medicina *intensiva*

REVIEW

Ten answers to key questions for fluid management in intensive care

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Abstract This review focuses on fluid management of critically ill patients. The topic is addressed based on 10 single questions with simplified answers that provide clinicians with the basic information needed at the point of care in treating patients in the Intensive Care Unit. The review has didactic purposes and may serve both as an update on fluid management and as an introduction to the subject for novices in critical care.

There is an urgent need to increase awareness regarding the potential risks associated with fluid overload. Clinicians should be mindful not only of the indications for administering fluid loads and of the type of fluids administered, but also of the importance to set safety limits. Lastly, it is important to implement proactive strategies seeking to establish negative fluid balance as soon as the clinical conditions are considered to be stable and the risk of deterioration is low.

Diez respuestas a preguntas clave para el manejo de fluidos en cuidados intensivos

Resumen Esta revisión se centra en el manejo de fluidos en el paciente crítico. Discutimos el tema con un enfoque basado en 10 preguntas individuales con respuestas simplificadas, que ofrecen al personal clínico la información básica necesaria, a pie de cama, para tratar a los pacientes en las unidades de cuidados intensivos. Esta revisión tiene propósitos didácticos y puede servir tanto como actualización sobre el manejo de fluidos como una introducción al tema para los que comienzan a tratar a pacientes críticos.

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Existe una necesidad urgente de aumentar la conciencia sobre los riesgos potenciales asociados con la sobrecarga de líquidos. Los médicos deben tener en cuenta no solo las indicaciones para administrar una carga de fluidos, sino también el tipo de fluidos administrados y la importancia de establecer límites de seguridad. Finalmente, es necesario implementar estrategias proactivas que tengan como objetivo un balance negativo de líquidos tan pronto como las condiciones clínicas del paciente crítico se consideren estables y el riesgo de deterioro sea bajo.

Introduction

The purpose of this short review is to answer ten key questions regarding the administration of intravenous fluid in the intensive care (ICU) setting, a topic that is receiving growing attention for the increased awareness on the potential risks associated with fluid overload. The decision to infuse fluid in order to revert acute circulatory dysfunction leading to shock is based on a basic physiological concept: a symptomatic fluid loss (absolute or relative) should be replaced to revert symptoms. Fluid resuscitation in the context of circulatory shock is focused on aggressive and rapid fluid infusion (eventually associated with the administration of systemic vasopressors) in order to restore blood pressure. The target of rapid fluid administration is to improve cardiac preload, and consequently cardiac output and peripheral perfusion.[1,2] While aggressive and prompt fluid resuscitation in the early phase of shock is a recommended intervention,[2,3] hemodynamic targets in already resuscitated patients and safety limits indicating whether or not fluid infusion should be considered are not well-defined yet.[2,4] Indeed, once hemodynamic stability has been reached, fluid management should be tailored. It is overtly evident that a targeted fluid management is of pivotal importance to improve the outcome of critically ill patients, as both hypovolemia and hypervolemia are harmful.[1] Clearly hypovolemia may lead to decreased organ perfusion, but the side effects of fluid overload are increasingly recognized. Table 1 summarizes these side effects at different organ level.

For such reasons, ICU clinicians should be aware of the indications for administering fluids in the already resuscitated critically ill patients, possibly pursuing a standardized approach as both the amount of fluids and the rate of administration influence the cardiovascular response. When deciding to administer fluids to the critically ill patient, it is pivotal to set the limits of safety for fluid challenges, understanding the risks associated with even small amounts of extra fluids. Furthermore, it is becoming relevant for ICU clinicians to implement pro-active strategies aiming at negative fluid balances already in the initial phase of recovery from critical illness. Moreover, several types of fluids are available for clinical use. Although the existing evidence is currently supporting the use of crystalloid solutions in most ICU patients, there is not an ''ideal'' fluid for all patients and, as for many other medical treatments, ''one size does not fit all''.

1. How intravenous fluids should be defined? Fluids should be considered as drugs.

This is an easy and short answer. Fluids are drugs and therefore, physicians should be aware of the same limitations as they are for any other medication used in clinical practice: clear indication, precise amount to be administered at a set rate, and safety issues that may prompt stopping administration if undesired side effects occur. Such a drug, the hemodynamic effects of fluid administration may be assessed by considering the pharmaco-dynamic analysis of fluid challenge.[5] In other words, the dose and the rate of administration of a fluid challenge may produce a different impact on right ventricular filling and, in turn, on the rate of fluid responders (FR). These aspects have been not entirely explained and, as a matter of facts, fluid challenge amount and rates for their administration are not fixed.[6,7] As for other drugs such as antibiotics, fluids utilization have been described according to the four ''D's'': drug, duration and dosing and de-escalation, with the latter receiving increasing attention over the recent years.[8] As expected, the rate of complications with fluid therapy increases with under- or over-dosing and targeting the correct fluid balance remains a clinical challenge, as one size does not fill all patients and/or conditions.[9]

2. What a fluid challenge is? The fluid challenge is a test to assess ''preload responsiveness''.

Fluid challenges should be distinguished from the fluid bolus (or fluid loading). The latter refers to the administration of a large volume of fluid given rapidly for rescue purposes to reverse an acute hemodynamic instability and often performed without close hemodynamic monitoring. On the other hand, a fluid challenge represents a test performed to assess the hemodynamic effects of a definite (lower) amount of fluids administered in the belief that it will increase the mean systemic filling pressures, which is the driving force for the venous return. Physiologically, improving preload conditions with fluid administration will increase the stroke volume (SV). A positive response to fluid administration generates a significant increase in SV, it is called ''fluid responsiveness'' (FR) and it is present in healthy individuals and of course in patients with circulatory shock.[10] Therefore, in patients with ''preload-responsiveness'' (physiologically better defined as ''bi-ventricular responsiveness''), a fluid

Table 1 Systemic effects of fluid overload.

Organ/system	Some effects of fluid overload
Central nervous system	Jugular vein congestion
	Increased backward venous pressure affecting brain perfusion
	Electrolyte shifts and increase in cerebral edema
	Risk of worsening neuronal damage (i.e. in TBI patients)
Respiratory	Worsening gas exchanges and pulmonary edema
	Prolonged time to liberation from MV and increased incidence of VAP
	Pleural effusions and increased need for thoracentesis
Cardiovascular	RV volume and/or pressure overload
	Pulmonary edema secondary to LV diastolic dysfunction
	LV dilatation especially if pre-existing impaired LV systolic function
	Disturbance in cardiac conduction and arrhythmias
Renal, hepatic and gastrointestinal	Increased splanchnic congestion with worsening splanchnic perfusion
	Increased need for diuretic therapy and/or RRT
	Worsening hepatic function
	Increased risk of intra-abdominal hypertension and abdominal compartment syndrome
Skin and muscles	Increased tissue edema with impaired peripheral perfusion
	Compromised wound healing and development of pressure ulcers
	Loss of muscular tissue, decreased mobility

challenge will increase preload and in turn SV and cardiac index (CI). On the other hand, a ''fluid unresponsive'' patient will not significantly increase the SV after fluid administration, and inappropriate fluid administration is likely contributing to venous congestion and fluid overload.

In other words, the fluid challenge should be administered only under preload-dependency condition (i.e. cardiac performance laying on the step part of Frank-Starling curve, see further), in already resuscitated patients. The decision to administer fluids assumes that the plateau of cardiac performance as described by the Frank-Starling curve has not been reached; in other words, the heart is performing in the steep part of the curve, when an increase in preload is followed by an increase in the SV. However, the clinical assessment of the position of patient's cardiac performance in the Frank-Starling curve is rather complex, and this evaluation at the ICU bedside for the prediction of FR is not always used.[11]

It is pivotal to understand that administration of fluids is a ''non-reversible'' action and the risk of fluid overload is behind the corner. Considering the negative impact on patient's outcomes of fluid overload both in the ICU setting[12-15] and in the surgical patient,[16] whenever feasible clinicians should evaluate FR before giving a fluid challenge. Therefore, an advanced hemodynamic monitoring should be in place (or echocardiography should be performed) as the assessment of FR cannot rely only on arterial blood pressure measurements.[17] Once again, the evaluation of FR and the administration of a fluid challenge applies to the already resuscitated and properly monitored ICU patients. On the other hand, evaluating FR is challenging during the resuscitation of the hypotensive patients in the emergency department as in most cases invasive hemodynamic monitoring is not yet in place. In these cases, fluid boluses (loading) are performed under the assumption that the patient is in the steep part of the Frank-Starling curve, as long as there are not obvious contraindications to fluid administration.

As a matter of fact, preload responsiveness does not necessarily imply the need of fluid administration to improve tissue perfusion (see further, question n 7).

3. When should I give a fluid challenge? The fluid challenge should be given to a responsive patients needing stabilization with limited risk of overload.

The fluid challenge is a diagnostic approach to hemodynamic management which aims at identifying the patients who respond to fluid administration with an increase in SV and CI. Unfortunately, in the clinical practice fluid challenges are still given with large worldwide variability in the indications, amount, rate and safety limits adopted (if any!) both clinically[11] and in research studies.[6]

From theoretical perspectives, in presence of signs of tissue dysoxia (see Table 2), fluids are given in order to improve oxygen delivery (DO_2) through an increase in SV and CI in the presence of the following three conditions:

- signs of hemodynamic instability and/or hypo-perfusion (high or increasing values of lactates, prolonged capillary refill time and skin mottling, increased CO_2 gap, abnormal $ScvO_2$),
- FR (often described as ''preload responsiveness'', possibly better if reported as ''biventricular responsiveness''),
- limited risks of fluid overload, so that the fluid administration has a low risk of worsening tissue perfusion (i.e. aggravating peripheral edema), gas exchanges (increase in extravascular lung water) and/or cardiac performance (i.e. right ventricular dilatation).

4. Does an increase in cardiac index after fluid administration mean improving the DO_2? This is not always the case.

Table 2 Assessment of tissue dysoxia at the bedside.

	Advantages	Drawbacks	Clinical utility
CRT and Skin mottling	-Easy to perform -Costless	-Both are operator dependent and affected by ambient and skin temperature -CRT is influenced by the different duration of pressure applied. Best method for performing CRT is still debated -Skin mottling is of difficult evaluation in patients with dark skin	Both are part of a simple clinical examination at bedside. If CRT ≤ 2 s, should be considered normal, higher values may indicate perfusion defects. Skin mottling may be equally helpful but should be evaluated with a standardized scale (from 0 indicating no mottling, to 5 where extremely severe mottling area going beyond the fold of the knee)
Lactate	-Available as POC -Reference value available -Does not distinguish the etiology of shock	-Normal values do not exclude acute circulatory dysfunction -Not a direct measure of tissue perfusion -Systemic values affected by clearance and by overall perfusion	Lactate normalization may indicate successful resuscitation. Persistence of severe hyperlactatemia for a prolonged period is associated with negative prognosis.
$ScVO_2$	-Available as POC -Reference value available -May help distinguishing between causes of shock	-Need for a CVC in the superior cava vein (or a pulmonary artery catheter, in which case a sample for evaluation of SVO_2 can be performed). Normal or high values are less indicative of the degree of shock.	The optimization of low $ScVO_2$ (<70%) has been successfully used in a protocolized approach to septic shock.
$\triangle PCO_2$	-Available as POC -Reference value available -May help distinguishing between causes of shock	-Need for both arterial and central venous blood gas analysis -Need for a CVC in the superior cava vein and of an arterial catheter or sample.	High values (>6 mmHg) can identify inadequately resuscitated patients (insufficient blood flow to the tissues).

Adapted from Messina A. et al. Fluid administration for acute circulatory dysfunction using basic monitoring. Ann Transl Med. 2020 Jun;8(12):788, with permission.
CRT, capillary refill time; $ScVO_2$, central venous oxygen saturation; $\triangle PCO_2$, the venous-to-arterial CO_2 tension difference; SBP, systolic blood pressure; MAP mean arterial pressure; CO, cardiac output; CVC, central venous catheter; ICU, intensive care unit.

Clinicians should be aware of three main factors interposing between an improved DO_2 and the oxygen utilization. First, as shown in the left side of Fig. 1, an increase in CI will ultimately contribute to an improved DO_2, providing that the arterial concentration of oxygen (CaO_2, right side of figure) remains unchanged. Fluid administration causes some degree of hemodilution with drop in hemoglobin levels; moreover, in case of elevated lung permeability also the oxygen saturation (SaO_2) may drop. As example, the indexed DO_2 in a patient with Hb = 9 g/dl, SaO_2 = 97% and CI = 2.7 L/min is 316 ml/min/m². Assuming a good hemodynamic response to the administration of fluids ($\triangle$CI = +15%, CI = 3.1 L/min), if a concomitant drop in both Hb (i.e. 8.4 g/dl) and SaO_2 (95%) occur, then the ultimate increase in DO_2 will be marginal (indexed DO_2 = 331 ml/min/m²).

Second, a straightforward assumption that increasing CI translates into greater DO_2 has a pitfall in the role of the microcirculation. Indeed, the percentage of perfused vessels (study of microcirculation using microscopy) does not always follows linearly the increases in CI.[18] In practice, the macro/micro-circulation coherence is not always preserved with large variability in the microcirculatory response at the end of fluid challenge.[19] While in some patients an increase in CI produces recruitment at microcirculatory level, in others the fluid redistribution and the interstitial leakage of fluids may decrease O_2 diffusion, potentially worsening the DO_2.

Finally, a third limitation is beyond the microcirculation and relies on alterations at cellular level and in particular on the mitochondria ability to uptake and properly use the O_2 delivered. The most typical case is seen in septic patients where O_2 extraction and utilization at cellular level is profoundly impaired.[20]

5. How fluid-responsiveness should be assessed in clinical practice? Fluid-responsiveness should be assessed using dynamic variables, being aware of the limitations of each test
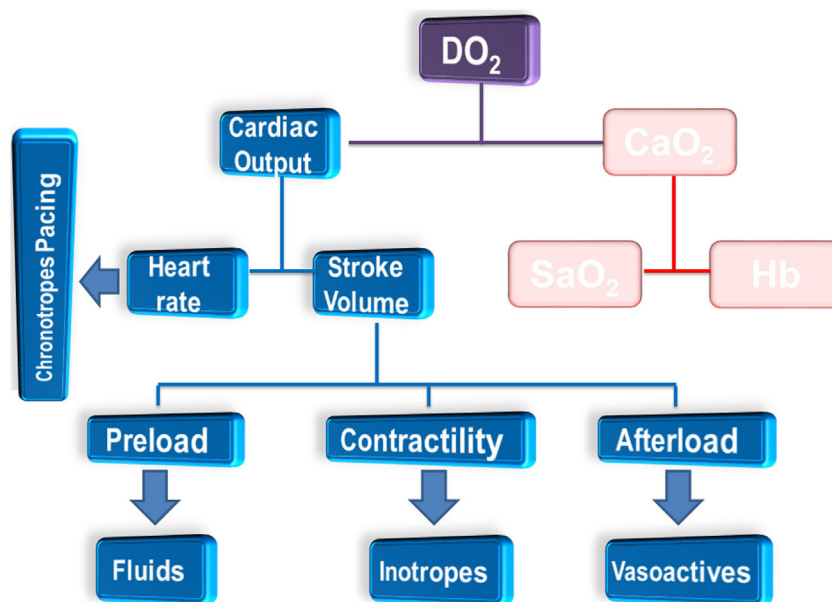
Figure 1 Factors conditioning the oxygen delivery (DO_2) to tissues and interventions from hemodynamic perspectives. The right side of the figure is intentionally left in shadow as the focus of the review is not the approach from transfusion and ventilatory perspective. CaO_2: arterial concentration of oxygen; Hb: hemoglobin; SaO_2: saturation of oxygen.

While it seems clear from scientific perspective that static hemodynamic parameters (such as central venous pressure, CVP) have poor performance[21] and should not be used to assess FR in critically ill patients, several dynamic parameters have been investigated and are potentially useful. In this regard, the heart-lung interaction during positive pressure ventilation plays a pivotal role in the interpretation of hemodynamic variations. Indeed, the swing in intra-thoracic pressure during mechanical ventilation and the consequent cyclic changes in venous return are a prerequisite for most tests of FR.

The most studied index for FR evaluates the cyclic variability of pulse pressure (difference between systolic and diastolic arterial pressure), and the possibility of FR is most commonly considered when pulse pressure variation is $\geq 13\%$.[22–25] A similar concept applies to the variability in SV (requiring advanced hemodynamic monitoring or echocardiography) with a slightly lower threshold to identify FR.[21,23] However, these two tests can be trustworthy only in a minority of ICU patients, since their reliability relies on presence of sinus rhythm, controlled mechanical ventilation with no spontaneous breathing efforts, tidal volume ≥ 8 ml/kg of ideal body weight, lung compliance ≥ 30 ml/cmH2O, and no increase in intra-abdominal pressure (as main limitations).[26]

Clinicians should be aware that, when ventilating with low tidal volumes (i.e. 6 ml/kg), there is an option to perform a tidal volume challenge technique for assessing FR, as described by Myatra and colleagues.[27] The authors tested the hypothesis that absolute changes in pulse pressure variation or in SV variation produced by an increase in the tidal volume from 6 to 8 ml/kg for only one minute would discriminate FR from non-responders.[27] As the widespread use of protective ventilation would impair the performance of several dynamic tests, the tidal volume challenge test may offer the opportunity to evaluate FR even in these patients, decreasing the risk of falsely negative results.[28] However, it should be noted that this promising test has been evaluated in a small-sized single center study,[27] or on elective neurosurgical patients in the operating room.[29]

The echocardiographic evaluation of the variation in inferior vena cava diameter has received a great attention due to the increasing use of critical care echocardiography.[30] However, its reliability seems lower than thought before,[31,32] and it shares many limitations as the above described tests. Similarly, variation in superior vena cava with transesophageal echocardiography may be used in selected patients.[33] Unfortunately, also these index showed limited clinical applicability, when applied in a large ICU population.[34]

When limitations preclude the use of these tests, ICU clinicians should keep in mind the applicability of two other options: the passive leg raising and the end-expiratory occlusion test. These maneuverers have different hemodynamic impact, and for the correct interpretation of their cardiovascular effects an advanced hemodynamic monitoring should be in place measuring the CI. Importantly, clinicians should remember that cut-offs for defining fluid-responsiveness is 15% variation in CI for passive leg raising and only 5% for end-expiratory occlusion test. More details on these tests are provided elsewhere[35,36]; we would like to remind the importance of maneuvers as these ones that do not require fluid administration and therefore have the advantage of being reversible (fluid are not given and there is no risk of overload due to these tests).

6. If an indication to give fluid exists, how should I give them? I should give fluids closely monitoring effects (and safety limits), and standardized approach

Once the FR has been evaluated and provides indications for a fluid challenge, we suggest that clinicians follow the same approach they use for any drug prescription, having a clear idea on

- the type and amount of fluid to be given,
- the rate of administration, and
- what are the safety limits to stop infusion.

Moreover, it would be ideal to agree and standardize the practice of performing fluid challenges within each group of ICU. The type of fluid is a complex decision and may vary according to patient's characteristics, underlying disease and concomitant electrolyte/metabolic conditions (see further questions 8 and 9). Although there is no established recommendation on the amount of fluids that should be used, the proportion of FR to fluid challenges varies greatly according to the amount given, as shown in a recent study on postoperative cardiac patients (1 ml/kg: 20%; 2 ml/kg: 35%; 3 ml/kg: 45%; 4 ml/kg: 60%, in all cases given in 5 min).[37] Moreover, a systematic review showed that the rate of administration may play a more important role and the proportion of FR is lower in studies performing a fluid challenge in more than 30 min.[7] This is probably due to the increased redistribution/leak in critically ill patients over longer periods of administration. Although no guidelines has been established, it is authors opinion that fluid challenges should be given in reasonable amount (4 ml/kg) and in a relatively short timeframe (5–10 min), possibly adopting a standardized approach in each ICU. Safety limits (i.e. monitoring an abrupt increase in CVP is a possible safety limit during fluid challenge, especially if coupled with a no significant improvement in CI) should be always set in the mind of clinicians prescribing a fluid challenge. Moreover, while tests for FR are predictive measures, clinicians should perform the final evaluation on the result of their fluid challenge at the bed-space, keeping in mind that the largest variation in CI occurs within one minute of fluid challenge, and that effects on variation of CVP (safety measure) are lost after 10 min.[5]

7. When clinicians should be more careful in fluid administration? Several clinical conditions suggest a caution approach to fluid administration

Being ''fluid-responder'' in a test for ''preload-responsiveness'' is a physiologic condition and under conditions of tested FR, several circumstances should be taken into account when ultimately deciding if fluids should be given. Describing in details all the conditions where even a small extra amount of fluids can be harmful is beyond the scope of the present manuscript. However, we summarize the most common conditions that should be kept in mind by clinicians prescribing a fluid challenge.

- Right ventricular dysfunction: even a tiny amount of fluids may over-distend the failing right heart and in many cases it is very difficult to revert it. Moreover, right ventricular failure is associated with false positives in tests for FR.[28]
- Left ventricular diastolic dysfunction: in cases of increased left atrial pressure due to increased left ventricular filling pressures and diastolic dysfunction, an

extra amount of fluid may worsen further the heart performance and, more importantly, it may further increase backward pressure on the pulmonary circulation with worsening oxygenation. Of note, diastolic dysfunction is associated with worse outcome in sepsis[38,39] and higher failure in weaning from mechanical ventilation.[40,41]
- Acute lung injury: in case of increased lung permeability fluids easily move to the extravascular space with increase in alveolar water and deterioration of pulmonary edema. For this reason, patients with acute respiratory distress syndrome seem to benefit from a conservative fluid strategy approach.[42,43]
- Kidney injury: although de-hydration is a cause of acute kidney injury, most ICU patients are not de-hydrated. Clinicians should keep in mind that in case of already established kidney damage, the excess of fluid cannot be easily removed (i.e. by increasing does of diuretics), and renal replacement may be the only option. Moreover, an increased CVP and backward pressure on kidneys may decrease their perfusion pressure, creating a vicious circle.[44]
- Hepatic and Gastrointestinal: the effects of venous congestions produce similar issues at gastrointestinal and hepatic level, with the risk of worsening their perfusion. Patients at risk of intra-abdominal hypertension may experience aggravation of their clinical conditions with interstitial leakage of fluids.[45]

Of note, it has been recently tested the ability of a point-of-care ultrasound assessment of venous congestion (so-called ''VEXUS), which focus on daily ultrasound assessment of hepatic, portal, intra-renal vein Doppler and inferior vena cava ultrasound. In a pioneer single-center study conducted during the first 72 hours after cardiac surgery, the authors were able to identify five prototypes of venous excess combining the above ultrasound parameters.[46] These findings deserve further attention and validation.

8. Is there any differences between classes of crystalloids? Yes. Balanced solutions have better profile, but one size does not fit all patients.

Crystalloids are the most commonly used intravenous fluids, and although in a very simplified approach they can be classified in unbalanced and balanced solutions according to the concentration of electrolytes. The first group embrace solutions containing different concentration of sodium and chloride only (most commonly 0.9%, 3%, 7.5%) with strong ion difference equal to 0. On the opposite the group of balanced solutions have different electrolytes composition and a positive value of strong ion difference, ranging between 27 (Acetate Malate and Ringers' solutions) and 50 (Acetate Gluconate solution). The detailed description of all the solutions is beyond the scope of the present manuscript, and readers are referred elsewhere.[47]

One of the greatest issues that should be considered at the bed-space when using unbalanced solutions (i.e. saline solution) is the higher load of chloride administered. This exposes the patient to greater risks of hyper-chloremic acidosis and renal injury.[48] Two recent single-center, pragmatic, multiple-crossover trials from the same group of

authors have recently compared balanced (Lactate Ringer or Acetate Gluconate) vs saline solution 0.9% in the ICU setting,[49] or in non-critically ill adult patients admitted to the Emergency Department.[50] In the study on ICU patients, the use of balanced crystalloids reduced the major adverse kidney events within 30 days (composite outcome of in-hospital mortality, new renal replacement therapy, and persistent renal dysfunction). Interestingly, these results were achieved despite a low amount of fluids given, with a median around 1000 ml for both groups from admission to day 30 or discharge, whichever came first.[49] In the study in non-critically ill adults, there were no difference in hospital-free days between groups but also in this study the group randomized to balanced crystalloids reported lower incidence of major adverse kidney events within 30 days (secondary outcome).[50] These reported effects on kidney function may be explained by the dose-dependent hyper-chloremic acidosis as this condition favors the contraction of vascular smooth muscles, potentially reducing renal per-fusion, causing harmful effects on renal function even at low doses.[51] There is preclinical evidence that administration of saline solutions causes not only hyper-chloremic metabolic acidosis, but also inflammation, hypotension and acute kid-ney injury.[52]

It is apparent that, when deciding to administer a crys-talloid solution, in most cases a balanced one may be preferred, but some peculiarities should be always kept in mind. As examples, these solutions contain potassium and could be contraindicated in case of renal failure and risk of dialysis; furthermore, these solutions are slightly hypo-tonic (range 277–304 mOsm/L) and their use in patients with traumatic brain injury should be very cautious to avoid aggravation of cerebral edema.[53] Moreover, lactate buffered solutions (i.e. Lactate Ringer) may potentially cause a small increases in serum lactate concentration, especially among patients with impaired hepatic function.[54] Of note, the Sur-viving Sepsis Campaign recommends crystalloids as fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock with no specific indications between balanced or unbalanced solutions.[2] As the present manuscript is written during the recent pandemic of coronavirus disease we remind readers that expert consensus for patients in shock suggests buffered crystalloid solutions over unbalanced[55] and to take in high consideration the risk of renal injury.[56]

In summary, there is not an ideal solution fitting for all critically ill patients, as there is not an ideal antibiotic for all infections.

9. Is there any differences between crystalloids and col-loids? Yes, and there are important differences between types of colloids

Colloids have been introduced in the clinical practice because of their theoretical capability to remain longer in the intravascular space as compared to crystalloids, for the generation of higher osmotic pressure in the cir-culation due to the presence of macromolecules in the solution. Examples of colloids are albumin, hydroxyl-ethyl-starch (HES), gelatins and dextran. Albumin is a natural colloid dissolved in an unbalanced solution (saline), gelatins and HES (with the exception of the unbalanced Voluven®)

are balanced solutions with a positive strong ion difference (range 28–56). Colloids particles are too large to pass semi-permeable membranes such as capillary membranes; thus colloids should theoretically remain longer in the intravas-cular space than crystalloids, possibly reducing the amount of fluids administered. However, one should keep in mind that such theoretical conditions are subverted in critically ill patients, where increased permeability, endothelial dam-age and several other factors affect the trans-membrane shift of fluids. Indeed, despite theoretical advantages, col-loids have mostly failed in showing advantage in critically ill patients. Importantly, a differentiation should be made between natural colloids (albumin) and synthetic colloids.

Albumin – A landmark trial in 2004 showed that 4% albu-min for fluid resuscitation in critically ill patients resulted in similar outcomes at 28 days as compared with saline solu-tion 0.9%, despite albumin significantly reduced the overall amount of fluids given (saline solution to albumin adminis-tration ratio during the first 4 days was 1.4).[57] Interestingly, the secondary analyses showed an increased risk of death in patients with traumatic brain injury, but on the con-trary there was a trend toward lower mortality in septic patients receiving albumin ($p = 0.09$). This led to the design of a randomized controlled trial in patients with severe sep-sis comparing albumin 20% replacement (to keep plasmatic values ≥ 3 g/dl) to crystalloids alone. The ALBIOS study (pub-lished 10 years later) showed that albumin did not improve the rate of survival at 28 and 90 days, but a reduction in 90-day mortality was seen in the post hoc analysis for the albumin group in patients with septic shock.[58] There is conflicting evidence on the role of albumin in critically ill patients with sepsis. Two meta-analyses included studies in whom patients received crystalloids as well as synthetic colloids in the control arm, and showed no difference in the mortality rates between groups.[59,60] On the contrary, a third meta-analysis including as control group patients receiving only crystalloids found that 90-day mortality of patients in septic shock was significantly lower with albumin.[61]

Synthetic colloids – In three large RCTs comparing syn-thetic colloids (HES) and crystalloids the ratio of crystalloids to HES administered has been mostly in the range of 1.0–1.2 (decrease up to 20% of the volume administered in the HES group), far less than expected.[62–64] Only one RCT showed a more pronounced reduction in the volume of fluids admin-istered in the HES group, with a ratio of 1.5.[65] The small reduction in the volume of fluids administered does not seem clinically relevant and, on the contrary, it is counter-balanced by known side-effects of HES such as the renal injury.[63,64] There also no data supporting advantages in long-term outcomes and cost-effectiveness analysis.[66] In January 2018, the European Medical Agency safety commit-tee recommended suspending the marketing authorizations of these medicines because they continued to be used in crit-ically ill patients and patients with sepsis despite restrictions already introduced 5 years earlier.[67] Although starches have been subsequently reintroduced on the market (provided that training, controlled access and warnings on the pack-aging are implemented), HES solutions have several con-traindications (sepsis or critically illness, renal impairment or ongoing renal replacement therapy, severe coagulopathy, intracranial or cerebral hemorrhage, burn injuries, severe hyperkalemia, hypernatremia, hyper-chloremia, impaired

hepatic function, congestive heart failure, organ transplant). The use of HES should be restricted to the initial phase of volume resuscitation and to acute blood loss when crystalloids alone are not considered sufficient.

10. When should I start taking fluids off? As soon as possible if the patient is not at risk of shock

As already mentioned fluid overload is defined an increase in 10% of body weight from ICU admission.[8,68–71] Regarding the approach with fluid therapy, progression of critical illness and fluid administration has been conventionally divided in four stages. The initial phase is represented by the ''resuscitation'' (or salvage) period where fluids are given in large amount to support end-organ perfusion and maintain vital signs during life-threatening conditions associated with impaired tissue perfusion. As result there is a rapidly growing curve of fluid balance. This period is followed by the ''optimization'', a phase where fluid administration starts to be tailored according to targeted hemodynamic and perfusion variables, still with a trend toward more positive fluid balance. The third phase is known as ''stabilization'' and fluids are only used for ongoing maintenance. By this time the patient has reached the peak of cumulative fluid balance (curve of fluid balance plateaus), is not anymore in a shock state (or at imminent risk), and possibly some fluids are starting to be mobilized and removed.

The last phase is called ''evacuation'' (or de-escalation) and it lasts much longer than the previous periods, from days to weeks. It refers to late goal-directed fluid removal associated with conservative fluid management. Indeed, during de-escalation becomes important to achieve a negative fluid balance with elimination of fluid excess gained during the most severe stages of critical illness. De-escalation with fluid removal has been described as the fourth ''D'' of fluid therapy (together with ''drug'', ''duration'' and ''dosing''), likewise it happens for other drugs (i.e. antibiotics). During this period the oral intake should be promoted, and unnecessary intravenous fluids should be avoided. Retrospective evidence has suggested that negative fluid balance on day 3 of ICU stay accomplished with de-resuscitation is associated with improved patient outcomes.[72] It is currently under investigation the role of conservative fluid administration and de-resuscitation in order to improve patients' recovery after critical illness.[73] In order to achieve negative fluid balance, clinicians pursuing aggressive de-resuscitation may use diuretics and eventually renal replacement therapy. However, they should balance the risk of being too aggressive with fluid removal as hypovolemia may trigger hemodynamic deterioration and hypo-perfusion with end-organ damage.

Conclusions

In conclusion we provide a short summary with key question and answer aiming at increasing the basic knowledge on the fluid management of critically ill patients. The manuscript spans from the indications, the modalities of administration and the safety limits when deciding to perform a fluid challenges, and emphasizes the increasing awareness on the importance of active de-resuscitation.

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Not applicable.

Consent for publication

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Availability of data and material

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Authors' contributions

FS and MA designed the review and the format, and wrote the initial draft. AM and MC critically revised the draft and made substantial changes. All the authors agreed on the manuscript content.

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References

1. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1795–815. PubMed PMID: 25392034. Pubmed Central PMCID: PMC4239778. Epub 2014/11/14. eng.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–77. PubMed PMID: 28101605.
3. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369:1243–51. PubMed PMID: 24066745.
4. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42:1695–705. PubMed PMID: 27686349.
5. Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. Crit Care Med. 2016;44:880–91. PubMed PMID: 26683506. Epub 2015/12/20. eng.
6. Messina A, Longhini F, Coppo C, Pagni A, Lungu R, Ronco C, et al. Use of the fluid challenge in critically ill adult patients: a systematic review. Anesth Analg. 2017;125:1532–43. PubMed PMID: 28514324. Epub 2017/05/18. eng.
7. Toscani L, Aya HD, Antonakaki D, Bastoni D, Watson X, Arulkumaran N, et al. What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis. Crit Care. 2017;21:207. PubMed PMID: 28774325. Pubmed Central PMCID: PMC5543539. Epub 2017/08/05. eng.
8. Malbrain M, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management

and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8:66. PubMed PMID: 29789983. Pubmed Central PMCID: PMC5964054. Epub 2018/05/24. eng.

9. Boulain T, Cecconi M. Can one size fit all? The fine line between fluid overload and hypovolemia. Intensive Care Med. 2015;41:544–6. PubMed PMID: 25656354. Epub 2015/02/07. eng.

10. Kattan E, Ospina-Tascón GA, Teboul JL, Castro R, Cecconi M, Ferri G, et al. Systematic assessment of fluid responsiveness during early septic shock resuscitation: secondary analysis of the ANDROMEDA-SHOCK trial. Crit Care. 2020;24:23. PubMed PMID: 31973735. Pubmed Central PMCID: PMC6979284. Epub 2020/01/25. eng.

11. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med. 2015;41:1529–37. PubMed PMID: 26162676. Pubmed Central PMCID: 4550653.

12. Kox M, Pickkers P. ''Less is more'' in critically ill patients: not too intensive. JAMA Internal Med. 2013;173:1369–72. PubMed PMID: 23752755. Epub 2013/06/12. eng.

13. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. Crit Care Med. 2017;45:386–94. PubMed PMID: 27922878. Epub 2016/12/07. eng.

14. Jozwiak M, Silva S, Persichini R, Anguel N, Osman D, Richard C, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med. 2013;41:472–80. PubMed PMID: 23263578. Epub 2012/12/25. eng.

15. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344–53. PubMed PMID: 16424713. Epub 2006/01/21. eng.

16. Raghunathan K, McGee WT, Higgins T. Importance of intravenous fluid dose and composition in surgical ICU patients. Curr Opin Crit Care. 2012;18:350–7. PubMed PMID: 22732434. Epub 2012/06/27. eng.

17. Monge García MI, Barrasa González H. Why did arterial pressure not increase after fluid administration? Med Intensiva. 2017;41:546–9. PubMed PMID: 28499615. Epub 2017/05/14. eng spa.

18. Pottecher J, Deruddre S, Teboul JL, Georger JF, Laplace C, Benhamou D, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. Intensive Care Med. 2010;36:1867–74. PubMed PMID: 20725823. Epub 2010/08/21. eng.

19. Bakker J, Ince C. Monitoring coherence between the macro and microcirculation in septic shock. Curr Opin Crit Care. 2020;26:267–72. PubMed PMID: 32332288. Epub 2020/04/26. eng.

20. Kohoutová M, Dejmek J, Tůma Z, Kuncová J. Variability of mitochondrial respiration in relation to sepsis-induced multiple organ dysfunction. Physiol Res. 2018;67 Suppl. 4:S577–82. PubMed PMID: 30607965. Epub 2019/01/05. eng.

21. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37:2642–7. PubMed PMID: 19602972. Epub 2009/07/16. eng.

22. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a ''gray zone'' approach. Anesthesiology. 2011;115:231–41. PubMed PMID: 21705869. Epub 2011/06/28. eng.

23. Hernández G, Cavalcanti AB, Ospina-Tascón G, Zampieri FG, Dubin A, Hurtado FJ, et al. Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK – a randomized controlled trial. Ann Intensive Care. 2018;8:52. PubMed PMID: 29687277. Pubmed Central PMCID: PMC5913056. Epub 2018/04/25. eng.

24. Teboul JL, Monnet X, Chemla D, Michard F. Arterial pulse pressure variation with mechanical ventilation. Am J Respir Crit Care Med. 2019;199:22–31. PubMed PMID: 30138573. Epub 2018/08/24. eng.

25. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review meta-analysis. Crit Care. 2014;18:650. PubMed PMID: 25427970. Pubmed Central PMCID: PMC4258282. Epub 2014/11/28. eng.

26. Biais M, Ehrmann S, Mari A, Conte B, Mahjoub Y, Desebbe O, et al. Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: the grey zone approach. Crit Care. 2014;18:587. PubMed PMID: 25658489. Pubmed Central PMCID: PMC4240833. Epub 2015/02/07. eng.

27. Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The changes in pulse pressure variation or stroke volume variation after a ''tidal volume challenge'' reliably predict fluid responsiveness during low tidal volume ventilation. Crit Care Med. 2017;45:415–21. PubMed PMID: 27922879. Epub 2016/12/07. eng.

28. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. Ann Intensive Care. 2016;6:111. PubMed PMID: 27858374. Pubmed Central PMCID: 5114218.

29. Messina A, Montagnini C, Cammarota G, De Rosa S, Giuliani F, Muratore L, et al. Tidal volume challenge to predict fluid responsiveness in the operating room: an observational study. Eur J Anaesthesiol. 2019;36:583–91. PubMed PMID: 31021879. Epub 2019/04/26. eng.

30. Vieillard-Baron A, Millington SJ, Sanfilippo F, Chew M, Diaz-Gomez J, McLean A, et al. A decade of progress in critical care echocardiography: a narrative review. Intensive Care Med. 2019;45:770–88. PubMed PMID: 30911808. Epub 2019/03/27. eng.

31. Charbonneau H, Riu B, Faron M, Mari A, Kurrek MM, Ruiz J, et al. Predicting preload responsiveness using simultaneous recordings of inferior and superior vena cavae diameters. Crit Care. 2014;18:473. PubMed PMID: 25189403. Pubmed Central PMCID: PMC4175634. Epub 2014/09/06. eng.

32. Zhang Z, Xu X, Ye S, Xu L. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: systematic review and meta-analysis. Ultrasound Med Biol. 2014;40:845–53. PubMed PMID: 24495437. Epub 2014/02/06. eng.

33. Maybauer MO, Asmussen S, Platts DG, Fraser JF, Sanfilippo F, Maybauer DM. Transesophageal echocardiography in the management of burn patients. Burns. 2014;40:630–5. PubMed PMID: 24035579. Epub 2013/09/17. eng.

34. Vignon P, Repesse X, Begot E, Leger J, Jacob C, Bouferrache K, et al. Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated patients. Am J Respir Crit Care Med. 2017;195:1022–32. PubMed PMID: 27653798.

35. Silva S, Jozwiak M, Teboul JL, Persichini R, Richard C, Monnet X. End-expiratory occlusion test predicts preload responsiveness independently of positive end-expiratory pressure during acute respiratory distress syndrome. Crit Care Med. 2013;41:1692–701. PubMed PMID: 23774335. Epub 2013/06/19. eng.

36. Monnet X, Teboul JL. Assessment of fluid responsiveness: recent advances. Curr Opin Crit Care. 2018;24:190–5. PubMed PMID: 29634494. Epub 2018/04/11. eng.

37. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. Crit Care Med. 2017;45:e161–8. PubMed PMID: 27655325. Epub 2016/09/23. eng.

38. Sanfilippo F, Corredor C, Arcadipane A, Landesberg G, Vieillard-Baron A, Cecconi M, et al. Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis. BJA. 2017;119:583–94.

39. Sanfilippo F, Corredor C, Fletcher N, Landesberg G, Benedetto U, Foex P, et al. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. Intensive Care Med. 2015. PubMed PMID: 25800584. Epub 2015/03/25. Eng.

40. Sanfilippo F, Di Falco D, Noto A, Santonocito C, Morelli A, Bignami E, et al. Association of weaning failure from mechanical ventilation with transthoracic echocardiography parameters: a systematic review and meta-analysis. Br J Anaesth. 2020. PubMed PMID: 32988600. Epub 2020/09/30. eng.

41. Sanfilippo F, Murabito P, La Rosa V, Oliveri F, Astuto M. Successful spontaneous breathing trial, early reintubation and mechanisms of weaning failure. Intensive Care Med. 2020;46:1960–1. PubMed PMID: 32661616. Pubmed Central PMCID: PMC7358284. Epub 2020/07/15. eng.

42. van Mourik N, Metske HA, Hofstra JJ, Binnekade JM, Geerts BF, Schultz MJ, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: an observational cohort study. PLOS ONE. 2019;14:e0224563. PubMed PMID: 31665179. Pubmed Central PMCID: PMC6821102. Epub 2019/10/31. eng.

43. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564–75. PubMed PMID: 16714767. Epub 2006/05/23. eng.

44. Monge García MI, Santos Oviedo A. Why should we continue measuring central venous pressure? Med Intensiva. 2017;41:483–6. PubMed PMID: 28188063. Epub 2017/02/12. eng spa.

45. Malbrain ML, De Laet I, De Waele JJ, Sugrue M, Schachtrupp A, Duchesne J, et al. The role of abdominal compliance, the neglected parameter in critically ill patients - a consensus review of 16. Part 2: Measurement techniques and management recommendations. Anaesthesiol Intensive Therapy. 2014;46:406–32. PubMed PMID: 25432559. Epub 2014/11/30. eng.

46. Beaubien-Souligny W, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J. 2020;12:16. PubMed PMID: 32270297. Pubmed Central PMCID: PMC7142196. Epub 2020/04/10. eng.

47. Martin C, Cortegiani A, Gregoretti C, Martin-Loeches I, Ichai C, Leone M, et al. Choice of fluids in critically ill patients. BMC Anesthesiol. 2018;18:200. PubMed PMID: 30579331. Pubmed Central PMCID: PMC6303886. Epub 2018/12/24. eng.

48. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566–72. PubMed PMID: 23073953. Epub 2012/10/18. eng.

49. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378:829–39. PubMed PMID: 29485925. Pubmed Central PMCID: PMC5846085. Epub 2018/02/28. eng.

50. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, et al. Balanced crystalloids versus saline in non-critically ill adults. N Engl J Med. 2018;378:819–28. PubMed PMID: 29485926. Pubmed Central PMCID: PMC5846618. Epub 2018/02/28. eng.

51. Malbrain M, Langer T, Annane D, Gattinoni L, Elbers P, Hahn RG, et al. Intravenous fluid therapy in the perioperative and critical care setting: executive summary of the International Fluid Academy (IFA). Ann Intensive Care. 2020;10:64. PubMed PMID: 32449147. Pubmed Central PMCID: PMC7245999. Epub 2020/05/26. eng.

52. Semler MW, Kellum JA. Balanced crystalloid solutions. Am J Respir Crit Care Med. 2019;199:952–60. PubMed PMID: 30407838. Pubmed Central PMCID: PMC6467313. Epub 2018/11/09. eng.

53. Oddo M, Poole D, Helbok R, Meyfroidt G, Stocchetti N, Bouzat P, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med. 2018;44:449–63. PubMed PMID: 29500701. Epub 2018/03/04. eng.

54. Shin WJ, Kim YK, Bang JY, Cho SK, Han SM, Hwang GS. Lactate and liver function tests after living donor right hepatectomy: a comparison of solutions with and without lactate. Acta Anaesthesiol Scand. 2011;55:558–64. PubMed PMID: 21342149. Epub 2011/02/24. eng.

55. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46:854–87. PubMed PMID: 32222812. Pubmed Central PMCID: PMC7101866. Epub 2020/03/31. eng.

56. Ballesteros Sanz M, Hernández-Tejedor A, Estella Á, Jiménez Rivera JJ, González de Molina Ortiz FJ, Sandiumenge Camps A, et al. Recommendations of the Working Groups from the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) for the management of adult critically ill patients in the coronavirus disease (COVID-19). Med Intensiva. 2020;44:371–88. PubMed PMID: 32360034. Pubmed Central PMCID: PMC7142677 declared the disease caused by SARS-CoV-2 (COVID-19) as a pandemic. The spread and evolution of the pandemic is overwhelming the healthcare systems of dozens of countries and has led to a myriad of opinion papers, contingency plans, case series and emerging trials. Covering all this literature is complex. Briefly and synthetically, in line with the previous recommendations of the Working Groups, the Spanish Society of Intensive, Critical Medicine and Coronary Units (SEMICYUC) has prepared this series of basic recommendations for patient care in the context of the pandemic. Epub 2020/05/04. Recomendaciones de «hacer» y «no hacer» en el tratamiento de los pacientes críticos ante la pandemia por coronavirus causante de COVID-19 de los Grupos de Trabajo de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC). eng.spa.

57. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56. PubMed PMID: 15163774. Epub 2004/05/28. eng.

58. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412–21. PubMed PMID: 24635772. Epub 2014/03/19. eng.

59. Jiang L, Jiang S, Zhang M, Zheng Z, Ma Y. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. PLoS ONE. 2014;9:e114666. PubMed PMID: 25474401. Pubmed Central PMCID: PMC4256427. Epub 2014/12/05. eng.

60. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ. 2014;349:g4561. PubMed PMID: 25099709. Pubmed Central PMCID: PMC4106199 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Epub 2014/08/08. eng.

61. Xu JY, Chen QH, Xie JF, Pan C, Liu SQ, Huang LW, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. Crit Care. 2014;18:702. PubMed PMID: 25499187. Pubmed Central PMCID: PMC4284920. Epub 2014/12/17. eng.

62. Futier E, Garot M, Godet T, Biais M, Verzilli D, Ouattara A, et al. Effect of hydroxyethyl starch vs saline for volume replacement therapy on death or postoperative complications among high-risk patients undergoing major abdominal surgery: the FLASH randomized clinical trial. JAMA. 2020;323:225–36. PubMed PMID: 31961418. Pubmed Central PMCID: PMC6990683 Drager Medical, GE Healthcare, Edwards Lifesciences, and Orion Pharma and lecture fees from Fresenius Kabi, Baxter, and Fisher & Paykel Healthcare. Dr Godet reported receiving personal fees from Draeger, General Electris, and Baxter. Dr Biais reported receiving personal fees from Edwards Lifesciences and Maquet Critical Care. Dr Ouattara reported receiving honoraria for consulting from LFB, Orion Pharma, Abiomed, Vifor Pharma, Nordic Pharma, and Masimo. Dr Lescot reported receiving personal fees from Fresenius Kabi, B. Braun Medical, Nestle, Nutricia, and Merck Sharp & Dohme and grants and personal fees from Baxter. Dr Asehnoune reported receiving personal fees from Fresenius, Baxter, and Fisher & Paykel. Dr Leone reported receiving personal fees from Merck Sharp & Dohme, Pfizer, Aguettant, 3M, Octapharma, Aspen, and Orion and personal fees and nonfinancial support from Amomed. Dr Jaber reported receiving personal fees from Drager, Fisher & Paykel, Medtronic, Fresenius-Xenios, and Baxter. No other disclosures were reported. Epub 2020/01/22. eng.

63. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11. PubMed PMID: 23075127. Epub 2012/10/19. eng.

64. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34. PubMed PMID: 22738085. Epub 2012/06/29. eng.

65. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809–17. PubMed PMID: 24108515. Epub 2013/10/11. eng.

66. Taylor C, Thompson K, Finfer S, Higgins A, Jan S, Li Q, et al. Hydroxyethyl starch versus saline for resuscitation of patients in intensive care: long-term outcomes and cost-effectiveness analysis of a cohort from CHEST. Lancet Respir Med. 2016;4:818–25. PubMed PMID: 27324967. Epub 2016/06/22. eng.

67. https://www.ema.europa.eu/en/medicines/human/referrals/hydroxyethyl-starch-hes-containing-medicinal-products [accessed 26.06.20].

68. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113:740–7. PubMed PMID: 25204700. Pubmed Central PMCID: PMC6863743. Epub 2014/09/11. eng.

69. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Therapy. 2014;46:361–80. PubMed PMID: 25432556. Epub 2014/11/30. eng.

70. O'Connor ME, Prowle JR. Fluid overload. Crit Care Clin. 2015;31:803–21. PubMed PMID: 26410146. Epub 2015/09/28. eng.

71. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care. 2012;16:R197. PubMed PMID: 23075459. Pubmed Central PMCID: PMC3682299. Epub 2012/10/19. eng.

72. Silversides JA, Fitzgerald E, Manickavasagam US, Lapinsky SE, Nisenbaum R, Hemmings N, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. Crit Care Med. 2018;46:1600–7. PubMed PMID: 29985214. Epub 2018/07/10. eng.

73. Silversides J, Marshall J, Ferguson A, Blackwood B, McAuley D. Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) – a pilot randomised controlled trial of conservative fluid administration and deresuscitation in critical illness: study protocol. Crit Care Horiz. 2018:9–15.