A volume responsiveness guided fluid resuscitation strategy for sepsis and septic shock

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**Introduction**

Sepsis, defined as: “life threatening organ dysfunction caused by dysregulated host response to infection” is one of the leading cause of mortality worldwide(1). Sepsis is recognized to encompass a wide range of cardiovascular derangements resulting in tissue hypoperfusion and life threatening organ dysfunction(1–3). For the last decade, international guidelines have focused their attention on achieving optimal tissue/organ perfusion as one of the key mechanisms to counteract the fatal derangements characteristic for this condition(4–6). Modulating intravascular fluid volume, vascular tone and cardiac function by means of fluid, blood and vasopressor infusion has been established as the cornerstone of resuscitation for patients with sepsis and septic shock(4–7).

While optimizing tissue perfusion and oxygen delivery is accepted as a fundamental principle for resuscitation in sepsis; clinical markers to guide fluid transfusion and the means of achieving resuscitation goals remain controversial(8–15). Original study by Rivers et al. was the first to introduce the concept of Early Goal Directed Therapy, the first protocolised care for sepsis that showed a decrease in 28 and 60 day mortality (RR 0.58 (0.39-0.87) p=0.01 and RR 0.67 (0.56-0.96) p=0.03 respectively) compared to a standard therapy group(8). These results were further supported by a multi-center randomized controlled trial(9) and eventually was adopted by the international guidelines for the management of sepsis and septic shock(4).

Since then, static endpoint guided aggressive fluid transfusion, 30 ml/kg within the first 3 hours of care with continuation of fluid resuscitation aiming to achieve

1. central venous pressure of 8-12 mm Hg and
2. Mean arterial pressure ≥ 65 mm Hg
3. Urine output ≥ 0.5 ml.kg.hr
4. Superior Vena Cava oxygen saturation (ScVo2) or mixed venous oxygen saturation (SVo2) of 70 or 65% respectively

has become the cornerstone for fluid transfusion in septic patients.

Although adherence to early goal directed therapy bundle has resulted in a decrease in mortality from sepsis worldwide, it is unclear whether the reduction was attributed to aggressive fluid transfusion or adherence to the early goal directed therapy bundle as a whole.(13) Recently, 3 large multi-center randomized controlled trials, a meta-analysis of early goal directed therapy and a number of clinical reviews have questioned the scientific validity of original Rivers trial and the benefits anticipated from aggressive fluid transfusion(10–14,16). In contrast, emerging body of evidence supports volume responsiveness guided fluid resuscitation strategy as a more effective and a less harmful strategy for resuscitating patients with sepsis and septic shock(17,18); volume responsiveness was defined as an increase in stroke volume by 10-15% after 200-250 ml fluid bolus(19).

**Physiology pertinent to sepsis and fluid resuscitation**

To achieve resuscitation goal of increased organ perfusion and oxygen delivery, fluid transfusion should increase stroke volume. According to Frank-Starling principle, considerable increase in stroke volume is seen until an optimal ventricular preload value is achieved after which, further increases in preload induce negligible changes in stroke volume and a large increase in extra vascular lung water; which was demonstrated to be an independent predictor for mortality(20–22) Therefore in order for fluid transfusion to be effective, ventricles must be functioning on an ascending limb of frank starling curve. (Figure 1.)
In closed, cardiovascular system cardiac output = venous return. In his landmark study Guyton defined venous return gradient (pressure difference in mean systemic pressure (Pms) and right atrial pressure (Pra)) to be the governing force for venous return \(^{(23)}\). This concept could easily be grasped using Hagen-Poiseuille’s law, which states that flow \((Q)\) equals to a pressure difference between upstream and downstream pressures divided by the resistance in the system.

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Q = \frac{P_1 - P_2}{R}
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In this equation Pms and Pra are upstream and downstream pressures respectively.\(^{(24)}\) Interestingly fluid transfusion doesn’t increase Pms and Pra in a uniform fashion\(^{(25,26)}\). Due to restraining effect of pericardium, heart compliance is considerably lower than the compliance of venous system, and therefore fluid over-transfusion increased Pra more than Pms, decreasing venous return gradients, acting as a congestant for forward flow and eventually compromising microcirculation\(^{(25,26)}\). Therefore, as expected, patients who responded to fluid resuscitation, increased their venous return gradient, unlike patients not responsive to fluid therapy\(^{(17)}\). Based on two physiologic mechanisms discussed above, in order for a fluid transfusion to be effective in achieving resuscitation goals 1. ventricles should be operating on an ascending portion of a frank starling curve and 2. Fluid transfusion should increase venous return gradient. Logically, only those who are assessed to be fluid responsive should be treated with fluid transfusion\(^{(27–30)}\).

**Deleterious effects of aggressive fluid resuscitation in patients with sepsis and septic shock**

Achieving and maintaining supra-normal central venous pressure not only acted as a congestant to venous return but also increased the release of natriuretic peptides\(^{(3)}\). Natriuretic peptides play an important role in sepses induced increase in vascular permeability and tissue edema. By accumulating or mobilizing blood from compliant splanchnic veins, normal central venous pressure is expected to be seen during compensated hypovolemia, normovolemia and compensated hypervolemia.\(^{(31)}\) Guiding fluid resuscitation based on central venous pressure measurements is scientifically flawed.\(^{(31)}\) Central venous pressure was shown to have no prognostic value in determining circulating blood volume and predicting fluid responsiveness in septic patients with urea under the receiver operator characteristic curve of about 0.5 \(^{(32–34)}\). Between low and high central venous pressure groups, high central venous pressure measurement was the only significant predictor for impaired microcirculatory flow, with no statistically
significant association with differences in mean arterial pressure, cardiac index and perfusion pressure. Using ScVO2 measurements to guide fluid therapy was demonstrated to have no beneficial effect on improving outcome, but rather increased healthcare associated costs and length of intensive care unit stay.

Fluid loading per early goal directed therapy guideline, was associated with fluid overload and increased mortality. Most influential data regarding deleterious effects of large fluid boluses came from ‘Fluid Expansion as Supportive Therapy (FEAST)’ study. The only randomized controlled trial comparing fluid boluses with conservative fluid management strategy in treatment of septic shock. This multi-center, randomized, controlled trial assessed 48 and 4 week mortality rates in children between 60 days and 12 years, presenting with septic shock in Africa, treated either with fluid bolus (20-40 ml/kg in 1 hour, with additional 20 ml/kg if shock persisted) or maintenance fluid therapy (2.5-4 ml/kg/hr). At the fifth interim review, based on the data collected from 2995 children, study committee, decided to halt the trial due to statistically significant increase in mortality risk in fluid bolus group, RR 1.45; 95% CI, 1.13 to 1.86; P=0.003. Reanalysis of the study by the authors found that mortality difference between bolus and control group correlated well with increasing severity of the condition, highest being in patients presenting with shock, acidosis and respiratory derangement and in patient with combined shock and acidosis. Interestingly 48 hour mortality was significantly higher in fluid non-responders compared to fluid responders, both groups having significantly higher mortality at 48 hour point compared to no-bolus group. In contrast, patients presenting with respiratory or neurologic abnormality alone and/or less severe shock had lower mortality difference between bolus and no-bolus groups. Most importantly, cardiovascular collapse contributed to increased mortality in bolus group the most. Although some concerns exist regarding the generalizability of the study, particularly in “developed” countries, the results presented in this exceptionally well designed study and its re-analysis support previously discussed physiologic bases of fluid resuscitation and come in agreement with accumulating evidence on deleterious effects of ‘unguided’ fluid boluses. Particularly by showing that

1. The importance of ‘guiding’ fluid therapy increases in line with the severity of shock, questioning our long standing belief that fluid boluses are self-evidently beneficial, especially in those with severe shock.
2. Treating fluid non-responders with fluid boluses increases mortality more than in patients who are fluid responsive, once again highlighting the importance of guiding fluid therapy.
3. Fluid boluses increase mortality by inducing cardiovascular collapse, possibly by exacerbating sepsis induced diastolic dysfunction.

For decades it has been known that sepsis and septic shock was associated with left ventricular systolic dysfunction, which paradoxically predicted increased survival, mechanism of which still remains unclear. But not until recently has adequately powered study addressed the issue of diastolic dysfunction caused by sepsis. In a prospective cohort study 239 patients presenting with sepsis or septic shock were analyzed using echocardiography. Study revealed that about 40% of patients had isolated diastolic dysfunction, while 14% was diagnosed with both systolic and diastolic dysfunction. Fluid boluses in this patient population increased central venous pressure with decrease or no change in stroke volume index; fluid boluses in patients with non-compliant heart increased sepsis induced pulmonary congestion, tissue edema and risk of death.

Luminal side of vascular endothelium is covered by a complex layer of endothelial glycocalyx, mainly functioning as a vascular permeability barrier. Recent study done on patients with good cardiovascular health has demonstrated that volume loading with 20 ml/kg induced significant increase in release of atrial natriuretic peptide. As shown in the study, hypervolemia induced increase in natriuretic peptides demonstrated the ability to shift fluid from intra to extravascular compartment by directly disrupting endothelial glycocalyx. Atrial natriuretic peptide induced shedding of endothelial glycocalyx could be one of the mechanisms of tissue edema in patients with sepsis and positive fluid balance. In light of this finding transfusing fluids to only selected patient population, identified as fluid responders seems particularly important.
While great number of patients with sepsis and septic shock is identified to be fluid non-responsive (15)(39), pursuing aggressive fluid resuscitation strategy as recommended by early goal directed therapy not only subjects them to harmful consequences of fluid overtransfusion, but could also considerably delay the administration of norepinephrine. It has been shown that early initiation of norepinephrine infusion strongly predicted survival (40). By selectively activating alpha adrenergic receptors on venous capacitance vessels, norepinephrine effectively mobilized blood from skin and splanchnic circulation while at the same time decreasing resistance to venous return through beta 2 adrenergic receptor stimulation (31). Through the mechanism described above norepinephrine significantly increases venous return gradient by selectively increasing mean circulatory pressure with no measurable change in right atrial pressure and positively effects microcirculation, largely reversing the disarrangements caused by sepsis and septic shock. Therefore, patients identified as fluid non-responders, could greatly benefit from early norepinephrine infusion, while avoiding deleterious effects of unneeded fluid over-transfusion.

**Conclusion**

The data of basic science and clinical trials show that in a great number of cases, aggressive fluid transfusion can be counterproductive for achieving resuscitation goals in patients with sepsis and septic shock. Large number of septic patients are not responsive to fluid therapy and aggressive fluid resuscitation carries a considerable risk of increasing mortality in these patient population. Central venous pressure and venous oxygen saturation demonstrated to have no predictive value in guiding fluid therapy and improving outcome. Assessing fluid responsiveness allows physician to differentiate fluid responsive patients from fluid unresponsive ones and guid fluid transfusion accordingly; avoiding potentially fatal over-transfusion and allowing early initiation of norepinephrine infusion. Emerging body of evidence has created a fertile ground for adequately powered study to assess the benefits of fluid responsiveness guided fluid management strategy.

**References:**


