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GUIDELINES

A Thai guideline summary in management of pediatric septic shock

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ABSTRACT:

Sepsis-associated organ dysfunction, particularly septic shock, is a prevalent critical illness characterized by increased morbidity and mortality, particularly in children. Recognizing the imperative to enhance outcomes, a septic shock guideline tailored for pediatric patients was formulated. This guideline strives to establish an evidence-based framework for the effective management of septic shock and sepsis-associated organ dysfunction in Thai children. Key components encompass the prompt identification and stabilization of patients, meticulous titration of fluids and vasoactive agents, initiation of empirical antimicrobial therapy, judicious infectious source control, respiratory support, administration of sedation and analgesia, blood and blood product transfusion, correction of electrolyte imbalances, management of metabolic derangements, renal replacement therapy, and the implementation of multimodal monitoring. The objective is to optimize management, achieving therapeutic goals while continuously reassessing the patient's condition. Additionally, this guideline demonstrates adaptability by tailoring its suggestions to the resources available in Thailand's medical facilities. Recognizing the diverse capabilities of healthcare institutions, the guideline endeavors to ensure its implementation is practical and feasible.

Keywords: Pediatric; Septic shock; Thai guideline; Management

INTRODUCTION

Pediatric septic shock stands as a critical condition and a major cause of mortality in critically ill children globally. In Thailand, the prevalence ranges from 2.1% to 23%, with mortality rates reaching 11% to 40% [1-3]. Recognizing the gravity of this issue, the Thai Society of Pediatric Respiratory and Critical Care Medicine (TPRC) took proactive initiatives by developing Thai pediatric sepsis and septic shock guidelines in 2018. In 2020, the Surviving Sepsis Guidelines for Children highlighted a significant turning point in the field [4]. These recommendations provided a comprehensive, evidence-based approach to managing septic shock and organ dysfunction associated with sepsis in pediatric patients. Redefining septic shock as a severe infection that causes cardiovascular dysfunction and sepsis-associated organ dysfunction as a severe infection that causes organ dys-

function without hypotension was a significant revision. Nevertheless, it is essential to recognize that these guidelines were mainly developed without specific consideration of varying healthcare resources. Numerous studies have contributed to the changing paradigm of pediatric septic shock management over the past few years. These studies have yielded new insights, updated strategies, and refined methods for enhancing the well-being of affected children. It is essential to acknowledge these advancements to ensure that guidelines remain current and reflect the most recent medical knowledge [5]. The TPRC has responded dynamically to these developments by revising the clinical practice guidelines. A notable feature is the adjustment of recommendations according to the readiness and resources of medical facilities at various levels, ranging from small hospitals to large regional hospitals with high potential. This tiered approach acknowledges the diverse capabilities and limitations of healthcare facilities, ensuring that the guidelines remain practical and implementable across different settings. A prior study examined the characteristics and outcomes of pediatric severe sepsis and septic shock in nine PICUs across three Asian countries, finding that despite adherence to guidelines with prompt fluid and inotropic support, PICU mortality remains high. The result revealed that the use of fluid and inotropic supports was associated with improved hemodynamic response and an increased survival rate [3]. Pediatric septic shock is a major concern in Thailand as well as throughout the world, necessitating the establishment of reliable and flexible guidelines. The TPRC's initiative to develop and revise guidelines reflects a commitment to improving outcomes for critically ill children, taking into consideration both local resources and the changing medical landscape. In order to effectively treat pediatric septic shock in a variety of healthcare settings, it remains critical to blend evidence-based practices with adaptable, resource-aware approaches. This review will summarize some of the current evidence-based interventions, discuss controversial aspects, and identify potential areas for enhancement. Early diagnosis and prompt intervention, including the administration of antibiotics, fluid resuscitation, and vasoactive medications, are the most crucial measures in managing sepsis. In Thailand, hospitals are classified using the Geographic Information System, aligning with the criteria of the Ministry of Public Health. This classification spans from Level 1 Subdistrict Health Promoting Hospitals (primary care) to Level 4 Central Hospitals (tertiary care or medical school), each serving specific roles in the healthcare system. Understanding these levels is crucial for tailoring guidelines to different healthcare facilities.

DEFINITIONS [4,6,7]

Presently, the diagnostic terminology has been revised to encompass septic shock and sepsis-associated organ dysfunction, effectively discarding the terms severe sepsis and Systemic Inflammatory Response Syndrome (SIRS). This adjustment arises from the recognition that SIRS may not always stem from an infection, and the term severe sepsis could be semantically similar to septic shock.

KEY MESSAGES:

- Quick identification and resuscitation matter: Rapid identification and prompt resuscitation significantly enhance outcomes in pediatric septic shock and sepsis-associated organ dysfunction.
- Key steps for initial stabilization and treatment: providing oxygen, fluid resuscitation, empirical antimicrobial therapy, and vasoactive agents within 60 minutes is crucial.
- Integrative hemodynamic monitoring: hemodynamic reassessment guides ongoing resuscitation, and intensive care unit monitoring supports organ dysfunction management.

Infection is defined as a confirmed infection through culture, polymerase chain reaction (PCR) testing, or possessing distinct attributes that unequivocally indicate infection (e.g., white blood cells isolated from sterile body fluid, chest radiographs displaying pneumonia patterns, etc.).

Sepsis is defined as a condition wherein infection primarily causes illness and tissues respond to the infection. Sepsis-associated organ dysfunction is defined as the condition of sepsis and organ dysfunction, characterized by normal blood pressure.

Septic shock is defined as patients with sepsis who had hypotension, were receiving vasoactive medication, or exhibited signs and symptoms of impaired perfusion (e.g., abnormal consciousness, capillary refill exceeding two seconds, weak pulse, cold extremities or flash capillary refill, bounding pulse, wide pulse pressure, or urine output less than 1 mL/kg/hour).

Fluid refractory shock is defined as patients who remain in a state of shock despite the administration of 40-60 mL/kg of fluid resuscitation.

Catecholamine-resistant shock is defined as patients who remain in a state of shock and are receiving catecholamines such as dopamine (10 mcg/kg/min, or epinephrine or norepinephrine 0.1-0.2 mcg/kg/min).

Refractory shock is defined as a patient who remains in shock despite receiving high dosages of an inotropic agent, vasopressor, or vasodilator and maintains the body's equilibrium in terms of hormones (including thyroid, hydrocortisone, or insulin) and metabolism (including glucose and calcium).

ANTIMICROBIAL THERAPY AND SOURCE CONTROL OF THE INFECTION

Administering timely and targeted empirical antibiotics is paramount in sepsis management, initiated within the first hour of diagnosis, considering local infection patterns [7, 8]. The appropriateness of previously admin-

istered antibiotics should be evaluated for patients transferred from other hospitals. Blood cultures, preferably obtained prior to antibiotic initiation, should not cause delays; if challenging, antibiotics can precede blood culture collection [9, 10]. Culturing other relevant body fluids based on the patient's condition is recommended. The choice of initial antibiotics should be guided by suspected microorganisms and patterns of local epidemiology (Table 1) and tailored for immunocompromised patients as specified in Table 2. After obtaining culture results, adjust antibiotic therapy to be more specific, considering pathogen susceptibility to different antibiotics. In hospitals with procalcitonin measurement capabilities, procalcitonin testing, coupled with clinical assessment, aids decisions on antibiotic regimen changes or discontinuation [11]. For very small children lacking accessible veins for intravenous antibiotics, consider intramuscular administration until intravenous access is established. Toxic shock syndrome (TSS) is a rapid-onset illness caused by toxins from Staphylococcus aureus and Streptococcus pyogenes, marked by fever, rash, hypotension, involvement of multiple organs, and skin desquamation. The mortality rates in children for streptococcal and staphylococcal TSS are 5-10% and 3-5%, respectively, which is lower than the 30-80% seen in adults for streptococcal TSS [12]. TSS management includes prompt identification, robust fluid resuscitation and vasopressor support, source control, targeted antibiotics, clindamycin, and IV immunoglobulin for adjunctive therapy, and vigilant monitoring for surgical intervention needs [13].

Source control of infection: Patients with septic shock should undergo evaluation for potential source control interventions, such as the drainage of abscesses, debridement of necrotic tissue, or removal of infected devices. Source control is crucial in pediatric septic shock management to directly target and eradicate the origin of infection. We recommend source control as promptly as feasible following resuscitation, optimally within 6–12 hours of diagnosis.

INITIAL FLUID RESUSCITATION

It is advisable to establish intravenous access as quickly as possible with the most experienced personnel available. In cases where intravenous access cannot be established promptly, intraosseous access is recommended, especially in patients with profound shock. If intravenous access cannot be secured within 90 seconds, with a maximum of up to three puncture attempts, intraosseous access should be considered [14]. The recommended initial resuscitation fluid is isotonic crystalloids, administered quickly at 10-20 mL/kg within 15-20 minutes, and can be repeated 2-3 times up to 40-60 mL/kg. Colloids in the same quantity may be an alternative, with additional colloids considered for further administration. During each fluid administration, vigilant assessment for fluid overload through physical examination, such as lung, heart sounds, and palpating the liver, is crucial. Monitor clinical signs closely throughout fluid administration and utilize additional assessment tools to guide fluid responsiveness. Central venous catheters (CVCs) are instrumental for administering intravenous fluids, medications such as vasopressors, blood products, and facilitating frequent blood sampling. Although CVCs permit central venous pressure (CVP) and central venous oxyhemoglobin saturation ($ScvO_2$) monitoring to assess therapeutic responses, evidence from randomized studies suggests the clinical benefit of these measurements may be restricted [15]. Point-of-care ultrasonography (POCUS) is highlighted as

Table 1. Empirical antimicrobial therapy and common organisms in community acquired sepsis.

Age	Organisms	Empirical antimicrobial agents	Comments
Neonatal	- Bacteria: E. coli & enteric gram-negative bacilli, group B Streptococci, Coagulase negative Staphylococcus - Virus: herpes simplex virus, enterovirus - Fungus: Candida	Ampicillin or Cefotaxime ± Aminoglycoside	High incidence area of Listeria monocytogenes suggests use Ampicillin consider Acyclovir when suspected HSV infection
1-3 month	- S. pneumoniae, H. influenzae type b, Salmonella, N. meningitidis, Group B Streptococci, E. Coli	Cefotaxime ± Aminoglycoside	
3 month-5 year	- S. pneumoniae, H. influenzae type b, Salmonella, N. meningitidis, S. aureus	Cefotaxime or Ceftriaxone ± Aminoglycoside If MRSA [74]: vancomycin, linezolid, daptomycin or ceftaroline	Suspected toxic shock syndrome recommend Cloxacillin or Cefazolin plus Clindamycin ± Aminoglycoside
> 5 years	- S. pneumoniae, S. aureus, S. pyogenes, Salmonella, N. Meningitidis	Cefotaxime or Ceftriaxone ± Aminoglycoside If MRSA [74]: vancomycin, linezolid, daptomycin or ceftaroline	

+Ceftriaxone is a broad-spectrum cephalosporin that may be one option to treat methicillin-susceptible Staphylococcus aureus (MSSA). Although MSSA may be susceptible to ceftriaxone, the minimum inhibitory concentration (MIC) is generally two- to four-fold higher than other susceptible bacterial pathogens. MRSA: methicillin resistance Staphyloccocus aureus.

Table 2. Empirical antimicrobial therapy and common organisms in pediatric sepsis with immunocompromised host.

Conditions	Organisms	Empirical	Comments
Asplenia or abnormal function of spleen	Encapsulated organism (S. pneumoniae, H. influenzae type b, N. meningitidis, K. pneumoniae), E coli	Cefotaxime/Ceftriaxone/Ceftazidime + Aminoglycoside or Cefipime or Piperacilin/tazobactam	Recommend Ceftazidime in endemic are of Meliodosis
Neutropenia	Enteric gram-negative bacilli, P. aeruginosa, S. aureus, Candida, Aspergillus, Zygomycosis	Carbapenem + Aminoglycoside	Consider start vancomycin when 1. Suspected CLABSI 2. History of drug resistance S. pneumoniae or MRSA 3. Blood culture positive to gram-positive 4. Severe mucositis
B cell defect	S. pneumoniae, H. influenzae type b, S. aureus, Salmonella, Shigella, Campylobacter, Enterovirus	Cefotaxime/Ceftriaxone + Macrolide	Consider use IVIG
Chronic granulomatous disease	S. aureus, Salmonella, S. marcescens, K. pneumoniae, Aspergillus, Nocardia	Cefotaxime/Ceftriaxone	Consider antifungal when clinical not improve
Compliment deficiency	S. pneumoniae, H. influenzae type b, N. meningitidis	Cefotaxime/Ceftriaxone	

Table 3. Fluid administration in pediatric patients based on level of care and sepsis severity.

Condition	PICU or respiratory support available	PICU and respiratory support not available
Sepsis-associated organ dysfunction (no hypotension)	10-20 mL/kg in 15-20 min, max 40-60 mL/kg in 1st hour	10 mL/kg in 1st hour
Septic shock	10-20 mL/kg in 15-20 min, max 40-60 mL/kg in 1st hour	10-20 mL/kg in 15-20 min, max 40 mL/kg in 1st hour

an effective tool for hemodynamic assessment in pediatric patients, with respiratory variation in aortic blood flow peak velocity emerging as the most examined predictor of fluid responsiveness, showing high sensitivity and specificity. However, evidence is insufficient to support the use of POCUS for guiding fluid therapy in children who are breathing spontaneously [16,17]. Regular and thorough monitoring is essential to guide fluid management and ensure an optimal response to resuscitation efforts. Excessive fluid administration poses a risk of complications, including pulmonary edema and worsening heart failure, potentially increasing mortality.

In resource-limited settings lacking advanced respiratory supportive and intensive care, we advise against the use of a fluid bolus in patients with normal blood pressure [4]. However, we suggest administering a fluid bolus of up to 40 mL/kg over the first hour if hypotension is present. Fluid administration should follow the guidelines outlined in Table 3. Recommended isotonic crystalloids include 0.9% saline and balanced salt solutions such as Ringer's lactate or Ringer's acetate, while 5% albumin is the recommended colloid option. However, normal saline demonstrated more adverse effects, including hyperchloremic metabolic acidosis, acute kidney injury (AKI), and increased mortality, when compared to balanced salt solutions [18-20]. Although high-quality pediatric research is limited, a balanced salt solution is recommended over normal saline as the primary volume expander in pediatric septic shock, as endorsed by the 2020 Surviving Sepsis Campaign International Guidelines [4]. A recent blinded multicenter parallel-group study revealed that children with septic shock who underwent fluid resuscitation with PlasmaLyte exhibited a significantly lower incidence of new and/or progressive acute kidney injury compared to those administered with normal saline within the first 7 days of hospitalization [21]. Unfortunately, plasmayte is currently unavailable in Thailand. The potential risk associated with Ringer's solution lies in its hypo-osmolarity and low sodium content compared to plasma. In the absence of PlasmaLyte, and considering specific conditions like hyponatremia or suspected increased intracranial pressure, normal saline can be an alternative [4]. Dextran, starch, or gelatin are not recommended due to their potential to cause acute kidney injury [22]. The first hour resuscitation in pediatric septic shock was outlined at Figure 1 and 2.

VASOACTIVE SUPPORT

The vasoactive medication should be initiated promptly upon the diagnosis of fluid refractory shock or in children exhibiting signs of fluid intolerance with inadequate tissue perfusion. The medication can be started using peripheral intravenous access without differentiating whether the patient has a cold or a warm shock. According to a prior study, there were significant differences

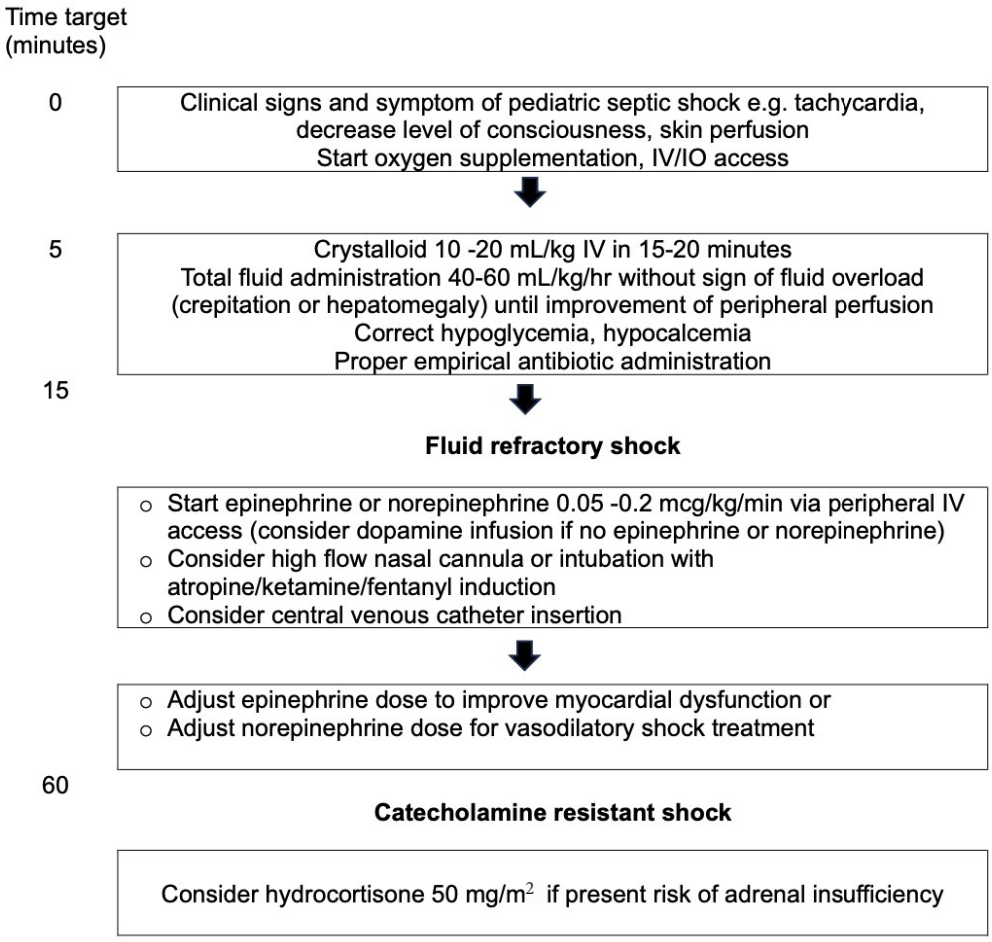

Figure 1. The 1st hour resuscitation in pediatric septic shock.

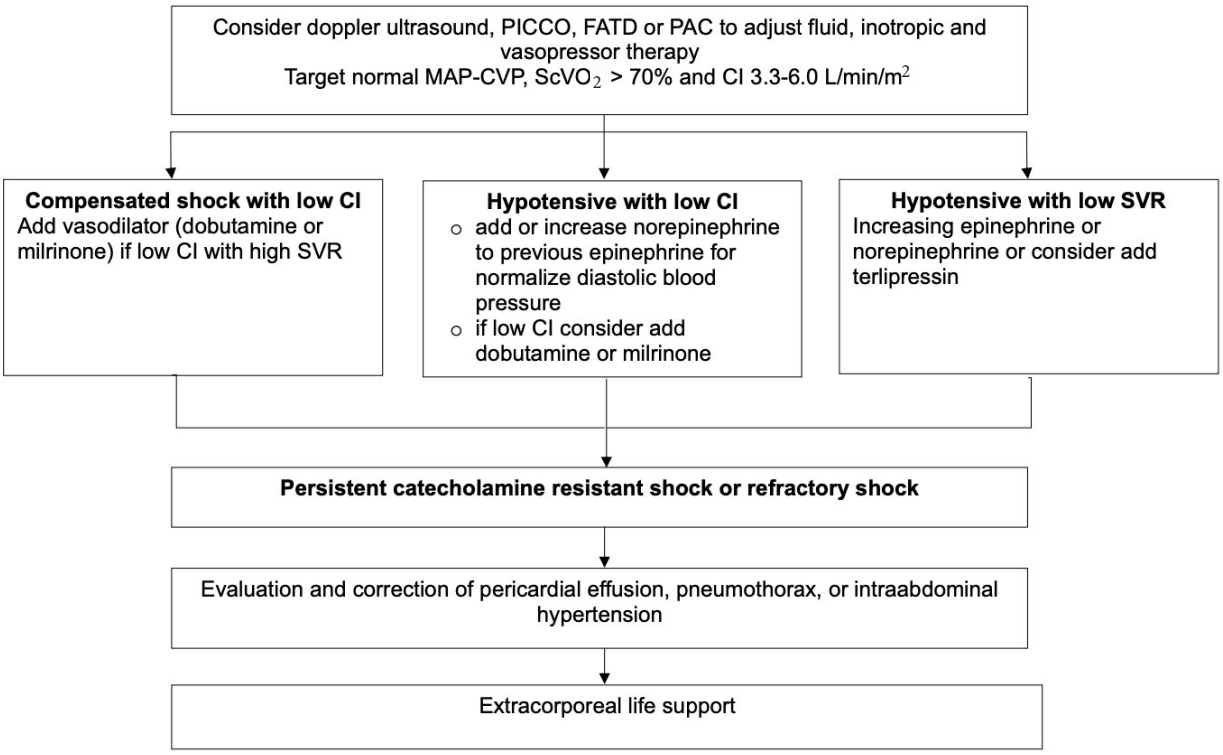

Figure 2. The treatment of pediatric septic shock after 1st hour resuscitation.

between physical examinations and cardiac output monitoring modalities [23]. Thus, the new terms of myocardial dysfunction and vasodilatory shock are introduced in this guideline to replace cold and warm shocks.

Both epinephrine and norepinephrine can be used as first-line vasoactive medications. The initial dose for epinephrine infusion is suggested in septic shock children with suspected myocardial dysfunction, while norepinephrine should be used in septic shock children with vasodilatory shock. Dopamine is not recommended as the first-line medication in centers with access to epinephrine, owing to the higher mortality rate compared with epinephrine [24,25].

In children with normal blood pressure and hemoglobin > 10 g/dL who have poor cardiac contractility, a cardiac index < 3.3 L/minute/m^2, central venous oxygen saturation ($ScvO_2$) < 70%, or non-declining high lactate, inotropic medications such as dobutamine or milrinone can be considered. Epinephrine can also be considered in children who received norepinephrine as the first-line vasoactive medication [7]. In children with refractory vasodilatory shock, terlipressin can also be considered [26]. There is growing evidence to use methylene blue for septic shock refractory to fluid and catecholamine therapy. A dose of 1 mg/kg intravenous, followed by a continuous infusion at 0.25 mg/kg per hour, may be used. A recent systemic review showed the safety and potential benefits for children with refractory shock, although more study is still warranted. [27] The doses and mechanisms of action of vasoactive medications are shown in Table 4 [28].

RESPIRATORY SUPPORT AND MECHANICAL VENTILATION

For stable patients exhibiting only tachypnea without oxygen desaturation or respiratory distress, oxygen administration through a low-flow nasal cannula (2-5 L/min) or a non-rebreathing mask (6-10 L/min) is suggested. In cases of altered consciousness, shock, or respiratory distress, oxygen administration with a non-rebreathing mask (6-10 L/min) or high-flow nasal cannula (HFNC) is recommended, accompanied by close monitoring. In severe cases or worsening respiratory status leading to respiratory arrest or fatigue, endotracheal intubation is advised. Patients with a Glasgow Coma Score (GSC) of 8 or below should be intubated for airway protection. Continuous monitoring of patients using pulse oximetry and arterial blood gas is essential.

In cases of respiratory failure or persistent hemodynamic instability, even after treatment with 40-60 mL/kg of fluid bolus and vasoactive medication, endotracheal intubation is recommended. The use of a cuffed endotracheal tube is suggested, and the endotracheal tube size is calculated using specified formulas by age. Patients with pediatric acute respiratory distress syndrome (PARDS) should receive mechanical ventilation using lung-protective strategies based on the severity, as outlined in the Pediatric Acute Lung Injury Consensus Conference-2 group (PALICC-2) guideline [29].

ENDOTRACHEAL INTUBATION

Endotracheal intubation, which requires sedation and a transition to positive pressure ventilation, carries a risk of hemodynamic deterioration. Clinicians should prepare to administer additional treatment, such as a fluid bolus or vasoactive medication, if necessary. Considering premedication with atropine before endotracheal intubation is advisable to reduce the incidence of bradycardia, particularly in young children younger than 1 year. Ketamine is the recommended sedative agent for use in patients with shock due to its lower likelihood of causing hypotension [30]. Etomidate should be avoided because of its adrenal suppression effect [7, 31]. Propofol should also be avoided because it can cause hypotension due to its vasodilatory effect. The use of neuromuscular blocking agents (NMBA) can facilitate endotracheal intubation but should be avoided in patients with risk of difficult airways.

SEDATION AND ANALGESIA

Sedation and analgesia are required for intubated patients. Fentanyl is the preferred analgesic agent, as it is less likely to induce hypotension compared to morphine. Midazolam is frequently used as a continuous intravenous sedative agent. In hemodynamically unstable patients, propofol and dexmedetomidine should be avoided because they can cause hypotension. In addition, dexmedetomidine can also induce bradyarrhythmia, which further worsens cardiac output. Continuous infusion of NMBA may be necessary to prevent endotracheal tube displacement, facilitate patient-ventilator synchronization, or reduce oxygen con-

Table 4. Vasoactive medications (doses and mechanism of action).

Vasoactive drugs	Dose
Dopamine	- 5-9 mcg/kg/min (stimulate beta-adrenergic receptor, increased contractility and heart rate) - 10-20 mcg/kg/min (stimulate alpha-adrenergic receptor, increased systemic vascular resistance)
Dobutamine	- 5-20 mcg/kg/min (stimulate beta-adrenergic receptor, increased contractility, heart rate and vasodilatation)
Epinephrine	- 0.05-0.2 mcg/kg/min (stimulate beta-adrenergic receptor, increased contractility and heart rate) - > 0.2 mcg/kg/min (stimulate alpha-adrenergic receptor, increased systemic vascular resistance)
Norepinephrine	- 0.05-2 mcg/kg/min (stimulate alpha-adrenergic receptor, increased systemic vascular resistance)
Milrinone	- 0.25-0.75 mcg/kg/min (stimulate cAMP and inhibit phosphodiesterase 3, increase contractility and vasodilatation)
Terlipressin	- 1-20 mcg/kg/hr (stimulate vasopressin receptor, increased systemic vascular resistance)

sumption as supportive treatment for shock. Cisatracurium is the preferred NMBA because its clearance is not affected by renal or hepatic dysfunction.

RENAL REPLACEMENT THERAPY AND EXTRACORPOREAL BLOOD PURIFICATION

Sepsis-associated acute kidney injury (S-AKI) is defined by the presence of acute kidney injury (AKI) diagnosed using the Kidney Disease Improving Global Outcome (KDIGO) criteria in septic patients without other significant contributing factors causing AKI [32-34]. The main pathophysiology in the development of S-AKI is still not well understood but is believed to result from a decrease in global renal blood flow, severe systemic inflammation, microcirculatory failure, and acute tubular necrosis. Renal replacement therapy (RRT) using an extracorporeal device with the mechanisms of diffusion, convection, or both is a well-recognized supportive management approach once S-AKI is diagnosed. However, the timing of the initiation and cessation of RRT has been a subject of long-standing debate. In resource-limited facilities where RRT via extracorporeal circuit is not available, peritoneal dialysis can be considered as an alternative mode of RRT [35-36].

Novel extracorporeal therapies using similar devices but employing the mechanism of adsorption have been developed and extensively studied in recent decades. These therapies aim to balance circulating pro- and anti-inflammatory cytokines in septic patients. RRT is the therapy of choice for the treatment of fluid overload resistant to diuretics and for addressing metabolic disturbances not amendable by medications. On the other hand, blood purification is designed to reduce cytokine levels to mitigate the host's inflammatory response and attain hemodynamic stability. Calculating percentage fluid overload (%FO) aids in optimizing fluid management, guiding tailored therapies, assessing risk, and optimizing resuscitation strategies. It is calculated by taking the difference between fluid intake (L) and fluid output (L), dividing by the baseline body weight (kg), and then multiplying by 100.

Potential benefits of RRT in sepsis include the treatment of fluid overload and metabolic disturbances unresponsive to medications, but RRT is not associated with other PICU outcomes [37]. The potential benefits of blood purification in sepsis encompass the reduction of various pro-inflammatory cytokines levels (IL-1β, IL-6, IL-8, and TNF-α), a decreased vasopressor-inotropic score (VIS), a lowered Pediatric Logistic Organ Dysfunction (PELOD-2) score at 72 hours, a shortened ICU length of stay, and a reduced mechanical ventilator day [38-42]. Different adsorptive columns exhibit varying reported benefits, though specific details for each adsorptive column are not fully described for simplicity of recommendation. Possible risks entail the need for a dialysis catheter, which requires clinicians and nursing specialists [4]. Pediatric dosing and regimen recommendations indicate that current evidence does not support the use of high-volume RRT, suggesting a usual pediatric dose of 1,000-2,000 mL/1.73 m^2/hour or 25-35 mL/kg/hour of dialysate or replacement fluid flow, with a blood flow rate starting at 3-5 mL/kg/min [43-47]. For extracorporeal blood purification therapy, the adsorptive cartridge should be connected in series configuration with the RRT circuit.

CORTICOSTEROIDS

Proposed mechanisms of corticosteroids involve multiple effects on vascular tone, including upregulation of angiotensin receptors on vascular smooth muscle cells (VSMC), inhibition of nitric oxide synthesis, stimulation of the release of calcium from intracellular storage, and blunting endothelium-dependent vasodilatation. These mechanisms enhance the effects of vasoconstrictors like alpha-adrenergic agonists, angiotensin-II, arginine vasopressin, endothelin, and thromboxanes. Additionally, corticosteroids exhibit cardiovascular effects beyond vascular tone, including a positive inotropic effect and bradycardia, with incompletely described mechanisms. [48-49].

Critical Illness-Related Corticosteroid Insufficiency (CIRCI) is distinct from adrenal insufficiency and is characterized by relative insufficiency in critically ill patients [50]. The 2017 SCCM-ESICM guideline recommends employing either a random cortisol level less than 10 mcg/dL or a 250-mcg ACTH stimulation test that results in a change in serum cortisol level less than 9 mcg/dL at 60 minutes for the diagnosis of CIRCI. However, in the context of limited laboratory resources in the Thai public health system, clinicians are recommended not to await confirmatory tests but to consider corticosteroid treatment for pediatric septic shock patients who are not responsive to fluid and vasoactive medications, if deemed necessary. Potential benefits of corticosteroids for septic shock include decreased 28-day mortality, improved shock reversal at day 7, a reduced Sequential Organ Failure Assessment (SOFA) score at day 7, and a shortened ICU length of stay (LOS) [51-57]. Possible risks encompass new infections, hyperglycemia, hypernatremia, critical illness-related myopathy, and neuromuscular weakness [51-53, 55-57]. Pediatric dosing and regimen recommend hydrocortisone at 50 mg/m^2 IV initially, followed by 50 mg/m^2/day divided 6-8 hours IV for 3-7 days, or until vasoactive drugs are successfully discontinued for at least 12 hours [58]. Alternative dosing is 2 mg/kg IV initially, followed by 1 mg/kg/day divided over 6-8 hours of IV.

BLOOD PRODUCT TRANSFUSION

Oxygen delivery (DO_2) and arterial oxygen content (CaO_2) are critical parameters in the context of shock, a clinical syndrome where DO_2 fails to meet the metabolic demands of the body. The relationship between oxygen delivery, cardiac output, and CaO_2 are key determinants of the adequacy of DO_2. The arterial oxygen content primarily relies on the oxygen carried by hemoglobin, with

a lesser contribution from dissolved oxygen in plasma. In this relationship, both hemoglobin (Hb) and arterial oxygen saturation play crucial roles in supplying vital organs with oxygen. Clinicians aiming to enhance oxygen supply can consider increasing either oxygen supplements or raising Hb levels through packed red blood transfusion. Despite several studies attempting to determine the optimal Hb level for pediatric septic shock, a large pediatric randomized controlled trial in 2007 found no significant differences in any PICU outcomes between transfusion-restrictive (Hb >7 g/dL) and transfusion-liberal (Hb >9.5 g/dL) groups [59]. The Surviving Sepsis Campaign guidelines recommend against routine prophylactic platelet transfusion for nonbleeding pediatric septic shock patients with thrombocytopenia and against prophylactic plasma transfusion for those with coagulation abnormalities. These suggestions apply to children who are not bleeding but present with sepsis-associated organ dysfunction [4]. A systematic review with expert consensus suggests that for critically ill pediatric patients undergoing invasive procedures outside the operating room (OR), platelet transfusion may be considered if platelet counts are at or below 20,000/mm^3. It also advises that plasma transfusion might be considered for those with an International Normalized Ratio (INR) over 2.5, weighing the transfusion risks against the clinical scenario [60]. To minimize transfusion-associated adverse events, encompassing both infectious and non-infectious complications, the following recommendations are made for Thai clinicians treating pediatric septic shock. We recommended transfusing packed red cells to maintain a Hb level > 7.0 g/dL, consider diuretics in patients at risk for fluid overload during or after transfusion, avoid platelet transfusion if platelet levels are > 20,000/mm^3, refrain from fresh frozen plasma transfusion for coagulopathy without bleeding, and use clinical judgment for blood product transfusion before invasive procedures in patients with coagulopathy and no clinical bleeding.

ENDOCRINE AND METABOLIC MANAGEMENT

Children with limited glycogen storage are susceptible to severe hypoglycemia during septic shock. Frequent monitoring, at least every 6 hours, is crucial, and to prevent hypoglycemia, intravenous fluids with 5-10 percent dextrose are recommended. We recommend maintaining a blood glucose level between 80-180 mg/dL [61,62]. Calcium dysregulation usually occurs in critically ill children and is associated with organ dysfunction [63]. We recommend targeting normal blood calcium levels in children with septic shock requiring vasoactive infusion support.

In cases of fluid-refractory catecholamine-resistant septic shock, the effectiveness of HAT therapy, which includes hydrocortisone, ascorbic acid, and thiamine, remains uncertain due to conflicting study results [64-66]. Therefore, further information and robust evidence are necessary to evaluate the potential role of HAT therapy as a rescue intervention for this condition. If HAT therapy is considered to be helpful, the specific dosages and administration intervals are as follows: hydrocortisone 1 mg/kg/dose (maximum 50 mg/dose) IV every 6 hours, thiamine 4 mg/kg/dose (maximum 200 mg/dose) IV infusion over 30-60 minutes once or twice daily, and vitamin C 30 mg/kg/dose (maximum 1,500 mg/dose) IV infusion over 30–60 minutes every 6 hours [67-69].

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Currently, there is insufficient conclusive evidence to support the routine use of IVIG in critically ill children with sepsis. We advise against its general use in cases of septic shock or sepsis-associated organ dysfunction [70]. However, there may be potential benefits for selected patients, such as those with suspected toxic shock syndrome. In such cases, consideration may be given to IVIG administration at a dosage of 1 g/kg/dose on day 1, followed by 0.5 g/kg/dose IV infusion over 6 hours on days 2 and 3 [71]. Furthermore, other pediatric populations that might derive benefits from IVIG include children with necrotizing fasciitis or those with an underlying disease of primary immunodeficiency. We suggest against the use of pentaglobulin in children with septic shock or sepsis-associated organ dysfunction [71].

SODIUM BICARBONATE ADMINISTRATION

We were unable to provide a specific recommendation on the routine use of sodium bicarbonate in children with septic shock or sepsis-associated organ dysfunction. However, in our clinical practice, there is a preference for administering 7.5% $NaHCO_3$ at a dosage of 1 mL/kg intravenously over 60 minutes in patients with hemodynamically unstable and severe metabolic acidosis (pH < 7.15) [72]. Close monitoring is essential during the infusion due to potential complications, including hypernatremia, hypokalemia, hypocalcemia, and fluid overload. It is important for patients to have normalized carbon dioxide levels before the administration of 7.5% $NaHCO_3$ to prevent hypercapnia.

PLASMA EXCHANGE (PE)

Current evidence suggests that plasma exchange (PE) is not generally effective as a therapy for septic shock [73]. However, PE may be beneficial for a specific subgroup of pediatric patients with thrombocytopenia-associated multiple organ failure (TAMOF) and should be considered in such cases. The efficacy of PE is well-established in conditions such as thrombotic thrombocytopenic purpura, a type of thrombotic microangiopathy that is associated with significantly reduced levels of ADAMTS-13. While randomized controlled trials are limited in number, various case series have demonstrated the potential benefits of PE in managing TAMOF [74-75].

Table 5. Summarize the septic shock resuscitation bundle for various levels of hospitals.

	Primary care	General hospital	Tertiary or quaternary hospital
Patient screening	Early recognition tool	- Early recognition tool - Diagnosis initial presentation of poor tissue perfusion or organ dysfunction	- Early recognition tool - Diagnosis poor tissue perfusion or organ dysfunction with additional assessment tools
Diagnosis	Early detection and refer	- Prompt diagnosis - Categorize patients into septic shock and sepsis-associated organ dysfunction - Evaluate shock stage - Search for the location of infection	- Prompt diagnosis - Categorize patients into septic shock and sepsis-associated organ dysfunction - Evaluate shock stage - Search for the location of infection
Initial treatment	- Oxygen - IV fluid	- Oxygen, respiratory support - Obtain culture from source of infection and blood culture	- Oxygen, respiratory support - Obtain culture from source of infection and blood culture
Antibiotic administration with controlled source of infection	Early refer for IV antibiotic	- Administrate empirical antibiotic as soon as possible (within 1 hour in septic shock or 3 hours in sepsis-associated organ dysfunction patients)	- Administrate empirical antibiotic as soon as possible (within 1 hour in septic shock or 3 hours in sepsis-associated organ dysfunction patients) - Control the causative source - Consider medication adjustments and appropriate interventions based on culture results
Initial fluid resuscitation	- Obtain one large bore IV access - In hypotensive patient, isotonic crystalloid bolus 10-20 mL/kg in 15-20 minutes (maximum 40 mL/kg or any signs of fluid overload) - In non-hypotensive patient, isotonic crystalloid bolus 10 mL/kg in 60 minutes	- Obtain 2 large bore IV access - Consider intraosseous if unable to establish IV access - Isotonic crystalloid bolus 10-20 mL/kg in 15-20 minutes, repeat 2-3 doses as needed in 1st hour (stop fluid bolus if present of any signs of fluid overload) - Evaluate signs of fluid overload	- Obtain 2 large bore IV access - Consider intraosseous if unable to establish IV access - Isotonic crystalloid bolus 10-20 mL/kg in 15-20 minutes, repeat 2-3 doses as needed in 1st hour (stop fluid bolus if present of any signs of fluid overload) - Evaluate signs of fluid overload with other tools such as ultrasound - Consider use 5% albumin as option fluid bolus
Inotropic and vasopressor	Early refer	- Epinephrine or norepinephrine 0.05-0.2 mcg/kg/min to raise blood pressure to the target level when blood volume is adequate (at least 40 mL/kg) - If no improvement, consider a referral	- Epinephrine or norepinephrine 0.05-0.2 mcg/kg/min to raise blood pressure to the target level when blood volume is adequate (at least 40-60 mL/kg) - Consider dobutamine or milrinone in poor myocardial contractility with normal blood pressure - Consider central venous catheter insertion to prevent extravasation
Blood component		If blood bank available consider transfusion - Red blood cell 10 mL/kg in unstable patient with Hb level less than 10 g/dL or in stable patient with Hb level less than 7 g/dL - Platelet in patient who has active bleeding, undergoes invasive procedure with platelet level less than < 50,000/mm^3, coagulopathy with platelet level less than < 20,000/mm^3, platelet level less than < 10,000/mm^3 - FFP 10 mL/kg in patient with coagulopathy along with bleeding or undergoes invasive procedures	Consider transfusion - Red blood cell 10 mL/kg in unstable patient with Hb level less than 10 g/dL or in stable patient with Hb level less than 7 g/dL - Platelet in patient who has active bleeding, undergoes invasive procedure with platelet level less than < 50,000/mm^3, coagulopathy with platelet level less than < 20,000/mm^3, platelet level less than < 10,000/mm^3 - FFP 10 mL/kg in patient with coagulopathy along with bleeding or undergoes invasive procedures

	Primary care	General hospital	Tertiary or quaternary hospital
Continuous renal replacement therapy (CRRT)		- Consider initiating CRRT when a patient is in stage 3 or higher of Acute Kidney Injury (AKI) and is unresponsive to standard treatment	- Consider initiating re when a patient is in stage 2 or higher of Acute Kidney Injury (AKI) and is unresponsive to standard treatment
Respiratory support	O_2 administration	- O_2 administration - Consider High flow nasal cannula - Consider intubation in patient who has respiratory failure or prolong shock	- O_2 administration - Consider High flow nasal cannula or Bilevel positive pressure ventilation - Consider intubation with cuffed tube in patient who has respiratory failure or prolong shock - Use lung protective strategies in patient with ARDS
Sedation		-Use sedative medication with minimal hemodynamics disturbance -Sedative medication for intubated patient	- Use sedative medication with minimal hemodynamics disturbance - Sedative medication for intubated patient with sedation scale or protocol
Monitoring		Mean arterial pressure, urine output, capillary refill time	- Mean arterial pressure, urine output, arterial lactate, $ScvO_2$, tissue perfusion

THERAPEUTIC ENDPOINTS

The targets for pediatric septic shock include achieving a capillary refill time of less than 2 seconds, no difference in the quality of pulses between peripheral and central, warm extremities, urine output greater than 1 mL/kg/hour, a normal level of consciousness, and maintaining a threshold heart rate based on age (90-160 beats per minute for infants, 70-150 beats per minute for children). Additionally, central venous oxygen saturation ($ScvO_2$) should be kept above 70%, anion gap below 16, lactate below 2 mmol/L, and cardiac index (CI) within the range of 3.3-6.0 L/minute/m^2 if equipment is available [1]. The management of pediatric septic shock across different hospital levels, including primary, secondary, and tertiary hospital, is outlined in Table 5.

CONCLUSION

The Thai pediatric septic shock management guideline emphasizes evidence-based strategies, including early recognition, fluid and vasoactive agent titration, empirical antimicrobial therapy, and holistic care. With a focus on adaptability to local resources, the guideline aims to optimize outcomes across Thailand's varied healthcare settings.

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