REVIEW

Open Access

CrossMark

Fluid resuscitation in human sepsis: Time to rewrite history?

Liam Byrne[1,2*] and Frank Van Haren[1,2]

Abstract

Fluid resuscitation continues to be recommended as the first-line resuscitative therapy for all patients with severe sepsis and septic shock. The current acceptance of the therapy is based in part on long history and familiarity with its use in the resuscitation of other forms of shock, as well as on an incomplete and incorrect understanding of the pathophysiology of sepsis. Recently, the safety of intravenous fluids in patients with sepsis has been called into question with both prospective and observational data suggesting improved outcomes with less fluid or no fluid. The current evidence for the continued use of fluid resuscitation for sepsis remains contentious with no prospective evidence demonstrating benefit to fluid resuscitation as a therapy in isolation. This article reviews the historical and physiological rationale for the introduction of fluid resuscitation as treatment for sepsis and highlights a number of significant concerns based on current experimental and clinical evidence. The research agenda should focus on the development of hyperdynamic animal sepsis models which more closely mimic human sepsis and on experimental and clinical studies designed to evaluate minimal or no fluid strategies in the resuscitation phase of sepsis.

Background

Sepsis is a significant global health problem. The worldwide incidence of sepsis is increasing, with current estimates between 20 and 30 million cases annually [1–5]. The mortality of septic shock, the most severe form of sepsis, continues to be higher than 50% [5, 6]. The cost associated with a single admission of a patient with sepsis has been estimated to be in excess of Euro 20,000 [7, 8]. The treatment of sepsis has not significantly changed over the past 40 years, with the currently used therapies of antibiotics, source control, fluid resuscitation and judicious use of vasopressors recommended in a familiar form in the literature as far back as 1970 [9].

Fluid resuscitation remains the most enduring of sepsis treatments predating even antibiotics. Its beginnings date to the European cholera epidemic of the 1830s, where it was first used to replace the losses associated with cholera diarrhoea [10]. In modern practice, fluid resuscitation has developed to encompass both corrections of absolute and relative hypovolemic states with the additional goal of augmenting cardiac output to restore organ perfusion pressure and improve oxygen transport to cells [5, 11, 12].

Unfortunately, there is no agreed uniform definition of fluid resuscitation in the literature. Fluid administration is not necessarily the same as fluid resuscitation. It is important to differentiate between fluid substitution and volume substitution in intensive care patients, a distinction that has not always been appreciated sufficiently in the design of fluid studies [13]. For the sake of simplicity and consistency, we define fluid resuscitation for sepsis in this review as the administration of intravenous fluids to correct sepsis-induced tissue hypoperfusion. This definition is consistent with the surviving sepsis guidelines and implies a targeted approach to a clinical problem [12].

The following article reviews the rationale for the introduction of fluid resuscitation as treatment for sepsis and highlights a number of significant concerns based on current experimental and clinical evidence.

*Correspondence: Liambyrne.syd@gmail.com
[2] Intensive Care Unit, The Canberra Hospital, Canberra, Australia
Full list of author information is available at the end of the article

Springer Open

Evolution of fluid resuscitation as a therapy for septic shock

R. Hermann was a German chemist working in Moscow during the second cholera pandemic in 1830. He proposed injecting water into the circulation to replace lost fluid after observing haemoconcentration in cholera patients. His clinician colleague Jaehnichen subsequently injected a cholera patient intravenously with 6 oz. of water, which resulted in a notable improvement in the patient's pulse. However, the patient died 2 h later [14, 15]. When the cholera pandemic arrived in England, in 1831 O'Shaughnessy, on also demonstrating haemoconcentration in cholera patients, recommended intravenous fluids to "restore blood to its natural specific gravity" and "restore its deficient saline matters" [16]. This leads to Latta's first successful attempts at fluid resuscitation with crystalloid solutions [10, 14–16]. Despite these and other initial reports of success during the pandemic, the practice did not achieve widespread use [10].

Fluid resuscitation was re-discovered some 30 years later as a treatment for severe haemorrhage. In 1864, Goltz was the first to suggest that loss of intravascular volume rather than a loss of oxygen carrying capacity might be the central mechanism of death in haemorrhagic shock [17]. This was supported by the experiments of Konecker and Sander, who found that dogs who were haemorrhaged 50% of their blood volume could be successfully resuscitated with a crystalloid solution [17]. Following these initial experiments, numerous clinical reports described the successful use of intravenous fluids in cases of major surgical and obstetric haemorrhage. Fluid resuscitation then began to be recommended as a treatment for haemorrhage [18–22].

The development of a new paradigm for the condition "shock" accompanied the expansion of the use of intravenous fluids. Prior to the nineteenth century, "shock" remained a concept without a clear definition [23, 24]. It was recognised that many different insults could lead to this common terminal syndrome [23, 24]. Theories on pathogenesis were numerous and varied, and focused mainly around primary nervous system failure or exhaustion of "vital energies" [23, 25]. Parallel developments in medical technology, such as the development of the sphygmomanometer in 1903, led to the ability to reliably and non-invasively measure blood pressure [24]. Experiments by Crile and others showed that injuries such as trauma, manipulation of internal organs and electrocution were able to produce a syndrome of systemic hypotension [25, 26]. On that basis, Mummery and Crile redefined shock as a condition with inadequate systemic blood pressure as its hallmark [24, 27]. Crile's later experiments demonstrated intravenous saline as one of the few therapies capable of improving blood pressure in shock

[27, 28]. By the early 1900s, several articles appeared recommending fluid boluses as an effective therapy for the undifferentiated syndrome of "shock" [29, 30].

The ability to measure cardiac output fundamentally changed the paradigm of shock again. The increased understanding of circulatory pathophysiology allowed the differentiation and description of shock by Blalock into the different subtypes recognisable today [31]. The subtype of vasodilatory shock (vasogenic in the original article) accounts for the dominant phenotype seen in human septic shock and endotoxemia [9, 32–35]. The ability to measure cardiac output led to the observation of an association between the development of a hyperdynamic circulation and survival in both experimental models and clinical septic shock [35–37]. This compelling finding along with the increased lactate and oliguria of sepsis was interpreted as evidence of potentially reversible tissue hypoperfusion [35–37]. The logical response to this was to introduce therapies which increase cardiac output, with the aim to overcome relative hypoperfusion and therefore improve patients' outcomes [35–37]. This theory of pathogenesis of organ dysfunction and death in sepsis has been the dominant paradigm since its inception in 1960s [38, 39]. However, evidence is accumulating, suggesting this paradigm may be fundamentally incorrect.

Changing understanding of sepsis and resuscitation

The case for tissue hypoperfusion in hyperdynamic sepsis was based on the occurrence of an increased lactate, oliguria and delivery-dependent oxygen consumption, with each finding attributed to occur due to inadequate blood flow. It was then assumed that fluid resuscitation would produce clinically relevant improvements in cardiac output able to reverse pathological tissue hypoperfusion. This example of linear clinical reasoning based on physiology is likely to be overly simplistic, and each element can be challenged by current evidence.

Increased lactate in sepsis

Tissue hypoperfusion leading to tissue hypoxia was thought to be the dominant mechanism accounting for the increased lactate seen in sepsis [37, 40, 41]. This theory has been challenged by the following observations. Direct tissue oximetry in hyperdynamic sepsis failed to show tissue hypoxia. Instead, skeletal muscle partial pressure of oxygen in patients with sepsis was found to be elevated [42, 43]. Similarly, experimental animal models attempting to demonstrate impaired cellular oxidative bioenergetics or abnormal lactate/pyruvate ratios have not demonstrated evidence of critically impaired oxidative metabolism during sepsis [44–47]. More recently, an

alternative mechanism has been proposed to explain the increased lactate of sepsis. Aerobic production mediated by increased Na/K^{ATPase} activity has been demonstrated to be a significant contributor to the lactate of sepsis in both human and animal models [44, 48]. Microdialysis measurements in septic patients showed that skeletal muscle lactate was significantly higher than blood lactate levels, indicating that there is net contribution of lactate to the circulation by skeletal muscle, despite an increased skeletal muscle partial pressure of oxygen [42, 43, 48]. This theory was supported by the observation that further lactate production could be abolished and the gradient eliminated by locally inhibiting Na/K^{ATPase} [48].

The production and clearance of lactate during sepsis is a complex, nonlinear and still poorly understood process. The current evidence suggests that elevated blood lactate level during sepsis is not a reliable indicator of tissue hypoxia [49].

Oliguria in sepsis

Oliguria in patients with sepsis is widely regarded as a surrogate for renal tissue hypoperfusion and often used as a trigger for fluid resuscitation. There is, however, little direct clinical evidence of renal hypoperfusion during sepsis. While the available clinical observational data are limited in both size and quality, where accurate estimates of renal blood flow in sepsis have been reported blood flow has been demonstrated to be markedly increased [50]. Experimental models have demonstrated variable findings with both reduced and increased renal plasma flow reported. It is important to point out that many animal models produce hypodynamic sepsis, which may explain some of this variation. In models of hyperdynamic sepsis, which more accurately mimic the clinical syndrome of human septic shock, increased renal blood flow has been demonstrated [50]. For example, in an ovine model of hyperdynamic septic shock, oliguria occurred despite dramatic increases in both cardiac output and renal artery blood flow [51]. These observations strongly suggest that oliguria is not a function of decreased renal perfusion during sepsis.

More importantly, clinical studies both in sepsis and in other conditions such as burns have shown that fluid resuscitation based on oliguria often has minimal to no effect on urine output and fails to reduce renal dysfunction [52–56].

Delivery-dependent oxygen consumption

The observation that oxygen consumption can be increased by increasing oxygen delivery in patients with sepsis is often referred to as "delivery-dependent oxygen consumption" [37, 41]. Its presence has been used to infer reversible tissue hypoperfusion and tissue hypoxia

in hyperdynamic sepsis [41]. However, the observed increase in oxygen consumption with increased oxygen delivery may be entirely accounted for by coupled effects, such as increased myocardial oxygen consumption and forced increases in renal oxygen consumption, rather than reversal of hypoxia [44]. Secondly, delivery-dependent oxygen consumption has also been observed in the setting of chronically ill patients operating at their baseline. This indicates that the presence of delivery-dependent oxygen consumption may not necessarily indicate critical tissue hypoxia [44, 57]. As Dantzker et al. [58] observed (it) "may represent the normal physiological behaviour of the system rather than an abnormal manifestation of oxygen extraction".

Effectiveness of resuscitation therapies on achieving haemodynamic targets

Fluid resuscitation exerts its potentially therapeutic effect by increasing the stressed volume of the circulation leading to increased venous return and cardiac output [59]. Recently, attempts have been made to quantify the potency of fluid administration to achieve this in sepsis. Studies in healthy individuals show increases in blood volume of 25–30% immediately after administration with 10–15% persisting 4 h after the infusion [60]. However, sepsis is known to produce changes in vascular permeability and the glycocalyx structure that may decrease the retention of fluids in the vascular compartment [59]. In an animal model of sepsis and fluid bolus resuscitation, only 0.6% of the fluid bolus remained in the circulation after 20 min [61]. Similar results have been demonstrated in humans with sepsis, with rapid redistribution of a fluid bolus out of the vascular compartment [62–64]. Clinically this translates into very small and short-lived effects of fluid bolus therapy on haemodynamic parameters such as blood pressure, heart rate, cardiac output and urine output [52, 65]. An improved understanding of the physiological effects of fluid administration has led to the development of a revised Starling equation. This new model of transvascular fluid exchange is based on recent research and considers the contributions of the endothelial glycocalyx layer, the endothelial basement membrane and the extracellular matrix [66].

The effect of vasopressors, increasing the stressed volume in the venous circulation, has been relatively overlooked until recently. In patients admitted to intensive care with septic shock, temporary reductions in noradrenaline infusion dose produced corresponding reductions in mean systemic filling pressure and cardiac output [67]. This supports previous observations of increased cardiac output and preload with vasopressor use in patients with septic shock [68, 69]. Interestingly, in a recently published PRCT, the addition of levosimendan

to augment cardiac output in patients with sepsis failed to show improvements in clinically relevant outcome parameters [70]. In another study comparing the early use of vasopressin and norepinephrine with or without hydrocortisone, similar clinical outcomes were demonstrated across groups demonstrating a range of possible therapeutic approaches to the haemodynamic management of sepsis [71].

These studies highlight that interventions other than fluid resuscitation could be applied to manipulate haemodynamic variables such as cardiac output in sepsis. The comparative effectiveness of these therapies remains unclear.

Preclinical evidence for the use of fluid resuscitation in sepsis

Several experimental studies in animals have investigated both the effectiveness of fluid resuscitation in improving the septic shock state and its effect on sepsis mortality.

In animal models of septic shock, fluid resuscitation resulted in modest improvements in a number of physiological variables. The most consistent finding from large animal models of sepsis is that of a short-term improvement in cardiac output associated with fluid resuscitation, with the effect dissipating rapidly after the termination of infusion [72–74]. Similarly, a number of studies have demonstrated modest improvements in gastrointestinal perfusion with fluid resuscitation [73]; however, this finding is not consistent in all the animal studies [74]. These results support the observation that, although gastrointestinal mucosal blood flow is impaired in septic shock, treatment strategies specifically aimed at improving gastrointestinal perfusion such as fluid resuscitation have generally failed to correct mucosal perfusion abnormalities and failed to show improve important clinical endpoints [75].

There are several small and large animal models that demonstrate improvements in mortality with fluid resuscitation. For example, in murine models of both caecal ligation and puncture and endotoxemia, fluid resuscitation has consistently been shown to improve mortality when compared to no treatment and to provide additive benefit to both antibiotics and corticosteroids [76–79]. Similarly, fluid resuscitation improved mortality in porcine and canine models of endotoxemia and peritonitis, respectively [80, 81].

The key problem with these animal studies, as briefly mentioned earlier, is the paucity of models that mirror the clinical presentation of sepsis in humans. The response to both sepsis and endotoxaemia in humans is different to commonly used murine, ovine and porcine models [82]. The dominant clinical form of sepsis in humans appears to be hyperdynamic sepsis, characterised by increased cardiac output and decreased systemic vascular resistance (SVR) [9, 32, 33, 35]. When challenged with intravenous endotoxin, humans also develop a hyperdynamic circulation [34]. This contrasts with the response seen in most large and small animal models, where hypodynamic shock after sepsis or endotoxemia predominates [72–74, 76–78, 82, 83]. These disparities occur from both the design characteristics of the models and the differences in human and experimental animal physiology. For example, both pigs and sheep have large numbers of pulmonary intravascular macrophages that are sensitive to circulating endotoxin. Activation leads to the rapid development of pulmonary hypertension and right heart dysfunction in ovine and porcine models of both sepsis and endotoxemia [82]. A similar clinical presentation of hypodynamic shock is seen in most murine models [76–78]. The dominance of hypodynamic models in the animal literature makes direct extrapolation of the effects of fluid resuscitation to human sepsis particularly problematic. The animal literature supports the conclusion that fluid resuscitation is effective for hypodynamic models of sepsis; however, it yields little insight on its effect in hyperdynamic septic shock.

Clinical evidence for the use of fluid resuscitation in sepsis

Despite its widespread use, the clinical evidence supporting fluid resuscitation in sepsis remains conflicted. Prior to 2001, its use hinged on physiological justification and a long history of use, as there were no randomised controlled trials (RCTs) that tested fluid resuscitation as an intervention for septic shock. The landmark study of early goal-directed therapy (EGDT) by Rivers et al. and the subsequent single-centre and multicentre follow-up RCTs in China were the first prospective studies suggesting benefit of the use of fluids in septic shock [84–86]. These studies demonstrated the benefits of a multi-intervention approach to the initial management of sepsis. Because fluid resuscitation was a central therapy of EGDT, these studies have been interpreted as strong support for the effectiveness of fluid resuscitation. Accordingly, these studies of EGDT are the cited references for the surviving sepsis guidelines recommending fluid resuscitation as the first haemodynamic intervention for patients in septic shock (1C recommendation—strong recommendation with low-quality evidence) [12]. However, while this body of evidence may support a multifaceted therapeutic approach that includes fluid resuscitation, this does not provide evidence for its effectiveness as an independent therapy. Fluid resuscitation was one of many potentially beneficial interventions that were unevenly distributed between groups, in both frequency and timing of use, including antibiotics,

vasopressors, corticosteroids and intensity of medical care [84–86]. Recently, three large RCTs of EGDT have been published [87–89]. In these trials, patients assigned to EGDT received significantly more fluids than patients receiving standard care. EGDT consistently failed to show an improvement in mortality for patients with septic shock, but was associated with more ICU admissions and increased utilisation of ICU resources [90]. These findings do not support the systematic use of EGDT, of which more aggressive fluid resuscitation is a component, in the management of patients with septic shock.

The observational data on the effects of fluid resuscitation in sepsis are conflicting, with studies suggesting equivocal, beneficial and negative effects on mortality.

In one study in 2796 patients across 77 intensive care units to determine the effectiveness of surviving sepsis guidelines recommended therapies, regression modelling showed that fluid challenge for hypotension or elevated lactate had no association with outcome (OR 1.01; 0.73–1.39) [91]. However, several retrospective reviews of septic patients, totalling more than 3000 patients, did report positive associations between increased early resuscitation volumes and improved mortality [92–95]. On the other hand, an increasing number of studies link fluid overload in septic patients to worse outcomes [96–99]. A positive fluid balance has been associated with increased mortality in sepsis in a number of studies, but it remains unclear whether it is a causative factor [6, 100]. For example, in a retrospective analysis of the "vasopressin in septic shock trial" (VASST), an inverse relationship between mortality and fluid balance within the first 12 h was demonstrated [98]. Of great concern were the findings of the "fluid challenges in intensive care" (FENICE) study, a large global inception cohort study [101]. This study showed that methods to predict fluid responsiveness are not used routinely by clinicians when prescribing fluid resuscitation, and safety limits for fluid resuscitation are rarely applied. Importantly, there was no statistically significant difference in the proportion of patients who received further fluids after the previous fluid bolus between those with a positive, with an uncertain or with a negatively judged response to fluids. In other words, patients who were proven to be not fluid responsive continued to receive the same amount of subsequent fluid boluses as did fluid responsive patients. This current practice undoubtedly increases the risk of fluid overload in critically ill patients [102].

Conversely, a conservative fluid strategy may improve patient outcomes, as was shown in the "fluids and catheters treatment trial" (FACTT) [103]. In this study, 1000 patients with acute lung injury were randomised into a conservative and a liberal strategy of fluid management using explicit protocols, which were applied for seven days. Patients in the conservative strategy arm showed significantly improved lung function and shorter duration of mechanical ventilation and intensive care without increasing non-pulmonary organ failures.

Considering the dose–effect relationship and side effects of fluids, fluid therapy should be regarded like other drug therapy with specific indications and tailored recommendations for the timing, type and dose of fluid. Based on this, a conceptual model with four phases of intravenous fluid therapy was recently proposed, which include resuscitation, optimisation, stabilisation and evacuation (ROSE) [104]. Specific strategies for fluid minimisation and de-escalation or de-resuscitation have been reported [105–107]. For example, in a recently published study, in which a protocol restricting resuscitation fluid was compared with standard care after initial resuscitation patients with septic shock showed that patient-centred outcomes all pointed towards benefit with fluid restriction [108]. The concept of de-resuscitation is further strengthened by a post hoc analysis of the RENAL study, which showed that a negative mean daily fluid balance was consistently associated with improved clinical outcomes [109]. A further and more detailed discussion of fluid minimisation, de-escalation or de-resuscitation is outside the scope of this review.

To provide a definitive answer to the crucial question what the true effect of fluid administration in the resuscitation phase of human sepsis is, we need high-level evidence from RCTs that compare fluid resuscitation versus no fluid resuscitation. This approach requires clinical equipoise between these two treatment arms, and therefore perhaps a shift in the way clinicians consider fluid resuscitation. Currently, the only randomised controlled trial of fluid resuscitation in sepsis is the "fluid expansion as supportive therapy trial" (FEAST) [110]. The investigators randomised 3141 (of a planned 3600) children with severe sepsis to receive fluid resuscitation with either 40 ml/kg of 0.9% saline or 4% albumin or no volume resuscitation. The trial was stopped early for harm, demonstrating a 40% increase in mortality in both the volume resuscitation arms. Much has been made with regard to the correct interpretation of these findings [111–113]. It has been suggested that the findings are specific to the unique population with a high incidence of malaria (57%), severe anaemia <5 g/dl (32%) and acidosis (base deficit >8 mmol/l, 51%) with saline and albumin causing disease-specific deterioration and worsening of both anaemia and acidosis [111, 112]. However, the published subgroup analysis does not support these conclusions with similar point estimates for harm independent of prior malaria, baseline haemoglobin and base deficit [110]. Surprisingly, the increase in

mortality did not appear to be related to complications of fluid overload but rather to delayed cardiovascular collapse [114].

Conclusion

Fluid resuscitation is recommended and widely used as the first-line resuscitative therapy for all patients presenting with septic shock. This practice seems mainly based on historical beliefs and an incomplete or incorrect understanding of the pathophysiology of sepsis.

Viewed as a whole, the bench-to-bedside evidence supporting fluid resuscitation as treatment for sepsis remains remarkably weak and highly conflicting. In addition, the indiscriminate use of fluid resuscitation, specifically beyond the initial resuscitation phase, has the potential to cause significant harm.

Although absence of evidence does not equal evidence of absence, one could argue there is an urgent need for better evidence. The research agenda should focus on the development of hyperdynamic animal sepsis models which more closely mimic human sepsis and on experimental and clinical studies designed to evaluate minimal or no fluid strategies in the resuscitation phase of sepsis.

The recent history of intensive care medicine has taught us that overly aggressive attempts to "normalise physiology", focusing on numbers, may be harmful. Perhaps the most important contribution towards improved outcomes of intensive care patients has been the removal of ineffective and potentially harmful treatments. Until proven otherwise, fluid resuscitation for sepsis fits that description.

Author details
[1] Australian National University Medical School, Canberra, Australia. [2] Intensive Care Unit, The Canberra Hospital, Canberra, Australia.

References

1. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546–54.
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. Crit Care Med Baltim. 2005;33(11):2555.
3. Sundararajan V, MacIsaac CM, Presneill JJ, Cade JF, Visvanathan K. Epidemiology of sepsis in Victoria, Australia. Crit Care Med. 2005;33(1):71–80.
4. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Crit Care. 2006;10(2):R42.
5. Daniels R. Surviving the first hours in sepsis: getting the basics right (an intensivist's perspective). J Antimicrob Chemother. 2011;66(suppl 2):ii11–23.
6. Vincent J, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med Baltim. 2006;34(2):344.
7. Suffredini AF, Munford RS. Novel therapies for septic shock over the past 4 decades. JAMA. 2011;306(2):194–9.
8. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med Baltim. 2001;29(7):1303–10.
9. Winslow EJ, Loeb HS, Rahimtoola SH, Kamath S, Gunnar RM. Hemodynamic studies and results of therapy in 50 patients with bacteremic shock. Am J Med. 1973;54(4):421–32.
10. Cosnett J. The origins of intravenous fluid therapy. The Lancet. 1989;333(8641):768–71.
11. Hollenberg S, Ahrens T, Astiz M, Chalfin D, Dasta J, Heard S, et al. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med. 1999;27(3):639–60.
12. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228.
13. van Haren F, Zacharowski K. What's new in volume therapy in the intensive care unit? Best Pract Res Clin Anaesthesiol. 2014;28(3):275–83.
14. Awad S, Allison SP, Lobo DN. The history of 0.9% saline. Clin Nutr. 2008;27(2):179–88.
15. Barsoum N, Kleeman C. Now and then, the history of parenteral fluid administration. Am J Nephrol. 2002;22(2–3):284–9.
16. O'shaughnessy W. Experiments on the blood in cholera. The Lancet. 1831;17(435):490.
17. Foëx B. How the cholera epidemic of 1831 resulted in a new technique for fluid resuscitation. Emerg Med J. 2003;20(4):316–8.
18. Richards B. Case of severe post-partum haemorrhage successfully treated by intra-venous injection of saline fluid. The Lancet. 1888;131(3359):67.
19. Jennings CE. The intra-venous injection of fluid for severe haemorrhage. The Lancet. 1882;120(3081):436–7.
20. The intra-venous injection of saline fluid. The Lancet. 1894;143(3672):105–6.
21. Coates W. Two cases of intra-venous injection of fluids for severe haemorrhage. The Lancet. 1882;120(3096):1110–2.
22. Thomas WT. Injection of saline solution in shock. The Lancet. 1898;152(3926):1390–1.
23. Millham FH. A brief history of shock. Surgery. 2010;148(5):1026–37.
24. Manji RA, Wood KE, Kumar A. The history and evolution of circulatory shock. Crit Care Clin. 2009;25(1):1–29.
25. Lockhart Mummery J. The physiology and treatment of surgical shock and collapse. I. Lancet. 1905;1:696–703.
26. Crile GW. An experimental research into surgical shock: an essay awarded the Cartwright Prize for 1897. Philadelphia: JB Lippincott; 1899.
27. Pilcher LS. Blood-pressure in surgery and the treatment of surgical shock. Ann Surg. 1904;39(2):310.
28. Soto-Ruiz KM, Varon J, George W. Crile: a visionary mind in resuscitation. Resuscitation. 2009;80(1):6–8.
29. The nature and treatment of wound shock. The Lancet. 1918;191(4932):375–6.
30. The treatment of shock. The Lancet. 1908;172(4428):102–3.
31. Blalock A. Shock and hemorrhage. Bull N Y Acad Med. 1936;12:610–6.
32. Villazon S, Sierra U, Lopez S, Rolando M. Hemodynamic patterns in shock and critically ill patients. Crit Care Med. 1975;3(6):215–21.
33. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med. 1987;15(10):923–9.

34. Suffredini AF, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA, et al. The cardiovascular response of normal humans to the administration of endotoxin. N Engl J Med. 1989;321(5):280–7.

35. MacLean LD, Mulligan WG, McLean A, Duff JH. Patterns of septic shock in man—a detailed study of 56 patients. Ann Surg. 1967;166(4):543.

36. Dietzman RH, Ersek RA, Bloch JM, Lillehei RC. High-output, low-resistance gram-negative septic shock in man. Angiology. 1969;20(11):691–700.

37. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis 1, 2. Am Rev Respir Dis. 1986;134(5):873–8.

38. Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004;32(9):1928–48.

39. Rivers EP, Coba V, Visbal A, Whitmill M, Amponsah D. Management of sepsis: early resuscitation. Clin Chest Med. 2008;29(4):689–704.

40. Dantzker D. Oxygen delivery and utilization in sepsis. Crit Care Clin. 1989;5(1):81–98.

41. Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH. Oxygen delivery and consumption in patients with hyperdynamic septic shock. Crit Care Med. 1987;15(1):26–8.

42. Boekstegers P, Weidenhöfer S, Kapsner T, Werdan K. Skeletal muscle partial pressure of oxygen in patients with sepsis. Crit Care Med. 1994;22(4):640–50.

43. Boekstegers P, Weidenhöfer S, Pilz G, Werdan K. Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. Infection. 1991;19(5):317–23.

44. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA. 1992;267(11):1503–10.

45. Jepson M, Cox M, Bates P, Rothwell N, Stock M, Cady E, et al. Regional blood flow and skeletal muscle energy status in endotoxemic rats. Am J Physiol Endocrinol Metabol. 1987;252(5):E581–7.

46. Hotchkiss R, Long R, Hall J, Shires G, Brouillard R, Millikan W, et al. An in vivo examination of rat brain during sepsis with 31P-NMR spectroscopy. Am J Physiol Cell Physiol. 1989;257(6):C1055–61.

47. Hotchkiss RS, Song S-K, Neil JJ, Chen RD, Manchester JK, Karl IE, et al. Sepsis does not impair tricarboxylic acid cycle in the heart. Am J Physiol Cell Physiol. 1991;260(1):C50–7.

48. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert P-E. Relation between muscle $Na^+K^+ATPase$ activity and raised lactate concentrations in septic shock: a prospective study. The Lancet. 2005;365(9462):871–5.

49. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. The Lancet. 1999;354(9177):505–8.

50. Langenberg C, Bellomo R, May C, Wan L, Egi M, Morgera S. Renal blood flow in sepsis. Crit Care. 2005;9(4):R363.

51. Langenberg C, Wan L, Egi M, May C, Bellomo R. Renal blood flow in experimental septic acute renal failure. Kidney Int. 2006;69(11):1996–2002.

52. Bihari S, Prakash S, Bersten AD. Post resuscitation fluid boluses in severe sepsis or septic shock: prevalence and efficacy (price study). Shock. 2013;40(1):28–34.

53. Lammi MR, Aiello B, Burg GT, Rehman T, Douglas IS, Wheeler AP, et al. Response to fluid boluses in the fluid and catheter treatment trial. Chest. 2015;148(4):919–26.

54. Dries DJ, Waxman K. Adequate resuscitation of burn patients may not be measured by urine output and vital signs. Crit Care Med. 1991;19(3):327–9.

55. Pruitt BA Jr. Protection from excessive resuscitation: "pushing the pendulum back". J Trauma. 2000;49(3):567–8.

56. Egal M, Erler NS, de Geus HR, van Bommel J, Groeneveld AB. Targeting oliguria reversal in goal-directed hemodynamic management does not reduce renal dysfunction in perioperative and critically ill patients: a systematic review and meta-analysis. Anesth Analg. 2016;122(1):173–85.

57. Mohsenifar Z, Jasper A, Koerner S. Relationship between oxygen uptake and oxygen delivery in patients with pulmonary hypertension. Am Rev Respir Dis. 1988;138(1):69–73.

58. Dantzker DR, Foresman B, Gutierrez G. Oxygen supply and utilization relationships: a reevaluation. Am Rev Respir Dis. 1991;143(3):675–9.

59. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. Br J Anaesth. 2016;116(3): 339–49.

60. Chowdhury AH, Cox EF, Francis ST, 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(1):18–24.

61. Bark BP, Öberg CM, Grände P-O. Plasma volume expansion by 0.9% NaCl during sepsis/systemic inflammatory response syndrome, after hemorrhage, and during a normal state. Shock. 2013;40(1):59–64.

62. Sánchez M, Jiménez-Lendínez M, Cidoncha M, Asensio M, Herrero E, Collado A, et al. Comparison of fluid compartments and fluid responsiveness in septic and non-septic patients. Anaesth Intensive Care. 2011;39(6):1022.

63. Nunes TSO, Ladeira RT, Bafi AT, de Azevedo LCP, Machado FR, Freitas FGR. Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation. Ann Intensive Care. 2014;4(1):1.

64. Marx G, Vangerow B, Burczyk C, Gratz K, Maassen N, Meyer MC, et al. Evaluation of noninvasive determinants for capillary leakage syndrome in septic shock patients. Intensive Care Med. 2000;26(9):1252–8.

65. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care. 2014;18(6):1.

66. 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(3):384–94.

67. Persichini R, Silva S, Teboul J-L, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med. 2012;40(12):3146–53.

68. Hamzaoui O, Georger J-F, Monnet X, Ksouri H, Maizel J, Richard C, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care. 2010;14(4):1.

69. Monnet X, Jabot J, Maizel J, Richard C, Teboul J-L. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. Crit Care Med. 2011;39(4):689–94.

70. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med. 2016;375(17):1638–48.

71. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA. 2016;316(5):509–18.

72. Rahal L, Garrido AG, Cruz RJ Jr, Silva E, Poli-de-Figueiredo LF. Fluid replacement with hypertonic or isotonic solutions guided by mixed venous oxygen saturation in experimental hypodynamic sepsis. J Trauma Acute Care Surg. 2009;67(6):1205–12.

73. Garrido A, Poli de Figueiredo L, Cruz RJ Jr, Silva E. Rocha e Silva M. Short-lasting systemic and regional benefits of early crystalloid infusion after intravenous inoculation of dogs with live *Escherichia coli*. Braz J Med Biol Res. 2005;38(6):873–84.

74. Lagoa CE, de Figueiredo LF, Cruz RJ, Silva E, Silva MR. Effects of volume resuscitation on splanchnic perfusion in canine model of severe sepsis induced by live *Escherichia coli* infusion. Crit Care. 2004;8(4):R221.

75. van Haren FM, Sleigh JW, Pickkers P, Van der Hoeven JG. Gastrointestinal perfusion in septic shock. Anaesth Intensive Care. 2007;35(5):679–94.

76. Ottosson J, Dawidson I, Brandberg A, Idvall J, Sandor Z. Cardiac output and organ blood flow in experimental septic shock: effect of treatment with antibiotics, corticosteroids, and fluid infusion. Circ Shock. 1991;35(1):14–24.

77. Ottosson J, Persson T, Dawidson I. Oxygen consumption and central hemodynamics in septic shock treated with antibiotics, fluid infusions, and corticosteroids. Crit Care Med. 1989;17(8):772–9.

78. Smith E III, Slivjak M, Egan J, Gagnon R, Arleth A, Esser K. Fluid resuscitation improves survival of endotoxemic or septicemic rats: possible contribution of tumor necrosis factor. Pharmacology. 1993;46(5):254–67.

79. Wilson MA, Chou MC, Spain DA, Downard PJ, Qian Q, Cheadle WG, et al. Fluid resuscitation attenuates early cytokine mRNA expression after peritonitis. J Trauma. 1996;41(4):622–7.

80. Natanson C, Danner RL, Reilly JM, Doerfler ML, Hoffman WD, Akin GL, et al. Antibiotics versus cardiovascular support in a canine model of human septic shock. Am J Physiol Heart Circ Physiol. 1990;259(5):H1440–7.
81. Oi Y, Åneman A, Svensson M, Ewert S, Dahlqvist M, Haljamäe H. Hypertonic saline-dextran improves intestinal perfusion and survival in porcine endotoxin shock. Crit Care Med. 2000;28(8):2843–50.
82. Schmidhammer R, Wassermann E, Germann P, Redl H, Ullrich R. Infusion of increasing doses of endotoxin induces progressive acute lung injury but prevents early pulmonary hypertension in pigs. Shock. 2006;25(4):389–94.
83. Bressack MA, Morton N, Hortop J. Group B streptococcal sepsis in the piglet: effects of fluid therapy on venous return, organ edema, and organ blood flow. Circ Res. 1987;61(5):659–69.
84. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
85. Early Goal-Directed Therapy Collaborative Group of Zhejiang Province. The effect of early goal-directed therapy on treatment of critical patients with severe sepsis/septic shock: a multi-center, prospective, randomized, controlled study. Chin Crit Care Med. 2010;22(6):331.
86. Lin S-M, Huang C-D, Lin H-C, Liu C-Y, Wang C-H, Kuo H-P. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock. 2006;26(6):551–7.
87. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11.
88. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. New Engl J Med. 2014;370(18):1683–93.
89. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, et al. Goal-directed resuscitation for patients with early septic shock. New Engl J Med. 2014;371(16):1496–506.
90. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, 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(9):1549–60.
91. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med. 2009;180(9):861–6.
92. Lee SJ, Ramar K, Park JG, Gajic O, Li G, Kashyap R. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: a retrospective cohort study. CHEST J. 2014;146(4):908–15.
93. Garland A, Kumar A, Waechter J. Early administration of crystalloid fluids reduces mortality in septic shock. Am J Respir Crit Care Med. 2010;181:A4097.
94. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. CHEST J. 2009;136(1):102–9.
95. Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. JAMA. 1991;266(9):1242–5.
96. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality. J Intensive Care Med. 2014;29(4):213–7.
97. Smith SH, Perner A. Higher vs. lower fluid volume for septic shock: clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort. Crit Care. 2012;16(3):R76.
98. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259–65.
99. Samoni S, Vigo V, Resendiz LI, Villa G, De Rosa S, Nalesso F, et al. Impact of hyperhydration on the mortality risk in critically ill patients admitted in intensive care units: comparison between bioelectrical impedance vector analysis and cumulative fluid balance recording. Crit Care. 2016;20:95.
100. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock the effect of increasing fluid balance on mortality. J Intensive Care Med. 2013:0885066613478899.
101. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study—a global inception cohort study. Intensive Care Med. 2015;41(9):1529–37.
102. Vandervelden S, Malbrain ML. Initial resuscitation from severe sepsis: one size does not fit all. Anaesthesiol Intensive Ther. 2015;47:s44–55.
103. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75.
104. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740–7.
105. Malbrain ML, Van Regenmortel N, Owczuk R. It is time to consider the four D's of fluid management. Anaesthesiol Intensive Ther. 2015;47:s1–5.
106. Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock: a pilot study. Chest. 2015;148(6):1462–9.
107. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014;46(5):361–80.
108. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695–705.
109. Investigators RRTS, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Crit Care Med. 2012;40(6):1753–60.
110. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95.
111. Southall D, Samuels M. Treating the wrong children with fluids will cause harm: response to 'mortality after fluid bolus in African children with severe infection'. Arch Dis Child. 2011;96(10):905–6.
112. Ford S, Visram A. Mortality after fluid bolus in African children with sepsis. N Engl J Med. 2011;365(14):1348.
113. Myburgh J, Finfer S. Causes of death after fluid bolus resuscitation: new insights from FEAST. BMC Med. 2013;11(1):1.
114. Maitland K, George EC, Evans JA, Kiguli S, Olupot-Olupot P, Akech SO, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med. 2013;11(1):1.