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Initial resuscitation from severe sepsis: one size does not fit all

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Abstract

Over recent decades many recommendations for the management of patients with sepsis and septic shock have been published, mainly as the Surviving Sepsis Campaign (SSC) guidelines. In order to use these recommendations at the bedside one must fully understand their limitations, especially with regard to preload assessment, fluid responsiveness and cardiac output. In this review we will discuss the evidence behind the bundles presented by the Surviving Sepsis Campaign and will try to explain why some recommendations may need to be updated. Barometric preload indicators, such as central venous pressure (CVP) or pulmonary artery occlusion pressure, can be persistently low or erroneously increased, as is the case in situations of increased intrathoracic pressure, as seen with the application of high positive end-expiratory pressure, or in situations with increased intra-abdominal pressure. Chasing a CVP of 8 to 12 mm Hg may lead to under-resuscitation in these situations. On the other hand, a low CVP does not always correspond to fluid responsiveness and may lead to over-resuscitation and all the deleterious effects on end-organ function associated with fluid overload. We will suggest the introduction of new variables and more dynamic measurements. During the initial resuscitation phase, it is equally important to assess fluid responsiveness, either with a passive leg raising manoeuvre or an end-expiratory occlusion test. The use of functional hemodynamics with stroke volume variation or pulse pressure variation may further help to identify patients who will respond to fluid administration or not. Furthermore, ongoing fluid resuscitation beyond the first 24 hours guided by CVP may lead to futile fluid loading. In patients that do not transgress spontaneously from the Ebb to Flow phase of shock, one should consider (active) de-resuscitation guided by extravascular lung water index measurements.

Key words: sepsis guidelines, bundle care, resuscitation

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During recent decades many important studies have been published which provide recommendations regarding resuscitation, including guidelines for the clinician caring for a patient with severe sepsis or septic shock [1–13]. The use of a combination of individual strategies to facilitate rapid adoption of (un)proven therapies, to benchmark performance, and to improve patient outcomes is called bundled care. Although care bundles are simple, uniform and have universal practical applicability, the bar needs to be raised [14]. A 2001 study by Rivers *et al.* (referred to hereafter as 'the Rivers study') was the first to show that the institution of early goal-directed therapy (EGDT) upon admission to the emergency room (ER) can significantly reduce the mortality of patients in severe sepsis and septic shock [1].

Due to the complexity of hemodynamics in sepsis, the goals of treatment are much more difficult to define with certainty than in other forms of shock. The limitations of care bundles include a lack of agreement on hemodynamic goals for management of patients with sepsis, proposing that this lack of consistency may contribute to heterogeneity in treatment effects for clinical trials of novel sepsis therapies. Moreover, the relative contributions of each element of the bundle are not known [15, 16].

The Surviving Sepsis Campaign (SSC) was launched as a collaboration of three professional organizations at the European Society of Intensive Care Medicine's annual congress in Barcelona in 2002 (www.survivingsepsis.org) and the SSC guidelines were first published in 2004 and revised

twice afterwards in 2008 and in 2012 [17–19]. The algorithm used in these guidelines was adopted from the Rivers' study. They provide a 6-hour bundle aimed at achieving the initial resuscitation of sepsis-induced hypoperfusion. Therefore, during the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as a part of a treatment protocol [19]:

- CVP 8–12 mm Hg
- MAP ≥ 65 mm Hg
- Urine output ≥ 0.5 mL kg^{-1} h^{-1}
- Superior vena cava oxygenation saturation ($S_{cv}O_2$) or mixed venous oxygen saturation (S_vO_2) 70% or 65%, respectively.

Despite the fact that this initiative is a great step forward in the standardisation of the initial management of patients with sepsis and septic shock, and the authors and co-workers on this project have to be congratulated, some recommendations may have limitations when applied at the bedside.

THE (LACK OF) EVIDENCE BEHIND THE SSC TARGETS

A recent multi-Society Statement clearly states that [20]: "The results of clinical research, pathophysiologic reasoning, and clinical experience represent different kinds of medical knowledge crucial for effective clinical decision making […] Each kind of medical knowledge has various strengths and weaknesses when utilized in the care of individual patients […] No single source of medical knowledge is sufficient to guide clinical decisions […] No kind of medical knowledge always takes precedence over the others." The importance of this statement at this point and time for medicine in general cannot be underestimated and some summarized it as follows: "It reflects the swing of the pendulum away from rigidly adhering to evidence based medicine principles and expresses the growing disappointment from randomized controlled clinical trials as a guide to clinical decisions." Furthermore "bundling" therapies may result in unintended side effects, particularly if the patient population is not the same as the one that was originally studied. For example, some sepsis treatments have been studied in sepsis, others in severe sepsis, and others in septic shock, yet we bundle them all together in the SSC guidelines [21, 22].

THE FIRST TARGET IS TO REACH A CVP OF 8–12 MM HG

This target became part of the bundle, having come from the Rivers' study. It is noteworthy that in this RCT, both the standard group and the GDT group were treated with a CVP to from 8 to 12 mm Hg. This recommendation is based on the previously stated practice parameters [15]: "In most patients with septic shock, cardiac output will be optimized at filling pressures between 12–15 mm Hg. Increases above this range, increase the risk for developing pulmonary oedema." The thresholds used by Hollenberg originate from an article written in 1983, entitled: "Optimum left heart filling pressure during fluid resuscitation of patients with hypovolemic and septic shock". The total population of this study was only 20 patients while the analysis was limited to 15 patients. The effect of increasing filling pressures on cardiac performance was examined in those 15 patients undergoing fluid resuscitation for hypovolemic and septic shock. Moreover, in 2 patients the protocol was terminated early because of the inability to increase the wedge pressure by 10 mm Hg, despite administration of 5 and 8 litres of normal saline solution, respectively [23]. This is where the chain of evidence leading to the CVP threshold of 8–12 mm Hg used in the SSC guidelines stops, as was nicely investigated, eloquently discussed and concluded by Perel [22].

Using pressures to measure preload has been found to be inaccurate, particularly in patients ventilated with intermittent positive pressure ventilation (IPPV), (auto) positive end expiratory pressure (PEEP), post-cardiac surgery, obesity and those with intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS) [24–29]. It is a step forward that the latest version of the SSC guidelines does mention the possible effects of increased intrathoracic pressure (ITP) and intra-abdominal pressure (IAP) on CVP.

However, Perel continued his analysis of the evidence behind the SSC and found that in one of the references to justify this statement, the SSC guidelines refer to a review that lacks evidence to support the statement that a higher CVP should be aimed for in a patient on mechanical ventilation [30]. This review clearly states that filling pressures have a low predictive value in estimating fluid responsiveness during mechanical ventilation and that using them to guide fluid therapy can lead to inappropriate therapeutic decisions. Thus, chasing the 8–12 mm Hg CVP target may institute aggressive fluid resuscitation in a certain group of patients with low CVP values, which may lead to fluid overload, and may aggravate pulmonary oedema. The opposite will happen in patients with high CVP that are in fact responders. Here fluids are withheld with a possible risk of hypoperfusion and, thus, under-resuscitation (Fig. 1) [29]. A recent analysis of the SSC results, based on 15,022 voluntary submitted data, showed that attainment of a CVP of 8 mm Hg and $S_{cv}O_2$ > 70% did not influence survival in patients with septic shock [31]. Another trial even showed that patients with a CVP less than 8 mm Hg who had received less fluid, had a better survival than those who had a CVP of about 12 mm Hg [32]. Moreover, Marik's meta-analysis, incorporating recent studies that investigated indices predictive of fluid responsiveness, showed that there are no data to support the widespread practice of using CVP to guide fluid therapy [33]. Indeed, Marik nicely elaborates on this issue with his tale of seven mares [34].

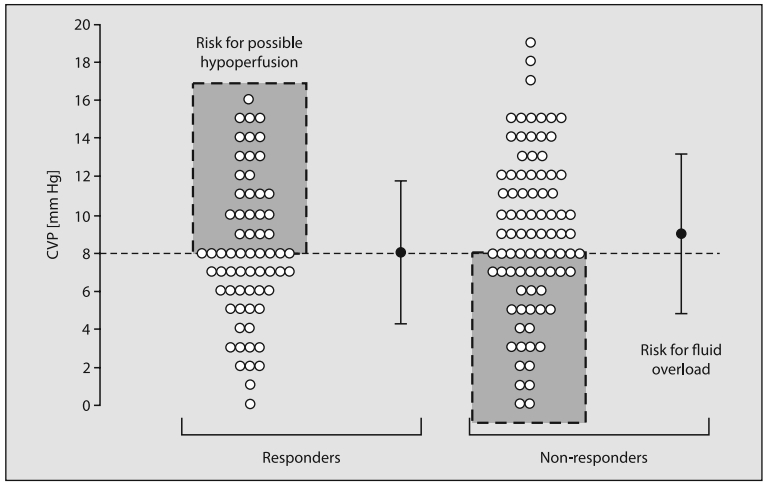

Figure 1. Inability of central venous pressure (CVP) to discriminate between fluid responders and non-responders. Adapted from Osman *et al.* [29]

The leadership of the SSC has believed since its inception that both the SSC Guidelines and the SSC performance improvement indicators will evolve as new evidence that improves our understanding of how best to care for patients with severe sepsis and septic shock becomes available [19]. The May 2015 update of the SSC (http://www.survivingsepsis.org/bundles) explains that there are indeed limitations to ventricular filling pressure estimates as surrogate for fluid resuscitation and that we possibly should use a dynamic measure of fluid responsiveness, including cardiac output (CO) in combination with volumetric preload indices. However, the latter have yet to be included into the SSC guidelines.

Moreover, the River's group recently published an update on early sepsis management where they in fact admit that aggressive fluid resuscitation in the late stages of the sepsis spectrum may increase morbidity [35]. As such, the global clinical picture should be given greater weight than an isolated value. However, they remain convinced that CVP-guided fluid administration in the early stages of sepsis might decrease mortality. They refer to Walkey's study on early central venous catheter (CVC) introduction in sepsis as evidence to support this statement [36]. Unfortunately, this study clearly states that an increased use of early CVC placement is not correlated with an increased quality of care in general, including concurrent implementation of other elements of the Surviving Sepsis bundle (e.g., early antibiotic administration) besides CVP measurement.

Recommendations:

- Barometric preload indicators, such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP), should not be used to guide fluid resuscitation in septic patients.
- Chasing a static CVP target of 8 to 12 mm Hg as a resuscitation endpoint may lead to over- or under-resuscitation and should be abandoned.

THE SECOND TARGET IS TO MAINTAIN A MAP > 65 MM HG

This recommendation is based on the findings of small studies, which showed no significant differences in lactate levels or regional blood flow when the MAP was elevated to more than 65 mm Hg in patients with septic shock, indicating that a target of 65 mm Hg should be sufficient in most cases [37, 38]. In the past, some authors suggested that a higher blood-pressure target might be better, for example to maintain kidney function [39, 40].

Recently, the SEPSISPAM investigators showed in a RCT that targeting a MAP of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation, did not result in significant differences in mortality [2]. Moreover, analogous with cerebral perfusion pressure defined as CPP = MAP – IAP, one could also calculate abdominal perfusion pressure APP = MAP – IAP, which seems a better resuscitation endpoint in patients with abdominal hypertension [41]. Therefore, the ideal MAP target should be based on pre-existing hypertension and co-morbidities.

Recommendations:

- Chasing a static MAP target of 65 mm Hg may be too low or too high and, as such, MAP should be tailored individually.
- In patients with abdominal hypertension, abdominal perfusion pressure (APP), calculated as MAP minus intra-abdominal pressure, may be a better resuscitation endpoint.

THE THIRD TARGET IS A URINE OUTPUT OF 0.5 ML KG^{-1}H^{-1}

Urine output has classically been adopted as the primary endpoint to guide resuscitation in burn care. The prevailing view has deemed it appropriate to target a diuresis of greater than 0.5 mL kg^{-1} h^{-1} in adults and 1 mL kg^{-1} h^{-1} in the paediatric population. This endpoint, however, has been brought into question by various studies that have shown no correlation between urine output and invasively derived physiologic variables. Moreover, urine output is unable to identify fluid responders after a fluid challenge and it is inaccurate as a resuscitation target. Decreased urinary output can easily mislead the clinician as, while it may be the result of intravascular hypovolemia, it equally could also be caused by IAH and ACS [42]. In the latter situation, a vicious cycle is established with further fluid loading. This will cause even more intestinal oedema and visceral swelling, leading to increasing IAP, venous hypertension and deteriorating renal function.

Recommendation:

- Urine output is a poor endpoint that may lead to over- or under estimation of fluid resuscitation: needs and, as such, can no longer be recommended.
- However, in situations with limited monitoring techniques, it may still be used to guide fluid resuscitation

THE FOURTH TARGET TO REACH IS AN $S_{CV}O_2$ OF 70%

Rivers showed that during fluid resuscitation, $S_{cv}O_2$ increases, suggesting a concomitant increase in CO. As such, $S_{cv}O_2$ can be used as a surrogate for CO [1, 43]. In the Rivers study the baseline $S_{cv}O_2$ value is around 50%. These observed $S_{cv}O_2$ values are extremely low compared to the normal $S_{cv}O_2$ value of about 75%. Moreover, in septic patients, the $S_{cv}O_2$ is usually normal or even supranormal due to a reduced oxygen extraction ratio, which is characteristic of septic shock [44, 45]. This can easily be calculated using the Fick Formula (the oxygen extraction ratio is approximately equal to $(1 - S_{cv}O_2)$). Only Rivers found such a low $S_{cv}O_2$ of 50%. Recent studies have indeed found much higher $S_{cv}O_2$ values in septic shock patients, either in the emergency department or on admission to the ICU [13, 46]. In two of these studies, the mean $S_{cv}O_2$ was 72% to 74% [47, 48]. A normal/high $S_{cv}O_2$ may be due to reduced O2 extraction and does not necessarily indicate adequate tissue oxygenation.

Further evidence of the fact that the $S_{cv}O_2$ values of Rivers' patients are not characteristic for all septic patients can be found in a later study of Rivers himself and his colleagues, in which patients of both the usual treatment and the EGDT groups of their original study were combined and then divided into three resuscitation groups. These included firstly, a group with severe global tissue hypoxia (lactate of greater than or equal to 4 mmol L^{-1} and $S_{cv}O_2$ of less than 70%), secondly, a group with moderate global tissue hypoxia (lactate of greater than or equal to 2 mmol L^{-1} and $S_{cv}O_2$ of less than 70%), and finally, a group with resolved global tissue hypoxia (lactate of less than or equal to 4 mmol L^{-1} and $S_{cv}O_2$ of greater than or equal to 70%) [49]. However, one group of patients was still missing: patients with high lactate and high $S_{cv}O_2$ or, thus, those with severe global tissue hypoxia and low O_2 extraction. In a multicenter European study [39], it was found, however, that out of 44 septic patients, 10 (23%) had lactate levels of greater than or equal to 2 mmol L^{-1} and $S_{cv}O_2$ values above 70% [50].

Perel performed a highly impressive bench-to-bedside analysis of the Rivers study showing that the extremely low $S_{cv}O_2$ values seen in Rivers' patients on admission to the ER indicate that these patients must have had very low CO's [22]. He stated that the most likely cause for these low CO's was probably a combination of pre-existing co-morbidities and profound hypovolemia, which may have developed due to a late arrival to the hospital (ethnic group, low socioeconomic status, no insurance) [22]. The very significant hypovolemic element of their shock was successfully corrected by aggressive fluid loading which was guided by a simple protocol that may be unsuitable for many ICU septic patients [22]. Interestingly, Perel also compared the co-morbidity of the Rivers' patients to those included in the CORTICUS (Corticosteroid Therapy of Septic Shock) study and concluded that Rivers' patients had significantly more severe co-morbidities [22, 51]. Whether or not $S_{cv}O_2$ should be used is not a problem of evidence-based medicine but rather a problem of *generalizability* and extrapolation of the Rivers' study results to other patient populations.. Therefore, it was very disappointing that even in the third revision of the SSCG guidelines the Rivers protocol was still perceived as high-grade evidence [19]. The Rivers single-center study dates back to 2001 and has never been repeated, until recently. The results have been recommended for *all* hypotensive and/or hyperlactatemic septic patients, both in and outside the ER regardless of the fact that this study was, so far up to then, the only evidence for the effectiveness of the hemodynamic protocol suggested in the SSC guidelines.

Recommendation:

- As chasing an $S_{cv}O_2$ target of 70% in isolation does not make sense, $S_{cv}O_2$ should always be seen in relation to previous history, co-morbidities and actual lactate levels.

DO NOT IGNORE THE NEW EVIDENCE

First came the ProCESS trial, which concluded that protocol-based resuscitation of patients in whom septic shock was diagnosed in the ER did not improve outcomes [3]. The patients (in total 1,341) were randomly assigned to protocol-based EGDT, a protocol-based standard treatment, or to usual care. There were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support.

Table 1. Overview of studies on GDT

Author	Year	Ref	n	Setting	Mortality EGDT	Mortality Control
Rivers	2001	[1]	263	ER	38/130 (29.2%)	59/133 (44.4%)
Wang	2006	[8]	33	NA	4/16 (25%)	7/17 (41.2%)
De Oliveira*	2008	[7]	102	mixed	6/51 (11.8%)	20/51 (39.2%)
EGDT	2010	[9]	314	NA	41/163 (25.2%)	64/151 (42.4%)
LACTATE	2010	[13]	348	ICU	58/171 (33.9%)	77/177 (43.5%)
Jones	2010	[6]	300	ER	34/150 (22.7%)	25/150 (16.7%)
Tian	2012	[10]	71	NA	12/19 (63.2%)	12/34 (35.3%)
Yu	2013	[11]	50	NA	6/23 (26.1%)	5/25 (20%)
Lu	2014	[12]	82	NA	7/40 (17.5%)	7/42 (16.7%)
PROCESS	2014	[3]	1341	ER	92/439 (21%)	167/902 (18.5%)
SEPSISPAM	2014	[2]	776	ICU	142/388 (36.6%)	132/388 (34%)
ARISE	2014	[4]	1600	ER	147/792 (18.6%)	150/796 (18.8%)
PROMISE	2015	[5]	1260	ER	184/623 (29.5%)	181/620 (29.2%)
Total			6491		771/3005 (25.7%)	906/3486 (26%)

EGDT — early goal directed therapy; ER — emergency room; ICU — intensive care unit; NA — not available, n: number of patients included; *paediatric patients from ER, ward and ICU

This was soon followed by a second RCT, the ARISE study, showing that EGDT did not reduce all-cause mortality at 90 days in critically ill patients presenting to the emergency department with early septic shock [4]. In total, 1600 patients were randomly assigned in a 1:1 ratio to receive either EGDT bundle care or usual care for 6 hours.

Finally, in the latest RCT, the ProMISE trial, patients were randomly assigned to receive either EGDT (a 6-hour resuscitation protocol) or usual care [5]. The primary clinical outcome was all-cause mortality at 90 days. The investigators enrolled 1,260 patients, with 630 assigned to EGDT and 630 to usual care. In patients with septic shock that were identified early and received intravenous antibiotics and adequate fluid resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.

The SSC explains that a large number of observational studies have shown significant mortality reduction compared to historical controls. Although this may be the case, closer analysis reveals that the beneficial effects may solely depend on the proper use of antibiotics. The early administration of antibiotics, and the right antibiotic, may be the secret to success of the Surviving Sepsis Campaign [52]. Although the use of bundles in order to ensure timely delivery of treatments with recognized benefits may be important in the ER and ICU, on the other hand, the institution of current sepsis bundles may force physicians to provide unproven or even harmful care, particularly if the patient population is not the same as the one originally studied [21].

Table 1 summarizes the different RCT's on GDT in the critically ill. In total, around 6,491 patients have been studied in 13 trials. All patients were available for mortality analysis while overall mortality was 25.8 % (1677 of 6491 patients). The mortality in the GDT group was 771/3005 (25.7%) compared to 906/3486 (26%) in the control group. EGDT did not confer a reduction in overall mortality (pooled OR 0.94 [95 % CI 0.84–1.05]; P = NS) (Fig. 2). There was evidence of heterogeneity (I^2 = 62%; P = 0.27).

ARE WE COMPLIANT WITH THE BUNDLES WE PRETEND TO USE?

The SSC guidelines attempt to include nearly every aspect of critical care potentially related to sepsis, perhaps losing focus in the process. As discussed previously, the evidence behind some of the elements of the bundles is not strong (e.g. CVP) and the bundles are turned into quality measures on which providers will be benchmarked, even though clinicians may correctly disagree with some of the recommendations [53]. It seems that other factors may also play a role: pharmaceutical, financial, political, legal etc. A Chinese study showed that only 47% of surveyed intensivists believed that CVP should be used to guide resuscitation, while 86% used it because of the SSC guidelines [54, 55]. Despite the hype and pressure, full compliance with all applicable elements of the sepsis resuscitation bundle was only 21.6% in the USA and 18.4% in Europe [56]. Finally the SSC leadership concluded: "The strong recommendation for achieving a CVP of 8 to 12 mm Hg and an $S_{cv}O_2$ of 70% in the first 6 hours of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet the standard of care as verified by practice data. The publication of the initial results of the international SSC performance improvement program demonstrated that adherence to CVP and $S_{cv}O_2$ targets for initial resuscitation was low" [57]. As discussed above, these reservations on the Rivers protocol have already been raised by others and are based on its

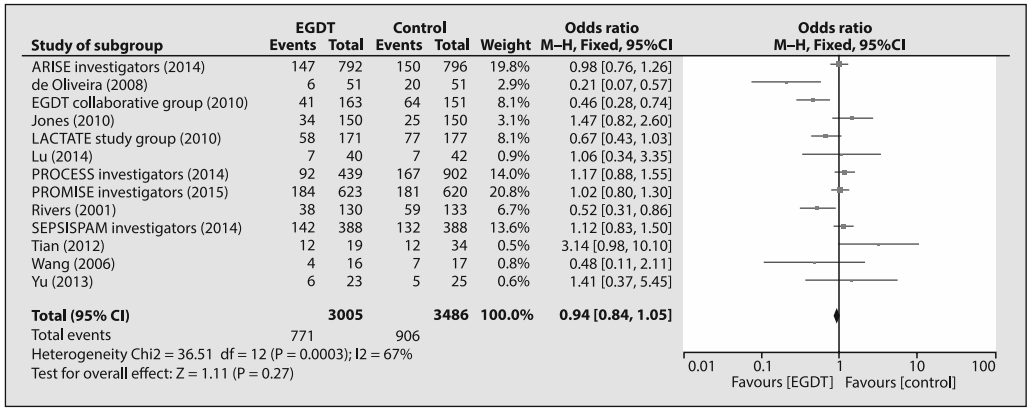

Figure 2. Forrest plot. Effect of EGDT on mortality in patients presenting to the emergency room or ICU with septic shock. Primary mortality outcome is given for each study. The control was usual care or another non- EGDT resuscitation strategy. Fixed-effect model: the individual points denote the OR of each study and the lines either side, the 95 % confidence intervals. OR: odds ratio, CI: confidence interval.

perceived physiological flaws (having the same targets of CVP in both arms) and on the possibility that the patients of the Rivers study do not represent all septic patients [22].

After the release of the 3rd SSC guidelines in 2013, the authors anticipated the growing international criticism [19]. In response to comments and questions, the SSC leadership has provided additional background regarding the guideline recommendation regarding measurement of CVP, $S_{cv}O_2$ and lactate. The performance indicators for bundle compliance now call for *measuring* CVP and $S_{cv}O_2$, and re-measuring lactate if the initial lactate was elevated. The rationale for the indicators' being *measurement*, and not target achievement, is that the decision to give more fluid or add inotropes to the resuscitation should be based on the entire clinical picture (www.survivingsepsis.org/SiteCollectionDocuments/Guidelines-Statement-Leadership-CVP-ScvO2-Lactate-Measurements.pdf).

Only recently, after 10 years of lively discussions and debate, CVP and $S_{cv}O_2$ were removed from the 6-hour bundle in April 2015 (http://www.survivingsepsis.org/News/Pages/SSC-Six-Hour-Bundle-Revised.aspx). However, the SSC leadership still keeps recommending measuring these parameters. With the publication of 3 trials that do not demonstrate the superiority of required use of a central venous catheter (CVC) to monitor central venous pressure (CVP) and central venous oxygen saturation ($S_{cv}O_2$) in all patients with septic shock who have received timely antibiotics and fluid resuscitation compared with controls or in all patients with lactate > 4 mmol L^{-1}, the SSC Executive Committee has revised the improvement bundles [3–5]. Therefore, finally, the 6-hour bundle has been updated as follows:

- To be completed within 3 hours of time of presentation (defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review):
  1. Measure lactate level
  2. Obtain blood cultures prior to administration of antibiotics
  3. Administer broad spectrum antibiotics
  4. Administer 30 mL kg^{-1} crystalloid for hypotension or lactate ≥ 4 mmol L^{-1}
- To be completed within 6 hours of time of presentation:
  5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
  6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol L^{-1}, volume status and tissue perfusion needs to be re-assessed and the findings documented with:
     a. either:
        i. repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.
     b. or two of the following:
        ii. measure CVP
        iii. measure $S_{cv}O_2$
        iv. bedside cardiovascular ultrasound
        v. dynamic assessment of fluid responsiveness with passive leg raising or fluid challenge
  7. Re-measure lactate if initial lactate elevated

ALTERNATIVE SOLUTIONS TO SSC TARGETS

IMPROVING BAROMETRIC PRELOAD INDICATORS

As stated above, the CVP and PAOP may be erroneously increased in patients with increased ITP [58]. The latest revision of the SSC guidelines still advocates initial

fluid management based on CVP measurements with the usual targets of 8 to 12 mm Hg. However, using pressures to measure preload has been found to be inaccurate time and time again, particularly, as discussed above, in patients ventilated with intermittent positive pressure ventilation (IPPV), (auto) PEEP, post-cardiac surgery, obesity and those with IAH and ACS [24, 27–29, 58]. Although it is re-assuring and noteworthy that the latest version of the SSC guidelines does mention the possible effects of increased ITP and IAP on CVP, it advises that: "In mechanically ventilated patients or those with known pre-existing decreased ventricular compliance, a higher target CVP of 12 to 15 mm Hg should be achieved to account for the impediment in filling. Similar consideration may be warranted in circumstances of increased abdominal pressure. Elevated CVP may also be seen with pre-existing clinically significant pulmonary artery hypertension, making use of this variable untenable for judging intravascular volume status". Moreover, they properly refer to previous publications on this topic [59–61]. Within this respect, the compliance of the thorax and the abdomen are key elements in order to explain the index of transmission of a given pressure from one compartment to another: "The use of lung-protective strategies for patients with ARDS […] has been widely accepted, but the precise choice of tidal volume […] may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure chosen, the compliance of the thoraco-abdominal compartment […]"[19]. This recently led to the recognition of the polycompartment syndrome [28, 62]. Instituting aggressive fluid resuscitation in patients with low CVP values may lead to fluid overload, which may aggravate pulmonary oedema, especially in those patients in whom sepsis is associated with acute respiratory distress syndrome (ARDS) and severe pulmonary dysfunction [22]. We therefore disagree with the SSC guidelines' statement that "a low CVP is still a good indicator of someone needing fluid resuscitation". Many patients with a low CVP are in fact non-responders [29, 63, 64].

The SSC leadership could have referred to the excellent paper by Teboul *et al.* with a calculation of the index of transmission that is dependent on dynamic lung compliance [65].

$$IT = (CVP_{ei} - CVP_{ee})/(P_{plat} - PEEP)$$

The higher the compliance (e.g. emphysema), the higher the IT and vice versa, the lower the compliance (lung fibrosis, ARDS), the lower IT. This is easy to understand, as the denominator is the same in the formula to calculate C_{dyn} and IT.

$$C_{dyn} = TV/(P_{plat} - PEEP)$$

Hence, the transmural CVP can be estimated as follows:

$$CVP_{tm} = CVP_{ee} - IT \times PEEP$$

Moreover, we have previously suggested a correction formula based on ITP or IAP (with an average index of transmission between abdomen and thorax of 50% [26,58]):

$$CVP_{tm} = CVP_{ee} - ITP = CVP_{ee} - IAP/2$$

Albeit far from perfect, these correction formulas for PEEP and IAP may better reflect the true preload status and thus may improve the value of the barometric preload indices. Teboul *et al.* demonstrated the biggest risk in these recommendations again, in a study showing that CVP is not a reliable predictor of volume responsiveness. They found no difference in CVP values of septic patients who are responders or non-responders (responder = cardiac index increase after fluid challenges) [29].

Recommendation:

- Transmural filling pressures, or their estimates, may better reflect the true preload status (especially in patients with high PEEP and IAP) and thus could be a better resuscitation endpoint.

VOLUMETRIC PRELOAD INDICATORS

Volumetric estimates of preload status, such as global end-diastolic volume index (GEDVI) and right ventricular end-diastolic volume index (RVEDVI), are of significant value in the assessment of traumatically injured patients. This volumetric assessment is especially useful in patients with increased IAP or patients with changing ventricular compliance and elevated ITP in whom traditional barometric preload indicators are elevated and difficult to interpret, since they are zero-referenced against atmospheric pressure [26, 58, 66–68].

Reliance on such pressures to guide resuscitation can lead to inappropriate therapeutic decisions, under- or over--resuscitation, and organ failure [28]. Correction of the GEDVI for the corresponding global ejection fraction can further improve its predictive value [69]. One must, however, take into account that no good normal values exist for GEDVI in different patient populations [70]. The same static volumetric targets, although better than those which are barometric, may not apply to all patients [71]. A recent meta-analysis showed that baseline values for GEDVI are around 694 mL m^{-2} in surgical and 788 mL m^{-2} in septic patients [70] and thus below the upper limit of normal of 850 mL m^{-2}, as was recently used as target for initiating a fluid challenge [72]. We must remember that no single parameter can improve outcome. This can only be achieved by a good protocol [73].

Recommendation:

- Volumetric preload indicators (like right ventricular or global end diastolic volume) are superior compared to

Table 2. Overview of recommendations regarding the initial resuscitation and resuscitation endpoint in patients with sepsis and septic shock

Resuscitation endpoints	
1. Monitoring	Every patient with septic shock should be adequately monitored with regard to cardiac output, fluid status, fluid responsiveness and organ perfusion.
2. Cardiac output	When treating shock patients, by definition, CO should be monitored to identify patients with low or high CO and to assess the response to treatment.
3. Barometric preload	Barometric preload indicators, such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP), should not be used to guide fluid resuscitation in patients with septic shock.
	Chasing a static CVP target of 8 to 12 mm Hg as resuscitation endpoint may lead to over- or under resuscitation and should be abandoned.
	Transmural filling pressures, or their estimates, may better reflect the true preload status (especially in patients with high PEEP and IAP) and thus could be a better resuscitation endpoint.
4. Perfusion pressure	Chasing a static mean arterial pressure (MAP) target of 65 mm Hg may be too low or too high and, as such, MAP should be tailored individually.
	In patients with abdominal hypertension, abdominal perfusion pressure (APP), calculated as MAP minus intra-abdominal pressure (IAP), may be a better resuscitation endpoint.
5. Urine output	Urine output is a poor endpoint that may lead to over- or under estimation of fluid resuscitation and, as such, can no longer be recommended.
	However, in situations with limited monitoring techniques, urine output can still be used to guide fluid resuscitation.
6. Mixed venous saturation	As chasing an $S_{cv}O_2$ target of 70% in isolation does not make sense, $S_{cv}O_2$ should always be seen in relation to previous history, co-morbidities and actual lactate levels.
7. Volumetric preload	Volumetric preload indicators (such as right ventricular or global end diastolic volume) are superior compared to those which are barometric and are recommended to guide fluid resuscitation, especially in septic patients with increased intrathoracic pressure or IAP.
	If the GEDVI is high, the measurement needs to be corrected for the global ejection fraction, as this leads to a more accurate estimation of preload.
8. Fluid responsiveness	Fluid resuscitation in septic patients should be guided by physiological parameters (SVV or PPV) or tests that are able to predict fluid responsiveness (passive leg raising or endexpiratory occlusion test).
9. Fluid balance	An excessive positive daily and cumulative fluid balance should be avoided.
10. Lung water	The use of the extravascular lung water index (EVLWI) is recommended to guide de-resuscitation in septic patients not transgressing spontaneously from the Ebb to Flow phase
11. Perfusion	Fluid resuscitation should only be given/increased in case of evidence of tissue hypoperfusion (base deficit, lactate etc.).

APP — abdominal perfusion pressure; CO — cardiac output; CVP — central venous pressure; EVLWI — extravascular lung water index; GEDVI — global end-diastolic volume index; IAP — intra-abdominal pressure; MAP — mean arterial pressure; PAOP — pulmonary artery occlusion pressure; PEEP — positive end expiratory pressure; PPV — pulse pressure variation; SVV — stroke volume variation

those which are barometric and are recommended to guide fluid resuscitation, especially in septic patients with increased IAP.

- If the GEDVI is high, the measurement needs to be corrected for the global ejection fraction as this leads to a more accurate estimation of preload.

FLUID RESPONSIVENESS

A significant relationship between values of CVP has not been found to identify responders from non-responders. Different techniques are available to assess fluid responsiveness [74, 75]. However, there are certain limitations to the use of functional hemodynamic monitoring, such as stroke volume variation (SVV) or pulse pressure variation (PPV). The patient needs to be in regular sinus rhythm, while the presence of atrial fibrillation, along with ventricular or supraventricular extra systoles, limit their use [76]. The patient also needs to be fully mechanically ventilated without spontaneous breathing, while tidal volumes must be above 6 mL kg^{-1} [77, 78]. The presence of right heart failure and conditions related to increased ITP or IAP will increase the baseline values of the functional hemodynamic parameters making them less reliable, unless we define new thresholds [79, 80]. In such situations (or thus in patients with diminished respiratory compliance) other techniques are available in order to assess fluid responsiveness, such as the use of a passive leg raise (PLR) or end-expiratory occlusion (EEO) test [81–84]. However, the PLR may result in a false negative response in conditions of increased IAP due to diminished venous return [85, 86]. The administration of repeated fluid boluses until the patient is no longer fluid responsive cannot be advocated [72, 73, 87].

Recommendation:

- Fluid resuscitation in septic patients should be guided by physiological parameters or tests that are able to predict fluid responsiveness.

CARDIAC OUTPUT MONITORING

Cardiac output (CO) is the main determinant of oxygen delivery and shock is defined by an imbalance between oxygen delivery and oxygen consumption. Physical examination and vital signs alone often fail to reflect significant alterations in CO [50]. Because of the complexity of assessment of clinical variables in septic patients, direct measurement of CO by invasive hemodynamic monitoring is advisable as it is, therefore, very useful for proper decision-making in the critically ill [88]. Furthermore, perioperative optimisation has resulted in better or altered outcomes [89–92].

The main two reasons to measure CO are firstly, the identification of patients who have low (or high) CO values that are not evident clinically (in order to stratify patients between those having cardiac vs. septic shock) and secondly, to assess the response to diagnostic (eg. passive leg raising test) and therapeutic (eg. fluid bolus) intervention. Based on the available evidence, we cannot agree with the SSC guidelines statement that: "The efficacy of these (CO) monitoring techniques to influence clinical outcomes from early sepsis resuscitation remains incomplete and requires further study before endorsement" [19]. As repeatedly stated previously by Perel and others, physiological examination, i.e. observing multiple parameters on the monitor in real time should be considered to be (at least) as important as the classic physical examination [76, 92–94].

Recommendation:

- By definition, when treating shock patients, CO should be monitored to identify patients with low or high CO and to assess the response to treatment.

FLUID BALANCE AND DE-RESUSCITATION

As early as 1942, the concept of a dual metabolic response to bodily injury was introduced. In direct response to initial pro-inflammatory cytokines and stress hormones, the *Ebb phase* represents a distributive shock characterised by arterial vasodilatation and transcapillary albumin leakage abating plasma oncotic pressure [95]. Arterial underfilling, microcirculatory dysfunction and secondary interstitial oedema lead to systemic hypoperfusion and regional impaired tissue use of oxygen. In this early stage of shock, adequate fluid therapy comprises goal directed filling to prevent development into multiple organ dysfunction syndrome (MODS). Patients with a higher severity of illness need more fluids to reach cardiovascular optimization. Therefore, at this point fluid balance may be considered a biomarker of critical illness, as proposed by Bagshaw *et al.* [96]. Classically, patients overcoming shock attain homeostasis of pro-inflammatory and anti-inflammatory mediators within three days. Subsequent hemodynamic stabilization and restoration of plasma oncotic pressure set off the *Flow phase*, with resumption of diuresis and mobilization of extravascular fluid resulting in negative fluid balances. Recent studies have shown that conservative late fluid management (CLFM) with 2 consecutive days of negative fluid balance within the first week of stay is a strong and independent predictor of survival [97]. In this context, the global increased permeability syndrome (GIPS) has been introduced, characterized by high capillary leak index (CLI, expressed as CRP over albumin ration), excess interstitial fluid and persistent high extravascular lung water (EVLWI), no CLFM achievement and progressive organ failure [98]. GIPS represents a 'third hit' following acute injury with progression to MODS [99]. The dual response to acute inflammatory insult is characterized by a crucial turning point on day 2 to 3. Lower EVLWI and pulmonary vascular permeability indices (PVPI) [100] at day 3 of shock were shown to correlate with better survival. As adverse effects of fluid overload in states of capillary leakage are particularly pronounced in the lungs, monitoring of EVLWI may offer a valuable tool to guide fluid management in the critically ill. It must be stated that EVLWI can never be a trigger to start fluids but it is rather a safety parameter in order to define the extent of capillary leak and to guide de-resuscitation [73, 101]. In this hypothesis (change in) EVLWI has a prognostic value as a reflexion of the extent of capillary leakage, rather than as a quantification of lung function impairment by lung water [98]. The proposed Berlin definition for ARDS, therefore, has no real added value compared to the previous AECC definition [102]. Thus, the value of EVLWI in combination with PVPI should "by definition" by part of a future ARDS definition [101, 103].

Recommendation:

- An excessive positive cumulative fluid balance should be avoided.
- The use of extravascular lung water is recommended to guide de-resuscitation in septic patients not transgressing spontaneously from the Ebb to Flow phase.

CONCLUSION

One could come to the erroneous conclusion that protocols may not have a role in the treatment of septic shock as suggested by some and as was the conclusion in a recent meta-analysis showing that EGDT is not superior to usual care for emergency department patients with septic shock but is associated with increased utilisation of ICU resources [104, 105]. However, Rivers *et al.* have started one of the most important change processes in modern critical care and the SSC has probably saved many lives. The methodology that was part of Rivers, ProCESS, ARISE and ProMISE studies can be applied in clinical practice to ensure early diagnosis and treatment for all patients with septic shock.

As we know that time is of the essence, the elements we should focus on in order to save lives, are the early recognition of sepsis, early source control, early administration of

antibiotics, early adequate volume resuscitation, and clinical assessment of the adequacy of circulation. However, the thresholds and targets suggested by the SSC to guide initial resuscitation cannot be extrapolated to all septic patients and may be potentially harmful in selected patients. Take home messages for the reader can therefore be summarized as follows: With regard to EGDT it is not advisable to guide the initial fluid resuscitation based on CVP measurements since they expose the patient to possible over-resuscitation along with all the deleterious effects of fluid overload, and, in some situations with increased ITP, also to under-resuscitation. No single parameter has ever improved survival, as only a good protocol or algorithm can. However, each patient is unique and, as such, also merits individualized personalized care. As the best fluid is the one that has not been given to the patient (that is, one which is unnecessary), it is advisable not to perform fluid bolus administrations until the patient is no longer fluid responsive but rather to assess responsiveness with passive leg raising or end-expiratory occlusion tests instead. Despite its limitations, dynamic functional hemodynamic monitoring can provide further insights towards the identification of fluid responders. In many situations, volumetric preload indicators have been proven superior over those which are barometric. Taking this into account the global ejection fraction can further improve them. By definition, CO should be measured in all patients with septic shock (especially when $S_{cv}O_2$ is low), as this is the gold standard in order to assess the effect of fluids (e.g. a 15% increase in baseline CO). Ongoing fluid resuscitation beyond the initial 24-48 hours cannot be recommended, unless a safety parameter, such as extravascular lung water, is taken into account. De-resuscitation needs to be considered in those patients who do not transgress spontaneously from the Ebb to Flow phase. Finally, a future ARDS definition should "by definition" take into account the value of EVLWI in combination with the PVPI. Only recently, the American National Quality Forum (NQF) formulated a new interpretation with regard to adherence to the Severe Sepsis and Septic Shock Management Bundle quidelines (NQF#0500) and state that measuring central venous pressure and central venous oxygen saturation is still preferred (http://www.qualityforum.org) [106]. All patients also need to receive a fluid bolus of 30 mLs kg^{-1} regardless of weight and fluid responsiveness and regardless of the fact that they may have pulmonary edema, renal failure or end-stage heart failure. The NQF also announced that hospitals are required to submit data on the SSC bundle adherence starting from October 1, 2015 with the risk for penalisation if they fail to do so. This is really freightening as it means that the American Federal Government seems to support overzealous futile fluid resuscitation. At least some food for further thought [106].

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