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The SEP-1 quality mandate may be harmful: How to drown a patient with 30 mL per kg fluid!

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The updated surviving sepsis campaign (SSC) guidelines state: "We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL kg^{-1} of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence)" [1]. Both the Federal Government in the United States of America (USA) and the authors of the SSC decree there are no exceptions to this rule; surprisingly, they mandate that patients with pneumonia or acute lung injury be intubated so that they can receive the potentially harmful 30 mL kg^{-1} fluid bolus [2]. This can only be described as reckless, and clearly one size may not fit all [3]. It is critical to stress that the SSC recommendation and the SEP-1 mandate are devoid of any supporting scientific evidence, indeed, a strong body of scientific evidence suggests that such an approach may be harmful [4].

SHEDDING NEW LIGHT ON THE PENUMBRA

Several important recent publications shed light on the SSC guidelines requiring the administration of 30 mL kg^{-1} crystalloid within the first 3 hours. We believe that this should lead to the abandonment of the federally mandated SEP-1 protocol. In our opinion as well as many other thought leaders in the USA and abroad that the continued enforcement of the SEP-1 protocol is scientifically, morally and ethically unacceptable [5, 6]. It is noteworthy that in response to the publication of the 2016 Surviving Sepsis Campaign Guidelines (SSCG) [1], the Editors of Critical Care Medicine and Intensive Care Medicine respectively have stated that: "As clinicians, we are bound to deviate from guidelines when such deviation is reasonably expected to improve an individual patient outcome. As clinical scientists, we are bound to evaluate the prevailing standard against emerging alternatives. These three imperatives are inseparable. We therefore caution against any quality metric or reimbursement policy that mandates slavish adherence to a particular recommendation" [7]. Furthermore, Mitchell Levy, one of the architects of SEP-1, has stated that the SSC Guidelines do not represent the best distillation of scientific information, that they do not need to be rigidly followed and that a 20 mL kg^{-1} fluid bolus may be harmful (Stated under oath, in Civil Action No. 15-CP-02-00794, State of South Carolina, County of Aiken, in the Court of Common Pleas, Second Judicial Circuit). Even more confusion has arisen following the recent pro-con series by a number of authors of the SSCG, confirming a plea for common sense [8, 9]. In addition to the 30 mL kg^{-1} bolus, SEP-1 mandates measurement of a serum lactate within 3-hours

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of presentation in all septic patients with repeat measurement within 6 hours if the initial lactate level is elevated. This mandate is also without a scientific basis. A recent analysis which included 16 studies found that 6-hour lactate measurement compliance was unrelated to mortality. Furthermore, it should be noted that in the development of the qSOFA score (SEPSIS-3) the "addition of lactate measurement did not meaningfully improve predictive the validity" [10].

POTENTIAL DANGERS

In a recent study from Mayo Clinic, Kelm and colleagues demonstrated that the SSC approach to fluid resuscitation results in fluid overload in 67% of patients with fluid overload being an independent predictor of death with an odds ratio 1.92 (1.16–3.22) [11]. Acheampong and Vincent recently demonstrated that a large positive fluid balance starting on ICU day two was an independent predictor of death [12]. In the largest study to date, day one fluid intake (from all sources) was analysed in a representative sample of 23,513 patients with severe sepsis and septic shock in the USA [13]. In this analysis, it was demonstrated that American clinicians administer far less fluid than recommended by the SSC, that over-resuscitation (> 5 L) significantly increases the risk of death while under-resuscitation was associated with a small but statistically significant survival advantage [13]. These findings debunk the SSC and SEP-1 mandate, and are in keeping with an expanding body of scientific knowledge, including that of the landmark FEAST study [14], that have demonstrated that large fluid boluses and a large cumulative fluid balance increase the risk of death in patients with sepsis and a variety of other syndromes.

The idea of giving large fluid boluses to patients with sepsis is illogical, reflects a poor understanding of human physiology and is likely harmful. As stated previously: "The gold standard for testing fluid responsiveness is a fluid challenge. The technique consists of infusing a small quantity of fluid in a short period of time, enough to increase the preload and test the response of the ventricle according to the Frank–Starling principle" [15, 16]. Furthermore, the paper states that "fluid therapy is not except from undesirable effects" and must therefore be closely titrated [15].

In the FENICE study which analyzed the use of fluid boluses in 2213 patients from 311 centers across 46 countries the median fluid bolus was 500 mL (IQR 500–999) [17]. Almost all bedside clinicians agree that the most effective approach to fluid resuscitation is to give a 500 mL bolus of crystalloid and then for the clinician (at the bedside) to monitor the response. If the patient demonstrates no hemodynamic benefit; then it makes no sense to give more fluids. If the patient demonstrates a hemodynamic benefit, then the clinician may decide to cautiously give a second bolus. Giving 2 L rapidly can be harmful and may result in severe adverse sequela. In order to justify the use of large volumes of fluid in patients with severe septic shock, it has been claimed that in the early goal directed therapy (EGDT) patients "received large amounts of crystalloid" prior to enrollment. It is however noteworthy that in the recent VANISH trial (conducted between 2013 and 2015) on average 1134 mL fluid was administered in the 4 hours prior to enrollment (and escalation of the dose of vasopressor) [18].

The idea of dosing a fluid bolus in an adult patient based on body weight is unusual. Fluid boluses in the ICU, operating room, emergency room are almost never given in a "dosage" of mL kg^{-1} body. Crystalloid solutions are usually provided in 1 L bags; less commonly in 500 mL and 250 mL bags. Consequently, standard practice around the world is to provide a fluid boluses of 500 mL (as demonstrated by the FENICE study). It would appear that the origin of dosing fluid by body weight comes from a small study in 34 pediatric patients with septic shock published by Carcillo *et al.* in 1991 [19]. In this study, patients who received greater than 40 mL kg^{-1} (n = 9) were reported to have an improved survival.

According to Guytonian physiology the cardiac output (CO) and venous return (VR) are equal, and any parameter that determines VR will therefore also determine CO. An increase in venous return will result in an increase in cardiac output. In order for venous return to increase the pressure gradient for venous return must increase, i.e. the increase in mean circulating filling pressure (MSFP) must be greater than the increase in CVP [15]. In a dose titration study performed in post cardiac surgery patients, the authors demonstrated that a fluid bolus of about 300 mL is required to reliably increase MCFP [20]. In septic patients with an increased unstressed volume it is likely that a 500 mL fluid bolus would achieve the same effect. The physiologic effects of large fluid boluses have not been studied in contemporary medicine. In the healthy individuals, the heart is able to regulate filling pressures (the CVP) by increasing the end-diastolic volume. However, septic patients frequently have diastolic dysfunction [21], and a large fluid bolus likely exceed the hearts ability to compensate causing the CVP (and PCWP) to increase significantly and thereby preventing an increase in the gradient of venous return. Therefore, a large fluid bolus may fail to increase CO when compared to a smaller bolus. In addition, the increase in filling pressures are associated with serous hemodynamic consequences including pulmonary edema (high PCWP) and venous congestion (high CVP) leading to kidney and hepatic injury [22]. Furthermore, the rapid increase in filling pressures may counteract the compensatory mechanism that occur in shock resulting in cardiovascular collapse; this is one of the mechanism that has been postulated to account for the increased mortality in the FEAST trial [14].

Only two studies have been conducted to date which have explored the clinical outcome of patients with severe sepsis and/or septic shock randomized to receive large fluid boluses vs. standard of care. In the study by Andrews *et al.* [23] adult patients with septic shock were randomized to receive a 2 L fluid bolus as compared to standard of care. In the FEAST study children with severe sepsis were randomized to a bolus of Saline or Albumin (40 mL kg^{-1}) or no bolus [14]. In both studies, the patients who received the large fluid boluses had a significantly higher mortality than the standard treatment group.

Administration of large amounts of crystalloid fluids is unphysiologic and may lead to fluid accumulation, fluid overload, poly-compartment syndrome and associated morbidity and mortality [4, 24, 25]. Instead of giving a fluid bolus in a blind (protocolized mandated) fashion or until the patient is no longer fluid responsive (with the risk of fluid overload and pulmonary edema), the clinician should assess whether or not the patient will be a fluid-responder. This "fluid responsiveness" can be examined with either the passive leg raising test or the end-expiratory occlusion test or via the use of functional hemodynamics looking at stroke volume, systolic pressure or pulse pressure variations [26, 27].

Moreover, recent clinical trials suggest that protocolized resuscitation strategies, which are also mandated by Rory's Regulations, may paradoxically lead to increased lengths of stay in the ICU and in the hospital and higher costs [3, 28–31]. The regulations may also lead to antibiotic overuse, if hospitals, in an attempt to increase their adherence to guidelines, give antibiotics to patients who are not infected [32]. In a study among 49,331 patients at 149 hospitals, 40,696 (82.5%) had the 3-hour bundle completed within 3 hours [31]. However, the results showed that more rapid administration of antibiotics, but not rapid completion of an initial bolus of intravenous fluids, were associated with lower risk-adjusted in-hospital mortality [31].

ONE SIZE DOES NOT FIT ALL

Protocols can be helpful in specific situations and may have shown benefits in clinical trials. So-called evidence-based protocols and checklists frequently remind clinicians to do the obvious, but may also contain as part of a bundle, elements that are not based on the best current evidence [33]. However, so-called quality improvement programs frequently call for implementation of the total bundle. A simple understanding of cardiovascular physiology and the pathological changes that occur with sepsis together with a review of the medical literature clearly highlights the dangers of the SEP-1 mandate forcing physicians to give qualifying patients a 30 mL kg^{-1} bolus of crystalloid, regardless of their comorbidities. It is important to emphasize that in general, sepsis is not a volume depleted state (with the main pattern being vasoplegia) and that not all patients in septic shock are responsive to fluids. This is not a new concept and was elegantly demonstrated in a series of studies performed at the NIH in the late 80's, showing that most patients in septic shock were unable to increase left ventricular end-diastolic volume (LVEDV) and stroke volume in response to a fluid challenge [34, 35]. Some patients with sepsis are dehydrated (due to poor oral intake, etc) and may respond to small boluses of fluid. However, the mandate to give a 30 mL kg^{-1} bolus of fluid (with the exception of severe burn injury) may lead to "salt water drowning" [22], and is unsupported by the scientific literature. It is remarkable that the US Federal Government has mandated that physicians use a therapeutic intervention that is scientifically unproven; this is unprecedented in the history of medicine.

Furthermore, quality and regulatory bodies frequently require compliance with all elements of the "bundle" even those that may be potentially harmful [33]. These organizations maintain that if all the elements of the "bundle" are not met no credit should be given for any of the elements. There are, however, no scientific data to support this concept and the assertion that "the movement to all-or-none performance assessment is an important milestone in the journey to high quality health care," is potentially dangerous and may not improve patient outcomes when simple common-sense interventions are packaged with other more complex interventions that are unproven or harmful [33].

OPTIONS FOR THE FUTURE

Recent evidence suggests that patients with sepsis may have improved outcomes when treated with a conservative, physiologically guided fluid strategy and state-of-the-art supportive care together with a novel pharmacologic intervention [3, 4, 36, 37]. Following this strategy patients with sepsis and septic shock may not develop progressive organ failure, with a reported mortality of less than 10%, this being despite poor compliance with the SEP-1 mandate (only 11%) [37].

As already mentioned above, an interesting development was the publication in Chest of a paper entitled "Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study" [37]. The response to this retrospective hypothesis generating study has been very favorable; except from many of the "sepsis experts" who consider this study to be "Fake Science", "Tooth Fairy Science", "Snake Oil Quality Evidence" and worse. Vivid discussions followed on social media (Table 1). However, unlike EGDT the protocol proposed in the Chest paper is based on an impressive body of scientific research dating back to 1949 [37]. Furthermore, this protocol is devoid of any major side effects. Safety monitoring of oxalate levels in the at-risk patients (chronic renal failure) has been

Table 1. Discussions on Social Media blog sites regarding "Chest" paper [37]

• http://groceryuniquedepot.com/blog/vitamin-c-news/vitamin-c-as-sepsis-treatment-should-doctors-wait-for-proof-or-treat-virginian-pilot/
• http://groceryuniquedepot.com/blog/vitamin-c-news/vitamin-c-for-sepsis-researchers-want-to-study-treatment-while-others-move-ahead-with--trial-virginian-pilot/
• http://thesgem.com/2017/04/sgem174-dont-believe-the-hype-vitamin-c-cocktail-for-sepsis/
• http://www.thebottomline.org.uk/summaries/icm/marik/
• http://www.emlitofnote.com/?p=3832
• http://rebelem.com/the-marik-protocol-have-we-found-a-cure-for-severe-sepsis-and-septic-shock/
• https://emcrit.org/emcrit/edited-marik-metabolic-sepsis/
• http://stemlynsblog.org/vitamin-sceptic/
• https://www.pharmacyjoe.com/vitamin-c-hydrocortisone-and-thiamine-for-severe-sepsis-and-septic-shock/
• http://www.everydayebm.org/case-based-learning/2017/3/26/vitamincsepsis
• https://emcrit.org/pulmcrit/metabolic-sepsis-resuscitation/
• https://www.youtube.com/watch?v=PZyq70iUFLM&t=845s

Table 2. Stepwise approach in sepsis management

Early diagnosis
— Clinical examination
— Biomarkers: procalcitonin, complete blood count and white blood cell differentiation
Early administration of the correct antibiotics, in the correct dose
Source control
Conservative, physiologic approach to fluid resuscitation
— R.O.S.E concept and 4 phase
• Resuscitation
• Optimization
• Stabilization
• Evacuation
— Treat fluids as drugs, consider the 4 D's
• Drug
• Dose
• Duration
• De-escalation
— Ask the 4 questions of fluid therapy
• When to start fluid resuscitation?
• When to stop fluid resuscitation?
• When to start fluid removal?
• When to stop fluid removal?
Early use of norepinephrine
Consider the "metabolic resuscitation protocol"
— Steroids, Vitamin C and thiamine
Multidisciplinary team approach to patient care
State-of-the-art evidence based supportive care

performed; and these levels have been consistently in the safe range (data on file). Prospective validation is under way in multi-center RCTS, while anecdotal reported results are consistent with the findings of the primary study. It is important to emphasize that an essential component of this strategy is a conservative, physiologic based approach to fluid resuscitation (Table 2).

THE BOTTOM LINES

In summary, there is now scientific evidence, supported by legal precedent that not only are the EGDT, SSC and SEP-1 protocols of limited benefit to patients if blindly followed, they are potentially harmful [3, 38–40]. These protocols violate the American Medical Association (AMA) and American College of Physicians (ACP) code of ethics [41, 42], and the basic Hippocratic Principle of Medicine, "*Primum Non Nocere*". We have entered the era of precision medicine and the SEP-1 mandate must be abandoned immediately, before additional patients are harmed. In addition to the harm caused to patients, the SEP-1 mandate has created an administrative nightmare that has wasted many work hours and hundreds of thousands of dollars [5]. It is time to consider the four D's of fluid therapy and to treat fluids as drugs, with the type of fluid, the dose, the duration and de-escalation all being equally important [43].

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improve survival of critically ill by bringing together physicians, nurses, and others from throughout the world and from a variety of clinical disciplines. The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The IFA website (http://www.fluidacademy.org) is now an official SMACC affiliated site (Social Media and Critical Care) and its content is based on the philosophy of FOAM (Free Open Access Medical education — #FOAMed). The site recently received the HONcode quality label for medical education (https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739).

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