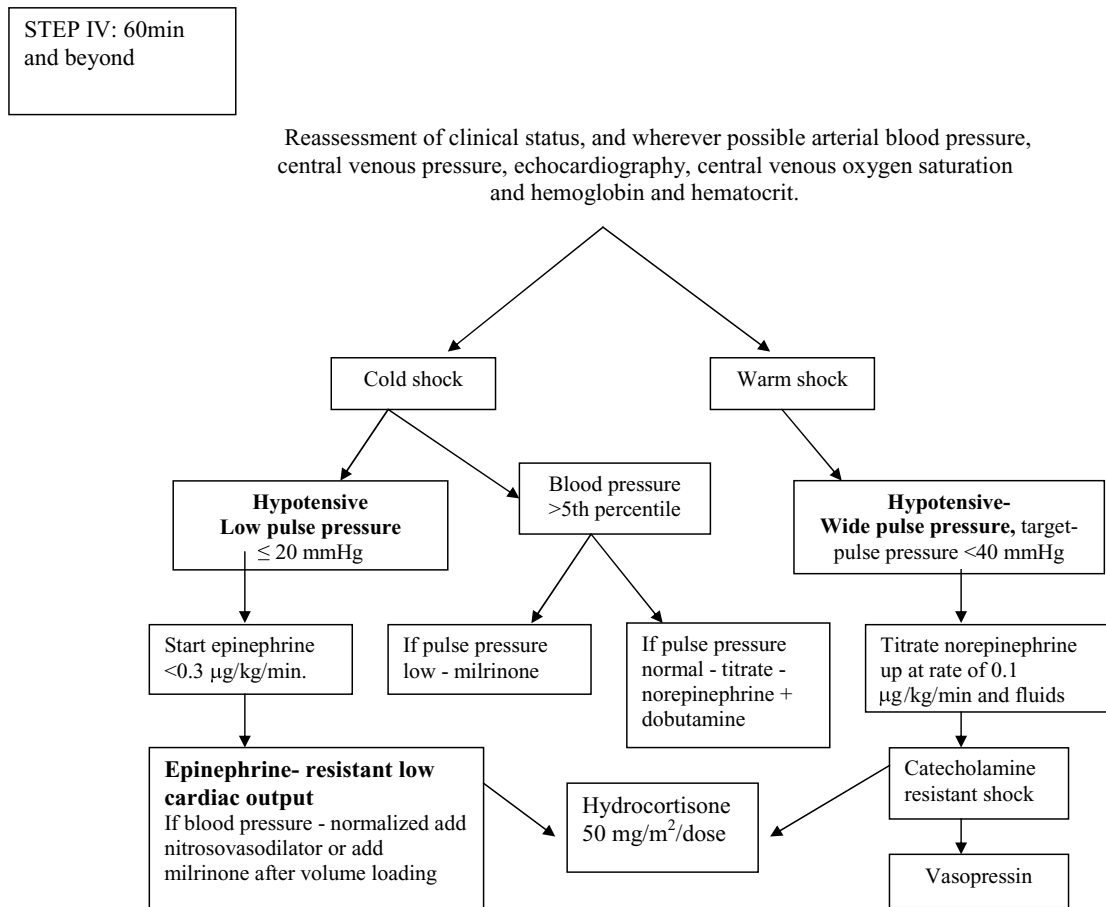
8.4.2.1. Recommendations

Corticosteroids should be given to those children with catecholamine resistant shock who have proven adrenal insufficiency or are at risk for adrenal insufficiency. Children at risk for adrenal insufficiency include those who have or are suspected to have pituitary or adrenal abnormalities, who have received corticosteroids for chronic illness or those who present with septic shock and purpura [4]. Corticosteroids should not be used routinely in children with septic shock [57].

Stress doses of hydrocortisone should be given intravenously 2 mg/kg [36] or 50 mg/m^2 followed by 50 $\text{mg}/\text{m}^2/\text{day}$ in four divided doses intravenously for 5 to 7 days [57].

Adrenal insufficiency (absolute/relative) is common in children with severe sepsis and septic shock [58–60]. In most of the studies, a poor adrenal reserve (inadequate increase in cortisol after corticotropin stimulation) or absolute adrenal insufficiency was associated with catecholamine refractory shock and /or poor outcome [4,36].

The enthusiasm associated with use of low dose (physiological stress doses) corticosteroids for a longer



BP = Blood pressure; PE = Pulmonary edema; ICU = Intensive care unit.

Note: Plan epinephrine infusion if bradycardia, blood pressure remains low or falls with cold shock* at any step in protocol. Relief of tamponade, such as pneumothorax, or pericardial tamponade, increased intra abdominal pressure due to fluid should be considered at any point.

Fig. 2b. Management algorithm for treatment of pediatric septic shock for resource limited countries recommended by Indian Academy of Pediatrics intensive care chapter. Algorithm for initial assessment and treatment within first hr, and dopamine/dobutamine resistant shock.

duration because of beneficial results in terms of mortality reduction and reversal of shock especially in patients showing catecholamine resistance has come down [3,61,62]. The recent large trials in adults have been discouraging [63].

At present, there is insufficient evidence to determine role of low dose hydrocortisone in children with septic shock. In an exploratory study from Chandigarh, there was a trend towards earlier reversal of shock and lower inotropes requirement in the hydrocortisone treated patients as compared to controls; however, the difference was not statistically significant [64]. There is no large randomized study in children to support the use of corticosteroids in septic shock. There is also a concern

about higher mortality and adverse effects associated with use of corticosteroids in children with septic shock in retrospective studies [66].

There are no clear guidelines for best dose of steroids in children with septic shock. The group recommends stress doses of hydrocortisone until reversal of shock for pediatric sepsis patients with catecholamine resistant shock (Level 2).

Up to this point most of the interventions can be performed in a peripheral setting and should be followed as the guideline in resource limited situation. Further management requires transfer of the patient to a PICU, reassessment of the patient's clinical status, arterial BP, CVP, echocardiography and hemoglobin (Hb) and

hematocrit. Generally, a low CVP will be an indication for more fluids, low BP for more vasopressors, poor contractility of myocardium on echocardiography for titrating up the dose of inotropes and low hematocrit an indication for packed cell transfusion.

8.4.3. Vasoactive drug therapy: Further titration

At this stage, children in shock may be classified into two broad categories: Warm shock and cold shock [4, 51].

Children in cold shock may be further categorized in two sub-groups. First are children with low BP. 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 such as nitroprusside and nitroglycerine, which are pure vasodilators with very short half life, or milrinone having both vasodilator as well as inotropic effects [51,66–68]. Nitrovasodilators are used as first line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular resistance. Use of phosphodiesterase inhibitor milrinone (50–75 $\mu\text{g}/\text{kg}/\text{min}$) should be strongly considered if low cardiac and high vascular resistance state persists in spite of epinephrine and nitrovasodilators. Starting milrinone may require additional fluid bolus, and titrating up the dose of epinephrine to check the vasodilatation and maintain BP [4,67,68].

Second category is that of children with normal BP. In these children, further action would depend on the pulse pressure. If the pulse pressure is low phosphodiesterase inhibitor such as milrinone [67,68] (Level 1) would be the drug of choice. However, if the pulse pressure is normal or high, norepinephrine and dobutamine should be titrated up [4].

Children with 'warm shock' are likely to have a wide pulse pressure. A vasopressor norepinephrine is the drug of choice in such patients. Norepinephrine causes a clinically significant increase in mean arterial pressure due to its vasoconstrictor effects, with little changes in heart rate or cardiac output. It should be used only to restore adequate values of mean arterial pressure that is sufficient to restore urine output. The usual dose is 0.05–1.00 $\mu\text{g}/\text{kg}/\text{min}$ [26,27].

8.4.4. Vasopressin in shock

Vasopressin therapy may be considered as a last resort if patient has warm shock with low BP unresponsive to norepinephrine [66,67]. In pediatric patients, suggested dose is 0.3 to 2 $\text{mU}/\text{kg}/\text{min}$ (equivalent to

0.0003 to 0.002 $\text{U}/\text{kg}/\text{min}$ or 0.01 to 0.12 $\text{U}/\text{kg}/\text{hr}$) [68]. The infusion should be titrated to optimize BP and perfusion [70,71].

There is a limited experience with vasopressin in children as a rescue therapy in catecholamine resistant shock; there are no large trials to define its place [72, 73]. Moreover, plasma vasopressin is high in children with septic shock and vasopressin may have deleterious effects on renal functions and platelet counts [74–76]. At this time, there is no evidence to support inclusion of vasopressin in the management protocol for pediatric septic shock.

8.4.5. Vasoactive drugs-Practice points

Accurate dose delivery is an important component of vasoactive drug therapy. This can only be achieved with infusion pumps. When infusion pumps are not available, the infusions may be given using micro-infusion sets whose drop size has been standardized (and confirmed by the user). When several infusions are being administered through the same intravenous access close monitoring of actual delivery of each infusion should be ensured. Even a small change in rates of infusion of vasoactive drugs can have a profound effect on the circulatory status; constant monitoring of the drops rate in such situations is required. One should avoid administering boluses of fluid 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. These drugs can be infused through the IO route until the time that an intravenous access becomes available [26,27].

A meticulous search for the causes of persistent catecholamine resistant shock should be made if therapeutic goals are not achieved in spite of adequate volume loading and high doses of appropriate vasoactive agents. One must rule out mechanical causes for catecholamine resistant shock, such as tamponade due to pericardial effusion, pneumothorax or increased intraabdominal pressure. This is all the more important in resource limited situations where extracorporeal membrane oxygenation is not available [10,11].

9. Other issues in management

9.1. Blood and component therapy

About 40% of all adult intensive care unit patients and 14% of children admitted to PICU received erythro-

Table 8
Transfusions recommendations

Variables	Transfusion trigger (g/L)	Goal (g/L)
General critically ill (no acute bleeding)	70	70–90
Critically ill with septic shock after first 6 hr	70	70–90
Critically ill with septic shock within first 6 hr	80–100	100
Critically ill with chronic cardiac disease	70	70–90
Critically ill with acute cardiac disease	70	100

cyte transfusions in western countries [77,78]. Given the poor nutritional background of infants and young children in India and other resource limited countries, the incidence of anemia is higher in this population [79].

Optimal Hb for a critically ill child with severe sepsis is not known. It can be argued that higher Hb would increase the oxygen content of the blood and may therefore benefit the tissues and organs oxygen delivery. However, this strategy has not proved beneficial to critically ill patients in several trials [80]. These as well as the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) trial strongly argue in favor of a restrictive transfusion strategy recommending erythrocyte transfusions to only those critically ill children whose Hb is ≤ 7 g/dL [81]. However, TRIPICU study excluded children with hemodynamic instability; therefore, the results cannot be extrapolated to children with septic shock [81].

The early goal directed therapy trial in adults used a goal of 30% hematocrit (approximately 10 g/dL Hb) during the resuscitation phase of septic shock along with other interventions and showed a clear benefit [52]. Hence, a recommendation for maintaining a somewhat higher Hb level of 10 mg/dL during the resuscitation phase is being made here too due to demonstrated physiological instability (Table 8). These recommendations may not apply to premature infants, children with severe hypoxemia, or cyanotic heart disease and to children who are actively bleeding.

9.2. Fresh frozen plasma (FFP)

Coagulation disturbances are common in patients with severe sepsis and septic shock. However, correction of these abnormalities do not improve outcome in all the patients and unnecessarily exposes the child to the risks of blood product transfusions [82]. FFP is indicated in only those patients with coagulation abnormalities that have any of the following: active bleeding, before surgery, before invasive procedure, and to reverse warfarin effect. Routine use of FFP to correct laboratory-clotting abnormalities is not indicated. When required the FFP infusion should be given relatively rapidly to achieve effective factor levels [3,4].

9.3. IVIG

IVIG may be considered in children with severe sepsis (Grade 2C) if cost is not an issue. It is known that endogenous and exogenously administered IVIG can neutralize endotoxins (IgM is more potent than IgG) and can attenuate the overshooting inflammation in patients of sepsis [83]. There is evidence that it has some benefit in children, and may possibly have some benefit in neonates. A recently published randomized control trial of polyclonal IVIG in pediatric sepsis showed a significant reduction in mortality and fewer complications [84]. However, large clinical trials, recent consensus guidelines, and a very recent editorial do not recommend widespread use of IVIG in patients with severe sepsis or septic shock [3,85–87]. Cost being an additional consideration in resource limited settings use of IVIG is not routinely recommended in patients of severe sepsis and septic shock.

9.4. Deep venous thrombosis prophylaxis

Use of deep venous thrombosis prophylaxis is recommended in postpubertal children with severe sepsis (Grade 2C) [3,4].

9.5. Stress ulcer prophylaxis

Therapy may be individualized. There are no graded recommendations [3,4].

9.6. Renal therapy

Continuous veno-venous hemofiltration may be clinically useful in children with anuria/severe oliguria and fluid overload. There are no graded recommendations. No large randomized trials comparing continuous veno-venous hemofiltration with intermittent dialysis exists.

9.7. Sedation/Analgesia

Sedation protocols with a sedation goal are recommended when sedation of critically ill mechanically ventilated patients with sepsis is required (Grade 1D) [3,4].

10. Summary and conclusions

Severe sepsis remains one of the most important causes of child-mortality in resource-limited countries. Several promising interventions that have been included in ACCM/Pediatric Advance Life Support guidelines to treat severe sepsis and septic shock in children can significantly reduce the mortality. These cannot be uniformly applied and practiced in resource-limited circumstances because of several barriers. Nonetheless, there is evidence that application of some of interventions using a time-sensitive protocol and clinical therapeutic end-points can bring down mortality in resource-limited settings. These interventions include early oxygen therapy, fluid resuscitation with normal saline 40–60 mL/kg (sometimes up to 90–110 mL/kg) to restore intravenous volume, dopamine infusion through peripheral vein in fluid refractory shock, early intubation and ventilation, and early appropriate antibiotic therapy. The expert group is of consensus that above interventions could easily be applied in resource limited circumstances even at primary and/or secondary level health facilities and recommends these along with correction of hypoglycemia and hypocalcemia. Therapeutic interventions recommended after these steps include use of epinephrine or nor-epinephrine, inodilators, stress dose corticosteroid in suspected or proven adrenal insufficiency, and CVP monitoring and echocardiography to guide vasoactive drugs. These recommendations are based on consensus, have insufficient evidence and need transfer to a PICU. Strict glycemc control is not recommended. Evidence is emerging on benefit of use of vasopressin as vasopressor, renal replacement therapy and use of plasmapheresis.

Further research evaluating individual components of guidelines and relative benefit of each of these interventions in resource limited setting is needed, as also the benefit of adherence with guidelines and standardized set orders. There is a need to answer issue of fluid resuscitation in severely malnourished children with septic shock, establish through randomized clinical trials choice of inotropic and vasopressor therapy in initial management, dose and timing of use of corticosteroids, administration of blood and blood products, protective mechanical ventilation, glycemc control, techniques of renal replacement therapy etc.

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