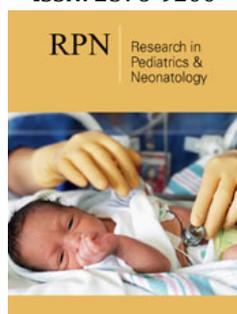


## Restrictive Versus Liberal Fluid Bolus Therapy in Pediatric Septic Shock: Should It Be Debated

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### Opinion

To date, sepsis has contributed significantly to the child mortality rate, which is around 8.9% in developed countries to 14.2% in developing countries [1-3]. The most common cause of death (23.1-34.6%) was refractory shock [2-4], of which most occurred in the first 3 days [5]. An additional hour of persistent shock was associated with >2-fold increased odds of mortality [6]. This shows that early treatment of septic shock is one of the keys to reduce sepsis mortality.

Fluid bolus is the main therapy for pediatric septic shock. International consensus recommends fluid bolus therapy (FBT) 10-60mL/kg in the first hour, accompanied by monitoring for hepatomegaly or increased work of breathing [7]. Resuscitation practice consistent with these guidelines can reduce mortality [6,8,9]. Current international guideline was based on some outstanding pioneer studies; unfortunately, all of them are retrospective observational and single-center studies, with a small sample size. Thus, it needs to be reevaluated whether the effectiveness of FBT in daily practice, certainly has a causal relationship with patient survival, or it was just a representation of lower severity illness in the survivor group.

FEAST (Fluid expansion as Supportive Therapy) trial, the first randomized control trial (RCT) study, with many subjects (3141 subjects) and multicenter in Africa, became the starting point for re-evaluation of FBT in recent years. In subjects with severe infections accompanied by impaired consciousness, respiration and perfusion, this study showed FBT of normal saline or 5% albumin given 20-40mL/kg in 1 hour increased mortality compared to maintenance fluid administration (RR=1.45, 95% CI, 1.13 -1.86; p=0.003) [10]. Although some conditions were considered as research limitation (absent mechanical ventilation, positive malaria and anemia [Hb<5g/dL] in most subjects), inevitably these results sparked debate which underlies several studies or clinical trial to compare the efficacy of restrictive and liberal FBT.

Before determining its effect on the outcome, it is necessary to take into consideration what is the definition of "restrictive and liberal"? Is it based on the volume of each bolus, the total volume of resuscitation, the total daily volume, or the rate of delivery? This must be established in order to produce same operational definition of the study. This definition is also important to determine the factors that most influence the patient's outcome.

A pilot study in UK compared bolus volumes of 10mL/kg (maximum 500mL per bolus) and 20mL/kg (maximum 1000mL per bolus) in 15 minutes. The maximum volume in 4 hours was 120mL/kg. As a result, the total volume of resuscitation in the restricted group was lower than conservative (14.5% vs 25.7mL/kg, p <0.001); however, there were no differences in mortality, length of PICU and hospital stay, and PICU free days in 30 days [11]. It has to be noticed that this study conducted in the developed countries with adequate facilities and low disease severity. Moreover, the total volume of conservative group resuscitation was 20.7mL/kg in the first hour and 25.7mL/kg in 4 hours; much less than the FBT volume in international guidelines. Consequently, the results could not simply generalize in the daily practice.

Another study in the adult population with septic shock compared the restrictive ( $\leq 60$ mL/kg in 72 hours) and conservative groups (no volume limit). Similar to studies in children,

there were differences in total fluid volume in 72 hours between the restrictive and conservative groups (47.1mL/kg vs. 61.1mL/kg, respectively;  $p=0.01$ ); however there were no differences in mortality, incidence of organ failure, ICU and hospital length of stay, or serious adverse effects within 30 days [12]. The 72 hour fluid volume in this study was far less than the international guidelines and several previous studies, including: Rivers (168mL/kg) , [13] Process (108-130mL/kg), [14] Promise (98mL/kg), [15] or arise (108-109mL/kg) [16]. The total volume in 72 hours consisted of resuscitation and non-resuscitation (maintenance) fluids. This revealed that organ perfusion may still be adequate with a small volume of resuscitation, because patients still get additional maintenance fluid afterwards.

Designed to compare restrictive and liberal FBT, however those two studies were unable to solve the problem because the FBT volumes given were less than international guidelines and daily practices. In the pediatric studies, low severity illnesses might be the reason why such patients responded to the small volumes of FBT [11]. In adult studies, unblinded intervention methods and a tendency to limit the FBT volume in daily practice cause both groups got smaller volumes [12]. Therefore, it seems that so far there has not been an adequate study to determine the effect of different FBT volumes on patient outcomes.

The rate of fluid delivery also must be considered, since some study demonstrated its impact to the outcome. Two RCTs in a population of septic shock children in India, suggested rapid fluid bolus administration is associated with increased morbidity. The first RCT stated that the incidence of liver enlargement was greater in group who received 40mL/kg in 15 minutes than the 20mL/kg in 20 minutes (70% vs 35.6%, respectively;  $p < 0.01$ ) [17]. The second study showed a reduced risk of mechanical ventilation and increased oxygenation index (OI) in the bolus group 15-20 minutes compared to 5-10 minutes (43% vs 68%; relative risk, 0.63; 95% CI, 0.42–0.93) [18]. Nevertheless, single-center studies and small sample size may be the limitation of both studies.

Increased morbidity and mortality after FBT are associated with impaired respiratory and neurology function. In addition, it was caused by hyperchloremic acidosis, decreased relative hemoglobin levels, and the possibility of ischemic-reperfusion injury [19-21]. Several studies have shown post-FBT hypervolemia damages endothelial glycocalyx (EGL) integrity thereby increasing vascular leakage [22,23]. Leakage of fluid into the interstitial space leads to edema and organ dysfunction [24]. It should also be noted that the risk of mortality increases with the severity of shock or if there are accompanying disorders, for example: respiratory and neurological disorders [21]. Therefore, it seems that the outcome of pediatric patients with septic shock is not only determined by volume or rate of fluid delivery. The severity of the disease and the amount of organ dysfunction also determine the patient's response to FBT and its outcomes.

Referring to the term "one size does not fit all", the use of FBT should consider the physiological factors of each patient. Not all patients respond well to large volumes of FBT, because there

is a risk of volume overload and vascular leakage. Vice versa, patients who respond to FBT will face the risk of hypoperfusion if restricted FBT volume is given. The Starling curve has explained that stroke volume (and cardiac output) is strongly influenced by the level of myocardial contractility [25,26]. In case of hypotensive shock or septic cardiomyopathy, it can be predicted that patients tend to be refractory to FBT and need vasoactive drugs. Septic cardiomyopathy itself is associated with increased mortality [27,28]. An observational retrospective study in Dengue shock syndrome (DSS) showed a decrease of myocardial contractility in most subjects. Accordingly, the mortality in restrictive FBT group was 53% lower than the liberal group, suggesting high amount of fluid volume may harmful in case of myocardial depression [29].

For this reason, giving FBT in a septic shock child should not merely consider the volume and rate of delivery. Measurement of myocardial contractility should be the main parameter to determine the appropriate FBT methods. Noninvasive techniques for measuring left ventricular systolic function by echocardiography or inotropy index by Doppler (USCOM) provide a lot of information about myocardial contractility under emergency conditions [30,31]. It is also important to measure fluid-responsiveness as a surrogate marker of FBT. Passive leg raising (PLR) and respiratory variation in aortic blood flow peak velocity are the most reliable methods in pediatric patients [32]. If myocardial contractility and fluid-responsiveness measurements become part of the protocol for managing septic shock, FBT can be adjusted to each patient's condition. Then, it will be unnecessary to debate the efficacy between restrictive and liberal FBT.

Furthermore, the same operational definition of volume and rate of delivery must be applied in the next studies. Variables that affect the outcome -such as: illness severity at presentation, time to obtain emergency management, time to get vasoactive agents, speed of antibiotic administration, availability of mechanical ventilation and hemodynamic support, daily fluid balance, and causative microorganisms- should also be analyzed in studies of pediatric septic shock. In this fashion, it provides comprehensive datas that important in developing a septic shock protocol.

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