REVIEW ARTICLE

Advances in the Management of Pediatric Septic Shock: Old Questions, New Answers

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Septic shock in children is associated with high mortality, especially in developing countries. Management includes early recognition, timely antibiotics, aggressive fluid resuscitation, and appropriate vasoactive therapy, to achieve the therapeutic end points. The evidence at each step in management has evolved over the past decade with a paradigm shift in emphasis from a 'protocolized care' to an 'individualized physiology-based care'. This shift mirrors the general trend one observes in critical care with respect to various treatment modalities i.e. moving away from a liberal to a more conservative approach be it fluids, ventilation, transfusion, antibiotics or insulin. The age-old questions of how much fluid to give, what inotropes to start, when to administer antibiotics, are steroids indicated and when to consider extracorporeal therapies in refractory shock are finding new answers from the recent spate of evidence. It is therefore imperative for all of us to be aware of the recent changes in management, to enable us to adopt an evidenced based approach while managing children with septic shock. In this review, we have tried to summarize the key changes in evidence that have occurred over the past decade at various steps in the management of pediatric septic shock.

Keywords: *Blood transfusion, Corticosteroids, Inotropes, Sepsis.*

Pediatric sepsis and septic shock remain a major cause of morbidity and mortality worldwide, despite advances in vaccines, antibiotics and intensive care. Sepsis accounts for about 6 million neonatal and childhood deaths a year, accounting for 60-80% of annual child mortality [1]. It is also one of the major contributors towards increased healthcare utilization costs. Timely management with fluids, vasopressors and antibiotics along with good supportive care has always been the cornerstone of treatment to improve outcomes. However, over the last decade, management of septic shock has undergone a paradigm shift from protocolized guidelines-based approach like early goal-directed therapy to an individualized physiology-based approach. The focus now is also moving away from aggressive fluid and transfusion targets to a more conservative approach. Additionally, more knowledge has been generated in the areas of fluid responsiveness, hemodynamic monitoring and biomarker-based diagnosis of sepsis. In this review, we have tried to summate in a question-answer format some of the key evidence that has emanated out of sepsis-related research and their impact on the existing practice guidelines.

Is early goal-directed therapy still the way forward?

Severe sepsis- and septic shock-related mortality in the absence of a protocolized management prior to 2001 was to the tune of 40-50%. That is when the landmark trial by Rivers, *et al.* [2], by showing a significant decrease in mortality, changed the way septic shock was to be managed over the next several years. They compared a time-bound strategy called the early goal-directed therapy (EGDT), akin to the ones used in acute myocardial infarction and trauma, to the usual care. This was followed by about 70 observational and randomized controlled studies showing a survival benefit. This paved the way for EGDT to be incorporated by the Surviving Sepsis Campaign into the resuscitation bundle, and soon became the standard of care worldwide. EGDT comprises of early recognition of high-risk patients with sepsis, timely administration of appropriate antibiotics, sending appropriate cultures, achieving source control, followed by early hemodynamic stabilization by optimizing preload (central venous pressure targeted with fluids), contractility (inotropic agents) and afterload (mean arterial pressure targeted with vasopressors). The arterial oxygen content is optimized by maintaining hemoglobin targets (blood transfusion and oxygen supplementation), and decreasing oxygen consumption (unloading respiratory muscle load by mechanical ventilation and sedation). The recent American College of Critical Care Medicine/Pediatric Advanced Life Support (ACCM/PALS) guidelines [3] recommend each institution to organize these practice parameters into various bundles like 'recognition

bundle', 'resuscitation and stabilization bundle' and 'performance bundle' for effective delivery and improvement of the process of care of these patients. These practice parameters formed the basis of best practice recommendations for management of sepsis in an intensive care setting until recently, when three large, multicenter, randomized controlled studies failed to replicate the same mortality benefit of EGDT [4-6]. The above trials challenged the necessity of targeting each of the components of the 6-hour resuscitation bundle. Though there were no children enrolled in these trials, they provided compelling evidence that the major components of the 6-h sepsis resuscitation bundle in EGDT does not provide additional benefit over usual care. The three trials independently demonstrated an all-time low mortality and emphasized more on systems-based protocolized approach, to eliminate undue delay in recognition and treatment of sepsis in emergency departments. This marks a new beginning in sepsis care, where interventions remain 'early' and 'goals' remain the same, but the emphasis is more on clinician intuition rather than strict targets for central venous pressure >8 mmHg or $ScVO_2$ >70. Thus, though the current body of evidence points towards a trend for eliminating protocolized approach, it must be individualized and refined to suit the patient physiology and more importantly the setting in which such a patient is treated.

What is the new evidence in relation to fluid resuscitation in septic shock?

Type of fluid

There is no consensus on the type of first-line fluid that should be used during resuscitation of septic shock. Evidence suggests that crystalloids whether balanced or not, are the most preferred. There are increasing reports of hyperchloremia and acute kidney injury when 'chloride liberal' normal saline is used [7,8]. In view of their restricted chloride content and lesser risk of acute kidney injury, currently balanced solutions are being promoted as a better alternative. Hypo-oncotic albumin solutions have also been suggested in patients requiring large volumes for fluid resuscitation. The hydroxyethyl starches have been demonstrated to increase mortality and hence should not be used in patients with septic shock [9]. While we await more answers on the use of albumin and balanced solutions, normal saline remains the standard of care [10].

Volume of fluid

The conventional teaching in septic shock emphasizes the need for aggressive fluid resuscitation to offset the massive capillary leak that is the major culprit for hypovolemia in these children. On the same lines, the current pediatric Surviving Sepsis Guidelines suggest that fluid resuscitation should be aggressive with repeated boluses of 20 mL/kg, so much so that some children may require as much as 200 mL/kg of fluid to achieve therapeutic endpoints [11]. The guidelines also recommend initiation of vasoactive therapy in patients with fluid-refractory shock defined as the presence of persistent signs of shock despite at least 60 mL/kg IV fluid boluses. Though evidence has shown reduced mortality and morbidity when the ACCM guidelines were followed, these recommendations for the volume of fluid resuscitation has emanated mainly from observational studies and expert opinions. Such an aggressive stand on fluid resuscitation in septic shock has recently been questioned by the Fluid Expansion as Supportive Therapy (FEAST) trial [12], which demonstrated increased mortality in children who received fluid boluses as compared to maintenance fluids, particularly in malnourished and anemic children. This study inferred that rapid fluid resuscitation may not be the best therapeutic strategy across the board for all children, especially in resource-limited settings where facilities to provide advanced ventilation and hemodynamic support are inadequate. This study threw open several questions regarding aggressive fluid resuscitation that until a few years back was considered the standard of care. Furthermore, subsequent studies [13-15] also suggested that excessive fluid resuscitation in patients with septic shock is associated with fluid overload, and increased morbidity and mortality.

The optimal volume of fluid resuscitation and the timing of initiation of vasoactive support in order to achieve therapeutic targets in children with septic shock are some other questions for which it is important to seek answers. Restricting maintenance fluids after initial fluid resuscitation and use of diuretics for fluid removal termed as 'de-resuscitation' is a useful strategy associated with increased number of ventilator-free days and shorter length of ICU stay [16]. The results of an ongoing trial [17] that plans to compare a goal-directed fluid-sparing strategy *vs* usual aggressive fluid strategy might provide more knowledge on this issue.

Assessment of fluid responsiveness – what works and what does not?

The clinical signs like heart rate and systolic blood pressure have been found to be poorly predictive of fluid responsiveness. Similarly, static variables like central venous pressure, preload estimates from thermodilution and ultrasound dilution were also poorly predictive of fluid responsiveness. Among the dynamic variables

(which reflect the ventilation-induced variation in stroke volume), respiratory variation in aortic blood flow peak velocity was the only variable which consistently predicted fluid responsiveness in children across six studies with a sensitivity of 92% and specificity of 85% [18]. At the bedside; however, the hemodynamic changes induced during the passive leg raising (PLR) test have been reported to be good predictor of fluid responsiveness in a meta-analysis of 23 trials with a sensitivity of 86% and specificity of 92% [19]. Additionally, these measurements were reliable irrespective of mode of ventilation, type of fluid, PLR starting position, and measurement technique. Studies in children have demonstrated similar effect with the difference in cardiac index/ stroke volume with passive leg raising (ΔCI-PLR or ΔSV-PLR) being good predictors of fluid responsiveness [20,21].

Ultrasound-guided resuscitation of septic shock

The classification of septic shock into 'warm' or 'cold' shock based on clinical assessment is often inaccurate given the complex derangements in myocardial function, vascular tone and distribution of blood flow. Bedside focused echocardiography is complementary to clinical examination as one can visualize the heart and great vessels directly. Ultrasound-guided fluid resuscitation is well established in adults but still in infancy stage in children due to lack of pediatric studies. In a cohort of 48 cases of fluid-refractory catecholamine-resistant septic shock (despite 60 mL/kg of fluid bolus and vasoactive drugs), uncorrected hypovolemia (33%) and decreased cardiac function (39.6%) were identified as causes of hypo-perfusion using focused ultrasound [22]. Also, shock being a dynamic state may swing from cold to warm or *vice versa* in the same child at different time points. A low systemic vascular resistance may masquerade clinically as a cold shock in presence of septic myocardial dysfunction and inadequate fluid resuscitation. Once the stroke volume improves following volume resuscitation and targeted inotrope therapy, the underlying warm vasodilatory state becomes clinically more apparent. This information is difficult to arrive at by physical examination even by experienced clinicians.

Only three to six hours of focused training has been found to be sufficient to infer useful data on volume responsiveness and cardiac contractility. However, the lack of formal training and certification process and limited availability of ultrasound devices restricts its widespread use in resource-limited settings.

Should epinephrine replace dopamine as the first choice of inotrope in fluid-refractory septic shock?

There is a paucity of research regarding the choice of first-line vasoactive drug in children with fluid-refractory septic shock. Two recently published randomized trials report the superiority of epinephrine over dopamine with respect to resolution of shock within the first hour, lower Sequential Organ Function Assessment score on day 3 [23], more organ failure-free days (24 *vs* 20 d; $P = 0.022$), and lower mortality [24]. The recent ACCM/PALS guidelines support use of peripheral infusion of epinephrine 0.05– 0.3 mcg/kg/min as the first line inotrope in fluid refractory shock based on the recent evidence [3]. As regards the safety of peripheral administration of inotropes, the recent literature suggests that the short-term infusion of vasoactives through peripheral cannula is safe in a closely monitored setting and can act as a bridge before establishment of a central venous access [25]. However, dopamine being the time-tested inotrope can be administered safely through a peripheral line in a resource-limited setting, and given the limitations of these trials, it continues to be first line inotrope to be used in day to day clinical practice. More studies are needed to identify patients who may not respond to dopamine and further individualize the inotropic choice.

Does first-hour antibiotic matters anymore?

Early identification and treatment with appropriate antibiotics are considered the two most important cornerstones in management of children with sepsis. A delay in administration of appropriate antibiotic was shown to be associated with an increased mortality of 7.6% for each hour delay, 8.5 % for a 6-hour delay and 8% increase in progression to septic shock for every hour delay [26-28]. Two retrospective studies in children with sepsis reported an increased odds of ICU and 1-year mortality for a delay of >3 hours for first or appropriate antibiotic administration [29,30]. The emphasis of early and appropriate antibiotics in sepsis only got cemented further on. However, a recent meta-analysis of 8 studies including 11,017 patients, evaluating the timing of antibiotic administration after sepsis/septic shock recognition with mortality has brought out evidence to the contrary [31]. There was no significant increase in mortality with every hour delay from less than 1 hour to more than 5 hours from the time of identification of septic shock [31]. Despite this controversial evidence, early administration of antibiotics sounds more rational, and therefore continues to be recommended and followed.

Should steroids be used in septic shock?

The utility of steroids in sepsis lacks definitive evidence and consensus. Though the pathophysiological basis for starting steroids like sepsis-induced adrenal suppression,

inotrope unresponsiveness, and the exaggerated inflammatory response is strong, it is not backed by strong evidence. Despite this, the surviving sepsis campaign guidelines state that hydrocortisone should be considered for a catecholamine-resistant septic shock with suspected or proven adrenal insufficiency. Adrenocorticotropic hormone stimulation test to prove adrenal insufficiency is however not routinely recommended. The adjunctive data from RESOLVE study [32] reported no obvious hemodynamic benefit or difference in outcomes with the administration of steroids in pediatric septic shock. Similarly, a systematic review [33] of 8 studies failed to prove an improvement in mortality or modification of shock duration, although the review was limited by small poorly performed trials. Furthermore, two recent retrospective cohorts in pediatric septic shock not only failed to demonstrate a benefit with steroids but showed an increase in new culture positivity rate, prolonged duration of antibiotic therapy and increased mortality [34,35]. A retrospective analysis of clinical practice revealed that the use of stress dose hydrocortisone correlated with severity of illness irrespective of the random serum total cortisol levels [36]. Notably, the outcomes like PICU and hospital length of stay and ventilation-free days were worse with the use of stress dose hydrocortisone irrespective of random cortisol levels. A randomized controlled trial for steroids in pediatric septic shock is much awaited to resolve this controversy. A feasibility study [37] of performing such a trial revealed that the major barrier was the high empiric usage of steroids by physicians.

Is there a change in blood transfusion targets in septic shock?

ACCM-PALS guidelines recommend a target hemoglobin of 10 g/dL to achieve adequate tissue oxygen delivery in children with septic shock [38]. This target however lacked a consensus. Studies in critically ill adults and children were moving away from liberal to restrictive transfusion strategy to prevent transfusion-related complications [39,40]. In this context, the need to maintain target hemoglobin of 10 g/dL in septic shock seemed out of place and needed a relook. A multicenter randomized trial evaluating ideal hemoglobin target in patients with septic shock, allocated to lower (Hb ≤7.0 g/dL) and higher thresholds (Hb ≤9.0 g/dL), demonstrated no significant difference in the 90 days mortality, rate of ischemic events or use of life support among these groups [40]. Furthermore, two recent trials [4,5] compared usual care arm with a mean Hb of 7.5 g/dL against EGDT arm with Hb of 10 g/dL. There was no difference in outcomes among these groups suggesting that blood transfusion does not have any added benefit as part of a protocolized therapy.

Should biomarker be routinely used to differentiate SIRS from sepsis?

Sepsis is defined as systemic inflammatory response syndrome (SIRS) with suspected or proven infection. However, it is difficult to differentiate it clinically from other causes of SIRS. Various biomarkers like C-reactive protein, procalcitonin, interleukin-6, human neutrophil gelatinase have been evaluated for their utility in diagnostic, prognostic and therapeutic monitoring. Procalcitonin is a specific marker for bacterial infection and helps in diagnosis and deciding duration of antibiotics. Serial trends rather than a single value helps in judging the clinical response to therapy. No single biomarker has the best diagnostic accuracy to differentiate sepsis from other inflammatory disorders.

Recently, in the Pediatric sepsis biomarker risk model (PERSEVERE), a combination of five biomarkers was found to reliably identify children at risk of death and those with higher illness severity from pediatric septic shock [41]. Such biomarker-based risk stratification could possibly pave way for assessing the efficacy of less proven therapies. Also, three gene expression diagnostics, based on genome-wide expression, that could help differentiate patients with sepsis from those with noninfectious inflammation have been developed and found to be useful [42]

Utility of extracorporeal life support therapies

Shock persisting despite optimization of preload, vasoactives, source control, appropriate antibiotics and correction of identifiable factors (intraabdominal hypertension, pneumothorax or pericardial tamponade, adrenal insufficiency) may require Extracorporeal membrane oxygenation (ECMO) therapy. A retrospective analysis of a database, revealed utilization of ECMO in 2.3%, renal replacement therapy in 6% and combination of both in 1% of children with septic shock [43]. The utilization of extracorporeal therapies was higher in those with multi organ dysfunction syndrome (MODS). Although mortality rates of about 48% have been reported for such children on ECMO [43], recent trends have been very encouraging; survival rates on ECMO of about 70-75% have been reported by experienced centers [44,45].

The concept of 'de-resuscitation' is gaining momentum, as evidence has clearly shown that fluid overload acts as a 'third hit' phenomenon resulting in increased mortality due to organ dysfunction. Therefore, after initial resuscitation and stabilisation, transition to a negative fluid balance needs to be aggressively achieved

KEY MESSAGES

- Emphasis on systems-based approach, to eliminate undue delay in recognition and treatment of sepsis in emergency departments.
- Focus on 'individual physiology' and the setting in which the patient is being treated.
- 'Optimal' fluid resuscitation, timely initiation of vasoactive support to achieve therapeutic targets followed by early targeted 'de-resuscitation'.
- Dynamic variables of fluid responsiveness (which reflect the change in cardiac output with respirophasic variation or during passive leg raising test) are more useful.
- Epinephrine is gaining momentum over dopamine as the first line inotrope.
- Restrictive transfusion targets are equally efficacious compared to higher targets.
- Extracorporeal membrane oxygenation (ECMO) and Continuous renal replacement therapy (CRRT) may be employed to improve outcomes in refractory shock and therapeutic plasma exchange to reverse Multi-organ dysfunction syndrome (MODS).

with restricted maintenance fluid, targeted diuresis or RRT. Use of continuous renal replacement therapy (CRRT) in severe sepsis not only helps in fluid removal but also in removal of toxic metabolites and inflammatory mediators. Early institution of CRRT in patients with MODS has been shown to reduce mortality [46,47] and hence the recent ACCM/PALS guidelines recommend use of either diuretics, peritoneal dialysis or CRRT in patients with fluid overload of more than 10% and impaired renal function [3].

Therapeutic plasma exchange (TPE) is indicated in thrombocytopenia associated multiorgan dysfunction (TAMOF) in which low ADAMTS-13 levels lead to widespread intravascular microthrombi and multiorgan dysfunction [48]. TPE in such patients may replenish ADAMTS-13 protease which helps cleave the ultra-large von Willebrand factor multimers and resolve organ dysfunction. A meta-analysis of adult trials reported a lower mortality with plasma exchange and hemoperfusion in patients with sepsis [49]. Similar beneficial effect has been demonstrated in a pediatric case series where TPE was shown to be an useful adjunct to reverse TAMOF [50]. Combining TPE with CRRT in an extracorporeal life support circuit in sepsis induced MODS was found to have high survival of about 71% [51]. TPE may therefore be tried as an adjunct to reverse MODS, after initial resuscitation.

CONCLUSION

Current evidence is moving away from protocolized early goal-directed therapy and entering a new age which emphasizes more on individualized approach to the treatment of septic shock. We are moving away from aggressive fluid resuscitation and liberal blood transfusion to a more restrictive regimen. Echocardiographic and Doppler based assessments of respirophasic variations in cardiac output for assessment of fluid responsiveness have replaced the static parameters like heart rate, blood pressure and central venous pressure. We are probably close to dismantling dopamine as the first choice inotrope in pediatric septic shock. We, however, await more answers on first hour antibiotics, type of fluids and steroids in septic shock. Extracorporeal therapies like ECMO, CRRT are being increasingly used for patients with refractory shock, resulting in an improved survival. Further research on biomarker-based risk stratification could possibly pave way for the assessing efficacy of less proven therapies.

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