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Editorial

Fluid Balance in Sepsis: Have We Resolved the Controversies?

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Sepsis is a global challenge with approximately 20-30 million cases per year, world-wide. The mortality due to septic shock is very high and have ranged as high as 50%. The cost associated with management of severe sepsis and septic shock can impose a significant financial burden to the countries health care system [1-4]. Despite hundreds and thousands of articles published and billions of dollars spent in the sepsis research world-wide, the management of sepsis remains focused on fluid resuscitation, antibiotics administration, source control and use of vasopressors. Despite significant research, the management of fluid balance has remained controversial at the best. In 2001, Mannuel Rivers from Michigan came up with early-goal directed therapy (EGDT) which formed the basis of the sepsis management for almost a decade and formed the basis for Surviving Sepsis Campaign. It emphasized, on early placement of SvO_2 Catheter placement, fluid therapy directed based on achieving mean arterial pressure (MAP) and central venous pressure (CVP) and also potential for PRBC and inotrope use. Over the years, this was publicized and carried out as the holy grail in the management of the patient with sepsis. Regulatory agencies as well as the hospital system jumped on it, despite very little data to support it [4-9]. Mortality for sure improved, with recognition of issues with early diagnosis and treatment. The credit was given to EGDT for improvement in the mortality [2,3]. Over the years, the data started emerging on concrete role of early appropriate antibiotics in the management of sepsis. The early aggressive fluid resuscitation bolus dose changed from 20 ml/kg to 30 ml/kg from 2004 to 2012 surviving sepsis guidelines [3,4]. In the interim, the role of SVO2 catheter, vasopressin, central venous catheter, transfusion and inotrope use came in questions and were proven not to be of beneficial as stated in EGDT or so-called sepsis bundle. The fluid resuscitation and bolus therapy were still pushed, though data were emerging that patient who have received higher volume had the higher mortality (the issue was dragged on as if it is overall fluid balance or early fluid bolus. The early bolus and resuscitation were felt to be of beneficial, especially in patients who received the volume in first three hours vs. the second three hour of the sepsis bundle of EGDT as study shown by Lewis and Ramar., *et al* [10].

To resolve the issue of fluid resuscitation in sepsis, ProCESS (USA), ProMISe (UK) and ARISE (Australia/New Zealand) trial were undertaken. All these three, multi-center randomized trials showed no difference in mortality between EGDT based on protocol versus standard therapy. The believers of Rivers trail and the EGDT still promoted the EGDT as it has shown to have benefit in mortality since surviving sepsis campaign and EGDT has been implemented based on several small non-randomized trails [11,12].

In the interim, the data emerged and suggested the role of early appropriate use of antibiotics as the major component in improving the mortality. Another study (FENICE) trial, which was fluid challenge in intensive care unit, also raised an important point that methods used to predict the fluid responsiveness were also not routinely used and patient who were fluid responsive or fluid un-responsive received the same amount of fluid. This raises a big question and emphasized the education and training in the diagnostic modality in the assessment of fluid balance.

As for the liberal versus restrictive fluid resuscitation, the only randomized trial to address this study so far is from African country among children (FEAST) trial. This trail was conducted among children with severe sepsis with either 40ml/kg of saline or 4% albumin when compared with no volume resuscitation. The trial was stopped early showing 40% increase in mortality among both volume resuscitation arms [13,14].

To resolve this challenging and controversial issue, The Heart, Lung and Blood Institute and the Early Treatment of Acute Lung Injury Trial Network developed the CLOVERS trial enrolling more

than 40 centers to address this issue, comparing liberal and resuscitative strategy for the first 24 hours of septic shock. The liberal strategy will consist of IV fluid management similar to that of usual care group as in ProCESS, ARISE and ProMIse trial and restrictive strategy will consists of early vasopressor initiation after the initial fluid bolus of 3L with additional fluid administered only for the signs of intravascular volume depletion [14]. We hope that this will help address the issue of fluid balance and administration among septic patients. The author of this editorial still feels and believes that till the time we cannot address and find an easy and effective method and technology to accurately assess the volume status and differentiate between the fluid responsive and fluid un-responsive patients, we still will be circling back to the same issue.

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