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# Approach to Fluid Therapy in the Acute Setting

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## Abstract

In the acute medicine, fluid therapy is a common intervention. Clinicians may have different preferences in prescribing the fluids—the type, the volume and rate, and the monitoring of response—but there is a growing argument in the literature for a more consistent and evidence-based approach to these prescriptions. This coincides with the call to treat fluids as drugs and to strategize the fluid management of individual patients. A good start toward observing this call will be an appreciation of the underlying physiology. The hemodynamic, biochemical, and microcirculatory responses to fluid therapy will influence the end-organ and clinical effects. In translating these physiological insights into practice, recent studies in several acute cohorts like trauma, sepsis, and postoperative and intensive care offer valuable guides. With all this in mind, the chapter aims to review the optimal approach to fluid therapy in the acute setting, from the understanding of the relevant basic sciences to the practice at the bedside.

**Keywords:** intravenous infusions, crystalloid solutions, colloids, emergency medicine, critical care

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## 1. Introduction

Majority of patients, in the early and immediate phase of their presentations to the hospital, will require fluid therapy. These fluids are given for various indications, from hemodynamic instability to the delivery of medications [1]. The clinical scenarios that demand the administration of fluids in the acute phase of these patients' stay in the hospital are often complex, yet the task in deciding the fluid regimen is often delegated to junior staff who may lack the necessary insight and experience [2]. Such attitude is compounded by the inadequate knowledge, among the doctors, on the essentials of intravenous fluids like the electrolyte components [3].

Intravenous fluids are drugs, and like other drugs, there are potential complications. In the acute setting where these fluids are commonplace, it is imperative that the practice aims at administering the right patient the right fluids, at the right volume and rate, with the right overall fluid balance.

2. Fluids and physiology

Water is the most important and abundant element of the human body, and the physiology that surrounds it is extensive. The following principles are at best, the foundations toward an informed fluid practice.

2.1. The body fluid compartments

Water, on average, makes up 60% of the total body weight. The percentage will vary depending on the gender and the fat content in the body. There is an inverse correlation between the water content of the body and the fat content as adipose tissue contains less water than lean tissue. This explains why women have lower percentages of water than men as they have a higher percentage of adipose tissue.

Water in the body is functionally distributed among the two main body fluid compartments, the intracellular fluid (ICF) and the extracellular fluid (ECF) (Figure 1). The ICF constitutes approximately two-thirds of the total body water or 40% of the body weight and the ECF the remaining one-third or 20% of the body weight [4]. Water crosses between the ICF and the ECF through aquaporin channels in the cell membrane to attain osmotic equilibrium. The cell

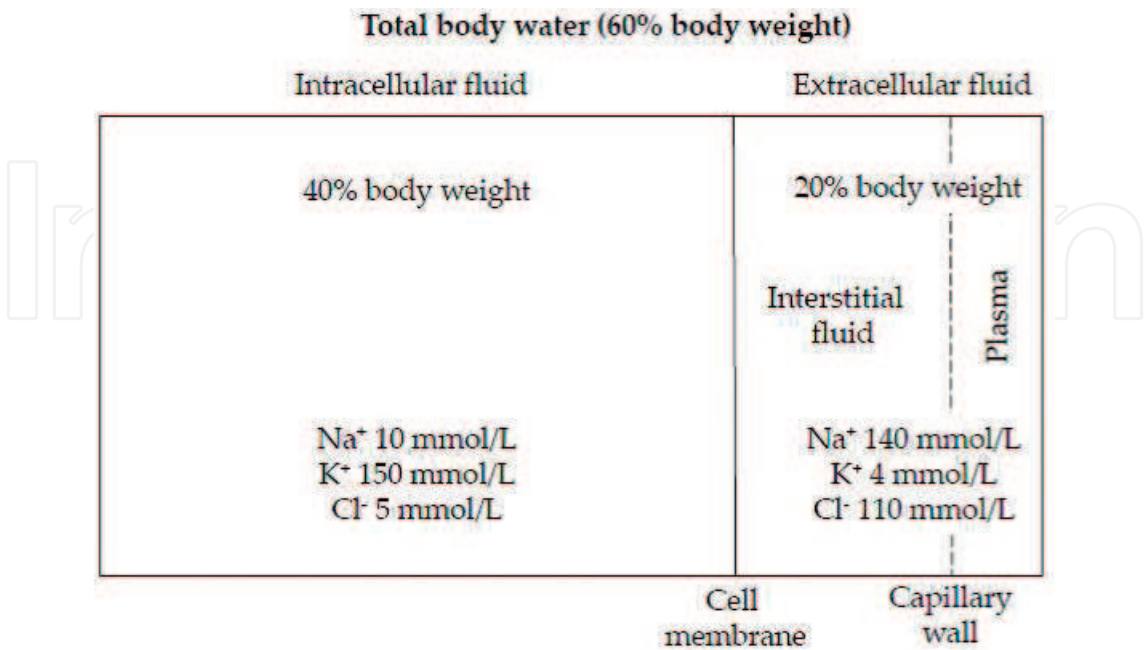


Figure 1. The distribution of total body water.

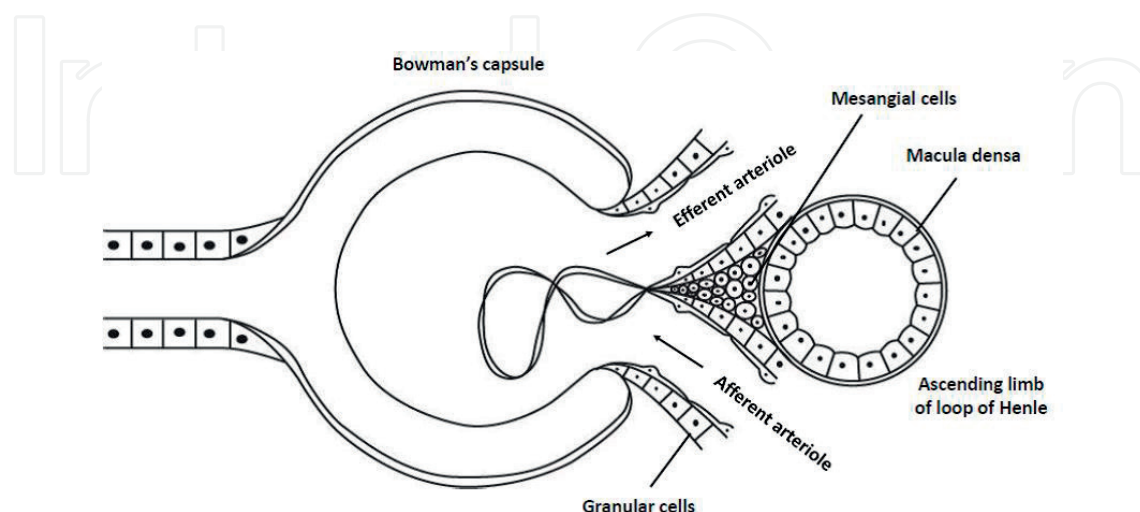
membrane also contains active pumps and transporters that distribute individual solutes, including electrolytes. These electrolytes account for the effective osmolality (tonicity) that governs the water movement. The mechanisms of these electrolyte movements are further defined by the Gibbs-Donnan effect of the nondiffusible large anions like protein. The end results are an ICF compartment with potassium ( $K^+$ ) as the predominant ion and an ECF compartment with sodium ( $Na^+$ ) and chloride ( $Cl^-$ ) as the predominant ions [5].

The ECF is further divided into the interstitial fluid and the plasma compartments, the two separated by the capillary wall. Except for plasma proteins and blood cells, the pores on the capillary wall permit the flux of water and small solutes. This contributes to the two compartments having almost similar electrolyte composition with only small differences contributed by the Gibbs-Donnan effect of the plasma proteins. By volume, these plasma proteins constitute 7% of the plasma volume with the remaining 93% plasma water. As a side note, these proteins are solids in the plasma, and the changes in their plasma load will affect the water-based measurements of plasma electrolyte concentrations [6].

## 2.2. The body fluid regulation

A complex interaction of regulatory mechanisms from different organs helps the body to maintain an effective fluid volume in different circumstances. The key pathway that underpins this volume regulation is the hormonally mediated renin-angiotensin II-aldosterone-system (RAAS), with the faster neutrally mediated baroreceptor reflex contributing an indirect role through its interplay of the pressure regulation. In the context of the fluid therapy scope of the chapter, the RAAS will be elaborated below.

The RAAS pathway is activated by a decrease in the renal perfusion pressure, detected by the juxtaglomerular apparatus (JGA) (**Figure 2**). In the JGA, the reduced renal perfusion stimulates the granular cells of the afferent arteriole to secrete the proteolytic enzyme renin through a direct intrarenal baroreceptor activity and detection of reduced sodium chloride concentrations by the macula densa in the wall of the ascending limb of the loop



**Figure 2.** The juxtaglomerular apparatus.

of Henle. Besides these mechanisms, the renin release is also controlled by renal sympathetic nerves and angiotensin II.

Renin as an enzyme will then catalyze the conversion of angiotensinogen, a large protein produced in the liver, to angiotensin I, a decapeptide. This is the rate-limiting step of the RAAS pathway (**Figure 3**). Angiotensin I has little biologic activity apart from being the precursor to angiotensin II. Its conversion to angiotensin II involves the removal of two amino acid moieties by the angiotensin-converting enzyme (ACE). ACE is primarily located in the pulmonary capillaries, but it is also found in the kidney epithelial cells.

The ultimate objective of the RAAS, through the activities of angiotensin II and aldosterone as summarized in **Figure 3**, is the preservation of effective fluid volume and pressure. The RAAS demonstrates the strong interconnection between the body fluid and electrolytes in maintaining the fluid homeostasis. In the acute setting, this interconnection is very relevant given the frequent alterations of the electrolyte contents of the body in the acute phase of illness. The assessment of electrolytes in the acute patients should, therefore, be comprehensive and extend beyond the laboratory results. For example, the assessment should also consider the potential electrolyte losses from the gastrointestinal tract, a common organ affected in acute illnesses [7].

2.3. The microcirculation model

The classic microcirculation model, based on the semipermeability of the capillary and post-capillary venule walls, and the presence of hydrostatic and oncotic pressure gradients across these walls had for long described the flux of fluids and electrolytes between the plasma and the interstitial fluid [8, 9]. The identification of the endothelial glycocalyx layer, a web of membrane-bound glycoproteins and proteoglycans on the luminal side of endothelial cells, has now challenged the classic model [10, 11]. The colloid oncotic pressure from the sub-glycocalyx space is a key determinant of the trans-capillary flow. The disruption to the integrity of the glycocalyx layer, or the “leakiness,” in a number of acute situations like sepsis [12], trauma, and postsurgery, has been attributed to the development of interstitial edema

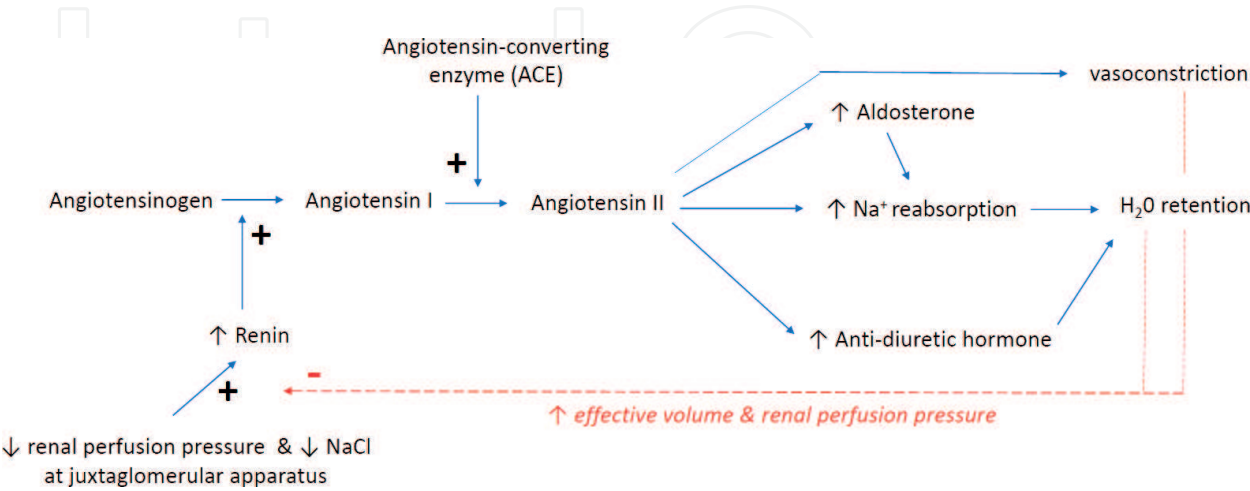
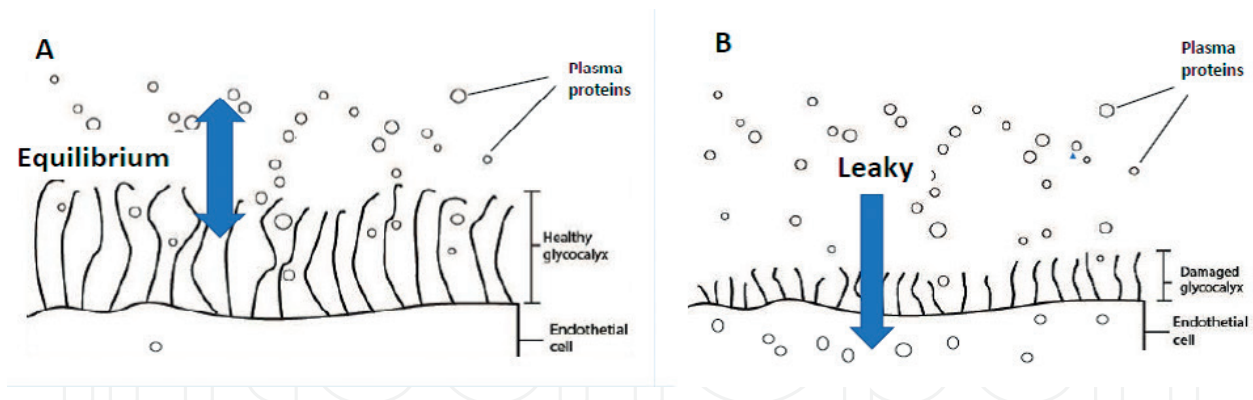


Figure 3. The renin-angiotensin II-aldosterone-system (RAAS).





**Figure 4.** The endothelial glycocalyx layer in healthy, equilibrium state (A) and damaged, leaky state (B) that leads to interstitial edema.

in various organs of the body (**Figure 4**). Appreciation of the dynamics of glycocalyx in the microcirculation of the acute cohort of patients will be integral in their fluid resuscitation and in future fluid research in such population [13, 14].

### 3. The types of fluids

The history of intravenous fluids began during the cholera pandemic in Europe in the 1830s. The success of Thomas Latta in using a saline solution to resuscitate dying cholera patients paved the way for the widespread use of intravenous fluids and the research to refine their contents [15]. The early milestones in intravenous fluid therapy included the first experiment with albumin in 1834 [16] and the attempt by Sydney Ringer to develop a physiological solution for cardiac contractility with his Ringer's solution in 1876 [17]. Ringer's solution was modified by Alexis Hartmann in 1932 by including lactate to help overcome the acidosis in dehydrated pediatric patients [18]. The gelatins and other solutions with larger molecules only broke into the scene during the Second World War [19], although the first study in humans was performed in 1915 [20]. It is interesting that the history behind the most common type of fluids used, the 0.9% saline, is unclear. The present-day 0.9% saline, often called the "normal saline," has far higher sodium and chloride concentrations than Latta's 1832 saline solution. The only possible connection to 0.9% saline in the history was the in vitro studies of Hamburger in the 1890s that described 0.9% NaCl as an "indifferent solution" in which erythrocytes were least likely to lyse [21, 22].

From the above breakthroughs, the science of intravenous fluids has grown progressively, especially in the last couple of decades. Whether medicine will find an answer to the ideal intravenous fluid will be debatable, but more evidence has emerged in the comparison between the different types of fluids available.

#### 3.1. Crystalloids

Crystalloids are solutions containing salts in the form of electrolytes and small molecules. The composition of commonly available crystalloids is given in **Table 1**.

|                 | Plasma | 0.9% NaCl | Hartmann's | Plasmalyte 148® | Sterofundin® |
|-----------------|--------|-----------|------------|-----------------|--------------|
| Sodium          | 140    | 150       | 131        | 140             | 140          |
| Potassium       | 5      | 0         | 5          | 5               | 4            |
| Chloride        | 100    | 150       | 111        | 98              | 127          |
| Calcium         | 2.2    | 0         | 2          | 0               | 2.5          |
| Magnesium       | 1      | 0         | 1          | 1.5             | 1            |
| Bicarbonate     | 24     | 0         | 0          | 0               | 0            |
| Lactate         | 1      | 0         | 29         | 0               | 0            |
| Acetate         | 0      | 0         | 0          | 27              | 24           |
| Gluconate       | 0      | 0         | 0          | 23              | 0            |
| Maleate         | 0      | 0         | 0          | 0               | 5            |
| Real osmolality | 287    | 286       | 254        | 273             | 287          |

Plasma-Lyte 148®: Baxter International, Deerfield, IL, USA; Sterofundin®: B Braun, Melsungen, Germany. All concentrations in mmol/L; osmolality in mosmol/kg.

**Table 1.** The composition of commonly used crystalloids.

Based on their differing compositions, crystalloids have been divided into saline solutions and balanced solutions. Saline solutions, chiefly the 0.9% NaCl solutions, are differentiated from the rest of crystalloids by their high contents of sodium and chloride. These concentrations of 150 mmol/L, especially for chloride, are much higher than the plasma concentrations. The 0.9% saline has thus been described as supra-physiological, and the name “normal saline” has been put to question [23, 24]. Balanced solutions, on the other hand, are other solutions like Hartmann’s, Plasmalyte 148®, and Sterofundin® that contains more closely resemble human plasma concentrations. These solutions achieve lower sodium and chloride concentrations through the addition of other electrolytes and buffers like lactate and acetate.

The debate is ongoing as to which will be the better choice for the acute population of patients, saline or balanced solutions. While saline is cheap and is still the most commonly used crystalloid in the world, there are significant concerns with its effect on acid-base balance and kidney function. The high chloride contents of saline contribute to the hyperchloremic or strong ion acidosis [25–27], and this has been well shown in different studies in different acute populations [28–30]. Given that acidosis is a common biochemical presentation in the acute setting, such acidosis could confuse patients’ assessment. This has made a case for suggesting balanced solutions as the fluid of choice, even when saline has always been the conventional prescription like in diabetic ketoacidosis [31, 32].

On the other hand, the potential risk of acute kidney injury (AKI) from the use of saline is a main research agenda. Changing the intravenous fluid practice from chloride-rich fluids (0.9% saline, 4% succinylated gelatin, or 4% albumin) to chloride-restrictive fluids (Hartmann’s solution, Plasma-Lyte 148, and 20% albumin) had been shown to reduce the incidence of AKI in the intensive care and emergency department populations in a single-center, open label sequential trial

[33–35]. Among the explanations suggested for the higher AKI incidence with the chloride-rich fluids like saline is the renal vasoconstrictive response to the high chloride delivery to the macula densa of JGA, a mechanism similar to the regulatory tubuloglomerular feedback [36, 37]. Similar trends of results implicating saline with AKI have been repeated in large retrospective trials [38, 39]. However, the only three large randomized trials comparing saline with balanced solutions to date have shown inconsistent results. These cluster randomized trials either showed no difference in renal outcomes [40] or a significant increase in major adverse kidney events within 30 days in the saline group for both the intensive care and emergency department populations [41, 42].

While large multicenter randomized controlled trials are ongoing to provide stronger evidence on the issue of saline [43, 44], there has been a notable shift in clinical practice with an increasing use of the balanced solutions [45]. 0.9% saline, nonetheless, remains the fluid of choice for patients with metabolic acidosis, hyponatremia, and traumatic brain injury, the latter attributed to its relatively high osmolality.

### 3.2. Colloids

Colloid solutions are characterized by the large molecules suspended in carrier solutions that would also contain electrolytes. The colloid osmotic pressure or oncotic pressure generated by these large molecules helps to retain fluid in the intravascular space longer. The composition of the commonly available colloids is in **Table 2**.

The volume effect of colloid, when compared to crystalloid, has traditionally been thought to be at a 1:3 ratio. This gives colloid a perceived advantage in reducing the volume of fluid

|                 | Plasma | Gelofusine® | Albumex®4 | Albumex®20 | Voluven® (HES 6% 130/0.4) |
|-----------------|--------|-------------|-----------|------------|---------------------------|
| Sodium          | 140    | 154         | 140       | 48-100     | 154                       |
| Potassium       | 5      | 0           | 0         | 0          | 0                         |
| Chloride        | 100    | 125         | 128       | 19         | 154                       |
| Calcium         | 2.2    | 0           | 0         | 0          | 0                         |
| Magnesium       | 1      | 0           | 0         | 0          | 0                         |
| Bicarbonate     | 24     | 0           | 0         | 0          | 0                         |
| Lactate         | 1      | 0           | 0         | 0          | 0                         |
| Acetate         | 0      | 0           | 0         | 0          | 0                         |
| Malate          | 0      | 0           | 0         | 0          | 0                         |
| Octanoate       | 0      | 0           | 6.4       | 32         | 0                         |
| Real osmolality | 287    | 271         | 260       | 130        | 298                       |

HES: hydroxyethyl starch. Gelofusine®: B Braun, Melsungen, Germany; Albumex®: CSL Limited, Victoria, Australia; Voluven®: Fresenius-Kabi, Bad Homburg, German. All concentrations in mmol/L; osmolality in mosmol/kg.

**Table 2.** The composition of commonly used colloids.



infused during resuscitation. However, data from recent large multicenter trials on the use of different types of colloids suggested a smaller colloid: crystalloid ratio, between 1:1.1 and 1:1.6 [46–49]. The finding of smaller volume effect advantage from colloid than previously thought adds to the predominant concern on the use of colloid—its effects on the kidney.

Strong evidence emerged in the last decade demonstrating a significant association between the risk of renal dysfunction, measured as AKI, and the need for renal replacement therapy, with the use of hydroxyethyl starch in the acute population of sepsis and intensive care [46, 47]. There are also doubts from observational data on the renal safety of another choice of colloid, the gelatins, in the septic population [50, 51]. The hyperoncotic albumin solutions (20–25%), on the other hand, have been associated with increased risk of renal events when used in cardiac surgery [52] and in patients in shock [53].

Besides these renal effects, colloids are more expensive than crystalloids, and there has been an absence of their clinical superiority over crystalloids in the mortality outcome of studies on different acute populations [49, 54, 55]. All these lead to the call for caution in the use of colloids. The recent Surviving Sepsis Guidelines, for example, strongly recommend against the use of hydroxyethyl starches and place albumin and gelatins as a second choice to crystalloids in sepsis fluid resuscitation [56].

## 4. Delivering fluid therapy

Following an evidence-informed choice of fluid, the next set of decisions will be equally crucial: how to administer the fluid, how to measure the patient's response to the fluid, and how much fluid should be given. Strategizing intravenous fluid delivery to an acute patient should include a well thought-out plan for these three important elements.

### 4.1. Resuscitation and the fluid challenge

A key aim of the fluid resuscitation in the acute setting is to exert a hemodynamic impact, increasing the venous return and the stroke volume. To achieve this, the concept of fluid challenge or fluid bolus was introduced almost four decades ago [57, 58]. The fluid challenge is a targeted administration approach through the delivery of a small amount of fluid over a short period of time, with an assessment of the fluid responsiveness [59].

The administration of fluid challenge has been one of the most diverse practices in fluid therapy. Recent attempts at identifying the global patterns in fluid challenge have provided valuable information. A global inception cohort study on fluid challenge involving 2213 patients across ICUs in 46 countries revealed a median amount of fluid challenge volume of 500 ml, a median time of 24 min, a median rate of fluid administration of 1000 ml/h, and a predominant choice of crystalloids [60]. Interestingly, categorizing patients as fluid responsive, non-fluid responsive, or uncertain fluid responsive did not make any difference to the receipt of further fluid administration in this study. In another study on the worldwide fluid challenge practices, involving 3138 intensive care specialists from 30 countries, more than 80% respondents

defined the fluid bolus therapy as delivery of more than 250 mL of either colloid or crystalloid fluid over less than 30 minutes, with crystalloids the most acceptable [61]. These numbers only reflect the majority views on the fluid challenge and must be interpreted in the context of the other aspects of an acute fluid strategy—the fluid responsiveness and the fluid balance.

#### 4.2. Fluid responsiveness

Clinical assessment is always an integral component of any fluid therapy approach. Identifying body volume repletion and the likelihood to respond to fluid resuscitation should begin with the background history and elicitation of signs of volume deficits, from the peripheral temperature gradient and capillary refill time [62] to the tachycardia, decreased mean arterial pressure, and oliguria. However, reliance on these clinical signs alone for assessment of volume status and responsiveness could be misleading [63–65]. For instance, an increase in the mean arterial pressure following a fluid challenge could be a result of the changes in the arterial vascular tone rather than a true increase in cardiac output.

Beyond clinical signs, the indices of fluid responsiveness—both static and dynamic—have been extensively studied. The static index of central venous pressure (CVP), arguably the most commonly used measure of fluid responsiveness, has long been shown to have no meaningful relationship to fluid volume and should be abandoned [66]. Similarly, the more invasive static index measurement of pulmonary artery occlusion pressure (PAOP) has its limitations and does not predict fluid responsiveness [67, 68].

The dynamic indices of fluid responsiveness work on the basis of inducing a change in preload and following up the effects on stroke volume and cardiac output [69]. There are different versions of these dynamic measurements with many evolving around the respiratory variation of hemodynamic indices. Examples include the pulse pressure variation (PPV), the pulse contour-derived stroke volume, the inferior vena cava (IVC) parameters assessed by ultrasonography, and the descending aortic blood flow assessed by esophageal Doppler [70–75]. There are, however, limitations to the observations of these respiratory variations. Some of these are of practical significance, like the need for tidal volumes of >7 mL/kg, the absence of spontaneous ventilatory efforts, and the absence of arrhythmia.

An approach to assessment of fluid responsiveness that is not affected by the practical ventilatory limitations above is the passive leg raising, PLR [76]. The postural change in PLR transfers around 300 mL of venous blood from the lower body to the heart. The advantage of this is it is an endogenous fluid challenge that is rapidly reversible [77]. To date, the PLR has been deemed as the most reliable measure of fluid responsiveness [78], although an increase in the intra-abdominal pressure or pain could give a false-negative result [79].

It is important to recognize that fluid responsiveness does not necessarily mean that fluid challenges must be given. It also does not mean that patients should be receiving fluid challenges until they are no longer fluid responsive. The hemodynamic benefits of the fluid boluses should be weighed against the risks of accumulating positive fluid balance, with a strong consideration of the use of vasopressors like noradrenaline to improve organ perfusion [80].

### 4.3. The importance of fluid balance

Fluid accumulation in the acute setting is a frequent event. While everything is geared toward early and aggressive fluid resuscitation, as it should be, less emphasis is given toward the risks associated with fluid accumulation and overload. As fluid overload is shown to contribute to poorer outcomes in different acute populations [81–84], it becomes imperative to achieve the right balance between overcoming hypovolemia and organ hypoperfusion and avoiding the dangers of fluid overload [85].

A common quantitative definition of fluid overload in the literature is a percentage fluid accumulation of >10%, determined by dividing the cumulative fluid balance in liter by the patient's baseline body weight and multiplying by 100% [86, 87]. This is, however, on the assumption that the patient is volume depleted on admission to the acute unit, which is not necessarily the case as some patients have already been accumulating fluid by then. The negative effects of the excess fluid have been shown in various organ systems. In a large RCT, higher cumulative fluid balance was associated with longer mechanical ventilation duration and length of ICU stay and without reducing the incidence of shock and the need for renal replacement therapy [88]. In managing intra-abdominal hypertension and abdominal compartment syndrome, poorer outcomes have been attributed to fluid overload [89, 90], a phenomenon linked to capillary leak and tissue edema. While fluid is often aggressively given to prevent AKI, the association between fluid overload and poorer renal outcomes has been evident [86, 91, 92], prompting questions on the cause-effect relationship between fluid overload and AKI [93].

A comprehensive fluid strategy will require a close monitoring of the fluid balance. In this context, a mindset of fluids as drugs will promote careful considerations of the indications and the doses of the fluids, recognizing that more is not always better.

## 5. Conclusion

In conclusion, fluid therapy in the acute setting is a challenging and complex task for the clinicians. Two areas that are beyond the scope of the chapter—the specific needs of the different subpopulations of acute patients and the different access to resources at different locations of practice—further add to the complexity. Emerging evidence on various facets of fluid therapy has helped to offer some consistency in approach in what has been a very diverse practice. The underpinning principle should be fluids are drugs that must be chosen and prescribed correctly, as wrong choice and doses lead to adverse effects.

### Conflict of interest

The author declares no competing interest.

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