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Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force

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Intensive Care MedIntensive Care MedIntensive Care MedAbstract

An international team of experts in the field of fluid resuscitation was invited by the ESICM to form a task force to systematically review the evidence concerning fluid administration using basic monitoring. The work included a particular emphasis on pre-ICU hospital settings and resource-limited settings. The work focused on four main questions: (1) What is the role of clinical assessment to guide fluid resuscitation in shock? (2) What basic monitoring is required to perform and interpret a fluid challenge? (3) What defines a fluid challenge in terms of fluid type, ranges of volume, and rate of administration? (4) What are the safety endpoints during a fluid challenge? The expert panel found insufficient evidence to provide recommendations according to the GRADE system, and was only able to make recommendations for basic interventions, based on the available evidence and expert opinion. The panel identified significant gaps in the scientific evidence on fluid administration outside the ICU (excluding the operating theater). Globally, scientific communities and health care systems should address these critical gaps in evidence through research on how basic fluid administration in resource-rich and resource-limited settings can be improved for the benefit of patients and societies worldwide.

Keywords: Fluids, Fluid Responsivenss, Intensive Care, Shock

Introduction

Acute circulatory dysfunction related to sepsis or other conditions is often managed in intensive care units (ICUs). Its detection and initial management can occur in different hospital settings; fluid resuscitation, as part of the treatment, is frequently started in pre-ICU facilities such as general wards, emergency departments (ED), postoperative recovery rooms, or intermediate care units.

A recent survey performed among practicing intensivists in Europe demonstrated considerable heterogeneity in the way intravenous (IV) fluids are administered in shock states, including the criteria used as triggers, targets, and safety limits for fluid input [1].

There is a paucity of data regarding initial fluid management in pre-ICU hospital settings. A wide range of approaches is observed because of the diverse backgrounds of professionals involved in initial resuscitation and the availability of only simple physiological

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monitoring. This fact is worrying since, as stated above, fluid resuscitation is started in the great majority of cases before ICU admission, and the quality of management in this phase is likely to affect patient outcome.

Therefore, the European Society of Intensive Care Medicine (ESICM) appointed a panel of experts to review the literature and provide recommendations on principles of IV fluid administration for acute circulatory dysfunction with basic monitoring in pre-ICU hospital settings. The task force was also instructed to adapt recommendations for resource-limited settings including low-income countries and settings where more advanced monitoring is traditionally less common (e.g. general wards).

Expert panel methodology

An international team of experts in emergency treatment of circulatory dysfunction and failure was invited by the ESICM to form a task force to evaluate fluid administration using basic monitoring, with a special focus on low-intensity monitoring environments within hospital and resource-limited settings. Experts were selected based on their research output, reputation, and background, with the aim of gathering the best expert opinion and representing the different settings for which this paper is relevant.

The aim of the task force was to answer four main questions pertaining to adults in circulatory dysfunction and failure:

- What is the role of clinical assessment in initiating fluid resuscitation in circulatory failure?
- What basic monitoring is required to perform and interpret a fluid challenge?
- What defines a fluid challenge in terms of fluid type, ranges of volume, and rate of administration?
- What are the safety endpoints during a fluid challenge?

Due to the scarce amount of evidence (with even scarcer data in resource-limited settings) found on the subject, it was not possible to perform a systematic analysis as called for by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology [2]. Recommendations of the group of experts were made based on expert opinion, online and face-to-face meetings, and email exchange.

For each question, pairs/trios of experts were assigned the task of reviewing the literature and presenting their findings to the rest of the group.

A subgroup of authors (TB, MD, SJ, MM) was specifically tasked with ensuring that the review and statements were adequate for application in resource-limited settings.

An initial online conference call was held on February 15, 2016, to review progress and contributions. This was followed by a face-to-face 1-day conference held in Brussels in March 2016.

A medical writer (Sophie Rushton-Smith, Ph.D.) was present and recorded the minutes of the discussion.

The manuscript was completed as an expert panel recommendations paper; the draft was then sent to all authors and approved before submission.

Fluid therapy for patients outside the ICU

Intravenous fluid therapy is one of the most common interventions in the hospital. However, little guidance is available for clinicians regarding the endpoints of fluid resuscitation [3]. In many settings, clinicians face several challenges when deciding whether to give fluids, including less clinical certainty regarding anatomical and circulatory diagnoses and limited access to advanced hemodynamic monitoring.

It is likely that patients in the ED and wards are generally treated as potential fluid responders, with fluids commonly being the initial therapy to correct arterial hypotension. However, few data are available to identify patients who may benefit from fluid administration in this context. The risk of harm is real—a randomized trial of children with fever and circulatory impairment in sub-Saharan Africa showed increased mortality with the use of fluid boluses, in spite of initial circulatory improvement [4, 5]. In the ICU setting, the risk of both over- and under-resuscitation is well described in adults, but there are very limited data from other settings [4, 6–9], which further complicates clinician guidance in these settings.

Physiological monitoring in the ED and non-ICU wards

The variation in practice around the world is wide, but poorly documented. The resuscitation area at the EDs, postoperative recovery rooms, and intermediate care units in high-income countries usually offer invasive and non-invasive monitoring of blood pressure (BP), heart rate (HR), respiratory rate, urine output, central venous pressure (CVP), and point-of-care (POC) blood gas and lactate analyses; ultrasound/echocardiography techniques are becoming more widely available. In wards, specific hemodynamic monitoring is generally lacking, with the exception of intermittent non-invasive BP, HR, and urine output measurements.

What is the role of clinical variables to trigger and guide fluid resuscitation in shock?

What defines a clinical assessment?

The purpose of the clinical examination in the initiation of IV fluid administration is to identify patients at risk of or in acute circulatory failure who are likely to benefit from fluid. Acute circulatory dysfunction can be detected by a thorough clinical examination including assessment of the three windows of tissue perfusion—altered mentation, skin perfusion, and oliguria—in combination with tachycardia and arterial hypotension [10]. Although from a physiological point of view, arterial hypotension is not mandatory for the diagnosis of circulatory shock, hypotension is important to recognize and is defined as a fall in arterial systolic blood pressure (SBP) to < 90 mmHg, or by > 40 mmHg in previously hypertensive patients in the presence of clinical signs attributed to organ hypoperfusion [11]. The major challenge is in recognizing acute circulatory failure at the early stages, in which both systemic compensatory mechanisms and metabolic adaptations at the microcirculatory level still maintain adequate oxygen delivery, at least to vital organs. When recognized at these stages, acute circulatory dysfunction can be treated and hypoperfusion-induced organ dysfunction may be prevented [11, 12].

In pre-ICU hospital settings that lack advanced laboratory testing or hemodynamic monitoring, the task of identifying early stages of circulatory dysfunction relies mainly on the clinical examination and basic laboratory testing. The physical examination should also include assessment of jugular vein distention, hydration status, and skin temperature, color and turgor, as well as chest auscultation. Mental status and the presence of disorientation or confusion should also be assessed. All these examination methods can be used to identify patients in shock and to potentially trigger fluid administration. Clinical examination, looking at mental state, SBP, and respiratory rate, is the basis of the recently proposed Quick Sequential Organ Failure Assessment (qSOFA) score for the early recognition of sepsis [13].

In 2013, the UK National Institute for Health and Care Excellence (NICE) produced a guideline for fluid administration [14], which suggested that the assessment for fluid requirements should be based on an "ABCD" assessment for hypovolemia. The guideline states that indications for fluid resuscitation may include a pulse > 90 beats/min, SBP < 100 mmHg, capillary refill time (CRT) > 2 s, respiratory rate > 20/min, and UK National Early Warning Score (NEWS) ≥ 5. However, the evidence for these indications for IV fluid is very sparse [14, 15].

None of these indicators is sensitive or specific when used alone. However, there is some evidence that using a combination of two or more physiological variables increases the sensitivity and specificity of a diagnosis of impending collapse [16]. These examination methods should therefore be used together to identify patients in shock and potentially trigger fluid administration [11].

Lactate and acid base status

Increased lactate levels are a hallmark of shock, even in the absence of overt physiological derangement [17–21]. Metabolic screens including acid base status and lactate may improve the detection of critical illness beyond clinical examination alone [22]. However, blood gas and lactate analyzers are not always available in health care facilities outside the ICU. The increasing availability of POC capillary lactate measurement devices may help to overcome this obstacle. Although lower precision could be a challenge, the benefit of having wide access to lactate measurements may outweigh this. Trends may be more relevant than isolated values [23].

Arterial blood pressure

Arterial BP is the complex product of the interaction between the blood ejected by the heart and the arterial load; the arterial load comprises the mechanical properties of the arterial system (such as arterial compliance or systemic vascular resistance) and the arterial wave reflections [24, 25]. As organ blood flow depends on mean arterial pressure (MAP), the arterial system modulates vascular tone to keep tissue perfusion pressure constant. Although arterial BP can be measured in adults in nearly all settings, many wards do not have oscillometric BP devices available. This means that MAP cannot be measured and that SBP and diastolic blood pressure (DBP), as well as pulse pressure (PP), must be determined instead, and MAP derived from SBP and DBP. If only SBP and DBP are available, MAP can be calculated as:

$$\mathrm{MAP} = [(2 \times \mathrm{DBP}) + \mathrm{SBP}]/3.$$

In resource-limited settings, BP measuring devices are often not available [26–30].

Blood pressure-related triggers for fluid administration

In the absence of advanced hemodynamic monitoring, hypotension and tachycardia are frequent triggers for fluid loading.

Fluid loading is obviously indicated if tachycardia and hypotension are attributed to fluid or blood loss. In hemorrhagic shock, both hypotension and tachycardia can be used as indicators of hypovolemia (and its severity) [31–34], but these are neither sensitive nor specific.

In practice, in the initial resuscitation phases of shock, both tachycardia and hypotension should prompt the clinician to start fluid resuscitation unless there are clear indications of severe cardiac failure.

How can heart rate be interpreted in the absence of flow monitors to guide fluid resuscitation?

The contribution of HR to cardiac output (CO) and BP regulation is crucial, and tachycardia is an important early sign of shock [10]. However, tachycardia in shock could be partly due to other factors including pain, stress, anemia, inflammation, and fever. In addition, bradycardia can be present in extreme hypovolemia. The specific HR value to guide resuscitation has been poorly studied. It is obvious that a decrease in HR after a fluid challenge should lead us to suspect some pre-existing hypovolemia. However, the HR response in studies testing the fluid responsiveness in ICU patients is quite variable [35–39]. Thus, HR appears to be a rather poor index for guide resuscitation and should not be used alone to predict fluid responsiveness.

The shock index

The "shock index", which was originally described in trauma patients [40], is the ratio of HR divided by SBP (HR/SBP), with a normal range of 0.5–0.7 in healthy adults. Research has established that the shock index has a linear inverse relationship to CO and stroke volume (SV) [41]. A value of ≥ 1 has been associated with adverse outcome [42]. Several studies indicate that the shock index correlates with the extent of hypovolemia in severely injured patients, as reflected by higher rates of massive transfusion, morbidity, and mortality [43]. The relevance of the shock index has also been demonstrated in patients with sepsis [44, 45]. Therefore, it may be calculated during initial assessment of an acute circulatory dysfunction and could be a trigger for fluid loading. Unfortunately, it lacks specificity, as it would also be increased in cardiogenic and obstructive shock.

Can arterial blood pressure help in the decision to start fluid resuscitation?

Knowledge of the MAP value alone is not sufficiently decisive to trigger fluid resuscitation. A low MAP can be associated with non-hypovolemic shock, for which the place of fluid therapy is not predominant. Conversely, during hypovolemia, MAP can be maintained due to compensatory mechanisms that increase vascular resistance [11, 46].

A low PP (e.g. < 40 mmHg) suggests that SV is low and in the presence of shock would encourage the infusion of fluids, except if signs of pulmonary edema or heart failure are present [47, 48].

The SBP value alone cannot be of much help when deciding whether to infuse intravenous fluids, since a value lower than normal (e.g. 90 mmHg) can be associated with either a normal DBP (e.g. 70 mmHg) or a low DBP (e.g. 40 mmHg). The DBP value cannot directly inform the need to administer fluid therapy. The main determinants of DBP are related to arterial tone and HR. Therefore, a low DBP (< 50 mmHg) suggests low arterial tone, especially in the case of tachycardia, suggesting the need for early vasopressors. Patient characteristics are also very important [49]. Patients with chronic hypertension might require a higher level of MAP to maintain their organ autoregulation. BP values must be interpreted and individualized for this reason as well.

The amplitude of the respiratory variation in PP (PPV) is a marker of fluid responsiveness in patients with hemodynamic instability receiving mechanical ventilation (MV) [50]. However, PPV cannot be reliably interpreted in many clinical conditions [51, 52]. In situations where PPV cannot be assessed, passive leg raising (PLR) has been proposed as an alternative test to predict fluid responsiveness [53]. The reliability of this test is good when CO changes are assessed in real time, but is less satisfactory when only changes in arterial PP are assessed. For these reasons, PPV has no role in general wards, but could eventually be assessed in postoperative recovery rooms, EDs, and intermediate care units where invasive arterial BP measurement is possible and the patient is anesthetized or deeply sedated.

Can fluid-induced changes in arterial blood pressure during fluid administration help to assess the effects of fluid administration on cardiac output?

When vascular tone is intact, an increase in MAP after fluid administration is likely to be an indicator of a positive hemodynamic response in terms of CO; however, when the vascular tone is altered, the absence of an increase in MAP is not an indicator of the absence of a positive response. Arterial BP is a regulated variable, and MAP can remain unchanged despite an increase in CO, as variations in the arterial system may ultimately determine the effects of fluids in arterial BP [54]. Unlike changes in MAP, changes in PP could theoretically better follow the changes in CO induced by fluid infusion. However, there are discordant data [46–48], and it is generally accepted that an increase in PP after a fluid bolus predicts an increase in CO with high specificity but rather poor sensitivity.

Does central venous pressure have a role in guiding fluid resuscitation?

Several meta-analyses have shown very poor predictive values for CVP as a predictor of fluid responsiveness [55, 56]. We believe that aligning the results of systematic reviews supports a recommendation against the insertion of a central line for the measurement of CVP to guide fluid resuscitation. However, the topic is not completely without controversy [57]. In a recent study, the lack of resources to treat sepsis (including reduced availability of central lines and CVP measurements) was associated with increased mortality [58].

Pragmatically, we suggest that if the patient has a central line in place, CVP measurements may be considered, mainly as a safety limit/endpoint.

Increasing CVP during fluid challenge may have negative predictive power for fluid responsiveness [11]. This physiological reasoning and a stop rule using the CVP was proposed by Weil and Vincent in the revised fluid challenge technique [59–61].

In practice, CVP should not be used to predict or guide fluid resuscitation but may be used as a safety endpoint if available.

Jugular venous pressure (JVP)

The JVP is the indirectly observed pressure over the venous system via visualization of the internal jugular vein. The clinical expectation is that JVP correlates with right atrial pressure or CVP, and thus a low JVP could reinforce the indication of fluid administration if clinically indicated for other reasons, and a high JVP could be used as a safety limit for fluid loading [30]. In clinical practice, however, especially in the ED, assessment of JVP is technically complex and physiologically difficult to interpret, subject to considerable inter-observer variability, and not well correlated with CVP. An increase in JVP might be an unreliable and potentially dangerous endpoint to stop fluid loading in resource-limited settings without the availability of mechanical ventilation. In practice, even though JVP could be seen as an attractive option in settings where no other monitoring technique is available, using a JVP-based approach may result in excessive fluid loading, fluid overload, and harm.

Is there a role for other bedside variables to trigger and guide fluid resuscitation?

Urinary output

During acute circulatory dysfunction, several neurohormonal compensatory mechanisms are activated with the objective of preserving central blood volume. Secondary functional changes in renal blood flow, glomerular filtration, or tubular function may result in oliguria as a clinical manifestation of this response [95]. However, oliguria is a non-specific symptom and could also be present in mild dehydration without hypoperfusion, certain hormonal states (e.g. adequate or inadequate antidiuretic hormone secretion), and major surgery. More importantly, oliguria may not reflect renal or systemic hypoperfusion during early circulatory dysfunction. In addition, it might be difficult to obtain on admission to the ED or in medical wards. Thus, although fluids should be given to oliguric patients when hypovolemia is the potential cause of oliguria, in real life, fluid challenges in critically ill patients are frequently given for oliguria not only as a trigger but also as a target even when hypovolemia is not the cause [11]. In fact, 18% of fluid boluses in the FENICE study were indicated for this specific reason [1].

Renal blood flow can be preserved or even increased in septic shock, and extra fluids could alter renal perfusion by increasing venous congestion [62, 63]. In addition, robust evidence supports the concept that one of the main pathophysiological mechanisms in acute kidney injury associated with septic shock and major surgery is the presence of profound intrarenal microcirculatory abnormalities that are not related to global hypoperfusion in resuscitated patients [64].

Accordingly, fluid administration does not necessarily lead to restoration of normal diuresis [65, 66]. Urine output is a variable that takes time to change and is influenced by factors other than hemodynamic status. Therefore, chasing an increase in urine output with fluid challenges represent a dangerous strategy that can lead to fluid overload.

Clinical assessment of the skin to assess peripheral perfusion

During circulatory dysfunction, the compensatory neurohumoral response redistributes flow to vital organs by reducing the flow to non-vital vasculatures such as the skin. Subjective assessment of the temperature of the extremities [67–69], visualization of mottling central to peripheral temperature difference [70], and CRT have been validated and shown to be relatively reproducible [73, 74]. Few data are available to quantify how changes in CRT respond to fluid resuscitation. Its simplicity makes this approach a very attractive tool for perfusion monitoring in pre-ICU, ICU, and resource-limited settings. Abnormal peripheral perfusion, either at admission or its persistence after initial resuscitation, is related to morbidity and mortality in patients with acute circulatory dysfunction [67, 71–74].

Peripheral perfusion as a trigger or guide for fluid resuscitation

Peripheral perfusion is a rapid flow-responsive parameter that could be used in pre-ICU settings as both a trigger and a target for early shock resuscitation [75]. Van Genderen et al. [76] undertook a proof-of-concept randomized controlled trial (RCT) comparing early fluid resuscitation targeted on peripheral perfusion versus standard care, demonstrating that this approach may be safe, and associated with less fluid administration and organ dysfunction. An important ongoing RCT, the ANDROMEDA-SHOCK study (ClinicalTrials.gov identifier: NCT03078712) is aimed at demonstrating the superiority of peripheral perfusion over lactate as a target for early septic shock resuscitation [77].

Despite these considerations, clinical assessment of perfusion has not attained a definite role in current septic shock resuscitation guidelines, and it was used as a trigger for fluid resuscitation in < 8% of cases in the FENICE study [1]. Several concerns about the evaluation of peripheral perfusion have been raised, including inter-observer variability, dispersion of normal values, influence of ambient temperature and skin color, and feasibility in certain settings [103]. However, these limitations may be compensated by the fact that non-invasive clinical evaluation of peripheral perfusion may be used as a surrogate of more invasive and complex monitors, at least during initial resuscitation, and is easily accessible with minimal training and associated costs.

It is also important to keep in mind that these are indices of poor tissue perfusion but do not give insight into the cause of hypoperfusion. They should be used to trigger fluid administration in the context where hypovolemia is likely.

What defines a fluid challenge in terms of type of fluid, range of volume, and rate of administration?

Fluid loading vs. fluid challenge

It is important to describe differences between the concepts of fluid loading and fluid challenge [60].

Fluid loading is the rapid administration of fluids without necessarily monitoring the response in real time. This approach is frequently taken in the ED or pre-ICU setting when confronting severe life-threatening hypotension and hypoperfusion. In contrast, the fluid-challenge technique is a test of the cardio-circulatory system, evaluating whether the patient has a preload reserve that can be used to increase the SV and CO with additional volume (fluid responsiveness), and as an expected consequence, improve tissue oxygenation [60].

The physiological rationale when administering fluids in acute circulatory dysfunction is to improve tissue perfusion [78, 79]. Although several studies have shown that hemodynamic optimization with fluids is associated with improved outcome when applied in the perioperative period and in the initial stabilization of sepsis [80–85], it is important to remember that a "one size fits all" approach is unlikely to work. For instance, fluid bolus therapy was associated with worse outcome in children with severe febrile illness in Africa, although it is important to remember that in this study the majority of children had severe anemia [4]. A recent trial from Zambia reported that early, protocolized fluid resuscitation and vasopressor use in adult patients increased in-hospital mortality compared with usual care [86]. However, the infusion was not titrated to any usual hemodynamic target, as they were not available. The amount of fluids was higher than 20–30 mL/kg, and all patients received 4 L of fluids regardless of hemodynamic improvement. Fluids were interrupted only in the presence of fluid overload. Notably, both aforementioned studies were performed in settings without adequate resources to provide mechanical ventilation. A prospective observational study from Myanmar reported that a conservative fluid resuscitation strategy of intravenous fluids was safe in adult malaria patients without shock or acute respiratory failure [87].

Currently, limited data are available in the literature to confirm the standard method for performing a fluid challenge. A fluid challenge should consist of a volume large enough to raise the mean systemic filling pressure [88] and increase venous return and thus CO in preload-responsive patients. Its effects can be transient, with maximum changes occurring immediately at the end of fluid administration [89]. Most of the literature in which fluid challenges are used as part of a fluid optimization protocol come from studies in the perioperative period or when investigating fluid responsiveness in critically ill patients [90–93]. The majority of studies in non-surgical patients use 500 mL of fluid given in < 30 min [56, 90, 94]. A recent study showed that 4 ml/kg, compared to 1, 2, or 3 mL/kg, increased the sensitivity of the fluid challenge when the response was measured with a CO monitor [95]. Extrapolating these studies to a situation with basic monitoring, where CO monitoring is not available, is not without problems.

In recent years, various studies have shown no benefit for colloid fluids versus crystalloids, while increasing the risk of nephrotoxicity [83, 96, 97]. In most conditions,

unless blood products are required and available, as during hemorrhagic shock. Human albumin is the only colloid that has not shown risks of nephrotoxicity [98]. If colloid resuscitation is considered, human albumin may be used as an alternative to crystalloids in the context of septic shock resuscitation [99]. However, in resource-limited settings, this approach may not be available or feasible due to its costs. Among crystalloids recent evidence suggest that when large volumes are used balanced solutions should be preferred to normal saline [100, 101]. There is not sufficient evidence however to recommend to abandon completely normal saline, especially if no other fluids are available. This is particularly true in resource-limited settings.

What are the safety endpoints during a fluid challenge?

While the goal of a fluid challenge is to improve tissue perfusion, fluid administration can actually impair tissue perfusion if fluids are not needed or not tolerated. For this reason, it is important to use both goals and safety limits.

The revised fluid challenge technique was proposed by Vincent and Weil in 2006 [59], in which an increase in CO (or a clinical surrogate such as MAP) was used as an endpoint and CVP changes as safety endpoints. In the FENICE study [1], the increase in arterial BP was rated as the most frequently used variable to interpret the response to fluid challenges. Interestingly, safety limits were used in only 28% of the patients, with CVP being the most commonly used variable.

Evidence as to the best way to perform a fluid challenge in terms of goals and safety endpoints is scarce. In practice, dynamic changes in CVP during a fluid challenge can be used to determine whether sufficient volume has been given and whether fluid infusion must be slowed or stopped because of (relative) right ventricular overload. Variables based on clinical examination may also include lung auscultation and measurement of JVP. These, however, would detect only late signs of poor tolerance. They should thus be used only with the integration of other variables and as extra information.

Special considerations in resource-limited settings

Septic patients in low-resource settings presenting with signs of hypoperfusion are severely ill, and timely interventions, such as fluid resuscitation, are critical. However, a careful clinical assessment of fluid requirements and fluid overload is desirable.

One of the clinical signs of fluid overload is an increase in extravascular lung water resulting in impaired pulmonary gas exchange. Clinically, this translates not only to changes in ventilatory mechanics with associated clinical symptoms (e.g. increased work of breathing, dyspnea, obstructive breathing pattern, increased respiratory rate, typical cough, fine end-inspiratory crackles), but also increased oxygen requirements. In settings where oxygen supplies are not consistent and mechanical ventilators are unavailable, timely detection of fluid overload is essential. Thus far, no evidence exists to guide clinicians in how to titrate fluid resuscitation and which safety endpoints to use in resource-limited settings. Two recent trials from Zambia found that regular assessment of JVP, respiratory rate, and oxygen saturation in patients with severe sepsis was not sufficient to indicate fluid overload early enough, as protocolized fluid resuscitation was associated with an increased rate of acute respiratory failure and in-hospital mortality [86, 102]. These findings appear to be in line with the results from the FEAST trial, which also showed worse outcomes when higher volumes of fluids were given [4, 5]. Interestingly, these outcomes were observed despite the fluid bolus group showing signs of improved perfusion [4]. As discussed previously, these studies are not without limitations, and it would be wrong to extrapolate their findings to every resource-limited setting.

In practice, given the lack of scientific evidence, no recommendations can be made on safety endpoints for fluid resuscitation in resource-limited settings. Clinicians can only be advised to use their physical examination skills and clinical acumen to predict or recognize fluid overload early. This is even more relevant in children and patients with severe malaria, in whom clinical signs are more difficult to interpret [103] and a cautious fluid resuscitation strategy might be associated with better outcomes [87].

Summary/conclusions

Optimal fluid administration is complex, and several questions remain, both in and outside the ICU. Disappointingly, we found very little research on fluid administration with basic monitoring in either non-resource-limited or resource-limited settings.

We found relevant gaps in the scientific evidence on fluid administration outside the ICU (excluding the operating theater). In particular, there is almost no evidence about how best to perform fluid administration and improve patient-centered outcomes. For instance, despite the fact that blood pressure is the most commonly used variable to guide fluid administration at the bedside, there is no evidence on how best to use it. In summary,

Table 1 Statements and recommendations

Statements and recommendations on identification of circulatory dysfunction and triggering of fluid administration
1. Acute circulatory dysfunction can be recognized by a thorough clinical examination including assessment of the three windows of tissue perfusion—altered mentation, skin abnormalities, and oliguria—together with a combined analysis of heart rate and blood pressure
2. Whenever possible, we recommend measuring blood lactate concentrations and integrating this information with clinical examination
3. The purpose of fluid administration during hypovolemia is to improve tissue perfusion through increased cardiac output
4. We suggest that, in a clinical context of hypovolemia such as bleeding, severe diarrhea, and trauma, the presence of hypotension and tachycardia or oliguria should trigger fluid administration
5. The absence of arterial hypotension does not exclude hypovolemia and the need for fluid administration
6. We recommend individualizing fluid resuscitation in all patients
Definitions of fluid loading and fluid challenge
7. Fluid loading consists of rapid administration of a large amount of fluids in suspected hypovolemia
8. The fluid-challenge technique is a test of the cardio-circulatory system, evaluating whether the patient has a preload reserve that can be used to increase the SV and CO with additional volume (fluid responsiveness)
9. We recommend fluid loading in the presence of overt hypovolemia
10. We recommend avoiding fluid loading in the absence of overt hypovolemia (with the exception in septic shock)
11. When performing a fluid challenge, we suggest infusing 150–350 mL (or 4 mL/kg) in < 15 min
Statements and recommendations on fluid administration and assessment of the response
12. During fluid administration, a positive response to fluids is suggested by a marked improvement in the triggering variables
13. When vascular tone is decreased, a lack of improvement in triggering variables (e.g. arterial BP) does not exclude a positive response to fluids
14. The kinetics of a response in urine output to fluid administration is notoriously slow. Oliguria as a target for fluid resuscitation is problematic, since it can easily lead to fluid overload and worsening renal function
15. Skin vasoconstriction can be easily assessed and monitored during fluid resuscitation
16. We recommend that peripheral perfusion be assessed by evaluating systematic hemodynamic and other perfusion parameters and monitored during fluid resuscitation
17. We recommend that peripheral perfusion assessment include at least subjective evaluation of skin temperature, skin mottling, and capillary refill time
18. Jugular vein pressure alone should not be used to guide fluid administration, as its assessment with respect to treatment is complex, and this approach may lead to fluid overload
19. A visible increase in jugular vein pressure before or during fluid loading should alert the clinician to reconsider fluid administration after a more comprehensive cardiac evaluation
20. In elderly patients or those with arteriosclerosis or chronic arterial hypertension, a low pulse pressure (e.g. less than 40 mmHg) indicates that stroke volume is low
21. A lack of increase in MAP does not exclude a positive response to fluid administration
22. We suggest looking at the arterial pulse pressure changes for tracking changes in stroke volume after fluid infusion, an increase in pulse pressure being an acceptable indicator of changes in stroke volume. The absence of an increase in pulse pressure does not exclude a positive response to fluid challenge in terms of CO
23. In the initial resuscitation of septic shock patients, we recommend fluid loading of up to 30 ml/kg, tailored according to individual considerations such as the perceived degree of hypovolemia and potential cardiovascular risks of fluid loading
24. The shock index might be calculated during initial assessment of acute circulatory dysfunction and could be a trigger for fluid loading
25. A fluid challenge consists of the administration of a fluid bolus while evaluating its effectiveness and tolerance
26. We suggest the use of crystalloids as the initial resuscitation fluid in most cases of acute circulatory failure (except when blood products are required and available)
27. A concomitant increase in BP with a decrease in HR is suggestive of a positive response to fluid resuscitation
28. We recommend against the insertion of a central line with the only purpose to measure CVP to guide fluid resuscitation
29. We recommend against the targeting of any specific value of CVP for fluid resuscitation
30. If CVP is measured, a marked rise during rapid fluid administration should be interpreted to reflect poor tolerance
31. We suggest stopping fluid administration when clinical signs of fluid intolerance occur and to reassess the patient's ongoing requirements for fluids
Research recommendations
32. We recommend that scientific communities and researchers invest in research in the field of basic fluid administration
33. We recommend a specific research focus on fluid administration in resource-limited settings

our work has found evidence to recommend only basic interventions, based more on physiological rationales than high-quality RCTs.

We believe that the scientific communities and health care systems should address these gaps in knowledge by initiating a series of studies to examine how fluid administration can be standardized to improve patient outcomes in both resource-rich and resource-limited settings (Table 1).

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