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REVIEW

Paediatrics: how to manage septic shock

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Abstract

Background: Septic shock is a common critical illness associated with high morbidity and mortality in children. This article provides an updated narrative review on the management of septic shock in paediatric practice.

Methods: A PubMed search was performed using the following Medical Subject Headings: "sepsis", "septic shock" and "systemic inflammatory response syndrome". The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies and reviews. The search was limited to the English literature and specific to children.

Results: Septic shock is associated with high mortality and morbidity. The outcome can be improved if the diagnosis is made promptly and treatment initiated without delay. Early treatment with antimicrobial therapy, fluid therapy and vasoactive medications, and rapid recognition of the source of sepsis and control are the key recommendations from paediatric sepsis management guidelines.

Conclusion: Most of the current paediatric sepsis guideline recommendations are based on the adult population; therefore, the research gaps in paediatric sepsis management should be addressed.

Keywords: antibiotics, critical care, inotropes, intensive care, lactate, organ dysfunction, paediatrics, sepsis, septic shock, systemic inflammatory response syndrome.

Citation

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Introduction

Sepsis, sepsis syndromes, septic shock and multiorgan system failure are important and common conditions encountered in the paediatric intensive care unit (PICU) setting.[1,2] The severity in host response to infection is a continuum from sepsis to septic shock and multiorgan system failure. Septic shock is a subset of sepsis in which cellular, metabolic and circulatory abnormalities can result in organ dysfunction and increase mortality substantially.[1,3–12] Children, immunocompromised individuals and old-aged individuals are more commonly affected as their immunity is weaker than that in healthy adults. Severe sepsis in the paediatric age group has similar prevalence, morbidity and mortality rates to those reported in critically ill adults.[1] This article provides an updated narrative review on the diagnosis and management of septic shock in children.

Methods

An extensive PubMed search of all human studies in English was conducted in December 2020 using the following Medical Subject Headings: "sepsis", "septic shock" and "systemic inflammatory response syndrome". The search strategy included meta-analyses, randomized controlled trials, observational studies and reviews published within the past 10 years including a population aged from birth to 18 years, and published in English. A more general review of the subject matter was also performed and this summary is therefore based on but not limited to the aforementioned publications.

Review

Definition

The Surviving Sepsis Campaign was formed in 2001 by the Society of Critical Care Medicine and European Society of Intensive Care Medicine with the aim of developing evidence-based guidelines to manage and resuscitate patients with sepsis.[12] The first paediatrics definitions for sepsis and organ dysfunction were published in 2005 by an international expert

panel that modified the published adult consensus.[11] The latest Surviving Sepsis Campaign international guidelines in paediatrics were published in 2020.[12]

Sepsis is defined as a dysregulated host response to infection, causing life-threatening organ dysfunction, whilst septic shock is sepsis with circulatory, cellular or metabolic dysfunction.[6] Systemic inflammatory response syndrome is a clinical entity of systemic inflammation caused either by infectious or noninfectious aetiologies and conceptualized as the body's systemic response to an insult, where the presence of at least two of four criteria, namely core temperature, heart rate, respiratory rate and leukocyte count, must be present.[11,13] Sepsis-associated organ dysfunction is defined as severe infection leading to cardiovascular and/or noncardiovascular organ dysfunction.[12] The Pediatric Logistic Organ Dysfunction (PELOD) score is one of the validated scoring systems to classify organ dysfunction in paediatric patients.[14]

The American College of Critical Care Medicine defines shock from a clinical, haemodynamic and oxygen utilization perspective.[12,15,16] From the clinical perspective, septic shock should ideally be diagnosed by using clinical signs, including temperature (hypothermia/hyperthermia), alteration of mental status and peripheral perfusion (warm shock *versus* cold shock), before hypotension occurs.[16] Haemodynamic variables include perfusion pressure (mean arterial pressure — central venous pressure) and cardiac output, whilst oxygen utilization can be measured through central venous oxygen saturation ($ScvO_2$).[16]

Dopamine-resistant fluid-refractory shock is defined as persistent shock despite ≥60 mL/kg fluid resuscitation and dopamine administration of up to 10 µg/kg/min. Catecholamine-resistant shock is defined as persistent shock after continuous catecholamine infusion following initial fluid resuscitation. Lastly, refractory shock is persistent shock despite the use of vasopressors, inotropes, vasodilators and maintenance of hormonal (thyroid, hydrocortisone, insulin) and metabolic (glucose, calcium) homeostasis.[17] The European Society of Paediatric and Neonatal Intensive Care defined refractory septic shock as blood lactate levels greater than 8 mmol/L or an increase of 1 mmol/L in lactate levels after 6 hours of resuscitation and high vasoactive dependency or myocardial dysfunction.[18]

As most sepsis definitions are based on adult data, a systemic review to evaluate the specific criteria used to identify children with sepsis is under way by the Pediatric Sepsis Definition Taskforce.[13]

Epidemiology

Sepsis is one of the leading causes of morbidity and mortality in children worldwide, with the mortality rate from septic shock ranging from 25% to 50%.[9,11,12,19,20] It is estimated that sepsis and sepsis-related deaths contributed to 19.7% of all global deaths in 2017.[21] According to a large-scale point prevalence study involving PICU data from 26 countries, the prevalence of sepsis appears to be higher in developing countries but the mortality was not significantly different to that in patients treated in North America, Europe and Australia/New Zealand compared with Asia, Africa and South America.[1,22] The burden of sepsis is also higher among people living in areas with a lower sociodemographic index.[21]

Severe sepsis accounts for 6–8% of PICU admissions.[1] There was an 81% increase in the number of cases of severe paediatric sepsis in the United States from 1995 to 2005, attributed to the increased survival of patients at high risk such as children with complex medical conditions and very low birthweight and premature infants.[22,23] The risk factors for severe sepsis and septic shock include malignancy, immunosuppression, malnutrition, invasive procedures, major surgery, burns, trauma, previous antibiotic treatment, prolonged hospitalization, and an underlying genetic susceptibility.[1,9,12,19,24–27] The most common underlying cause of sepsis in a large-scale global study among all age groups and locations was diarrhoeal disease and the most common underlying cause of sepsis-related death was lower respiratory infection.[21]

Aetiology

Sepsis is frequently seen in patients with comorbid conditions that predispose to infections such as diabetes or any immunocompromising diseases.[7,28] In the majority of patients with sepsis, an infectious focus can usually be identified, except in patients who are immunocompromised with neutropenia. Before antibiotic exposure, gram-positive bacteria were the principal culprits behind sepsis. Gram-negative bacteria then became the key pathogens causing septic shock. In recent years, the rates of severe sepsis and septic shock due to gram-positive organisms have been on the rise due to the more frequent use of invasive procedures and vascular access among the critically ill. Consequently, gram-positive and gram-negative microorganisms are now equally likely to be causative bacteria in patients with septic shock. In one study, the most frequent sites of infection were the respiratory tract (about 40%) followed by the bloodstream (19%).[1]

Pathophysiology

The pathophysiology of septic shock involves complex interactions between the host immune system and the pathogen.[29–34] Pattern recognition receptors, including nucleotide oligomerization domain, leucine-rich repeat proteins, toll-like receptors and cytoplasmic caspase activation and recruiting domain helicases, are involved in the initiation of the sepsis response. These receptors modulate the adaptive immune response and trigger the innate immune response to infection.[29,30] Bacterial pathogens and various bacterial cell wall components induce a variety of pro-inflammatory mediators that in turn initiate sepsis and shock. The complement system is also activated, which enhances the tissue damage. Excessive nitric oxide (NO)

production, following the cytokine-dependent induction of the inducible NO synthase, is the modulator that mediates the action of most vasodilators and precipitates haemodynamic alterations of septic shock.[35] The overproduction of NO during sepsis is the most important cause of the vasopressor-resistant hypotension that characterizes septic shock. Poor cellular oxygen utilization and tissue organ dysfunction due to mitochondrial dysfunction result during sepsis.[36] Organ dysfunction and death due to disseminated intravascular coagulopathy and microvascular thrombosis may also result.[37–39]

The vascular maldistribution and endothelial dysfunction characteristics of distributive shock as well as myocardial dysfunction result in inadequate delivery of oxygen to vital tissues. These pathophysiological changes can be refractory to endogenous-released vasoactive hormones (such as epinephrine and norepinephrine) during shock.[20,30,36,38–40]

Clinical manifestations

The clinical manifestations of septic shock include hypotension, reliance on vasoactive agents to maintain normotension and signs of inadequate tissue perfusion. Evidence of inadequate tissue perfusion includes prolonged capillary refill, oliguria, metabolic acidosis and elevated serum lactate (>4 mmol/L). Dysregulated host responses to infection occupy a continuum from sepsis to severe sepsis to septic shock and multiple organ dysfunction syndrome.[3,4,5,10,19,41] In children, hypotension induced by sepsis often persists despite intravenous fluid administration.[1,11,24] The patient goes into a state of acute circulatory failure with tissue hypoperfusion (manifested by a lactate concentration >4 mmol/L) and persistent arterial hypotension despite adequate fluid resuscitation.[3–5]

In severe sepsis and septic shock, changes occur at the cellular and microvascular levels with diffuse activation of coagulation and inflammatory cascades, capillary endothelial leakage, and dysfunctional utilization of nutrients and oxygen. It is important to recognize that this process is under way when its effects may not be immediately obvious on clinical examination or from the patient's vital signs.[5,42] Apart from hypotension, common clinical manifestations include tachypnoea, tachycardia, abnormal pulse (diminished, weak, bounding pulse), abnormal capillary refill time (central refill ≥3 seconds or flash refill <1 second), altered body temperature (fever higher than 38.0°C or hypothermia lower than 36.0°C) and an abnormal mental status (e.g. apprehension, anxiety, agitation, obtundation, coma). Pallor or mottled skin are signs signifying poor tissue perfusion in septic shock. There is no unified criteria to support specific haemodynamic targets for children, yet the latest Surviving Sepsis Campaign guidelines suggest targeting a mean arterial pressure between the 5th and 50th percentile for age and to use advanced haemodynamic monitoring, including cardiac output/cardiac index, systemic vascular resistance, stroke index and $ScvO_2$, if available.[12]

It is generally considered that there are four clinical stages of sepsis. In stage 1, the patient has increased volume requirements, mild respiratory alkalosis, oliguria, elevated blood glucose and increased insulin requirements. In stage 2, the patient is tachypnoeic, hypocapnic, and hypoxemic and develops liver dysfunction and haematologic abnormalities. In stage 3, the patient develops shock with azotaemia, acid–base disturbances and coagulation abnormalities. In stage 4, the patient is oliguric or anuric, vasopressor dependent, and may develop lactic acidosis and ischaemic colitis.[43]

In children with refractory shock, potentially reversible causes, including unrecognized morbidities, unrecognized source of infection, pericardial effusion, pneumothorax, hypoadrenalism, hypothyroidism, ongoing blood loss, excessive immunosuppression or immunocompromise, must be considered and addressed.[16]

Diagnosis

Septic shock is diagnosed in a child with sepsis if there is evidence of inadequate tissue perfusion, hypotension persists after initial fluid resuscitation, and the patient has to rely on vasoactive agent administration to maintain normotensive state. Evidence of inadequate tissue perfusion can be in the form of oliguria, prolonged capillary refill, elevated serum lactate level and metabolic acidosis.

It is very important to identify any potential source of infection. Common infections in children with sepsis are pneumonia, bloodstream, skin or urinary tract infections, and, less commonly, meningitis. One report demonstrated that 67% of patients had multiorgan dysfunction at sepsis recognition, with 30% going on to develop progressive multiorgan dysfunction.[1] Haemodynamic monitoring and pulse oximetry are indicated in patients with septic shock. Septic shock is clinically identified by a vasopressor requirement to maintain a minimum systolic blood pressure (60 mmHg for term infants <1 month, 70 mmHg for 1–12 months, 70 + (2 × age in years) mmHg for children aged between 1 and 10 years, 90 mmHg for children older than 10 years) and serum lactate level >2 mmol/L or 18 mg/dL after hypovolemia is corrected.[4,12,44]

Differential diagnosis

The differential diagnosis for sepsis includes a range of noninfectious and inflammatory conditions with systemic symptomatology such as of systemic inflammatory response syndrome and hyperinflammatory syndromes (e.g. haemophagocytic lymphohistiocytosis).[45,46]

Laboratory evaluation

In patients with septic shock, white blood cell count can be elevated or depressed for age or be in the presence of >10% of immature neutrophils.[11,24] At least two sets of blood cultures are required to identify the causative organism(s), one should

be drawn through the skin and one through a vascular access device (e.g. central venous catheter and arterial lines) that has been in place for >48 hours.[24] Bacteria are only present in the blood in approximately 30% of cases.[47] Cultures of other sources of infection potentially present in other samples, including wounds, urine, cerebrospinal fluid or respiratory secretions, should be carried out. Where possible, blood culture should be obtained before initiation of antimicrobial treatment; however, the screening of sepsis must not delay the prompt administration of antibiotics.[24]

Central venous pressure and central venous oxygen saturation should be monitored if initial blood lactate is ≥4 mmol/L or if blood pressure remains low within 6 hours despite vigorous fluid resuscitation of 30 mL/kg.[24] Raised blood lactate >2 mmol/L at intensive care unit (ICU) admission is associated with worse outcomes. Monitoring of trends in blood lactate is recommended in addition to clinical assessment to guide the management of septic shock in children.[12,24,48] It is important to determine the source of infection that requires emergent source control within 12 hours.[24] Radiological investigations and interventions might be necessary if there is evidence suggestive of perforated internal organs or deep-site infections to detect and remove the source of infection.[49]

Complications

In septic shock, end-organ dysfunction can involve multiple organs.[50] Complications include acute respiratory distress syndrome (ARDS), encephalopathy, multifocal necrotizing leukoencephalopathy, hepatic dysfunction, renal failure and cardiac failure.

Management

The most important aspects of medical therapy for patients with septic shock in the ICU setting are underpinned by crystalloid fluid administration, early administration of broad-spectrum antibiotics, adequate oxygen delivery, rapid source identification and control, and support of organ failure or dysfunction.[12,24,51–53]

Initial resuscitation

Many deaths occur within the first 48–72 hours of treatment, whilst mortality is associated with late PICU referral, delay in inotrope resuscitation and delay in restoration of normal blood pressure and capillary refill; early identification and appropriate treatment is crucial to improve outcomes for children with sepsis.[12,16,22] The Surviving Sepsis Campaign guidelines recommend an initial resuscitation algorithm and systematic screening for sepsis in children. Within 1 hour of initial recognition of septic shock, the following six steps should be performed: (1) obtain intravenous/intraosseous access; (2) collect blood culture; (3) start empiric broad-spectrum antibiotics; (4) measure lactate; (5) administer fluid bolus if shock persists; and (6) start vasoactive agents if shock persists.[54]

Patients with severe septic shock might require intubation and mechanical ventilation for optimal pulmonary support. Mechanical ventilation with adequate sedation eliminates the work of breathing and metabolic demands of respiration. The patient might develop paediatric ARDS, and low-tidal volume ventilatory strategies have been advocated to manage ARDS and minimize alveolar injury. It is recommended to keep tidal volume to <6 mL/kg and plateau pressures below 30 mL H_2O.[24,51] A high positive end-expiratory pressure is often required to prevent alveolar collapse at the end of expiration.[55]

The American College of Critical Care Medicine recommended that each institution should implement their own adopted bundles to guide management of septic shock and these should include the following elements: (1) a recognition bundle to trigger rapid identification of patients with suspected septic shock; (2) a resuscitation and stabilization bundle tailor to the consensus of that individual institution; and (3) a performance bundle to monitor, improve and audit adherence to the recommended practice.[16]

Fluid resuscitation therapy

Fluid resuscitation and haemodynamic support should be given to children with septic shock.[56] Hypotension in septic shock contributes to poor tissue perfusion. The latest Surviving Sepsis Campaign international guidelines suggest administrating 40–60 mL/kg of fluid over the first hour and the amount should be titrated according to clinical response and frequent assessment of cardiac output.[12] In the non-PICU setting, fluid resuscitation should be more cautious and the guidelines suggest administrating up to 40 mL/kg over the first hour.[12] Fluid administration can be titrated by frequent reassessment of the clinical markers of cardiac output (e.g. heart rate, blood pressure, capillary refill time, level of consciousness and urine output) and withhold when there are signs of fluid overload (e.g. hepatomegaly or pulmonary oedema).[12] Fluid overload should be avoided as it is associated with a risk for prolonged mechanical ventilation, acute kidney injury and increased mortality.[57] If resources are available, serial lactate measurement and advanced haemodynamic monitoring should also be used.[12]

For improvement of the preload state (expanding intravascular and interstitial fluid spaces), isotonic crystalloid fluids (isotonic sodium chloride solution (normal saline), lactated Ringer solution and Plasma-Lyte) are the standard intravenous fluids used for initial volume expansion and resuscitation to maintain an adequate circulating intravascular volume.[52] There is evidence to suggest that using balanced crystalloids for initial resuscitation of a paediatric patient with sepsis is associated with a decreased prevalence of acute kidney injury, shorter duration of vasoactive infusions and improved survival when compared with unbalanced crystalloids.[12,58]

Colloids provide oncotic expansion of plasma volume. They expand plasma volume to a greater degree than isotonic crystalloids and reduce the tendency of cerebral and

pulmonary oedema. Approximately 50% of the administered colloid stays in the intravascular compartment. Although the routine use of colloids for initial fluid resuscitation is not recommended in sepsis, it can be considered for the maintenance of cardiac output and preload intravascular volume expansion.[12] Albumin is the colloid of choice; 25% solutions are indicated for raising oncotic pressure, whereas the 5% solutions are indicated for expanding plasma volume.[12]

Vasopressors and inotropes

Vasopressors and inotropes may be indicated in patients refractory to fluid resuscitation. Adequate fluid resuscitation is a prerequisite for using vasopressors or inotropes in patients with septic shock as vasopressor may worsen organ perfusion in inadequately volume-resuscitated patients.[59] The inflammatory response of septic shock can lead to a complex interaction between pathological vasodilatation, relative and absolute hypovolemia, direct myocardial depression, and altered blood flow distribution.[59] Inotropes are adrenergic agonists commonly used in sepsis to offset cardiovascular derangement, whilst vasopressors augment the cerebral and coronary blood flow during the low-flow state in shock.

Vasopressor and inotrope therapy can be titrated with clinical signs and advanced haemodynamic monitoring, targeting a mean arterial pressure between the 5th and 50th percentile for age in children.[12] The aim of therapy should be aimed at restoring normal physiology to maintain perfusion pressure above the critical point to maintain adequate levels of oxygen delivery tissue and organs to avoid flow-dependent tissue hypoxia.[16,59] Advanced haemodynamic monitoring (e.g. cardiac output/cardiac index, systemic vascular resistance, stroke index and $ScvO_2$) is recommended as blood pressure might not reflect cardiac output.[12,16] A cardiac index between 3.3 and 6 L/min/m^2 is associated with the best outcomes in patients with septic shock.[16]

Common agents used in children with septic shock are norepinephrine, epinephrine, dopamine, dobutamine and vasopressin. The evidence to support the use of one specific vasoactive drug over another in children is limited and controversial in the literature. The latest Surviving Sepsis Campaign guidelines in children recommended using either epinephrine or norepinephrine, rather than dopamine in children with septic shock.[12] In patients requiring high-dose catecholamines, vasopressin receptor agonists can be added.[12]

Norepinephrine is indicated for septic shock with protracted hypotension after adequate replacement of intravascular volume. It stimulates both α-adrenergic and β1-adrenergic receptors, thereby increasing vasoconstriction, cardiac contractility and heart rate, and increases systemic blood pressure and cardiac output. Norepinephrine is the first-line agent for fluid-refractory hypotensive hyperdynamic shock in adults but there are no controlled studies comparing norepinephrine to dopamine and/or epinephrine in children.[16,52,56,60–63]

Epinephrine stimulates both β-adrenergic and α-adrenergic receptors, with potent inotropic and chronotropic effects. There are no studies to compare the effects of epinephrine and norepinephrine, but early administration of epinephrine was associated with increased survival when compared with dopamine.[12,64]

Dopamine stimulates both dopaminergic and adrenergic receptors. The haemodynamic effect is dose dependent. It is believed that lower doses of dopamine predominately stimulate the dopaminergic receptors that produce mesenteric and renal vasodilation, whilst at higher doses, they induce renal vasodilation and increase cardiac contractility. Dopamine was once a popular inotrope; however, it can cause tachycardias and arrhythmias.[12,60–62,65] Dobutamine is a sympathomimetic amine that produces systemic vasodilation and increases the inotropic state with stronger β than α effects. The drug is used if there is evidence of sepsis-related tissue hypoperfusion and myocardial dysfunction. Both dobutamine and dopamine are the drugs of choice for improving myocardial contractility, with dopamine preferred in patients with hypotension. Higher dosages of dobutamine may cause tachycardia and exacerbate cardiac ischaemia.

Vasopressin is an antidiuretic hormone with vasopressor activity by promoting the contraction of smooth muscle throughout the vascular bed of the renal tubular epithelium. Vasoconstriction is increased in portal, intrahepatic, splanchnic, cerebral, coronary, peripheral and pulmonary vessels. The effects of vasopressin are not affected by α-adrenergic receptor downregulation in patients with sepsis; therefore, vasopressin can be considered as rescue therapy in patients in vasodilatory shock not responding to high-dose catecholamines.[12,16]

Vasoactive agents should be started as soon as possible, preferably within 60 minutes of resuscitation, through peripheral venous access or intraosseous access if central venous access is not avaliable.[12,16] Epinephrine or dopamine is preferred to norepinephrine for peripheral infusion.[12] Short-term delivery of vasoactive agents via peripheral venous access appears to be safe and the incidence of extravasation is low.[66]

Antimicrobial agents

Empiric antibiotic therapy is the only proven effective medical treatment in septic shock and should be started promptly within 1 hour of recognition.[12,52,56] Broad spectrum with one or more antibiotics should be used to provide the necessary wide coverage for a wide range of potential pathogens where gram-positive or gram-negative bacteria are the most common causes of sepsis in children.[12] In children who are immunocompromised with sepsis, anti-pseudomonal third-generation cephalosporin or carbapenem should be started and an antifungal should be considered to cover invasive fungal infections.[12] In children with chronic health conditions requiring frequent hospital visits, antimicrobials to cover atypical pathogens and resistant bacteria, for example,

methicillin-resistant *Staphylococcus aureus*, might be needed. All antibiotics should initially be administered intravenously in therapeutic dosages.

Nutrition

A normal glucose level below 10 mmol/L is recommended and intravenous insulin might be needed for glycaemic control.[12] Partial or full enteral feeding delivered via a feeding tube is considered the best approach to providing nutrition for a patient contraindicated for oral intake in the first 7 days of sepsis. Nevertheless, omega-3 fatty acids are generally not recommended as immune supplements in septic shock. The usage of prokinetic agents, such as domperidone, metoclopramide and erythromycin, is recommended for patients with sepsis unable to tolerate enteral feeding. However, these agents may precipitate QT prolongation and provoke ventricular arrhythmia and torsades de pointes. The usage of prokinetic agents should be reviewed daily and stopped if no longer needed.[6]

Stress ulcer prevention

H_2 antagonist and proton pump inhibitors are useful in a person at risk of developing upper gastrointestinal bleeding, for example, on mechanical ventilation for >48 hours, persistent shock, or those with liver disease, coagulation disorders, renal replacement therapy or receiving treatment with corticosteroids.[6,12]

Corticosteroids

Corticosteroids are anti-inflammatory drugs that may maintain vascular tone in shock states.[52,56] Currently, the evidence for improved outcomes with the use of corticosteroids is marginal. Results from clinical studies remain controversial and the latest version of the paediatric Surviving Sepsis Campaign guidelines does not have specific recommendations about hydrocortisone use.[12] In this context, low-dose hydrocortisone is recommended in fluid-refractory and catecholamine-resistant shock, although catecholamine resistance remains poorly defined. These medications may be beneficial if treatment is initiated within 8 hours of severe septic shock, especially in adreno-suppressed patients. Exogenous hydrocortisone administration may improve outcomes and increase mean arterial pressure in patients with septic shock who have persistent hypotension despite vasopressor support and adequate crystalloid resuscitation. Low-dose hydrocortisone for 5–7 days may lead to improved outcomes.[52,67] Adjunctive hydrocortisone should always be considered in children with congenital adrenal hyperplasia, hypothalamic–pituitary–adrenal axis disorders, multiple endocrinopathies, receiving treatment of acute or chronic corticosteroids, ketoconazole, or etomidate.[12,68]

Immunoglobulin and miscellaneous medications

The beneficial effects of intravenous immunoglobulin (IVIG) for sepsis are not proven and therefore not recommended.[6] Monoclonal and polyclonal IVIG have not been shown to lower death rates in newborns and adults with sepsis.[69] Evidence for the use of IgM-enriched polyclonal preparations of IVIG is not consistent.[69] Patients with toxic shock syndrome or necrotizing fasciitis may benefit from IVIG.[12] The use of antithrombin to treat disseminated intravascular coagulation associated with severe sepsis is also not beneficial. Recombinant activated protein C (namely drotrecogin alfa) usage in sepsis is controversial.[70] A 2011 Cochrane review showed no evidence of efficacy in reduction of mortality and its use is thus not recommended.[71]

Renal replacement therapy and continuous blood purification techniques

Continuous renal replacement therapy may be beneficial if indicated. As fluid overload is often associated with substantial morbidity and mortality in the critically ill child with septic shock, renal replacement therapy can be used to treat or prevent fluid overload.[12,57] Some techniques of continuous blood purification may provide a solution for addressing refractory sepsis by removing inflammatory pro-cytokines from the body.[72–74] Plasma exchange is not recommended as it does not improve survival for septic shock.[6,12]

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygen (ECMO) can be provided in venovenous mode for respiratory support alone or in venoarterial mode for both respiratory and circulatory support. It is a complex, high-risk therapy in children and requires a specialized system of care available in a limited number of tertiary children's hospitals in high-income countries. Whether or not the use of ECMO in severe paediatric septic shock confers an outcome benefit remains uncertain. Venovenous ECMO is currently recommended for the treatment of refractory hypoxia, including due to severe sepsis.[75] Venoarterial ECMO may be used as a rescue therapy in refractory circulatory shock due to sepsis.[12] Survival may be better in patients receiving high ECMO flows (>150 mL/kg/min at 4 hours after institution of ECMO) *versus* standard flow or no ECMO.[76] However, the evidence base is not strong and a commonly agreed definition of refractory shock is lacking.

Monitoring in the PICU

In addition to advanced haemodynamic monitoring, laboratory tests in the PICU setting usually include serial blood gas analysis, complete blood count with a leukocyte differential, blood coagulation profiles (e.g. activated partial thromboplastin time, prothrombin time, fibrinogen levels), blood chemistry (e.g. sodium, bicarbonate, chloride, calcium, magnesium, phosphate, lactate, glucose), renal function tests (e.g. blood urea nitrogen and creatinine), hepatic function tests (e.g. albumin, bilirubin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and lipase), and tests to identify the source of infection (e.g. blood cultures, Gram stain and culture of secretions and tissue, urinalysis and urine cultures). Radiologic studies (such as chest, abdominal, extremity radiography, abdominal

ultrasonography, abdomen or head CT) may be indicated to evaluate patients with septic shock suspected of having an uncontrolled source of infection.

Surgery

After initial resuscitation and administration of antibiotics, patients with focal infections may need definitive surgical treatment. Certain conditions do not respond to standard therapy for septic shock unless the source of infection is surgically removed (e.g. mediastinitis, empyema, intra-abdominal sepsis (perforation, abscesses), cholangitis, pancreatic abscesses, renal abscess, pyelonephritis, infective endocarditis, deep cutaneous or perirectal abscess, septic arthritis, infected prosthetic device and necrotizing fasciitis). Any suspected necrotizing fasciitis or deep abscess should be drained in the surgical suite.

Prevention

The key to preventing the occurrence of sepsis is the successful implementation of public health measures against infections, including good hygiene practices, ensuring widespread access to vaccination programmes, improved sanitation, availability of water, quality of water, and other infection prevention and control practices both in the community and healthcare settings. Early diagnosis, appropriate and timely clinical management of sepsis, fluid resuscitation and optimal antimicrobial use are crucial to maximizing the likelihood of survival of patients with septic shock.[77]

Prognosis

Serum lactate is a useful marker in determining prognosis. Patients with a lactate level >4 mmol/L have a mortality of 40% and those with <2 mmol/L have a mortality of less than 15%.[78] Several prognostic stratification systems have been developed, such as Mortality in Emergency Department Sepsis, Acute Physiology And Chronic Health Evaluation II (APACHE II) and Pediatric Index of Mortality 3 (PIM3).[79,80] Case fatality rates are similar for culture-negative and culture-positive severe sepsis. Of the individual covariates, the risk of death is most strongly influenced by the severity of underlying disease. Septic shock is also a strong predictor of both short-term and long-term mortality. Some patients may experience long-term severe cognitive decline following an episode of severe sepsis.[81] Adult and adolescent patients with septic shock can be clinically identified by having serum lactate levels >2 mmol/L and requiring a vasopressor to maintain a mean arterial pressure of >65 mmHg in the absence of hypovolemia. This combination is associated with hospital mortality rates of over 40%.[3,4] Patients usually recover in 2–3 weeks following prompt treatment. However, the condition can be fatal within hours.[82]

Mortality due to septic shock can only be reduced with prompt resuscitation, supportive and target treatment. Prognosis is worse in patients with premorbid conditions such as immunodeficiency and malignancy.[9,11,19] In children, initial usage of epinephrine and more than one inotrope are associated with death.[20] Critically ill patients with septic shock treated in a children's hospital emergency department who receive antibiotics within ≤1 hour were significantly more ill than those treated later, but they were not at higher risks of new or progressive multiple organ dysfunction syndrome or death.[83]

Conclusion

Sepsis is one of the leading causes of morbidity and mortality worldwide. Mortality is associated with delayed recognition and treatment; therefore, the Surviving Sepsis Campaign advocates an initial resuscitation algorithm for children with sepsis to improve survival.[12,16,22,54] Each institution should implement their own sepsis management bundle to trigger the rapid identification of septic shock, guide resuscitation and stabilization, and audit performance to recommended practice.[16] Most of the current paediatric sepsis guideline recommendations are based on the adult literature, with research gaps in many areas. Therefore, we believe that the following should be addressed in priority: sepsis and shock definition in children, haemodynamic monitoring targets, and evidence to support recommendation of vasoactive medications and the indication and timing of ECMO initiation to improve sepsis survival and outcomes.

Key practice points

- Sepsis is one of the leading causes of morbidity and mortality worldwide. Mortality is associated with delayed recognition and treatment.
- The Surviving Sepsis Campaign advocates an initial resuscitation algorithm for children with sepsis to improve survival – within 1 hour of initial recognition of septic shock, the following six steps should be performed: (1) obtain intravenous/intraosseous access; (2) collect blood culture; (3) start empiric broad-spectrum antibiotics; (4) measure lactate; (5) administer fluid bolus if shock persists; and (6) start vasoactive agents if shock persists.

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