Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data

Neil J Glassford¹,², Glenn M Eastwood¹,³ and Rinaldo Bellomo¹,²*

Abstract

Fluid bolus therapy (FBT) is a standard of care in the management of the septic, hypotensive, tachycardic and/or oliguric patient. However, contemporary evidence for FBT improving patient-centred outcomes is scant. Moreover, its physiological effects in contemporary ICU environments and populations are poorly understood. Using three electronic databases, we identified all studies describing FBT between January 2010 and December 2013. We found 33 studies describing 41 boluses. No randomised controlled trials compared FBT with alternative interventions, such as vasopressors. The median fluid bolus was 500 ml (range 100 to 1,000 ml) administered over 30 minutes (range 10 to 60 minutes) and the most commonly administered fluid was 0.9% sodium chloride solution. In 19 studies, a predetermined physiological trigger initiated FBT. Although 17 studies describe the temporal course of physiological changes after FBT in 31 patient groups, only three studies describe the physiological changes at 60 minutes, and only one study beyond this point. No studies related the physiological changes after FBT with clinically relevant outcomes. There is a clear need for at least obtaining randomised controlled evidence for the physiological effects of FBT in patients with severe sepsis and septic shock beyond the period immediately after its administration.

Introduction

All critically ill patients receive intravenous (IV) fluids, which are given to maintain physiological homeostasis, or as a vehicle for drug administration, or as direct therapeutic administration to correct perceived haemodynamic instability [1-4]. In these situations, where there is a perceived reduction in venous return and cardiac output secondary to vasodilatation and/or hypovolaemia, using IV fluid to increase intravascular volume is believed to effectively compensate for these changes in vascular tone by increasing stroke volume in accordance with the Frank-Starling principle [5-10].

Several mechanisms for delivering IV fluids, both diagnostically and therapeutically under such circumstances, have been described. These include Weil central venous pressure (CVP)-guided fluid challenge technique [10-13], the timed and rapid infusion methods favoured by Shoemaker [7,8,14-16] and, more recently, techniques involving echocardiographic or ultrasonographic assessment of fluid responsiveness following low-volume IV infusion [17]. However, the current standard of care in the management of septic, hypotensive, tachycardic and/or oliguric patients is fluid bolus therapy (FBT), where IV fluid is rapidly administered in discrete boluses [18-21]. While the ideal fluid bolus would be a discrete volume of a specific fluid administered at a specified rate, accounting for individual patient features and with a defined aim (Figure 1) [11], there is no current agreement regarding exactly what defines a fluid bolus. Moreover, although strong overall consensus regarding the importance of FBT exists [18-20], there appears to be little randomized controlled information on the magnitude and duration of its physiological effects, or on the direct positive impact of FBT on patient outcome in sepsis as an independent intervention [22].

In contrast, an expanding body of evidence suggests that FBT may contribute to a positive fluid balance, which, in turn, is independently associated with a variety of adverse outcomes in the critically ill [23-28]. Recent
experimental evidence suggests rapid fluid infusion can also damage the endothelial glycocalyx [29,30], a structure already at risk in patients with sepsis [31], leading to endothelial disruption and organ dysfunction [32,33]. It appears that we need a better understanding of both the current evidence base for FBT and how best to apply it in the clinical setting [34,35].

Accordingly, we systematically reviewed the contemporary literature to determine current practice and to identify the independent effects of FBT on both physiological and patient-centred outcomes in the management of severe sepsis and septic shock in critical care practice.

**Methods**
We interrogated the MEDLINE, CENTRAL and EMBASE electronic reference databases using a combination of search terms (Figure 2). The reference lists of retrieved articles were examined for additional studies of potential relevance.
The search was carried out in December 2013. To achieve contemporary relevance results were arbitrarily limited to this decade (2010 to 2013) and to English language studies in humans. Paediatric studies were excluded. This search defined a set of records of studies of fluid administration or haemodynamic optimization in patients with severe sepsis or septic shock.

The abstracts of these records were examined to identify those studies of potential relevance. These manuscripts were retrieved and examined manually in accordance with our inclusion criteria. The studies to be included in the review were checked to ensure they had not been retracted subsequent to their publication.

**Study inclusion criteria**

**Population of included studies**
We considered clinical studies of any type describing a population of patients suffering from severe sepsis or septic shock. We also included those studies of shock or circulatory failure where either the majority of patients, or a defined subgroup of patients, had severe sepsis or septic shock.

**Intervention - fluid bolus administration**
For the purposes of this study a fluid bolus was a defined volume of a defined fluid administered over a defined time period. We recognised that most studies do not describe FBT in ideal terms (Figure 1) and therefore studies describing at least two of the three criteria were included in the review.

**Comparator - alternatives to fluid administration**
Any studies comparing FBT with the initiation of vasoactive medication, the increase of such medication or observation as an alternative to the administration of FBT were included in the review.

**Between groups analysis**
Where studies included in the review assigned patients to multiple treatment arms, each treatment group was treated as an individual group.

**Outcome - physiological effects of bolus administration**
Subsets of studies were selected from those describing FBT. The first included those reporting changes in cardiac output, heart rate, mean arterial pressure, central venous pressure, venous oxygen saturation, blood lactate concentration, urine output or haemoglobin concentration following FBT; for the purposes of inclusion, studies could describe changes in any or all of the haemodynamic parameters listed, but the direction, magnitude and duration of the change had to be extractable from tables or figures contained in the paper. The second group included those reporting non-physiological, patient-centred outcomes. Our primary outcome of interest was mortality at all reported time points. Secondary outcomes of interest included duration of ICU and hospital stay, duration of mechanical ventilation, and need for continuous renal replacement therapy (CRRT). We did not contact authors for additional information or individual patient data.

**Data collection**
We collected data on study type, study setting and location, study population and the aims of the study. Due to our acceptance of multiple types of study, we chose not to adopt a methodological scoring system. We examined the definition of a fluid bolus in each study fulfilling our criteria and recorded the type and volume of fluid used, as well as the rate of administration. We identified the trigger and end-points for fluid bolus administration, the number of boluses administered and the use of red cell transfusions and vasoactive medication as part of the experimental protocol. We identified the demographic group in which subsequent observations were recorded. In those studies describing the physiological effects of bolus administration, we recorded the absolute change in cardiac output, heart rate, mean arterial pressure, venous oxygen saturation, blood lactate concentration, urine output and haemoglobin concentration. In those studies reporting patient-centred outcomes we recorded mortality at all reported time points, duration of ICU and hospital stay, duration of mechanical ventilation, and need for CRRT.

**Statistical analysis**
We expected grossly heterogeneous results across different study types and study protocols. A meta-analysis approach could not be applied. Results are therefore presented as crude medians with full ranges. These exclude alternative units of measure, which are reported separately - for example, the median may be given in millilitres, followed by individual reporting of ml/kg.

**Results**

**Electronic search**
Our search strategy identified 2,956 articles over the period 2010 to 2013. Of these, 2,875 were excluded as duplicates, irrelevant, paediatric research or having been published in a language other than English. Of the 81 potentially relevant publications identified, 33 met our inclusion criteria (Figure 3) [36-68]. In total, 17 of these described the physiological changes occurring following FBT [36,39,40,45,46,48,50,53-55,57,59,60,62,63,65,66] and seven studies described patient-orientated outcome measures [37,42,43,49,58,59,64].

**Relevant contemporary studies**
The study details, population, size and aims are presented in Table 1. We identified 22 prospective observational
studies, four retrospective observational studies, two quasi-experimental studies, and five randomised controlled trials (RCTs). Of the five RCTs, none compared FBT with a control intervention; two actually reported the impact of blood volume analysis on protocolized resuscitation [64,67]; two compared hypertonic versus isotonic fluids [51,65]; and one actually compared two vasopressors and reported fluid data as an addendum [38]. Additional study data can be found in the electronic supplemental material (Additional file 1: Table S1).

Pre-fluid bolus therapy fluid administration
Fluid resuscitation prior to study recruitment and FBT was described in 10 studies. In the five studies describing finite volumes of resuscitation fluid, the median volume administered was 2,200 ml (range 1,000 to 5,060 ml) [38,47,51,53,58]. The five remaining studies reported weight-dependent volumes of between 20 and 30 ml/kg of resuscitation (Table 2) [41,43,49,56,57].

Initiation and cessation of fluid bolus therapy
Across the 33 studies, 19 predetermined clinical or physiological features triggered FBT. In the remaining 14 studies, FBT was triggered by clinical judgment in eight, by hypotension in two, simply by the diagnosis of severe sepsis or septic shock in two, and remained unspecified in two (Table 2).

In the majority of studies (18 of 33) FBT ceased at the end of the bolus in question; 10 studies used predetermined immediate changes in physiological variables as end-points; four studies did not define the physiological end-points of fluid resuscitation (Table 2).

Defining fluid bolus therapy
Overall, 41 forms of FBT were described, fully or in part, in 33 studies. They are presented in Table 2. In 20 studies, the fluid type was fixed; in 13 more than one fluid type was used. In six studies the fluid type was not identified beyond the generic crystalloid or colloid. The fluid most commonly used as a bolus was 0.9% saline (17 studies), followed by 6% hydroxyethyl starch (eight studies). On the other hand, 4% albumin was used in only four studies [38,53,59,65], 4% gelatin in only three [38,48,66], physiological lactated solutions in only two [59,61], and 20% albumin and blood products in only one [38].

The median amount of fluid administered as a finite volume was 500 ml (range 100 to 1,000 ml). However, 20 ml/kg and 7 ml/kg were individually reported as weight-dependent boluses. The median number of boluses (24 studies) was 1 (range 0.68 to 10). Rates of administration were defined for 31 of 41 boluses with a median rate of 30 minutes (range 10 to 60 minutes).

Haemodynamic changes after fluid bolus therapy
Comparing different interventions
No RCTs compared the haemodynamic changes induced by FBT with observation or vasopressor administration or inotropic drug administration or continuous low dose IV fluid infusion or any combination of the above. The only study comparing FBT with an alternative intervention was a single, non-randomized, prospective, observational study that compared acute circulatory failure patients treated with FBT (500 ml of saline) or with increased norepinephrine dose according to clinician preference [55]. The two groups had clearly different baseline characteristics and were not directly compared.
| First author | Journal | Year | Aims of study | Location | Institution(s) | Study type | Population size |
|--------------|---------|------|---------------|----------|----------------|------------|-----------------|
| Bihari [36]  | Shock   | 2013 | Investigation of the use and effects of fluid boluses in septic patients following primary resuscitation | Australia | Single centre, academic ICU | Prospective observational study | 50 patients with severe sepsis or septic shock |
| Castellanos-Ortega [37] | Critical Care Medicine | 2010 | Evaluation of the impact of a standardised EGDT response to sepsis | Spain | Single centre, academic ICU | Quasi-experimental study | 480 patients with septic shock |
| De Backer [38] | New England Journal of Medicine | 2010 | Assessing the effect of noradrenaline as first-line vasopressor on mortality | Europe | 8 centres, mixed ICUs | Randomised clinical trial | 1,679 patients with shock requiring vaspressor therapy. 1,044 patients with sepsis |
| Dong [39] | World Journal of Emergency Medicine | 2012 | Investigating the relationship between stroke volume index and passive leg raising and fluid responsiveness | China | 2 centres, general ICUs | Prospective observational study | 32 mechanically ventilated patients with septic shock |
| Freitas [40] | British Journal of Anaesthesia | 2013 | Evaluation of the predictive value of automated PPV for fluid responsiveness in patients with sepsis and low tidal volumes | Brazil | Single centre, academic ICU | Prospective observational study | 40 patients with low tidal volume ventilation and severe sepsis or septic shock requiring a fluid challenge |
| Gaieski [41] | Critical Care Medicine | 2010 | Evaluation of the impact of a standardised EGDT response to sepsis on time to antibiotic administration and survival | USA | Single centre, academic ICU | Retrospective observational study | 261 patients with severe sepsis and septic shock undergoing EGDT |
| Hamzaoui [42] | Critical Care | 2010 | Evaluation of the cardiac consequences of early administration of noradrenaline | France | Single centre, academic ICU | Prospective observational study | 105 patients with septic shock requiring vasopressor commencement following initial fluid resuscitation |
| Hanzeika [43] | Supportive Care in Cancer | 2013 | Evaluation of the impact of a standardised EGDT response to sepsis | USA | Single centre, academic ED | Retrospective observational study | 200 patients with cancer and severe sepsis or septic shock presenting to ED |
| Jacob [44] | Critical Care Medicine | 2012 | Evaluation of the impact of early monitored sepsis management | Uganda | 2 centres, medical/treatment centres | Prospective observational study | 671 patients with severe sepsis presenting within office hours |
| Khwannimit [45] | European Journal of Anaesthesiology | 2012 | Comparing SW by Vigileo with PPV by monitor to predict fluid responsiveness | Thailand | Single centre, academic ICU | Prospective observational study | 42 patients with septic shock who were mechanically ventilated with tidal volumes >8 ml/kg requiring fluid resuscitation |
| Lakhal [46] | Intensive Care Medicine | 2013 | Identification of fluid responsiveness from IABP and NIBP | France | 3 centres, academic ICU | Prospective observational study | 130 patients with circulatory failure requiring a fluid challenge. 58 patients with septic shock |
| Lanspa [47] | Journal of Critical Care | 2012 | Assessment of CVP and shock index to predict haemodynamic response to volume expansion when compared with CVP alone | USA | Single centre, academic ICU | Prospective observational study | 25 patients with septic shock over 14 years of age |
| Study settings, size, population and aims (Continued) |
|------------------------------------------------------|
| Machare-Delgado [48] Journal of Intensive Care Medicine 2011 Predicting fluid responsiveness by comparing SVV and inferior vena caval respiratory variation by ECHO during mechanical ventilation USA Single centre, medical academic ICU Prospective observational study 25 mechanically ventilated vasopressor-dependent patients who required a fluid challenge. 22 patients with severe sepsis or septic shock |
| MacRedmond [49] Quality and Safety in Health Care 2010 Evaluation of the impact of implementing a quality initiative on the management of severe sepsis and septic shock Canada Single centre, ICU Quasi-experimental study 74 patients with severe sepsis or septic shock admitted via ED |
| Mahjoub [50] Intensive Care Medicine 2012 Assessment of the impact of volume expansion on patients with left ventricular dysfunction France Single centre, academic ICU Prospective observational study 83 mechanically ventilated patients with sepsis-induced circulatory failure |
| McIntyre [51] Journal of Critical Care 2012 Feasibility study comparing the effects of 5% albumin versus 0.9% saline for resuscitation in septic shock Canada 6 centres, academic ED and ICU Randomised clinical trial 50 patients with refractory hypotension and sepsis |
| Monnet [52] Critical Care 2010 Comparing haemodynamic changes induced by noradrenaline and volume expansion using Vigileo and PICCO France Single centre, academic medical ICU Prospective observational study 80 patients with sepsis-induced circulatory failure |
| Monnet [53] Critical Care Medicine 2011 Assessing the effects of noradrenaline on haemodynamics in sepsis France Single centre, academic medical ICU Prospective observational study 25 patients with sepsis-induced fluid-responsive acute circulatory failure with DBP <40 mmHg, or requiring noradrenaline |
| Monnet [54] Critical Care Medicine 2013 Comparing ScvO2 and markers of anaerobic metabolism as predictors of unfavourable changes in oxygen extraction France Single centre, academic medical ICU Prospective observational study 51 patients with acute circulatory failure undergoing transpulmonary thermodilution monitoring, 40 patients with septic shock |
| Monnet [55] Critical Care Medicine 2011 Investigation of the utility of pulse pressure as a surrogate for changes in cardiac output France Single centre, academic medical ICU Prospective observational study 373 patients with acute circulatory failure requiring a fluid challenge or the introduction or dose increase of noradrenaline. 338 patients with septic shock |
| O’Neill [56] Journal of Emergency Medicine 2012 Evaluation of the most difficult elements of a SSC protocol to implement in a community-based ED USA Single centre, community ED Retrospective observational study 79 with severe sepsis or septic shock remaining hypotensive following 2,000 ml of fluid resuscitation |
| Ospina-Tascon [57] Intensive Care Medicine 2010 Evaluation of the effects of fluid administration on microcirculatory alterations in sepsis Belgium Single centre, academic ICU Prospective observational study 60 patients with severe sepsis requiring fluid challenge, 37 within 24 hours of diagnosis, 23 after 48 hours |
| Patel [58] Annals of Pharmacotherapy 2010 Investigation of the implementation and effects of introducing the SSC guidelines USA Single centre, community ICU Prospective observational study 112 patients with sepsis or septic shock |
| Study ID | Journal | Year | Aim | Setting | Size | Population | Aims |
|---------|---------|------|-----|--------|------|------------|-----|
| Pierrakos [59] | Intensive Care Medicine | 2012 | Evaluation of the correlation between changes in MAP and CI following fluid challenge | Belgium | Single centre, academic ICU | Prospective observational study | 51 patients with septic shock undergoing invasive haemodynamic monitoring and requiring a fluid challenge |
| Pottecher [60] | Intensive Care Medicine | 2010 | Assessment of sublingual microcirculatory changes in response to fluid challenge | France | 2 centres, academic ED | Prospective observational study | 25 mechanically ventilated patients with severe sepsis or septic shock within 24 hours of ICU admission demonstrating pre-load dependency |
| Sanchez [61] | Anaesthesia and Intensive Care | 2011 | Measuring the response to a fluid load in patients with and without septic shock | Spain | Single centre, academic ICU | Prospective observational study | 32 patients requiring invasive monitoring. 18 patients with septic shock |
| Schnell [62] | Critical Care Medicine | 2013 | Assessment of the effects of a fluid challenge on Doppler-based renal resistive index in critically ill patients | France | 3 centres, academic ICUs | Prospective observational study | 35 mechanically ventilated patients with real-time cardiac monitoring requiring a fluid challenge. 30 patients with sepsis |
| Sturgess [63] | Anaesthesia and Intensive Care | 2010 | Comparison of aortic corrected flow time, BNP and CVP as predictors of fluid responsiveness | Australia | Single centre, private ICU | Prospective observational study | 10 patients with septic shock requiring a fluid challenge |
| Trof [64] | Critical Care Medicine | 2012 | Comparison of volume-guided and pressure-guided hemodynamic management in shocked patients | Netherlands | 2 centres, academic ICU | Randomised clinical trial | 120 patients with shock requiring invasive haemodynamic monitoring and >48 hours of ICU admission. 72 patients with sepsis |
| van Haren [65] | Shock | 2012 | Evaluation of the effects of hypertonic versus isotonic fluid administration in patients with septic shock | Netherlands | Single centre, academic ICU | Randomised clinical trial | 24 patients with septic shock enrolled within 24 hours of admission |
| Wacharasint [66] | Journal of the Medical Association of Thailand | 2012 | Evaluation of the effectiveness of three dynamic measures of fluid responsiveness in septic shock patients | Thailand | Single centre, medical ICU | Prospective observational study | 20 patients with sepsis and acute circulatory failure with invasive haemodynamic monitoring stable for 15 minutes prior to inclusion |
| Yu [67] | Shock | 2011 | Evaluation of the effects of blood volume analysis compared with pulmonary artery catheter monitoring | North America | Single centre, academic ICU | Randomised clinical trial | 100 patients requiring resuscitation for shock. 69 patients with severe sepsis or septic shock |
| Zhang [68] | Journal of Critical Care | 2012 | Investigation of the association between plasma protein levels and subsequent pulmonary oedema | China | Single centre, academic ICU | Retrospective observational study | 62 patients with sepsis undergoing transpulmonary thermodilution assessment requiring fluid |

BNP, B-type natriuretic peptide; CI, cardiac index; CVP, central venous pressure; DBP, diastolic blood pressure; ECHO, echocardiogram; ED, Emergency Department; EGDT, early goal directed therapy; IABP, intra-arterial blood pressure; MAP, mean arterial blood pressure; NIBP, non-invasive blood pressure; PICCO, pulse contour cardiac output monitoring; PPV, pulse pressure variation; ScvO₂, central venous oxygen saturation; SSC, Surviving Sepsis Campaign; SVV, stroke volume variation.
| First author               | Year Initial | Resuscitation | Bolus fluid type | Bolus fluid volume (ml) | Bolus fluid rate (minutes) | Physiological trigger for fluid administration | Physiological end-point for fluid administration | Number of boluses administered | Vasoactive administration? | Packed red cell transfusion? |
|---------------------------|--------------|----------------|------------------|-------------------------|---------------------------|----------------------------------------------|----------------------------------------------|--------------------------------|-----------------------------|-----------------------------|
| Bihari [36]               | 2013         | Undefined      | 4% albumin       | 750                     | <30                       | Clinician defined                           | Clinician defined                           | 2                              | Yes                         | Not described               |
| Castellanos-Ortega [37]   | 2010         | Undefined      | Crystalloid      | 1,000                   | 30                        | Hypotension                                 | CVP ≥8 mmHg, MAP ≥65 mmHg, ScvO₂ ≥70%      | Not described                   | Yes                         | Not described               |
| De Backer [38]            | 2010         | 500 ml colloid or 1,000 ml crystalloid | Colloid          | 1,000                   | Not defined                | MAP <70 mmHg; SBP <100 mmHg, altered mental state; mottled skin; oliguria >1 hour; hyperlactataemia | Not described                   | Not described                   | Yes                         | Not described               |
| Dong [39]                 | 2012         | Undefined      | 6% HES           | 500                     | 30                        | SBP <90 mmHg or >40 mmHg drop or need for vasopressors, oliguria >1 hour; mottled skin; HR >100 bpm | End of infusion                           | 1                              | Not described                   | Not described               |
| Freitas [40]              | 2012         | Undefined      | 6% HES           | 7 ml/kg (max 500)       | 30                        | Clinician defined                           | End of infusion                           | 1                              | Yes                         | No                          |
| Gaieski [41]              | 2010         | 20-30 ml/kg    | 0.9% saline      | 500                     | 15-20                     | CVP <8 mmHg                                 | CVP >8 mmHg                                | Not described                   | Yes                         | Yes                         |
| Hamzaoui [42]             | 2010         | Undefined      | 0.9% saline      | 1,000                   | Not defined                | Underdefined                               | Underdefined                               | Not described                   | Yes                         | Yes                         |
| Hanzeika [43]             | 2013         | 20 ml/kg       | Undefined        | 1,000                   | 60                        | Severe sepsis                               | SBP >90 mmHg, MAP <65 mmHg                 | Not described                   | Yes                         | No                          |
| Jacob [44]                | 2012         | Undefined      | 0.9% saline      | 1,000                   | 60                        | SBP <100 mmHg or hyperlactataemia           | SBP increased by 10 mmHg for 2 consecutive hours to >90 mmHg | Up to 10                        | No                          | Not described               |
| Khwannimit [45]           | 2012         | Undefined      | 6% HES           | 500                     | 30                        | Clinician defined                           | End of infusion                           | 1                              | Yes                         | No                          |
| Lakhal [46]               | 2013         | Undefined      | 4% gelatin       | 500                     | 30                        | One or more of SBP <90 mmHg, MAP <65 mmHg, requiring vasoactive medication, oliguria, skin mottling, hyperlactataemia | End of infusion                           | 1                              | Yes                         | Not described               |
| Table 2 Description of fluid boluses, triggers, physiological end-points and primary confounders (Continued) |
|--------------------------------------------------|
| Lanspa [47] 2012 | 5,060 ml | Crystalloid (or equivalent colloid) | 20 ml/kg | <20 | Clinician defined | End of infusion | 1.36 | Yes | Yes |
| Machare-Delgado [48] 2011 | Undefined | 0.9% saline | 500 | 10 | Clinician defined | End of infusion | 1 | Not described | No |
| MacRedmond [49] 2010 | 25 ml/kg | 0.9% saline | 500 | <15 | MAP <65 mmHg | End of infusion | 1 | Not described | Yes |
| Mahjoub [50] 2013 | Undefined | 0.9% saline | 500 | 20 | SBP <90 mmHg and/or need for vasopressor drugs and/or persistent lactic acidosis | End of infusion | 1 | Yes | Not described |
| McIntyre [51] 2012 | 2,400 ml | 0.9% saline or 4% albumin | 500 | STAT | Undef         | End of infusion | 1 | Yes | Not described |
| Monnet [52] 2010 | Undefined | 0.9% saline | 500 | 30 | SBP <90 mmHg, SBP drop >50 mmHg if HT, and one or more of HR >100, skin mottling or oliguria | End of infusion | 1 | Yes | Not described |
| Monnet [53] 2011 | 2,200 ml | 0.9% saline | 500 | 10 | SBP <90 mmHg, SBP drop >50 mmHg if HT, and one or more of HR >100, skin mottling or oliguria | End of infusion | 1 | Yes | Not described |
| Monnet [54] 2013 | Undefined | 0.9% saline | 500 | 30 | SBP <90 mmHg, SBP drop >50 mmHg if HT, and one or more of HR >100, skin mottling or oliguria | End of infusion | 1 | Yes | Yes |
| Monnet [55] 2011 | Undefined | 0.9% saline | 500 | 20 | SBP <90 mmHg, SBP drop >50 mmHg if HT, and one or more of HR >100, skin mottling or oliguria | End of infusion | 1 | Yes | Not described |
| O’Neill [56] 2012 | 20 ml/kg | 0.9% saline | 500 | 15 | CVP <8 mmHg; MAP <65 mmHg; ScvO$_2$ < 70% | End of infusion | 0.68 | Yes | Not described |
| Ospina-Tascon [57] 2010 | Undefined | CSL 4% albumin | 1,000 | 30 | MAP <65 mmHg | End of infusion | 1 | Yes | Not described |
| Patel [58] 2010 | 2,000 ml | Normal saline | Undefined | 30 | SBP <90 mmHg; MAP <65 mmHg | End of infusion | 1 | Yes | Not described |
| Pierrakos [59] 2012 | Undefined | CSL 6% HES | 100 | 30 | Clinician defined | End of infusion | 1 | Yes | Not described |
| Author         | Year | Definition | Type of Solution | Dose             | Time | MAP Criteria | End of Infusion | STAT | Primary Confounders                                                                 |
|---------------|------|------------|------------------|------------------|------|--------------|----------------|------|-------------------------------------------------------------------------------------|
| Pottecher     | 2010 | Undefined  | HES 6% or 0.9% saline | 500, 30 MAP <65 mmHg, skin mottling or oliguria | End of infusion 1 | Yes           | Not described                |
| Sanchez       | 2011 | Undefined  | Crystalloid      | 1,000 ITBVI >900 ml/ml or EVLWI >10 ml/kg | Hypotension with perfusion abnormalities |
| Schnell       | 2013 | Undefined  | Crystalloid      | 500, 15-30 Clinician defined | Clinician defined                      |
| Sturgess      | 2010 | Undefined  | Colloid          | 4% albumin       | 250, 15 MAP >65 mmHg, ScvO2 > 70%, lactate clearance, diuresis >0.5 ml/kg/hour, restoration of peripheral perfusion deficits |
| Trof          | 2012 | Undefined  | HES or 4% gelatin | 250-500 EVLWI <10 ml/kg or >10 ml/kg with GEDVI <850 ml/m²; PAOP >18 mmHg; MAP <65 mmHg, HR >100, ScvO2 < 70%, oliguria; peripheral perfusion deficits, hyperlactatemia |
| van Haren     | 2012 | Undefined  | 6% HES in 0.9% saline | 500, 15 Septic shock | End of infusion 1 | Yes           | Not described                |
| Wacharasint   | 2013 | Undefined  | HES 6% or 7.2% saline | 250, 15 MAP >65 mmHg, ScvO2 > 70%, lactate clearance, diuresis >0.5 ml/kg/hour, restoration of peripheral perfusion deficits |
| Yu            | 2011 | 30 ml/kg in 1,000 ml increments | Crystalloid or colloid | 250-500 SBP <90 mmHg or requirement for vasopressors | End of infusion 1 | Yes           | Not described                |
| Zhang         | 2012 | Undefined  | Crystalloid or colloid | 250-500 SBP <90 mmHg; HR >100 bpm; UO >0.5 ml/kg/hour; lactate clearance; SmvO2 > 70% | Pre-defined rise in CVP | Not described | Yes                        |

CSL, compound sodium lactate solution; CVP, central venous pressure; EVLWI, extra-vascular lung water index; HES, hydroxyethyl starch; HR, heart rate; HT, hypertensive; GEDVI, global end diastolic volume index; ITBVI, intrathoracic blood volume index; MAP, mean arterial blood pressure; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; ScvO2, central venous oxygen saturation; SmvO2, mixed venous oxygen saturations; STAT, statim/immediately; SvO2, venous oxygen saturation; UO, urine output.
Temporal trends in physiological changes following fluid bolus therapy
The temporal change in physiological parameters following FBT is described in 31 different groups across 17 studies (Table 3).

Immediately post-infusion
Ten studies reported the physiological state after bolus administration in 18 groups immediately post-administration. In the six studies describing changes in cardiac index immediately post-FBT, cardiac index increased by a median of 800 ml/minute/m² (range 0 to 1,300 ml/minute/m²). The median reduction in heart rate at the end of a fluid bolus (eight studies) was 2 bpm (range 10 to 0 bpm reduction) and the median increase in mean arterial pressure (eight studies) was 7 mmHg (range 1 to 15.2 mmHg). The median increase in CVP across five studies was 3.2 mmHg (range 2.3 to 5.2 mmHg). Only a single study reported the effect on venous oxygen saturation, blood lactate concentration or haemoglobin concentration. No study reported the effect on urine output.

Thirty minutes post-administration
Five studies reported the physiological effects of FBT 30 minutes after administration. Cardiac index increased by a median of 300 ml/minute/m² (range -400 to 600 ml/minute/m²) in three studies. The median reduction in heart rate (five studies) was 2 bpm (range 11 bpm reduction to 0.3 bpm increase) and the median increase in mean arterial pressure (five studies) was 7.5 mmHg (range 3 to 11 mmHg). The median increase in CVP across four studies was 3 mmHg (range 2 to 5.25 mmHg). There was a median increase in central venous saturation of 2% (range 4% reduction to 8% increase) across two studies. Changes in other indices are reported in Table 3.

Sixty minutes post-administration
Only three studies reported the physiological effects of FBT 60 minutes after administration (Figure 4) [36,57,65]. Cardiac index increased by a median of 300 ml/minute/m² (range -300 to 400 ml/minute/m²) in two studies. The median reduction in heart rate 60 minutes after a fluid bolus (three studies) was 1 bpm (range 11 bpm reduction to 2 bpm increase) and the median increase in mean arterial pressure (three studies) was 3 mmHg (range 2 to 7 mmHg). The median increase in CVP across three studies was 2 mmHg (range 1 to 3 mmHg). There was a median increase in central venous saturation of 1% (range 0.4% to 2% increase) across two studies.

Beyond 1 hour post-fluid bolus therapy
Only one study reported the effects of FBT at 120, 180 and 240 minutes after administration (Figure 4) [65].

Comparing responders and non-responders
Overall, 10 studies compared the physiological responses to FBT administration between groups defined by changes in a physiological variable. Patients were defined as either responders or non-responders depending on the response exhibited. Different variables are used in different studies: stroke volume index (five studies), cardiac index or output (three studies), increase in oxygen consumption (one study) or aortic blood flow rate (one study). All reported changes only within 30 minutes of FBT completion (Additional file 1: Table S2).

In the six studies describing changes in cardiac index, cardiac index increased by a median of 850 ml/minute/m² (range 600 to 1,300 ml/minute/m²) in fluid responders compared with 200 ml/minute/m² (range 0 to 1,000 ml/minute/m²) in non-responders. The median increase in mean arterial pressure (10 studies) in responders was 9.5 mmHg (range 7 to 15.2 mmHg) versus 4.8 mmHg (range 1 to 13 mmHg) in non-responders. Similarly, the median increase in central venous pressure (six studies) was 3 mmHg (range 2.6 to 3.4 mmHg) in responders versus 3.7 mmHg (range 2 to 5.2 mmHg) in non-responders. The median decrease in heart rate (nine studies) was 3.3 bpm in responders (range 1.5 to 10 bpm decrease) and 1.2 bpm in non-responders (range 0 to 4 bpm decrease). Information on changes in venous oxygen saturation, blood lactate concentration, and blood haemoglobin concentration in the few studies reporting such data are presented in Additional file 1: Table S2.

Additional comparisons
The physiological effects of FBT grouped by speed of FBT delivery (Additional file 1: Table S3) and by class of fluid administered (Additional file 1: Table S4) have also been presented. There is no consistent pattern demonstrated across or between groups.

Relationship between physiological changes after fluid bolus therapy and clinical outcome
Overall, seven studies described clinically orientated outcomes [37,43,44,49,58,59,64]. All reported the effects of complex interventions, such as early goal-directed therapy. No studies examined the relationship between FBT and outcome directly (Tables 4 and 5).

Discussion
We examined the contemporary literature on FBT in severe sepsis and septic shock and identified 33 original studies describing the characteristics of a fluid bolus, 17 of which also describe the associated physiological
| First author | Fluid given | Group | Time from completion of fluid administration until physiological measurement (minutes) | Measure of central tendency | Change in cardiac output estimation (bpm) | Change in heart rate (bpm) | Change in mean arterial pressure (mmHg) | Change in central venous pressure (mmHg) | Change in venous oxygen saturation (%) | Change in blood lactate concentration (mmol/l) | Change in urine output (mL/min) | Change in haemoglobin concentration (g/L) |
|--------------|-------------|-------|------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------------------|--------------------------|-----------------------------------------|-----------------------------------------|----------------------------------------|------------------------------------------|-------------------------------|-----------------------------------------|
| Machare-Delgado [48] | 500 ml of 0.9% saline over 10 minutes | Responders: >10% SVI increase | 0 | Mean | +3.99 ml/min/m²/beat | | | | | | | |
| | 500 ml of 0.9% saline over 10 minutes | Non-responders: >10% SVI increase | 0 | Mean | +0.57 ml/min/m²/beat | | | | | | | |
| Dong [39] | 500 ml of 6% HES over 30 minutes | Responders: >15% SVI increase | 0 | Mean | +600 ml/min/m² | -1.5 | +15.2 | +3.2 | | | |
| | 500 ml of 6% HES over 30 minutes | Non-responders: <15% SVI increase | 0 | Mean | +300 ml/min/m² | -1.2 | +4.8 | +2.3 | | | |
| Khwannimit [45] | 500 ml of 6% HES over 30 minutes | Responders: >15% SVI increase | 0 | Mean | +1300 ml/min/m² | -3.3 | +9.5 | +3.4 | | | |
| | 500 ml of 6% HES over 30 minutes | Non-responders: <15% SVI increase | 0 | Mean | +200 ml/min/m² | -0.9 | +3.9 | +5.2 | | | |
| Lakhal [46] | 500 ml of 4% gelatin over 30 minutes | Responders: >15% SVI increase | 0 | Mean | +900 ml/min/m² | -6 | +14 | +3 | | | |
| | 500 ml of 4% gelatin over 30 minutes | Non-responders: <15% SVI increase | 0 | Mean | +0 ml/min/m² | -3 | +7 | +4.5 | | | |
| Mahjoub [50] | 500 ml of 0.9% saline over 20 minutes | Responders: >10% SVI increase | 0 | Mean | +1,000 ml/min | -4 | +7 | +2.6 | | | |
| | 500 ml of 0.9% saline over 20 minutes | Non-responders: >10% SVI increase | 0 | Mean | +300 ml/min | -3 | +1 | +2.9 | | | |
| Monnet [53] | 500 ml of 0.9% saline over 10 minutes | All patients | 0 | Mean | +800 ml/min/m² | -7 | +8 | +5 | | | |
| Study | Fluid Type | Volume | Duration | Responders & % Increase | Non-Responders & % Increase | Mean | Median | 30 mins | 30 mins |
|-------|------------|--------|----------|--------------------------|-----------------------------|------|--------|---------|---------|
| Monnet [55] | 500 ml of 0.9% saline over 20 minutes | | | Responders: >15% CI increase | Non-responders: <15% increase in CI | Mean | | 0 | -2 | +11 |
| Monnet [54] | 500 ml of 0.9% saline over 30 minutes | | | Responders: >15% VO2 increase | Non-responders: <15% increase in VO2 | Mean | | 0 | -2 | +7 | +1% | -1.9 | -7 |
| Schnell [62] | 500 ml of 0.9% saline over 15-30 minutes | | | Responders: >10% increase in aortic blood flow | Non-responders: <10% increase in aortic blood flow | Median | | 0 | -10 | +7 |
| Sturgess [63] | 250 ml of 4% albumin over 15 minutes | | | All patients | | Mean | | +7.5% ml/beat | |
| | Haemodynamic indices measured 30 minutes after fluid bolus administration | | | | | Mean | | 0 | -10 | +7 |
| Freitas [40] | 7 ml/kg, maximum 500 ml of 6% HES over 30 minutes | | | Responders: >15% CO increase | Non-responders: <15% increase in CO | Mean | | 0 | -2 | +11 | +3 | +8% | -0.1 |
| Pierrakos [59] | 500 ml of 6% HES or 1,000 ml of CSL over 30 minutes | | | Responders: >10% increase in CI | Non-responders: <10% increase in CI | Mean | | 0 | -4 | +8 | +3 | +3% |
| Pottecher [60] | Up to 500 ml of 6% HES or 0.9% saline over 30 minutes | | | All patients | | Mean | | 0 | -2 | +7 |
### Table 3 Physiological effects grouped by measurement time (Continued)

| Study            | Fluid Type                  | Measurement Time | Treatment Details                                                                 | Measurement Time | Mean    | +470 ml/min/m² | +0.3 | +9.2 | +5.25 |
|------------------|-----------------------------|------------------|-----------------------------------------------------------------------------------|------------------|---------|----------------|-------|-------|-------|
| Wacharasint [66] | All patients                | 30               | 500 ml of 6% HES over 30 minutes                                                  |                  | Mean    | +470 ml/min/m² | +0.3 | +9.2 | +5.25 |
| van Haren [65]   | Hypertonic bolus            | 30               | 250 ml of 6% HES in 7.2% saline over 15 minutes                                   |                  | Mean    | +300 ml/min/m² | -11   | +4    | +2    |
|                  | Isotonic bolus              | 30               | 500 ml of 6% HES in 0.9% saline over 15 minutes                                   |                  | Mean    | -400 ml/min/m² | -1    | +5    | +4    | -0.2  | -8    |
|                  | Isotonic bolus              | 60               | 500 ml of 6% HES in 0.9% saline over 15 minutes                                   |                  | Median  | +0    | +2    | +2    | +0.4% | -0.2  | No change |
|                   | 500-750 ml of 4% albumin,   |                  | Bihari [36] 500-750 ml of 4% albumin, blood, 20% albumin FFP, 4% gelatin or platelets administered over less than 30 minutes |                  | Median  | +0    | +2    | +2    | +0.4% | -0.2  | No change |
|                   | 20% albumin FFP, 4% gelatin  |                  | Patients with early sepsis                                                       |                  | Median  | +300 ml/min/m² | +2    | +2    | +3    | +2%   | -0.2  |
|                   | or platelets administered   |                  | Patients with late sepsis                                                        |                  | Median  | +300 ml/min/m² | -9    | +7    | +1    | +1%   | +0.1  |
| van Haren [65]   | Hypertonic bolus            | 60               | 250 ml of 6% HES in 7.2% saline over 15 minutes                                   |                  | Mean    | +400 ml/min/m² | -11   | +6    | +1    | -0.3  | -9    |
|                  | Isotonic bolus              | 60               | 500 ml of 6% HES in 0.9% saline over 15 minutes                                   |                  | Mean    | -300 ml/min/m² | -1    | +3    | +3    | -0.1  | -12   |
Table 3 Physiological effects grouped by measurement time (Continued)

| van Haren [65] | Haemodynamic indices measured greater than 60 minutes after fluid bolus administration |
|----------------|--------------------------------------------------------------------------------------|
| 250 ml 6% HES in 7.2% saline over 15 minutes | Hypertonic bolus 120 Mean (+300 ml/min/m²) -7 +7 +2 0.0 +13 -6 |
| 500 ml 6% HES in 0.9% saline over 15 minutes | Isotonic bolus 120 Mean (-300 ml/min/m²) +0 +1 +2 -0.3 -30 -9 |
| 250 ml 6% HES in 7.2% saline over 15 minutes | Hypertonic bolus 180 Mean (+100 ml/min/m²) -3 +6 +3 -0.3 -9 |
| 500 ml 6% HES in 0.9% saline over 15 minutes | Isotonic bolus 180 Mean (+0 ml/min/m²) +3 +5 +3 -0.2 -6 |
| 250 ml 6% HES in 7.2% saline over 15 minutes | Hypertonic bolus 240 Mean (+100 ml/min/m²) +1 +3 +3 -0.3 -3 -8 |
| 500 ml 6% HES in 0.9% saline over 15 minutes | Isotonic bolus 240 Mean (-200 ml/min/m²) +3 +0 +3 -0.2 -40 -4 |

CI, cardiac index; CO, cardiac output; CSL, compound sodium lactate; FFP, fresh frozen plasma; HES, hydroxyethyl starch; SVI, stroke volume index; VO₂, oxygen delivery.
changes. We found heterogeneity of triggers, amount, fluid choice and speed of delivery for FBT, which was administered to achieve heterogeneous physiological targets. We similarly found heterogeneity of physiological changes after FBT. In addition, no RCTs compared FBT with an alternative intervention. Finally, no study related physiological changes after FBT to clinically relevant outcomes.

FBT is a widespread intervention in the management of the critically ill septic patient, despite lack of a consistent definition or use of terminology. Our study demonstrates that no contemporary RCTs exist that compare FBT with alternative interventions. The only study comparing FBT to an alternative intervention was a single, non-randomized, prospective, observational study that compared acute circulatory failure patients treated with FBT (500 ml of saline) or with increased norepinephrine dose according to clinician preference. The two groups had clearly different baseline characteristics and were not directly compared [55]. Alternative interventions to FBT may include a diagnostic low-volume FBT [17], classic fluid challenge [11,12], low-volume FBT and low-dose vasopressor therapy, or cardiac output-guided therapy. Despite the availability of such strategies and the availability of non-invasive cardiac output monitoring, these alternative approaches have not been studied.

Understanding which patient will be fluid responsive is a vital part of rationalising fluid therapy [69]. However, there are multiple different definitions of fluid responsiveness, each dependent on different interventions and different measurements. It would appear that there is little evidence to suggest a consistently different response to FBT based on pre-intervention physiology, as fluid responsiveness is often tautologically and retrospectively defined by participants’ responses to the therapy. A full review of this topic is beyond the scope of this review, though this information is available elsewhere [69,70].

The contribution of FBT to a positive fluid balance remains poorly understood. In a recent observational study, Bihari and colleagues [36] found that a median of 52.4% of fluid balance on the first, 30.8% on the second and 33.2% on the third study day consisted of FBT. In the Fluid and Catheter Treatment Trial [27] and Sepsis Occurrence in Acutely Ill Patients [71] studies, increasing fluid balance was associated with increased risk of acute kidney injury and mortality. In a retrospective study of septic shock patients in a North American university hospital, non-survivors had a significantly greater positive net fluid balance than survivors over the first 24 hours from onset [34]. Our study also shows little or no evidence for any persisting beneficial physiological changes following FBT. These observations suggest the
| First author | Journal | Year | Control group | ICU mortality | Hospital mortality | Other | Intervention group | ICU mortality | Hospital mortality | Other |
|--------------|---------|------|----------------|---------------|-------------------|------|---------------------|---------------|-------------------|------|
| MacRedmond [49] | Quality and Safety in Health Care | 2010 | Before protocolised resuscitation | 19/37 | | | After protocolised resuscitation | 10/37 | | |
| Pierrakos [59] | Intensive Care Medicine | 2012 | Responders (>10% increase in CI) | 13/25 | | | Non-responders (<10% increase in CI) | 11/26 | | |
| Patel [58] | Annals of Pharmacotherapy | 2010 | Pre-intervention | 32/53 | | | Post-intervention, significantly more fluid and less vasoactives | 12/59 | | |
| Castellanos-Ortega [37] | Critical Care Medicine | 2010 | Pre-intervention | 51/96 | 55/96 | | Post-intervention, significantly more fluid | 117/384 | 144/384 | |
| Traf [64] | Critical Care Medicine | 2012 | Pulmonary artery catheter-guided resuscitation | 13/34 | 15/34 | | Transpulmonary thermodilution-guided resuscitation | 17/38 | 21/38 | |
| Hanzelka [43] | Supportive Care in Cancer | 2013 | Pre-intervention | 28-day: 38/100 | Post-intervention, significantly quicker resuscitation | | 28-day: 20/100 | | |
| Jacob [44] | Critical Care Medicine | 2012 | Pre-intervention | 30-day: 126/245 | Post-intervention, significantly quicker resuscitation with significantly larger volumes of fluid at 6 and 24 hours | | 30-day: 257/426 | | |

CI, cardiac index.
| First author | Journal                                | Year       | Control group                                                                 | LOS in ICU (days) | LOS in hospital (days) | MV (days) | CRRT                      | Intervention group                                                                 | LOS in ICU (days) | LOS in hospital (days) | MV (days) | CRRT |
|--------------|----------------------------------------|------------|-------------------------------------------------------------------------------|-------------------|------------------------|-----------|---------------------------|---------------------------------------------------------------------------------|-------------------|------------------------|-----------|------|
| MacRedmond [49] | Quality and Safety in Health Care      | 2010       | Before protocolised resuscitation                                             | 8                 |                         |           | CRRT                      | After protocolised resuscitation                                                | 7                 |                         |           |      |
| Castellanos-Ortega [37] | Critical Care Medicine                | 2010       | Pre-intervention                                                              | 9.9               | 26.5                   |           |                          | Intervention group, significantly more receive fluid                            | 9.1               | 30.6                   |           |      |
| Hanzelka [43] | Supportive Care in Cancer              | 2013       | Pre-intervention                                                              | 5.1               | 10.3                   |           |                          | Post-intervention, significantly quicker resuscitation                          | 2.5               | 8.1                    |           |      |
| Trof [64]    | Critical Care Medicine                 | 2012       | Pulmonary artery catheter-guided resuscitation                              | 15                | 25                     | 13        |                          | Transpulmonary thermodilution-guided resuscitation                              | 11                | 27                     | 10        |      |
| Patel [58]   | Annals of Pharmacotherapy              | 2010       | Pre-intervention                                                              | 6                 | 9.5                    | 7.5       | 8/53                      | Post-intervention, significantly more fluid and less vasoactives                | 5                 | 9                      | 7         | 0/59 |

CRRT, continuous renal replacement therapy; LOS, length of stay; MV, mechanical ventilation.
need for RCTs comparing FBT with alternative interventions and well-defined triggers and physiological outcomes.

This review has several strengths. To our knowledge this is the first review of the contemporary literature on FBT in critically ill patients with severe sepsis.

We are the first to explore the contemporary features of a FBT, and the first to produce a summary of the physiological changes associated with FBT in septic, critically ill patients, including data from RCTs, and observational and quasi-experimental studies. Our wide search criteria, use of three separate sources and hand searching references reduced the risk of inclusion bias and makes it unlikely that we missed relevant studies.

Our study also has some limitations. Our assessments of physiological changes are necessarily limited to the measures of central tendency provided in tables and graphs in the studies identified. We have only provided crude median results in an attempt to provide a rough estimate of possible effect. We limited our search to the present evolving decade. It is unlikely that current clinical practice is better reflected by earlier studies. Indeed, in comparing our results with similar, earlier studies, the reported physiological changes are similar [14,71-75]. We did not account for the effect of vasoactive medications beyond noting their administration. It appears obvious that the mixed and differential inotropic/vasopressor/lusitropic/chronotropic effects of different vasoactive medications are likely to have an effect on the physiological changes reported, as would the administration of blood products. Inadequate information was provided in the studies to make such adjustments possible. FBT is normally part of a complex intervention - the resuscitation of the critically ill patient. As well as the initiation and manipulation of vasoactive medications, analyses must contend with the impact of the use of mechanical ventilation, CRRT, and antibiotic administration. These confounders were not reliably reported in the studies identified and could not be evaluated. In addition, the perceived haemodynamic success of an intervention often depends on the trajectory of the patient's clinical course. Unfortunately no such information was available from the studies reviewed.

Conclusion

FBT in severe sepsis and septic shock is described in 33 articles in the contemporary literature. Only 17 of these studies report the physiological changes associated with FBT. Evidence regarding the efficacy of FBT compared with alternative interventions is lacking. Crucially, no studies relate the physiological changes after FBT to clinically relevant outcomes. In light of recent studies highlighting the association between FBT and fluid administration in general and harm, there is a clear need for at least obtaining randomised controlled evidence for the physiological effects of FBT over the immediate (0 to 4 hours) post-intervention period in patients with severe sepsis and septic shock.

Additional file

Additional file 1: Electronic Supplement. Containing: Appendix 1 (Electronic Search Strategies); Table S1: Study inclusion criteria, definitions of sepsis and definitions of hyperlactataemia; Table S2: Physiological effects grouped by intervention type and comparison; Table S3: Physiological effects grouped by speed of FBT delivery; Table S4: Physiological effects of FBT grouped by fluid class.

Abbreviations

CRRT: Continuous renal replacement therapy; CVP: Central venous pressure; FBT: Fluid bolus therapy; IV: Intravenous; RCT: Randomised controlled trial.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NJG: study design, electronic search design, literature search, study selection, data extraction, data handling/analysis, manuscript preparation, manuscript revision, and manuscript submission. GME: literature search, study selection, manuscript revision, and manuscript submission. RB: study design, electronic search design, data analysis, manuscript preparation, manuscript revision, and manuscript submission. All authors read and approved the final manuscript.

Author details

1. Department of Intensive Care, Austin Hospital, Melbourne, Victoria 3084, Australia. 2. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria 3004, Australia. 3. School of Nursing and Midwifery, Faculty of Health, Deakin University, Burwood, Victoria 3125, Australia.

Published online: 27 December 2014

References

1. Holliday MA, Segar WE: The maintenance need for water in parenteral fluid therapy. Pediatrics 1957, 19:823 832.
2. Network SIG: Postoperative management in adults. A practical guide to postoperative care for clinical staff. In SIGN Guidelines. Healthcare Improvement Scotland; Edinburgh: 2004.
3. Powell-Tuck J, Gosling P, Lobo DN, Allison SP, Carlson GL, Gore M, Lewington AJ, Pearsie RM, Mythen MG: British consensus guidelines on intravenous fluid therapy for adult surgical patients (GIFTSUP). [http://www.bapen.org.uk/pdfs/bapen_pubs/giftsuspdf.pdf].
4. Resuscitation Council UK: Advanced Life Support Manual. 6th edition. London: Resuscitation Council (UK); 2011.
5. Carey JS, Mohr PA, Brown RS, Shoemaker WC: Cardiovascular function in hemorrhage, trauma and sepsis: determinants of cardiac output and cardiac work. Ann Surg 1969, 170:910 921.
6. Hall JE: Cardiac output, venous return and their regulation. In Guyton and Hall Textbook of Medical Physiology. 12th edition. Edited by Hall JE, Guyton AC. Philadelphia, PA: Saunders Elsevier; 2011:229 241.
7. Shoemaker WC: Pathophysiologic mechanisms in shock and their therapeutic implications. Am J Surg 1965, 110:337 341.
8. Shoemaker WC, Carey JS, Mohr PA, Brown RS, Monson DO, Yao ST, Kho LK, Stevenson A: Hemodynamic measurements in various types of clinical shock. Analysis of cardiac output and derived calculations in 100 surgical patients. Arch Surg 1966, 93:189 195.
9. Udovič VN, Weil MH, Sambhi MP, Rosoff L: Hemodynamic studies on clinical shock associated with infection. Am J Med 1963, 34:461 469.
10. Weil MH: Current concepts on the management of shock. Circulation 1957, 16:1097 1105.
11. Vincent JL, Weil MH: Fluid challenge revisited. Crit Care Med 2006, 34:1333 1337.
50. Mahjoub Y, Benoit-Fallet H, Alarpteanu N, Lome E, Levraud M, Seydi AA, Amennouche N, Slama M, Dupont H. Improvement of left ventricular relaxation as assessed by tissue Doppler imaging in fluid-responsive critically ill septic patients. *Intensive Care Med* 2012, 38:1461–1470.

51. McIntyre LA, Fergusson DA, Cook DJ, Rowe BH, Bagshaw SM, Easton D, Emond M, Finfer S, Fox-Robichaud A, Gaudet C, Green R, Hebert P, Marshall J, Rankin N, Stott J, Timmou M, Pagliarello J, Turgeon AF, Worster A, Zarychanski R. Canadian Critical Care Trials Group: fluid restriction with 5% albumin versus normal saline in early septic shock: a pilot randomized, controlled trial. *J Crit Care* 2012, 27:317.e311–317.e316.

52. Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul JL. Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010, 14:R109.

53. Monnet X, Jabot J, Maizeil J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care 2011*, 39:589–594.

54. Monnet X, Julien F, At-Hamou N, Lequoy M, Gosset C, Jozwiak M, Persichini R, Anguel N, Richard C, Teboul JL. Lactate and venaocutaneous carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. *Crit Care Med* 2013, 41:1412–1420.

55. Monnet X, Letierce A, Hamzaoui O, Chemla D, Anguel N, Osman D, Richard C, Teboul JL. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. *Crit Care Med* 2011, 39:1394–1399.

56. O’Neill R, Morales J, Jule M. Early goal-directed therapy (EGDT) for severe sepsis/septic shock: which components of treatment are more difficult to implement in a community-based emergency department? *J Emerg Med* 2012, 42:503–510.

57. Ospina-Taascon G, Neves AP, Occhipinti G, Donadello K, B?chele G, Simion D, Fabre D, Collard A, Santacruz M. Early goal-directed therapy (EGDT) for severe sepsis/septic shock: which components of treatment are more difficult to implement in a community-based emergency department? *J Emerg Med* 2012, 42:503–510.

58. Patel GW, Roderman N, Gehring H, Saad J, Bartek W. Assessing the effect of the Surviving Sepsis Campaign treatment guidelines on clinical outcomes in a community hospital. *Ann Pharmacother* 2010, 44:1733–1738.

59. Pieracker C, Velissaris D, Scolletta S, Heenen S, De Backer D, 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, 38:422–428.

60. Pottecher J, Deruddre S, Teboul JL, Georges JF, Laplace C, Benhamou D, Vicaut E, Duranteau J. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in patients with severe sepsis. *Intensive Care Med* 2010, 36:949–955.

61. Schulman CA, Pressler S, Duranteau J, Canet E, Gery P, Franci S, De Backer D. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med* 2010, 36:1867–1874.

62. Sanchez M, Jimenez-Lendinez M, Cidoncha M, Anguel N, Osman D, Richard C, Teboul JL. Fluid restriction with 5% albumin versus normal saline in early septic shock: a pilot randomized, controlled trial. *J Crit Care* 2012, 27:317.e311–317.e316.

63. Schneid DR, Camous L, Gujornach S, Duranteau J, Canet E, Gery P, Dumenil AS, Zeni F, Azoulay E, Darmon M. Renal perfusion assessment by renal Doppler during fluid challenge in sepsis. *Crit Care Med* 2013, 41:1214–1220.

64. Sturgess DJ, Pascoe RS, Scala G, Venkatesh B. A comparison of transcutaneous Doppler corrected flow time, b-type natriuretic peptide and central venous pressure as predictors of fluid responsiveness in septic shock: a preliminary evaluation. *Anaesth Intensive Care* 2011, 39:1022–1029.

65. Trof RJ, Beishuizen A, Cornet AD, Wtt RJ, Gibbes AR, Groeneveld AB. Volume-limited versus pressure-limited hemodynamic management in septic and nonseptic shock. *Crit Care Med* 2012, 40:1177–1185.

66. van Haren FMP, Sleight J, Boerma EC, La Pine M, Bahr M, Pickkers P, Van Der Hoeven JG. Hypertonic fluid administration in patients with septic shock: a prospective randomized controlled pilot study. *Shock* 2012, 37:269–275.

67. Wacharasint P, Lertamornpong A, Wattanatham U, Wongsa A. Predicting fluid responsiveness in septic shock patients by using 3 dynamic indices: is it all equally effective? *J Med Assoc Thai* 2012, 95:5149–5156.

68. Yu M, Pei K, Moran S, Edwards KD, Domingo S, Steinerman S, Ghows M, Takiguchi S, Tan A, Lurie F, Takanishi D Jr. A prospective randomized trial using blood volume analysis in addition to pulmonary artery catheter, compared with pulmonary artery catheter alone, to guide shock resuscitation in critically ill surgical patients. *Shock* 2011, 35:220–228.

69. Zang Z, Lu B, Ni H, Sheng X, Jin N. Prediction of pulmonary edema by plasma protein levels in patients with sepsis. *J Crit Care* 2012, 27:623–629.

70. Zarychanski R, Canadian Critical Care Trials Group. Fluid restriction with 5% albumin versus normal saline in early septic shock: a pilot randomized, controlled trial. *J Crit Care* 2012, 27:317.e311–317.e316.
Author/s: Glassford, NJ; Eastwood, GM; Bellomo, R

Title: Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data

Date: 2014-01-01

Citation: Glassford, N. J., Eastwood, G. M. & Bellomo, R. (2014). Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. CRITICAL CARE, 18 (6), https://doi.org/10.1186/s13054-014-0696-5.

Persistent Link: http://hdl.handle.net/11343/261377

File Description: Published version

License: CC BY