Editorial

Aristotle and the art of fluid resuscitation in sepsis

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"It is better to rise from life as from a banquet—neither thirsty nor drunken." —Aristotle

Sepsis is a common and commonly fatal condition, leading to significant mortality in hospitalized patients, particularly in intensive care units (1). The presentation of sepsis is variable, and the people it affects are diverse, which has created much debate as to the best approach to reduce morbidity and mortality. It is well documented that early intervention with aggressive supportive care, with an emphasis on appropriate antibiotic administration, source control, and volume resuscitation reduces mortality and improves outcomes. In recent years, we have discovered that some of the interventions which had previously been accepted as beneficial in severe sepsis and septic shock have either been found to be ineffective or potentially harmful (2-6). The available evidence has now coalesced largely around early and appropriate antibiotic administration, source control when possible, and volume resuscitation as the most beneficial interventions.

Early and effective fluid resuscitation remains a cornerstone of sepsis therapy, and it is known to reduce mortality and improve outcomes. In a recent meta-analysis of early goal-directed therapy (EGDT) for septic shock, both the usual care and EGDT treated patients received the same amount of volume during the resuscitation, on average. However, in the usual-care groups across the three trials studied, the volume of IV fluid resuscitation was based on the best judgement of the bedside clinician, rather than a protocol (6). Without a set protocol to drive fluid administration, such as that proposed by Rivers *et al*. in 2001, the amount of fluids needed for resuscitation in sepsis is open for debate, and there is no clear guideline as to how much fluid is harmful or effective (7).

It is in this context that Sakr *et al*. describe the results of an international cohort of septic patients receiving fluid resuscitation in sepsis, entitled "*Higher Fluid Balance Increases the Risk of Death from Sepsis: Results from a Large International Audit*." This study was designed to investigate the hypothesis that a positive fluid balance in septic patients after the initial 24-hour resuscitation period would be independently associated with mortality. In the study, patients were stratified according to quartiles of cumulative fluid balance at 24 hours and then at 3 days following intensive care unit (ICU) admission. They found that higher cumulative fluid balance at day 3, but not within the first 24 hours, following ICU admission was independently associated with an increased risk of mortality. Of 1,808 patients studied, 60.7% had septic shock. The overall ICU mortality rate was 27.6%, with a hospital mortality rate of 37.3%. This is somewhat higher than other global and regional estimates of mortality from sepsis, with a recent global estimate of mortality at 17% for sepsis and 26% for severe sepsis over the decade of 2005–2015 (8). The patient population was largely medical, but did include approximately one third surgical patients. Illness severity scores were similar across all groups, but were higher in those who received a greater volume of fluid following ICU admission. Comorbidities were similar across all groups of patients. Most infections were respiratory in nature, but abdominal infections became increasingly prevalent

as the total fluid balance increased. Additionally, septic shock was more common in those patients with the greatest fluid balance following ICU admission. The cumulative fluid intake was similar in survivors and nonsurvivors within the study, but fluid output was less in nonsurvivors, leading to a more positive fluid balance in those patients. This difference was more pronounced on the third day following hospital admission. They observed a stepwise increase in the risk of death with increasing fluid balance at the 3-day mark, but not in quartiles of 24 hours following hospital admission. These findings further bolster the prevailing evidence that overzealous fluid administration to patients in sepsis may ultimately be detrimental. Perhaps the most well-known evidence to this effect is supplied by the Fluids and Catheters Therapeutic Trial (FACTT) trial, which demonstrated that conservative strategies in fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing non-pulmonary organ failure (9).

While a judicious approach to fluid administration in sepsis is warranted, we believe that a cautious approach to these data and their implications is necessary to ensure that patients receive appropriate volume resuscitation and are not under-treated. One commonly encounters an over-abundance of concern regarding volume resuscitation in the settings of heart failure, chronic kidney disease, or other comorbid conditions which may predispose patients to volume overload. These concerns often lead to under-resuscitation and poor initial therapy with IV fluids, prolonging illness and worsening outcomes in general. Microcirculatory derangements are common in sepsis, and likely play a pivotal role in the development of organ dysfunction, due to the role these derangements play in creating tissue hypoxia. Perfusion at the microcirculatory level is known to be altered in patients with sepsis, characterized by a decrease in vascular density as well as an increased number of capillaries with dysfunctional or absent flow (10). While no therapy has been proven to specifically increase microcirculatory flow, it is known that fluid resuscitation does aid in improvement, regardless of macrocirculatory or hemodynamic status (11). Poor microvascular perfusion is also a predictor of outcome in severe sepsis, with one study identifying the proportion of perfused small vessels in patients as an independent predictor of outcome in severe sepsis (12).

Without a protocol to guide the administration of IV fluid to every patient with sepsis, it is left to the individual clinician's judgement to determine the amount of fluid appropriate to administer to each septic patient, often based on subjective factors. This can lead clinicians to err toward under-resuscitation in the initial phases of sepsis, as a great deal of consideration is generally given to the idea that any medical therapy should "first do no harm". Therefore, there is a need for objective guidance for the appropriate volume resuscitation of septic patients. Such objective measures could be made with a PA catheter, but this technique has been largely abandoned, because it is invasive, technically hazardous, subject to operator error, and produces results that are often difficult to interpret, especially as overall intensivist experience with the catheters wanes. Central venous pressure has historically been used as a surrogate marker for volume status, but this measure is inaccurate and ineffective (13). Since that time, a number of other more dynamic measures of volume status have been investigated, each with specific strengths. Earlier methods, especially those dependent on arterial waveform derived variables, while effective, are limited in application to patients who are mechanically ventilated and not spontaneously breathing (14). Others, such as echocardiography are not as effective in the very critically ill, and transesophageal echocardiography, while effective, is invasive and cannot be practically performed with enough frequency to be clinically useful. Bedside ultrasound to inspect variations in inferior vena cava and/or superior vena cava diameter has been studied but remains prone to misinterpretation in a variety of clinical settings. Further evolution in the area has provided us with means to determine volume responsiveness which may be more universally applied to a variety of patients in the ICU setting. Passive leg raising, fluid challenges, and ventilator-directed modalities such as an end-expiratory occlusion test have been used in concert with reliable noninvasive and minimally invasive measures of cardiac output (CO) and stroke volume (SV) to determine fluid responsiveness (15-17).

Currently, we use passive leg raising or conventional fluid challenges in concert with a Non-invasive Cardiac Output Monitor (NICOM) to guide volume resuscitation in our medical ICU. It is our goal to administer IV fluids only to those patients who can be proven to be responsive to volume, with demonstrable changes in SV and CO following the fluid bolus or leg raising maneuver. A retrospective cohort study in our Medical ICU comparing guided IV fluid administration with usual care in severe sepsis and septic shock found that fluid balance was significantly lower in the NICOM guided group, with a concurrent reduction in ICU length of stay, a reduction in duration of vasopressor

use, and less need for mechanical ventilation (18). This study found that early fluid administration, measured at 4 hours was not different between the groups, while volume was significantly less in the SV guided group by 24 hours and for the entire ICU stay. Additionally, dialysis was less common in the SV guided group. These results suggest that early aggressive volume resuscitation is appropriate for the majority of patients with severe sepsis, while the data also bolster the concept that fluid administration performed under the objective, dynamic guidance of CO and SV monitoring is beneficial, with the potential to avoid many of the pitfalls encountered with overzealous fluid resuscitation in sepsis.

Early, appropriate resuscitation is key to survival in sepsis, with the first hours of the resuscitation especially critical; delays in therapy lead to worsening overall mortality and outcomes. Over a decade ago, Kumar *et al*. reported that delays in antibiotic administration in septic shock confer additional mortality (19). More recently, it was demonstrated that hourly delays in antibiotic administration are associated with increased risk of hospital mortality, even if antibiotics are administered within a 6-hour window (20). Furthermore, we demonstrated that antibiotic delays are associated with increased risk of progression to septic shock in patients presenting to the emergency department with severe sepsis (21). Similar to the evidence supporting early, appropriate antibiotic administration, there is emerging evidence that fluid administration in the early phases of sepsis also reduces mortality. One recent retrospective cohort study found that increased fluid administration within the first three hours was associated with decreased mortality in severe sepsis and septic shock (22). Other studies demonstrate equivalent outcomes related to fluid administration within the first 24 hours of sepsis resuscitation, even while demonstrating poorer outcomes associated with late fluid administration or with volume overload, including the study by Sakr *et al*. (23,24).

Perhaps most germane to the idea that the appropriate use of fluids is beneficial is a study conducted by Murphy *et al*. in 2009, which retrospectively analyzed cohorts of septic patients and compared hospital mortality among groups achieving appropriate initial fluid resuscitation (initial fluid bolus of >20 mL/kg prior to and achievement of a central venous pressure of >8 mmHg within 6 h after the onset of therapy with vasopressors) and/or conservative late fluid management (even-to-negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset). Only those patients who met both goals of appropriate initial fluid resuscitation and conservative late fluid management experienced reduced mortality in the study (25).

The study by Sakr *et al*. further confirms other evidence throughout recent literature that early fluid administration is generally not harmful, but excessive IV fluid administration and poor fluid balance in the later phases of sepsis is associated with worse outcomes by a variety of measures. Every septic patient should receive fluid resuscitation specific to their individual physiology, and the best means of doing so at this time involves guidance by dynamic measures of CO and SV. Objective physiologic evidence should guide volume resuscitation early in the disease course to ensure that all patients with sepsis receive adequate initial resuscitation with the goal of improving end-organ perfusion, in turn improving outcomes. As the data demonstrate, careful attention to volume status does not end following the initial resuscitation of sepsis, and we agree with the investigators that fluid balance is a critical factor in outcomes later in the course of disease, dictating judicious IV fluid administration as well as the aggressive use of diuretics when feasible to encourage negative fluid balance.

The detrimental effects of volume overload on organ function and overall physiology are well known, hazardous, and important to avoid. However, the detrimental effects of inadequate resuscitation in the initial phase of sepsis are also known, and also potentially hazardous to patients. We must continually perform a delicate balancing act when providing resuscitation in severe sepsis, recognizing that IV fluids should be treated as a medication, only administering them when appropriate, and discontinuing them when no longer needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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