

## REVIEW ARTICLE

# A rational approach to fluid therapy in sepsis

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## Abstract

Aggressive fluid resuscitation to achieve a central venous pressure (CVP) greater than 8 mm Hg has been promoted as the standard of care, in the management of patients with severe sepsis and septic shock. However recent clinical trials have demonstrated that this approach does not improve the outcome of patients with severe sepsis and septic shock. Pathophysiologically, sepsis is characterized by vasoplegia with loss of arterial tone, venodilation with sequestration of blood in the unstressed blood compartment and changes in ventricular function with reduced compliance and reduced preload responsiveness. These data suggest that sepsis is primarily not a volume-depleted state and recent evidence demonstrates that most septic patients are poorly responsive to fluids. Furthermore, almost all of the administered fluid is sequestered in the tissues, resulting in severe oedema in vital organs and, thereby, increasing the risk of organ dysfunction. These data suggest that a physiologic, haemodynamically guided conservative approach to fluid therapy in patients with sepsis would be prudent and would likely reduce the morbidity and improve the outcome of this disease.

**Key words:** central venous pressure; fluid therapy; pulmonary edema; sepsis; septic shock

## Editor's key points

- The authors review, in detail, the physiology of hypo- and hypervolaemia, and the effects of venodilation and arteriodilation.
- They contend that universal, aggressive fluid administration in septic shock carries considerable risk, and that a haemodynamically-guided, conservative approach is likely to produce better outcome.
- They also argue that early norepinephrine therapy is likely to improve outcome.

In the 19<sup>th</sup> century, patients with cholera dying from hypovolaemic shock were treated by venesection or blood-letting.<sup>1 2</sup> This treatment was considered the standard of care for this disorder. In the first part of the 21<sup>st</sup> century patients with septic shock were treated with massive amounts of crystalloids, approaching 17 litres in the first 72 h of hospitalization.<sup>3 4</sup> This

approach was considered the standard of care and endorsed by International Guidelines.<sup>5–7</sup> Clearly, these treatment approaches failed to appreciate the pathophysiological changes of both disorders and that the prescribed treatments were harmful. Cholera is a disease associated with profound volume depletion through diarrhoea that requires replacement with i.v. fluids.<sup>1 2</sup> Severe sepsis and septic shock however, are not associated with volume loss. Sepsis is characterized by arterio- and venodilation together with microcirculatory and myocardial dysfunction, with septic patients being poorly responsive to fluid administration. Nevertheless, aggressive fluid resuscitation to achieve a central venous pressure (CVP) greater than 8 mm Hg ('Early Goal Directed Therapy' - EGDT), has been considered the standard of care in the management of patients with severe sepsis and septic shock.<sup>5–7</sup> However, recent multicentre clinical trials (ProCESS, ARISE and PROMISE) and a meta-analysis of EGDT have demonstrated that this approach does not improve the outcome of patients with severe sepsis and septic shock.<sup>8–11</sup> This article reviews the haemodynamic changes associated with sepsis and provides a rational approach to fluid management in this complex disorder.

## Pertinent normal cardiovascular physiology

The amount of blood pumped out of the heart (cardiac output) is equivalent to venous return (volume entering the right atrium).<sup>12</sup> According to Guyton, venous return is determined by the pressure gradient between the peripheral veins and the right atrium (CVP).<sup>13</sup> The venous system can be divided into two theoretical compartments, the unstressed and stressed volume.<sup>14</sup> The intravascular volume that fills the venous system to the point where intravascular pressure starts to increase is called unstressed volume, whereas the volume that stretches the veins and causes intravascular pressure to increase is called the stressed volume. The mean circulatory filling pressure (MCFP) is conceptualized as the pressure distending the vasculature, when the heart is stopped (zero flow) and the pressures in all segments of the circulatory system have equalized.<sup>14 15</sup> The stressed venous system is the major contributor to the MCFP.<sup>14 15</sup> The MCFP in humans is normally in the range of 8–10 mm Hg.<sup>14 15</sup> The MCFP is the major determinant of venous return.

The venous system has a large vascular capacitance and a constant compliance in which an increased blood volume is associated with a relatively small change in the MCFP.<sup>14</sup> However, because of the restraining effects of the pericardium and cardiac cytoskeleton, the diastolic compliance of the normal heart (both left and right ventricles) reduces as distending volume increases; consequently, with large volume fluid resuscitation, the cardiac filling pressures (particularly on the right side, i.e. CVP) increase faster than the MCFP, decreasing the gradient for venous return.<sup>16–18</sup> Organ blood flow is determined by the difference in the pressure between the arterial and venous sides of the circulation. The mean arterial pressure (MAP) minus the CVP is therefore the overall driving force for organ blood flow. A high CVP therefore decreases the gradient for venous return, while at the same time decreasing organ driving pressure and therefore blood flow. Venous pressure has a much greater effect on microcirculatory flow than the MAP; provided that the MAP is within an organ's autoregulatory range, the CVP becomes the major determinant of capillary blood flow.<sup>19 20</sup>

According to the Frank-Starling principle, as left-ventricular (LV) end-diastolic volume (i.e. preload) increases, LV stroke volume (SV) increases until the optimal preload is achieved, at which point the SV remains relatively constant.<sup>21</sup> This optimal preload is related to the maximal overlap of the actin-myosin myofibrils. Fluid administration will only increase SV if two conditions are met, namely: i) that the fluid bolus increases the MCFP more than it increases the CVP, thereby increasing the gradient for venous return, and ii) that both ventricles are functioning on the 'ascending limb' of the Frank-Starling curve.<sup>22 23</sup>

The vascular endothelium is coated on the luminal side by a web of membrane-bound glycoproteins and proteoglycans known as the endothelial glycocalyx.<sup>24–26</sup> The glycocalyx plays a major role as a vascular barrier, preventing large macromolecules moving across the endothelium, preventing leucocyte and platelet aggregation and limiting tissue oedema. An intact endothelial glycocalyx is a prerequisite of a functioning vascular barrier.<sup>27</sup> Increased cardiac filling pressures after aggressive fluid resuscitation increase the release of natriuretic peptides.<sup>28 29</sup> Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx.<sup>30–32</sup> Damage to the glycocalyx profoundly increases endothelial permeability. In addition, increased natriuretic peptides inhibit the lymphatic propulsive motor activity reducing lymphatic drainage.<sup>33–35</sup>

## Vascular dysfunction with sepsis

Septic shock is primarily a vasoplegic state with arterial and venous dilatation, as a result of failure of the vascular smooth muscle to constrict.<sup>36</sup> Vasoplegic shock is believed to be because of increased expression of inducible nitric oxide synthetase with increased production of nitric oxide (NO), activation of  $K_{ATP}$  channels resulting in hyperpolarisation of the muscle cell membrane, increased production of natriuretic peptides (which act synergistically with NO) and a relative vasopressin deficiency.<sup>36</sup> Arterial dilatation results in systemic hypotension. However, more importantly, profound venodilation occurs in the splanchnic and cutaneous vascular beds increasing the unstressed blood volume, decreasing venous return and cardiac output.<sup>14 15</sup> As approximately 70% of the blood volume is within the venous system, changes in venous blood volume play a major role in determining venous return.<sup>15</sup>

Sepsis is characterized by increased expression and activation of endothelial adhesion molecules with adhesion and activation of platelets, leucocytes and mononuclear cells and activation of the coagulation cascade.<sup>37</sup> This results in a diffuse endothelial injury, microvascular thrombosis, gaps between the endothelial cells (paracellular leak) and shedding of the endothelial-glycocalyx.<sup>38 39</sup> The combination of these mechanisms contributes to a reduction in functional capillary density, heterogeneous abnormalities in microcirculatory blood flow and increased capillary permeability.<sup>40 41</sup>

## Cardiac changes with sepsis

Myocardial depression in patients with septic shock was first described in 1984 by Parker and colleagues<sup>42</sup> using radionuclide cineangiography. In a series of 20 patients, these investigators reported a 50% incidence of LV systolic dysfunction. Notably, in this study the initial ejection fraction and ventricular volumes were normal in non-survivors and these indices did not change during serial studies; it is likely that these patients had significant diastolic dysfunction. The initial studies evaluating cardiac function in sepsis focused on LV systolic function. However, LV diastolic dysfunction has emerged as a common finding in patients with severe sepsis and septic shock.<sup>43</sup> Adequate filling during diastole is a crucial component of effective ventricular pump function. Diastolic dysfunction refers to the presence of an abnormal LV diastolic distensibility, filling, or relaxation, regardless of LV ejection fraction. Predominant diastolic dysfunction appears to be at least twice as common as systolic dysfunction in patients with sepsis.<sup>43</sup> In the largest study to date ( $n=262$ ), Landesberg and colleagues<sup>44</sup> reported diastolic dysfunction in 54% of patients with sepsis while 23% of patients had systolic dysfunction. Brown and colleagues<sup>45</sup> performed serial echocardiograms in 78 patients with severe sepsis or septic shock. In this study 62% of patients had diastolic dysfunction on at least one echocardiogram. Unlike systolic LV dysfunction, diastolic dysfunction is an important prognostic marker in patients with sepsis.<sup>43–45</sup> Diastolic dysfunction is becoming increasingly recognized in the community, particularly in patients with hypertension, diabetes, obesity and with advancing age.<sup>46–48</sup> These conditions are associated with an increased risk of sepsis and may therefore further increase the prevalence and severity of diastolic dysfunction in patients with sepsis. Patients' with diastolic dysfunction respond very poorly to fluid loading.<sup>44</sup> This was demonstrated in a landmark study published by Ognibene and colleagues<sup>49</sup> in 1988, who reported an insignificant increase LV stroke work index and LV end-diastolic volume index in patients with septic

shock who received a fluid challenge. In these patients, fluid loading will increase cardiac filling pressures, increase venous and pulmonary hydrostatic pressures with the increased release of natriuretic peptides with minimal (if any) increase in SV. Furthermore, as reviewed above, aggressive fluid resuscitation in itself causes diastolic dysfunction which will compound the pre-existing and/or sepsis-induced diastolic dysfunction.

## Fluid responsiveness

The widely accepted rationale behind fluid resuscitation in sepsis is to improve cardiac output and organ perfusion, thereby limiting organ dysfunction. Logically, therefore, the only reason to resuscitate a patient with fluid (give a fluid bolus) would be to cause a clinically significant increase in SV. A patient whose SV increases by 10–15% after a fluid challenge (250–500 ml) is considered to be a fluid responder.<sup>50</sup> Nonetheless, according to the Frank-Starling principle, as the preload increases, SV increases until the optimal preload is achieved, at which point the SV remains relatively constant.<sup>50</sup> If the fluid challenge does not increase SV, volume loading serves the patient no useful benefit and is likely harmful. The adverse effects of fluid loading when a patient is on the flat portion of the Frank-Starling curve, is related to the curvilinear shape of the left ventricular pressure-volume curve, resulting from altered diastolic compliance at higher filling pressures.<sup>16–18</sup> As the patient reaches the plateau of his/her Frank-Starling curve, atrial pressures increase, increasing venous and pulmonary hydrostatic pressures which combined with the increased release of natriuretic peptides, causes a shift of fluid into the interstitial space, with an increase in pulmonary and tissue oedema (see Fig. 1). Tissue oedema impairs

oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage and disturbs cell-cell interactions.<sup>52–53</sup> Increased right atrial pressure (CVP) is transmitted backwards increasing venous pressure in vital organs, with a profound effect on microcirculatory flow and organ function.<sup>19</sup> The kidney is particularly affected by increased venous pressure, which leads to increased renal sub-capsular pressure and reduced renal blood flow and glomerular filtration rate.<sup>52</sup>

## Fluid responsiveness and the haemodynamic effects of fluids in patients with sepsis

Studies in heterogeneous groups of critically ill and injured patients and those undergoing surgery have reproducibly demonstrated that only about 50% of haemodynamically unstable patients are fluid responders.<sup>50–56</sup> This is a fundamental concept which is not widely appreciated,<sup>57–58</sup> and challenges the widely accepted notion that fluid administration is the ‘cornerstone of resuscitation’.<sup>5–7–59</sup> As a result of the effects of sepsis on the venous capacitance vessels and myocardial function, it is likely that less than 40% of hypotensive patients with severe sepsis or septic shock are ‘fluid responders’.<sup>60–62</sup>

The goal of fluid resuscitation is to increase the stressed blood volume and MCFP more than the CVP, and thereby increase the pressure gradient for venous return. However the ability of crystalloids (the most common fluid used for the resuscitation of patients with sepsis) to expand the intravascular volume is poor. Chowdhury and colleagues<sup>63</sup> reported that in healthy volunteers, only 15% of a crystalloid bolus remained in the intravascular space at 3 h, with 50% of the infused volume being in the

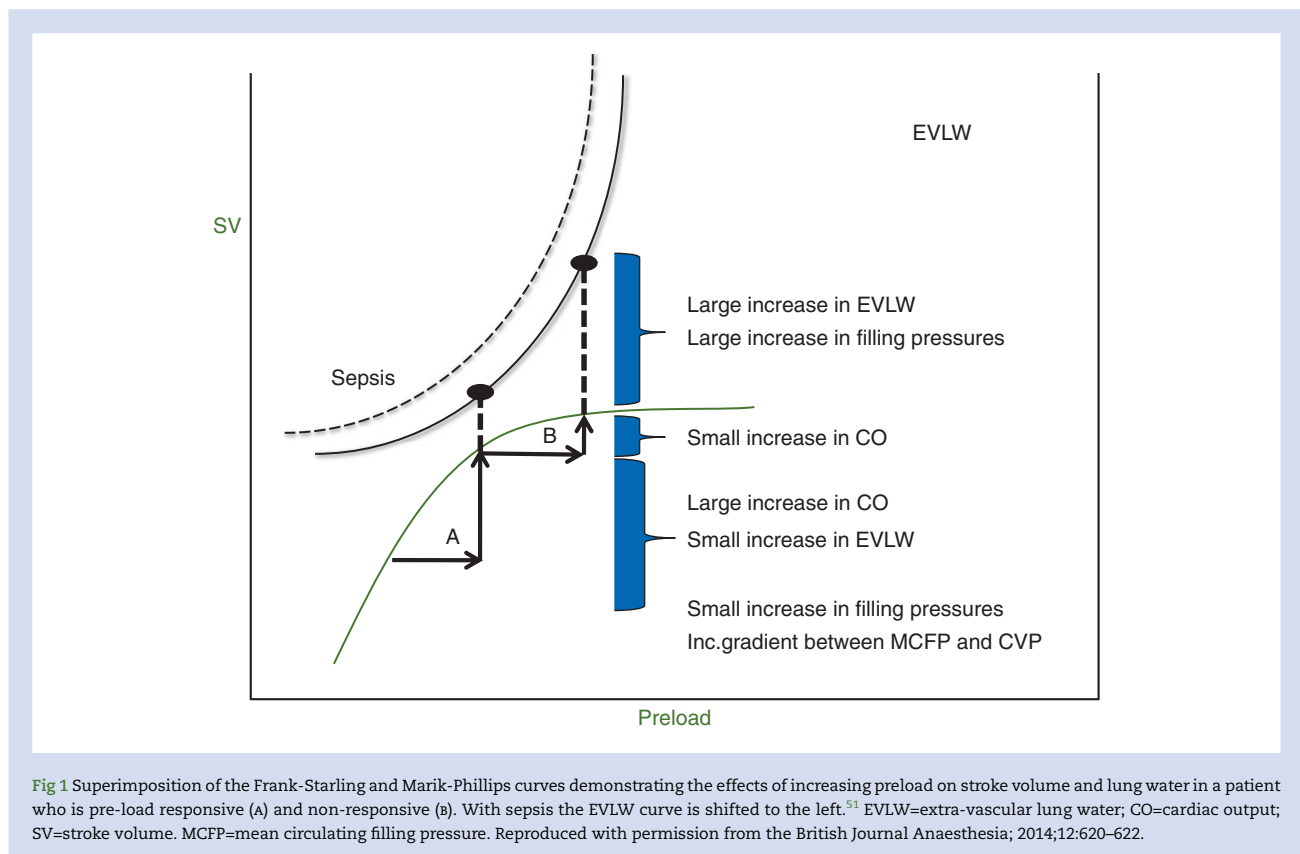


Fig 1 Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume and lung water in a patient who is pre-load responsive (A) and non-responsive (B). With sepsis the EVLW curve is shifted to the left.<sup>51</sup> EVLW=extra-vascular lung water; CO=cardiac output; SV=stroke volume. MCFP=mean circulating filling pressure. Reproduced with permission from the British Journal Anaesthesia; 2014;12:620–622.

extravascular extracellular compartment. In patients with sepsis and in experimental models, less than 5% of a crystalloid bolus remains intravascular an hour after the end of the infusion.<sup>64 65</sup> It is therefore likely that the haemodynamic effects of a fluid bolus (in the fluid responders) are short-lived, with the net effect being the shift of fluid into the interstitial compartment with tissue oedema. Nunes and colleagues<sup>66</sup> demonstrated that in fluid responders, the SV returned to baseline 60 min after a crystalloid bolus. Glassford and colleagues<sup>67</sup> performed a systematic review which examined the haemodynamic response of fluid boluses in patients with sepsis. These authors reported that while the mean arterial pressure (MAP) increased by 7.8 (3.8) mm Hg immediately after the fluid bolus, the MAP had returned close to baseline at one h with no increase in urine output. In a retrospective analysis of the ARDSnet Fluid and Catheter Treatment Trial (FACTT),<sup>68</sup> Lammi and colleagues<sup>62</sup> examined the physiological effect of 569 fluid boluses (15 ml kg<sup>-1</sup>; 1025±243 ml) in 127 patients (the majority of whom were septic), randomized to the pulmonary artery catheter arm of the study. The FACTT trial required reassessment of the haemodynamic profile one h after the fluid bolus, if the indication for fluids was shock, ineffective circulation, or low urine output and four h if the indication was a low pulmonary artery occlusion pressure (PAOP).<sup>68</sup> Fifty-eight percent of fluid boluses were given for shock or poor urine output/ineffective circulation, with 42% of boluses given for a low PAOP. In this study, only 23% of patients were fluid responders (increase in CI > 15%). There was a small increase in the MAP (78.3 16.4 to 80.4 16.5 mm Hg) while the urine output did not change in the 1–4 h after the fluid bolus.

Monge-Garcia and colleagues<sup>69</sup> measured the effects of a fluid bolus on arterial load in patients with septic shock. In this study 67% of patients were fluid responders, however the MAP increased in only 44% of these patients (pressure responder). Overall there was a significant reduction in effective arterial elastance (Ea) and systemic vascular resistance (SVR), this effect being most marked in the pre-load responders who were pressure non-responders. Additional studies have demonstrated a decrease in SVR after fluid resuscitation in patients with sepsis.<sup>70 71</sup> This suggests that fluid boluses should be considered vasodilator therapy, in patients with sepsis and that aggressive fluid resuscitation may potentiate the hyperdynamic state.

In summary, these studies demonstrate that the majority of patients with severe sepsis and septic shock are not fluid responders. Furthermore, the haemodynamic changes in the fluid responders are small, short-lived and likely to be clinically insignificant. However, aggressive fluid resuscitation will likely have adverse haemodynamic consequences including an increase in cardiac filling pressures, damage to the endothelial glycocalyx, arterial vasodilation and tissue oedema. Consequently, the concept that aggressive fluid resuscitation is the 'cornerstone of resuscitation' of patients with severe sepsis and septic shock needs to be reconsidered.<sup>5–7 59</sup> Indeed, it is likely that aggressive fluid resuscitation increases the morbidity and mortality of patients with sepsis (see section below). Nevertheless the updated Surviving Sepsis Campaign Guidelines, published after the publication of the ProCESS, ARISE and PROMISE studies<sup>8–10</sup> mandate the administration of '30 ml kg<sup>-1</sup> crystalloid for hypotension or lactate ≥ 4 mmol Litre<sup>-1</sup> within 3 h of presentation to hospital.<sup>72</sup> This recommendation is problematic as the majority of hypotensive patients with septic shock will not respond to fluids; this approach is likely to lead to 'salt water drowning' with an increase in the morbidity and mortality of these patients.<sup>73</sup> Furthermore, as discussed below, an increased blood lactate is unlikely to be associated with anaerobic metabolism, or inadequate oxygen

delivery, and attempts at increasing oxygen delivery do not increase oxygen consumption or lower lactate concentrations. Indeed such an approach has been demonstrated to increase the risk of death of critically ill patients.<sup>74</sup>

These data suggest that only patients who are fluid responsive should be treated with fluid boluses. Furthermore, the patients' fluid responsiveness and the risk/benefit ratio of fluid administration needs to be determined before each fluid bolus.<sup>75</sup> As the haemodynamic response to a fluid challenge is very short-lived and large fluid boluses (20–30 ml kg<sup>-1</sup>) are associated with severe volume overload, the mini-fluid bolus approach (200–500 ml) to fluid therapy is recommended.<sup>76</sup> The passive leg raising manoeuvre (PLR) and the fluid bolus test coupled with real-time SV monitoring, are currently the only techniques which have an acceptable degree of clinical accuracy, which can be used for determining fluid responsiveness.<sup>51</sup> Because of its ease of use, simplicity, high diagnostic accuracy, inherent safety and short procedure time (less than 5 min to perform) the PLR is the preferred method to assess fluid responsiveness in the emergency department, hospital ward and ICU.<sup>51 75</sup> The PLR manoeuvre is performed by lifting the legs passively from the horizontal position and is associated with the gravitational transfer of blood (about 300 ml) from the lower limbs and abdomen toward the intrathoracic compartment.<sup>75 77 78</sup> The PLR manoeuvre has the advantage of reversing its effects once the legs are returned to the horizontal position.<sup>75 79 80</sup> Therefore, the PLR manoeuvre is considered a reversible or 'virtual' fluid challenge. The ability of the PLR manoeuvre to serve as a test of preload responsiveness has been confirmed in multiple studies performed in critically ill patients. A meta-analysis, which pooled the results of eight studies, confirmed the excellent value of PLR to predict fluid responsiveness in critically ill patients with a global area under the ROC curve of 0.95 (95% CI, 0.92–0.95).<sup>81</sup> In an updated meta-analysis which evaluated 21 studies, we report a pooled ROC AUC of 0.93–0.95 (Monnet X, Marik P, Teboul JL; submitted for publication). As the maximal haemodynamic effects of PLR occur within the first min of leg elevation,<sup>75 80</sup> it is important to assess these effects with a method able to track changes in cardiac output or SV on a real-time basis. It is important to note that the change in bp after a PLR or fluid challenge is a poor guide to fluid responsiveness; SV may increase without a significant change in bp.<sup>70</sup> Furthermore, unlike techniques to determine fluid responsiveness based on heart-lung interactions, the PLR manoeuvre can be performed in spontaneously breathing patients, patients with cardiac arrhythmias and those receiving low tidal volume ventilation.<sup>75 51</sup>

The chest radiograph, CVP, central venous oxygen saturation (ScvO<sub>2</sub>) and ultrasonography, including the vena-caval collapsibility index, have limited value in guiding fluid management and should not be used for this purpose.<sup>54 82–86</sup> Furthermore, it has been well established that physical examination cannot be used to predict fluid responsiveness and physical examination is unreliable for estimating intravascular volume status.<sup>87</sup> It is therefore very troubling that the updated *Surviving Sepsis Campaign Guidelines* which are now federally mandated in the USA (SEP-1 Early Management Bundle, #0500 Severe Sepsis and Septic Shock: management Bundle) require either a 'focused exam by a licensed independent practitioner', or measurement of the CVP or ScvO<sub>2</sub>, or bedside cardiovascular ultrasound, to assess the volume status of the patient with severe sepsis and septic shock.<sup>88</sup> It should be noted that the area under the receiver operator characteristic (ROC) curve of the CVP, for predicting fluid responsive is approximately 0.5, which is considered a 'completely useless test'.<sup>54 89 90</sup> Furthermore, it is important to emphasize

that a normal CVP is between 0–2 mm Hg; this is necessary to ensure adequate venous return and cardiac output (as discussed above). In addition, while the change in CVP in response to a fluid challenge is still widely promoted as a method to guide fluid therapy,<sup>57</sup> this technique has no physiologic basis and is unable to predict fluid responsiveness with any degree of accuracy.<sup>54–91</sup> Furthermore, it should be noted that with the exception of measuring dynamic changes in the carotid Doppler peak velocity,<sup>86–92–93</sup> bedside ultrasound including the inferior vena caval distensibility index cannot accurately predict fluid responsiveness.<sup>51–82–85–86</sup> It is somewhat astonishing that the ScvO<sub>2</sub> is still being recommended to guide the resuscitation of critically ill septic patients and is being used as an indicator of the quality of care delivered.<sup>72–88</sup> Monitoring the ScvO<sub>2</sub> in patients with sepsis has no scientific basis, as patients with sepsis usually have a normal or increased ScvO<sub>2</sub>,<sup>94–95</sup> and a high (ScvO<sub>2</sub> > 90%) rather than low ScvO<sub>2</sub> has been demonstrated to be an independent predictor of death.<sup>96</sup> Three large randomized controlled trials (ProCESS, ARISE and PROMISE) have now demonstrated that titrating therapy to a ScvO<sub>2</sub> > 70% does not improve outcome,<sup>8–10</sup> but rather increases the risk of organ dysfunction, length of ICU stay and increased use of resources and costs.<sup>10</sup> These observations must lead to the conclusion that the original EGDT study was not scientifically valid and that no aspect of this study should be used to guide the management of patients with severe sepsis and septic shock.<sup>3–97–98</sup>

In addition to targeting a CVP greater than 8 mm Hg, the Surviving Sepsis Campaign guideline recommends ‘targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion’.<sup>7</sup> This recommendation is based on the notion that an elevated lactate is a consequence of tissue hypoxia and inadequate oxygen delivery.<sup>95</sup> However, these assertions are likely wrong.<sup>99</sup> Hotchkiss and Karl<sup>100</sup> in a seminal review published over 20 yr ago, demonstrated that cellular hypoxia and bioenergetic failure does not occur in sepsis. It has now been well established that epinephrine released as part of the stress response in patients with severe sepsis, stimulates Na<sup>+</sup> K<sup>+</sup>-ATPase activity. Increased activity of Na<sup>+</sup> K<sup>+</sup> ATPase leads to increased lactate production under well-oxygenated conditions in various cells, including erythrocytes, vascular smooth muscle, neurons, glia, and skeletal muscle.<sup>101–102</sup> While

sepsis is considered to be a ‘hypermetabolic’ condition oxygen consumption and energy expenditure are broadly comparable with that of normal people, with energy expenditure decreasing with increasing sepsis severity.<sup>103–105</sup> Therefore, there is no requirement that oxygen delivery increase with sepsis. Indeed, increasing oxygen delivery in patients with sepsis does not increase oxygen consumption nor decrease lactate concentrations.<sup>106–107</sup> The critical oxygen delivery threshold for humans (both septic and non-septic) is approximately 3.8 (1.5) ml min<sup>-1</sup> kg<sup>-1</sup> (270 ml min<sup>-1</sup> in a 70 kg patient).<sup>108</sup> These values translate into a cardiac output of approximately 2 Litre min<sup>-1</sup>; it is likely that only pre-terminal moribund patients with septic shock would have such a low cardiac output.

### Evidence supporting the deleterious effects of aggressive fluid resuscitation

The harmful effects of aggressive fluid resuscitation on the outcome of sepsis are supported by experimental studies and data accumulated from clinical trials.<sup>109–110</sup> Multiple clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patient with sepsis.<sup>29–111–120</sup> The most compelling data that fluid loading in sepsis is harmful, comes from the landmark ‘Fluid Expansion as Supportive Therapy (FEAST)’ study performed in 3141 sub-Saharan children with severe sepsis.<sup>121</sup> In this randomized study, aggressive fluid loading was associated with a significantly increased risk of death. After the Rivers’ Early Goal Directed Therapy trial,<sup>3</sup> which formed the basis for the concept of early aggressive fluid resuscitation, a number of EGDT studies have been published.<sup>4–8–10–122</sup> An analysis of these studies demonstrates a marked reduction in mortality over this time period (see Fig. 2). While all these studies emphasized the early use of appropriate antibiotics, the decline in the amount of fluids administered in the first 72 h is striking. Furthermore as illustrated in Fig. 3 there is a very strong correlation between the amount of fluid administered (in first 6 h) and the target CVP. It should be noted that the CVP in the usual arm of both the ARISE (The Australasian Resuscitation in Sepsis Evaluation) and ProMISE (Protocolised Management in Sepsis) trials was greater than 10 mm Hg, being almost identical to the EGDT arm, and with

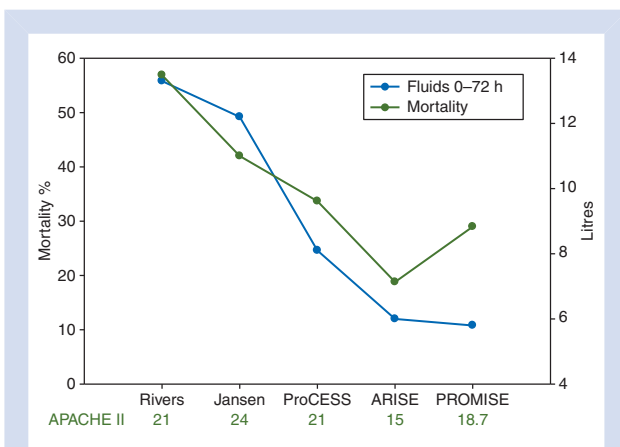


Fig 2 Fluid administered between enrolment and 72 h and 90-day mortality in the control arm of the Early Goal Directed Therapy (EGDT) Studies performed between 2001 and 2015. APACHE II=APACHE II Severity of illness scoring system (0–71).

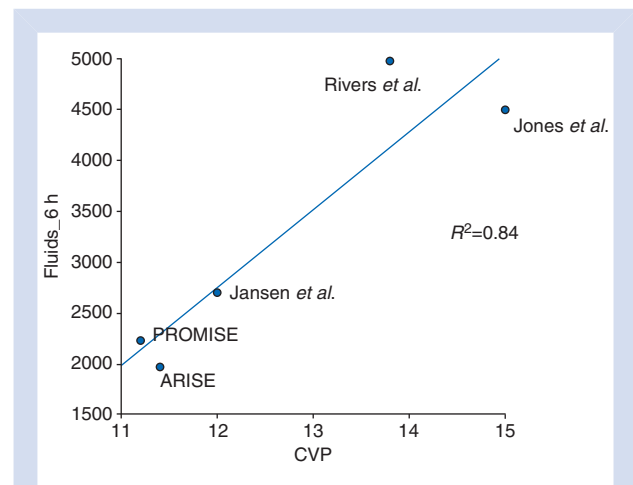


Fig 3 Fluid administered between enrolment and 6 h and central venous pressure (CVP) at h in the Early Goal Directed arm of the EGDT studies performed between 2001 and 2015.

almost an identical amount of fluid being administered in the usual arm, as in the active EGDT arm in both studies.<sup>9 10</sup> Clinicians seem compelled to give fluid when the CVP is less than 8 mm Hg; the only solution to this pervasive problem is to stop measuring the CVP.

### A haemodynamically-guided conservative fluid resuscitation strategy

These data strongly support a haemodynamically-guided fluid resuscitation strategy in patients with severe sepsis and septic shock. Furthermore, from an evolutionary point of view, humans have evolved to deal with hypovolemia and not hypervolemia. Large fluid boluses may counter the life preserving homeostatic mechanisms in unstable critically ill patients, increasing the risk of death.<sup>123</sup> In some patients, hypotension and tachycardia do resolve with limited fluid resuscitation. It is likely that many of these patients have super-added dehydration as a result of poor oral intake and a delay in seeking medical attention. However, fluids alone will not reverse the haemodynamic instability of patients with more severe sepsis; in these patients, fluids alone are likely to exacerbate the vasodilatory shock and increase the capillary leak and tissue oedema. Based on these data, the initial resuscitation of patients with septic shock should logically include at most 500 ml boluses of crystalloid (Ringer's lactate), to a maximum of about 20 ml kg<sup>-1</sup>.<sup>124</sup> Ideally, fluid resuscitation should be guided by the determination of fluid responsiveness.<sup>50 51</sup> Normal saline is an 'unphysiologic' solution that should be avoided, except in patients with acute neurological injuries. Normal saline causes a hyperchloraemic metabolic acidosis<sup>125-128</sup>; it decreases renal blood flow<sup>63</sup> increasing the risk of renal failure.<sup>129</sup> In patients with sepsis, the use of normal saline as compared with physiologic salt solutions, has been associated with an increased risk of death.<sup>130</sup> Similarly, synthetic starch solutions increase the risk of renal failure and death in patients with sepsis and should be avoided.<sup>131 132</sup>

The septic patient with an intra-abdominal catastrophe, who requires urgent surgical intervention, represents a sub-group of patients that may require more aggressive fluid resuscitation. However, overly aggressive fluid resuscitation will likely result in intra-abdominal hypertension, which is associated with a high risk of complications and death.<sup>133 134</sup> In these patients continuous SV monitoring is essential and ongoing fluid requirements should be guided by the trend in the SV and the haemodynamic response to a mini-fluid bolus. In addition, perioperative, intra-abdominal pressure monitoring is required in these patients.<sup>133</sup>

Norepinephrine should be initiated in those patients who remain hypotensive (MAP < 65 mm Hg) despite this initial, limited fluid strategy.<sup>124 135</sup> Norepinephrine increases arterial vascular tone increasing bp and organ blood flow. Venous capacitance vessels are much more sensitive to sympathetic stimulation than are arterial resistance vessels, consequently low dose  $\alpha$ -1 agonists cause greater veno- than arterio-constriction.<sup>136</sup> In septic patients,  $\alpha$ -1 agonists mobilize blood from the unstressed reservoirs in the splanchnic circulation and skin, thereby increasing venous return and cardiac output. In a porcine endotoxic shock model, Datta and Magder<sup>137</sup> demonstrated that norepinephrine increased the MCFP, leading to an increase in venous return. Similarly in patients with septic shock, Persichini and colleagues<sup>138</sup> demonstrated that decreasing the dose of norepinephrine, decreased the MCFP with a decrease in venous return and cardiac output. In a cohort of patients with septic shock Kozieras and colleagues<sup>139</sup> demonstrated that norepinephrine increased

cardiac index, systemic vascular resistance and central blood volumes (intrathoracic blood volume, global end-diastolic volume), as measured by transpulmonary thermodilution. In this study extra-vascular lung water (EVLW) remained unchanged. Hamzaoui and colleagues<sup>140</sup> demonstrated that the early administration of norepinephrine increased preload, cardiac output and MAP largely reversing the haemodynamic abnormalities of severe vasodilatory shock. Abid and colleagues<sup>141</sup> demonstrated that the early use of norepinephrine in patients with septic shock was a strong predictor of survival. These studies demonstrate that in patients with septic shock, the early use of norepinephrine restores the stressed blood volume, increasing the MCFP, venous return and cardiac output. The increase in the stressed blood volume is as a result of the mobilisation of blood, rather than the short-lived effect of a volume expander. Therefore unlike fluids, the effect of  $\alpha$ -1 agonists on venous return is enduring and not associated with tissue oedema.  $\alpha$ -1 agonists should not be used in patients with hypovolaemic shock (e.g. cholera) who are already vasoconstricted; in this setting,  $\alpha$ -1 agonists will cause severe vasoconstriction, impairing organ blood flow. However, in septic veno- and arterio-dilated patients,  $\alpha$ -1 agonists increase venous return, increase stroke volume and increase arterial tone, thereby increasing organ blood flow.<sup>142-144</sup> Digital and limb ischaemia and ischaemic skin lesions are extremely rare with the use of norepinephrine,<sup>145</sup> occurring usually with high dosages and usually when used together with vasopressin.<sup>146 147</sup> Furthermore, uncontrolled disseminated intravascular coagulation (DIC) plays a contributing role in these patients.<sup>148</sup> We are unaware of any reported patients with digital or limb ischaemia associated with the early use of norepinephrine. In our experience the early use of norepinephrine appears to reduce the peak and total dose of vasopressors administered. It is noteworthy that norepinephrine may be safely given through a well-functioning peripheral venous catheter,<sup>149</sup> precluding the requirement for emergent central venous catheterization, which is generally regarded as an obstacle to the early use of norepinephrine. In experimental sepsis models, norepinephrine appears preferable to epinephrine and phenylephrine as a first-line therapy in restoring haemodynamic stability.<sup>150 151</sup> Dopamine as opposed to norepinephrine is associated with an increased risk of arrhythmias and death in patients with sepsis and should be avoided.<sup>152-154</sup>

### Conclusions

An emerging body of basic science and clinical studies supports the concept of a haemodynamically-guided, restricted fluid resuscitation strategy in patients with severe sepsis and septic shock. Initial fluid resuscitation should be limited and guided by an assessment of fluid responsiveness. Norepinephrine increases preload, systemic vascular resistance and cardiac output and its use in patients with persistent hypotension is recommended early in the course of septic shock. Early bedside echocardiographic assessment of cardiac function is recommended to guide further haemodynamic management. Adequately powered, randomized, controlled trials, are urgently required to demonstrate the benefits of the early use of norepinephrine and a conservative, haemodynamically-guided fluid resuscitation strategy.

### Authors' contributions

Writing paper: P.M., R.B.

Revising paper: both authors

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## Declaration of interest

In the last 5 yr P.M. has received an honorarium from Pulsion Medical, manufacture of the PiCCO haemodynamic device for a lecture delivered at an international Critical Care Symposium (about 1000 GBP) and an honorarium from Cheetah Medical, manufacturer of the NiCOM haemodynamic device for a lecture delivered at medical grand rounds (about 1500 GBP). R.B. has no conflicts of interest to declare.

## References

- Cosnett JE. The origins of intravenous fluid therapy. *Lancet* 1989; **1**: 768–71
- MacGillivray N. Dr Latta of Leith: pioneer in the treatment of cholera by intravenous saline infusion. *J R Coll Physicians Edinb* 2006; **36**: 80–5
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368–77
- Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739–46
- Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; **32**: 858–73
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis Campaign: International guidelines for management of severe sepsis and septic shock. 2008. *Crit Care Med* 2008; **36**: 296–327
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. 2012. *Crit Care Med* 2013; **41**: 580–637
- Yealy DM, Kellum JA, Huang DT, et al. A Randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683–93
- Peake SL, Delasney A, Bailey M, et al. Goal-directed resuscitation for patients with Early Septic Shock. *N Engl J Med* 2014; **371**: 1496–506
- Mouncey PR, Osborn TM, Power S, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301–11
- Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMiSe investigators. *Intensive Care Med* 2015; **41**: 1549–60
- Funk DJ, Jacobsen E, Kumar A. The role of venous return in critical illness and shock-part I: physiology. *Crit Care Med* 2013; **41**: 250–7
- Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; **35**: 123–9
- Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiol* 2008; **108**: 735–48
- Peters J, Mack GW, Lister G. The importance of the peripheral circulation in critical illnesses. *Intensive Care Med* 2001; **27**: 1446–58
- Applegate RA, Johnston WE, Vinten-Johansen J, Klopfenstein HS, Little WC. Restraining effect of intact pericardium during acute volume loading. *Am J Physiol* 1992; **262**: H1725–33
- Tyson GS, Maier GW, Olsen CO, Davis JW, Rankin JS. Pericardial influences on ventricular filling in the conscious dog. An analysis based on pericardial pressure. *Circ Res* 1984; **54**: 173–84
- Fragata J, Areias JC. Effects of gradual volume loading on left ventricular diastolic function in dogs: implications for the optimisation of cardiac output. *Heart* 1996; **75**: 352–7
- Vellinga NA, Ince C, Boerma EC. Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis. *BMC Anesthesiol* 2013; **13**: 17
- Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010; **6**: 107–15
- Starling EH. *The Linacre Lecture on the Law of the Heart, Given at Cambridge, 1915*. London: Longmans, 1918; 27
- Marik PE. The physiology of volume resuscitation. *Curr Anesthesiol Rep* 2014; **4**: 353–9
- Cecconi M, Aya HD, Geisen M, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. *Intensive Care Med* 2013; **39**: 1299–305
- Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth* 2012; **108**: 384–94
- Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Archiv - Eur J Physiol* 2007; **454**: 345–59
- Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* 2010; **87**: 198–210
- Jacob M, Chappell D, Rehm M. The ‘third space’—fact or fiction? *Best Practice & Research. Clinical Anaesthesiology*. 2009; **23**: 145–57
- Ueda S, Nishio K, Akai Y, et al. Prognostic value of increased plasma levels of brain natriuretic peptide in patients with septic shock. *Shock* 2006; **26**: 134–9
- Zhang Z, Zhang Z, Xue Y, Xu X, Ni H. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resus Emerg Med* 2012; **20**: 86
- Bruegger D, Jacob M, Rehm M, et al. Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. *Am J Physiol Heart Circ Physiol* 2005; **289**: H1993–99
- Berg S, Golster M, Lisander B. Albumin extravasation and tissue washout of hyaluronan after plasma volume expansion with crystalloid or hypooncotic colloid solutions. *Acta Anaesthesiol Scand* 2002; **46**: 166–72
- Bruegger D, Schwartz L, Chappell D, et al. Release of atrial natriuretic peptide precedes shedding of the endothelial glycocalyx equally in patients undergoing on- and off-pump coronary artery bypass surgery. *Basic Res Cardiol* 2011; **106**: 1111–21
- Atchison DJ, Johnston MG. Atrial natriuretic peptide attenuates flow in an isolated lymph duct preparation. *Eur J Physiol* 1996; **431**: 618–24
- Anderson WD, Kulik TJ, Mayer JE, Anderson WD, Kulik TJ, Mayer JE. Inhibition of contraction of isolated lymphatic ducts by atrial natriuretic peptide. *Am J Physiol* 1991; **260**: R610–4

35. Ohhashi T, Watanabe N, Kawai Y, Ohhashi T, Watanabe N, Kawai Y. Effects of atrial natriuretic peptide on isolated bovine mesenteric lymph vessels. *Am J Physiol* 1990; **259**: H42–7
36. Landry DW, Oliver JA. Pathogenesis of vasodilatory shock. *N Engl J Med* 2001; **345**: 588–95
37. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. *Intensive Care Med* 2010; **36**: 1286–98
38. Goldenberg NM, Steinberg BE, Slutsky AS, Lee WL. Broken barriers: a new take on sepsis pathogenesis. *Sci Translation Med* 2011; **3**: 88ps25
39. Hernandez G, Bruhn A, Ince C. Microcirculation in sepsis: new perspectives. *Curr Vasc Pharm* 2013; **11**: 161–9
40. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; **166**: 98–104
41. Trzeciak S, Rivers E. Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. *Crit Care* 2005; **9** (suppl 4): S20–6
42. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med* 1984; **100**: 483–90
43. Sanfilippo F, Corredor C, Fletcher N, et al. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. *Intensive Care Med* 2015; **41**: 1004–13
44. Landesberg G, Gilon D, Meroz Y, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J* 2012; **33**: 895–903
45. Brown SM, Pittman JE, Hirshberg EL, et al. Diastolic dysfunction and mortality in early severe sepsis and septic shock: a prospective, observational echocardiography study. *Crit Ultrasound J* 2012; **4**: 8
46. Cheitlin MD. Cardiovascular physiology—changes with aging. *Am J Geriatr Cardiol* 2003; **12**: 9–13
47. Pieske B, Wachter R. Impact of diabetes and hypertension on the heart. *Curr Opin Cardiol* 2008; **23**: 340–9
48. Russo C, Jin Z, Homma S, et al. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol* 2011; **57**: 1368–74
49. Ognibene FP, Parker MM, Natanson C, Shelhamer JH, Parrillo JE. Depressed left ventricular performance: response to volume infusion in patients with sepsis and septic shock. *Chest* 1988; **93**: 903–10
50. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Crit Care* 2011; **1**: 1
51. Marik PE, Lemson J. Fluid responsiveness: An evolution of our understanding. *Br J Anaesth* 2014; **112**: 620–2
52. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. *Nat Rev Nephrol* 2014; **10**: 37–47
53. Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. *Crit Care* 2012; **16**: 302
54. Marik PE, Cavallazzi R. Does the Central Venous Pressure (CVP) predict fluid responsiveness: An update meta-analysis and a plea for some common sense. *Crit Care Med* 2013; **41**: 1774–81
55. Biais M, Ehrmann S, Mari A, et al. Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: the grey zone approach. *Crit Care* 2014; **18**: 587
56. Cannesson M, Le MY, Hofer CK, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a “gray zone” approach. *Anesthesiol* 2011; **115**: 231–41
57. Vincent JL, Pelosi P, Pearse R, et al. Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. *Crit Care* 2015; **19**: 224
58. Wilms H, Mittal A, Haydock MD, van den Heever M, Devaud M, Windsor JA. A systematic review of goal directed fluid therapy: Rating of evidence for goals and monitoring methods. *J Crit Care* 2014; **29**: 204–9
59. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; **32**: 1928–48
60. Smith B, Phillips R, Madigan V, West M. Decreased mortality, morbidity and emergency transport in septic shock: A new protocol based on advanced noninvasive haemodynamics and early antibiotics [abstract]. *Crit Care Med* 2013; **40**: 1–17
61. Mallat J, Meddour M, Durville E, et al. Mini-fluid challenge in patients with low-volume mechanical ventilation: the decrease in pulse pressure and stroke volume variations accurately predicts fluid responsiveness. *Br J Anaesth* 2015; **115**: 449–56
62. Lammi MR, Aiello B, Burg GT, et al. Response to fluid boluses in the fluid and catheter treatment trial. *Chest Advance Access published on May 28, 2015*. doi: 10.1378/chest.15-0445
63. Chowdhury AH, Cox EF, Francis S, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; **256**: 18–24
64. Sanchez M, Jimenez-Lendinez M, Cidoncha M, et al. Comparison of fluid compartments and fluid responsiveness in septic and non-septic patients. *Anaesth Intensive Care* 2011; **39**: 1022–9
65. Bark BP, Oberg CM, Grande PO. Plasma volume expansion by 0.9% NaCl during sepsis/systemic inflammatory response syndrome, after hemorrhage, and during a normal state. *Shock* 2013; **40**: 59–64
66. Nunes T, Ladeira R, Bafi A, de Azevedo L, Machado F, Freitas F. Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation. *Ann Intensive Care* 2014; **4**: 25
67. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. *Crit Care* 2014; **18**: 2557
68. Wioedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564–75
69. Monge-Garcia MI, Gonzalez PG, Romero MG, et al. Effects of fluid administration on arterial load in septic shock patients. *Intensive Care Med* 2015; **41**: 1247–55
70. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De BD, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? *Intensive Care Med* 2012; **38**: 422–8
71. Monnet X, Chemla D, Osman D, et al. Measuring aortic diameter improves accuracy of esophageal Doppler in assessing fluid responsiveness. *Crit Care Med* 2007; **35**: 477–82
72. Surviving Sepsis Campaign; 6 hour bundle revised. <http://www.survivingsepsis.org/News/Pages/SSC-Six-Hour-Bundle-Revised.aspx> 2015. (Accessed 4-9-2015)
73. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. *Ann Intensive Care* 2014; **4**: 21
74. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the



- treatment of critically ill patients. *N Engl J Med* 1994; **330**: 1717–22
75. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid!. *Crit Care* 2015; **19**: 18
  76. Marik PE. Fluid therapy in 2015 and beyond: The mini-fluid challenge and mini-fluid bolus approach. *Br J Anaesth* 2015; **115**: 347–9
  77. Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med* 2008; **34**: 659–63
  78. Teboul JL, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care* 2008; **14**: 334–9
  79. Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. *Chest* 2002; **121**: 1245–52
  80. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; **34**: 1402–7
  81. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med* 2010; **36**: 1475–83
  82. Wetterslev M, Haase N, Johansen RR, Perner A. Predicting fluid responsiveness with transthoracic echocardiography is not yet evidence based. *Acta Anaesthesiol Scand* 2013; **57**: 692–7
  83. Muller L, Bobbia X, Toumi M, et al. Respiratory variations of inferior vena cava diameter predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care* 2012; **16**: R188
  84. Juhl-Olsen P, Vistisen ST, Christiansen LK, Rasmussen LA, Frederiksen CA, Sloth E. Ultrasound of the inferior vena cava does not predict hemodynamic response to early hemorrhage. *J Emerg Med* 2013; **45**: 592–7
  85. Corl K, Napoli AM, Gardiner F. Bedside sonographic measurement of the inferior vena cava caval index is a poor predictor of fluid responsiveness in emergency department patients. *Emergency Medicine Australasia* 2012; **24**: 534–9
  86. Ibarra-Estrada MA, Lopez-Pulgarin JA, Mijangos-Mendez JC, Diaz-Gomez JL, Aguirre-Avalos G. Variation in carotid peak systolic velocity predicts volume responsiveness in mechanically ventilated patients with septic shock: A prospective cohort study. *Crit Ultrasound J* 2015; **7**: 12
  87. Saugel B, Ringmaier S, Holzapfel K, et al. Physical examination, central venous pressure, and chest radiography for the prediction of transpulmonary thermodilution-derived hemodynamic parameters in critically ill patients: A prospective trial. *J Crit Care* 2011; **26**: 402–10
  88. NQF #0500. Severe Sepsis and Septic Shock: management Bundle, January 5 2015, update. [www.qualityforum.org](http://www.qualityforum.org). 2015. National Quality Forum. (Accessed 15 May 2015)
  89. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr* 2007; **96**: 644–7
  90. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. *Intensive Care Med* 2003; **29**: 1043–51
  91. Marik PE, Baram M, Vahid B. Does the central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; **134**: 172–8
  92. Song Y, Kwak YL, Song JW, Kim YJ, Shim JK. Respirophasic carotid artery peak velocity variation as a predictor of fluid responsiveness in mechanically ventilated patients with coronary artery disease. *Br J Anaesth* 2014; **113**: 61–6
  93. Marik PE, Levitov A, Young A, Andrews L. The use of NICOM (Bioreactance) and Carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest* 2013; **143**: 364–70
  94. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest* 1993; **103**: 900–6
  95. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; **369**: 840–51
  96. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO<sub>2</sub>) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; **55**: 40–6
  97. Burton TM. New therapy for sepsis infection raises hope but many questions (lead article). *The Wall Street Journal* August 14th, 2008. New York, NY, Dow Jones and Company, Inc. (Accessed 14 August 2008)
  98. Marik PE. The demise of early goal-directed therapy for severe sepsis and septic shock. *Acta Anaesthesiol Scand* 2015; **59**: 561–7
  99. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care* 2014; **18**: 503
  100. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetics failure in sepsis. *JAMA* 1992; **267**: 1503–10
  101. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet* 1999; **354**: 505–8
  102. James JH, Fang CH, Schrantz SJ, Hasselgren PO, Paul RJ, Fischer JE. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest* 1996; **98**: 2388–97
  103. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. *Crit Care Med* 1999; **27**: 1295–302
  104. Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Gretten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med* 1993; **21**: 1012–9
  105. Subramaniam A, McPhee M, Nagappan R. Predicting energy expenditure in sepsis: Harris-Benedict and Schofield equations versus the Weir derivation. *Crit Care Resusc* 2012; **14**: 202–10
  106. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; **269**: 3024–9
  107. Marik PE, Bellomo R. Lactate clearance as a target of therapy in sepsis: a flawed paradigm. *OA Critical Care* 2013; **1**: 3
  108. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993; **270**: 1724–30
  109. Brandt S, Regueira T, Bracht H, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. *Crit Care* 2009; **13**: R186
  110. Rehberg S, Yamamoto Y, Sousse L, et al. Selective V(1a) agonism attenuates vascular dysfunction and fluid accumulation in ovine severe sepsis. *Am J Physiol Heart Circ Physiol* 2012; **303**: H1245–54

111. Rosenberg AL, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; **24**: 35–46
112. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344–53
113. Alsous F, Khamiees M, DeGirolamo A, moateng-Adjepong Y, Manthous CA. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest* 2000; **117**: 1749–54
114. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; **136**: 102–9
115. Chung FT, Lin SM, Lin SY, Lin HC. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respiratory Medicine* 2008; **102**: 956–61
116. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; **12**: R74
117. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76**: 422–7
118. Micek SC, McEnvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Crit Care* 2013; **17**: R246
119. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure increase mortality. *Crit Care Med* 2011; **39**: 259–65
120. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 2015; **19**: 251
121. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; **364**: 2483–95
122. Jansen TC, van BJ, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; **182**: 752–61
123. Maitland K, George EC, Evans JA, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. *BMC Medicine* 2013; **11**: 68
124. Marik PE. Early management of severe sepsis: Current concepts and controversies. *Chest* 2014; **145**: 1407–18
125. Scheingraber S, Rehm M, Sehmsich C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiol* 1999; **90**: 1265–70
126. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock* 1998; **9**: 364–8
127. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 2001; **93**: 817–22
128. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab) normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clinical Science* 2003; **104**: 17–24
129. Mohd Yunus N, Bellomo R, Hegarty C, Stoty D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566–72
130. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. *Crit Care Med* 2014; **42**: 1585–91
131. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.4 versus Ringers Acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34
132. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38–0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *Br Med J* 2013; **346**: f839
133. Kirkpatrick AW, Roberts DJ, De WJ, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190–206
134. Malbrain ML, Marik PE, Witters I, et al. De-resuscitation in the critically ill: What, why, when and how? Results of a meta-analysis and systematic review on the impact of fluid overload on morbidity and mortality. *Anesthesiology Intensive Therapy* 2014; **46**: 361–80
135. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; **370**: 1583–93
136. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med* 2011; **39**: 689–94
137. Datta P, Magder S. Hemodynamic response to norepinephrine with and without inhibition of nitric oxide synthase in porcine endotoxemia. *Am J Respir Crit Care Med* 1999; **160**: 1987–93
138. Persichini R, Silva S, Teboul JL, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med* 2012; **40**: 3146–53
139. Kozieras J, Thuemer O, Sakka SG. Influence of an acute increase in systemic vascular resistance on transpulmonary thermodilution-derived parameters in critically ill patients. *Intensive Care Med* 2007; **33**: 1619–23
140. Hamzaoui O, Georger JF, Monnet X, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care* 2010; **14**: R142
141. Abid O, Akca S, Haji-Michael P, Vincent JL. Strong vasopressor support may be futile in the intensive care unit patient with multiple organ failure. *Crit Care Med* 2000; **28**: 947–9
142. Di Giantomasso D, May CN, Bellomo R. Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. *Intensive Care Med* 2003; **29**: 1774–81
143. Di Giantomasso D, Morimatsu H, May CN, Bellomo R. Intrarenal blood flow distribution in hyperdynamic septic shock: Effect of norepinephrine. *Crit Care Med* 2003; **31**: 2509–13
144. Jhanji S, Stirling S, Patel N, Hinds CJ, Pearse RM. The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. *Crit Care Med* 2009; **37**: 1961–6
145. Hayes MA, Yau EH, Hinds CJ, Watson JD. Symmetrical peripheral gangrene: association with noradrenaline administration. *Intensive Care Med* 1992; **18**: 433–6

146. Dunser MW, Mayr AJ, Tur A, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003; **31**: 1394–8
147. Anantasit N, Boyd JH, Walley KR, Russell JA. Serious adverse events associated with vasopressin and norepinephrine infusion in septic shock. *Crit Care Med* 2014; **42**: 1812–20
148. Hotchkiss RS, Levy JH, Levi M. Sepsis-induced disseminated intravascular coagulation, symmetrical peripheral gangrene, and amputations. *Crit Care Med* 2013; **41**: e290–1
149. Cardenas-Garcia J, Schaub KF, Belchikov YG, Narasimhan M, Koenig SJ, Mayo PH. Safety of peripheral intravenous administration of vasoactive medication. *J Hosp Med* 2015; **10**: 581–5
150. Ducrocq N, Kimmoun A, Furmaniuk A, et al. Comparison of equipressor doses of norepinephrine, epinephrine, and phenylephrine on septic myocardial dysfunction. *Anesthesiol* 2012; **116**: 1083–91
151. Minneci PC, Deans KJ, Banks SM, et al. Differing effects of epinephrine, norepinephrine, and vasopressin on survival in a canine model of septic shock. *Am J Physiol Heart Circ Physiol* 2004; **287**: H2545–54
152. Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Marik PE. Norepinephrine or dopamine for septic shock: A systematic review of randomized clinical trials. *J Intensive Care Med* 2011; **27**: 172–8
153. De Baker D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. *Crit Care Med* 2011; **40**: 725–30
154. Fawzy A, Evans SR, Walkey AJ. Practice patterns and outcomes associated with choice of initial vasopressor therapy for septic shock. *Crit Care Med* 2015; **43**: 2141–6

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