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Management of Septic Shock in Pediatric Emergency Departments

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Abstract:
Septic shock in pediatric patients causes severe infection that can lead to systemic inflammation and cardiovascular compromise. The objective of this study is to review the updates of the literature regarding the management of septic shock in pediatric emergency departments. The researcher employed the most research engines to collect the cited literature including Science Direct, Pub Med, Google Scholar, and others. The present study introduced the topic from various points including diagnosis and treatment options.

INTRODUCTION

Septic shock in pediatric patients causes severe infection that can lead to systemic inflammation and cardiovascular compromise (Nolt *et al.*, 2021). Pediatric sepsis occurs at a higher rate compared to adults and carries an elevated mortality rate (Grace and Barcellini, 2020). Delay in the administration of empirical intravenous antibiotics is associated with increased sepsis and septic shock-related mortality for pediatric patients (Chiu and Legrand, 2021; Weatherhead *et al.*, 2020; Zarbock *et al.*, 2023). Healthy critical care guidelines recommend the use of wide-spectrum empiric antimicrobial treatment within one hour of the identification of sepsis or septic shock in pediatrics (Alkhatib, 2021; Arashova, 2023; Markwart *et al.*, 2020). Thus, the emergency department is at the frontline for the timely diagnosis and management of septic shock in children (Crombie and LaCasce, 2021; Henderson *et al.*, 2020).

Understanding the demographics and epidemiology of septic shock is essential (Smith *et al.*, 2021). In resource-rich countries, the median prevalence of severe sepsis and various subpopulations are well described with an overall mortality rate of 10–16% (Peshimam and Nadel, 2021). A multinational study of septic shock in the pediatric emergency department confirmed the diagnosis of septic shock in a small percentage, with a mean age of 29 days (Gorantiwar and de Waal, 2021). Since the epidemiology of sepsis changes with the host, the cost, the nature of the host-pathogen interaction, and the environment, a deeper understanding of septic shock due to the general pathogens in pediatrics is needed (Bayazeed *et al.*, 2024). Untreated septic shock mortality rates in children are high: a significant percentage of children with septic shock die for each hour of delayed treatment (Burgunder *et al.*, 2022). Given the large treatment window, it is most likely that many children who fulfill the strict criteria for septic shock have undiagnosed septic shock (De Lima *et al.*, 2024). Pediatric septic shock behaves differently than adult septic shock; children exhibit a unique pathophysiology, distributive shock, an overwhelming proinflammatory response and a parallel anti-inflammatory response (Borankulova and Sazonov, 2024). There are additional nuances in treating pediatric septic shock, as the management must be adapted to the unique physiology of neonates, infants, and older children (Zaki *et al.*, 2024). There are generally accepted guidelines that describe normal cardiovascular variables in term neonates and children of various ages and stages of development, some of which vary wildly from adult values. These guidelines use the best available evidence to recommend that children receive prompt, adequate, and early therapy. This strategy encourages fluid resuscitation, vasoactive medications as needed, routine transfusions of red blood cells when hematocrit falls below a certain level, and corticosteroids in children who require high-dose vasopressors (Alkhalaf *et al.*, 2023).

Pathophysiology of Septic Shock in Children

Septic shock is a complex interplay between immune, inflammatory, and cardiovascular mechanisms (Dallan *et al.*, 2020). Most cases of septic shock in children will occur in response to systemic invasive infections; however, sources including otitis media, upper respiratory infections, and soft tissue infections have also been described. In general, infections trigger a systemic, pro-inflammatory response (Garcia *et al.*, 2020). Vasodilation and increased vascular permeability lead to a relative hypovolemic state, while systemic myocardial dysfunction precipitates the cardiogenic component of septic shock (Hilarius *et al.*, 2020). In comparison to adults, children demonstrate unique infectious, immune responses, and cardiovascular profiles that may influence the prevalence and severity of sepsis and septic shock (Bulatova *et al.*, 2020; Sehgal *et al.*, 2020; Shah *et al.*, 2020; Weiss *et al.*, 2020).

Many ER presentations are due to direct sepsis, as the source is usually clinically apparent (Garcia *et al.*, 2020). Classifying the source of sepsis has been proposed, but not widely adopted (Sehgal *et al.*, 2020). Some are bacterial and include viruses and fungi, and some are due to infections from bacteria expressing specific virulence factors, such as toxic shock syndrome (Schlapbach *et al.*, 2024). There is debate about whether infections of viral or fungal etiology lead to an increased number of affected organs in comparison to a bacterial source (Sehgal *et al.*, 2020). Many pathogenic organisms have been implicated in pediatric septic shock, including the most frequently isolated organism (*Streptococcus pneumonia*) (Hilarius *et al.*, 2020). Bacteria, however, are the primary cause of pediatric septic shock, given the existing immune system's robustness towards fungi and the absence of local immunity, such as the case with *Candida* spp. (Weiss *et al.*, 2020).

The possible relationship between recognition of the pathogen, the response/non-response of the immune system, and the occurrence of septic shock needs to be considered concerning the development of newer strategies that evaluate pathogen antecedents of septic shock in the emergency department (Iqbal *et al.*, 2021; Prout *et al.*, 2020). Current reliable tests are not available, and therefore, it is crucial to maintain vigilance during assessment of pediatric patients for septic shock (Hazwani *et al.*, 2020). Early perception and acknowledgment of the progression of pediatric septic shock are necessary; however, additional potential causes of death include cardiovascular collapse, coma, and pulmonary hypoxemia occurring at an unpredictable time (Prout *et al.*, 2020). Septic shock, caused by an over-exuberant release of circulating inflammatory mediators, is characterized by increased myocardial dysfunction and an altered cellular immune function (Sehgal *et al.*, 2020). It results in multi-organ involvement, and the individual constantly deteriorates to a hypodynamic shock. Several reviews postulate a genetic and molecular search for children that may influence morbidity in septic shock, although definitive evidence is still in the form of Phase 1 studies (Hazwani *et al.*, 2020).

Recognition and Diagnosis of Septic Shock in Pediatric Emergency Departments

Severe sepsis and septic shock are currently the leading causes of morbidity and mortality in pediatric patients presenting to pediatric emergency departments (Schlapbach *et al.*, 2020). To manage septic shock effectively, recognition and timely diagnosis are critical (La Via *et al.*, 2024). Clinical features indicating the presence of septic shock can include altered mental status, poor perfusion, and often significant abnormalities in vital signs (Liu *et al.*, 2022). Sepsis can be distinguished from septic shock by the use of diagnostic criteria including the presence of severe hypotension, which is indicative of end-stage hemodynamic compromise (Gavelli *et al.*, 2021).

Using a systematic, standardized approach that incorporates the use of clinical scoring systems and clinical or laboratory tests can aid in the early recognition of patients with septic shock (Hilarius *et al.*, 2020). A detailed history and physical examination represent the most important tools for the recognition and diagnosis of pediatric septic shock (Garcia *et al.*, 2020). Near-continuous assessment of patient status and rapid, serial reassessment should be performed throughout the evaluation of the critically ill pediatric patient (Weiss *et al.*, 2020). However, early identification of pediatric septic shock can be extremely challenging for some clinician populations, given that children of differing ages may have atypical presentations or may have numerous causes for alterations in mental status or the presence of vital sign abnormalities (Depinet *et al.*, 2022; Harley *et al.*, 2022).

Patients typically present in a hyperdynamic septic shock with warm extremities, bounding peripheral pulses, and capillary refill in less than seconds (Karunarathna *et al.*, 2024). In the hypodynamic form, cardiovascular compensation is lost with diminished pulses, prolonged capillary refill, and cool extremities (Ushay, 2011). It is crucial to initiate immediate therapy and promptly perform a radiological check to search for the origin of sepsis, define any organ damage, and monitor the response to therapy (Mateo-Sidrón, 2023). An early broad-spectrum intravenous antibiotic treatment for severe sepsis is strongly recommended. Source control remains a cornerstone of effectively managing sepsis and septic shock (Banothu *et al.*, 2023).

Initial Stabilization and Resuscitation in Pediatric Septic Shock

Initial stabilization and resuscitation are essential parts of early intervention for pediatric patients with septic shock (Lenjani *et al.*, 2024). New evidence-based protocols in adults have informed the development of resuscitation guidelines in pediatric sepsis and septic shock (Gómez-Ríos *et al.*, 2024). Early recognition and goal-directed therapy in the ED have shown decreased mortality and decreased progression to multiorgan system failure in adult patients (Figueroa-Uribe *et al.*, 2021). Appropriate initial care in children is not only vital to decreasing the progression of septic shock, but it is also essential in disease progression and survival (Howard *et al.*, 2023; Long *et al.*, 2023). Therefore, optimal initial stabilization and resuscitation are important to all emergency physicians who must resuscitate pediatric sepsis and septic shock in the ED (Brant-Zawadzki *et al.*, 2024; Jayaprakash *et al.*, 2020).

Hemodynamic support in children and adults can make a significant difference in terms of organ perfusion, organ failure, and survival (Obonyo, 2020). It is imperative to begin volume expansion as soon as possible to prevent multiorgan system failure (Pfortmueller *et al.*, 2024). Hypovolemia is typically profound in critically ill patients who are in septic shock. In the first minutes or hours of resuscitation, the capacity for profuse sweating and polyuria is replaced by a profound edema-forming state as a child or adult who is acutely ill becomes hypovolemic (Kashani *et al.*, 2022). This condition results in significantly decreased organ perfusion, leading to progressive organ failure, cardiovascular collapse, and death. Early septic shock is also associated with cardiac dysfunction (Guarino *et al.*, 2023). All children's hospitals and most general EDs are equipped with the tools required to manage not only adult septic shock but also pediatric septic shock emergencies (Moschopoulos *et al.*, 2023). Starling forces play a significant role in capillary leakage because they are proportional to arterial pressure (Durand *et al.*, 2023). By volume expanding the child until arterial pressure can rise back into the capillaries, this pressure can be decreased. By giving a fluid challenge to a sweating child, we can tell in advance who is going to swell up significantly. We can use central venous pressure and pulse pressure as the best guides versus urine output, to determine when to volume expand and when to move on to vasopressors (Cinel *et al.*, 2020). Moreover, central venous pressure and pulse pressure can guide us to a volume that may be better to start vasopressor therapy than continue to volume expand an already hypervolemic patient. The use of a scale rather than a liberal approach during the acute phase after fluid resuscitation prevents global edema in pediatric and adult septic shock (Gazmuri and de Gomez, 2020).

Fluid Resuscitation

Fluid resuscitation is key in the initial management of pediatric septic shock (Malbrain *et al.*, 2020). It is first-line therapy to restore effective circulation and may be life-saving (Ismail and Elbaih, 2020).

For fluid resuscitation to be efficient and fast, every effort should be made to rapidly get IV access, and, if needed, to develop arteriovenous access (Ismail and Elbaih, 2020; Röher and Fideler, 2024). The choice of fluids to use should be carefully chosen, taking into account that current recommendations are to administer boluses of isotonic fluid to achieve the fastest hemodynamic stability (Edwards and Hoareau, 2021; Röher and Fideler, 2024).

Initial infusions should usually be administered as fast boluses (10–20 mL/kg, in a rapid 5–20 min administration, and possibly repeated), adapted to the clinical situation and hemodynamic parameters' responses (Zampieri *et al.*, 2021). In cases of inadequate response after early fast fluid resuscitation, observing other clinical signs (preferably blood pressure and diuresis) is essential for ongoing management and discussing therapy intensification (vasopressors, mainly inotropes, need for PICU admission) (Piehl and Park, 2021). Very severe risks are related to inadequate volumes (under-resuscitation) and excessive volumes (over-resuscitation). Because both are common, some risks are related to any fluid resuscitation as such, involving not only the amounts but also the characteristics of the individuals (comorbidities, illness evolution, and characteristics) (Messina *et al.*, 2024). Monitoring for each child should be individualized according to sepsis severity, context, and access to monitors (Alves *et al.*, 2023; Kietzmann, 2024). In clinical practice, one of the most important aspects, after ensuring a good maneuver, is to assess the patient's reaction to the fluid administration, in order to be able to adapt it afterward and to measure it: echo examination, USCOM, or PPV test (Saoraya *et al.*, 2021). In addition, the diagnosis or treatment of other pathologies may be associated (Christoforidis *et al.*, 2022).

Vasopressor Therapy

Vasopressor therapy should be administered to children who remain in septic shock despite the provision of intravenous fluid resuscitation managed under hemodynamic monitoring (Barboza *et al.*, 2020). Once children have been diagnosed with fluid-refractory septic shock and have achieved intravenous fluid resuscitation, begin vasopressor therapy (Russell *et al.*, 2021).

Vasopressor administration should be personalized to include a prescription to treat a child with age and size-related agents (Lee *et al.*, 2022). Healthcare facilities must have age-specific, weight-based vasopressors to support the effective prescription of vasopressor regimens for infants and children (Teja *et al.*, 2023). During vasopressor treatments, continuous monitoring of perfusion and organ function and the response of dosage and pressure is recommended (Ranjit and Natraj, 2024a). Urine output and other cardiovascular outcomes should be selected as targets for vasopressor therapy together with physical examination and advanced monitoring (Chacko, 2020; Ranjit and Natraj, 2024b).

Potential vasopressors based on the previous experience of pediatric shock therapy are norepinephrine, epinephrine, and dopamine (Wen and Xu, 2020). Norepinephrine has been increasingly used in adults and can be used in pediatrics (Manolopoulos *et al.*, 2020). The concentration of norepinephrine is usually 0.05 mcg/kg/min, and it can be increased up to 2 mcg/kg/min (Siva *et al.*, 2024). However, marked individual variation may occur in the response recommended for each child (Jha *et al.*, 2021). In the case of side effects and hypotension, norepinephrine should be given simultaneously with continuous pressure therapy (Rheingold and Silverstein, 2024). Among potential side effects are nose, toes, and finger ischemia. Vasoactive agents prefer norepinephrine over dopamine, especially if norepinephrine therapy fails. Adverse side effects, unrelated to dosage or rate, raise attention to the potential of hypotension during discontinuation (Chow *et al.*, 2020). As for dopamine endpoints, neither beat nor systolic arterial pressure nor urine output were relevant. Further studies found no superiority in either serum or in subgroups (Gupta *et al.*, 2022). In adults, as in children with absolute hypotension, specific pediatric data are not available; the appropriate dosage should be titrated (Chow *et al.*, 2020). Dopamine side effects include myocardial ischemia, tachyarrhythmias, and local skin irritations, particularly in continuous peripheral therapy, and rarely core for dopamine blockage (Jha *et al.*, 2021). Optimally, fewer patients should have correct myocardial functioning (Gupta *et al.*, 2022).

Antimicrobial Therapy in Pediatric Septic Shock

Antimicrobial therapy is a fundamental component in the management of septic shock, which is mainly aimed at treating the underlying infection (Niederman *et al.*, 2021; Strich *et al.*, 2020). The first hour of recognition of septic shock is crucial, when initial resuscitation and antimicrobial therapy significantly improve outcomes (Basodan *et al.*, 2022; Seok *et al.*, 2020). Currently, there is clear scientific evidence of a significant linear and/or curvilinear trend between the timing of antimicrobial therapy and lower morbidity and mortality rates in critically ill adult and pediatric patients (Im *et al.*, 2022). Each quarter-hour of delay in antimicrobial therapy is correlated with a higher incidence of in-hospital mortality (Busch and Kadri, 2020; Landersdorfer and Nation, 2021).

Current guidelines recommend initiating empirical antibiotic therapy that covers the most likely pathogens and local antibiotic resistance patterns, immediately after the blood culture has been sampled, to ensure appropriateness and effectiveness of the treatment (Ashraf and Iqbal, 2020; Semret *et al.*, 2020). Most of these recommendations are based on drugs licensed for use in adults because many prospective trials have confirmed their safety and efficacy, and antibiotic treatment strategies applicable to adult patients can also be extrapolated to pediatric patients (De Rose *et al.*, 2021). However, we should keep in mind that many physiological factors can significantly influence the pharmacokinetics and pharmacodynamics of an antibiotic, such as renal and metabolic capabilities, weight, and the development of the immune system (Mahrous *et al.*, 2020). The choice of empirical antimicrobials should follow local guidelines related to resistance patterns, but efficacy, safety, tissue penetration, and the ability to obtain appropriate dosing seem to be of paramount importance (Rule *et al.*, 2021). Once the results of cultures are available, antibiotics should be de-escalated to the narrowest spectrum of antimicrobials to provide a clear microbiological focus and medical history (Iqbal and Ashraf, 2021; Khasawneh *et al.*, 2023). At the same time, clinicians should be aware of other concomitant or secondary infections, such as fungal or viral infections, the latter of which are more frequently associated with older age (Ashraf and Iqbal, 2021; Fabre *et al.*, 2022; Iqbal, 2020; Iqbal *et al.*, 2019b). Often, viral and fungal biomarkers may help to decide whether or not to introduce antiviral and antifungal agents. Fungal infections are closely related to immune status, various comorbidities, central venous catheters, and prolonged antibacterial therapy (Verboom *et al.*, 2021). Given the encouraging results of medicinal plants that have few or no side effects and are readily available, natural substances have drawn a lot of interest for the treatment of many clinical complications (Ashraf *et al.*, 2020; Iqbal *et al.*, 2019a; Iqbal and Ashraf, 2019; Shahzad *et al.*, 2017; Zaynab *et al.*, 2018). In summary, the choice of antimicrobial therapy should be guided by source control and adapted to the age and immune status of the patient (Kuzniewicz *et al.*, 2020). In addition, a closely monitored strategy should be used for the subsequent step-down based on culture results (Mizrahi *et al.*, 2022).

CONFLICT OF INTEREST

Authors hereby declare that they have no conflict of interest.

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