ACTA MEDICA LITUANICA. 2012. Vol. 19. No. 3. P. 136–145

Pediatric sepsis and septic shock: definitions and treatment algorithms

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Sepsis remains one of the leading causes of morbidity and mortality in children despite improved understanding of the pathophysiology leading to better clinical management and survival. Recent studies have identified several areas that must be addressed by the clinician in order to continue to impact the morbidity and mortality associated with sepsis. In this review, we discuss the evidence in several of these areas including recognition of shock, initial resuscitation and fluid therapy, use of inotropes and vasopressors, identification and control of the source of infection, maintenance of oxygen delivery and ventilation. The overall goal is to provide the bedside clinician with an updated systematic approach to treat sepsis in children.

Key words: pediatric sepsis, septicemia, septic shock, SIRS

INTRODUCTION

Sepsis is a major cause of morbidity and mortality in children, with an estimated 42 000 cases per year in the United States, and an associated case fatality rate of 10% (1). In the United Kingdom, infection accounts for more than 10% of deaths in children, 4 years of age and approximately 1 000 children with severe sepsis are admitted to pediatric intensive care units (PICUs) annually (2). Up to 20% of children admitted to PICUs with severe sepsis die. In the Italian multicenter study (15 PICUs with 2 741 patients enrolled), authors report severe sepsis and septic shock mortality rate of 17.7% without underlying disease and 50.8% in children with existing comorbidities (3). The reported mortality from severe sepsis / septic shock in 9 Japanese PICUs was ~19% (4). In a trial conducted in Latvia, Gardovska and colleagues reported 24.4% case fatality rate (5). The aim of this article was to systematically review the evidence from studies evaluating the management of sepsis and septic shock in children. Data sources: electronic databases, including PubMed, EMBASE and references from identified articles between January 1992 and June 2012 were used for a literature search relating to pediatric sepsis and septic shock.

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DEFINITIONS AND PEDIATRIC AGE NORMS

Epidemiological studies of the incidence and outcome of sepsis and clinical trials of treatment options in this syndrome require standardized definitions of the syndrome and patient classification that are universally accepted. Part of this challenge historically has been the lack of an adequate, standardized definition of sepsis, prompting

an international panel of experts from the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) to propose the now familiar consensus definitions for the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in 1992 (6). Severe sepsis is defined as sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic). These definitions have been modified for use in critically ill children with sepsis by the International Pediatric Sepsis Consensus Conference (IPSCC) (7). The American College of Critical Care Medicine (ACCM) Clinical Practice Parameters for Hemodynamic Support in Pediatric and Neonatal Patients in septic shock further defines shock according to response to therapy as fluid refractory / dopamine resistant, catecholamine resistant, and refractory shock (7). Multiple organ failure is defined as failure of more than one organ. The greater the number of concomitant organ failures, the greater the risk of mortality. Multiple organ failure is generally observed in septic shock patients who receive delayed resuscitation or inadequate source-control therapies. Multiple organ failure is also observed in septic shock patients who have an underlying primary or acquired immunodeficiency that prevents timely eradication of infection. Systemic inflammatory response syndrome (SIRS) was introduced as the first step of the activation of inflammatory cascade caused by infections or different pathogenic mechanisms (i. e. burns, pancreatitis, and trauma). The systemic inflammatory response syndrome (SIRS) is defined by the presence of at least two of the following four criteria: 1) core temperature >38.5 °C or <36 °C; 2) tachycardia in the absence of pain, fever, drug therapy or bradycardia; 3) tachypnea or need for mechanical ventilatory support; 4) increased or decreased peripheral white blood cell (WBC) count. These definitions gained a wide popularity and became a standard classification for studies conducted in adult patients. Differences in definitions and classifications for sepsis, severe sepsis, septic shock and organ dysfunction that had been used in pediatric studies have made it difficult to compare incidence and outcomes in children (3). In 2005 pediatric age norms of vital signs and laboratory variables of various age groups were published (8). Later, in 2007, previous guidelines were updated and published in 2009 (9). The 2002 guidelines were based on consensus of experts; however, the 2009 guidelines incorporated the findings of numerous studies that challenged the original assumptions. The guidelines place a heavy emphasis on the early recognition and aggressive goal-directed treatment (within the first hour) of sepsis and septic shock. Early and aggressive treatment of shock at any stage may halt the progression to later stages and may negate the need for complex, expensive therapies that are not available for many children in many parts of the world.

CHANGES IN THE REVISED GUIDELINES

There are two major changes between the 2002 guidelines (8) and the updated 2007 guidelines (9). First, it is now recommended that inotropes should be administered through a peripheral or intraosseous line before central access is available. This conclusion is based on the observation that few practitioners in the emergency setting were able to establish central venous access before 2 hours. A delay in administration of inotropes was associated with a 20-fold increased mortality risk. Second, it is now recommended that high-flow heated and humidified oxygen be provided by a face mask or nasal cannula to increase oxygen content of the blood until more definitive therapy is available. Third, although implied in 2002, it is now unequivocally recommended that antibiotics be administered within the first hour.

RECOGNITION OF SEPTIC SHOCK

The inflammatory triad of fever, tachycardia, and vasodilation is common in children with benign infections in the emergency department. Septic shock is suspected when children with this triad have a change in mental status manifested as irritability, inappropriate crying, drowsiness, confusion, poor interaction with parents, and lethargy or are becoming unarousable. The clinical diagnosis of septic shock is made in children who (1) have a suspected infection manifested by hypothermia or hyperthermia and (2) have clinical signs of inadequate tissue perfusion including any of the following: decreased or altered mental status, prolonged capillary refill of more than 2 seconds (cold shock),

diminished pulses (cold shock), mottled cool extremities (cold shock), or flash capillary refill (warm shock), bounding peripheral pulses and wide pulse pressure (warm shock), or decreased urine output of less than 1 ml/kg per hour. Hypotension is not necessary for the clinical diagnosis of septic shock; however, its presence in a child with clinical signs suggestive of an infection is confirmatory. Shock can be recognized as a progression of hemodynamic abnormalities beginning with tachycardia, which is then followed by hypotension in the case of warm shock, or prolonged capillary refill in the case of cold compensated shock. Children have limited cardiac reserve compared to adults. The adult resting heart rate is 70 beats/min, therefore twofold increase in heart rate from 70 to 140 beats/min can be easily tolerated and used to maintain cardiac output when stroke volume is decreased. Similar mechanisms are not possible in babies and infants. A resting heart rate of 140 beats/min in a baby cannot be doubled to 280 beats/min because diastolic filling time is too short. Because of this limited cardiac reserve, as cardiocirculatory compromise progresses, infants and children vasoconstrict their peripheral tissue microvascular beds in an attempt to maintain cardiac preload and perfusion pressure in the central organs, including the brain, heart, and kidney. This stage of "compensated shock" can be clinically recognized as prolongation in capillary refill time to 2 seconds. If circulatory insufficiency progresses beyond this point, hypotension occurs with ensuing circulatory collapse and failure and eventual cardiac arrest. Patients with hypotension and prolonged capillary refill are considered to have decompensated shock. Mortality risks increase as the patient progresses through this time-sensitive pathology. McCloskey and colleagues (10) examined 5 tertiary care hospitals with 4 856 patients enrolled and they found that although only 7% of the children were referred for shock, 40% had shock defined by the presence of prolonged capillary refill of more than 3 seconds and / or hypotension. Use of the Pediatric Advanced Life Support (PALS) / Advanced Pediatric Life Support (APLS) recommended resuscitation in the emergency room resulted in a 2-fold reduction in mortality and functional morbidity in these children. These multicenter findings were very similar to the single-center report of Han and colleagues (11), who found that every hour's delay in PALS/APLS resuscitation in the emergency room was associated with a 40% increase in mortality in children with septic shock. In a similar study from UK where 17 PICU were audited with 200 pediatric septic shock patients, the targets set by the 2002 ACCM-PALS guideline for fluid administration and inotropic support were not achieved in the majority of critically ill children. Overall fluid and inotrope management suggested by the 2002 ACCM-PALS guideline was not followed in 62% of shocked children. Failure to reverse shock by the time of PICU admission was independently associated with mortality (12).

IDENTIFICATION AND CONTROL OF THE SOURCE OF INFECTION

In patients with severe sepsis / septic shock, source control is an integral component of therapy. That encompasses all the physical measures that can be used to control a focus of infection and modify factors that promote microbial growth or impair host antimicrobial defenses. Every child who presents with sepsis should be evaluated for a source of infection amenable to source control. The methods of source control predominantly include the drainage of infected fluid collections, debridement of infected tissue, and removal of devices or foreign bodies. Examples of source control that must be initiated in the pediatric emergency department include the prompt removal of a tampon in a patient suspected of having toxic shock syndrome and early identification of necrotizing soft tissue infections so as to obtain a prompt surgical debridement. Such measures include abscess drainage, debridement, and removal of devitalized infected tissue or infected prostheses. Establishing a definitive microbial cause of severe sepsis / septic shock is difficult during initial evaluation. Nonetheless, identification of the organisms and antimicrobial susceptibilities can be important in subsequent management. Kumar et al. (13) in their study found that administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%. Broad initial antibiotics coverage is recommended that is tailored to the potential source of infection and according to local hospital sensitivity and resistance patterns.

AIRWAY MANAGEMENT AND VENTILATION

On admission, the staff should ensure a patent airway and appropriate protective airway reflexes are present, especially if there is any alteration in the mental status. They should make a rapid assessment of the work of breathing, air exchange, and measure oxygen saturation non-invasively when pulse oximetry is available. When any degree of distress or abnormal respiratory function is noted, the patient should be placed on 100% high-flow humidified oxygen to ensure maximal oxygen saturation. In the presence of metabolic acidosis related to septic shock, the work of breathing associated with the compensatory respiratory alkalosis can be substantial and contribute, along with fever, to a significant portion of oxygen consumption. In addition, myocardial dysfunction, which is often present in children with sepsis, can be partially ameliorated by the application of positive pressure ventilation by achieving a decrease in afterload (provided impairment of preload is not too great). Therefore, early preventive intubation and positive pressure mechanical ventilatory support should be strongly considered in this setting. This approach is supported in part by the clinical practice position article from a group that reported low mortality (~5%) in meningococcal septic shock by intubating and mechanically ventilating all children who required >40 ml/kg volume resuscitation (14). Often, the combination of increased lung vascular permeability with aggressive fluid resuscitation that is necessary to restore intravascular volume and maintain organ perfusion pressure (defined as the difference between the mean arterial pressure minus the mean central venous pressure) contributes to the development of pulmonary edema. In children, the related changes in lung compliance and loss of functional residual capacity tremendously increase the work of breathing ultimately leading to respiratory failure that necessitates endotracheal intubation and mechanical ventilatory support. The presence of substantially increased work of breathing or, alternatively, ominous signs of hypoventilation, impaired mental status, or obtundation are all indications for instituting mechanical ventilatory support which holds additional benefit in decreasing the overall oxygen consumption, especially when combined with analgesia and / or sedation. Because of the often dramatic effect the initiation of positive pressure ventilation can have on the hypovolemic patient in decreasing preload and thus, cardiac output, it is strongly suggested that intravascular volume depletion be corrected prior to instituting positive pressure ventilation and that additional volume expansion be readily available in this setting.

FLUID THERAPY AND CARDIOVASCULAR SUPPORT

Initial resuscitation and fluid management

The management of shock initially entails obtaining rapid peripheral intravenous or intraosseous access. If the liver is not enlarged and the patient does not have rales on lung examination, then isotonic fluid boluses should be pushed initially in boluses of 20 ml/kg with reassessment of the liver size and breath sounds in the lungs. If the liver is enlarged and / or rales are heard, then further fluid resuscitation is deferred, and the patient is administered a peripheral inotrope. Antibiotics should be pushed intravenously as soon as possible, not later than recommended 60 minutes after the admission. Blood sampling should be obtained for rapid evaluation of blood glucose and ionized calcium as well as blood culture. In the case of newborns, a prostaglandin infusion should be begun until ductal-dependent congenital heart disease is ruled out. The fluid boluses and inotrope infusions should be titrated to the goals of threshold heart rates and blood pressure for age and a capillary refill of 2 seconds or less. Close adherence to these guidelines will result in resolution of shock in about 90% of cases. Patients who fail to respond will require more aggressive therapy, including assisted ventilation and manipulation of inotropes and / or vasopressors. If the child remains in shock despite these interventions, then clinicians skilled in intubation and central line placement from the emergency room, critical-care unit, or other settings can intravenously administer atropine plus ketamine for intubation (if in respiratory distress) and / or central line placement. Central norepinephrine can be used to treat hypotension and adrenaline to treat cold shock. Recently, a trial of early hemodynamic resuscitation to normal physiologic parameters, or early goal-directed therapy, was conducted in adult patients with severe sepsis / septic shock and revealed a significant mortality reduction (15). Early

goal-directed therapy is an algorithmic approach to hemodynamic optimization and resolution of global tissue hypoxia within the first 6 hours of disease presentation. The strategy targets normal oxygen delivery by optimizing preload, afterload, oxygen content, and contractility to achieve a balance between tissue oxygen delivery and consumption. Placement of central access at the superior vena cava / right atrium or right atrium / inferior vena cava junction allows for further goal-directed therapy toward maintaining a central venous oxygen saturation ($ScvO_2$) of greater than 70% (using blood transfusion if the hemoglobin <10 g/dl, inotropes, and vasodilators). In settings where cardiac output can be measured, a goal cardiac index of greater than 3.3 l/min per m^2 and less than 6.0 L/min/m^2 should be attained. De Oliveira and his group in Brazil (16) conducted a similar randomized controlled trial in a pediatric population. In this cohort of 102 children with severe sepsis, similar early goal-directed therapy was implemented to achieve and maintain superior vena caval oxygen (SVC O_2) saturation >70%. In the study 28-day mortality was significantly lower in the intervention group (11.8% vs. 39.2%) with significantly fewer new organ dysfunctions. Interestingly, SVC O_2 saturation on admission carried a prognostic value, as the mortality rate was significantly higher in patients who presented with SVC O_2 saturation <70% (41.9% vs. 24.3%; OR = 3.04 (1.43–8.79); p = 0.006). Though only a single center study and mortality rates trended higher in both groups as compared to rates reported from other recent pediatric sepsis studies, these results support the concept that a strategy of achieving early restoration of adequate organ perfusion pressure, espoused by early goal directed therapy, may improve outcome in children with septic shock. These guidelines have great relevance to clinical practice and organization in the emergency care setting. Those involved in triage will need to assess heart rate, blood pressure, and capillary refill measurements in all patients and promptly move patients to a suitable location for definitive therapy when they meet the criteria. Intravenous and intraosseous lines, fluids, high-flow oxygen mask or nasal cannula, antibiotics, and inotrope infusions will need to be prepared and be readily available. A reference table of goal heart rates, blood pressures, and shock index for age will also need to be readily available to guide goal-directed therapy.

Resuscitation of septic patients by means of one or more fluid boluses is recommended by guidelines from multiple relevant organizations and as a component of surviving sepsis campaigns. The technique is considered a key and life-saving intervention during the initial treatment of severe sepsis in children and adults. Such recommendations, however, are only based on expert opinion and has a weak physiological support and limited experimental evidence. Despite these limitations, fluid bolus therapy (20 to 40 ml/kg) is widely practiced and is currently considered a cornerstone of the management of sepsis. This paradigm is now challenged by the findings published recently where authors demonstrate that a more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in adults with septic shock (17). Murphy and colleagues in adults having acute lung injury demonstrate that an approach that combines both adequate initial fluid resuscitation followed by conservative late-fluid management was associated with improved survival (18). No therapeutic benefit of fluid challenge was found in a large (2 804 adult patients enrolled) multicenter study in Spain (19). A large randomized controlled trial in septic children in Sub-Saharan Africa, led by Maitland, shows that in pediatric patients bolus fluid resuscitation with either albumin or saline, as compared with the control, increased the absolute risk of death at 48 hours by 3.3% and the risk of death, neurologic sequelae, or both at 4 weeks by nearly 4% (20). Arikan with colleagues in their study demonstrated that increasing fluid overload during the PICU stay was associated with worsening oxygenation, longer duration of ventilation, and hospital length of stay (21). These findings support an opinion that the concept of large fluid bolus resuscitation in sepsis needs to be investigated further. Fluid resuscitation may be lifesaving in patients with severe sepsis, especially in the earliest phases of treatment. Following initial resuscitation, however, fluid boluses often fail to augment perfusion and may be harmful**.** Massive amount of fluids, mostly saline, rapidly clears intravascular space and accumulates in tissue, leading to interstitial edema and fluid overload. In the presence of sepsis there is a pertinent risk for the development of acute kidney injury (AKI) that rapidly turns situation to critical. In this context, 2007 guidelines recommend fluid removal using

diuretics and renal replacement therapies in patients who have been adequately fluid resuscitated but cannot maintain their native urine output. When a patient has indications for a fluid bolus, the potential for harm should be considered and, if there is reasonable potential for harm, a careful assessment of clinical signs (liver enlargement, "wet" lung) and fluid balance or advanced hemodynamic monitoring in the resource rich environment using bedside ultrasonography, $SvcO_2$, femoral artery thermodilution (FATD) provide real time quantitative measurements of vascular resistance and cardiac index, systolic volume variations (SVV), GEDW and extravascular lung water which would provide more objective data to optimize therapy. These variables should be used to limit fluid infusion only to patients who will benefit. Obviously, there is room for much further study to identify whether this or some other fluid restrictive approach confers improved outcomes in resuscitated septic patients. These aspects probably will be the object of discussions when current guidelines will be updated.

Inotropes and vasopressors

When fluid therapy does not reach established goals, inotropes and/or vasopressors should be added. The decision of which agent to add in the setting of fluid refractory, dopamine-resistant shock is based on the underlying cause of cardiovascular compromise and the presenting hemodynamic profile. In the pediatric population it is more common to have low cardiac output with increased systemic vascular resistance as compared to adults who most often present with high cardiac output and low systemic vascular resistance (22). Dopamine remains the most common first choice of inotropic agents for patients with fluid-refractory shock. Dopamine possesses dose-dependent agonist effects on dopaminergic and adrenergic (α and β) receptors. Thus, dopamine provides inotropic support via β-adrenergic stimulation in the general dosing range of 5–10 μg/kg/min and vasopressor activity via α-adrenergic stimulation in the higher dosing range (~10–20 μg/kg/min). More recently, dopamine has lost some favor as the first line inotropic agent because of a number of reported and theoretic adverse effects. Dopamine functionally suppresses neutrophils by attenuating the chemo attractant effect of interleukin-8 (23). It also interferes with the neuroendocrine system by suppressing the release of many anterior pituitary hormones, including growth hormone, TSH and prolactin. Because prolactin typically enhances monocytes, B-cell and T-cell responses and may prevent their programmed cell death (apoptosis), the use of dopamine may aggravate immune dysfunction and increase susceptibility to infection. Therefore, clinicians are increasingly choosing low-dose epinephrine to achieve β-adrenergic-mediated inotropic support as the first line therapy for fluid refractory shock. When the hemodynamic resuscitation end-points are not achieved with adequate fluid and dopamine/low-dose epinephrine administration, further management of this so called state of "fluid-refractory, dopamine-resistant shock" is dictated by the clinical context. The decision of which agent to add in the setting of fluid refractory, dopamine-resistant shock is based on the underlying cause of cardiovascular compromise and the presenting hemodynamic profile. In the pediatric population it is more common to have low cardiac output with increased systemic vascular resistance as compared to adults who most often present with high cardiac output and low systemic vascular resistance (22). As a result, low-dose epinephrine is chosen as the second line inotropic agent most often. Epinephrine provides inotropic support via β_1 receptor stimulation and modest vasodilatation via β_2 receptor stimulation when administered at low concentrations (0.02–0.3 μg/kg/min). Brierley and Peters in their study shows that septic shock secondary to central venous catheter (CVC) associated infection was typically "warm shock" (15 of 16 patients, 94%), with high cardiac index and low systemic vascular resistance index (24). In contrast, this pattern was rarely seen in community-acquired (CA) sepsis in 2 of 14 patients, 14%, where a normal or low cardiac index was predominant. The consequence of their findings is that a vasoconstrictor, such as norepinephrine, is a realistic first-line agent if rapid, noninvasive, hemodynamic assessment is available and the classic low SVRI / high cardiac index pattern is demonstrated for a child with an indwelling CVC in the setting of fluid-resistant septic shock. Brierley and Peters findings demonstrate that the manifestation of septic shock in children is cause dependant, with CVC infection leading to the "adult-type" pattern with high CO and low

systemic vascular resistance, in comparison with CA infections. As a result, low-dose epinephrine is chosen as the second line inotropic agent most often. Epinephrine provides inotropic support via β_1 receptor stimulation and modest vasodilatation via β_2 receptor stimulation when administered at low concentrations (0.02–0.3 μg/kg/min). Though epinephrine possesses these beneficial cardiovascular effects, it also possesses some adverse properties. Epinephrine stimulates gluconeogenesis and glycogenolysis and inhibits the action of insulin, leading to an adverse profile of dysregulated serum glucose which may impact outcomes. In the setting of low systemic vascular resistance (SVR), higher concentrations of epinephrine (>0.3 μg/kg/min) are used to provide vasopressor effect via α_1 stimulation. Furthermore, given the observation that the SVR is often high (clinically presenting as "cold" shock), vasodilator therapy should be considered in the adequately volume resuscitated, relatively normotensive patient who remains mottled with evidence of end-organ malperfusion (e. g. elevated lactate, decreased urine output, delayed capillary refill). In less common hemodynamic state in pediatric severe sepsis of high cardiac output and low SVR, a vasopressor such as norepinephrine, which provides vasoconstriction via α_1 receptor stimulation, is the most commonly used. Norepinephrine also provides some minimal inotropic support via its less predominant β_1 receptor stimulation. When simultaneous lusitropic action is required, milrinone should be administered. Milrinone is a type III phosphodiesterase (PDE) inhibitor that may have a synergistic effect with β adrenergic agonists since the latter agents stimulate intracellular production of cAMP while the PDE inhibitors further increase intracellular cAMP by blocking its degradation. Since the PDE inhibitors do not depend on a receptor mechanism, they maintain their action even when the β adrenergic receptors are down regulated or have reduced functional responsiveness as may be the case in sepsis. A caveat to its use is that it possesses a long elimination half-life, which is more pronounced in patients with renal dysfunction, so that milrinone should be discontinued at the first sign of hypotension or excessively diminished systemic vascular resistance. Because of this, some clinicians prefer to employ a much shorter-acting, more easily titratable vasodilator (e. g. nitroprusside) to decipher the clinical response to afterload-reduction, which can be immediately discontinued in the event of unacceptable hypotension.

MAINTENANCE OF OXYGEN DELIVERY

The cornerstone of conventional therapy in sepsis remains the maintenance of adequate oxygen delivery in the face of myocardial depression, capillary leak, acidosis, and massive cytokine release. Adequate oxygen delivery (DO_2) to maintain tissue oxygenation requires sufficient tissue perfusion and oxygen content as determined by the following equation:

$$DO_2\ (mL/min) = CO \times CaO_2 = [HR \times SV] \times$$
$$\times [(1.34 \times Hb \times SaO_2) + (0.0031 \times Pa\ O_2)],$$

where DO_2 is oxygen delivery, CaO_2 is arterial oxygen content, CO is cardiac output, SV is stroke volume, HR is heart rate, and PaO_2 is arterial partial oxygen tension. A number of studies of adults in selected patient subpopulations have suggested improved outcomes when achieving supra-normal levels of oxygen delivery (25, 26). Whether this improves outcomes in children has not been conclusively shown. Ultimately, we may discover this approach to be ineffective as suggested by the observation that septic patients often have a diminished ability to extract oxygen such that increasing oxygen delivery will not improve oxygen extraction at the cellular level. For these reasons the best assessment of adequate oxygen delivery and uptake includes a combination of measures of adequate perfusion (such as lactate level and urine output) in addition to blood pressure and SVC oxygen saturation. An adequate hemoglobin level is an important factor in providing sufficient oxygen delivery. While there is no recommended target hemoglobin level for children, a hemoglobin concentration of 10 g/dl has been espoused for adults with cardiopulmonary compromise based on improved outcomes when this goal was achieved as part of EGDT (4). On the other hand, 637 stable, pediatric intensive care patients who had Hb < 9.5 g/dl were randomly assigned to a hemoglobin (Hb) threshold of 7 g/dl for red cell transfusion ("restrictive" group) or to a threshold of 9.5 g/dl ("liberal" strategy). In the restrictive group, there was 96% reduction in the number of patients who had any transfusion exposure and a 44% decrease in the number of red cell

transfusions administered (27). This was accomplished without any increase in the rates of new or progressive multiple organ dysfunction syndrome (MODS) or nosocomial infections and other important clinical parameters (23). This study only suggests a lower Hb threshold may be acceptable in a well-defined subset of stable pediatric intensive care patients. Broader extrapolation of these results should be tempered as the study subjects were characterized as less severely ill and did not include unstable patients with septic shock. Thus, it is generally recommended that blood transfusion be considered to aid in achieving a goal of increased CaO_2 in the setting of a low Hb concentration with targeting of the SVC O_2 saturation to be >70%.

CORTICOSTEROIDS

The physiologic response to sepsis is an increased level of stress hormones such as cortisol. Children with normal adrenal function are defined by an incremental increase in the cortisol level 9 μg/dl. They may benefit from hydrocortisone treatment if they do not have a functioning pituitary axis. Lack of endogenous production of ACTH will prevent production of cortisol and aldosterone, but not a normal incremental cortisol response to exogenously administered ACTH. This population of children is growing as the use of acute and chronic steroid treatment is becoming a common practice for patients with cancer, transplantation, asthma, croup, allergies and autoimmune disease. Although findings from small, single-center studies of septic shock suggested that prolonged administration of low doses of hydrocortisone could decrease requirements for vasopressors and improve survival, this therapeutic approach has only recently been validated in an adequately powered, multicenter, placebo-controlled study in France. Annane et al. studied patients as defined by more than 1 hour of fluid-unresponsive hypotension and a greater than 5 μg/kg/min requirement for dopamine or other vasopressors, such as norepinephrine or epinephrine. Administration of corticosteroids resulted in a 28-day mortality rate of 63% in the placebo group compared with 53% in the treatment group among patients who did not respond appropriately to adrenocorticotropic hormone (relative reduction in mortality rate of 16%) (28). In contrast, there was no improvement in survival when patients with an appropriate cortisol response to adrenocorticotropic hormone were treated with steroids. The time for receiving vasopressors was also significantly shortened when low-dose corticosteroids were administered to septic shock patients with inadequate adrenal reserve. Corticosteroid administration was not associated with increases in infectious complications, gastrointestinal bleeding, or mental status changes. The utility of routine corticosteroid supplementation for sepsis remains limited by the inability to reliably determine adrenal insufficiency within the time of emergency management. A large, multicenter trial of corticosteroid therapy in septic shock called CORTICUS (29) shows no survival benefit from corticosteroids in septic shock. Before corticosteroid treatment is started, an adrenocorticotropic hormone stimulation test or baseline cortisol level should be performed and corticosteroids continued only in patients who demonstrate inadequate adrenal response, as defined by an increase in serum cortisol less than 9 μg/dl (Grade C). Specific recommendations for children with septic shock suggested that hydrocortisone therapy should be reserved for use in children with catecholamine resistant shock and suspected or proven adrenal insufficiency (Grade 2C), but that children who have clear risk factors for adrenal insufficiency should be treated with stress-dose hydrocortisone. Aneja and Carcillo recommended titration of hydrocortisone dose to effect (30). The initial bolus of hydrocortisone can be between 2 and 50 mg/kg, followed by an infusion of 2–50 mg/kg/24 h. Overall, the recommendation for use of adjunctive corticosteroids for severe sepsis is currently graded as 2C, that is, a weak recommendation based on unclear trade off between desirable and undesirable corticosteroid effects and current low quality of evidence (31). These results are in conflict with those reported by Annane and coworkers (28) but agree with the findings of the recently published Corticus randomized controlled trial (29). Ferrer's study also does not support the use of steroids in septic shock (19). At present, a common approach in managing pediatric sepsis is to consider the use of exogenous steroids in patients with severe sepsis who are "fluid refractory" and on two or more vasoactive agents. This approach generally complies with the expert recommendations from the International Task Force of the American College of Critical Care Medicine (ACCCM).

CONCLUSIONS

In the management of sepsis, prompt recognition of the early signs and symptoms of sepsis and shock is of paramount importance. Diagnosis of the source of infection should be attempted and appropriate antibiotics administered without delay within 1 hour of presentation. Immediate measures to support circulation and counteract hypoxemia should be instituted. Volume resuscitation should be started immediately, and vasopressor support instituted if signs of shock persist despite adequate volume resuscitation. If signs of shock persist, transfusions of blood should be provided to maintain the hemoglobin of 8–10 g/dl. Frequent assessments, both clinical and laboratory, need to be performed to ensure that the interventions are effective and appropriate. Vasopressor and/or inotropic therapy should be provided based on the clinical presentation and ongoing physiologic derangements. Scv O_2 can help guide therapy. Although aggressive early fluid resuscitation followed by vasoactive agents (in those with persistent hypotension) remains the cornerstone of the management of patients with severe sepsis and septic shock, the endpoints of resuscitation should be based on validated physiologic variables that are individualized based on each patients comorbidities and unique clinical circumstances.

Received 2 July 2012
Accepted 1 August 2012

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SEPSIS IR SEPSINIS ŠOKAS PEDIATRIJOJE: APIBRĖŽIMAI IR GYDYMO ALGORITMAI

Santrauka

Nepaisant pagerėjusio patofiziologijos suvokimo, lėmusio geresnę klinikinę priežiūrą ir išgyvenamumą, sepsis išlieka viena pagrindinių vaikų sergamumo ir mirtingumo priežasčių. Naujose studijose išskirtos kelios sritys, į kurias klinicistui reikėtų atkreipti dėmesį siekiant paveikti su sepsiu siejamą sergamumą ir mirtingumą. Šioje apžvalgoje aptariama pradinio gaivinimo ir skysčių terapijos, inotropų ir vazopresorių, infekcijos šaltinio identifikacijos ir kontrolės, deguonies tiekimo ir ventiliacijos svarba. Pagrindinis tikslas – pateikti gydančiam klinicistui naujesnį sisteminį požiūrį į vaikų sepsio gydymą.

Raktažodžiai: sepsis, pradinis gaivinimas, skysčių terapija, inotropų ir vazopresorių naudojimas, deguonies tiekimas, ventiliacija