Review Article

Fluid Resuscitation in Sepsis: Reexamining the Paradigm

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Sepsis results in widespread inflammatory responses altering homeostasis. Associated circulatory abnormalities (peripheral vasodilation, intravascular volume depletion, increased cellular metabolism, and myocardial depression) lead to an imbalance between oxygen delivery and demand, triggering end organ injury and failure. Fluid resuscitation is a key part of treatment, but there is little agreement on choice, amount, and endpoints for fluid resuscitation. Over the past few years, the safety of some fluid preparations has been questioned. Our paper highlights current concerns, reviews the science behind current practices, and aims to clarify some of the controversies surrounding fluid resuscitation in sepsis.

1. Introduction

The incidence of severe sepsis varies between 20 and 30% in most intensive care units and is a leading cause of mortality [1]. Fluid resuscitation is one of the cornerstones of management. Though there is a consensus on the need for adequate fluid therapy, the timing, type, and quantity of fluid resuscitation remain controversial. Furthermore, the optimal monitoring technique to guide fluid therapy continues to be debated; with mounting and sometimes contradicting evidence, the ideal fluid strategy is increasingly elusive.

Contemporary understanding of the pathophysiology of sepsis supports intensive fluid resuscitation in the initial phase. SIRS and sepsis incite widespread inflammatory responses at tissue and cellular levels altering homeostasis. Resultant circulatory abnormalities (peripheral vasodilation, intravascular volume depletion, increased cellular metabolism, and myocardial depression) lead to an imbalance between oxygen delivery and demand, worsening end organ injury and failure.

In a landmark paper, Rivers and colleagues demonstrated early goal directed therapy, targeting a specific central venous pressure (CVP) and mixed central venous oxygen saturation (ScVO2), improved mortality by 16% [2]. In response, the surviving sepsis guidelines recommend early aggressive fluid resuscitation during the “golden” hours [3]. Although adequate fluid resuscitation makes eminent physiological sense, the optimal amount, and type of fluid remain unclear. Our paper aims to clarify these issues by reviewing the latest evidence guiding these practices.

2. Monitoring Fluid Resuscitation

2.1. Static Monitors. In sepsis, it is important to identify which patients will respond to volume resuscitation. In the critically ill, this means identifying the patient whose cardiac output will improve with fluid administration, called preload responsiveness. Traditionally, static indicators such as CVP have guided therapy. However, historic and recent evidence suggest CVP is a poor predictor of fluid responsiveness. In a systematic review on the usefulness of the CVP, Marik et al. concluded that it is neither a good indicator of volume status nor a predictor of responsiveness to fluid therapy [4]. It has been suggested that CVP no longer be used to guide fluid therapy [5]; although it remains in the surviving sepsis guidelines, some authors suggest that these recommendations should be revisited [5]. In fact, recent
evidence suggests CVP guided fluid resuscitation leads to venous congestion increasing the incidence of pulmonary complications in septic shock [6]. However, removal of CVP parameters from the guidelines may result in inadequate volume resuscitation and many centres continue to use static CVP measurement, despite evidence that it is an unhelpful guide for fluid administration. Furthermore, respiratory variation in the CVP is useful for predicting fluid responsiveness in spontaneously breathing patients [7].

Similarly, the pulmonary artery catheter (PAC) is unable to predict fluid responsiveness. Perhaps this is partly why the PAC is not associated with improved outcomes and its use has declined over the past two decades [8]. Although hemodynamic variables available from the PAC, such as the pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and derived variables, are helpful for determining the type of circulatory shock and assessing response to therapy, none of these parameters predict preload responsiveness [9]. Furthermore, recent evidence casts doubt on the accuracy of hemodynamic data obtained from PACs [10].

2.2. Dynamic Monitoring. The most useful indicators of preload responsiveness are phasic changes in stroke volume and systolic blood pressure during positive pressure mechanical ventilation [11]. Stroke volume variation (SVV) is the ratio of maximal stroke volume difference during several respiratory cycles and the mean stroke volume over the same period [12]. Since the arterial pulse pressure depends on the amount of blood ejected during each systole (stroke volume), the pulse pressure variation covaries with SVV [13]. During positive pressure ventilation, inspiration increases the intrathoracic pressure reducing the right ventricular (RV) filling and right ventricular output if the RV is volume responsive. This causes the left ventricular filling and left ventricular (LV) output to decrease over successive beats if the LV is also volume responsive [12]. A SVV of >15% in patients receiving a tidal volume of >8 mL/kg or an SVV of >10% in patients receiving a tidal volume of 6 mL/kg accurately predicts preload responsiveness in patients with a closed chest [14–16].

Commercially available monitors such as the PiCCO, LiDCOplus, Volume View/EV1000, and the FloTrac use pulse contour analysis to indirectly determine the cardiac output and stroke volume variation. Pulse contour analysis is based on the relationship of the stroke volume, aortic compliance, and systemic vascular resistance [17]. Complex algorithms that account for reflection waves and aortic impedance are used to analyse the arterial wave and derive the stroke volume. The LiDCO uses pulse power analysis to convert the arterial waveform into a volume-time waveform which makes it less dependent on the shape of the pulse wave [18]. Although these devices are dependent on accurate calibration to measure CO, SVV and PPV are not dependent on calibration and, therefore, less affected by reliability concerns associated with these devices.

2.3. Indicators of Tissue Perfusion. The ultimate goal of fluid resuscitation is adequate tissue perfusion. However, dynamic monitoring does not measure tissue perfusion. Indicators of adequate perfusion include SVO₂, ScVO₂, and lactate. The surviving sepsis group recommends targeting ScVO₂ of 70% within the first 6 hours of recognition of sepsis [19]. However, ScVO₂ may be normal or even elevated in sepsis, for example, in patients with chronic liver disease. In contrast, hyperlactatemia is a more consistent finding in severe sepsis [20]. Normalization of lactate can be a useful target, alongside other hemodynamic parameters. Jansen et al. demonstrated reduced hospital mortality when targeting normalisation of lactate in a multicentre RCT [21].

A potentially useful measure of tissue perfusion is gastric mucosal pH. Since splanchnic circulation is compromised early during hypoperfusion, gastric blood flow is reduced. Changes in gastric mucosal pH (pHi), measured using a tonometer, reflect the adequacy of splanchnic perfusion [22]. The pHi is determined using a fluid or air filled balloon tipped nasogastric tube. The balloon contents equilibrate with the gases in the gastric lumen; therefore, changes in carbon dioxide (CO₂) in the balloon reflect gastric luminal CO₂. The pHi is calculated from the gastric lumen CO₂ and blood bicarbonate; lower values indicate greater hypoperfusion. Although it is useful in prognosticating multiorgan failure and death in several conditions such as acute pancreatitis [23], trauma [24], and other critically ill patients [25], technical difficulties and potential sources of error in manual tonometer monitoring have prevented its widespread use [22]. Other tissue perfusion monitors such as Sidestream Dark Field imaging technique (SDF) [26], sublingual capnometry [27–29], and near infrared spectroscopy (NIRS) [30–33] have also been studied in critically ill patients. Although some studies have shown benefit, these monitors are not widely available and their clinical utility for delivery of bedside critical care remains to be established [33, 34].

3. Which Fluid?

Intravenous fluid therapy originated during the great cholera outbreak of the nineteenth century [35–38]. Fluids of various compositions were used, and studies tracing their composition indicate they resembled balanced crystalloids [39]. Balanced solutions are those with an electrolyte composition similar to that of plasma. However, the most commonly used crystalloid is 0.9% saline, which is not balanced. About 10 million litres of saline are used each year in the UK and 200 million litres are sold every year in the United States [40].

3.1. Crystalloids (Saline and Balanced Solutions). 0.9% saline is frequently referred to as “normal” saline. However, Awad and colleagues elegantly showed that this term entered medical practice based on colloquialism rather than sound physiological or scientific data [39]. There is certainly nothing normal about “normal” saline. The first documented use of “normal saline” was in the Lancet in 1888 [41]; however the solution described bore no resemblance to 0.9% saline. The widespread adoption of 0.9% saline was likely based on its
isotonicity, as described in a single in vitro experiment on red cell lysis as well as the convenience and low cost of production [42].

Although there is no consensus on the superiority of balanced solutions over 0.9% saline, contemporary understanding of acid-base balance and recent observational evidence favours balanced solutions. The Stewart physicochemical approach [43] to acid-base dictates that infusion of large quantities of 0.9% saline will result in hyperchloremic acidosis. The strong ion difference (SID-sum of all the strong cations minus sum of all the strong anions) of plasma is maintained by the greater concentration of sodium relative to chloride in the plasma. Electroneutrality is maintained by anions such as bicarbonate (HCO$_3^-$), weak acids (HA), and hydroxyl ion (OH$^-$). Decreases in the SID decrease the available “space” for these anions, ultimately reducing [OH$^-$]. However, the dissociation of water (kw) must remain constant. Since kw is directly proportional to the product of [OH$^-$] and hydrogen ion concentration [H$^+$], decreases in [OH$^-$] lead to increases in [H$^+$] causing acidosis. Infusing 0.9% saline provides relatively more chloride, compared to sodium, resulting in a reduction in the strong ion difference which in turn lowers the pH, causing hyperchloremic acidosis [44].

Few studies have compared balanced crystalloids and 0.9% saline in patients with sepsis. However, there is substantial animal evidence that hyperchloremia causes harmful effects. In dogs, hyperchloremia causes progressive renal vasoconstriction and a fall in GFR in denervated kidneys [45]. In animal sepsis models, infusions of 0.9% saline increase inflammatory cytokines, worsen hypotension and vasoconstriction and a fall in GFR in denervated kidneys. There is clearly mounting evidence suggesting that hyperchloremia associated with use of 0.9% saline does have significant clinical implications, cannot be ignored and should at least give pause to continued saline only resuscitation in sepsis. Table 1 summarizes the studies examining crystalloids.

3.2. Colloids. There are fundamental differences between crystalloids and colloids. Crystalloids are predominantly based on sterile water to which electrolytes have been added. Colloids have an additional “colloidal” component that does not freely diffuse across semipermeable membranes, in theory making them more effective volume expanders. Colloids are the preferred resuscitation fluids in Europe and Australasia [54]. Albumin, hydroxyethyl starch (HES), and gelatin are the three classes of colloid commonly used.

However, the safety profile of certain colloids in patients with sepsis has recently been challenged. In fact, safety concerns have existed since their introduction. Scheirhout and colleagues, in a meta-analysis of 37 RCTs in critically ill patients, found that resuscitation with colloids (albumins, gelatins, dextrans, and starches) increased risk of mortality by 4% (95% CI 0–8%) [55]. A separate French multicentre study found gelatins [odds ratio (OR) 4.81 (95% CI 2.01–11.51 P = 0.0005)] and dextrans [OR 3.83 (95% CI 1.17–12.60 P = 0.02)] were independent risk factors for anaphylactoid reactions [56]. Furthermore, Dextran 70 has been shown to decrease Factor VIII procoagulant activity, factor VIII related antigen, and ristocetin cofactor activity [57] resulting in coagulopathies.

Based on adverse outcome reports, such as renal dysfunction and coagulopathy, high molecular weight starches have already been phased out in favour of HES (130/0.42). The adverse effects of HES were considered benign, transitory, dose dependent, and related to only high molecular weight starches. However, HES (130/0.42) is not readily excreted and there is evidence it accumulates in the skin, liver, kidney, and reticuloendothelial system [58]. It is suggested that the lower degree of substitution and lower molecular weight of HES (130/0.42) facilitate greater uptake in the tubular epithelium leading to osmotic nephrosis and requirement of renal replacement therapy and, therefore, could be more harmful than its predecessors [58–60].

In the recent Crystalloid versus Hydroxyethyl starch Trial (CHEST), the effect of fluid resuscitation with HES (130/0.4) was compared with 0.9% saline among 7000 patients admitted to an intensive care unit [61]. The study found no difference in 90 day mortality between the groups; however, patients receiving HES required renal replacement therapy
acetate, the 6S trial [62]. The primary outcome of death or severe sepsis to receive either HES (130/0.42) or Ringer’s therapy (22% versus 16%, more patients in the HES group receiving renal replacement group compared to 43% in the Ringer’s group (dialysis dependence at 90 days occurred in 51% of the HES study also demonstrated more adverse events with the use of HES. The CRYSTMAS trial was a prospective multicentre, double blind randomized study comparing the hemodynamic efficacy and safety of HES (130/0.4) with 0.9% saline in severe sepsis. The authors found significantly less volume of HES was required to achieve hemodynamic stability (1379 ± 886 mL in HES versus 1709 ± 1164 mL in saline group, P = 0.0185) and found no difference in the rate of AKI or RRT [64]. Unfortunately, it lacked power to address renal safety, and based on current evidence, the FDA has issued a boxed warning for HES. It would appear the risks associated with HES use in sepsis outweigh any volume expansion benefits and its use in sepsis cannot currently be recommended. Given the concerns with synthetic colloids, albumin has reemerged as a good alternative. The recent surviving sepsis campaign guidelines advocate the use of albumin for volume expansion after the use of colloids [19].

Apart from the hemodynamic efficacy that albumin confers, it is reported to have antioxidant and anti-inflammatory activity [65]. The postulated mechanisms include an increase in plasma thiol levels, modulation of cytokine activity, binding of endotoxin, and protection of glycocalyx. It also alters drug binding and reduces nitric oxide, attenuating vasodilatation [66].

The SAFE study compared albumin and saline resuscitation in 6997 patients [67]. Twenty-eight-day mortality was no different between both groups (726 albumin group versus 729 0.9% saline group, P = 0.87). The study concluded that albumin and 0.9% saline are clinically equivalent for fluid resuscitation in the ICU. However, post hoc analysis of the sepsis subgroup indicates that resuscitation with albumin may reduce the mortality in patients with severe sepsis, confirming possible additional protective mechanisms conferred by albumin. Furthermore, a large meta-analysis showing resuscitation with albumin solutions in sepsis was associated with lower mortality [68]. Although many of the studies included had not used proper methodology, the results suggest that albumin does not have specific adverse effects in sepsis. Table 2 summarizes studies examining colloids.

| Author          | Year | Study design       | Sample size | Study fluid                      | Primary endpoint                                      | Comments                                                                 |
|-----------------|------|--------------------|-------------|----------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------|
| Wilcox [45]     | 1983 | Animal experiment  | 48          | Chloride rich solutions          | Regulation of renal blood flow                        | Increased renal vasoconstriction and ↓ GFR* with chloride rich solutions |
| Waters et al. [49] | 2001 | Prospective randomized study | 66          | 0.9% Saline versus lactated Ringer | Multiple outcomes studied                               | Increased use of blood products and acidosis with 0.9% Saline           |
| O’Malley et al. [50] | 2005 | Randomised clinical trial | 51          | 0.9% Saline versus lactated Ringer | Creatinine concentration on POD3b                     | No difference; but Ringer’s was associated with less hyperkalemia and acidosis |
| Shaw et al. [51] | 2012 | Observational      | 31,920      | 0.9% Saline versus balanced crystalloid | Major morbidity                                      | Higher mortality, increased transfusion requirements, dialysis requirements, and increased buffer requirements in saline group |
| Maitland et al. [52] | 2011 | Multicentric randomized trial | 3141        | Albumin bolus and saline bolus    | Mortality                                             | Boluses resulted in increased mortality                                  |

Table summarizing studies evaluating colloids. *Glomerular Filtration Rate, †Postoperative Day 3.
Table 2: Summary of studies evaluating colloids.

| Author | Year | Study design | Sample size | Study fluid | Primary endpoint | Comments |
|--------|------|--------------|-------------|-------------|------------------|----------|
| Schierhout and Roberts [55] | 1998 | Meta-analysis | 1315 | All colloids | Mortality | Increased mortality |
| Laxenaire et al. [56] | 1994 | Multicentre prospective | 19593 | All colloids | Adverse effects | Gelatins and dextran-independent risk for anaphylactoid reactions |
| Myburgh et al. [61] | 2012 | RCTa | 7000 | HESb versus 0.9% saline | 90-day mortality | HESb associated with increased incidence of RRT |
| Perner et al. [62] | 2012 | RCTa | 804 | HESb versus Ringer’s acetate | Death/dialysis dependence at 90 days | Death and dialysis dependence more in HES |
| Zarychanski et al. [63] | 2013 | Meta-analysis | 10,290 | HESb | Mortality and AKIc | Significant increase in risk of mortality and AKIc |
| Guidet et al. [64] | 2012 | RCTa | 196 | HESb versus 0.9% saline | Hemodynamic efficacy and safety | HESb better hemodynamic efficacy and no difference in AKIc |
| Finfer et al. [67] | 2004 | RCTa | 6997 | Albumin versus 0.9% saline | 28-day mortality | No difference |
| Myburgh et al. [72] | 2007 | Post hoc analysis of SAFE trial | 460 | Albumin versus 0.9% saline | Safety in TBId | Albumin unsafe for TBId |
| Delaney et al. [68] | 2011 | Meta-analysis | 1977 | Albumin | Safety for resuscitation | Albumin associated with lower mortality |
| Annane et al. [69] | 2013 | RCTa | 2857 | Colloids versus crystalloids | 28-day mortality | No difference |

Table summarizing studies evaluating colloids. aRandomized Controlled Trial, bHydroxyethyl starch, cAcute Kidney Injury, dTraumatic Brain Injury.

shock without sepsis or trauma). They used colloids (𝑛 = 1414; gelatins, dextrans, hydroxyethyl starches, 4% or 20% of albumin) or crystalloids (𝑛 = 1443; isotonic saline, hypertonic saline, or Ringers lactate) for fluid interventions, other than fluid maintenance throughout the ICU stay. There was no difference in 28-day mortality between the two groups (359 in colloid group versus 390 in crystalloid group, 𝑃 = 0.26). However, a secondary outcome, 90-day mortality, was lower in patients receiving colloids, but it is difficult to draw strong conclusions from this study due to the heterogeneity of fluid composition in the two groups.

From the many trials that have been carried out so far, it is clear that some synthetic colloids should be avoided in sepsis and that 0.9% saline may have disadvantages over balanced crystalloids. However, whether to select albumin over a crystalloid remains uncertain. Based on the SAFE study, one potential advantage of albumin is that less fluid is ultimately required to achieve hemodynamic end goals. This will only prove beneficial, if a more positive balance is associated with worse outcomes.

4. How Much Fluid?

Boyd and colleagues retrospectively reviewed the association of positive fluid balance at 12 hours and at 4 days in 778 patients of the Vasopressin in Septic Shock (VASST) study [70]. They found that the quartile that had the least positive balance at 12 hours [0.569 (0.405–0.799) for Quartile 1 and 0.581 (0.414–0.816) for Quartile 2] and at 4 days [0.466 (0.299–0.724) for Quartile 1 and 0.512 (0.339–0.775) for Quartile 2] had a lower hazard ratio relative to the quartile with the maximum positive balance. Furthermore we know that a fluid restrictive strategy is beneficial in patients with concomitant ARDS [71]. Although it is expected that 3 to 4 times the volume of crystalloids may be required to achieve the hemodynamic efficacy of colloids, the SAFE study found that the volume of saline used was only 40% more than albumin, perhaps because the clearance of crystalloids is decreased during the stress response of critical illness. Furthermore, there are settings where one fluid is clearly advantageous, such as sepsis patients with traumatic brain injury where albumin and hypotonic resuscitation fluids should be avoided [72]. Similarly, patients requiring fluid restrictive strategy, such as those with ARDS or concomitant abdominal compartment syndrome, might benefit from an albumin based strategy (Figure 1).

5. Conclusion

In conclusion, a perfect one-size-fits-all fluid strategy does not exist. In sepsis, clinicians should understand the limitations and potential benefits of each strategy. Each fluid should be considered a drug, with specific pharmacokinetic, pharmacodynamic, and adverse effect profiles, which can be carefully matched to the patient. Whichever fluid is chosen, resuscitation should be titrated to evidence based
Sepsis with hypotension

Preload responsive?
(PPV or SVV >15% in a mechanically ventilated patient or CVP variance in a spontaneously breathing patient)

Yes
Fluid resuscitation mandated
Considerations in fluid resuscitation
TBI
ARDS
Abdominal sepsis with compartment syndrome or chronic liver disease
0.9% saline preferred
Avoid albumin and hypotonic crystalloids
Consider restrictive fluid strategy
Consider albumin in addition to crystalloids
Avoid using only crystalloids, consider albumin

No
Consider early vasopressors/inotropes and confirm fluid status on bedside ECHO
All other sepsis
Balanced crystalloids preferred

Figure 1: Algorithm to guide fluid therapy in the septic patient.

targets, combining clinical assessment, such as signs of tissue perfusion with dynamic hemodynamic monitoring. Balanced crystalloids may be preferred first choice, followed by albumin, based on their comparative safety profiles. 0.9% saline should only be used after consideration of its potential to cause harm and current evidence would suggest starches (HES) should be avoided in sepsis.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

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References
[1] C. Alberti, C. Brun-Buisson, H. Burchardi et al., “Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study,” Intensive Care Medicine, vol. 28, no. 2, pp. 108–121, 2002.
[2] E. Rivers, B. Nguyen, S. Havstad et al., “Early goal-directed therapy in the treatment of severe sepsis and septic shock,” The New England Journal of Medicine, vol. 345, no. 19, pp. 1368–1377, 2001.
[3] R. P. Dellinger, M. M. Levy, J. M. Carlet et al., “Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock,” Critical Care Medicine, vol. 36, pp. 296–327, 2008.
[4] P. E. Marik, M. Baram, and B. Vahid, “Does the central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares,” Chest, vol. 134, no. 1, pp. 172–178, 2008.
[5] P. E. Marik, X. Monnet, and J. Teboul, “Hemodynamic parameters to guide fluid therapy,” *Annals of Intensive Care*, vol. 1, no. 1, pp. 2–9, 2011.

[6] R. Rajendram and J. R. Prowle, “Venous congestion: are we adding insult to kidney injury in sepsis?” *Critical Care*, vol. 18, p. 104, 2014.

[7] S. Magder, G. Georgiadis, and T. Cheong, “Respiratory variations in right atrial pressure predict the response to fluid challenge,” *Journal of Critical Care*, vol. 7, no. 2, pp. 76–85, 1992.

[8] S. Harvey, D. A. Harrison, M. Singer et al., “Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial,” *The Lancet*, vol. 366, no. 9484, pp. 472–477, 2005.

[9] A. Kumar, R. Anel, E. Bunnell et al., “Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects,” *Critical Care Medicine*, vol. 32, no. 3, pp. 691–699, 2004.

[10] P. E. Marik, “Obituary: pulmonary artery catheter 1970 to 2013,” *Annals of Intensive Care*, vol. 3, article 38, 2013.

[11] P. E. Marik, R. Cavallazzi, T. Vasu, and A. Hirani, “Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature,” *Critical Care Medicine*, vol. 37, no. 9, pp. 2642–2647, 2009.

[12] M. E. Cove and M. R. Pinsky, “Perioperative hemodynamic monitoring,” *Best Practice and Research: Clinical Anaesthesiology*, vol. 26, no. 4, pp. 453–462, 2012.

[13] J. Erlanger and D. R. Hooker, “An experimental study of blood pressure and of pulse pressure in man,” *John Hopkins Hospital Records*, vol. 12, pp. 145–378, 1904.

[14] M. Kobayashi, M. Koh, T. Irinoda, E. Meguro, Y. Hayakawa, and A. Takagane, “Stroke volume variation as a predictor of intravascular volume depression and possible hypotension during the early postoperative period after esophagectomy,” *Annals of Surgical Oncology*, vol. 16, no. 5, pp. 1371–1377, 2009.

[15] H. Berkenstadt, N. Margalit, M. Hadani et al., “Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery,” *Anesthesia and Analgesia*, vol. 92, no. 4, pp. 984–989, 2001.

[16] D. A. Reuter, T. W. Felbinger, C. Schmidt et al., “Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery,” *Intensive Care Medicine*, vol. 28, no. 4, pp. 392–398, 2002.

[17] L. J. Montenij, E. E. C. De Waal, and W. F. Buhre, “Arterial waveform analysis in anesthesia and critical care,” *Current Opinion in Anaesthesiology*, vol. 24, no. 6, pp. 651–656, 2011.

[18] M. Jonas, D. Hett, and J. Morgan, “Real time, continuous monitoring of cardiac output and oxygen delivery,” *International Journal of Intensive Care*, vol. 9, no. 1, pp. 33–42, 2002.

[19] R. P. Dellinger, M. M. Levy, A. Rhodes et al., “Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012,” *Critical Care Medicine*, vol. 41, no. 2, pp. 580–637, 2013.

[20] J. Bakker, M. W. N. Nijsten, and T. C. Jansen, “Clinical use of lactate monitoring in critically ill patients,” *Annals of Intensive Care*, vol. 3, article 12, 2013.

[21] T. C. Jansen, J. van Bommel, F. J. Schoonderbeek et al., “Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial,” *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 6, pp. 752–761, 2010.

[22] J. J. Kolkman, J. A. Otte, and A. B. J. Groeneveld, “Gastrointestinal luminal $P_{\text{CO}_2}$ tonometry: an update on physiology, methodology and clinical applications,” *British Journal of Anaesthesia*, vol. 84, no. 1, pp. 74–86, 2000.

[23] M. J. D. Bonham, F. M. Abu-Zidan, M. O. Simovic, and J. A. Windsor, “Gastric intramucosal pH predicts death in severe acute pancreatitis,” *British Journal of Surgery*, vol. 84, no. 12, pp. 1670–1674, 1997.

[24] O. C. Kirton, J. Windsor, R. Wedderburn et al., “Failure of splanchnic resuscitation in the acutely injured trauma patient correlates with multiple organ system failure and length of stay in the ICU,” *Chest*, vol. 113, no. 4, pp. 1064–1069, 1998.

[25] N. Maynard, D. Bihari, R. Beale et al., “Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure,” *Journal of the American Medical Association*, vol. 270, no. 10, pp. 1203–1210, 1993.

[26] P. T. Goedhart, M. Khalilzada, R. Bezemer, J. Merza, and C. Ince, “Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation,” *Optics Express*, vol. 15, no. 23, pp. 15101–15114, 2007.

[27] E. C. Rackow, P. O’Neill, M. E. Astiz, and C. M. Carpati, “Sublingual capnometry and indexes of tissue perfusion in patients with circulatory failure,” *Chest*, vol. 120, no. 5, pp. 1633–1638, 2001.

[28] P. E. Marik, “Sublingual capnography: a clinical validation study,” *Chest*, vol. 120, no. 3, pp. 923–927, 2001.

[29] P. E. Marik and A. Bankov, “Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients,” *Critical Care Medicine*, vol. 31, no. 3, pp. 818–822, 2003.

[30] H. Gómez, A. Torres, P. Polanco et al., “Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue $O_2$ saturation response,” *Intensive Care Medicine*, vol. 34, no. 9, pp. 1600–1607, 2008.

[31] D. E. Skarda, K. E. Mulier, D. E. Myers, J. H. Taylor, and G. J. Beilman, “Dynamic near-infrared spectroscopy measurements in patients with severe sepsis,” *Shock*, vol. 27, no. 4, pp. 348–353, 2007.

[32] A. Lima, J. van Bommel, T. C. Jansen, C. Ince, and J. Bakker, “Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients,” *Critical Care*, vol. 13, supplement 5, article S13, 2009.

[33] A. Lima, J. Van Bommel, K. Sikorska et al., “The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients,” *Critical Care Medicine*, vol. 39, no. 7, pp. 1649–1654, 2011.

[34] R. Bezemer, S. A. Bartels, J. Bakker, and C. Ince, “Clinical review: clinical imaging of the sublingual microcirculation in the critically ill—where do we stand?” *Critical Care*, vol. 16, no. 3, article 224, 2012.

[35] N. Howard-jones, “Cholera therapy in the nineteenth century,” *Journal of the History of Medicine and Allied Sciences*, vol. 62, no. 7, pp. 703–721, 2007.

[36] T. F. Baskett, “The resuscitation greats: William O’Shaughnessy, Thomas Latta and the origins of intravenous saline,” *Resuscitation*, vol. 55, no. 3, pp. 231–234, 2002.
[38] B. A. Foëx, “How the cholera epidemic of 1831 resulted in a new technique for fluid resuscitation,” Emergency Medicine Journal, vol. 20, no. 4, pp. 316–318, 2003.

[39] S. Awad, S. P. Allison, and D. N. Lobo, “The history of 0.9% saline,” Clinical Nutrition, vol. 27, no. 2, pp. 179–188, 2008.

[40] Baxter Healthcare Deerfield IL, “Derived from IMS Health Hospital supply index, GHX Market Intelligence data and Baxter internal sales data”.

[41] Dr. Churton, “A case of scirrhous of the pylorus, with excessive vomiting; repeated intravenous injections of saline solution; remarks,” The Lancet, vol. 132, no. 3396, pp. 620–621, 1888.

[42] E. A. Coller, V. S. Dick, and W. G. Maddock, “Maintenance of normal water exchange with intravenous fluids,” Journal of the American Medical Association, vol. 107, pp. 1522–1527, 1936.

[43] P. A. Stewart, “Modern quantitative acid-base chemistry,” Canadian Journal of Physiology and Pharmacology, vol. 61, no. 12, pp. 1444–1461, 1983.

[44] N. M. Yunos, R. Bellomo, D. Story, and J. Kellum, “Bench-to-bedside review: chloride in critical illness,” Critical Care, vol. 14, no. 4, article 226, 2010.

[45] C. S. Wilcox, “Regulation of renal blood flow by plasma chloride,” The Journal of Clinical Investigation, vol. 71, no. 3, pp. 726–735, 1983.

[46] J. A. Kellum, M. Song, and E. Almasri, “Hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis,” Chest, vol. 125, no. 1, pp. 243–248, 2004.

[47] J. A. Kellum, M. Song, and R. Venkataraman, “Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis,” Chest, vol. 130, no. 4, pp. 962–967, 2006.

[48] F. Zhou, Z. Y. Peng, J. V. Bishop et al., “Effects of Fluid Resuscitation With 0.9% Saline Versus a Balanced Electrolyte Solution on Acute Kidney Injury in a Rat Model of Sepsis,” Critical Care Medicine, vol. 42, 2014.

[49] J. H. Waters, A. Gottlieb, P. Schoenwald, M. J. Popovich, J. Sprung, and D. R. Nelson, “Normal saline versus lactated Ringer’s solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study,” Anesthesia and Analgesia, vol. 93, no. 4, pp. 817–822, 2001.

[50] C. M. N. O’Malley, R. J. Frumento, M. A. Hardy et al., “A randomized, double-blind comparison of lactated ringer’s solution and 0.9% NaCl during renal transplantation,” Anesthesia and Analgesia, vol. 100, no. 5, pp. 1518–1524, 2005.

[51] A. D. Shaw, S. M. Bagshaw, S. L. Goldstein et al., “Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-lyte,” Annals of Surgery, vol. 255, no. 5, pp. 821–829, 2012.

[52] K. Maitland, S. Kiguli, R. O. Opoka et al., “Mortality after fluid bolus in African children with severe infection,” The New England Journal of Medicine, vol. 364, no. 26, pp. 2483–2495, 2011.

[53] K. Maitland, E. C. George, J. A. Evans et al., “Exploring mechanisms of excess mortality with early fluid resuscitation: Insights from the FEAST trial,” BMC Medicine, vol. 11, no. 1, article no. 68, 2013.

[54] S. Finfer, B. Liu, C. Taylor et al., “Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units,” Critical Care, vol. 14, article R185, 2010.

[55] G. Schierhout and I. Roberts, “Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials,” British Medical Journal, vol. 316, no. 7136, pp. 961–964, 1998.

[56] M. C. Laxenaire, C. Charpentier, and L. Feldman, “Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study,” Annales Francaises d’Anesthese et de Reanimation, vol. 13, no. 3, pp. 301–310, 1994.

[57] J. Batte, F. Del Rio, and L. Fernandez, “Effect of dextran on factor VIII/von Willebrand factor structure and function,” Thrombosis and Haemostasis, vol. 54, no. 3, pp. 697–699, 1985.

[58] R. Bellmann, C. Feistritzer, and C. J. Wiederman, “Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies,” Clinical Pharmacokinetics, vol. 51, no. 4, pp. 225–236, 2012.

[59] H. P. Ferber, E. Nitsch, and H. Förster, “Studies on hydroxyethyl starch. Part II: changes of the molecular weight distribution for hydroxyethyl starch types 450/0.7, 450/0.5, 450/0.3, 300/0.4, 200/0.7, 200/0.5, 200/0.3 and 200/0.1 after infusion in serum and urine of volunteers,” Arzneimittelforschung, vol. 35, no. 3, pp. 615–622, 1985.

[60] M. L. Cittanova, I. Leblanc, C. Legendre, C. Mouquet, B. Riou, and P. Coriat, “Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients,” The Lancet, vol. 348, no. 9042, pp. 1620–1622, 1996.

[61] J. A. Myburgh, S. Finfer, R. Bellomo et al., “Hydroxyethyl starch or saline for fluid resuscitation in intensive care,” The New England Journal of Medicine, vol. 367, no. 20, pp. 1901–1911, 2012.

[62] A. Perner, N. Haase, A. B. Guttmersen et al., “Hydroxyethyl starch 130/0.42 versus Ringer’s acetate in severe sepsis,” The New England Journal of Medicine, vol. 367, no. 2, pp. 124–134, 2012.

[63] R. Zarzanchki, A. M. Abou-Setta, A. F. Turgeon et al., “Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation,” Journal of the American Medical Association, vol. 309, no. 7, pp. 678–688, 2013.

[64] B. Guidet, O. Martinet, T. Boulain et al., “Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 versus 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study,” Critical Care, vol. 16, article R94, 2012.

[65] M. Roche, P. Rondeau, N. R. Singh, E. Tarnus, and E. Bourdon, “The antioxidiant properties of serum albumin,” FEBS Letters, vol. 582, no. 13, pp. 1783–1787, 2008.

[66] J. S. Stamler, O. Jaraki, J. Osborne et al., “Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin,” Proceedings of the National Academy of Sciences of the United States of America, vol. 89, no. 16, pp. 7674–7677, 1992.
[70] J. H. Boyd, J. Forbes, T. Nakada, K. R. Walley, and J. A. Russell, "Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality," *Critical Care Medicine*, vol. 39, no. 2, pp. 259–265, 2011.

[71] A. L. Rosenberg, R. E. Dechert, P. K. Park, and R. H. Bartlett, "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," *Journal of Intensive Care Medicine*, vol. 24, no. 1, pp. 35–46, 2009.

[72] J. Myburgh, D. J. Cooper, S. Finner et al., "Saline or albumin for fluid resuscitation in patients with traumatic brain injury," *The New England Journal of Medicine*, vol. 357, no. 9, pp. 874–884, 2007.