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Shock

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Fluids in shock

Fluid management during shock from physiology to bedside

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Shock is a common life-threatening, generalised form of acute circulatory failure in critically ill patients, which is usually managed by infusing fluids to increase cardiac output and supply the systemic oxygen request. International guidelines recommend use of an aggressive fluid resuscitation in the early phases of shock. In this context, crystalloids, including balanced solutions, are suggested as first-line fluid therapy. However, a single physiological or biochemical measurement able to adequately assess the balance between cardiac output and perfusion pressure is still not available. Moreover, the haemodynamic targets and safety limits indicating whether or not to stop this treatment in already resuscitated patients are still undefined. A fluid should be considered as a drug and the intensivist should consider its pharmacodynamic and pharmacokinetic properties, and whether or not a patient is resistant to this therapy—before administration.

Why administer fluids? From physiology to bedside

Shock is a life-threatening, generalised form of acute circulatory failure affecting one-third of intensive care unit (ICU) patients (Sakr et al. 2006; Cecconi et al. 2014). It is associated with the imbalance between the oxygen delivery (DO_2) provided by the cardiac function, and the systemic oxygen request. The first variable is defined as the product of oxygen content and the cardiac output (CO), whereas inadequate cellular oxygen utilisation derives from a tissue oxygen request exceeding the DO_2, or to the cellular inability of using O_2. This latter condition is due to mitochondrial dysfunction (Brealey et al. 2002) and deregulated cell-signalling pathways during sepsis-induced multiple organ damage (Singer 2017). A large trial regarding dopamine or norepinephrine infusion for shock reversal in more than 1600 ICU patients demonstrated that septic shock occurred in the vast majority of ICU patients (62%), while cardiogenic shock (16%), hypovolaemic shock (16%) and other types of distributive (4%) or obstructive (2%) shock are less frequent. Fluid infusion to correct haemodynamic instability is a key, early and common intervention in ICU patients with shock (Myburgh and Mythen 2013; Rhodes et al. 2017).

The technique of fluid resuscitation to treat an episode of shock was first described by Dr. Thomas Latta nearly 200 years ago in a letter to the editor of *The Lancet* (Latta 1832). He injected repeated small boluses of a fluid solution equivalent to approximately ½ Ringers lactate and observed the clinical changes of his first patient (an elderly woman). The first bolus did not have any visible effect, but after multiple boluses (overall 2.8 litres) "soon the sharpened features, and sunken eye, and fallen jaw, pale and cold, bearing the manifest imprint of death's signet, began to glow with returning animation; the pulse returned to the wrist." To give fluids during shock and observe the clinical improvement of the patient at bedside seemed reasonable in 1831 and still makes sense! In fact, optimal fluid management is a key component to improve the outcome of haemodynamically unstable ICU patients, since both hypovolaemia and hypervolaemia are harmful (Cecconi et al. 2014).

When to administer fluids? Triggers and safety limits of fluid administration

While consensus exists regarding the need for aggressive fluid resuscitation in the early phases of shock (Rhodes et al. 2017), the haemodynamic targets and the safety limits indicating whether or not to stop this treatment in already resuscitated patients are still undefined (Hjortrup et al. 2016; Rhodes et al. 2017). Moreover, a single physiological or biochemical measurement able to adequately assess the balance between the changes in heart function and in DO_2, peripheral perfusion pressure and O_2 request, is not available. Surely, giving fluids to increase the cardiac output (CO) and, as a consequence, DO_2, seems reasonable.

CO is the dependent variable of the physiological interaction of cardiac function (described by the observations of Otto Frank and Ernest Starling more than 100 years ago) and venous return function (based on Guyton's relationship between the elas-

tic recoil of venous capacitance vessels, the volume stretching the veins, the compliance of the veins and the resistance of the venous system). In this context, fluids should be used to increase CO only if the plateau of cardiac function is not reached. At this point, in fact, and probably even before reaching this point, fluid administration does not increase CO and can be considered as futile or even harmful.

However, clinical assessment of the Frank-Starling curve position of the ventricle is complex and the prediction of fluid responsiveness in ICU patients is still challenging (Monnet et al. 2016). The fluctuations of arterial waveform caused by the fixed and constant insufflations in patients undergoing a >8 ml/kg controlled mechanical ventilation have been successfully tested to predict fluid responsiveness (Monnet et al. 2016). However, most ICU patients are protectively ventilated or retain to some extent spontaneous breathing activity (McConville and Kress 2012; Esteban et al. 2013; Mahjoub et al. 2014), making the changes in intrathoracic pressure neither fixed nor constant and, in turn, the dynamic indexes unreliable (Monnet et al. 2016).

In daily practice hypotension is usually indicated as the bedside trigger to start fluid administration and the mean arterial pressure (MAP) is the physiological target indicating whether or not to continue fluid infusion for most ICU physicians (Cecconi et al. 2015). The assumption that hypotension and shock are synonymous is misleading. In fact, restoring MAP above predetermined targets does not necessarily mean reverting shock, whereas MAP below guidelines' predefined thresholds does not necessarily indicate shock (Cecconi et al. 2014). Unfortunately, the physiological relationship between changes in systemic pressures and stroke volume becomes weak in previously resuscitated ICU patients, especially during an episode of septic shock (Dufour et al. 2011; Pierrakos et al. 2012; Lakhal et al. 2013). For these reasons, the MAP target should be individualised to each patient, combining the assessment of blood lactates, mixed venous oxygen saturation and veno-arterial carbon dioxide difference (Cecconi et al. 2014). Finally, during fluid administration, the assessment of the changes of both right and left ventricle filling pressures is useful as a safety limit to guide further infusion. In fact, despite static indexes are not reliable in predicting fluid responsiveness, the increase of filling pressures suggests that the ventricle is operating on the flat part of the Frank-Starling's curve.

Table 1. Clinical bedside triggers of fluid administration

Variable	Pros	Cons
Mean arterial pressure	• Target indicated in the guidelines • Easy to measure and to monitor	• Difficult to be tailored in some categories of patients (hypertensive, chronic renal failure)
Lactate	• The reduction is usually associated with shock reversal • Easy to measure • Early variation even in normotensive patients	• Not specific under certain conditions (poisoning, liver failure, shivering)
Capillary refill time	• Easy and costless • Good correlation with systemic perfusion	• Low sensitivity and specificity in vasculopathic patients
Oliguria	• High sensitivity	• Difficult to evaluate in previous renal failure patients • Need a few hours for defining a trend • Affected by diuretics use
Mottled skin	• High specificity	• Not always present or late sign of hypoperfusion

> "Fluid infusion to correct haemodynamic instability is a key, early and common intervention in ICU patients with shock"

How to administer fluids? Pharmacodynamic and pharmacokinetic of fluid administration

Fluids should be considered as a drug and, as a consequence, the ICU physician should assess whether or not a patient is resistant to this therapy—before administration. Unfortunately, the reliability in predicting fluid responsiveness and guiding fluid therapy of the physical bedside examination, chest radiography, central venous pressure and urine output (specifically in septic patients) is very limited (see Table 1).

An early fluid resuscitation with 30 ml/kg is suggested as the first-step approach to septic shock (Rhodes et al. 2017). On the one hand, a large initial fluid load seems suitable to revert acute hypovolaemia; on the other hand a tailored fluid therapy could prevent fluid overload after shock relapse (Hjortrup et al. 2016).

A modern approach to guide fluid therapy to revert an episode of haemodynamic instability should include a portioned fluid administration and bedside tests, aiming at revealing preload dependence. Repeated fluid challenges [(FCs); an infusion of small aliquots of 300 to 500 ml of fluid administered over 20-30 minutes, as indicated by the guidelines (Rhodes et al. 2017)] to assess fluid responsiveness should be preferred to a larger and continuous infusion of any fluid. Recent findings on postoperative patients suggest that the minimum volume required to perform an effective fluid challenge is 4 ml/kg infused over 5 minutes (Aya et al. 2015).

In principle, FCs should avoid or reduce ineffective fluid administration. However, the effect on haemodynamics should be only assessed by measuring the changes in CO. Recently, RACE (rapid assessment by cardiac echography) has been suggested as a first-line tool to evaluate the type of shock if the clinical examination does not lead to a clear diagnosis, even when used by a minimally trained intensivist (Cecconi et al. 2014; Finfer et al. 2018).

Table 2. Haemodynamic monitoring during shock

Variable	Pros	Cons
Echocardiography	• Prompt evaluation • Not invasive • Suggested as first-line haemodynamic evaluation after clinical examination • Rapid differentiation of the cause of shock	• Need learning curve for more precise measurements • Not yet available in all intensive care units • Operator/patient dependent • Not useful for continuous monitoring
Calibrated pulse contour methods	• Accurate in estimating cardiac output and trending cardiac function • Provide dynamic indexes of fluid responsiveness and also estimate systemic distribution of fluids	• Invasive and time-consuming • Not available in all intensive care units • Limited by cardiac arrhythmias or vascular abnormalities
Uncalibrated pulse contour methods	• Not or minimally invasive • Prompt measurement • Provide dynamic indexes of fluid responsiveness	• Questioned accuracy in critically ill patients • Not available in all intensive care units • Limited by cardiac arrhythmias or vascular abnormalities
Oesophageal Doppler	• Minimally invasive • Prompt measurement	• Contraindicated in those with oesophageal pathology • The acquisition of the optimal acoustic signal may require frequent repositioning • Difficult to use in awake patients

Despite the increasing number of haemodynamic tools measuring CO or its surrogates, continuous monitoring of cardiac function is far from being considered a standard in haemodynamically unstable ICU patients (Cecconi et al. 2015) (see Table 2). As a consequence, the outcome of a FC is often ambiguous in terms of haemodynamic response (responder/non-responder), leading to adjunctive and often futile fluid administration (Cecconi et al. 2015). Recently, a few studies evaluated the response to FC by considering the early variation of the stroke volume or dynamic indexes to a quick infusion of smaller portion of the entire FC (Marik 2015). On the other hand, the dose (ml/Kg) of a FC can also affect the percentage of responders to the test (Aya et al. 2015). In practice there is no standard way of performing a FC (Messina et al. 2017; Toscani et al. 2017). Studies investigating the different components (type of fluids, dose, speed and response) of a FC are largely awaited (Aya et al. 2017; Toscani et al. 2017; Bennett et al. 2018).

Finally, several haemodynamic tests have been proposed in the literature to evaluate the preload dependency of the right ventricle by increasing venous return before FC administration. Among them is the passive leg raising (PLR) test. PLR is performed by simultaneously lowering the trunk and raising the inferior limbs, changing the patient's position from semi-recumbent to a position in which the head and the trunk are horizontal and the legs are elevated at 45°(Monnet and Teboul 2015). This manoeuvre leads to an autotransfusion of about 300 ml of blood volume recruited from the capacitance veins of the legs and pushed to the heart; an increase in CO of about 10%-15% reliably predicts fluid responsiveness. Unfortunately, lower trunk trauma, increased intracranial pressure, low level of sedation and abdominal hypertension might limit PLR reliability.

> "the assumption that hypotension and shock are synonymous is misleading"

Which fluid in critically ill patients with shock?

The ideal fluid for patients in shock should have a composition as similar as possible to the extracellular fluid, to support cellular metabolism and avoid organ dysfunction, and should increase intravascular volume and persist over time, to optimise CO. Unfortunately, no ideal fluid exists, and the available fluid options are roughly divided in three groups: crystalloids, colloids, and blood products. The latter have few very specific indications including shock in trauma patients and haemorrhagic shock, and will not be discussed in this review (Stensballe et al. 2017).

Colloids are composed of large molecules designed to remain in the intravascular space for several hours, increasing plasma osmotic pressure and reducing the need for further fluids. Despite the theoretical advantages of this model, subsequent studies challenged this view in sepsis patients, where alterations in glycocalyx and endothelial permeability may lead to extravasation of colloid's large molecules (Brunkhorst et al. 2008), abolishing their primary advantage. Colloids are further divided into semi-synthetic colloids and albumin. The former includes hydroxyethyl starches, dextrans and gelatins and have demonstrated either no effect (Annane et al. 2013) or detrimental consequences in critically ill patients, increasing the risk of kidney injury (Myburgh et al. 2012; Perner et al. 2012) Thus, the use of semi-synthetic colloids in shock patients should be abandoned.

The role of albumin is still debated. While theoretically promising for its anti-inflammatory and anti-oxidant proprieties (Vincent 2009), and for its supposed longer intravascular confinement due to the interaction between its surface negative charges and endovascular glycocalyx (Vincent 2009), there is no clear evidence of its efficacy in critically ill patients (Finfer et al. 2004; Caironi et al. 2014). The use of albumin was associated with improved mean arterial pressure with an infusion of a lower volume, but the relative risk of mortality was similar to the crystalloid infusion (Caironi et al. 2014). A predefined subgroup analysis of the SAFE study suggested that the use of albumin should be avoided in patients with traumatic brain injury. Debate is still ongoing, and the safer indication for albumin use in shock patients is liver failure (Salerno et al. 2013).

On the other waterside of fluid therapy, crystalloids are composed of water and electrolytes.

Normal saline was the first crystalloid

solution to be used in humans. Its drawbacks are a very high concentration of chloride and high osmolarity, which were associated with nephrotoxicity and hyperchloraemic acidosis (Yunos et al. 2015). Several balanced solutions were later proposed, such as Ringer lactate (Hartman solution), Ringer acetate and PlasmaLyte. These solutions have *normal* chloride concentration, lower osmolarity (between 280 and 294) and are buffered with lactate or acetate to maintain fluid neutrality.

Two randomised studies were recently published to assess the effect of balanced solutions vs normal saline. The SPLIT trial, conducted in 4 ICUs, showed no advantage in either group (Young et al. 2015). The SMART trial was a monocentric study (5 ICUs/1 academic centre) and yielded similar results, with no difference in mortality or kidney injury using balanced solution vs normal saline (Semler et al. 2018). A significant difference in favour of PlasmaLyte was found in days free from renal replacement therapy and in a composite outcome of renal complications and mortality in the SMART trial (Semler et al. 2018). Both trials were cluster randomised, and negative trial results may also reflect the relatively small quantity of fluid infused in the two groups (median quantity less than 2 litres). Despite the lack of definitive evidence, balanced solutions have theoretical advantages that should be compared with the risk of hyperchloraemic acidosis after large volume resuscitation with normal saline. Consequently, balanced solutions are probably the best choice as a first-line fluid therapy in patients with shock.

Conclusions

Fluids are a crucial component of the resuscitation of patients in shock. A paradigm shift is taking place in fluid therapy, changing from the administration of large volume to a more targeted and personalised approach. Fluids should be considered as a drug, and should be administered after testing preload dependency and with continuous evaluation of preload dependency/CO response. Fluid therapy should be paired with timely monitoring of clinical and metabolic signs of shock. Despite the lack of definitive evidence, balanced crystalloids are the most promising fluids in patients in shock, while semi-synthetic colloids should be definitively avoided in this population. ■

Conflict of interest

Maurizio Cecconi is a consultant for Edwards Lifesciences, LiDCO and Cheetah Medical.

Abbreviations

CO cardiac output
FC fluid challenge
ICU intensive care unit
MAP mean arterial pressure

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/o1x