Evolving Definitions and Current Perspectives in Pediatric Sepsis: A Narrative Review

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ABSTRACT

Sepsis is a common yet potentially life-threatening condition affecting neonates and children worldwide, with a disproportionately large burden in Low and Middle-Income (LMIC) countries. Accurate estimation of global burden is hindered by a lack of standardisation of diagnostic criteria and scarce population-based data, especially in developing/LMIC countries. This narrative review chronicles the evolution of the definitions of pediatric sepsis and outlines the current perspectives in the management of pediatric septic shock. PubMed/Medline and Google Scholar were searched for relevant articles, until July 2024. The updated recommendations define pediatric sepsis, using a novel scoring matrix- The Phoenix Sepsis Score based on a 4-organ system model, marking a complete transition from Systemic Inflammatory Response Syndrome. Key strategies in the management of septic shock include early recognition, supporting the airway and breathing, blood investigations, source control, hemodynamic management, and supportive therapy. IV fluid bolus therapy, preferably with balanced crystalloids, is indicated only if hypotension is present (all settings), along with abnormal perfusion (only in high-income intensive-care settings). Recent research has shown significantly higher sepsis-attributable mortality with antibiotic institutions, only beyond 330 minutes. For IV fluid refractory shock, Norepinephrine (the first-line vasopressor in septic shock) is preferred in hypotension with vasodilatory shock; Epinephrine is preferred for hypotension with septic myocardial dysfunction. In normotension with persistent hypoperfusion, the inodilators-Dobutamine or Milrinone are indicated. Steroids are not advocated, and (RBC) transfusion is definitely recommended only if the Hb concentration is <5 g/dL. Renal Replacement Therapy remains the mainstay of treatment for established acute kidney injury and diuretic-refractory fluid overload. For pediatric refractory sepsis, veno-arterial Extracorporeal Membrane Oxygenation survival rates over 60% have been demonstrated. Further moderate/high-GRADE evidence is needed to fortify existing protocols, with due pragmatic considerations for resource-poor settings.

Keywords: Children, Definition, Epidemiology, Refractory Shock, Sepsis, Septic Shock Management.

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Introduction

Sepsis is a common yet potentially life-threatening condition affecting neonates and children worldwide. The word "sepsis" (from the Greek "sepsin," meaning "rot, make putrid"), has been used historically to describe infections usually bacterial, which if left untreated, could progress to shock and death.[1]

Globally, in 2017 there were 48.9 million cases of sepsis and 11 million sepsis-related deaths, accounting for 19.7% of all global deaths. Notably, half of all sepsis cases worldwide occurred in children; with those under the age of five accounting for an estimated 20 million cases and 2.9 million global deaths. Stark regional disparities exist, with nearly 85% of sepsis cases and sepsis-related deaths worldwide occurring in Low and Middle-Income (LMIC) countries in sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia.[2]

A systematic review of 23 studies included from 1979 to 2016, published in 2018, found an aggregate estimate of 48 (95% CI 27-86) sepsis cases and 22 (95% CI 14-33) severe sepsis cases in children per 100 000 person-years; with mortality ranging from 1% to 5% for sepsis and 9% to 20% for severe sepsis.[3] Among hospitalized children, the prevalence of severe forms of sepsis and shock ranges from 1- 26%. Mortality is even higher, about 5% in developed countries to nearly 35% in developing countries.[4]

Nevertheless, despite these data, the accurate estimation of global burden continues to be challenging, especially in developing/LMIC countries. Significant obstacles include the lack of standardisation of diagnostic criteria, with varying definitions of sepsis in the reviewed studies as also, scarce population-based data from low-income settings.[3]

This narrative review chronicles the evolution of the definitions of pediatric sepsis, enumerates the risk factors and causes of pediatric and neonatal sepsis, and proceeds to outline the current perspectives in the management of pediatric septic shock.

Methodology

PubMed/Medline and Google Scholar were searched for the relevant articles up to July 2024 to identify the literature on the global and regional burden, definitions of pediatric sepsis, risk factors and causes of pediatric and neonatal sepsis, and management of pediatric septic shock, by using the following keywords: 'burden', 'definition', 'epidemiology', 'etiology', 'risk factors', 'shock', 'sepsis', 'septic shock', 'children', 'sepsis management', 'shock management', 'first hour', 'intravenous fluids', 'vasoactive agents', 'hemodynamic monitoring', 'resistant shock', 'refractory shock', 'steroid' as well as combinations of the above. Since this is not a systematic review, the most relevant articles were identified from the results, while duly considering chronology, for inclusion in this narrative review.

Standardization of the Definitions of Pediatric Sepsis-Timelines

The first consensus definition of sepsis by the American College of Chest Physicians and Society of Critical Care Medicine in 1991, relied on the development of a Systemic Inflammatory Response Syndrome (SIRS) in response to an infection defined in the adult population as the presence of two or more of the following a) Temperature > 38 °C or < 36 °C b) Heart rate > 90/min c) Respiratory rate > 20/min or PaCO2 > 32 mmHg d) Leukocyte count > 12,000/mm3 or < 4000/mm3 or > 10% immature bands. In addition, the development of organ dysfunction was defined as 'severe sepsis'; and hypotension resistant to adequate fluid resuscitation, as 'septic shock'.[5]

Given that in the pediatric population, abnormal heart rate and respiratory rates are more common, the diagnostic definition was modified to include a mandatory requirement of abnormal leukocyte count or temperature.[6]

While it was dogmatically assumed that almost all septic patients have SIRS, but not all SIRS patients are septic, there were exceptional subgroups among hospitalized patients, especially the very young, who did not meet the criteria for SIRS on presentation, yet progressed to severe infection, multiple organ dysfunction and death. Indeed, bradycardia, a sign of SIRS in the neonatal period

could represent significant decompensation in older children.

Paediatric age-specific definitions for sepsis and severe sepsis were therefore revised in 2005 at the International Paediatric Sepsis Consensus Conference (IPSCC).[7] Sepsis was defined as SIRS plus suspected/proven infection; severe sepsis was defined as sepsis plus cardiovascular/acute respiratory dysfunction, or two or more organ dysfunctions (respiratory, renal, neurological, haematological, or hepatic); the septic shock was redefined as severe sepsis with cardiovascular dysfunction, factoring in the phenomenon that hypotension is a late marker of decompensated shock in children.[7]

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3 definitions) redefined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection' The Sepsis-3 definition removed 'severe sepsis' from the nomenclature, redefined septic shock as sepsis with 'profound circulatory, cellular, and metabolic abnormalities, associated with a greater risk of mortality than with sepsis alone' while including Mean Arterial Pressure (MAP) and serum lactate as clinical-laboratory requirements.[8] Thereafter, the development of the paediatric Sequential Organ Failure Assessment (pSOFA) by Matics et al facilitated the application of the Sepsis-3 guidelines to the paediatric cohort.[9]

In 2016, the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) experts defined and validated paediatric Refractory Septic Shock (RSS) characterised by evidence of myocardial dysfunction (3 points) and high blood lactate levels (1 point) despite high vasopressor treatment (1 point). A bedside score ≥2 or computed score ≥3.5 showed high discriminative power against the need for extracorporeal life support or death.[10]

In 2020, the Surviving Sepsis Campaign (SSC) International Guidelines developed evidence-based recommendations for the recognition and management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children.[11]

In 2022, Pediatric Organ Dysfunction Information Update Mandate (PODIUM) expert panel characterised data on single and multiple organ dysfunction to derive a final set of 43 contemporary criteria for pediatric organ dysfunction in an unwell child.[12]

Subsequently, the Society of Critical Care Medicine assembled a collaborative task force of 35 pediatric experts from six different countries to review international data based on more than 3 million hospital encounters in the U.S. and globally, including four lower-resource settings. Results were derived and validated to predict mortality in children with suspected or confirmed infection. Updated recommendations, defining sepsis in children were formulated, using a novel scoring matrix- The Phoenix Sepsis Score based on a 4-organ system model, and published in January 2024.

This includes criteria for respiratory (mechanical ventilation, PaO2:FIO2, and SpO2:FIO2 ratios), cardiovascular (mean arterial pressure, lactate level, and vasoactive medications), coagulation (platelet count, international normalized ratio, D-dimer, and fibrinogen), and neurologic (Glasgow Coma Scale and pupillary reaction) parameters. Septic shock is sepsis plus one or more points in the cardiovascular component of the Phoenix Sepsis Score (viz. severe hypotension, blood lactate >5 mmol/L, or vasoactive medication infusion). A score 2 or higher on the Phoenix Sepsis Score implies potentially life-threatening organ dysfunction.[13]

These criteria performed better than previous criteria across settings. Substantial changes in the newly proposed criteria compared to previous criteria include the removal of SIRS as a diagnostic factor and the elimination of severe sepsis as a separate condition.[14]

The Phoenix score has performed well even in low-income settings where lactate information was not available. Phoenix Sepsis Score is not designed as a screening tool for sepsis or to predict the risk of sepsis. Rather, it is designed to assist clinicians in identifying children with both infection and life-threatening organ dysfunction.[14]

The transition from SIRS to the Phoenix criteria is thus complete.

Risk Factors and Causes of Pediatric and Neonatal Sepsis

Common risk factors for pediatric sepsis include the presence of an underlying chronic disease, underlying immunodeficiency, indwelling central venous device, and bone marrow or solid organ transplantation.[15]

Sepsis can be caused by bacterial, viral, fungal, parasitic, and rickettsial infections, with bacteria and viruses being the most frequently identified.

In studies in non-resource-limited settings such as the US, Sweden, Australia, and New Zealand, the most common pathogens affecting previously healthy children were Staphylococcus aureus followed by Streptococci and Escherichia coli. In contrast, the most common pathogens in children with chronic diseases were S. aureus followed by Candida and Pseudomonas.[16–18]

About a third to half of children with sepsis do not have an identifiable pathogen, largely attributable to sepsis of viral etiology or limits in bacterial pathogen detection.[15]

In sepsis occurring within the first 28 days of life (neonatal sepsis), implicated organisms are those vertically transmitted from the vaginal tract and/or hospital-acquired infections. The most common isolated bacterial pathogen is Streptococcus agalactiae (group B streptococcus) followed by Escherichia coli. Viruses implicated include herpes simplex virus (HSV), usually due to vertical transmission, enterovirus and parechovirus.[19]

In LMIC settings, in contrast to high-income settings, community-acquired infections are more prevalent, along with vertical transmission. Hospital-based data implicate the most commonly associated bacterial pathogens to be Klebsiella species, Staphylococcus aureus, Enterobacterales, and non-typhoidal Salmonella.[20]

In young infants under 3 months of age, Escherichia coli, Group B streptococcus, and Staphylococcus aureus are most frequently identified. In patients with sepsis with febrile neutropenia, both gram-positive (coagulase-negative Staphylococcus, Staphylococcus aureus, Streptococcus pneumoniae, and viridans) and gram-negative organisms (Pseudomonas, Escherichia coli, Klebsiella) are common. In hospital-acquired bacterial infections, such as catheter-associated bloodstream infections, coagulase-negative Staphylococcus, followed by gram-negative organisms are the most commonly identified.[21]

Septic Shock Management

Initial management is vital, especially in the first 6 hours, and should be directed at early diagnostic and timely therapeutic interventions to interpret and treat hemodynamic derangements; and the institution of appropriate antibiotics and vasoactive agents. This initial management aimed at improving tissue perfusion and oxygen delivery an important constituent of early goal-directed therapy. Rivers et al found in-hospital mortality and APACHE 2 scores significantly lower (30.5 percent) in the group assigned to early goal-directed therapy, compared to standard therapy (46.5 percent).[22]

Key strategies in the management of septic shock include early recognition, hemodynamic management, and supportive therapy.[23]

In children with suspected or confirmed infection, “Sepsis” is identified using the Phoenix sepsis criteria as two or more points in the Phoenix Sepsis Score. This indicates potentially life-threatening organ dysfunction (respiratory,

cardiovascular, coagulation, and/or neurological). "Septic shock" is diagnosed in a subset of children with sepsis and cardiovascular dysfunction, implying a cardiovascular score of at least 1 point in the Phoenix sepsis score.[13]

Recognition of Septic Shock: Age-appropriate values for Tachycardia* disproportionate to fever, Tachypnea* (usually effortless, unless underlying lung pathology is present), Blood pressure* (SBP) <5th centile *, Temperature <36°C or >38.5°C, Capillary refill time >3 seconds or <1 second, Peripheral pulses (weak, absent or bounding), Central pulses (normal or bounding), decreased urine output and decreased conscious level are important clinical parameters to aid in the timely recognition of sepsis and septic shock. Age under 3 months, hypoperfusion (clinical and hemodynamic variables), and low-urine output, with or without hypotension are red flag clinical parameters aiding in the recognition of shock.[24]

Significantly, shock in newborn infants unlike adults and pediatric patients, is often recognized in the uncompensated phase by the presence of hypotension.[25]

Supporting the airway and breathing: The airway must be stabilized and hypoxemia should be addressed by supplemental oxygen or High-Flow Nasal Cannula (HFNC) or non-invasive ventilation using continuous positive airway pressure (CPAP).[26] In children with unstable airways or ventilation-perfusion mismatch, intubation and mechanical ventilation should be provided.

Blood investigations, Blood culture, Antibiotics and stewardship, Source control: Using two large-bore IV cannulas, initial investigations to be conducted include blood counts, CRP/procalcitonin, blood gas analysis, electrolytes, calcium, glucose, lactate, two sets of blood cultures and tests for organ dysfunction. Blood cultures must be obtained before the institution of antimicrobial therapy followed by the administration of the first dose of empirical IV antibiotic. Antibiotics should be initiated within 1 hour of recognition in children with septic shock and within 3 hours of recognition in children with sepsis-associated organ dysfunction without shock.[15] However, in a recently published study that included 19,515 children aged 29 days to less than 18 years over a 5-year period (2017-21) with a diagnosis of sepsis recognized within 1 hour of emergency department (ED) arrival, regression analysis identified that 3-day and 30-day sepsis-attributable mortality increased significantly with delays in antibiotic administration 330 minutes or longer from ED arrival.[27,28] The empiric antibiotic choice depends on the suspected site, likely pathogens, community/nosocomial source, local epidemiology, and immune status.[29] Antimicrobial coverage can then be narrowed down based on culture and susceptibility, and dosing optimized based on pharmacokinetic data.

If confirmed to be a source of sepsis, intravascular access devices should be removed after alternative access is obtained. Foci of undrained infection may not respond to antibiotics, hence control of microbial proliferation should be undertaken as source-control measures (physical measures to eradicate a focus of infection and eliminate or treat microbial proliferation and infection) to eradicate the source of infection.[30]

Intravenous fluid treatment: In LMIC settings, fluid bolus therapy is recommended only if all three WHO shock criteria (cold extremities, capillary refill time greater than 3 s and weak or fast pulse) are present (or) if there is hypotension (low systolic blood pressure < 50 mmHg < 1 year, < 60 mm Hg between 1-5 years and < 70 mm Hg > 5 years).[11,31]

The above recommendation stems from the FEAST trial conducted in 3 African countries which found that the 48-hour and 4-week mortality were significantly higher in the fluid-resuscitated group.[31]

In contrast, in settings where intensive care interventions such as ventilation and ionotropic support are available, 40–60 mL/kg isotonic fluid boluses are to be administered during the first hour as increments of 10–20 mL/kg. Thus, as per the SSC, fluid bolus therapy is indicated in pediatric sepsis only if hypotension is present (all settings), along with abnormal perfusion (only in high-income settings with ICU facilities).[11]

Non-invasive serial echocardiography can be used to recognise septic myocardial dysfunction and hypovolemia not apparent on clinical assessment and guide response to therapy by monitoring ventricular function, stroke volume, and systemic vascular resistance index (SVRI). This is critical since high stroke volume and low SVRI with absolute or relative hypovolemia characterises the hyperdynamic state in septic shock.[32]

Based on the available evidence, the SSC in 2020, recommended balanced crystalloids as the first line for fluid bolus therapy in pediatric sepsis instead of normal saline, albeit with low-grade quality of evidence.[11] The European Resuscitation Council in 2021 extended this recommendation into Paediatric Life Support for all critically ill children with circulatory failure.[33]

Between crystalloids and colloids, crystalloids are preferred; and among crystalloids, balanced crystalloids are preferred. The use of normal saline results in reduced bicarbonate concentration, a movement of H+ and K+ out of cells for electroneutrality, and hyperchloremic metabolic acidosis because of its zero (0) Strong Ion Difference (SID) ([Na+] = [Cl−]). SIDs of the balanced crystalloids Hartmann's solution[27], Ringer's lactate[27], Ringer's acetate[25], and Plasma-Lyte[50] are closer to Human plasma[40], unlike normal saline (0).[34–36]

Normal saline should be only preferred in hypovolemic hyponatremia or hypochloremic metabolic alkalosis (due to its higher [Na+] and [Cl−] content) and in patients at risk of increased intracranial pressure such as traumatic brain injury, diabetic ketoacidosis (due to its hypertonicity). Ringer's lactate is best avoided in the latter scenario due to its hypotonicity {osmolarity-Normal saline (308) vs Ringer's lactate (273) vs Human plasma (285 ± 10)}.[11]

In high-income settings, the SSC recommends fluid boluses of 10–20 ml/kg of ideal body weight, up to 40–60 ml/kg over the first hour of management, while dropping the previously recommended "5–10 min" duration.[11,37]

Excessive or repeated fluid boluses may exacerbate sepsis-induced vasodilatation, decreased venous return, capillary leak, interstitial fluid accumulation, pulmonary edema, or hepatomegaly.[38] Higher ICU mortality has been documented with fluid overload, especially over 10%.[39–43] Hence serial monitoring of dynamic indices such as central venous pressure, Pulse Pressure Variation (PPV), and Stroke Volume Variation (SVV) should be used to guide fluid bolus and vasoactive agent therapy.[32,44]

Vasoactive Agents

Persistent shock refractory to IV fluid bolus therapy calls attention to vasoactive agents. Vasoactive agents correct the vascular tone depression, increase preload by recruiting fluids from an expanded venous bed, and improve organ perfusion pressure thereby countering vasodilatation, a distinctive feature of septic shock; hence, SSC experts recommend norepinephrine (NE) as the first-line vasopressor in septic shock.[11]

Norepinephrine is a potent α1-agonist with some β1-adrenergic properties leading to increased venous and arterial tone, increased preload, and increased contractility. NE increases blood pressure primarily through its vasoconstrictive properties but has little effect on heart rate. The diastolic arterial pressure (DAP) is a marker of vascular tone. Below a certain critical autoregulation value of MAP, organ blood flow will decrease along with the decrease in MAP. Autoregulation mechanisms are impaired in

septic shock, rendering vital organs more vulnerable to hypotension.[45] Early NE administration could correct hypotension faster thereby preventing prolonged severe hypotension.[46]

Upon introduction of pressors, monitoring for new-onset/worsening respiratory distress, hypotension, and serial echocardiographic assessments for Left Ventricular (LV) systolic and diastolic function, Right Ventricular (RV) function, and persistent low or high vasomotor tone is essential, since pressors may unveil underlying myocardial dysfunction.[46]

Epinephrine which has α1, β1, and β2 agonist properties, while increasing venous and arterial tone, preload, and contractility like norepinephrine, also increases the heart rate. This could lead to tachycardia, increased myocardial oxygen consumption, lactic acidosis, and hyperglycemia.[47]

The recommended dose for Norepinephrine and Epinephrine, for Vasodilatory shock and Vasoconstrictor shock respectively, is 0.05-0.2 µg/kg/min.[48]

Vasopressin and its analogues are only second-line vasopressors, added to raise MAP to target or decrease NE dosage.[49] Persistent shock despite both norepinephrine and epinephrine infusions must prompt detailed evaluation for underlying pathology. A progressive tapering of catecholamine with regular monitoring may be beneficial and could be initiated for patients who show signs of shock from excess catecholamine.

The two most often used inodilators in pediatric septic shock are Dobutamine and Milrinone. Inodilators increase cardiac output (CO) by increasing heart muscle contraction similar to inotropes. They in addition also decrease systemic vascular resistance (inodilators) and hence the afterload. Dobutamine mainly has strong β1 and some β2 adrenergic receptor effects at low doses. The α1 adrenergic receptor effects at high doses may be superseded by its more prominent strong β1 activity and baroresponse.[50]

Milrinone is a phosphodiesterase 3 inhibitor, which can improve cardiac contractility, increase lusitropic function (improve diastolic relaxation), and decrease SVR with afterload reduction.[51]

If organ hypoperfusion persists after normalizing blood pressure, Dobutamine or Milrinone infusions may enhance cardiac output and microcirculation.

In summary, in Hypotension with vasodilatory shock, Norepinephrine (first-line vasopressor in septic shock) ±Epinephrine is titrated as indicated; whereas for Hypotension with septic myocardial dysfunction (SMD), epinephrine is preferred and norepinephrine considered. If BP is normal with persistent hypoperfusion with or without SMD, the inodilators-Dobutamine or Milrinone are indicated.[48]

RV dysfunction, pneumothorax, pericardial effusion, and high intra-abdominal pressures are possible important causes of Refractory shock and are to be ruled out by periodic clinical laboratory and echocardiographic assessments.[52,53]

Diuretic Use: Fluid overload would warrant diuretic use, only if the BPs are sustained above the 5th centile and there is no requirement for vasoactive drug dose escalation.[54]

Antibiotic Tapering: Broad-spectrum antibiotics should be narrowed down based on trending antimicrobial susceptibility reports/antibiograms.

Role of Mechanical ventilation and intubation: Although a trial of non-invasive mechanical ventilation in children responding to resuscitation would be justified, there is no recommendation for intubation in children with fluid or catecholamine-resistant septic shock. If, however, intubation is inevitable, acute

respiratory distress syndrome (ARDS) treatment recommendations (prone positioning, neuromuscular blockage, high (PEEP) are available.[15]

Patients with RV dysfunction may benefit by avoiding hypercapnia, hypoxemia, and maintaining pH >7.3 in addition to restricting plateau pressures to <25 cmH2O; whereas in subjects with normal RV function, standard lung-protective strategies, VT 5–6 mL/kg and plateau pressure < 30 cmH2O would be preferred.[48]

Role of corticosteroids: The beneficial role of steroids (hydrocortisone plus fludrocortisone vs placebo) in all-cause mortality reduction has been demonstrated in a multicenter, double-blind, randomized trial in adults.[55] However, given that a pediatric retrospective cohort study (RESOLVE)[56] and a meta-analysis (eight small RCTs all before 2009 and in LMICs, 6/8 in dengue shock setting)[57] failed to demonstrate evidence of benefit, and there is no published recent RCT in children, current recommendations do not advocate the use of steroids in cases where fluid and vasoactive medications are able to restore hemodynamic stability. However, steroids may or may not be used if hemodynamic stability is not achieved despite fluid and vasoactive medications.[37,58]

Enteral Nutrition: Early enteral nutrition can be commenced (within 48 hours). Importantly, insulin to target lower blood glucose levels should be avoided.[15]

Correction of Anemia: Seminal studies have provided evidence that certain populations of critically ill children benefit from a restrictive approach for (RBC) transfusion. In critically ill children or those at risk for critical illness, who are hemodynamically stable – (RBC) transfusion is 'recommended' if the Hb concentration is <5 g/dL, 'not recommended' at ≥7 g/dL, and 'reasonable to consider' based on clinical judgment between these values.[59]

Renal Replacement Therapy (RRT): Extracorporeal therapy such as RRT remains the mainstay of treatment for established acute kidney injury (AKI) and to prevent or treat diuretic-refractory fluid overload. Septic shock is the most common cause of AKI in critically ill patients. Several risk factors could contribute, including gram-negative infections, administration of vasoactive drugs, and mechanical ventilation. RRT removes cytokines in sepsis, dialyzable poisons, and toxins, and corrects severe resistant-to-treatment electrolyte disturbances.[60,61]

Extracorporeal Membrane Oxygenation (ECMO): ECMO is a rescue therapy in children with septic shock refractory to all other treatments; the best results for ECMO in sepsis and septic shock have been documented in neonates.[62] For respiratory support venovenous (VV) ECMO and for cardiopulmonary support, venoarterial (VA) ECMO may be applied. For pediatric refractory sepsis, venoarterial (VA) ECMO survival rates of over 60% have been demonstrated. Factors associated with in-hospital death after VA ECMO were high lactate and high creatinine at admission.[63]

Conclusion

Pediatric sepsis and shock have been described from historical times. Yet, actual estimates of sepsis incidence worldwide have been heavily influenced by then-prevailing sepsis definitions, which have evolved considerably over time, culminating in the most recently promulgated Phoenix sepsis score. Moreover, despite intravenous fluids having been advocated for sepsis shock treatment for the last two centuries, there is currently only low-grade evidence for the use of balanced crystalloids in pediatric sepsis shock management, the guideline varying with setting.

Nevertheless, more recent therapeutic interventions such as RRT and ECMO have revolutionized the management of pediatric septic shock. Further research is needed to ensure

fortification/modification of existing guidelines/protocols based on moderate to high-grade evidence, with due pragmatic considerations for resource-poor settings.

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