Severe sepsis is the leading cause of mortality among children aged under the age of 5 years. The four main causes of sepsis in children are pneumonia, malaria, measles and diarrhoea. Preventing sepsis is extremely important and immunization of children and regular hand hygiene proved to be very efficient and cost effective in avoiding the development of diseases that may lead to sepsis. Clinical symptoms of all stages of sepsis in children are often non specific, but early diagnosis is extremely important. The initial treatment of sepsis in children has to be adjusted to the developmental stadium, age, the capacity of its immune system and the likely cause of infection. In studies on children early administration of antimicrobial therapy proved to be efficient. Early management of septic shock should consist of rapid boluses of crystalloids and 5% albumin solutions and administration of vasoactive medications until hemodynamic stability is achieved.

Keywords: sepsis, children, septic shock, early management

INTRODUCTION

Sepsis is a leading cause of morbidity and is the most common cause of deaths (almost 60%) in children aged under 5 years1. Sepsis is a clinical syndrome presenting as a life-threatening organ dysfunction caused by a dysregulated host response to infection2. It occurs when normal pro-inflammatory host response exceeds its usual homeostatic constraints and becomes a generalized process3. The definition of sepsis in children is similar to adults, but the major difference is in the cutoff values of laboratory and clinical parameters. The most important steps in reducing the incidence of sepsis in children are to provide a safe living environment for them, to recognize and treat sepsis early and to prevent progression of sepsis from simple to more complex forms in order to prevent death and disabilities3.

The World Health Organization has stated that the four big causes of death in children worldwide are infectious diseases: pneumonia, diarrhea, malaria and measles. Severe sepsis was also more common in children with comorbidities. Despite the rising incidence of severe sepsis, the mortality rate has reduced from 10.3% to 8.9%. While any infection may precipitate sepsis, the most common pathogens are bacteria, viruses, and fungi. The type of pathogen varies according to host factors, including age, comorbidity, and geographic location1.

A child’s immune system is remarkably different from adults in terms of innate and adaptive immune function; in fact, full immunologic maturity is not reached until adolescence. A relatively suppressed immune system allows the newborn to tolerate colonization of previously sterile skin and gastrointestinal tract with normal bacterial flora without triggering an overwhelming inflammatory response. Both cellular and humoral immunity is suppressed and it reaches its adult adaptive and immune response levels only at the age of 2 years. The cumulative result of these deficits in immune function is that infants and some toddlers have markedly increased susceptibility to severe infection from various organisms, particularly viruses in children less than 2 years old. The primary mitigating factor during the first 6 months of life is transplacentally acquired maternal antibody (primarily IgG and IgA), a reason for expanding the recommendations for maternal immunization to include coverage of common pathogens associated with severe pediatric illness3.

Immunisation is the principal method of primary prevention, but global inequality exists in terms of access to existing vaccine products. Long term antimicrobial prophylaxis with antibiotics, antivirals, or antifungals is rec-
omended in immunocompromised patients with premorbid conditions as part of secondary prevention practices. Screening for sepsis in the asymptomatic population is not useful, but screening for maternal colonization with group B streptococci in pregnancy has been shown to reduce the burden of group B streptococci disease in newborns. Early onset GBS infection has a case fatality of 5–20%. Neonatal infection can occur when GBS ascends from the vagina to the amniotic fluid after the onset of labor or rupture of membranes. Therefore, US guidelines from 2002, recommend the universal screening of all pregnant women between 35 and 37 weeks of gestation to identify women at risk of transmitting group B streptococci to the newborn. These women were to receive intrapartum antibiotics, penicillin (preferred agent), ampicillin, or cefazolin given for >4 h before delivery. Dramatic reduction in early onset neonatal sepsis due to group B streptococci was achieved after the introduction of this program.

The initial clinical presentation of sepsis in children may be non-specific, especially in younger age groups. Laboratory tests, blood cultures and biomarkers, may be helpful in seeking of diagnosis but the final diagnosis has to be made initially using clinical judgement. Culture-negative sepsis appears in many children, without an identifiable pathogen. The two biomarkers most frequently used for pediatric patients are C reactive protein and serum procalcitonin, which shows the most potential in this area. IL-6 is a biomarker of choice for early diagnosis of sepsis and CD14 has been shown to be efficient in early diagnosing of bacterial and fungal neonatal sepsis as well. Older children may present with a focus of infection, infants and neonates usually present with non-specific symptoms and signs. In older infants and children, sepsis typically presents with features of systemic inflammatory response syndrome (Table 1.) In young infants and term and preterm neonates, the symptoms and signs of sepsis are often vague and non-specific. Sepsis in this age group often manifests initially as

| TABLE 1 |
| PAEDIATRIC SPECIFIC DEFINITIONS OF SYSTEMIC INFAMMATORY RESPONSE SYNDROME (SIRS) |
| SIRS | A response to a stimulus, which result in two or more of the following |
| Sepsis | SIRS with a suspected or confirmed bacterial, viral, or fungal cause |
| Severe sepsis | Sepsis and organ hypoperfusion or dysfunction of ≥2 organ systems |
| Septic shock | Sepsis with fluid refractory hypotension and signs of hypoperfusion. It has following signs of cardiovascular organ dysfunction that remain after initial fluid resuscitation (40ml/kg intravascularly in ≤1 h) |
| | • Decrease in BP (hypotension) <5th percentile for age or systole BP ≥2 SD below normal for age; OR |
| | • Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or epinephrine, or norepinephrine at any dose); OR |
| | • At least two of the following |
| | * Unexplained metabolic acidosis: base deficit >0.5mEq/L |
| | * Increased arterial lactate >2 times upper limit of normal |
| | * Oliguria: urine output <0.5 mL/kg/h |
| | * Prolonged capillary refill: >5 s |
| | * Core to peripheral temperature gap >3°C |
a change in the normal trends of observations for that child. Neonatal sepsis is usually classified in terms of timing of onset in relation to birth to early onset neonatal sepsis, occurring in the first 72 hours of life, and late onset neonatal sepsis, occurring after the first 72 hours of life.

**MANAGEMENT**

Contemporary protocols American College of Critical Care Medicine-Pediatric Advanced Life Support guidelines for the management of septic shock (ACCM-PALS) (2009,) and Surviving Sepsis Campaign (SSC) (2012,) are the main guidelines in recent years in the management of sepsis in children. According to SSC protocol the initial steps which should be taken in the early management of sepsis in children are initial resuscitation, timely antibiotics and source control, early fluid resuscitation and inotropes, vasopressor, vasodilator at "time zero".

**INITIAL RESUSCITATION**

Initial resuscitation implies early oxygen delivery by a face mask, nasopharyngeal continuous positive airway pressure (CPAP) or a high flow nasal cannula for respiratory distress and hypoxemia. In emergency inotropes and fluids can be administered via a peripheral intravenous or intraosseal line. Patients who require mechanical intubation, should be sedated cautiously in order to avoid hypotension.

Ketamine if not contraindicated is a drug of good choice, whereas etomidate is best avoided for its inhibitory effects on cortisol. Short acting barbiturates and propofol are also linked with haemodynamic instability and therefore should be used with reserve.

The main goal is to restore normal CRF =2 s, arterial blood pressure, pulse, mental status, warm body temperature and urine output > 1 mL/kg/hr in the first hour of resuscitation. It is best to target Scvo2 saturation greater than or equal to 70% and cardiac index between 3.3 and 6.0 L/min/m2. In children lactate clearance and lactate levels are not a good indicator in septic shock, because they usually have normal lactate levels in septic shock.

Adherence to ACCM-PALS protocol provided better survival among patients, by simply following the main steps of the protocol in the shortest possible time. Hospitals that followed the protocol had good results, by reducing the ICU (mean5.5 v 6.8 days) and hospital stay (mean 6.8 v 10.9 days), and mortality from 4.8% to 1.7%.

**FLUID MANAGEMENT**

In resource-rich settings, with mechanical ventilation and inotropes available, rapid intravenous (IV) access should be followed by an aggressive initial IV fluid bolus of 20 mL/kg of isotonic crystalloid or 5% albumin infused over 5-10/min. These should be titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses and level of consciousness. If patient is not responsive bolus should be repeated up to 40-60 mL/kg fluid (even 200 mL/kg) until hepatomegaly or rales appear. If hepatomegaly or rales develop, inotropic support should be implemented, not fluid resuscitation.

In resource limited settings, fluid therapy should be used cautiously and may even be contraindicated. A large study, “The fluid expansion as support therapy” (FEAST) trial, on numerous sub-Saharan African children, showed that 48-hour mortality was significantly higher (10.6, 10.5, and 7.3%) after rapid and massive fluid boluses. The patients had predominantly: malaria parasitemia (57%) and severe anemia (hemoglobin <5 g/dL, 32%). In these patients fluid bolus only contributed to the already reduced oxygen capacity of the blood.
ANTIBIOTICS AND SOURCE CONTROL

Empiric antibiotic therapy should be administered within 1 hr of “time 0” in sepsis. Similarly to adults, each hour delay in antibiotic administration has been associated with an approximately 8% increase in mortality. In one pediatric series, delays greater than three hours were associated with significantly increased odds of mortality (OR 4.0 [95% CI 1.3-12.1]) 16. In all patients blood cultures should be obtained whenever antibiotics are given, but this should not delay initiation of antibiotics 16. The epidemic and endemic ecologies (child’s age, history, comorbidities, drug intolerance, Gram stain data, and local resistance patterns) dictate empiric drug of choice. Antibiotics which can be given by rapid intravenous bolus should be the first therapeutic choice, followed by infusions of antibiotics, that must be delivered more slowly. Broad spectrum antibiotic cover is to be switched to narrow spectrum antibiotic after antibiotic therapy review has been carried out on a daily basis. It is best to administer intravenous antibiotics in a 5-7 day course for uncomplicated infections. In disseminated infections, or in immunocompromised patients prolonged courses of antimicrobials may be required 17.

Sepsis is caused by different antimicrobes in children of various age, therefore this should be taken in to account when choosing initial empiric antimicrobial therapy. Children are more prone to toxic shock than adults because of their lack of circulating antibodies to toxins. Children with severe sepsis and erythroderma and suspected toxic shock should be treated with clindamycin to reduce toxin production 16.

In all patients with an identifiable source of infection, early and aggressive source control is required 16.

INOTROPE, VASODILATOR AND VASOPRESSOR THERAPY

There is a potentially decreased myocardial reserve and contractility in the neonatal immature myocardium. Variability in the response to these agents exist across age. We still lack evidence-based data on strategies and efficacy of inotropes and vasopressors in the pediatric population.

Initiation of vasoactive therapy in children with septic shock is required if 40 to 60 mL/kg of fluid bolus was not effective. No central line present is not a contraindication for inotrope therapy, thus inotropes should be administered promptly through a peripheral intravenous or intraosseal line, as soon as there are needed. Cohort studies show that delay in the use of inotropic therapies is associated with major increases in mortality risk. In the initial resuscitation phase, inotrope/vasopressor therapy may be required to sustain perfusion pressure, even when hypovolemia has not yet been resolved. (Table 2.) Children with severe sepsis may move from one hemodynamic state to another. The initial choice of vasoactive agents is guided by physical findings, and hemodynamic state of patient. In cold shock states initial choice would be dopamine infusions at 5 mcg/kg/min to 10 mcg/kg/min. In shock resistant to dopamine, epinephrine infusion should be started at 0.05 to 0.3 mcg/kg/min. In warm shock, treatment should start with norepinephrine starting at 0.03 to 0.05 mcg/kg/minute. If dopamine infusion has already been started then norepinephrine can be added to dopamine 18.

In the case of extremely low systemic vascular resistance despite the use of norepinephrine, the use of vasopressin and terlipressin has been described in a number of case reports, yet evidence to support this in pediatric sepsis, as well as safety data, are still lacking. There is insufficient evidence to recommend or refute the use of vasopressin or its analogues in the treatment of refractory hypotension in neonates 19 and no clinical benefit of vasopressin for pediatric vasodilatory shock 20,21.

Patients with low cardiac output states and elevated systemic vascular resistance with normal blood pressure should be given vasodilator therapies in addition to inotropes. The choice of vasoactive agent is initially determined by the clinical examination; however, for the child with invasive monitoring in place and demonstration of a persistent low cardiac output state with high systemic vascular resistance and normal blood pressure despite fluid resuscitation and inotropic support, vasodilator therapy can reverse shock. Type III phosphodiesterase inhibitors (amrinone, milrinone, enoximone) and the calcium sensitizer levosimendan can be helpful because they overcome receptor desensitization 19.

Sepsis is a leading cause of mortality and critical illness worldwide, and the global prevalence of severe sepsis in pediatric intensive care units is 8.2% 21. It is important to say that patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities with significant health care and social implications 22, and therefore it is of vital importance to recognize and treat sepsis at early stages in the first hours from presentation.

SAŽETAK

Teška sepsa je vodeći uzrok mortaliteta kod dece mlađe od 5 godina. Cetiri glavna uzroka sepsa kod dece su pneumonija, malarija, male boganje i diareja. Prevencija sepsa je izuzetno važna i imunizacija dece i redovna higijena rujnu su se pokazali veoma efikasnim u sprečavanju oboljenja koja mogu dovesti do sepsa. Klinički simptomi svih stadijuma sepsa kod dece su često nespecifični, ali je rana dijagnoza ekstremno značajna. Iničijalno lečenje sepsa kod dece treba da bude prilagođeno razvojnom stadijumu, uzrastu, kapacitetu imunog sistema i verovatnom uzročniku infekcije. Studije kod dece su pokazale da je rana primena antibiotičke terapije efikasna. Rana faza lečenja sepičkog šoka treba da se sastoji od brzih bolusa kristaloida i rastvora 5% albumina, kao I primene vazoaktivnih lekova do postizanja hemodinamičke stabilnosti.

Ključne reči: sepsa, dece, sepični šok, rano zbrinjavanje
REFERENCES:


