SMGroup

Sepsis in Children

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KEY MESSAGES

- The hemodynamic response to sepsis, severe sepsis and septic shock in children can be different than in adults. Response changes in the first 48 hours of the disease and may include lowered, normal or even elevated cardiac output with lowered, normal or elevated systemic vascular resistance.
- Pediatric septic shock mortality is lower than in adults and the main factor determining the survival is low cardiac output. Therefore, the critical therapeutic target is the cardiac index value of 3.3 – 6 l/min/m^2.
- Thermoregulation disturbances, tachycardia and insufficient tissue perfusion are the fundamental criteria pointing to severe sepsis/septic shock. Capillary refill time is a useful indicator. Hypotension, on the other hand, does not have to be necessarily present.

- The “first hour” therapeutic measures are focused on following: securing the oxygenation and ventilation, maintaining/restoring the circulation with adequate tissue perfusion, restoring normal heart rate and antibiotics administration.
- Therapeutic measures to fulfill after the first hour include capillary refill time ≤ 2 seconds, warm periphery on extremities, no difference between central and peripheral pulsation quality, oxygen saturation in central venous blood > 70 %, cardiac index value 3.3 – 6.0 l/min/m^2 with normal perfusion pressure (MAP–CVP or MAP–IAP) for given age, diuresis > 1 ml/kg/hour and normal blood lactate, INR and anion gap values.

INTRODUCTION

Worldwide there are about 29000 deaths of children younger than 5 years each day. Almost three quarters of those deaths are caused by the six main causes: diarrhea (17%), malaria (8%), neonatal infections (10%), pneumonia (19%), premature birth (10%) and neonatal asphyxia (8%). Infections of various causes are therefore responsible for the majority of pediatric mortality [1].

The first guidelines of The American College of Critical Care Medicine – Pediatric Advanced Life Support (ACCM – PALS) for the diagnosis and treatment of pediatric sepsis were published in 2002 [2] a further revised in 2009 [3] and 2012 [4]. According to those guidelines, the critical measures determining the therapeutic outcome include rapid diagnosis, adequate fluid resuscitation, appropriate cardiovascular support and early antibiotic therapy. Despite the fact that ACCM – PALS guidelines are for sure the proper clinical practice, from the view of evidence based medicine there is not much proof to support each of those individual interventions. Majority of therapeutic recommendations for the pediatric septic shock is level C or D, according to Surviving Sepsis Campaign. Only exception is the recommendation not to administer the activated protein C, which is level B guideline [5].

There are also many publications supporting the efficiency of the ACCM – PALS guidelines. The retrospective study of authors from Pittsburgh, USA showed that compliance with the ACCM – PALS algorithm along with successful management of shock state in 75 minutes resulted in patient mortality of 8%, compared with mortality of 38% when the algorithm was not followed. Surprisingly, the right course of action was used only in 30% of patients [6]. The prospective study from 17 British pediatric ICUs showed that 62% of children in shock state were not treated according to ACCM – PALS guidelines with resulting mortality of 25%. The mortality of children in whom the algorithm was followed was 6%. Authors conclude that the main reasons for the wrong therapeutic approach include delayed diagnosis of shock state, delayed treatment initiation and pointless delay in central venous catheter insertion [7]. One study showed almost 100% survival of children with the dengue shock syndrome and adequate fluid resuscitation [8]. British authors proved that the delay in inotropic drugs administration is associated with the 23-times higher probability of death in children with meningococcal septic shock [9]. Studies from the St.

Mary Hospital in London, UK [10] and Sophia Hospital in Rotterdam, Netherlands [11] aimed on children with meningococcal sepsis showed that implementation of ACCM – PALS protocol resulted in mortality decrease from 22% to 2%, resp. from 20% to 1%. Randomized study from Brazil [12] showed that targeting the therapy on oxygen saturation in central venous blood over 70% resulted in mortality decrease from 39% to 12%.

It seems that there is some kind of barrier preventing the wider use of those guidelines in clinical practice. Reasons can include the lack of awareness and knowledge, disagreement or mistrust in the adequate guideline efficiency and also a kind of "force of habit" of the present clinical practice [13].

DIFFERENCES IN HEMODYNAMIC RESPONSE TO SEPSIS IN CHILDREN AND ADULTS

The main cause of death in adult septic shock is vasomotor paralysis. Myocardial dysfunction manifests itself by the decrease in ejection fraction, but the cardiac output (CO) is maintained or increased by two mechanisms: tachycardia and lowered systemic vascular resistance (SVR) [14]. Pediatric septic shock is linked with severe hypovolemia and children, therefore, often have a good response to aggressive volume resuscitation. The main factor determining survival in children is low CO – unlike in adults, where it is low SVR – therefore reaching the cardiac index (CI) of 3.3–6 l/min/m^2 increases survival. Another important difference is in the main determinant of oxygen consumption (VO_2) – in children it is the decrease in oxygen delivery (DO_2), not the oxygen extraction as in adults. Mortality can therefore be decreased by achieving the VO_2 > 200 ml/min/m^2 [15].

The hemodynamic profile in children with septic shock can be very variable and rapidly changes in the first 48 hours. Study including 50 children showed that 58% of patients had low CO along with normal or high SVR, 22% of patients had low CO and low SVR, and 20% had normal or elevated CO with low SVR. Mortality in the first group was 28%, in second 9%, and in third 10%, resp [15].

Clinical Signs and Hemodynamic Parameters

Shock should be diagnosed based on clinical picture, ideally before the onset of hypotension. Clinical signs include hypothermia or hyperthermia, altered mental state, bradycardia or tachycardia, peripheral vasodilatation (warm shock) or vasoconstriction with prolonged capillary refill time > 2 s (cold shock). Initial therapeutic approach must focus on the normalization of mental state, good peripheral perfusion (capillary refill time < 3 seconds), well palpable peripheral pulse and normal blood pressure and heart rate for given age (Table 1) [3].

Table 1: Heart rate and perfusion pressure target values [3].

Age category	Heart rate (/min)	Perfusion pressure (MAP – CVP or MAP – IAP)
On-term newborn	120 – 180	55
28 days – 1 year	120 – 180	60
1 year – 2 years	120 – 160	65
2 – 7 years	100 – 140	65
7 – 15 years	90 – 140	65

Abbreviations: MAP–Mean Arterial Pressure; CVP-Central Venous Pressure; IAP-Intra Abdominal Pressure.

Study of Carcillo and colleagues showed that different abnormalities in hemodynamic profile correspond with different mortality: tachycardia or bradycardia 3%, hypotension with capillary refill time < 3 seconds 5%, normal blood pressure with capillary refill time > 3 seconds 7%, and hypotension with capillary refill time > 3 seconds 33%. However despite the initial hemodynamic profile of the patient on admission, adherence to ACCM – PALS protocol resulted in 40% decrease in mortality [16].

Shock state can be evaluated and the treatment managed based on the hemodynamic parameters. Basic parameters include perfusion pressure and CO. Organ blood flow is directly proportional to the perfusion pressure and indirectly proportional to the SVR, which can be expressed as: CO = (MAP–CVP)/SVR. The therapeutic target is naturally to maintain the perfusion pressure above the critical point in a way to ensure the sufficient organ blood flow. Perfusion pressure is used as a parameter corresponding to organ blood flow. The above mentioned equation shows that organ blood flow (Q) correlates directly with the perfusion pressure and indirectly with the vascular resistance. In healthy heart the increase in SVR leads to hypertension with maintained CO. In the heart with insufficient ventricular function, however, the high SVR along with normal blood pressure leads to the decreased CO, which can further lead to the insufficient organ perfusion and shock. The CI values in the range of 3.3 – 6 l/min/m^2 in patients with the septic shock are linked with lower mortality. CI value in patients without the septic shock can be maintained above the 2 l/min/m^2. Achieving the requested CI values is however dependent on maintaining adequate heart rate (HR). With the high HR there is not enough time to fill coronary arteries and therefore the contractility along with CO decreases. Coronary perfusion can be further reduced by low diastolic pressure and/or high end-diastolic ventricular pressure. Coronary perfusion pressure can be improved by the administration of fluids (in the case of low stroke volume (SV)) or by increasing low contractility. Fluid administration and raising SV naturally lead to the decrease in HR and improvement in CO. Generally, children have limited capability of increasing the CO by heart rate because of physiologically higher HR compared to adults. Adult can compensate the fall in SV by increasing the HR to double, for example from 70 to 140 / min, but the child is not able to

use this compensatory mechanism, i.e. from 140 to 280 /min. Despite the fact that increasing the HR to maintain CO is also partially important in children, there is one rule – the younger the child is the less effective is this compensatory mechanism. Cardiovascular system responds to lower contractility and lower SV by vasoconstriction with the goal to maintain adequate blood pressure. Corresponding clinical picture includes cold extremities, poorly palpable peripheral pulse, prolonged capillary refill time and decreased pressure amplitude. In this clinical picture the right choice is to administer vasodilating drugs to decrease the heart afterload and fluids to increase the end-diastolic volume – this will result in lower heart rate and improved peripheral perfusion. It is certain that bradycardia is also the reason for low CO. Basic approach is to administer inotropic drugs with positive chronotropic effect. If the difference between diastolic blood pressure and central venous pressure is too small, it is time to add a vasopressor [3,4].

Shock therapy can also be directed based on oxygen parameters. As stated above, maintaining the CI value in the range of 3.3 to 6 ml/min/m^2 and VO_2 > 200 ml/min/m^2 improves survival of pediatric septic shock. Low CO is connected with higher oxygen extraction and therefore we can use the oxygen saturation in venous blood as an indirect indicator of the patient's CO. If DO_2 value is sufficient, the oxygen saturation in venous blood should be above 70%. As in adults, the therapy focused on achieving/maintaining $ScvO_2$ > 70% led to substantial decrease in mortality from 39% to 12% [12].

Septic Shock in Children – Diagnosis

Infection in children manifests itself by a triad of symptoms including fever, tachycardia and vasodilatation. If this triad is accompanied by nonspecific signs as lethargy, confusion, drowsiness, poor contact or in contrast irritation with parents, we must suspect the septic shock is present. Clinical picture of the septic shock in children with probable or proven infection include the following:

1. Hypothermia or hyperthermia

2. Insufficient tissue perfusion – prolonged capillary refill time > 2 seconds (cold shock)

- Weakened peripheral pulse (cold shock)
- Marbled cold extremities (cold shock)
- "Flash" capillary refill (warm shock)
- Diuresis decrease under 1 ml/kg/hour

Hypotension does not have to necessarily be present in pediatric septic shock, but the occurrence of hypotension is a definite proof of septic shock.

Septic Shock in Children – Therapy

First hour = basic urgent measures

Goals: Maintaining or restoring the patency of airway. Securing the oxygenation and ventilation. Restoring or maintaining the circulation; i.e. securing adequate perfusion and adequate blood pressure, restoring normal heart rate for given age.

Therapeutic targets: Main therapeutic targets include capillary refill time ≤ 2 seconds, normal vessel pulsation with no difference in peripheral and central regions, warm extremities, diuresis exceeding 1 ml/kg/hour, normal blood pressure for given age (noninvasive blood pressure monitoring is reliable only with well palpable pulse) and normal blood levels of glucose and ionized calcium.

Monitoring: Pulse oximetry, continuous ECG, blood pressure, pressure amplitude (result of the episodic character of heart contractions and elastic features of arterial vessels). Pressure amplitude value and diastolic blood pressure is used to distinguish between low systemic vascular resistance (high pressure amplitude caused by low diastolic blood pressure) and high systemic vascular resistance (low pressure amplitude). Further we should monitor body temperature, diuresis, blood glucose and ionized calcium values.

Respiration and securing the airway: Airway status and the quality of respiration should be closely monitored and maintained because of possible rapid changes in lung compliance a respiratory work. Because of the centrally driven hyperventilation patients can demonstrate respiratory alkalosis in the early phase of sepsis. Hypoxemia can develop with the progression of sepsis. Further with the development of secondary lung parenchyma damage or altered mental state there is enormous risk of respiratory acidosis. In the same way patient can demonstrate the onset of metabolic acidosis.

The decision about endotracheal intubation and initiation of artificial lung ventilation is based on the clinical picture – elevated respiratory work, hypoventilation or altered mental state. Hesitation with endotracheal intubation and lengthy waiting for laboratory results can have very devastating consequences. About 40% of the cardiac output is spent on respiratory work and therefore early intubation and artificial lung ventilation can reverse the development of the shock state. When possible before the intubation in the state of absolute hypovolemia and cardiac dysfunction, it is recommended to perform the fluid resuscitation and to administer vasoactive agents in order to suppress the onset of endogenous stress induced by intubation-facilitating agents.

Etomidate is not recommended for intubation. Ketamine and atropine can be used as a premedication. Benzodiazepines can be used as an induction agent and subsequent sedative with the maintenance of cardiovascular stability. When we are sure about the ability to maintain the airway patency, we can use short-acting non-depolarizing muscle blocker.

Cardiovascular system: Venous access must be secured very quickly. When we are not able to secure the reliable vascular access in a few minutes, one should use the intraosseous approach. Fluid resuscitation should be commenced immediately considering possible hepatomegaly and heart murmur. Murmur can however be present e.g. in children with pneumonia and therefore its meaning does not necessarily have to be the fluid overload. Fluid resuscitation in children with probable or proven pneumonia should be performed under strict monitoring of the respiratory work and oxygen saturation. In the intravenous fluid-resistant shock we are starting the peripheral inotropic support with the low-dose dopamine or epinephrine. Inotropic agents should be given as diluted solution when administered via peripheral vasculature. Higher dosing can cause peripheral ischemia because of the drug effect on alpha-adrenergic receptors and then the dose should be decreased. With the central venous access we can administer dopamine, epinephrine or norepinephrine based on the actual hemodynamic profile. Fluid infusion via the peripheral vein should only be stopped after the onset of centrally administered agents.

Fluid resuscitation: Administer rapid fluid bolus – 20 ml/kg (isotonic crystalloid or 5% albumin) – via the positive pressure infusion or „by hand". Monitor very closely for the signs of circulatory overload – increase in the respiratory work, murmurs, heart gallop or hepatomegaly. In the absence of these clinical signs repeated fluid boluses can be administered. First hour therapy in children usually requires 40 – 60 ml/kg of fluids. Low blood glucose and hypocalcemia must be corrected.

Hemodynamic support: Dopamine is administered via the central line. If the child is developing fluid-refractory or dopamine-resistant shock, administer epinephrine in the dose of 0.05– 0.3 μg/kg/minute in cold shock. In the warm shock, administer norepinephrine in the dose, which will restore normal perfusion and normal blood pressure.

Corticosteroid therapy: Hydrocortisone is indicated in children with acute adrenal cortex insufficiency or hypothalamus–*hypophysis–adrenal axis suppression* (purpura fulminans, congenital adrenal hyperplasia, hypothalamus–hypophysis axis abnormalities), who remain is shock state despite the epinephrine or norepinephrine therapy. Hydrocortisone can be administered in a bolus or in continual infusion with the dose 1–2 mg/kg/day. In stress state the dose of 50 mg/kg can be used, but it must be titrated to reverse the shock.

Stabilization – subsequent hemodynamic support following the first hour

Goals: Normal perfusion; reaching capillary refill time ≤ 2 seconds within few hours. Normal perfusion pressure value related to child's age (MAP–CVP or MAP–IAP). Central venous blood saturation ($ScvO_2$) > 70%, CI 3.3 – 6.0 l/min/m^2.

Therapeutic targets: Reaching capillary refill time ≤ 2 seconds within few hours, normal vessel pulsation with no difference in peripheral and central region, warm extremities, diuresis > 1 ml/kg/hour, cardiac preload optimization, CI 3.3–6.0 l/min/m^2 with normal perfusion pressure related to child's age (MAP–CVP or MAP–IAP). $ScvO_2$ > 70 %. Reaching normal blood lactate, INR and anion gap values.

Monitoring: Pulse oximetry, continuous ECG, continuous blood pressure monitoring, body temperature, central venous pressure/oxygen saturation in venous blood, pulmonary artery pressure/oxygen saturation, CO, blood glucose, blood lactate and calcium level monitoring, INR and anion gap values monitoring.

Fluid resuscitation: Fluid loss and persistent hypovolemia resulting from the increased vessel permeability (capillary leak) can last for several days. Fluid delivery must focus on reaching optimal perfusion pressure, CVP, *end-diastolic* pressure (measured by echocardiography) values, optimization of the PAWP (*pulmonary artery* wedge *pressure) and CO.*

Crystalloids are the fluid of choice in patients with hemoglobin level > 100 g/l. Children with hemoglobin level < 100 g/l must be given a red blood cell transfusion. Fresh frozen plasma administration is recommended in prolonged INR value. Following the initial septic shock fluid resuscitation when there is about 10% fluid overload and the kidneys are no longer able to eliminate excessive fluid, diuretics are indicated. Other possible choices are peritoneal dialysis or continuous renal replacement therapy (CRRT).

With elevated blood lactate level and increased anion gap it is necessary to ensure adequate oxygen delivery ($ScvO_2$ > 70%) and CI value > 3.3 l/min/m^2. This can be achieved by means of hemoglobin level > 100 g/l, adequate fluid delivery and vasoactive agent administration.

Blood glucose should be maintained in the range of 4.4 – 8.3 mmol/l using isotonic 10% dextrose solution. Insulin administration is indicated in hyperglycemia. Hypoglycemia prevention is critical. Solutions containing <10% dextrose cannot provide sufficient glucose delivery.

Hemodynamic support: Hemodynamic support in children is necessary in case of fluid-refractory and dopamine-resistant shock. Signs of the catecholamine-resistant shock in children include the following:

1. ↓ CO a ↑ SVR
2. ↑ CO a ↓ SVR
3. ↓ CO a ↓ SVR

Although heart failure is quite common in children with persistent shock, hemodynamic parameters can be completely variable in time.

If low perfusion pressure, low diuresis, acidosis and hypotension persist despite the established hemodynamic support, it is recommended to insert the thermodilution catheter to measure the minute cardiac output, intra-cardiac pressures, pulmonary artery pressures and pulmonary artery wedge pressure. Therapeutic measures should focus on achieving $ScvO_2$ > 70%, CI 3.3 – 6.0 l/min/m^2 and normal perfusion pressure related to child's age.

Septic shock with low CI, normal blood pressure and high SVR: This clinical picture is similar to cardiogenic shock. Cardiac afterload-increasing agents should be used, which will decrease myocardial workload, improve the minute volume and peripheral perfusion. In children with epinephrine-resistant shock and normal blood pressure vasodilating agent is indicated – drugs of choice include sodium nitroprusside or nitroglycerine. In case of toxicity resulting from the prolonged use of nitroglycerine (methemoglobinemia) or nitroprusside (cyanides or isothiocyanate serum levels elevation) or still low value of CI, it is recommended to substitute those drugs for milrinone or inamrinone. As stated above, longer degradation halftime of those drugs can lead to reversible toxicity, which includes hypotension, tachyarrhythmia, abnormal liver and renal functional tests. This toxicity is reversible using norepinephrine or vasopressin infusion. Adequately filled vascular compartment is necessary prior to the administration of the initial dose of milrinone or inamrinone. In case of low CI, levosimendan and/or enoximone administration should be considered. Triiodothyronine supplementation is recommended in decreased thyroid function. Hydrocortisone administration is recommended in hypothalamus–hypophysis–adrenal axis insufficiency.

Septic shock with low CI, low blood pressure and low SVR: Low diastolic pressure and low SVR should be increased by adding norepinephrine to the administered epinephrine. When the adequate blood pressure is reached, CI and $SvcO_2$ values can be increased using dobutamine or *phosphodiesterase III blockers* (PDE *III). T*riiodothyronine supplementation is recommended in decreased thyroid function and once again hydrocortisone administration is recommended inhypothalamus–hypophysis–adrenal axis insufficiency.

Septic shock with high CI, low blood pressure and low SVR: When hypotension persists despite the fluid resuscitation and norepinephrine titration, low-dose vasopressin, angiotensin or terlipressin can be administered to restore the blood pressure. CO and $SvcO_2$ monitoring is necessary during the administration of those drugs because of their vasoconstrictor properties. In case of strong vasoconstrictor effect it is necessary to lower the dose or to increase the inotropic support using epinephrine or dobutamine. As with other types of septic shock stated above, triiodothyronine and hydrocortisone supplementation is recommended in the case of insufficiency.

Refractory septic shock: The whole set of possible associated signs and symptoms must be evaluated in children with refractory shock (therapy is given in parentheses):Pericardial effusion (*pericardiocentesis)*

- Pneumothorax (thoracocentesis)
- Adrenal insufficiency (substitution therapy)
- Severe bleeding (blood loss coverage, hemostasis)
- Elevated intraabdominal pressure (peritoneal catheter, decompression)

- Necrotic tissue (focus removal)
- Hidden source of infection (elimination, antibiotics therapy, intravenous immunoglobulins in toxic shock)
- Excessive immunosuppression (immunosuppressive drugs removal)
- Primary or acquired immunodeficiency (growth factors administration)

When the therapy fails, the possible alternative therapeutic option is extracorporeal membrane oxygenation (*ECMO*). Currently, the patient survival rate using this method is 50%. Continuous renal replacement therapy (CRRT) using high flux filters (> 35 ml/kg/hour) must be considered in fluid-overloaded patients with septic shock and purpura [3,4].

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